expression of one or more of *ADGRG7, FN1, KCNA1, VSIG2, CNN1, ABCB1,ABCB4, COCH, MAGED4, IGSF5,PCP4, MARVELD3, MIR5188, FRZB, ELMOD1, MSI1, HPGD, TPBG, F5, THBS2, ECEL1P1/2, CPVL,LINC02258, CD86, DLK1, FOXF2, GMNC, GPR34, IGKV3-20, IGKV6D-21, TMEM255A, CDKN2A, CLEC5A, MARCH1, GPC3, HLA-DQA1, HLA-DRA, CYBB, GRM5,NOX4, IGKC,IGKJ1,IGKJ2, C3AR1, DCX, MMP2-AS1, LYVE1, FAM198B, FCGR1B, FOLR2, FCGR3A, TNFRSF11B, PSG4, KRT7, COL4A2, CTGF, COL9A3, COL1A2, FGFR2, NOTCH2, TGFBR1, IFNGR1, TGFBR2, NOTCH1, HLA-DPB1, IL18, JAG1, CD4, SPI1, PIK3R5, ITGB2, NFATC2, HLA-DPA1, HLA-DOA, IKZF1, IL10RA, MAPK10, BCL2, COL5A2, ROR2, ACKR1, CADM3, VIPR2, ADAM33, CADM3-AS1, TSHR, DPP10, CLIC6, TMEM30B, LGR6, CST4, ICA1, ALPK2, RARRES2, MMP19, DCDC2C, CST1, ITPRIPL1, WNT3, SLC5A1, ARSJ, GREB1L, SLC16A9, EPHB6, MROH9, ENOX1, PLAC9, KIF21B, ADAMTS12, ITIH5, ANXA3, PROS1, PTPN3,* or *DCLK1*. The therapeutic agents can be small molecule inhibitors, oligonucleotides, siRNAs, antibodies, RNAi, shRNA, miRNA, viral vectors, non-viral delivery, and CRISPR-Cas system, zinc finger nucleases, and TALENs. The method can further comprise treating the subject with one or more therapeutic agents that increase the amount of expression of one or more of *SAA2/4, NPBWR1, GFAP, DNER, INPP5D, SYNDIG1, CSF3, SPATA18, CLEC4GP1, OVCH1, LINC01811, CLIC5, FAM107A, PNMT, CYTL1, ,SERPINA3/4/5, TMOD1, HMGN2P17, GPRC5B, DRD2, PSPHP1, CDH12, IL17REL, ARC, UBE2W, RNU5E-1, CXCL8, LINC00881,LINC02029, CXCL3, RNU2-63P, CXCL2, RASD1, RNU6-1208P, UTY, CD24P4,RNU6-255P,TTTY14, KDM5DP1,TTTY10, NLGN4Y, RNU1-59P, ZFY, STK40, RNU5B-1, LINC01783,RNU1-6P, RNU1-5P, EPS8L1, LUM, KDR, SOD3, IRF1, JUN, SOCS3, NFIL3, FGFR4, NFKB1, SOD2, MAOA, CYCS, SNCA, PDHA1, UQCRH, COX7B, COX5B, NDUFV1, UQCRC2, NDUFA1, CYC1, UQCRB, VDAC2, COX4I1, SDHB, COX6B1,* or *MAOB*. The therapeutic agents can be gene replacement therapy, saRNA, RNAa, CRISPR-Cas system, increasing RNA transcription or translation, and cell-based therapies.

[0013] Another embodiment provides a method of monitoring treatment of Fuchs' endothelial corneal dystrophy (FECD) comprising: (a) obtaining a first sample from a subject; (b) detecting gene expression levels of one or more of *ADGRG7, FN1, KCNA1, VSIG2, CNN1, ABCB1,ABCB4, COCH, MAGED4, IGSF5,PCP4, MARVELD3, MIR5188, FRZB, ELMOD1, MSI1, HPGD, TPBG, F5, THBS2, ECEL1P1/2, CPVL,LINC02258, CD86, DLK1, FOXF2, GMNC, GPR34, IGKV3-20,*

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IGKV6D-21, TMEM255A, CDKN2A, CLEC5A, MARCH1, GPC3, HLA-DQA1, HLA-DRA, CYBB, GRM5,NOX4, IGKC,IGKJ1,IGKJ2, C3AR1, DCX, MMP2-AS1, LYVE1, FAM198B, FCGR1B, FOLR2, FCGR3A, TNFRSF11B, PSG4, KRT7, COL4A2, CTGF, COL9A3, COL1A2, FGFR2, NOTCH2, TGFBR1, IFNGR1, TGFBR2, NOTCH1, HLA-DPB1, IL18, JAG1, CD4, SPI1, PIK3R5, ITGB2, NFATC2, HLA-DPA1, HLA-DOA, IKZF1, IL10RA, MAPK10, BCL2, COL5A2, ROR2, ACKR1, CADM3, VIPR2, ADAM33, CADM3-AS1, TSHR, DPP10, CLIC6, TMEM30B, LGR6, CST4, ICA1, ALPK2, RARRES2, MMP19, DCDC2C, CST1, ITPRIPL1, WNT3, SLC5A1, ARSJ, GREB1L, SLC16A9, EPHB6, MROH9, ENOX1, PLAC9, KIF21B, ADAMTS12, ITIH5, ANXA3, PROS1, PTPN3, DCLK1, SAA2/4, NPBWR1, GFAP, DNER, INPP5D, SYNDIG1, CSF3, SPATA18, CLEC4GP1, OVCH1, LINC01811, CLIC5, FAM107A, PNMT, CYTL1, ,SERPINA3/4/5, TMOD1, HMGN2P17, GPRC5B, DRD2, PSPHP1, CDH12, IL17REL, ARC, UBE2W, RNU5E-1, CXCL8, LINC00881,LINC02029, CXCL3, RNU2-63P, CXCL2, RASD1, RNU6-1208P, UTY, CD24P4,RNU6-255P,TTTY14, KDM5DP1,TTTY10, NLGN4Y, RNU1-59P, ZFY, STK40, RNU5B-1, LINC01783,RNU1-6P, RNU1-5P, EPS8L1, LUM, KDR, SOD3, IRF1, JUN, SOCS3, NFIL3, FGFR4, NFKB1, SOD2, MAOA, CYCS, SNCA, PDHA1, UQCRH, COX7B, COX5B, NDUFV1, UQCRC2, NDUFA1, CYC1, UQCRB, VDAC2, COX4I1, SDHB, COX6B1, or *MAOB*; or detecting one or more skipped exon events as shown in Table 8 in the first sample obtained from the subject; (c) administering a treatment to the subject; (d) obtaining a second sample from the subject at a later time and detecting gene expression levels or skipped exon events of (b) in the second sample; and (e) comparing the first sample gene expression levels or skipped exon events with the second sample gene expression levels or skipped exon events.

[0014] The first sample and second sample can be corneal tissue, aqueous humor, plasma, serum, blood, tear film, trabecular meshwork, or a combination thereof. The treatment can comprise therapeutic agents that increase gene expression, therapeutic agents that decrease gene expression, steroidal eye drops, sodium chloride eye drops, keratoprosthesis implantation, therapeutic contacts, corneal transplant, endothelial keratoplasty, penetrating keratoplasty, prostaglandins, beta blockers, alpha-adrenergic agonists, carbonic anhydrase inhibitors, rho kinase inhibitors, miotic or cholinergic agents, or combinations thereof. The method can further comprise repeating steps (a)-(e) one, two, three, or more times.

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[0015] An additional embodiment provides a method of monitoring progression of Fuchs' endothelial corneal dystrophy (FECD) comprising: (a) obtaining a first sample from a subject; (b) detecting gene expression levels of one or more of *ADGRG7, FN1, KCNA1, VSIG2, CNN1, ABCB1,ABCB4, COCH, MAGED4, IGSF5,PCP4, MARVELD3, MIR5188, FRZB, ELMOD1, MSI1, HPGD, TPBG, F5, THBS2, ECEL1P1/2, CPVL,LINC02258, CD86, DLK1, FOXF2, GMNC, GPR34, IGKV3-20, IGKV6D-21, TMEM255A, CDKN2A, CLEC5A, MARCH1, GPC3, HLA-DQA1, HLA-DRA, CYBB, GRM5,NOX4, IGKC,IGKJ1,IGKJ2, C3AR1, DCX, MMP2-AS1, LYVE1, FAM198B, FCGR1B, FOLR2, FCGR3A, TNFRSF11B, PSG4, KRT7, COL4A2, CTGF, COL9A3, COL1A2, FGFR2, NOTCH2, TGFBR1, IFNGR1, TGFBR2, NOTCH1, HLA-DPB1, IL18, JAG1, CD4, SPI1, PIK3R5, ITGB2, NFATC2, HLA-DPA1, HLA-DOA, IKZF1, IL10RA, MAPK10, BCL2, COL5A2, ROR2, ACKR1, CADM3, VIPR2, ADAM33, CADM3-AS1, TSHR, DPP10, CLIC6, TMEM30B, LGR6, CST4, ICA1, ALPK2, RARRES2, MMP19, DCDC2C, CST1, ITPRIPL1, WNT3, SLC5A1, ARSJ, GREB1L, SLC16A9, EPHB6, MROH9, ENOX1, PLAC9, KIF21B, ADAMTS12, ITIH5, ANXA3, PROS1, PTPN3, DCLK1, SAA2/4, NPBWR1, GFAP, DNER, INPP5D, SYNDIG1, CSF3, SPATA18, CLEC4GP1, OVCH1, LINC01811, CLIC5, FAM107A, PNMT, CYTL1, SERPINA3/4/5, TMOD1, HMGN2P17, GPRC5B, DRD2, PSPHP1, CDH12, IL17REL, ARC, UBE2W, RNU5E-1, CXCL8, LINC00881,LINC02029, CXCL3, RNU2-63P, CXCL2, RASD1, RNU6-1208P, UTY, CD24P4,RNU6-255P,TTTY14, KDM5DP1,TTTY10, NLGN4Y, RNU1-59P, ZFY, STK40, RNU5B-1, LINC01783, RNU1-6P, RNU1-5P, EPS8L1, LUM, KDR, SOD3, IRF1, JUN, SOCS3, NFIL3, FGFR4, NFKB1, SOD2, MAOA, CYCS, SNCA, PDHA1, UQCRH, COX7B, COX5B, NDUFV1, UQCRC2, NDUFA1, CYC1, UQCRB, VDAC2, COX4I1, SDHB, COX6B1,* or *MAOB*; or detecting one or more skipped exon events as shown in Table 8 in the first sample obtained from the subject; (c) obtaining a second sample from the subject at a later time and detecting gene expression levels or skipped exon events of (b) in the second sample; and (d) comparing the first sample gene expression levels or skipped exon events with the second sample gene expression levels or skipped exon events.

[0016] The first sample and second sample can be corneal tissue, aqueous humor, plasma, serum, blood, tear film, trabecular meshwork, or a combination thereof. The method can further comprise repeating steps (a)-(d) one, two, three, or more times.

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[0017] A further embodiment provides a method of detecting glaucoma in a subject comprising detecting an increase in expression of *COCH* in a sample obtained from the subject.

[0018] The sample can be corneal endothelial cells, corneal tissue, aqueous humor, plasma, serum, blood, tear film, trabecular meshwork, or a combination thereof. The method can further comprise treating the subject with one or more therapeutic agents that decrease *COCH* expression, prescription eyedrops, oral medications, prostaglandins, beta blockers, alpha-adrenergic agonists, carbonic anhydrase inhibitors, rho kinase inhibitors, miotic or cholinergic agents, laser trabeculoplasty, trabeculectomy, drainage tubes, minimally invasive glaucoma surgery (MIGS), peripheral iridotomy, aqueous shunts, or combinations thereof. The treatment can be delivered to the anterior segment of the eye, posterior segment of the eye, corneal endothelial cells, or other cells of the anterior segment of an eye. The therapeutic agents can be small molecule inhibitors, oligonucleotides, siRNAs, antibodies, RNAi, shRNA, miRNA, and CRISPR-Cas system, zinc finger nucleases, and TALENs.

[0019] Yet another embodiment provides a method of monitoring treatment of glaucoma comprising: (a) obtaining a first sample from a subject; (b) detecting gene expression levels of *COCH* in the first sample obtained from the subject; (c) administering a treatment to the subject; (d) obtaining a second sample from the subject at a later time and detecting gene expression levels of *COCH* in the second sample; and (d) comparing the first sample gene expression levels with the second sample gene expression levels.

[0020] The sample can be corneal tissue, aqueous humor, plasma, serum, blood, tear film, trabecular meshwork, or a combination thereof. The treatment can be therapeutic agents that decrease *COCH* expression, prescription eyedrops, oral medications, prostaglandins, beta blockers, alpha-adrenergic agonists, carbonic anhydrase inhibitors, rho kinase inhibitors, miotic or cholinergic agents, laser trabeculoplasty, trabeculectomy, drainage tubes, minimally invasive glaucoma surgery (MIGS), peripheral iridotomy, aqueous shunts, or combinations thereof. The therapeutic agents can be small molecule inhibitors, oligonucleotides, siRNAs, antibodies, RNAi, shRNA, miRNA, viral vectors, non-viral delivery, CRISPR-Cas system, zinc finger nucleases, and TALENs. The method can further comprise repeating steps (a)-(e) one, two, three, or more times.

[0021] Still another embodiment provides a method of monitoring progression of glaucoma comprising: (a) obtaining a first sample from a subject; (b) detecting gene expression levels of *COCH* in the first sample obtained from the subject; (c) obtaining a second sample from the subject at a later time and detecting gene expression levels of *COCH* in the second sample; and (d) comparing the first sample gene expression levels with the second sample gene expression levels.

[0022] The sample can be corneal tissue, aqueous humor, plasma, serum, blood, tear film, trabecular meshwork, or a combination thereof. The method can further comprise repeating steps (a)-(d) one, two, three, or more times.

[0023] For purposes of summarizing, certain aspects, advantages, and novel features have been described herein. It is to be understood that not all such advantages may be achieved in accordance with any one particular embodiment. Thus, the disclosed subject matter may be embodied or carried out in a manner that achieves or optimizes one advantage or group of advantages without achieving all advantages as may be taught or suggested herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0024] The features, objects and advantages other than those set forth above will become more readily apparent when consideration is given to the detailed description below. Such detailed description makes reference to the following drawings, wherein:

[0025] **FIG. 1** show preparation of homogeneous tissue monolayers for analysis. **(A)** Human donor cornea in corneal viewing chamber with Optisol corneal storage media (Bausch & Lomb). **(B)** Corneal endothelium / Descemet's membrane monolayer being dissected from underlying stromal tissue. **(C)** Monolayer of corneal endothelial cells assumes a "scroll" shape. This single cell monolayer will be used for sequencing and other analyses. **(D)** Immunostaining of monolayer of cells with corneal endothelial specific marker, zonula occudens-1 (ZO-1) (nuclei-DAPI).

[0026] **FIG. 2** shows experimental scheme and sample cohorts. **(A)** Homogenous samples of corneal endothelium are surgically removed from normal, presymptomatic and, affected (FECD or FECD_NR) tissue bank donors or patients and used for RNAseq followed by data analysis. **(B)** Detailed description of tissue samples. **(C)** Dendrogram for four groups of samples and **(D)** all replicates. RIN:RNA integrity number. CTG18.1: the number of repeats on each chromosome.

[0027] **FIG. 3** shows intronic RNA stabilized in Pre_S and FECD_REP tissue and FECD_REP patient-derived F35T and F45SV corneal endothelial cells. **(A)**

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Representative RNAseq data showing relative read number for *TCF4* intron 2 RNA from each sample cohort. **(B)** Summary of RNA half-life of different cell lines after treatment with actinomycin D. The much longer half life of intron 2 up-stream RNA in F35T and F45SV cells is listed in the second row, sixth column and third row, sixth column. **(C)** Graphs of time-dependent RNA decay following treatment with actinomycin D.

[0028] **FIG. 4** shows RNAseq data demonstrates changes in splicing in pre-symptomatic, FECD_REP, and FECD_NR tissue. **(A)** Alternative splicing events in Pre_S, FECD_REP, and FECD_NR cohorts. **(B)** Overlap between sample cohorts for skipped exon (SE) events showing that late stage disease FECD_REP and Pre_S cohorts cluster differently from control or FECD_NR cohorts. **(C)** Heat map comparing inclusion levels of exons among 4 cohorts. The chosen SE events were based on the 313 significant skipped exon events identified in Pre_S tissues. The Pre_S cohort is more similar to FECD_REP than it is to the other two cohorts. **(D)** The similarity of Pre_S and FECD_REP is emphasized by a heat map comparing top 25 SE events in common between FECD_REP and Pre_S tissues and corresponding changes in FECD_NR and control tissues. **(E)** Identity of top 24 SE events in common between FECD_REP and Pre_S. Genes *COPZ2, MBNL2, SORBS1, KIF13A, CLASP1, ARHGEF10L, NUMA1,* and *VPS39* are also observed in RNAseq data from DM1 tissue, demonstrating substantial overlap despite different tissue origins. The threshold used in identifying the significant events: FDR < 0.001, |IncLevel Difference| >= 0.15.

[0029] **FIG. 5** show differential gene splicing is similar in Pre_S and FECD_REP tissue. **(A)** Representative Sashimi plots showing changes in alternative splicing for *MBNL2* and *SYNE1* transcripts in Control versus Pre_S and FECD_REP tissues. **(B)** Reverse-transcriptase PCR evaluation of RNA splicing changes in Control, Pre_S and FECD_REP tissue. All measurements used surgically prepared corneal endothelium from disease patients or donors detailed in Table 6.

[0030] **FIG. 6** shows RNAseq analysis of gene expression. **(A)** Overlap for gene expression of Pre-S, FECD_REP, and FECD_NR cohorts showing that Pre_S is more similar to FECD_REP than FECD_NR. Numbers indicate the number of differentially expressed genes identified in each individual region. **(B)** Volcano plots for Pre_S vs. Control, FECD_Rep vs. Control, FECD_NR vs. Control and FECD_REP vs. FECD_NR and top genes in each comparison. **(C)** Top 20

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upregulated (left side) and downregulated (right side) genes in Pre_S vs. control comparison. Where Rna-seq analysis finds similar reads for two or more genes, those genes are listed together.

[0031] **FIG. 7** shows changes in gene expression in Pre_S and FECD_REP tissue. qPCR evaluation of gene expression levels in Control, Pre_S, and FECD_REP tissue. All measurements used surgically prepared single cell monolayer corneal endothelium from disease patients or donors detailed in Table 6.

[0032] **FIG. 8** shows pathway analysis. **(A)** Top 25 pathways based on FECD_REP. The *p*-values for three cohorts for each pathway are shown in the last three columns. **(B)** Shared differentially expressed genes in Fibrosis pathway between Pre-S and FECD_REP. **(C)** Changes in Th1/2 pathway genes for FECD_NR and FECD_REP. **(D)** Significant expression level changes in genes involved in mitochondrial dysfunction seen in FECD_REP but not in FECD_NR. FPKM > 1.5, fold change > 1.5, FDR <=0.05.

[0033] **FIG. 9** shows expression profile of genes in Hepatic fibrosis pathway for Pre_S cohort. FPKM > 1.5, fold change > 1.5, FDR <=0.05. The six largest fold changes in gene expression (**FIG. 8**) are outlined in rectangles.

[0034] **FIG. 10** shows schematic diagram of FECD molecular and disease progression from CTG expanded repeat mutation at the *TCF4* locus to advanced FECD. Initially the GTC expansion expresses the CUG repeat RNA. Because the expanded repeat mutation that causes FECD-REP is a relatively common genetic mutation, Pre_S tissue is available for analysis. Pre_S tissue appears normal upon clinical observation. However, in Pre_S tissue foci can be detected, we observe changes in splicing and gene expression, the mutant intronic repeat is stabilized, and early signs of fibrosis pathway activation are apparent. In late stage disease, more pronounced changes in splicing and gene expression accompany clinically observable systems and loss of vision.

[0035] **FIG. 11** shows sample characterization and clustering. **(A)** Principle Component Analysis (PCA) plot showing the group relationship based on gene expression for four groups of samples. **(B)** PCA plot for all the replicates.

[0036] **FIG. 12** shows quality examination of all RNA samples used for RNA-seq. **(A)** Heatmap showing the gene body converge from 5- end to 3'-end for all the samples. **(B)** Gene body percentile plot from 5'- to 3'-end for all the samples.

[0037] **FIG. 13** shows RNA Electropherograms. **(A)** RNA Electropherogram for all the RNA-seq samples generated by Agilent Bioanalyzer 2100. **(B)** RNA Electropherogram for each of the RNA-seq samples generated by Agilent Bioanalyzer 2100. **(C)** RNA Electropherogram for all the RNA-seq samples generated by Agilent Bioanalyzer 2100.

[0038] **FIG. 14** shows expression levels of *TCF4*, *MBNL1*, and *MBNL2* mRNA. Measurements were made using RNAseq and corneal endothelial tissue samples from the four sample cohorts. No statistically significant differences were observed. Error bar stands for 95% confidence interval.

[0039] **FIG. 15** shows comparison of *TCF4* mRNA levels in FECD patient derived endothelial cell lines F35T, F45SV with VVM84 fibroblast cells by qPCR analysis. T-Test: F35T/VVM84, p=0.21; F45SV/VVM84, p=0.18; F35T/F45SV, p=0.82.

[0040] **FIG. 16** shows the upstream region of intron 2 is not retained in mature mRNA. Primers were designed to target exon 2 and exon 3. Amplification yielded a product consistent with complete removal of intron 2.

[0041] **FIG. 17** shows RNAseq data demonstrates changes in splicing in pre-symptomatic, FECD_REP, and FECD_NR tissue. **(A)** Alternative 5' splice site (A5SS) in Pre_S, FECD_REP, and FECD_NR cohorts (relative to control). **(B)** Alternative 3'-splice site (A3SS) in Pre_S, FECD_REP, and FECD_NR cohorts (relative to control). **(C)** Mutually exclusive exon (MXE) in Pre_S, FECD_REP, and FECD_NR cohorts (relative to control). **(D)** Retained intron (RI) in Pre_S, FECD_REP, and FECD_NR cohorts (relative to control). The threshold used in identifying the significant events: FDR < 0.001, |IncLevel Difference| >= 0.15. **(E)** Skipped exon events are shared among Pre_S, FECD_REP and DM1. **(F)** Details of 13 shared SE events among three groups, FECD_REP, Pre_S, and DM1. DM1 raw data was obtained from Gene Expression Omnibus (GSE86356) and analyzed similarly as the FECD data (visit DMseq.org for more information). **(G)** Basic functions of commonly shared genes listed in **(F)**.

[0042] **FIG. 18** shows quantification of mis-spliced genes in Pre_S, FECD_REP and healthy control endothelium tissues. **(A)** Ratio of selected exon exclusion verse inclusion found in samples by RNA_Seq analysis. **(B)** Ratio of the same exon exclusion verse inclusion verified in samples by RT-PCR showed in **FIG. 5**. T-Test: $^{**}p<0.01$, $^{***}p<0.001$ relative to exon exclusion ratio with control group.

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[0043] **FIG. 19** shows differential gene expression analysis with DeSeq2. **(A)** PCA plot for all 25 replicates from all genes analyzed by DeSeq2. **(B)** Boxplot showing the expression levels of 8 selected genes in Control, Pre_S, FECD_REP and FECD_NR tissue replicates. The results were obtained with CuffDiff. **(C)** Boxplot showing the expression levels of 8 selected genes in Control, Pre_S, FECD_REP and FECD_NR tissue replicates. The results were obtained with DeSeq2.

[0044] **FIG. 20** shows top differentially expressed genes in Pre_S tissues. **(A)** Boxplot showing the level of top 20 upregulated differentially expressed genes in Pre_S tissue replicates. **(B)** Boxplot showing the level of top 20 downregulated differentially expressed genes in Pre_S tissue replicates. A total of 215 differentially expressed genes were identified in Pre_S vs. Control. FPKM > 1.5, fold change > 1.5, FDR <=0.05.

[0045] **FIG. 21** shows detailed pathway analysis. **(A)**. Expression profile of genes in hepatic fibrosis pathway, all cohorts. FPKM > 1.5, fold change > 1.5, FDR <=0.05. **(B)** Expression profile of genes in Hepatic fibrosis pathway for Pre_S cohort. FPKM > 1.5, fold change > 1.5, FDR <=0.05. First column in each gene panel is control, second column is Pre_S, third column is FEDC_REP, fourth column is FEDC_NR. **(C)** Diagram of hepatic fibrosis / hepatic stellate activation pathway based on the comparison of FECD_REP versus Control tissue. Differentially expressed genes that are upregulated are pink and downregulated genes are green. Stars mark genes that also change in Pre_S tissue compared to Control samples. **(D)** Th1/2 activation pathway. FPKM > 1.5, fold change > 1.5, FDR <=0.05. **(E)** Gene expression changes for NFAT pathway. FPKM > 1.5, fold change > 1.5, FDR <=0.05. **(F)** Neuroinflammation Signaling Pathway. FPKM > 1.5, fold change > 1.5, FDR <=0.05. **(G)** Volcano plot of DE genes involved in mitochondrial dysfunction in FECD_REP. **(H)** A scatter 3D plot showing a group of genes involved in mitochondrial dysfunction are differentially expressed in FECD_REP, but not in FECD_NR. X-axis: gene list, y-axis: log2-fold change, z-axis: -log10(adjusted p-value).

[0046] **FIG. 22** shows top 20 upregulated (left side) and top downregulated (right side) genes in **(A)** FECD_REP vs. Control; **(B)** FECD_NR vs. Control. Where Rna-seq analysis finds similar reads for two or more genes, those genes are listed together.

[0047] **FIG. 23** shows the log2FC values and adjusted p-values for 42 fibrosis-pathway associated genes in FECD_REP and Pre_S. These genes were found to be differentially expressed in FECD_REP. For a gene to be considered expressed, its expression level has to be higher than 1.5 FPKM. NA in the following table denotes that a gene is not expressed or its level < 1.5 FPKM.

[0048] **FIG. 24** shows *COCH* mRNA expression is up-regulated in FECD samples. **(A)** *COCH* expression is up-regulated in corneal endothelial cells from FECD/REP, FECD/NR or Pre_Sym corneal tissues analyzed by RNA-seq. **(B)** Higher *COCH* expressions are verified in endothelial cells from FECD/REP or Pre_Sym corneal tissues by qPCR analysis. **(C)** *COCH* expression is up-regulated in FECD endothelial cell line.

[0049] **FIG. 25** shows TGFβ induces up-regulation of *COCH*. **(A)** *COCH* expression is up-regulated by adding increased concentration of TGFβ in HCN19 healthy control corneal endothelial cells. **(B)** TGFβ activated *COCH* in control corneal tissue.

[0050] **FIG. 26** shows cochlin is a secreted protein. **(A)** Western blot image of cochlin detected in FECD (F35T) corneal endothelial cell culture media. HCN19, healthy control endothelial cell line. **(B)** The full length cochlin band is confirmed by siRNA knocking down in F35T culture media. si173, anti-cochlin siRNA; siCM, non-complementary control siRNA.

[0051] **FIG. 27** shows secreted cochlin proteins were detected in FECD patient aqueous humor by ELISA assay.

[0052] **FIG. 28** shows cochlin deposits in FECD patient corneal tissue by immunofluorescence. **(A)** Cochlin may deposit in Descemet's membrane of FECD patient cornea tissue. **(B)** Cochlin deposits in trabecular meshwork of FECD donor cornea samples. Cross sections 4056-19-4596, 4056-19-4540 are FECD samples without repeat expansion; 4056-19-4463 is considered pre-symptomatic, which has no guttae, but with expanded CTG repeat (CTG repeat number: 18,73).

[0053] The following detailed description is merely exemplary in nature and is not intended to limit the invention or the applications of its use.

[0054] **Detection of an Increase of Expression of Marker Genes**

[0055] Provided herein are methods of detecting pre-symptomatic, advanced, early-onset, or age-related (late-onset) Fuchs' endothelial corneal dystrophy (FECD), glaucoma, or other ocular diseases in a subject comprising detecting an increase of

expression of one or more of *ADGRG7, FN1, KCNA1, VSIG2, CNN1, ABCB1,ABCB4, COCH, MAGED4, IGSF5,PCP4, MARVELD3, MIR5188, FRZB, ELMOD1, MSI1, HPGD, TPBG, F5, THBS2, ECEL1P1/2, CPVL,LINC02258, CD86, DLK1, FOXF2, GMNC, GPR34, IGKV3-20, IGKV6D-21, TMEM255A, CDKN2A, CLEC5A, MARCH1, GPC3, HLA-DQA1, HLA-DRA, CYBB, GRM5,NOX4, IGKC,IGKJ1,IGKJ2, C3AR1, DCX, MMP2-AS1, LYVE1, FAM198B, FCGR1B, FOLR2, FCGR3A, TNFRSF11B, PSG4, KRT7, COL4A2, CTGF, COL9A3, COL1A2, FGFR2, NOTCH2, TGFBR1, IFNGR1, TGFBR2, NOTCH1, HLA-DPB1, IL18, JAG1, CD4, SPI1, PIK3R5, ITGB2, NFATC2, HLA-DPA1, HLA-DOA, IKZF1, IL10RA, MAPK10, BCL2, COL5A2, ROR2, ACKR1, CADM3, VIPR2, ADAM33, CADM3-AS1, TSHR, DPP10, CLIC6, TMEM30B, LGR6, CST4, ICA1, ALPK2, RARRES2, MMP19, DCDC2C, CST1, ITPRIPL1, WNT3, SLC5A1, ARSJ, GREB1L, SLC16A9, EPHB6, MROH9, ENOX1, PLAC9, KIF21B, ADAMTS12, ITIH5, ANXA3, PROS1, PTPN3,* or *DCLK1*.

[0056] As used herein, the term "subject" refers to any individual or patient on which the methods disclosed herein are performed. The term "subject" can be used interchangeably with the term "individual" or "patient." The subject can be a mammal such as a human.

[0057] As used herein, the term "gene expression" or "expression" broadly refers to the level or presentation of a gene product in a cell, tissue, or subject. It should be appreciated that the gene product can be, for example, an RNA transcript or a protein. An RNA transcript can be one that encodes a protein. RNA transcripts can be non-protein-encoding, such as long non-coding RNA, long non-coding RNA between genes, non-coding RNA, miRNA, small nuclear RNA (snRNA), or other functional RNA.

[0058] As used herein, "detecting" or "measuring" means that a test or assay for detecting or measuring is performed. Such detection and/or measuring may result in a value of zero. Thus, if a test for detection or measuring results in a finding of no gene expression (expression of zero), the step of detecting or measuring the gene expression has nevertheless been performed.

[0059] RNA isolation and sequencing methods can be used to determine amounts of gene expression. Total RNA can be obtained using RNAseq, whole transcriptome sequencing using next generation DNA sequencing (NGS) technologies. The transcriptome is the complete set of transcripts in a cell, and their quantity, for a

specific developmental stage or physiological condition. NGS can reveal very rare mRNA, splice variants, allelic variants, and SNPs.

[0060] In RNAseq, a population of RNA (total or fractionated, such as poly(A)+) is converted to a library of cDNA fragments with adaptors attached to one or both ends. Each molecule, with or without amplification, is then sequenced in a high-throughput manner to obtain short sequences from one end (single-end sequencing) or both ends (pair-end sequencing). The reads are typically 30–400 bp, depending on the DNA-sequencing technology used. In principle, any high-throughput sequencing technology can be used for RNA-Seq, including, but not limited to, the Illumina IG, Applied Biosystems SOLiD, and Roche 454 Life Science. Ribosomal RNA can be depleted from total RNA using kits such as Ribominus™ (Thermo Fischer Scientific). Following sequencing, the resulting reads are either aligned to a reference genome or reference transcripts, or assembled de novo without the genomic sequence to produce a genome-scale transcription map that consists of both the transcriptional structure and/or level of expression for each gene. Transcriptomic data obtained are can be confirmed with, for example, quantitative reverse transcription polymerase chain reaction (qRT-PCR) analysis.

[0061] Moreover, gene expression data can be obtained from, and comparisons can be made between, a number of different methods. Methods can include, for example, western blotting, northern blotting, real-time PCR, nucleic acid hybridization (e.g., microarrays), and nucleic acid amplification methods (e.g., RT-PCR).

[0062] The amount of gene expression can be determined in a test sample and compared to the expression of a previous test sample from the same subject or test sample or control level. "Control level" or "control" is an expression level of the same gene found in a subject not suffering from FECD, glaucoma, ocular disease, or another degenerative disease.

[0063] Upregulated gene expression in FECD, glaucoma, or other ocular diseases as described herein can be increased about 10%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more as compared to control level. Alternately, gene expression can be increased 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80 or more fold compared to a control level.

[0064] Combinations of 2, 3, 4, 5, 6, 7 ,8 ,9 ,10, 20, 30, 40, 50, 60, 70, 80, 90, 100 or more of the upregulated genes can be detected in methods of detecting expression marker genes. One or more of the genes described below can be upregulated in a

patient having pre-symptomatic, advanced, early-onset, or age-related (late-onset) FECD, glaucoma, or other ocular diseases.

[0065] The *ADGRG7* (GeneID: 84873) gene encodes for adhesion G Protein-Coupled Receptor G7, which is a member of the adhesion GPCR family.

[0066] The *FN1* (GeneID: 2335) gene encodes for fibronectin 1, which is an extracellular matrix protein.

[0067] The *KCNA1* (GeneID: 3736) gene encodes for potassium voltage-gated channel subfamily A member 1, which is a voltage-gated potassium channel that mediates transmembrane potassium transport in excitable membranes, present primarily in the brain and the central nervous system, but also present in the kidney and eye.

[0068] The *VSIG2* (GeneID: 23584) gene encodes V-set and immunoglobulin domain-containing protein 2, which is a single-pass type I membrane protein that contains an Ig-like C2-type (immunoglobulin-like) domain and one Ig-like V-type (immunoglobulin-like) domain.

[0069] The *CNN1* (GeneID: 1264) gene encodes Calponin-1, which is a thin filament-associated protein that is implicated in the regulation and modulation of smooth muscle contraction. It is capable of binding to actin, calmodulin and tropomyosin.

[0070] The *ABCB1,ABCB4* (GeneID: 5243, GeneID: 5244) genes encode for ATP binding cassette subfamily B members 1 and 2, are members of the MDR/TAP subfamily of ATP-binding cassette transporters. These proteins transport molecules across extra- and intra-cellular membranes.

[0071] The *COCH* (GeneID: 1690) gene encodes cochlin, which is an extracellular matrix (ECM) protein highly abundant in the cochlea and vestibule of the inner ear, constituting the major non-collagen component of the ECM of the inner ear.

[0072] The *MAGED4* (GeneID: 728239) gene encodes melanoma-associated antigen D4, which may enhance ubiquitin ligase activity of RING-type zinc finger-containing E3 ubiquitin-protein ligases.

[0073] The *IGSF5, PCP4* (GeneID: 150084, GeneID: 5121) genes encode immunoglobulin superfamily member 5 and calmodulin regulator protein. IGSF5 is a protein that helps form an adhesion machinery at tight junctions and a PCP4 is protein that functions as a modulator of calcium-binding by calmodulin.

[0074] The *MARVELD3* (GeneID: 91862) gene encodes MARVEL domain-containing protein 3, which functions as a component of tight junctions, plays a role in paracellular ion conductivity.

[0075] The *MIR5188* (Gene ID: 100847004) gene is MicroRNA 5188.

[0076] The *FRZB* (GeneID: 2487) gene encodes secreted frizzled-related protein 3, which is a Wnt-binding protein.

[0077] The *ELMOD1* (GeneID: 55531) gene encodes ELMO domain-containing protein 1, which acts as a GTPase-activating protein (GAP) toward guanine nucleotide exchange factors like ARL2, ARL3, ARF1 and ARF6, but not for GTPases outside the Arf family.

[0078] The *MSI1* (GeneID: 4440) gene encodes RNA-binding protein Musashi homolog 1, which is an RNA binding protein that regulates the expression of target mRNAs at the translation level.

[0079] The *HPGD* (GeneID: 3248) gene encodes 15-hydroxyprostaglandin dehydrogenase [NAD(+)], which is an enzyme.

[0080] The *TPBG* (GeneID: 7162) gene encodes trophoblast glycoprotein, which is an antagonist of Wnt/β-catenin signaling pathway.

[0081] The *F5* (GeneID: 2153) gene encodes coagulation factor V, which is a regulator of hemostasis.

[0082] The *THBS2* (GeneID: 7058) gene encodes thrombospondin-2, which is a disulfide-linked homotrimeric glycoprotein that mediates cell-to-cell and cell-to-matrix interactions.

[0083] ECEL1P1&2 (GeneID: 100131546, GeneID: 347694), endothelin converting enzyme like 1 pseudogene 1, endothelin converting enzyme like 1 pseudogene 2, which are pseudo genes.

[0084] The *CPVL* (GeneID: 54504) gene encodes a carboxypeptidase and bears strong sequence similarity to serine carboxypeptidases.

[0085] LINC02258 (Gene ID: 110806294) (Long Intergenic Non-Protein Coding RNA 2258) is an RNA Gene, and is affiliated with the lncRNA class.

[0086] The *CD86* (GeneID: 942) gene encodes type I membrane protein that is a member of the immunoglobulin superfamily. Alternative splicing results in two transcript variants encoding different isoforms.

[0087] The *DLK1* (GeneID: 8788) gene encodes a transmembrane protein that contains multiple epidermal growth factor repeats that functions as a regulator of cell growth.

[0088] The *FOXF2* (GeneID: 2295) gene encodes forkhead box protein F2, which is a probable transcription activator for a number of lung-specific genes.

[0089] The *GMNC* (GeneID: 647309) gene encodes Geminin coiled-coil domain-containing protein 1, which regulates DNA replication.

[0090] The *GPR34* (GeneID: 2857) gene encodes probably G-protein coupled receptor 34.

[0091] The *IGKV3-20* (GeneID: 28912) gene encodes Immunoglobulin Kappa Variable 3-20, which is part of the V region of the variable domain of immunoglobulin light chains that participates in the antigen recognition.

[0092] The *IGKV6D-21* (Gene ID: 28870) gene encodes Immunoglobulin Kappa Variable 6-21, which is part of the V region of the variable domain of immunoglobulin light chains that participates in the antigen recognition.

[0093] The *TMEM255A* (GeneID: 55026) gene encodes transmembrane protein 255A.

[0094] The *CDKN2A* (GeneID: 1029) (cyclin-dependent kinase inhibitor 2A) gene encodes two proteins, including the INK4 family member p16 (or p16INK4a) and p14arf, which both act as tumor suppressors by regulating the cell cycle.

[0095] The *CLEC5A* (GeneID: 23601) gene encodes a member of the C-type lectin/C-type lectin-like domain (CTL/CTLD) superfamily.

[0096] The *MARCH1* (Gene ID: 55016) gene encodes E3 ubiquitin-protein ligase MARCHF1, which is an E3 ubiquitin-protein ligase that mediates ubiquitination of TFRC, CD86, FAS and MHC class II proteins, such as HLA-DR alpha and beta, and promotes their subsequent endocytosis and sorting to lysosomes via multivesicular bodies.

[0097] The *GPC3* (GeneID: 2719) gene encodes Glypican-3, which is a cell surface proteoglycan that bears heparan sulfate.

[0098] The *HLA-DQA1* (GeneID: 3117) gene encodes HLA class II histocompatibility antigen, DQ alpha 1 chain, which binds peptides derived from antigens that access the endocytic route of antigen presenting cells (APC) and presents them on the cell surface for recognition by the CD4 T-cells.

[0099] The *HLA-DRA* (GeneID: 3122) gene encodes HLA class II histocompatibility antigen, DR alpha chain, which binds peptides derived from antigens that access the endocytic route of antigen presenting cells (APC) and presents them on the cell surface for recognition by the CD4 T-cells.

[0100] The *CYBB* (GeneID: 1536) gene encodes Cytochrome b-245 heavy chain, which is a critical component of the membrane-bound oxidase of phagocytes that generates superoxide.

[0101] GRM5, NOX4, (GeneID: 2915, GeneID: 50507) glutamate metabotropic receptor 5, NADPH oxidase 4.

[0102] IGKC,IGKJ1,IGKJ2, (GeneID: 3514, GeneID: 28950, GeneID: 28949) (immunoglobulin kappa constant, immunoglobulin kappa joining 1, immunoglobulin kappa joining 2).

[0103] The *C3AR1* (GeneID: 719) gene encodes C3a anaphylatoxin chemotactic receptor, which is a receptor for the chemotactic and inflammatory peptide anaphylatoxin C3a.

[0104] The *DCX* (GeneID: 1641) gene encodes Neuronal migration protein doublecortin, which is a microtubule-associated protein required for initial steps of neuronal dispersion and cortex lamination during cerebral cortex development.

[0105] MMP2-AS1, (Gene ID: 107984884) MMP2 antisense RNA 1, is non-coding RNA.

[0106] The *LYVE1* (GeneID: 10894) gene encodes Lymphatic vessel endothelial hyaluronan receptor 1, which is a type I integral membrane glycoprotein. The encoded protein acts as a receptor and binds to both soluble and immobilized hyaluronan.

[0107] The *FAM198B* (Gene ID: 51313) gene encodes Golgi-associated kinase 1B.

[0108] The *FCGR1B* (Gene ID: 2210) is called the Fc Fragment of IgG Receptor Ib and it is a pseudogene.

[0109] The *FOLR2* (Gene ID: 2350) gene encodes Folate receptor beta, which is a member of the folate receptor (FOLR) family.

[0110] The *FCGR3A* (Gene ID: 2214; called Fc Fragment of IgG Receptor IIIa) gene encodes a receptor for the Fc portion of immunoglobulin G, and it is involved in the removal of antigen-antibody complexes from the circulation, as well as other responses, including antibody dependent cellular mediated cytotoxicity and antibody dependent enhancement of virus infections.

[0111] The *TNFRSF11B* (Gene ID: 4982) gene encodes Tumor necrosis factor receptor superfamily member 11B, which a cytokine receptor of the tumor necrosis factor (TNF) receptor superfamily.

[0112] The *PSG4* (Gene ID: 5672) gene encodes a pregnancy-specific glycoprotein (PSG).

[0113] The *KRT7* (Gene ID: 51350) gene encodes Keratin, type II cytoskeletal 7, which blocks interferon-dependent interphase and stimulates DNA synthesis in cells.

[0114] The *COL4A2* (GeneID: 1284) gene is called collagen type IV alpha 2 chain, and it encodes a protein which is a structural component of basement membranes.

[0115] The *CTGF* (GeneID: 1490) gene encodes connective tissue growth factor, which is a growth factor related to the ECM.

[0116] The *COL9A3* (GeneID: 1299) gene encodes collagen type IX alpha 3 chain, which is an ECM protein.

[0117] The *COL1A2* (GeneID: 1278) gene encodes collagen type I alpha 2 chain, which is a fibrillar forming collagen.

[0118] The *FGFR2*, (GeneID: 2263) gene encodes fibroblast growth factor receptor 2, which is a member of the fibroblast growth factor receptor family, where amino acid sequence is highly conserved between members and throughout evolution.

[0119] The *NOTCH2* (GeneID: 4853) gene encodes notch receptor 2, which a member of the Notch family. Members of this Type 1 transmembrane protein family share structural characteristics including an extracellular domain consisting of multiple epidermal growth factor-like (EGF) repeats, and an intracellular domain consisting of multiple, different domain types.

[0120] The *TGFBR1* (Gene ID: 7046) gene encodes transforming growth factor beta receptor 1, which forms a heteromeric complex with type II TGF-beta receptors when bound to TGF-beta, transducing the TGF-beta signal from the cell surface to the cytoplasm. The encoded protein is a serine/threonine protein kinase.

[0121] The *IFNGR1* (Gene ID: 3459) gene encodes interferon gamma receptor 1, which is the ligand-binding chain (alpha) of the gamma interferon receptor. Human interferon-gamma receptor is a heterodimer of IFNGR1 and IFNGR2.

[0122] The *TGFBR2* (Gene ID: 7048) gene encodes transforming growth factor beta receptor 2, which is a transmembrane protein that has a protein kinase domain, forms a heterodimeric complex with TGF-beta receptor type-1, and binds TGF-beta. This receptor/ligand complex phosphorylates proteins, which then enter the nucleus

and regulate the transcription of genes related to cell proliferation, cell cycle arrest, wound healing, immunosuppression, and tumorigenesis.

[0123] The *NOTCH1* (Gene ID: 4851) gene encodes notch receptor 1, which is a member of the NOTCH family of proteins. Members of this Type I transmembrane protein family share structural characteristics including an extracellular domain consisting of multiple epidermal growth factor-like (EGF) repeats, and an intracellular domain consisting of multiple different domain types.

[0124] The *HLA-DPB1* (Gene ID: 3115) gene encodes major histocompatibility complex, class II, DP beta 1, which belongs to the HLA class II beta chain paralogues. This class II molecule is a heterodimer consisting of an alpha (DPA) and a beta chain (DPB), both anchored in the membrane. It plays a central role in the immune system by presenting peptides derived from extracellular proteins.

[0125] The *IL18* (Gene ID: 3606) gene encodes interleukin 18, which is a proinflammatory cytokine of the IL-1 family that is constitutively found as a precursor within the cytoplasm of a variety of cells including macrophages and keratinocytes.

[0126] The *JAG1* (Gene ID: 182) gene encodes jagged canonical Notch ligand 1, which is the human homolog of the Drosophilia jagged protein. Human jagged 1 is the ligand for the receptor notch 1, the latter is involved in signaling processes.

[0127] The *CD4* (Gene ID: 920) gene encodes CD4 molecule, which is the CD4 membrane glycoprotein of T lymphocytes. The CD4 antigen acts as a coreceptor with the T-cell receptor on the T lymphocyte to recognize antigens displayed by an antigen presenting cell in the context of class II MHC molecules.

[0128] The *SPI1* (Gene ID: 6688) gene encodes Spi-1 proto-oncogene, which is an ETS-domain transcription factor that activates gene expression during myeloid and B-lymphoid cell development. The nuclear protein binds to a purine-rich sequence known as the PU-box found near the promoters of target genes, and regulates their expression in coordination with other transcription factors and cofactors.

[0129] The *PIK3R5* (Gene ID: 23533) gene encodes phosphoinositide-3-kinase regulatory subunit 5. Phosphatidylinositol 3-kinases (PI3Ks) phosphorylate the inositol ring of phosphatidylinositol at the 3-prime position, and play important roles in cell growth, proliferation, differentiation, motility, survival and intracellular trafficking. The PI3Ks are divided into three classes: I, II and III, and only the class I PI3Ks are involved in oncogenesis. This gene encodes the 101 kD regulatory subunit of the class I PI3K gamma complex, which is a dimeric enzyme, consisting of a 110 kD catalytic subunit

gamma and a regulatory subunit of either 55, 87 or 101 kD. This protein recruits the catalytic subunit from the cytosol to the plasma membrane through high-affinity interaction with G-beta-gamma proteins.

[0130] The *ITGB2* (Gene ID: 3689) gene encodes integrin subunit beta 2, which is an integrin beta chain, which combines with multiple different alpha chains to form different integrin heterodimers.

[0131] The *NFATC2* (Gene ID: 4773) gene encodes nuclear factor of activated T cells 2, which is a member of the nuclear factor of activated T cells (NFAT) family.

[0132] The *HLA-DPA1* (Gene ID: 3113) gene encodes major histocompatibility complex, class II, DP alpha 1, which belongs to the HLA class II alpha chain paralogues. This class II molecule is a heterodimer consisting of an alpha (DPA) and a beta (DPB) chain, both anchored in the membrane.

[0133] The *HLA-DOA* (Gene ID: 3111) gene encodes major histocompatibility complex, class II, DO alpha, which belongs to the HLA class II alpha chain paralogues. HLA-DOA forms a heterodimer with HLA-DOB.

[0134] The *IKZF1* (Gene ID: 10320) gene encodes IKAROS family zinc finger 1, which is a transcription factor that belongs to the family of zinc-finger DNA-binding proteins associated with chromatin remodeling.

[0135] The *IL10RA* (Gene ID: 3587) gene encodes interleukin 10 receptor subunit alpha, which is a receptor for interleukin 10. This protein is structurally related to interferon receptors.

[0136] The *MAPK10* (Gene ID: 5602) gene encodes mitogen-activated protein kinase 10, which is a member of the MAP kinase family. This kinase is specifically expressed in a subset of neurons in the nervous system, and is activated by threonine and tyrosine phosphorylation.

[0137] The *BCL2* (Gene ID: 596) gene encodes BCL2 apoptosis regulator, which an integral outer mitochondrial membrane protein that blocks the apoptotic death of some cells such as lymphocytes.

[0138] The *COL5A2* (Gene ID: 1290) gene encodes collagen type V alpha 2 chain, which is an alpha chain for one of the low abundance fibrillar collagens.

[0139] The *ROR2* (Gene ID: 4920) gene encodes receptor tyrosine kinase like orphan receptor 2. The protein encoded by this gene is a receptor protein tyrosine kinase and type I transmembrane protein that belongs to the ROR subfamily of cell surface receptors.

[0140] The *ACKR1* (Gene ID: 2532) gene encodes atypical chemokine receptor 1 (Duffy blood group). The protein encoded by this gene is a glycosylated membrane protein and a non-specific receptor for several chemokines.

[0141] The *CADM3* (Gene ID: 57863) gene encodes cell adhesion molecule 3. The protein encoded by this gene is a calcium-independent cell-cell adhesion protein that can form homodimers or heterodimers with other nectin proteins. The encoded protein has both homophilic and heterophilic cell-cell adhesion activity.

[0142] The *VIPR2* (Gene ID: 7434) gene encodes vasoactive intestinal peptide receptor 2. This gene encodes a receptor for vasoactive intestinal peptide, a small neuropeptide. Vasoactive intestinal peptide is involved in smooth muscle relaxation, exocrine and endocrine secretion, and water and ion flux in lung and intestinal epithelia.

[0143] The *ADAM33* (Gene ID: 80332) gene encodes DAM metallopeptidase domain 33. This gene encodes a member of the ADAM (a disintegrin and metalloprotease domain) family. Members of this family are membrane-anchored proteins structurally related to snake venom disintegrins, and have been implicated in a variety of biological processes involving cell-cell and cell-matrix interactions, including fertilization, muscle development, and neurogenesis. This protein is a type I transmembrane protein implicated in asthma and bronchial hyperresponsiveness.

[0144] The *CADM3-AS1* (Gene ID: 100131825) gene encodes CADM3 antisense RNA 1.

[0145] The *TSHR* (Gene ID: 7253) gene encodes thyroid stimulating hormone receptor. The protein encoded by this gene is a membrane protein and a major controller of thyroid cell metabolism. The encoded protein is a receptor for thyrothropin and thyrostimulin, and its activity is mediated by adenylate cyclase.

[0146] The *DPP10* (Gene ID: 57628) gene encodes dipeptidyl peptidase like 10. This gene encodes a single-pass type II membrane protein that is a member of the S9B family in clan SC of the serine proteases. This protein has no detectable protease activity, most likely due to the absence of the conserved serine residue normally present in the catalytic domain of serine proteases. However, it does bind specific voltage-gated potassium channels and alters their expression and biophysical properties.

[0147] The *CLIC6* (Gene ID: 54102) gene encodes chloride intracellular channel 6. This gene encodes a member of the chloride intracellular channel family of proteins.

[0148] The *TMEM30B* (Gene ID: 161291) gene encodes transmembrane protein 30B.

[0149] The *LGR6* (Gene ID: 59352) gene encodes leucine rich repeat containing G protein-coupled receptor 6. This gene encodes a member of the leucine-rich repeat-containing subgroup of the G protein-coupled 7-transmembrane protein superfamily. The encoded protein is a glycoprotein hormone receptor with a large N-terminal extracellular domain that contains leucine-rich repeats important for the formation of a horseshoe-shaped interaction motif for ligand binding.

[0150] The *CST4* (Gene ID: 1472) gene encodes cystatin S. The cystatin superfamily encompasses proteins that contain multiple cystatin-like sequences. This gene is located in the cystatin locus and encodes a type 2 salivary cysteine peptidase inhibitor. The protein is an S-type cystatin, based on its high level of expression in saliva, tears and seminal plasma.

[0151] The *ICA1* (Gene ID: 3382) gene encodes islet cell autoantigen 1. This gene encodes a protein with an arfaptin homology domain that is found both in the cytosol and as membrane-bound form on the Golgi complex and immature secretory granules.

[0152] The *ALPK2* (Gene ID: 115701) gene encodes alpha kinase 2.

[0153] The *RARRES2* (Gene ID: 5919) gene encodes retinoic acid receptor responder 2. This gene encodes a secreted chemotactic protein that initiates chemotaxis via the ChemR23 G protein-coupled seven-transmembrane domain ligand.

[0154] The *MMP19* (Gene ID: 4327) gene encodes matrix metallopeptidase 19. This gene encodes a member of a family of proteins that are involved in the breakdown of extracellular matrix in normal physiological processes, such as embryonic development, reproduction, and tissue remodeling, as well as in disease processes, such as arthritis and metastasis. The encoded protein is secreted as an inactive proprotein, which is activated upon cleavage by extracellular proteases.

[0155] The *DCDC2C* (Gene ID: 728597) gene encodes doublecortin domain containing 2C.

[0156] The *CST1* (Gene ID: 1469) gene encodes cystatin SN. The cystatin superfamily encompasses proteins that contain multiple cystatin-like sequences. This gene is located in the cystatin locus and encodes a cysteine proteinase inhibitor found in saliva, tears, urine, and seminal fluid.

[0157] The *ITPRIPL1* (Gene ID: 150771) gene encodes ITPRIP like 1.

[0158] The *WNT3* (Gene ID: 7473) gene encodes Wnt family member 3. The WNT gene family consists of structurally related genes which encode secreted signaling proteins. This gene is a member of the WNT gene family.

[0159] The *SLC5A1* (Gene ID: 6523) gene encodes solute carrier family 5 member 1. This gene encodes a member of the sodium-dependent glucose transporter (SGLT) family. The encoded integral membrane protein is the primary mediator of dietary glucose and galactose uptake from the intestinal lumen.

[0160] The *ARSJ* (Gene ID: 79642) gene encodes arylsulfatase family member J.

[0161] The *GREB1L* (Gene ID: 80000) gene encodes GREB1 like retinoic acid receptor coactivator.

[0162] The *SLC16A9* (Gene ID: 220963) gene encodes solute carrier family 16 member 9.

[0163] The *EPHB6* (Gene ID: 2051) gene encodes EPH receptor B6. This gene encodes a member of a family of transmembrane proteins that function as receptors for ephrin-B family proteins. Unlike other members of this family, the encoded protein does not contain a functional kinase domain. Activity of this protein can influence cell adhesion and migration.

[0164] The *MROH9* (Gene ID: 80133) gene encodes maestro heat like repeat family member 9.

[0165] The *ENOX1* (Gene ID: 55068) gene encodes ecto-NOX disulfide-thiol exchanger 1. The protein encoded by this gene is involved in plasma membrane electron transport pathways. The encoded protein has both a hydroquinone (NADH) oxidase activity and a protein disulfide-thiol interchange activity. The two activities cycle with a periodicity of 24 minutes, with one activity being at its peak when the other is at its lowest.

[0166] The *PLAC9* (Gene ID: 219348) gene encodes placenta associated 9.

[0167] The *KIF21B* (Gene ID: 23046) gene encodes kinesin family member 21B. This gene encodes a member of the kinesin superfamily. Kinesins are ATP-dependent microtubule-based motor proteins that are involved in the intracellular transport of membranous organelles.

[0168] The *ADAMTS12* (Gene ID: 81792) gene encodes ADAM metallopeptidase with thrombospondin type 1 motif 12. This gene encodes a member of the ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) protein family. Members of the family share several distinct protein modules, including a propeptide

region, a metalloproteinase domain, a disintegrin-like domain, and a thrombospondin type 1 (TS-1) motif. Individual members of this family differ in the number of C-terminal TS-1 motifs, and some have unique C-terminal domains. The enzyme encoded by this gene contains eight TS-1 motifs.

[0169] The *ITIH5* (Gene ID: 80760) gene encodes inter-alpha-trypsin inhibitor heavy chain 5. This gene encodes a heavy chain component of one of the inter-alpha-trypsin inhibitor (ITI) family members. ITI proteins are involved in extracellular matrix stabilization and in the prevention of tumor metastasis. They are also structurally related plasma serine protease inhibitors and are composed of a light chain and varying numbers of heavy chains.

[0170] The *ANXA3* (Gene ID: 306) gene encodes annexin A3. This gene encodes a member of the annexin family. Members of this calcium-dependent phospholipid-binding protein family play a role in the regulation of cellular growth and in signal transduction pathways. This protein functions in the inhibition of phopholipase A2 and cleavage of inositol 1,2-cyclic phosphate to form inositol 1-phosphate.

[0171] The *PROS1* (Gene ID: 5627) gene encodes protein S. This gene encodes a vitamin K-dependent plasma protein that functions as a cofactor for the anticoagulant protease, activated protein C (APC) to inhibit blood coagulation. It is found in plasma in both a free, functionally active form and also in an inactive form complexed with C4b-binding protein.

[0172] The *PTPN3* (Gene ID: 5774) gene encodes protein tyrosine phosphatase non-receptor type 3. The protein encoded by this gene is a member of the protein tyrosine phosphatase (PTP) family. PTPs are known to be signaling molecules that regulate a variety of cellular processes including cell growth, differentiation, mitotic cycle, and oncogenic transformation. This protein contains a C-terminal PTP domain and an N-terminal domain homologous to the band 4.1 superfamily of cytoskeletal-associated proteins.

[0173] The *DCLK1* (Gene ID: 9201) gene encodes doublecortin like kinase 1. This gene encodes a member of the protein kinase superfamily and the doublecortin family. The protein encoded by this gene contains two N-terminal doublecortin domains, which bind microtubules and regulate microtubule polymerization, a C-terminal serine/threonine protein kinase domain, which shows substantial homology to Ca2+/calmodulin-dependent protein kinase, and a serine/proline-rich domain in

between the doublecortin and the protein kinase domains, which mediates multiple protein-protein interactions.

[0174] **Detection of a Decrease of Expression of Marker Genes**

[0175] Provided herein are methods of detecting pre-symptomatic, advanced, early-onset, or age-related (late-onset) Fuchs' endothelial corneal dystrophy (FECD), glaucoma, and other ocular diseases in a subject comprising detecting a decrease of expression of one or more of *SAA2/4, NPBWR1, GFAP, DNER, INPP5D, SYNDIG1, CSF3, SPATA18, CLEC4GP1, OVCH1, LINC01811, CLIC5, FAM107A, PNMT, CYTL1, SERPINA3/4/5, TMOD1, HMGN2P17, GPRC5B, DRD2, PSPHP1, CDH12, IL17REL, ARC, UBE2W, RNU5E-1, CXCL8, LINC00881,LINC02029, CXCL3, RNU2-63P, CXCL2, RASD1, RNU6-1208P, UTY, CD24P4,RNU6-255P,TTTY14, KDM5DP1,TTTY10, NLGN4Y, RNU1-59P, ZFY, STK40, RNU5B-1, LINC01783,RNU1-6P, RNU1-5P, EPS8L1, LUM, KDR, SOD3, IRF1, JUN, SOCS3, NFIL3, FGFR4, NFKB1, SOD2, MAOA, CYCS, SNCA, PDHA1, UQCRH, COX7B, COX5B, NDUFV1, UQCRC2, NDUFA1, CYC1, UQCRB, VDAC2, COX4I1, SDHB, COX6B1, or MAOB*.

[0176] The amount of gene expression can be determined in a test sample and compared to the amount of gene expression in a previous test sample from the same subject or test sample or control level.

[0177] Downregulated gene expression in FECD, glaucoma, or other ocular diseases as described herein can be decreased about 10%, 25%, 30,%, 40%, 50%, 60%, 70%, 80%, 90%, or more compared to a control level. Alternately, gene expression can be decreased 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80 or more fold compared to a control level.

[0178] Combinations of 2, 3, 4, 5, 6, 7 ,8 ,9 ,10, 20, 30, 40, 50, 60, 70, or more of the downregulated genes can be detected in methods of detecting expression marker genes. One or more of the genes described below can be downregulated in a patient having FECD, glaucoma, or other ocular diseases.

[0179] *SAA2/4* (Gene ID: 6289, Gene ID: 6291) are serum amyloid A2 and serum amyloid A4. The *SAA2* gene encodes a member of the serum amyloid A family of apolipoproteins.

[0180] *NPBWR1* (GeneID: 2831) is neuropeptides B and W receptor 1.

[0181] GFAP (Gene ID: 2670) is glial fibrillary acidic protein. This gene encodes one of the major intermediate filament proteins of mature astrocytes. It is used as a marker to distinguish astrocytes from other glial cells during development.

[0182] *DNER* (Gene ID: 92737) is delta/notch like EGF repeat containing.

[0183] *INPP5D* (Gene ID: 3635) is inositol polyphosphate-5-phosphatase D. This gene is a member of the inositol polyphosphate-5-phosphatase (INPP5) family and encodes a protein with an N-terminal SH2 domain, an inositol phosphatase domain, and two C-terminal protein interaction domains.

[0184] *SYNDIG1* (Gene ID: 79953) is synapse differentiation inducing 1. This gene encodes a protein that belongs to the interferon-induced transmembrane family of proteins.

[0185] *CSF3* (Gene ID: 1440) is colony stimulating factor 3. This gene encodes a member of the IL-6 superfamily of cytokines.

[0186] *SPATA18* (Gene ID: 132671) is spermatogenesis associated 18. This gene encodes a p53-inducible protein that is able to induce lysosome-like organelles within mitochondria that eliminate oxidized mitochondrial proteins, thereby contributing to mitochondrial quality control.

[0187] *CLEC4GP1* (Gene ID: 440508) is C-type lectin domain family 4 member G pseudogene 1. *CLEC4GP1* is a pseudo gene.

[0188] *OVCH1* (Gene ID: 341350) is ovochymase 1.

[0189] LINC01811 (Gene ID: 101928114) is long intergenic non-protein coding RNA 1811.

[0190] *CLIC5* (Gene ID: 53405) is chloride intracellular channel 5. This gene encodes a member of the chloride intracellular channel (CLIC) family of chloride ion channels.

[0191] *FAM107A* (Gene ID: 11170) has sequence similarity to 107 member A.

[0192] *PNMT* (Gene ID: 5409) is phenylethanolamine N-methyltransferase. The product of this gene catalyzes the last step of the catecholamine biosynthesis pathway, which methylates norepinephrine to form epinephrine (adrenaline).

[0193] *CYTL1* (Gene ID: 54360) is cytokine like 1. C17 is a cytokine-like protein specifically expressed in bone marrow and cord blood mononuclear cells that bear the CD34 (MIM 142230) surface marker.

[0194] *SERPINA3/4/5* (Gene ID: 12/ Gene ID: 5267/ Gene ID: 5104) is serpin family A member 3/serpin family A member 4/serpin family A member 5. The proteins

encoded by these genes are members of the serpin family of proteins, a group of proteins that inhibit serine proteases.

[0195] *TMOD1* (Gene ID: 7111) is tropomodulin 1. This gene encodes a member of the tropomodulin family. The encoded protein is an actin-capping protein that regulates tropomyosin by binding to its N-terminus, inhibiting depolymerization and elongation of the pointed end of actin filaments and thereby influencing the structure of the erythrocyte membrane skeleton.

[0196] *HMGN2P17* (Gene ID: 100113373) is high mobility group nucleosomal binding domain 2 pseudogene 17. HMGN2P17 is a pseudogene.

[0197] *GPRC5B* (Gene ID: 51704) is G protein-coupled receptor class C group 5 member B. This gene encodes a member of the type 3 G protein-coupled receptor family. Members of this superfamily are characterized by a signature 7-transmembrane domain motif.

[0198] *DRD2* (Gene ID: 1813) is dopamine receptor D2. This gene encodes the D2 subtype of the dopamine receptor. This G-protein coupled receptor inhibits adenylyl cyclase activity.

[0199] *PSPHP1* (Gene ID: 8781) is phosphoserine phosphatase pseudogene 1. PSPHP1 is a pseudogene. This gene is significantly upregulated in Fanconi's anemia fibroblasts but downregulated or absent in fibroblasts from normal donors.

[0200] *CDH12* (Gene ID: 1010) is cadherin 12. This gene encodes a type II classical cadherin of the cadherin superfamily. Alternative splicing of this gene results in multiple transcript variants.

[0201] *IL17REL* (Gene ID: 400935) is interleukin 17 receptor E like.

[0202] *ARC* (Gene ID: 23237) is activity regulated cytoskeleton associated protein.

[0203] *UBE2W* (Gene ID: 55284) is ubiquitin conjugating enzyme E2 W. This gene encodes a nuclear-localized ubiquitin-conjugating enzyme (E2) that, along with ubiquitin-activating (E1) and ligating (E3) enzymes, coordinates the addition of a ubiquitin moiety to existing proteins.

[0204] *RNU5E-1* (Gene ID: 26829) is RNA, U5E small nuclear 1 and it is snRNA.

[0205] *CXCL8* (Gene ID: 3576) is C-X-C motif chemokine ligand 8. The protein encoded by this gene is a member of the CXC chemokine family and is a major mediator of the inflammatory response. The encoded protein is commonly referred to as interleukin-8 (IL-8). IL-8 is secreted by mononuclear macrophages, neutrophils, eosinophils, T lymphocytes, epithelial cells, and fibroblasts.

[0206] LINC00881,LINC02029 (Gene ID: 100498859, Gene ID: 105374177) are long intergenic non-protein coding RNA 881 and long intergenic non-protein coding RNA 2029.

[0207] *CXCL3* (Gene ID: 2921) is C-X-C motif chemokine ligand 3. This antimicrobial gene encodes a member of the CXC subfamily of chemokines. The encoded protein is a secreted growth factor that signals through the G-protein coupled receptor, CXC receptor 2.

[0208] *RNU2-63P* (Gene ID: 106480225) is RNA, U2 small nuclear 63, pseudogene.

[0209] *CXCL2* (Gene ID: 2920) is C-X-C motif chemokine ligand 2. This antimicrobial gene is part of a chemokine superfamily that encodes secreted proteins involved in immunoregulatory and inflammatory processes.

[0210] *RASD1* (Gene ID: 51655) is ras related dexamethasone induced 1. This gene encodes a member of the Ras superfamily of small GTPases and is induced by dexamethasone. The encoded protein is an activator of G-protein signaling and acts as a direct nucleotide exchange factor for Gi-Go proteins.

[0211] *RNU6-1208P* (Gene ID: 106480094) is RNA, U6 small nuclear 1208, pseudogene.

[0212] *UTY* (Gene ID: 7404) is ubiquitously transcribed tetratricopeptide repeat containing, Y-linked. This gene encodes a protein containing tetratricopeptide repeats which are thought to be involved in protein-protein interactions. The encoded protein is also a minor histocompatibility antigen which may induce graft rejection of male stem cell grafts.

[0213] *CD24P4,RNU6-255P,TTTY14* (Gene ID: 938, Gene ID: 106481258, Gene ID: 83869) are CD24 molecule pseudogene 4, RNA, U6 small nuclear 255 pseudogene, and testis-specific transcript, Y-linked 14 (ncRNA).

[0214] *KDM5DP1,TTTY10* (Gene ID: 359796, Gene ID: 246119) are lysine demethylase 5D pseudogene 1 and testis-specific transcript, Y-linked 10.

[0215] *NLGN4Y* (Gene ID: 22829) is neuroligin 4 Y-linked. This gene encodes a type I membrane protein that belongs to the family of neuroligins, which are cell adhesion molecules present at the postsynaptic side of the synapse, and may be essential for the formation of functional synapses.

[0216] *RNU1-59P* (Gene ID: 106480167) is RNA, variant U1 small nuclear 24, a pseudogene.

[0217] *ZFY* (Gene ID: 7544) is zinc finger protein Y-linked. This gene encodes a zinc finger-containing protein that may function as a transcription factor.

[0218] *STK40* (Gene ID: 83931) is serine/threonine kinase 40.

[0219] *RNU5B-1* (Gene ID: 26832) is RNA, U5B small nuclear 1, snRNA.

[0220] *LINC01783,RNU1-6P* (Gene ID: 100132147, Gene ID: 106480152) are long intergenic non-protein coding RNA 1783 and RNA U1 small nuclear 6 pseudogene.

[0221] *RNU1-5P* (Gene ID: 107105261) is RNA, U1 small nuclear 5, pseudogene.

[0222] *EPS8L1* (Gene ID: 54869) is Epidermal growth factor receptor kinase substrate 8-like protein 1.

[0223] The *LUM* (GeneID: 4060) gene encodes lumican, which is an extracellular matrix protein related to collagen fibril organization.

[0224] *KDR* (Gene ID: 3791) is kinase insert domain receptor. Vascular endothelial growth factor (VEGF) is a major growth factor for endothelial cells. This gene encodes one of the two receptors of the VEGF. This receptor, known as kinase insert domain receptor, is a type III receptor tyrosine kinase.

[0225] *SOD3* (Gene ID: 6649) is superoxide dismutase 3, which encodes a member of the superoxide dismutase (SOD) protein family.

[0226] *IRF1* (Gene ID: 3659) is interferon regulatory factor 1, which is a transcriptional regulator and tumor suppressor, serving as an activator of genes involved in both innate and acquired immune responses.

[0227] *JUN* (Gene ID: 3725) is Jun proto-oncogene, AP-1 transcription factor subunit, is the putative transforming gene of avian sarcoma virus 17. It encodes a protein which is highly similar to the viral protein, and which interacts directly with specific target DNA sequences to regulate gene expression.

[0228] *SOCS3* (Gene ID: 9021) is suppressor of cytokine signaling 3, which encodes a member of the STAT-induced STAT inhibitor (SSI), also known as suppressor of cytokine signaling (SOCS), family. SSI family members are cytokine-inducible negative regulators of cytokine signaling. The expression of this gene is induced by various cytokines, including IL6, IL10, and interferon (IFN)-gamma. The protein encoded by this gene can bind to JAK2 kinase, and inhibit the activity of JAK2 kinase.

[0229] *NFIL3* (Gene ID: 4783) is nuclear factor, interleukin 3 regulated, which is a transcriptional regulator that binds as a homodimer to activating transcription factor

(ATF) sites in many cellular and viral promoters. The encoded protein represses PER1 and PER2 expression and therefore plays a role in the regulation of circadian rhythm.

[0230] *FGFR4* (Gene ID: 2264) is fibroblast growth factor receptor 4. The protein encoded by this gene is a tyrosine kinase and cell surface receptor for fibroblast growth factors.

[0231] *NFKB1* (Gene ID: 4790) is nuclear factor kappa B subunit 1. This gene encodes a 105 kD protein which can undergo cotranslational processing by the 26S proteasome to produce a 50 kD protein. The 105 kD protein is a Rel protein-specific transcription inhibitor and the 50 kD protein is a DNA binding subunit of the NF-kappa-B (NFKB) protein complex.

[0232] *SOD2* (Gene ID: 6648) is superoxide dismutase 2. This gene is a member of the iron/manganese superoxide dismutase family. It encodes a mitochondrial protein that forms a homotetramer and binds one manganese ion per subunit. This protein binds to the superoxide byproducts of oxidative phosphorylation and converts them to hydrogen peroxide and diatomic oxygen.

[0233] *MAOA* (Gene ID: 4128) is monoamine oxidase A. This gene is one of two neighboring gene family members that encode mitochondrial enzymes which catalyze the oxidative deamination of amines, such as dopamine, norepinephrine, and serotonin.

[0234] *CYCS* (Gene ID: 54205) is cytochrome c, somatic. This gene encodes a small heme protein that functions as a central component of the electron transport chain in mitochondria. The encoded protein associates with the inner membrane of the mitochondrion where it accepts electrons from cytochrome b and transfers them to the cytochrome oxidase complex. This protein is also involved in initiation of apoptosis.

[0235] *SNCA* (Gene ID: 6622) is synuclein alpha. Alpha-synuclein is a member of the synuclein family, which also includes beta- and gamma-synuclein. Synucleins are abundantly expressed in the brain and alpha- and beta-synuclein inhibit phospholipase D2 selectively. SNCA may serve to integrate presynaptic signaling and membrane trafficking.

[0236] *PDHA1* (Gene ID: 5160) is pyruvate dehydrogenase E1 subunit alpha 1. The pyruvate dehydrogenase (PDH) complex is a nuclear-encoded mitochondrial multienzyme complex that catalyzes the overall conversion of pyruvate to acetyl-CoA

and CO(2), and provides the primary link between glycolysis and the tricarboxylic acid (TCA) cycle.

[0237] *UQCRH* (Gene ID: 7388) is ubiquinol-cytochrome c reductase hinge protein.

[0238] *COX7B* (Gene ID: 1349) is cytochrome c oxidase subunit 7B. Cytochrome c oxidase (COX), the terminal component of the mitochondrial respiratory chain, catalyzes the electron transfer from reduced cytochrome c to oxygen. This component is a heteromeric complex consisting of 3 catalytic subunits encoded by mitochondrial genes and multiple structural subunits encoded by nuclear genes.

[0239] *COX5B* (Gene ID: 1329) is cytochrome c oxidase subunit 5B. Cytochrome C oxidase (COX) is the terminal enzyme of the mitochondrial respiratory chain. It is a multi-subunit enzyme complex that couples the transfer of electrons from cytochrome c to molecular oxygen and contributes to a proton electrochemical gradient across the inner mitochondrial membrane. The complex consists of 13 mitochondrial- and nuclear-encoded subunits.

[0240] *NDUFV1* (Gene ID: 4723) is NADH:ubiquinone oxidoreductase core subunit V1. The mitochondrial respiratory chain provides energy to cells via oxidative phosphorylation and consists of four membrane-bound electron-transporting protein complexes (I-IV) and an ATP synthase (complex V). This gene encodes a 51 kDa subunit of the NADH:ubiquinone oxidoreductase complex I; a large complex with at least 45 nuclear and mitochondrial encoded subunits that liberates electrons from NADH and channels them to ubiquinone.

[0241] *UQCRC2* (Gene ID: 7385) is ubiquinol-cytochrome c reductase core protein 2. The protein encoded by this gene is located in the mitochondrion, where it is part of the ubiquinol-cytochrome c reductase complex (also known as complex III). This complex constitutes a part of the mitochondrial respiratory chain.

[0242] *NDUFA1* (Gene ID: 4694) is NADH:ubiquinone oxidoreductase subunit A1. The human NDUFA1 gene codes for an essential component of complex I of the respiratory chain, which transfers electrons from NADH to ubiquinone.

[0243] *CYC1* (Gene ID: 1537) is cytochrome c1. This gene encodes a subunit of the cytochrome bc1 complex, which plays an important role in the mitochondrial respiratory chain by transferring electrons from the Rieske iron-sulfur protein to cytochrome c.

[0244] *UQCRB* (Gene ID: 7381) is ubiquinol-cytochrome c reductase binding protein. This gene encodes a subunit of the ubiquinol-cytochrome c oxidoreductase

complex, which consists of one mitochondrial-encoded and 10 nuclear-encoded subunits. The protein encoded by this gene binds ubiquinone and participates in the transfer of electrons when ubiquinone is bound. This protein plays an important role in hypoxia-induced angiogenesis through mitochondrial reactive oxygen species-mediated signaling.

[0245] *VDAC2* (Gene ID: 7417) is voltage dependent anion channel 2. This gene encodes a member of the voltage-dependent anion channel pore-forming family of proteins that are considered the main pathway for metabolite diffusion across the mitochondrial outer membrane. The encoded protein is also thought to be involved in the mitochondrial apoptotic pathway via regulation of BCL2-antagonist/killer 1 protein activity.

[0246] *COX4I1* (Gene ID: 1327) is cytochrome c oxidase subunit 4I1. Cytochrome c oxidase (COX) is the terminal enzyme of the mitochondrial respiratory chain. It is a multi-subunit enzyme complex that couples the transfer of electrons from cytochrome c to molecular oxygen and contributes to a proton electrochemical gradient across the inner mitochondrial membrane. This gene encodes the nuclear-encoded subunit IV isoform 1 of the human mitochondrial respiratory chain enzyme.

[0247] *SDHB* (Gene ID: 6390) is succinate dehydrogenase complex iron sulfur subunit B. Complex II of the respiratory chain, which is specifically involved in the oxidation of succinate, carries electrons from FADH to CoQ. The complex is composed of four nuclear-encoded subunits and is localized in the mitochondrial inner membrane.

[0248] *COX6B1* (Gene ID: 1340) is cytochrome c oxidase subunit 6B1. Cytochrome c oxidase (COX), the terminal enzyme of the mitochondrial respiratory chain, catalyzes the electron transfer from reduced cytochrome c to oxygen. It is a heteromeric complex consisting of 3 catalytic subunits encoded by mitochondrial genes and multiple structural subunits encoded by nuclear genes. The mitochondrially-encoded subunits function in electron transfer, and the nuclear-encoded subunits may be involved in the regulation and assembly of the complex. This nuclear gene encodes subunit VIb.

[0249] *MAOB* (Gene ID: 4129) is monoamine oxidase B. The protein encoded by this gene belongs to the flavin monoamine oxidase family. It is a enzyme located in the mitochondrial outer membrane. It catalyzes the oxidative deamination of biogenic

and xenobiotic amines and plays an important role in the metabolism of neuroactive and vasoactive amines in the central nervous system and peripheral tissues.

[0250] **Detection of Skipped Exon Events**

[0251] In an embodiment, a method of detecting pre-symptomatic, advanced, early-onset, or age-related (late-onset) Fuchs' endothelial corneal dystrophy, glaucoma, or other ocular diseases can comprise detecting one or more skipped exon events as shown in Table 8 in a sample obtained from a subject. In an embodiment a combination of 2, 3, 4, 5, 10, 15, 20, 20, 30, 40, 50, 60, 70, 80, 90, 100, or more of skipped exon events shown in Table 8 can be detected.

[0252] The complex and diverse process alternative splicing (AS) involves removing noncoding intronic sequences and remaining exons to generate mature mRNA. AS is generally divided into five basic types according to the process: alternative 5' splice sites, alternative 3' splice sites, intron retention event, exon skipping (ES) events, and mutually exclusive exons. RNAseq can be used to evaluate splicing changes.

[0253] Strategies applied for differential splicing analysis can be divided into isoform-based or count-based. Isoform-based methods aim at reconstructing and quantifying full-length transcripts, prior to differential expression analysis. Statistical testing is then applied to identify significant differences in the relative transcript abundances between the different experimental conditions. Isoform-based methods can include, for example, Cufflinks/cuffdiff2 or DiffSplice.

[0254] Count-based methods include both exon-based and event-based approaches. In exon-based methods, read counts are assigned to different features, such as exons or junctions. Exon-based methods can include, for example, DEXSeq, edgeR, JunctionSeq, or limma. In event-based methods, splicing events themselves are quantified by calculating the percentage spliced in (PSI) values for each event, which measure the fraction of mRNAs expressed from a gene that contains a specific form of that event. Event-based methods can include, for example, dSpliceType, MAJIQ, rMATS, or SUPPA /SUPPA2.

[0255] In an embodiment, alternative splicing patterns can be validated by preparing cDNAs via reverse transcription, subsequent RT-PCR analysis, amplification products separated by gel electrophoresis, and qPCR.

[0256] In an embodiment, RNAseq or other suitable methods can be used to evaluate splicing changes in subjects (**FIG. 4**).

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[0257] In another embodiment, polymorphisms can be genotyped and RNA half-life can be measured.

[0258] *TCF4* CTG18.1 polymorphism genotyping was conducted using short tandem repeat (STR) and triplet repeat primed polymerase chain reaction (TP-PCR). *TCF4* RNA half-life was measured using qPCR.

[0259] Short tandem repeat analysis (STR) and triplet repeat primed polymerase chain reaction (TP-PCR) can be used in tandem. Short Tandem Repeat (STR) analysis is a common molecular biology method used to compare allele repeats at specific loci in DNA between two or more samples. A short tandem repeat is a microsatellite with repeat units that are 2 to 7 base pairs in length, polymerase chain reaction (PCR) is employed to discover the lengths of the short tandem repeats based on the length of the PCR product. TP-PCR can be performed on the samples in which the STR analysis revealed only one apparent allele or no alleles. Characteristic tracing patterns of the triplet repeat primed electropherograms can be used to distinguish samples. The TP-PCR assay is also used to screen for expanded alleles and it uses a locus-specific primer flanking the repeat together with paired primers amplifying from multiple priming sites within the repeat. Specificity is dictated by the fluorescently labeled, locus-specific primer. TP PCR gives a characteristic ladder on the fluorescence trace enabling the rapid identification of large pathogenic repeats that cannot be amplified using flanking primers. For example, *TCF4* CTG18.1 polymorphism genotyping can be conducted using short tandem repeat (STR) and triplet repeat primed polymerase chain reaction (TP-PCR). Gel Electrophoresis, Southern blot, or other methods of separation and detection can be used to identify samples.

[0260] Furthermore, RNA half-life can be measured using qPCR.

[0261] In an embodiment, the methods of detection described herein (i.e., detection of upregulation of genes, down regulation of genes, or skipped exon events) can detect early stage or late stage Fuchs' endothelial corneal dystrophy earlier than detection by the Krachmer grading scale. In an embodiment, the methods of detection described herein (i.e., detection of upregulation of genes, down regulation of genes, or skipped exon events) can detect early stage or late stage FECD before a patient is at G0, at G1, at G2, at G3, at G4, or at G5 of the Krachmer grading scale.

[0262] The Hodapp, Parrish, and Anderson System (HPA) system, a commonly used classification system, is based upon the overall extent of visual field depression

(calculated by the mean deviation value), the number of defective points in the Humphrey Statpac-2 pattern deviation probability map of the 24-2, SITA-STANDARD test, and proximity to damage to fixation point. In spite of its popularity, the HPA system has several limitations. There are only three stages of glaucoma classification: early, moderate, and severe. These broad categories make it difficult to monitor small, but meaningful, changes in functional loss over time. The system does not provide any information regarding the location and depth of defects in the visual field. Finally, the system is complicated and can be time-consuming, limiting its clinical use

[0263] A more continuous staging system was proposed by the Advanced Glaucoma Intervention Study (AGIS). The AGIS system is based on the number and depth of neighboring depressed test locations on the total deviation plot in the nasal area, upper hemifield, and lower hemifield. Visual fields are scored between 0 and 20, with 0 indicating no measured defective points and 20 indicating severe visual field depression. AGIS visual fields are placed into five stages of severity based on the 20-point scale. However, as this system contains a high number of parameters, it is difficult to manually use in the clinic.

[0264] Other methods, such as Brusini's Glaucoma Staging System (GSS), are based on Standard Automated Perimetry (SAP) indices, which serve as the standard for assessing visual field damage indices, such as the Visual Field (VF) indices. VF indices are used to acquire information on both the severity of defects and the type of damage. However, this method does not supply information regarding the location, shape, and morphology of defects, leading to overlapping classifications in some instances. The Enhanced Glaucoma Staging System was derived from the GSS and is considered to be more easily implemented with more severe staging of abnormal fields.

[0265] The University of São Paulo Glaucoma Visual Field Staging System (USP-GVFSS), proposed in 2009, uses four main parameters. These parameters include the Visual Field Index (VFI-a Humphrey Visual Field Test value), location of the defect, involvement of the blind spot, and number of hemifields affected. The SCHEIE (Systematic Classification of Humphrey visual fields-Easy Interpretation and Evaluation) grading system improves on the quantitative aspects of the USP-GVFSS and combines them with qualitative measurements for grading glaucomatous visual field defects.

[0266] In an embodiment, the methods of detection described herein (i.e., detection of upregulation of genes, down regulation of genes, or skipped exon events) can detect glaucoma earlier than detection by the HPA scale, the AGIS system, Brusini's Glaucoma Staging System, or the USP-GVFSS. In an embodiment, the methods of detection described herein (i.e., detection of upregulation of genes, down regulation of genes, or skipped exon events) can detect glaucoma before a patient is at the early, at the moderate, or at the severe grades of the HPA scale. In an embodiment, the methods of detection described herein (i.e., detection of upregulation of genes, down regulation of genes, or skipped exon events) can detect glaucoma before a patient is at the 0, at the 1, at the 2, at the 3, at the 4, at the 5, at the 10, at the 15, or at the 20 score of the AGIS system.

[0267] In an embodiment, the methods of detection described herein can detect early stage or late stage FECD or glaucoma before a patient displays elevated intraocular pressure. In an embodiment, the methods of detection described herein can detect early stage or late stage FECD or glaucoma before a patient displays intraocular pressure above about 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28 mm Hg intraocular pressure.

[0268] **Methods of Treatment**

[0269] In an embodiment, a method of detecting pre-symptomatic, advanced, early-onset, or age-related (late-onset) Fuchs' endothelial corneal dystrophy can comprise treating the subject with eyedrops, surgical interventions, or combinations thereof.

[0270] In some embodiments, medical or surgical treatment for FECD can be administered to a subject. Known methods of treatment include medical treatments of FECD to treat symptoms of early disease. Treatment can be steroidal eye drops, sodium chloride eyedrops, keratoprosthesis implantation, therapeutic contacts, corneal transplant, endothelial keratoplasty, and penetrating keratoplasty. FECD can also be treated with prostaglandins, beta blockers, alpha-adrenergic agonists, carbonic anhydrase inhibitors, rho kinase inhibitors, miotic or cholinergic agents (discussed in more detail below), or combinations thereof.

[0271] Medical management can include steroidal eyedrops, sodium chloride eyedrops, topical hypertonic saline, the use of a hairdryer to dehydrate the precorneal tear film, and therapeutic soft contact lenses. In using a hairdryer, the patient is instructed to hold a hairdryer at an arm's length or directed across the face, to dry out

the epithelial blisters. This can be done two or three times a day. It has also been reported that botulinum toxin can produce improvement lasting several months. Definitive treatment, however, (especially with increased corneal edema) is surgical in the form of corneal transplantation.

[0272] Surgical procedures, called posterior lamellar keratoplasty or endothelial keratoplasty, were initially popularized as deep lamellar endothelial keratoplasty (DLEK) and Descemet's stripping with endothelial keratoplasty (DSEK) for treatment of FECD. DLEK and DSEK avoid some of the surgical complications of PKP such as wound dehiscence and high postoperative astigmatism. DSEK has become the dominant procedure for patients with corneal disease restricted to the endothelium. It can be technically easier for the surgeon compared to DLEK, and may provide superior visual results. With DSEK, patients must remain supine (face up positioning) for 24 or more hours following the procedure while the transplanted tissue adheres to the overlying cornea.

[0273] Improved surgical instrumentation for DSEK, such as DSEK graft injectors, and technical improvements in the surgical technique have facilitated reduced complications and the potential to perform DSEK through very small (3 mm) sutureless incision.

[0274] Endothelial keratoplasty has been further refined to Descemet Membrane Endothelial Keratoplasty (DMEK), in which only a donor Descemet membrane and its endothelium is transplanted. With DMEK, 90% of cases achieve a best spectacle corrected visual acuity 20/40 or better, and 60% of cases 20/25 or better within 1-3 months, although complications such as graft failure and detachment remain challenges for the patient and surgeon.

[0275] Keratoprosthesis implantation is a procedure that involves full-thickness removal of the cornea and replacement by an artificial cornea. The Boston Type I Keratoprosthesis is currently the most commonly used keratoprosthesis device in the US. It consists of a clear plastic polymethylmethacrylate (PMMA) optic and back plate sandwiched around a corneal graft and secured with a titanium locking ring. After the device is assembled, a partial-thickness trephination is performed on the host cornea. Full-thickness resection of the patient's cornea is then completed using curved corneal scissors. The keratoprosthesis is then secured to host tissue using interrupted or running sutures. Generally, patients who have a history of multiple failed penetrating keratoplasty procedures are candidates for a keratoprosthesis transplant.

[0276] Glaucoma is a group of eye diseases encompassing a broad spectrum of clinical presentations, etiologies, and treatment modalities. Glaucoma causes pathological changes in the optic nerve, visible on the optic disk, and it causes corresponding visual field loss, resulting in blindness if untreated. Glaucoma is grossly classified into two categories: closed-angle glaucoma, also known as angle closure glaucoma, and open-angle glaucoma. Closed-angle glaucoma is caused by closure of the anterior chamber angle by contact between the iris and the inner surface of the trabecular meshwork. Closure of this anatomical angle prevents normal drainage of aqueous humor from the anterior chamber of the eye.

[0277] Open-angle glaucoma is any glaucoma in which the angle of the anterior chamber remains open, but the exit of aqueous through the trabecular meshwork is diminished. The exact cause for diminished filtration is unknown for most cases of open-angle glaucoma. Primary open-angle glaucoma is the most common of the glaucomas, and it is often asymptomatic in the early to moderately advanced stage. Patients may suffer substantial, irreversible vision loss prior to diagnosis and treatment. However, there are secondary open-angle glaucomas which may include edema or swelling of the trabecular spaces (e.g., from corticosteroid use), abnormal pigment dispersion, or diseases such as hyperthyroidism that produce vascular congestion.

[0278] In an embodiment, a method of detecting glaucoma in a subject can comprise treating the subject with eyedrops, oral medications, surgical interventions, or combinations thereof.

[0279] Glaucoma can be treated with, for example prostaglandins, beta blockers, alpha-adrenergic agonists, carbonic anhydrase inhibitors, rho kinase inhibitors, miotic or cholinergic agents. These agents can be delivered via, for example, eye drops or orally. Oral medication and eye drops can be administered 1, 2, 3, 4, 5, 6, or more times a day.

[0280] Prostaglandins can increase the outflow of the fluid in the eye (aqueous humor), thereby reducing eye pressure. Medicines in this category include latanoprost (Xalatan), travoprost (Travatan Z), tafluprost (Zioptan), bimatoprost (Lumigan) and latanoprostene bunod (Vyzulta).

[0281] Beta blockers can reduce the production of fluid in the eye, thereby lowering the pressure in the eye (intraocular pressure). Examples include timolol (Betimol, Istalol, Timoptic) and betaxolol (Betoptic).

[0282] Alpha-adrenergic agonists can reduce the production of aqueous humor and increase outflow of the fluid in the eye. Examples include apraclonidine (Iopidine) and brimonidine (Alphagan P, Qoliana).

[0283] Carbonic anhydrase inhibitors can reduce the production of fluid in the eye. Examples include dorzolamide (Trusopt) and brinzolamide (Azopt).

[0284] Rho kinase inhibitors lower eye pressure by suppressing the rho kinase enzymes responsible for fluid increase. It is available as netarsudil (Rhopressa) and Y-27632.

[0285] Miotic or cholinergic agents can increase the outflow of fluid from the eye. An example is pilocarpine (Isopto Carpine).

[0286] Advanced, early-onset, or age-related (late-onset) Fuchs' endothelial corneal dystrophy involves fluid buildup and can sometimes accompany glaucoma. In some embodiments, a method of detecting pre-symptomatic, advanced, early-onset, or age-related (late-onset) Fuchs' endothelial corneal dystrophy can comprise treating the subject with prostaglandins, beta blockers, alpha-adrenergic agonists, carbonic anhydrase inhibitors, rho kinase inhibitors, miotic or cholinergic agents as described herein.

[0287] In an embodiment, a method of detecting glaucoma in a subject can comprise treatment with laser therapy, such as laser trabeculoplasty, filtering surgery, such as a trabeculectomy, drainage tubes to drain away excess fluid to lower eye pressure, minimally invasive glaucoma surgery (MIGS), and peripheral iridotomy. Furthermore, glaucoma can be treated with implantation of aqueous shunts after failure of trabeculectomy or if trabeculectomy is unlikely to succeed. Trabeculectomy is a major surgery that is widely used and is augmented with topically applied anticancer drugs, such as 5-flurouracil or mitomycin-C to decrease scarring and increase the likelihood of surgical success.

[0288] **Methods for decreasing gene expression of upregulated genes**

[0289] In an embodiment a subject having early or late onset FECD, glaucoma, or other ocular disease can be treated by downregulating one or more of the genes described in the section entitled Detection of an Increase of Expression of Marker Genes herein.

[0290] In some embodiments, a method for decreasing gene expression of upregulated genes is provided. In some embodiments, the method of decreasing gene expression can include administration of antibodies, oligonucleotides, RNAi, siRNAs,

shRNA, miRNA, small molecules; CRISPR systems, or combinations thereof to a subject in need thereof.

[0291] Antibodies

[0292] Therapeutic agents of the present disclosure can include various antibodies or specific binding fragment thereof. The term "antibody" as used herein is used broadly and can encompass polyclonal antibodies, monoclonal antibodies as well as specific binding fragments thereof. An antibody molecule can be monospecific, idiospecific, heterospecific, or polyspecific. Antibody molecules can have specific binding sites that bind to specific antigenic determinants, epitopes, on antigens. "Specific binding fragments" can comprise a portion of the full-length antibody. The portion can generally be the antigen binding or a variable region of the antibody. Examples of antibody fragments include Fab, Fab', F(ab')2 and Fv fragments; diabodies; linear antibodies; single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

[0293] In an embodiment, antibodies can be used to target intracellular molecules. In effect, this would achieve gene downregulation at the post-translational level. This approach was given impetus by the development of the single chain variable fragment (scFv) antibody format, which facilitates the engineering and expression of functional antibodies within the intracellular environment. The recombinant antibody expressed within the confines of the intracellular environment is commonly referred to as an intrabody.

[0294] Antibodies can be used, for example, to decrease or downregulate gene expression for one or more of the upregulated genes disclosed herein. Antibodies that can bind to *COCH*, an upregulated gene, to decrease expression include, for example, ABIN951612, orb30939, AP51001PU-N, PA5-48475, OAAB09196, BS6944, or LS-C166910, among others. Antibodies that can bind to FN1, an upregulated gene, to decrease expression include, for example, AMAb91223, HPA027066, and ab2413, among others. Antibodies that can bind to THBS2, an upregulated gene, to decrease expression include, for example, HPA044304, A16231, and ab112543, among others. Antibodies to downregulate expression of other genes encoding proteins as described in the section entitled "Detection of an Increase of Expression of Marker Genes" are readily available.

[0295] Gene Therapy

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[0296] Gene therapy includes constructs designed to reduce the expression of a particular gene (DNA sequences coding for shRNA and miRNA, as well as siRNA that are delivered directly). All constructs can be delivered using the most common virus-based, as well as non-viral, methods. Therapeutic agents for decreasing gene expression of upregulated genes can include the use of oligonucleotides, RNAi, siRNA molecules, shRNA molecules, and miRNA molecules. Viral vectors or non-viral delivery can be used.

[0297] In another embodiment, viral vectors can be used for gene therapy. Adenoviruses, for example, are medium-sized, non-enveloped viruses with a nucleocapsid and a linear dsDNA genome. They are able to replicate in the nucleus of mammalian cells but do not efficiently integrate into the host's genome. AdVs are able to package approximately 8-30 kb of foreign DNA. Several AdV features are attractive for vector use. Adenoviral vectors are a common delivery method to introduce shRNA-expression cassettes (described below) into target cells in vitro. Another example is Adeno-associated viral vectors (AAV), one of the smallest viruses belonging to the genus Dependovirus and the family Parvoviridae. AAVs have a small, single-stranded DNA genome (4.8 kb) and are considered apathogenic in humans. The genome contains only two genes, which can be replaced with foreign ones, leaving only the terminal ITRs to allow high-level expression of the insert. However, the 5 kb packaging limit of AAV is still sufficient to accommodate at least eight individual shRNA expression cassettes.

[0298] In other embodiments, non-viral delivery can be used. Non-viral vectors are safer, of low cost, more reproducible and do not present DNA size limitations in comparison with viral vectors. For example, cationic liposomes associated with Tf form stable siRNA (described below) lipoplexes with reduced toxicity and enhanced specific gene knockdown activity compared to conventional lipoplexes. Thus, such formulations may constitute efficient delivery systems for therapeutic siRNA applications.

[0299] Oligonucleotides

[0300] Therapeutic agents of the present disclosure can include one or more antisense oligonucleotides targeting one or more of the genes, disclosed herein, with upregulated expression. The goal of the antisense approach is the downregulation of a molecular target, usually achieved by induction of RNase H endonuclease activity that cleaves the RNA-DNA heteroduplex with a significant reduction of the target gene

translation. Antisense oligonucleotides are short, synthetic, single-stranded oligodeoxynucleotides that are complementary to the mRNA target. Antisense oligonucleotides can be about 20 nucleotides long and can be selected to target either the methionine (AUG) initiation codon, blocking translation, or the splice sites, to block splicing. Antisense oligonucleotides can be synthesized using chemically modified nucleotides, for example (without limitation), phosphorothioates, 2'-*O*-methyl RNA, or locked nucleic acids, which can confer nuclease resistance. Antisense oligonucleotides can hybridize to target RNA in a sequence-specific manner. Antisense oligonucleotides can inhibit gene expression, modulate splicing of a precursor mRNA, or inactivate microRNA. Antisense oligonucleotides can work by inducing RNase H endonuclease activity that cleaves the RNA-DNA heteroduplex and thereby can reduce target gene translation, for example, *COCH*, the gene encoding the protein cochlin. Antisense oligonucleotides can also inhibit 5' cap formation, alter the splicing process (splice-switching), and sterically hinder ribosomal activity).

[0301] Antisense oligonucleotides can be used, for example, to decrease or downregulate gene expression for one or more of the upregulated genes disclosed herein Antisense oligonucleotides that can bind the mRNA of an upregulated gene such as mRNA of *COCH* or *FN1* to decrease expression. Examples include RNase H1-dependent antisense oligonucleotides, gapmer antisense oligonucleotides, and phosphorothioate antisense oligonucleotides, among others. For example, in FECD cases with an expanded intronic CUG tract in the *TCF4* gene that forms nuclear foci, the foci sequester splicing factors and impair splicing. Synthetic oligonucleotides complementary to the CUG repeat in the *TCG4* gene can reverse the splicing defect, inhibit foci, and reverse pathological changes in splicing.

[0302] RNAi

[0303] RNAi is a conserved biological response to double-stranded RNA that mediates resistance to both endogenous parasitic and exogenous pathogenic nucleic acids, and regulates the expression of protein-coding genes. RNAi interrogates gene function by blocking gene expression and analyzing its effect on phenotype. RNAi silences genes by generating knockdowns at the mRNA level.

[0304] siRNA

[0305] Therapeutic agents of the present disclosure can include one or more small interfering RNA (siRNA) targeting one or more of the upregulated genes disclosed herein. siRNA, also referred to as short interfering RNA or silencing RNA, is a class of

double-stranded RNA non-coding molecules, which can be about 20-25 base pairs long. siRNA can operate within the RNA interference (RNAi) pathway. An endoribonuclease, Dicer, can cleave long dsRNA forming siRNA. Long dsRNA can come from hairpin, complementary RNAs, and/or RNA-dependent RNA polymerases. An siRNA can also be transfected into a host cell. Once siRNA enters the target cell, proteins can come together to form the RNA-Induced Silencing Complex (RISC). After RISC forms, the siRNA can unwind to form two single stranded siRNA segments, the passenger strand and the guide strand. The passenger strand is degraded while the less thermodynamically stable guide strand remains part of the RISC and scans to find complementary mRNA. When the siRNA (part of RISC) binds to target mRNA, it induces mRNA cleavage. The cut mRNA is identified as abnormal by the cell and is degraded, thereby preventing translation and silencing the gene that encodes that mRNA, for example, *FN1*.

[0306] siRNA can be used, for example, to decrease or downregulate gene expression for one or more of the upregulated genes disclosed herein. For example, FNA siRNA can inhibit protein expression of FN1 (see EP2574930A1 and sequences disclosed within). siRNA that can inhibit expression of *COCH* can include, for example, NM_004086 (Rosetta Gene ID: HSG00288029; Entrez ID: 1690; probe ID 10023819878) from Sigma Aldrich. siRNA can inhibit expression of THBS2 can include, for example, NM_003247 (Rosetta Gene ID: HSG00242955; Entrez ID: 7058; probe ID 10023814096) from Sigma Aldrich. siRNAs are readily available for the other upregulated genes described in the section entitled "Detection of an Increase of Expression of Marker Genes".

[0307] shRNA

[0308] Therapeutic agents of the present disclosure can include one or more short hairpin RNA (shRNA) targeting one or more of the genes, disclosed herein, with upregulated expression. This shRNA, also referred to as small hairpin RNA or Hairpin Vector, is an artificial RNA molecule with a tight hairpin turn that can be used to silence target gene expression operating within the RNAi pathway. As discussed above, one method for gene knockdown can be transfection of exogenous siRNA, but transfected siRNA can degrade. An expression vector containing siRNA can be synthesized using shRNA. The expression vector can be viral or non-viral DNA vectors that encode shRNA. A common vehicle for shRNA delivery is viral transduction. Expression through AAV or adenovirus can prevent insertional mutagenesis since these vectors

remain episomal, but this approach leads to more transient expression since the vectors are lost through multiple rounds of cell division. Expression through lentivirus provides a stable solution through chromosomal integration, but this also presents the risk of insertional mutagenesis. The siRNA sequence can be modified to contain a short loop between the two strands, creating the shRNA. Dicer can process shRNA, which can provide an advantage over transfected siRNA, which can degrade more rapidly than shRNA.

[0309] The one or more shRNAs targeting one or more of the genes, disclosed herein, with upregulated expression can be, for example, one or more of those in table 1. shRNAs are readily available for the other genes described in the section entitled Detection of an Increase of Expression of Marker Genes.

[0310] Table 1. shRNA transcripts for upregulated genes.

Gene ID	Taxon	Gene Symbol	Gene Description	Current WT Transcripts
5243	human	*ABCB1*	ATP binding cassette subfamily B member 1	NM_001348946.2, NM_001348944.1, NM_001348945.1, NM_000927.4
5244	human	*ABCB4*	ATP binding cassette subfamily B member 4	XR_001744809.2, NM_018849.3, XM_011516313.3, XM_011516312.3, XM_011516315.3, XM_011516311.3, XM_017012323.2, NM_000443.4, XM_011516308.3, XM_011516310.3, XM_011516309.3, XR_001744810.2, NM_018850.2
84873	human	*ADGRG7*	adhesion G protein-coupled receptor G7	NM_032787.3, XM_011513245.2, NM_001308362.1
719	human	*C3AR1*	complement C3a receptor 1	NM_001326475.2, NM_001326477.2, NM_004054.4
942	human	*CD86*	CD86 molecule	NM_001206925.1, NM_006889.4, NM_001206924.1, NM_176892.1, NM_175862.5
1029	human	*CDKN2A*	cyclin dependent kinase inhibitor 2A	XM_011517675.2, XR_929159.2, XM_011517676.2, XM_005251343.1, NM_000077.4, NM_001195132.1, NM_058195.3, NM_058197.4, NM_001363763.2
23601	human	*CLEC5A*	C-type lectin domain containing 5A	NM_013252.3, NM_001301167.2, XM_017011916.2, XM_017011917.1, XM_017011915.1, XM_011515995.2
1264	human	*CNN1*	calponin 1	XM_017026289.1, XM_005259741.2, XM_024451361.1, NM_001308341.2, NM_001299.6, NM_001308342.2, XM_024451362.1
1690	human	*COCH*	cochlin	NM_001347720.1, XM_017021071.1, NM_001135058.1, XM_024449506.1, NM_004086.3
54504	human	*CPVL*	carboxypeptidase vitellogenic like	NM_001371256.1, NM_001371267.1, NM_001371263.1, NM_031311.5, NM_001371264.1, NM_001371257.1, NM_001371261.1, NM_001371268.1, NM_001371265.1, NM_001371255.1, NM_001371258.1, NM_001371260.1, NM_001371266.1, NM_001371262.1, NM_001348054.1, NM_019029.3, NM_001348052.1, XM_017012366.1, XM_011515437.1
1536	human	*CYBB*	cytochrome b-245 beta chain	NM_000397.4
1641	human	*DCX*	doublecortin	NM_000555.3, NM_178151.2, NM_001369370.1, NM_178152.3, XM_011530879.3, NM_001369372.1, NM_001195553.2, NM_001369371.1, NM_001369373.1, NM_001369374.1, NM_178153.3
8788	human	*DLK1*	delta like non-canonical Notch ligand 1	NM_003836.6, NM_001317172.2
347694	human	*ECEL1P2*	endothelin converting enzyme like 1 pseudogene 2	NR_028501.1
55531	human	*ELMOD1*	ELMO domain containing 1	NM_018712.4, XM_017017994.2, XM_017017995.2, NM_001308018.1, NM_001130037.1
2153	human	*F5*	coagulation factor V	NM_000130.5, XM_017000660.2

2210	human	*FCGR1B*	Fc fragment of IgG receptor Ib	XR_002959729.1, XR_001737041.2, NR_045213.2, NM_001017986.4, NM_001004340.4, XM_017000661.1, XM_017000662.1, XR_001737040.1, NM_001244910.1
2335	human	*FN1*	fibronectin 1	XM_017003692.1, XM_017003695.1, NM_001365524.1, XM_024452770.1, NM_001365521.1, NM_001365518.1, NM_001365522.1, XM_024452769.1, NM_212482.3, NM_001365517.1, NM_001365523.1, NM_001365519.1, NM_001365520.1, XM_005246402.1, XM_005246404.1, XM_005246410.1, XM_005246398.1, XM_005246397.1, XM_005246408.1, XM_005246411.1, XM_005246407.1, XM_005246399.1, XM_005246416.1, XM_005246403.1, XM_005246401.1, NM_054034.2, NM_002026.3, NM_212474.2, NM_212476.2, NM_212478.2, NM_001306131.1, NM_001306130.1, NM_001306129.1, NM_001306132.1
2350	human	*FOLR2*	folate receptor beta	XM_005273856.4, XM_024448412.1, NM_001113534.2, NM_001113536.2, NM_000803.5, NM_001113535.2
2295	human	*FOXF2*	forkhead box F2	NM_001452.2
2487	human	*FRZB*	frizzled related protein	NM_001463.4
51313	human	*GASK1B*	golgi associated kinase 1B	NM_016613.7, XM_024454078.1, XM_024454079.1, NM_001031700.3, NM_001128424.2
647309	human	*GMNC*	geminin coiled-coil domain containing	XR_924161.2, NM_001146686.3
2719	human	*GPC3*	glypican 3	NM_004484.4, NM_001164619.2, XM_017029413.2, NM_001164618.2, NM_001164617.2
2857	human	*GPR34*	G protein-coupled receptor 34	XM_005272597.4, NM_005300.4, NM_001097579.2
2915	human	*GRM5*	glutamate metabotropic receptor 5	NM_000842.4, NM_001143831.2, XM_011542792.1, XM_017017627.2, XM_006718828.4
3117	human	*HLA-DQA1*	major histocompatibility complex, class II, DQ alpha 1	XM_006715079.4, NM_002122.5
3122	human	*HLA-DRA*	major histocompatibility complex, class II, DR alpha	NM_019111.5
3248	human	*HPGD*	15-hydroxyprostaglandin dehydrogenase	NM_001363574.2, XR_938728.2, NM_000860.6, NM_001145816.2, NM_001256301.1, NM_001256306.1, NM_001256307.1, NM_001256305.1
150084	human	*IGSF5*	immunoglobulin superfamily member 5	NM_001080444.1, XM_011529472.2
3736	human	*KCNA1*	potassium voltage-gated channel subfamily A member 1	NM_000217.3
10894	human	*LYVE1*	lymphatic vessel endothelial hyaluronan receptor 1	NM_006691.4
728239	human	*MAGED4*	MAGE family member D4	NM_001272061.1, NM_001272063.2, NM_001272062.2, NM_001098800.3
55016	human	*MARCHF1*	membrane associated ring-CH-type finger 1	NM_017923.4, XM_011532055.3, NM_001166373.1, XM_017008334.1, XM_017008335.1, XM_017008336.1
91862	human	*MARVELD3*	MARVEL domain containing 3	NM_001017967.4, NM_052858.6, XM_011523449.3, NM_001271329.2
100847004	human	*MIR5188*	microRNA 5188	NR_049820.1
107984884	human	*MMP2-AS1*	MMP2 antisense RNA 1	NR_147198.1
4440	human	*MSI1*	musashi RNA binding protein 1	XM_011538363.2, XM_011538364.2, XM_006719404.3, XM_011538370.2, XM_011538362.2, XM_011538371.2, XM_011538365.2, XM_011538366.2, XM_006719403.3, XM_011538368.2, XM_011538361.3, NM_002442.4
50507	human	*NOX4*	NADPH oxidase 4	XM_017017842.1, XM_017017844.1, XM_011542857.2, XM_017017845.1, NM_001300995.1, NM_001291927.1, NM_001143836.3, XM_017017843.2, NM_001291929.2, NR_120406.2, XM_006718849.4,

				XM_017017841.2, NM_016931.5, NM_001143837.2, NM_001291926.2
5121	human	*PCP4*	Purkinje cell protein 4	NM_006198.3
7058	human	*THBS2*	thrombospondin 2	NM_003247.3
55026	human	*TMEM255A*	transmembrane protein 255A	NM_017938.3, NM_001104544.1, NM_001104545.1, XM_017029619.2, XR_001755706.2
7162	human	*TPBG*	trophoblast glycoprotein	NM_006670.4, NM_001166392.1
23584	human	*VSIG2*	V-set and immunoglobulin domain containing 2	NM_014312.5, NM_001329920.2
1490	human	*CCN2*	cellular communication network factor 2	NM_001901.3
1278	human	*COL1A2*	collagen type I alpha 2 chain	NM_000089.4
1284	human	*COL4A2*	collagen type IV alpha 2 chain	NM_001846.4
1299	human	*COL9A3*	collagen type IX alpha 3 chain	XM_017027666.1, XM_011528545.1, NM_001853.4
2214	human	*FCGR3A*	Fc fragment of IgG receptor IIIa	NM_000569.7, NM_001127592.2, NM_001329122.1, NM_001329120.1, NM_001127593.1, XM_024454064.1, NM_001127595.2, NM_001127596.2
51350	human	*KRT76*	keratin 76	NM_015848.4
5672	human	*PSG4*	pregnancy specific beta-1-glycoprotein 4	NM_002780.5, NM_213633.3, NM_001316339.2, XM_017027001.2, XM_017027002.2, XM_017026997.2, NM_001276495.1
4982	human	*TNFRSF11B*	TNF receptor superfamily member 11b	NM_002546.4
596	human	*BCL2*	BCL2 apoptosis regulator	XM_017025917.2, XR_935248.3, XM_011526135.3, NM_000633.2, NM_000657.2
920	human	*CD4*	CD4 molecule	NM_001195016.3, NM_001195014.3, XM_017020228.2, NM_001195015.3, NM_000616.5, NM_001195017.3
1290	human	*COL5A2*	collagen type V alpha 2 chain	NM_000393.5, XM_011510573.3
2263	human	*FGFR2*	fibroblast growth factor receptor 2	NM_001144915.1, NM_001144913.1, NM_001144916.1, NM_001320654.1, NM_001144914.1, NM_023029.2, NM_000141.4, NM_022970.3, XM_024447887.1, NM_001144917.2, NR_073009.2, XM_024447892.1, XM_017015924.2, XM_006717710.4, XM_017015920.2, XM_024447891.1, XM_006717708.3, NM_001144918.2, XM_017015921.2, XM_024447888.1, XM_024447890.1, XM_024447889.1, NM_001320658.2, NM_001144919.2, XM_017015925.2
3111	human	*HLA-DOA*	major histocompatibility complex, class II, DO alpha	NM_002119.4
3113	human	*HLA-DPA1*	major histocompatibility complex, class II, DP alpha 1	NM_033554.3, NM_001242524.2, NM_001242525.2
3115	human	*HLA-DPB1*	major histocompatibility complex, class II, DP beta 1	NM_002121.6
3459	human	*IFNGR1*	interferon gamma receptor 1	NM_000416.2, XM_011535794.1, XM_011535793.2, XM_006715470.3, NM_001363527.1, NM_001363526.1
10320	human	*IKZF1*	IKAROS family zinc finger 1	XM_017011669.1, XM_011515060.2, XM_011515077.2, XM_011515076.2, XM_011515062.2, XM_017011670.1, XM_011515070.2, XM_011515073.2, XM_017011668.1, XM_011515066.2, XM_011515074.2, XM_011515063.2, XM_011515072.2, XM_011515058.2, XM_017011667.1, XM_011515068.2, XM_011515069.2, XM_011515065.2, XM_011515071.2, XM_011515078.2, XM_011515075.2, NM_001291844.1, NM_001220770.2, NM_001291843.1, NM_001291841.1, NM_001220768.2, NM_001220767.2, NM_001291840.1, NM_001220771.2, NM_001291842.1, NM_006060.6, NM_001291837.2, NM_001291846.2,

				NM_001220765.3, NM_001291845.2, XM_011515064.3, XM_011515067.3, NM_001291839.2, NM_001291838.2, XM_011515059.3, NM_001291847.2, XM_011515061.3
3587	human	*IL10RA*	interleukin 10 receptor subunit alpha	XM_024448493.1, NR_026691.2, NM_001558.3
3606	human	*IL18*	interleukin 18	XM_011542805.1, XM_011542806.2, NM_001243211.2, NM_001562.4
3689	human	*ITGB2*	integrin subunit beta 2	NM_000211.5, XM_006724001.2, NM_001303238.2, NM_001127491.3
182	human	*JAG1*	jagged canonical Notch ligand 1	NM_000214.3
5602	human	*MAPK10*	mitogen-activated protein kinase 10	XR_001741289.1, XM_017008441.2, XM_024454145.1, XM_006714268.3, XM_005263135.4, XM_017008428.2, NM_002753.5, XM_017008453.2, XM_005263130.3, XM_024454141.1, NM_001363657.2, XM_024454144.1, XM_017008435.2, XM_024454142.1, NM_001351624.2, XM_017008436.2, XM_017008450.2, XM_017008434.2, XM_017008454.2, XM_017008433.2, XM_017008429.2, XM_005263131.3, XM_005263129.3, XM_024454146.1, XM_017008448.2, XM_024454143.1, XM_017008447.2, XM_017008432.2, XM_017008420.2, XM_024454149.1, NM_138982.4, XM_017008422.2, XM_017008452.2, XM_024454148.1, XM_011532117.3, XM_024454139.1, NM_001318069.2, XM_017008445.2, XM_017008423.2, XM_017008449.2, XM_006714269.3, XM_024454147.1, XM_017008427.2, XM_017008430.2, XM_011532120.3, XM_011532121.3, NM_138980.4, XM_011532118.3, XM_017008451.2, NM_001351625.2, XM_017008437.2, XM_024454140.1, NM_001318068.1, NM_001318067.1
4773	human	*NFATC2*	nuclear factor of activated T cells 2	XM_011528826.2, XM_011528824.2, XM_011528825.2, XM_017027851.1, XM_017027850.1, NM_001258296.2, NM_173091.4, NM_001258292.2, NM_001258294.2, NM_012340.5, NM_001258297.2, NM_001136021.3, NM_001258295.2
4851	human	*NOTCH1*	notch receptor 1	XM_011518717.2, NM_017617.5
4853	human	*NOTCH2*	notch receptor 2	NM_001200001.1, NM_024408.4
23533	human	*PIK3R5*	phosphoinositide-3-kinase regulatory subunit 5	NM_001251851.2, NM_001251852.1, NM_001251855.1, NM_001251853.1, NM_001142633.2, XM_005256580.3, NM_014308.3
6688	human	*SPI1*	Spi-1 proto-oncogene	XM_017018173.1, XM_011520307.1, NM_001080547.2, NM_003120.3
7046	human	*TGFBR1*	transforming growth factor beta receptor 1	NM_001130916.3, XM_024447658.1, NM_001306210.2, NM_004612.4, XM_011518950.2, XM_011518949.2, XM_011518948.2, XM_017015063.1
7048	human	*TGFBR2*	transforming growth factor beta receptor 2	NM_001024847.2, XM_011534043.2, XM_017007106.1, NM_003242.6, XM_011534045.3
2532	human	*ACKR1*	atypical chemokine receptor 1 (Duffy blood group)	NM_001122951.3, NM_002036.4
80332	human	*ADAM33*	ADAM metallopeptidase domain 33	XM_017028083.1, XM_017028082.1, XR_001754405.1, XM_006723640.1, XM_005260843.1, NM_001282447.2, NM_025220.4, NM_153202.3, XM_006723644.2, XM_011529366.1, XR_937151.1, XM_011529370.1, XR_937152.1, XM_011529367.1, XM_017028081.2, XM_017028080.2, XM_011529371.2, XR_002958534.1, XM_011529373.2
81792	human	*ADAMTS12*	ADAM metallopeptidase with thrombospondin type 1 motif 12	NM_030955.4, NM_001324512.2, NM_001324511.2, XM_017009909.1, XM_017009906.1, XM_017009907.1, XM_017009908.1, XM_017009905.1
115701	human	*ALPK2*	alpha kinase 2	NM_052947.4

306	human	*ANXA3*	annexin A3	NM_005139.3, XR_001741215.2
79642	human	*ARSJ*	arylsulfatase family member J	XM_011532239.2, XM_017008600.1, XM_011532238.3, XM_017008598.2, XM_017008594.2, XM_017008595.2, XM_017008592.2, XM_024454216.1, NM_024590.4, NM_001354210.2, XM_017008599.2, NM_001354211.2, XM_024454214.1, XM_017008593.2, XM_024454215.1, XM_017008597.2
57863	human	*CADM3*	cell adhesion molecule 3	XM_024448760.1, NM_021189.5, NM_001127173.3, NM_001346510.2
100131625	human	*CADM3-AS1*	CADM3 antisense RNA 1	NR_037870.1
54102	human	*CLIC6*	chloride intracellular channel 6	XM_017026406.1, NM_001317009.2, NM_053277.3
1469	human	*CST1*	cystatin SN	NM_001898.2
1472	human	*CST4*	cystatin S	NM_001899.2
728597	human	*DCDC2C*	doublecortin domain containing 2C	XM_006711894.4, NM_001365580.1, XR_001738921.2, XM_017004837.2, XM_017004836.2, NM_001287444.2, XR_001738920.2
9201	human	*DCLK1*	doublecortin like kinase 1	NM_001195415.1, XM_017020848.1, XM_017020847.1, NM_001195430.2, NM_001195416.2, NM_001330071.2, NM_004734.5, NM_001330072.2
57628	human	*DPP10*	dipeptidyl peptidase like 10	NM_001178034.1, NM_001321906.1, NM_001321914.1, XM_017004566.1, NM_001321905.2, NM_001178036.2, NM_001178037.2, XM_024453023.1, NM_001321912.2, NM_001004360.4, NM_001321907.2, NM_001321910.2, NM_001321913.2, NM_001321909.2, NM_001321911.2, NM_020868.6, NM_001321908.2
55068	human	*ENOX1*	ecto-NOX disulfide-thiol exchanger 1	NM_001127615.2, XR_001749594.1, XM_017020641.2, NM_001347965.2, NM_001347968.2, NM_017993.5, XM_011535127.3, NM_001347970.2, XR_001749593.2, NM_001242863.3, XM_024449374.1, NM_001347969.2, NM_001347963.2, XM_024449372.1, NR_145132.2, XM_011535126.3, XM_024449373.1, NM_001347967.2, XR_001749592.2, NM_001347964.2, NM_001347971.2, XM_024449371.1, NM_001347966.2, XM_017020642.2, XM_017020637.2
2051	human	*EPHB6*	EPH receptor B6	XM_011515881.3, XM_024446674.1, XM_024446675.1, NM_004445.6, XM_011515880.1, XM_011515879.1, XM_011515882.2, NM_001280795.2, NM_001280794.2, NR_104001.2
80000	human	*GREB1L*	GREB1 like retinoic acid receptor coactivator	XM_017025991.1, XM_017025988.1, XM_017025996.1, XM_017025989.1, XM_017025994.1, XM_017025990.1, XM_017025993.1, XM_017025995.1, XM_017025992.1, NM_001142966.2, XM_006722547.3, XM_011526179.3
3382	human	*ICA1*	islet cell autoantigen 1	XM_011515351.1, XM_011515349.1, XM_011515348.1, XM_011515354.1, XM_011515353.2, XM_011515357.2, XM_017012125.1, XM_017012116.1, NM_004968.3, NR_146929.2, NM_001350829.2, NM_001350833.2, NM_001350838.2, NM_001350826.2, NR_146928.2, NM_001350837.2, XM_024446741.1, XR_002956426.1, NM_001350825.2, NM_001276478.2, NM_001350823.2, NM_001350834.2, NM_001350831.2, XM_024446740.1, NM_001350836.2, XM_011515347.3, NM_001350819.2, NM_001350830.2, NM_001350828.2, NM_001350827.2, NR_146926.2, XM_011515356.3, NM_001350835.2, NM_001136020.3, NM_001350821.2, NM_001350832.2, XM_011515355.3, NM_022307.3, XR_002956427.1, NM_001350824.2, NM_001350820.2, NR_146927.2

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80760	human	*ITIH5*	inter-alpha-trypsin inhibitor heavy chain 5	NM_030569.7, XM_011519714.3, XM_011519713.3, NM_032817.6, NM_001001851.2
150771	human	*ITPRIPL1*	ITPRIP like 1	NM_001163523.1, NM_001163524.1, NM_001008949.2, XM_017003427.1, NM_001324490.1, NM_178495.6
23046	human	*KIF21B*	kinesin family member 21B	NM_001252102.2, NM_001252103.2, NM_017596.4, NM_001252100.2, XM_017000732.1, XM_017000731.1
59352	human	*LGR6*	leucine rich repeat containing G protein-coupled receptor 6	NM_001017404.1, NM_001017403.1, XM_011509840.2, XM_011509841.2, XM_011509844.2, XM_011509838.2, XM_017001996.1, XM_011509842.2, XM_011509846.2, XM_011509843.2, XM_005245404.3, XM_011509839.2, XM_017001997.1, XM_017001998.1, NM_021636.3
4327	human	*MMP19*	matrix metallopeptidase 19	XM_017019309.1, XM_006719401.3, XM_017019308.1, XR_429102.2, XM_011538359.1, XR_944553.1, NM_002429.6, NM_001272101.2, NR_073606.2
80133	human	*MROH9*	maestro heat like repeat family member 9	NM_001163629.1, XM_011510006.2, XM_011510007.2, XM_011510005.2, NM_025063.4
219348	human	*PLAC9*	placenta associated 9	NM_001012973.3, NM_001331125.2, NR_138551.2
5627	human	*PROS1*	protein S	NM_000313.4, NM_001314077.1
5774	human	*PTPN3*	protein tyrosine phosphatase non-receptor type 3	XM_006717203.4, NM_001145371.2, NM_001145372.2, NM_001145368.2, NM_002829.4, NM_001145369.1, XM_017014956.1, XM_006717201.3, XM_017014955.1, XM_006717197.3, XM_011518889.2, XM_006717199.3, XM_006717204.3, XM_006717202.3, XM_011518888.2, XM_017014957.1, NM_001145370.1, NR_026918.1
5919	human	*RARRES2*	retinoic acid receptor responder 2	XM_017012491.1, NM_002889.4
4920	human	*ROR2*	receptor tyrosine kinase like orphan receptor 2	XM_005252008.4, XM_017014763.1, XM_017014762.1, XR_001746315.1, XM_006717121.3, XM_005252009.3, NM_001318204.2, NM_004560.4
220963	human	*SLC16A9*	solute carrier family 16 member 9	XM_017015883.1, NM_001323979.1, NM_001323978.1, NM_001323981.1, NM_001323980.1, NM_001323977.1, NM_194298.2, XM_017015884.2, XM_024447878.1
6523	human	*SLC5A1*	solute carrier family 5 member 1	NM_000343.4, XM_011530331.1, NM_001256314.1
161291	human	*TMEM30B*	transmembrane protein 30B	NM_001017970.3
7253	human	*TSHR*	thyroid stimulating hormone receptor	NM_000369.3, NM_001142626.3, NM_001018036.3, XM_006720245.1, XM_005268039.1, XM_005268037.4, XM_011537119.2
7434	human	*VIPR2*	vasoactive intestinal peptide receptor 2	NM_001308259.1, NR_130758.1, NM_001304522.1, XM_005249561.3, XM_017012580.1, XM_006716107.2, XM_006716108.3, XM_011516550.2, XM_024446917.1, XM_024446916.1, XM_024446914.1, XM_024446915.1, XM_024446918.1, NM_003382.5
7473	human	*WNT3*	Wnt family member 3	NM_030753.5

[0311] miRNA.

[0312] MicroRNAs (miRNAs) are non-coding RNAs of 20–24 nucleotides in length that serve as central regulators of eukaryotic gene expression by targeting mRNAs for cleavage or translational repression and promoting mRNA degradation.

[0313] miRNAs that bind to mRNA of *COCH*, an upregulated gene, to decrease expression include, for example, hsa-mir-331-3p, hsa-mir-192-5p, hsa-mir-615-3p, hsa-mir-215-5p, and hsa-mir-1301-3p, among others. miRNAs that bind to mRNA of FN1, an upregulated gene, to decrease expression include, for example, hsa-mir-200b-3p, has-mir-1, has-mir-200c-3p, has-mir-26b-5p, and has-mir-615-3p, among others. miRNAs that bind to mRNA of THBS2, an upregulated gene, to decrease expression include, for example, miR-659-39, among others. miRNAs are readily available for the other genes described in the section entitled "Detection of an Increase of Expression of Marker Genes."

[0314] Small Molecule Therapeutics

[0315] Small-molecule gene-silencing strategies have rapidly evolved, driven largely by enhanced understanding of gene function in the pathogenesis of disease. Over this time, many genes have been targeted by specifically engineered agents from different classes of nucleic acid-based drugs in experimental models of disease to probe, dissect, and characterize further the complex processes that underpin molecular signaling. With the ongoing identification of new genes and an appreciation of their regulatory pathways and pathological roles, small-molecule antigen strategies have not only emerged as an important molecular approach to delineate the functions of these genes but also are now a clinical reality inching closer to mainstream therapeutics.

[0316] For example, pharmacologic targeting of *NTRK3* with the small molecule inhibitor entrectinib can be effective in both in vitro and in vivo models of desmoplastic small round cell tumor, a sarcoma for which *NTRK3* is a prominent neural marker (Ogura et al., *Clinical Cancer Research,* 27(4):2021).

[0317] Genome Editing

[0318] Genome editing changes the actual DNA sequence in the genome. Therapeutic agents can use molecular tools for genome editing to decrease gene expression of upregulated genes, Methods can include the CRISPR-Cas system, zinc finger nucleases, and TALENs.

[0319] Therapeutic agents can include one or more gene-editing compositions directed to target at least one sequence of a polynucleotide of an unregulated gene described herein. The one or more gene editing compositions can comprise at least one polynucleotide encoding an RNA-guided DNA endonuclease protein, and at least one guide RNA (gRNA) having a spacer sequence complementary to a polynucleotide

sequence of an upregulated gene described herein. These RNA-guided DNA endonucleases are directed by gRNA to cleave phosphodiester bonds within a polynucleotide chain. These gRNAs can be noncoding short RNA sequences that bind to complementary DNA sequences and can be used in DNA editing. One RNA-guided DNA endonuclease is CRISPR associated protein 9 (Cas9), which can cleave nearly any sequence complementary to the gRNA. However, any suitable RNA-guided DNA endonuclease can be used. The gRNA can confer target sequence specificity to the CRISPR-CAS9 system by first binding to the RNA-guided DNA endonuclease. Then, the gRNA sequence can guide the complex to a specific location on the DNA where RNA-guided DNA endonuclease performs its endonuclease activity cutting the target DNA strand.

[0320] CRISPR Systems

[0321] CRISPR interrogates gene function by blocking gene expression and analyzing its effect on phenotype. CRISPR generates knockouts at the DNA level. CRISPR-based genome editing requires two components: a guide RNA and a CRISPR-associated endonuclease protein (Cas). The guide RNA, analogous to a GPS system, directs the Cas nuclease to the specific target DNA sequence, which then cuts the DNA at that site. The most commonly used nuclease, SpCas9, is the one isolated from the bacterium *Streptococcus pyogenes*.

[0322] CRISPR systems can be used, for example, to decrease or downregulate gene expression for one or more of the upregulated genes disclosed herein. In an example, the following gRNA sequences uniquely target the *COCH* gene within the human genome. These gRNA sequences are for use with WT SpCas9, or as crRNA for use with WT SpCas9 protein, and introduce a DSB for genome editing. See, Sanjana *et al.,* Improved vectors and genome-wide libraries for CRISPR screening. Nat Methods. 2014 Aug;11(8):783-4:

[0323] Table 2. *COCH* CRISPR gRNA or crRNA

COCH CRISPR Guide RNA or crRNA 1	(GCTTCTGTATCGAGCATATG) (SEQ ID NO:23)
COCH CRISPR Guide RNA or crRNA 2	(ACCGGCTCCCTCGCTGCCCG) (SEQ ID NO:24)
COCH CRISPR Guide RNA or crRNA 3	(CACCCACCGAGGCCGAGAGC) (SEQ ID NO:25)

COCH CRISPR Guide RNA or crRNA 4	(TACACAGAGAATTCCTCAAG) (SEQ ID NO:26)
COCH CRISPR Guide RNA or crRNA 5	(CAGTCACCATGTCCGCAGCC) (SEQ ID NO:27)
COCH CRISPR Guide RNA or crRNA 6	(CCCGCGGGCAGCGAGGGAGC) (SEQ ID NO:28)

[0324] In another example, the following gRNA sequences uniquely target the *FN1* gene within the human genome. These gRNA sequences are for use with WT SpCas9, or as crRNA for use with WT SpCas9 protein, to introduce a DSB for genome editing. See Sanjana *et al.,* Improved vectors and genome-wide libraries for CRISPR screening. Nat Methods. 2014 Aug;11(8):783-4.

[0325] Table 3. *FN1* CRISPR gRNA or crRNA

FN1 CRISPR Guide RNA or crRNA 1	(GACCTACCTAGGCAATGCGT) (SEQ ID NO:29)
FN1 CRISPR Guide RNA or crRNA 2	(TACAAACCAACGCATTGCCT) (SEQ ID NO:30)
FN1 CRISPR Guide RNA or crRNA 3	(GCTCATAAGTGTCACCCACT) (SEQ ID NO:31)
FN1 CRISPR Guide RNA or crRNA 4	(GAATGGACCTGCAAGCCCAT) (SEQ ID NO:32)
FN1 CRISPR Guide RNA or crRNA 5	(TCACACACCTATGGGCTTGC) (SEQ ID NO:33)
FN1 CRISPR Guide RNA or crRNA 6	(GACTGTACCTGCATCGGGGC) (SEQ ID NO:34)

[0326] In yet another example, the following gRNA sequences uniquely target the *THBS2* gene within the human genome. These gRNA sequences are for use with WT SpCas9, or as crRNA for use with WT SpCas9 protein, to introduce a DSB for genome editing. See Sanjana *et al.,* Improved vectors and genome-wide libraries for CRISPR screening. Nat Methods. 2014 Aug;11(8):783-4.

[0327] Table 4. *THBS2* CRISPR gRNA or crRNA

THBS2 CRISPR Guide RNA or crRNA 1	(CCTCACCTTGCAGGTACACG) (SEQ ID NO:35)
THBS2 CRISPR Guide RNA or crRNA 2	(CTGCGCCAGTCCATCCTTTG) (SEQ ID NO:36)
THBS2 CRISPR Guide RNA or crRNA 3	(GCAGCATTCGCCTTCCACAA) (SEQ ID NO:37)
THBS2 CRISPR Guide RNA or crRNA 4	(CGAATGATAACCAGTTTCTC) (SEQ ID NO:38)
THBS2 CRISPR Guide RNA or crRNA 5	(AGCAAGAAGGGTTGCCAGCA) (SEQ ID NO:39)
THBS2 CRISPR Guide RNA or crRNA 6	(CCTAGTGTTTGAAAACTCTG) (SEQ ID NO:40)

[0328] Zinc Finger Nucleases

[0329] Zinc finger nucleases (ZFNs) are comprised of a chain of zinc finger proteins fused to a bacterial nuclease to produce a system capable of making site-specific double stranded DNA breaks to enable gene edits. ZFNs allow site-specific manipulation of the genome. For example, a ZFN-based method suited for the silencing of protein-coding and noncoding genes relies on the ZFN-mediated integration of RNA destabilizing elements into the human genome, e.g., poly(A) signals functioning as termination elements and destabilizing downstream sequences. The biallelic integration of poly(A) signals into the gene locus of the long ncRNA *MALAT1* resulted in a 1000-fold decrease of RNA expression. Thus, this approach is more specific and 300 times more efficient than RNA interference techniques. The opportunity to create a variety of loss-of-function tumor model cell lines in different cancer backgrounds will promote future functional analyses of important long noncoding RNA transcripts. ZFN's can be used to downregulate the upregulated genes described herein.

[0330] TALENs

[0331] Transcription Activator-Like Effector Nucleases (TALENs) are artificial restriction enzymes that consist of a TAL effector DNA-binding domain fused to the DNA nuclease domain from the enzyme FokI. The TAL effector DNA-binding domain is composed of 33-35 amino acid repeats, which differ from each other by two amino

acids (called the Repeat-Variable Di-residue (RVD)). The identity of those two amino acids determines which nucleotide each repeat will bind. A stretch of 12 to 31 repeats can be assembled in a row in order to target the TALEN to a specific DNA sequence in the genome.

[0332] In order for the nuclease domain to cut, the TALEN must dimerize. This means that two different TALENs must be supplied to the cell: one targeting each strand of DNA, separated by a small spacer sequence of 12-25 bp. After FokI cuts, it will cause a dsDNA break, which will be repaired by the cell's error-prone NHEJ pathway. As with CRISPR, this will sometimes result in InDel frameshift mutations which can knockout gene expression. Talens can be used to downregulate the upregulated genes described herein.

[0333] Therapeutic agents of the present disclosure can include one or more agents that can lower or reduce the amount of one of more of the upregulated genes in a patient or subject. The one or more agents can lower or reduce the amount of one or more of the upregulated genes by about 30% to about 90% in the patient or subject, or by about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90% or more. Alternatively, the one or more therapeutic agents can reduce the amount of one or more of the upregulated genes by about 1, 2, 3, 4, 5, 10, 20, 30 fold or more.

[0334] **Methods of Increasing Expression of Downregulated Genes**

[0335] In an embodiment a subject having pre-symptomatic, advanced, early-onset, or age-related (late-onset) FECD, glaucoma, or other ocular disease can be treated by downregulating one or more of the genes described in the section entitled "Detection of a Decrease of Expression of Marker Genes" herein.

[0336] In some embodiments, a method for increasing gene expression of downregulated genes is provided. In some embodiments, the method of increasing gene expression can include gene replacement therapy, CRISPR-Cas system, saRNA, RNAa, increasing RNA transcription or translation, or cell-based therapies.

[0337] Gene Therapy

[0338] Gene therapy includes the delivery of wild-type (WT) and modified genes, as well as constructs designed to reduce the expression of a particular gene (DNA sequences coding for shRNA and miRNA, as well as siRNA that are delivered directly).

[0339] RNAa/saRNA

[0340] RNA activation (RNAa) allows specific gene upregulation mediated by a small activating RNA (saRNA). RNA activation (RNAa) is a process mediated by RNAs to enhance gene expression. This pathway is highly regulated and evolutionarily conserved; therefore, there is enormous potential to apply this gene activation mechanism to target undruggable diseases. In an example, small activating RNAs (saRNA), which were designed to have complementary sequences to the promoter regions of E-cadherin, p21WAF1/CIP1(p21) and VEGF, mediate sequence specific mRNA transcription activation of the respective targeted genes in mammalian cells.

[0341] Increasing RNA Transcription/Translation

[0342] The primary control point for gene expression is usually at the very beginning of the protein production process — the initiation of transcription. RNA transcription makes an efficient control point because many proteins can be made from a single mRNA molecule. The quantity of mRNA transcript for a single gene directly reflects how much transcription of that gene has occurred. Tracking and regulating that quantity will therefore indicate how vigorously a gene is transcribed or expressed. Furthermore, amino acids act through a number of signaling pathways and mechanisms to mediate control of gene expression at the level of translation. Although phosphorylation of eIF2α leads to a suppression of global protein synthesis, accumulating evidence demonstrates that it also results in the derepression of translation of a number of specific mRNA.

[0343] Increasing the expression of *LUM* mRNA, a downregulated gene, can be accomplished through interaction with, for example, tetrachlorodibenzodioxin, valproic acid, phenylmercuric acetate, 4-(5-benzo(1,3)dioxol-5-yl-4-pyridin-2-yl-1H-imidazol-2-yl)benzamide, (6-(4-(2-piperidin-1-ylethoxy)phenyl))-3-pyridin-4-ylpyrazolo(1,5-a)pyrimidine, or 8-Bromo Cyclic Adenosine Monophosphate, among other compounds. Increasing the expression of GFAP mRNA, a downregulated gene, can be accomplished through, for example, interaction with resveratrol, cadmium chloride, and kainic acid, among others.

[0344] Cell-based Therapies

[0345] Although cell therapies have been used in medicine for several decades (e.g., blood transfusions), the use of cells manipulated *ex vivo* with therapeutic genes and then reintroduced into patients offers a new strategy by which to deliver gene-based medicines. The advantages of *ex vivo* genetic manipulation of cells include the ability to engineer highly purified cell populations and optimize the conditions for high-

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efficiency gene transfer outside the body. This obviates the issues of *in vivo* targeting of vectors and circulating host antibody responses. Furthermore, safety profiles of *ex vivo* modified cells can be stringently assessed prior to administration to the patient.

[0346] Cell therapies that can increase, for example, *LUM* expression include, for example, umbilical cord-derived mesenchymal stem cell therapy and corneal stromal stem cell therapy. Cell therapies that can increase *GFAP* expression include, for example, bone marrow stromal cell therapy. Cell therapies that can increase *CXCL8* expression include, for example, mesenchymal stem cell therapy using exogenous *CXCL8*.

[0347] Nucleic Acid Delivery & Expression

[0348] In certain embodiments, expression cassettes are employed to express a gene product, either for subsequent purification and delivery to a cell/subject, or for use directly in a genetic-based delivery approach. Expression requires that appropriate signals be provided in the vectors, and include various regulatory elements such as enhancers/promoters from both viral and mammalian sources that drive expression of the genes of interest in cells. Elements designed to optimize messenger RNA stability and translatability in host cells also are defined. The conditions for the use of a number of dominant drug selection markers for establishing permanent, stable cell clones expressing the products are also provided, as is an element that links expression of the drug selection markers to expression of the polypeptide.

[0349] Regulatory Elements

[0350] In certain embodiments, viral promotes such as the human cytomegalovirus (CMV) immediate early gene promoter, the SV40 early promoter, the Rous sarcoma virus long terminal repeat, rat insulin promoter and glyceraldehyde-3-phosphate dehydrogenase can be used to obtain high-level expression of the coding sequence of interest. The use of other viral or mammalian cellular or bacterial phage promoters which are well-known in the art to achieve expression of a coding sequence of interest is contemplated as well, provided that the levels of expression are sufficient for a given purpose. By employing a promoter with well-known properties, the level and pattern of expression of the protein of interest following transfection or transformation can be optimized. Furthermore, selection of a promoter that is regulated in response to specific physiologic signals can permit inducible expression of the gene product.

[0351] Genome Editing

[0352] CRISPR activation (CRISPRa) is a type of CRISPR tool that uses modified versions of CRISPR effectors without endonuclease activity, with added transcriptional activators on dCas9 or the guide RNAs (gRNAs). Like for CRISPR interference, the CRISPR effector is guided to the target by a complementary guide RNA. However, CRISPR activation systems are fused to transcriptional activators to increase expression of genes of interest. Such systems are usable for many purposes including but not limited to, genetic screens and overexpression of proteins of interest. The most commonly-used effector is based on Cas9 (from Type II systems), but other effectors like Cas12a (Type V) have been used as well.

[0353] Furthermore, selection of a promoter that is regulated in response to specific physiologic signals can permit inducible expression of the gene product.

[0354] **Methods of Monitoring Treatment**

[0355] In an embodiment, a method of monitoring treatment of pre-symptomatic, advanced, early-onset, or age-related (late-onset) Fuchs' endothelial corneal dystrophy can comprise obtaining a first sample from a subject and then detecting in the first sample one or more of: gene expression levels of one or more upregulated genes as described herein, gene expression levels of one or more downregulated genes as described herein, or skipped exon events as shown in Table 8. The method can further comprise treating the subject and then, later, obtaining a second sample from a subject and then detecting in the second sample gene expression levels or skipped exon events. Furthermore, the method can comprise comparing the first sample gene expression levels or skipped exon events with the second sample gene expression levels or skipped exon events.

[0356] In another embodiment, a method of monitoring treatment of glaucoma can comprise obtaining a first sample from a subject, detecting gene expression levels of *COCH* in the first sample, administering a treatment to the subject; obtaining a second sample from the subject and, later, detecting gene expression levels in the second sample, and comparing the first sample gene expression levels to the second sample gene expression levels. The sample of the method can be corneal tissue, aqueous humor, plasma, serum, blood, tear film, trabecular meshwork, or a combination thereof. The method further includes treating the subject with any suitable means including, for example, therapeutic agents that decrease *COCH* expression, prescription eyedrops, oral medications, prostaglandins, beta blockers, alpha-adrenergic agonists, carbonic anhydrase inhibitors, rho kinase inhibitors, miotic or

cholinergic agents, laser trabeculoplasty, trabeculectomy, drainage tubes, minimally invasive glaucoma surgery (MIGS), peripheral iridotomy, aqueous shunts, or combinations thereof. The method can be directed or performed in the anterior segment of the eye, posterior segment of the eye, corneal endothelial cells, or other cells of the anterior segment of the eye. The posterior segment of the eye comprises the back two-thirds of the eye, including the vitreous humor, the retina, the choroid, and the optic nerve. The anterior segment of the eye is the front-most region of the eye, and includes the cornea, iris, ciliary body, and lens. The anterior segment of the eye comprises the anterior chamber between the posterior surface of the cornea (i.e. the corneal endothelium) and the iris and the posterior chamber between the iris and the front face of the vitreous.

[0357] Detection methods

[0358] Gene expression changes in a patient with FECD or glaucoma can be detected using a variety of different methodologies. mRNA of one or more of the up- or down-regulated genes described herein can detected and quantified. Alternatively, one or more proteins associated with the up- or down-regulated genes described herein can be detected and quantified. Some methods include fluorescence in situ hybridization (FISH), immunodetection, western Blot, northern blot, or microarray.

[0359] Fluorescence In Situ Hybridization

[0360] FISH (fluorescent in situ hybridization) is a cytogenetic technique developed to detect and localize the presence or absence of specific nucleic acid sequences. FISH uses fluorescent probes that bind to targets (e.g., parts of the chromosome with which they show a high degree of sequence complementarity). Fluorescence microscopy can be used to find out where the fluorescent probe is bound. FISH is often used for finding specific features in DNA for use in genetic counseling, medicine, and species identification, but can also be used to detect and localize specific RNA targets (mRNA, lncRNA and miRNA) in cells and tissue samples. In this context, it can help define the spatial-temporal patterns of gene expression within cells and tissues.

[0361] The differences between the various FISH techniques are usually due to variations in the sequence and labeling of the probes; and how they are used in combination. Probes are divided into two generic categories: cellular and acellular. "In situ" in fluorescent in situ hybridization refers to the placement of the probe placed cellularly. These few modifications make possible all FISH techniques. Probe size is important because longer probes hybridize less specifically than shorter probes. A

short strand of DNA or RNA (often 10-25 nucleotides) which is complementary to a given target sequence, it can be used to identify or locate the target. The overlap defines the resolution of detectable features. A variety of other techniques use mixtures of differently colored probes. A range of colors in mixtures of fluorescent dyes can be detected, so that different targets can be identified by a characteristic color and a variety of ratios of colors.

[0362] Immunodetection

[0363] In further embodiments, there are immunodetection methods for identifying and/or quantifying gene expression. Some immunodetection methods include enzyme linked immunosorbent assay (ELISA), radioimmunoassay (RIA), immunoradiometric assay, fluoroimmunoassay, chemiluminescent assay, bioluminescent assay, and western blot to mention a few. The steps of various useful immunodetection methods have been described in the scientific literature, such as, e.g., Doolittle and Ben-Zeev (1999), Gulbis and Galand (1993), De Jager et al. (1993), and Nakamura et al. (1987). In general, the immunobinding methods include obtaining a sample and contacting the sample with a first antibody in accordance with embodiments discussed herein, as the case may be, under conditions effective to allow the formation of immunocomplexes. It is also possible to perform in vivo assays.

[0364] Contacting the chosen biological sample with an antibody under effective conditions and for a period of time sufficient to allow the formation of immune complexes (primary immune complexes) is generally a matter of simply adding the antibody composition to the sample and incubating the mixture for a period of time long enough for the antibodies to form immune complexes with, i.e. , to bind to proteins related to the up or downregulated genes disclosed herein. After this time, the sample-antibody composition, such as a tissue section, ELISA plate, dot blot or western blot, will generally be washed to remove any non-specifically bound antibody species, allowing only those antibodies specifically bound within the primary immune complexes to be detected.

[0365] The detection of immunocomplex formation may be achieved through the application of numerous approaches. These methods are generally based upon the detection of a label or marker, such as any of those radioactive, fluorescent, biological and enzymatic tags. Patents concerning the use of such labels include U.S. Patents 3,817,837, 3,850,752, 3,939,350, 3,996,345, 4,277,437, 4,275, 149 and 4,366,241, incorporated by reference herein. Of course, one may find additional advantages

through the use of a secondary binding ligand such as a second antibody and/or a biotin/avidin ligand binding arrangement, as is known in the art.

[0366] The antibody employed in the detection may itself be linked to a detectable label, wherein one would then simply detect this label, thereby allowing the amount of the primary immune complexes in the composition to be determined. Alternatively, the first antibody that becomes bound within the primary immune complexes may be detected by means of a second binding ligand that has binding affinity for the antibody. In these cases, the second binding ligand may be linked to a detectable label. The second binding ligand is itself often an antibody, which may thus be termed a "secondary" antibody. The primary immune complexes are contacted with the labeled, secondary binding ligand, or antibody, under effective conditions and for a period of time sufficient to allow the formation of secondary immune complexes. The secondary immune complexes are then generally washed to remove any non-specifically bound labeled secondary antibodies or ligands, and the remaining label in the secondary immune complexes is then detected.

[0367] Further methods include the detection of primary immune complexes by a two-step approach. A second binding ligand, such as an antibody that has binding affinity for the antibody, is used to form secondary immune complexes, as described above. After washing, the secondary immune complexes are contacted with a third binding ligand or antibody that has binding affinity for the second antibody, again under effective conditions and for a period of time sufficient to allow the formation of immune complexes (tertiary immune complexes). The third ligand or antibody is linked to a detectable label, allowing detection of the tertiary immune complexes thus formed. This system may provide for signal amplification if this is desired. One method of immunodetection uses two different antibodies. A first biotinylated antibody is used to detect the target antigen, and a second antibody is then used to detect the biotin attached to the complexed biotin. In that method, the sample to be tested is first incubated in a solution containing the first step antibody. If the target antigen is present, some of the antibody binds to the antigen to form a biotinylated antibody/antigen complex. The antibody/antigen complex is then amplified by incubation in successive solutions of streptavidin (or avidin), biotinylated DNA, and/or complementary biotinylated DNA, with each step adding additional biotin sites to the antibody/antigen complex. The amplification steps are repeated until a suitable level of amplification is achieved, at which point the sample is incubated in a solution

containing the second step antibody against biotin. This second step antibody is labeled, as for example with an enzyme that can be used to detect the presence of the antibody/antigen complex by histoenzymology using a chromogen substrate. With suitable amplification, a conjugate can be produced which is macroscopically visible.

[0368] Another known method of immunodetection takes advantage of the immuno-PCR (Polymerase Chain Reaction) methodology. The PCR method is similar to the Cantor method up to the incubation with biotinylated DNA, however, instead of using multiple rounds of streptavidin and biotinylated DNA incubation, the DNA/biotin/streptavidin/antibody complex is washed out with a low pH or high salt buffer that releases the antibody. The resulting wash solution is then used to carry out a PCR reaction with suitable primers with appropriate controls. At least in theory, the enormous amplification capability and specificity of PCR can be utilized to detect a single antigen molecule.

[0369] Western Blot or Northern Blot

[0370] The western blot (alternatively, protein immunoblot) is an analytical technique used to detect specific proteins in a given sample of tissue homogenate or extract. It uses gel electrophoresis to separate native or denatured proteins by the length of the polypeptide (denaturing conditions) or by the 3-D structure of the protein (native/non-denaturing conditions). The proteins are then transferred to a membrane (typically nitrocellulose or PVDF), where they are probed (detected) using antibodies specific to the target protein.

[0371] Samples may be taken from whole tissue or from cell culture. In most cases, solid tissues are first broken down mechanically using a blender (for larger sample volumes), using a homogenizer (smaller volumes), or by sonication. Cells may also be broken open by one of the above mechanical methods. However, it should be noted that bacteria, virus or environmental samples can be the source of protein and thus western blotting is not restricted to cellular studies only. Assorted detergents, salts, and buffers may be employed to encourage lysis of cells and to solubilize proteins. Protease and phosphatase inhibitors are often added to prevent the digestion of the sample by its own enzymes. Tissue preparation is often done at cold temperatures to avoid protein denaturing.

[0372] The proteins of the sample are separated using gel electrophoresis. Separation of proteins may be by isoelectric point (pi), molecular weight, electric charge, or a combination of these factors. The nature of the separation depends on

the treatment of the sample and the nature of the gel. This is a very useful way to determine a protein. It is also possible to use a two-dimensional (2-D) gel which spreads the proteins from a single sample out in two dimensions. Proteins are separated according to isoelectric point (pH at which they have neutral net charge) in the first dimension, and according to their molecular weight in the second dimension.

[0373] In order to make the proteins accessible to antibody detection, they are moved from within the gel onto a membrane made of nitrocellulose or polyvinylidene difluoride (PVDF). The membrane is placed on top of the gel, and a stack of filter papers placed on top of that. The entire stack is placed in a buffer solution which moves up the paper by capillary action, bringing the proteins with it. Another method for transferring the proteins is called electroblotting and uses an electric current to pull proteins from the gel into the PVDF or nitrocellulose membrane. The proteins move from within the gel onto the membrane while maintaining the organization they had within the gel. As a result of this blotting process, the proteins are exposed on a thin surface layer for detection (see below). Both varieties of membrane are chosen for their non- specific protein binding properties (i.e. , binds all proteins equally well). Protein binding is based upon hydrophobic interactions, as well as charged interactions between the membrane and protein. Nitrocellulose membranes are cheaper than PVDF, but are far more fragile and do not stand up well to repeated probings. The uniformity and overall effectiveness of transfer of protein from the gel to the membrane can be checked by staining the membrane with Coomassie Brilliant Blue or Ponceau S dyes. Once transferred, proteins are detected using labeled primary antibodies, or unlabeled primary antibodies followed by indirect detection using labeled protein A or secondary labeled antibodies binding to the Fc region of the primary antibodies.

[0374] The northern blot (RNA immunoblots for RNA isolation) is conceptually similar to western Blot. This type of blotting method is used to detect RNA. RNA is released once cells are broken open. Through northern blotting procedure, researchers can easily compare the cell type that contains the highest number of RNA. It also allows the researchers to find out if the cells from a certain disease contain less RNA or more RNA. It also helps in determining the progression of a certain disease based on RNA production. Northern blotting comprises the following steps: electrophoresis, transfer, and detection of specific sequences.

[0375] Microarray

[0376] DNA microarray technology is a high throughput technology for monitoring gene expression at the transcription level. Its use is akin to performing tens of thousands of northern blots simultaneously, and has the potential for parallel integration of the expression levels of an entire genome. A DNA microarray comprises DNA probes immobilized on a solid support such as a glass microscope slide. The DNA probes can be double stranded cDNA or short (25mers) or long (50-70mers) oligonucleotides of known sequences. An ideal DNA microarray should be able to interrogate all of the genes expressed in an organism.

[0377] In DNA microarrays using cDNA, the probes are PCR amplified from plasmid cDNA clones that have been purified and robotically printed onto coated glass slides. DNA microarrays using oligonucleotide have an advantage over cDNA microarrays because physical clones are not necessary. The oligonucleotides can either be previously synthesized and printed on glass slides, or can be synthesized directly on the surface of silicon or glass slides. Several print-ready oligonucleotide (60-70 mers) sets are commercially available for human, mouse and other organisms (cgen.com, operon.com).

[0378] Another technique for fabricating oligonucleotide microarrays chemically synthesizes the oligonucleotides (25 mers) on a silicon surface using photolithography techniques. (Affymetrix Inc., Santa Clara, Calif.). Originally such arrays were designed to detect single-nucleotide mutations, but now have applications for gene expression profiling studies. Yet another technique delivers single nucleic acids, which ultimately form longer oligonucleotides (60 mers), by ink-jet onto glass surfaces.

[0379] One method of utilizing gene expression data from microarrays is described by Tusher et al., PNAS 98(9) p. 5116-21, April, 2001. The method of Tusher is a statistical method titled Significance Analysis of Microarrays ("SAM"). The general approach in SAM is based on commonly used statistical tests, t-tests specifically, to find genes that discriminate between two classes in a gene-by-gene fashion. SAM uses replication of experiments to assign a significance to the discriminating genes in terms of a false discover rate. SAM therefore offers a method of choosing particular genes from a set of gene expression data, but does not offer a diagnosis based on those genes.

[0380] An embodiment provides methods of monitoring treatment of pre-symptomatic, advanced, early-onset, or age-related (late-onset) FECD, glaucoma, or other ocular disease. The methods can comprise obtaining a first sample from a

subject having early stage FECD, late stage FECD, or FECD and detecting gene expression levels and or skipped exon events in the first sample. The first sample can be, for example, corneal tissue, aqueous humor, plasma, serum, blood, tear film, or a combination thereof. Gene expression levels and or skipped exon events can be detected as described herein. The genes of interest can comprise one or more of the upregulated genes and downregulated genes as described herein. Skipped exon events can comprise one or more of those listed in Table 8. The subject can be administered a treatment as described herein. At this point, the treatment can be administered 1, 2, 3, 4 or more times for 1, 2, 5, 7, 14, 21, 28 days, or 1, 2, 3, 4, 5, 6, or more months before the next step. When ready to proceed with the method, a second sample can be obtained from the subject. The second sample can be obtained from the subject and gene expression levels and or skipped exon events for the second sample can be determined at any time after both the first sample is obtained, and the treatment is administered. The second sample can be, for example, corneal tissue, aqueous humor, plasma, serum, blood, tear film, trabecular meshwork, or a combination thereof. Gene expression levels and skipped exon events can be detected as described herein. The method further includes comparing the first sample gene expression levels or skipped exon events with the second sample gene expression levels or skipped exon events.

[0381] Additionally, an embodiment provides methods of monitoring treatment of glaucoma. The methods can comprise obtaining a first sample from a subject having glaucoma and detecting gene expression levels of *COCH* in the first sample. The first sample can be, for example, corneal tissue, aqueous humor, plasma, serum, blood, tear film, trabecular meshwork, or a combination thereof. Gene expression levels can be detected as described herein. The subject can be administered a treatment as described herein. At this point, the treatment can be administered 1, 2, 3, 4 or more times for 1, 2, 5, 7, 14, 21, 28 days, or 1, 2, 3, 4, 5, 6, or more months before the next step. When ready to proceed with the method, a second sample can be obtained from the subject. The second sample can be obtained from the subject and gene expression levels for the second sample can be determined at any time after both the first sample is obtained, and the treatment is administered. The second sample can be, for example, corneal tissue, aqueous humor, plasma, serum, blood, tear film, trabecular meshwork, or a combination thereof. Gene expression levels can be detected as described herein. The method further includes comparing the first sample gene

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expression levels with the second sample gene expression levels. The method can be directed or performed in the anterior segment of the eye, posterior segment of the eye, corneal endothelial cells, or other cells of the anterior segment of the eye.

[0382] Treatments for FECD can be those described herein such as therapeutic agents that increase gene expression, therapeutic agents that decrease gene expression, conjunctival flaps, anterior stromal puncture, phototherapeutic keratectomy, amniotic membrane transplantation, collagen cross-linking, delivery of hyperosmotic solutions, steroidal eye drops, sodium chloride eye drops, keratoprosthesis implantation, therapeutic contacts such as bandage contact lenses, corneal transplant, lamellar transplant such as Descemet's stripping automated endothelial keratoplasty (DSAEK) and Descemet's membrane endothelial keratoplasty (DMEK), endothelial keratoplasty, penetrating keratoplasty, or combinations thereof. FECD can also be treated with, for example, Rho-associated kinase (ROCK) inhibitors such as Y-27632, optionally combined with transcorneal freezing. FECD can also be treated with transplantation of cultured corneal endothelial cells as a sheet or by injection of a cell suspension into the anterior chamber, optionally in combination with ROCK inhibitor. FECD can further be treated with prostaglandins, beta blockers, alpha-adrenergic agonists, carbonic anhydrase inhibitors, rho kinase inhibitors, miotic or cholinergic agents described herein.

[0383] In another embodiment, treatment for glaucoma can be those described herein such therapeutic agents that decrease the amount of expression of *COCH*, prescription eyedrops, oral medications, prostaglandins, beta blockers, alpha-adrenergic agonists, carbonic anhydrase inhibitors, rho kinase inhibitors, miotic or cholinergic agents, laser trabeculoplasty, trabeculectomy, drainage tubes, minimally invasive glaucoma surgery (MIGS), peripheral iridotomy, aqueous shunts, or combinations thereof.

[0384] Where the treatment is intended to treat symptoms, delay progression of disease, or decrease expression for upregulated genes, and the expression for upregulated genes measured in the second sample of a subject is the same or lower than the expression for upregulated genes measured in the first sample of the subject, the efficacy of the treatment is likely. Additionally, where the treatment is intended to treat symptoms, delay progression of disease, or decrease expression for upregulated genes, and the skipped exon events detected in the second sample of a subject are

the same or fewer than the skipped exon events detected in the first sample of the subject, the efficacy of the treatment is likely.

[0385] Similarly, where the treatment is intended to treat symptoms, delay the progression of disease, or increase expression for downregulated genes, and the expression for downregulated genes measured in the second sample of a subject is the same or higher than the expression for downregulated genes measured in the first sample of the subject, the efficacy of the treatment is likely. Additionally, where the treatment is intended to treat symptoms, delay progression of disease, or increase expression for downregulated genes, and the skipped exon events detected in the second sample of a subject are the same or fewer than the skipped exon events detected in the first sample of the subject, the efficacy of the treatment is likely.

[0386] Where the treatment is intended to treat symptoms, delay progression of disease, or decrease expression of *COCH*, and the expression for *COCH* measured in the second sample of a subject is the same or lower than the expression for *COCH* measured in the first sample of the subject, the efficacy of the treatment is likely.

[0387] By "efficacious" is meant that the treatment leads to a reduction in expression of a pathologically upregulated gene, increase in expression of a pathologically down-regulated gene or a decrease in size, prevalence, formation of guttae in a subject. When treatment is applied prophylactically, "efficacious" means that the treatment prevents onset of FECD symptoms.

[0388] Several treatments can be administered to a subject over the course of the treatment of FECD, glaucoma, or other ocular diseases. Each treatment can have individual effect progression of disease and symptomology. Accordingly, the determination of a change in gene expression and skipped exon events can be assessed after the administration of a therapy, whether or not it is the first to be administered to the subject, and as many times as required to follow the changes in gene expression over time. The treatment or treatments can be adjusted as needed based on the changes in gene expression levels and skipped exon events over time.

[0389] Therefore, the steps of obtaining a first sample from a subject; detecting gene expression levels and or detecting one or more skipped exon event in the first sample; administering a treatment to the subject; obtaining a second sample from the subject at a later time and detecting gene expression levels or skipped exon events of in the second sample; and comparing the first sample gene expression levels or skipped exon events with the second sample gene expression levels or skipped exon events

can be repeated after each treatment regimen. Additionally, in cases of repeated measures, the latest amount gene expression or detection of skipped exon events in the sample of a subject can be compared to any one or to all of the previously measured samples to evaluate the changes over time and in response to the various treatments.

[0390] Furthermore, the steps of obtaining a first sample from a subject; detecting *COCH* gene expression levels in the first sample; administering a treatment to the subject; obtaining a second sample from the subject at a later time and detecting *COCH* gene expression levels in the second sample; and comparing the first sample *COCH* gene expression levels with the second sample *COCH* gene expression levels can be repeated after each treatment regimen. Additionally, in cases of repeated measures, the latest amount *COCH* gene expression in the sample of a subject can be compared to any one or to all of the previously measured samples to evaluate the changes over time and in response to the various treatments.

[0391] **Methods of Monitoring Progression of Disease**

[0392] An embodiment provides methods of detection of gene expression levels for monitoring the progression of a disease. The methods of detection can include Fluorescence In Situ Hybridization (FISH), immunodetection, western blot, northern blot, or microarray, as described above.

[0393] An embodiment provides methods of monitoring progression of pre-symptomatic, advanced, early-onset, or age-related (late-onset) FECD. The methods can comprise obtaining a first sample from a subject having early stage FECD, late stage FECD, or FECD and detecting gene expression levels and or skipped exon events in the first sample. The first sample can be, for example, corneal tissue, aqueous humor, plasma, serum, blood, tear film, trabecular meshwork, or a combination thereof. Gene expression levels and or skipped exon events can be detected as described herein. The genes of interest can comprise one or more of the upregulated genes and downregulated genes as described herein. Skipped exon events can comprise one or more of those listed in Table 8. A second sample can be obtained from the subject. The second sample can be obtained from the subject and gene expression levels and or skipped exon events for the second sample can be determined at any time after the first sample is obtained. The second sample can be, for example, corneal tissue, aqueous humor, plasma, serum, blood, tear film, trabecular meshwork, or a combination thereof. Gene expression levels and skipped

exon events can be detected as described herein. The method further includes monitoring the progression of disease by comparing the first sample gene expression levels or skipped exon events with the second sample gene expression levels or skipped exon events.

[0394] Additionally, an embodiment provides methods of monitoring progression of glaucoma. The methods can comprise obtaining a first sample from a subject having glaucoma and detecting gene expression levels of *COCH* in the first sample. The first sample can be, for example, FECD cell line, aqueous humor, trabecular meshwork, or a combination thereof. Gene expression levels can be detected as described herein. A second sample can be obtained from the subject. The second sample can be obtained from the subject and gene expression levels for the second sample can be determined at any time after the first sample is obtained. The second sample can be, for example, corneal tissue, aqueous humor, plasma, serum, blood, tear film, trabecular meshwork, or a combination thereof. Gene expression levels can be detected as described herein. The method further includes comparing the first sample gene expression levels with the second sample gene expression levels to monitor progression of disease overtime. The method can be directed or performed in the anterior segment of the eye, posterior segment of the eye, corneal endothelial cells, or other cells of the anterior segment of the eye.

[0395] Where the expression for upregulated genes measured in the second sample of a subject is the same or lower than the expression for upregulated genes measured in the first sample of the subject, the disease is not likely to have progressed. Additionally, where the skipped exon events detected in the second sample of a subject are the same or fewer than the skipped exon events detected in the first sample of the subject, the disease is not likely to have progressed. Similarly, where the expression for downregulated genes measured in the second sample of a subject is the same or higher than the expression for downregulated genes measured in the first sample of the subject, the disease is not likely to have progressed.

[0396] Where the expression for upregulated genes measured in the second sample of a subject is higher than the expression for upregulated genes measured in the first sample of the subject, the disease is likely to have progressed. Additionally, where the skipped exon events detected in the second sample of a subject are greater than the skipped exon events detected in the first sample of the subject, the disease is likely to have progressed. Similarly, where the expression for downregulated genes

measured in the second sample of a subject is the lower than the expression for downregulated genes measured in the first sample of the subject, the disease is likely to have progressed.

[0397] Where the treatment the expression for *COCH* measured in the second sample of a subject is the same or lower than the expression for *COCH* measured in the first sample of the subject, the disease is not likely to have progressed.

[0398] Where the treatment the expression for *COCH* measured in the second sample of a subject is the higher than the expression for *COCH* measured in the first sample of the subject, the disease is likely to have progressed.

[0399] Therefore, the steps of obtaining a first sample from a subject; detecting gene expression levels and or detecting one or more skipped exon event in the first sample; obtaining a second sample from the subject at a later time and detecting gene expression levels or skipped exon events of in the second sample; and comparing the first sample gene expression levels or skipped exon events with the second sample gene expression levels or skipped exon events can be repeated after each sample. Additionally, in cases of repeated measures, the latest amount gene expression or detection of skipped exon events in the sample of a subject can be compared to any one or to all of the previously measured samples to evaluate the changes over time.

[0400] The details of one or more variations of the subject matter described herein are set forth in the accompanying drawings and the description below. Other features and advantages of the subject matter described herein will be apparent from the description and drawings, and from the claims. The disclosed subject matter is not, however, limited to any particular embodiment disclosed.

[0401] The compositions and methods are more particularly described below and the Examples set forth herein are intended as illustrative only, as numerous modifications and variations therein will be apparent to those skilled in the art. The terms used in the specification generally have their ordinary meanings in the art, within the context of the compositions and methods described herein, and in the specific context where each term is used. Some terms have been more specifically defined herein to provide additional guidance to the practitioner regarding the description of the compositions and methods.

[0402] As used herein, the term "and/or" includes any and all combinations of one or more of the associated listed items. As used in the description herein and throughout the claims that follow, the meaning of "a", "an", and "the" includes plural reference as

well as the singular reference unless the context clearly dictates otherwise. The term “about” in association with a numerical value means that the value varies up or down by 5%. For example, for a value of about 100, means 95 to 105 (or any value between 95 and 105).

[0403] All patents, patent applications, and other scientific or technical writings referred to anywhere herein are incorporated by reference herein in their entirety. The embodiments illustratively described herein suitably can be practiced in the absence of any element or elements, limitation or limitations that are specifically or not specifically disclosed herein. Thus, for example, in each instance herein any of the terms "comprising," "consisting essentially of," and "consisting of" can be replaced with either of the other two terms, while retaining their ordinary meanings. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the claims. Thus, it should be understood that although the present methods and compositions have been specifically disclosed by embodiments and optional features, modifications and variations of the concepts herein disclosed can be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of the compositions and methods as defined by the description and the appended claims.

[0404] Any single term, single element, single phrase, group of terms, group of phrases, or group of elements described herein can each be specifically excluded from the claims.

[0405] Whenever a range is given in the specification, for example, a temperature range, a time range, a composition, or concentration range, all intermediate ranges and subranges, as well as all individual values included in the ranges given are intended to be included in the disclosure. It will be understood that any subranges or individual values in a range or subrange that are included in the description herein can be excluded from the aspects herein. It will be understood that any elements or steps that are included in the description herein can be excluded from the claimed compositions or methods.

[0406] In addition, where features or aspects of the compositions and methods are described in terms of Markush groups or other grouping of alternatives, those skilled

in the art will recognize that the compositions and methods are also thereby described in terms of any individual member or subgroup of members of the Markush group or other group.

[0407] The following are provided for exemplification purposes only and are not intended to limit the scope of the embodiments described in broad terms above.

[0408] **EXAMPLES**

[0409] These examples focus on isolating corneal tissue from FECD_REP, FECD_NR, Pre_S, and Control samples. *TCF4* CTG18.1 polymorphism genotyping was conducted using short tandem repeat (STR) and triplet repeat primed polymerase chain reaction (TP-PCR). Total RNA was isolated using RNAseq. Whole transcriptomic sequencing data was analyzed to determine differentially expressed or spliced genes. *TCF4* RNA half-life was measured using qPCR. Differential gene expression and alternative splicing patterns were validated by preparing cDNAs via reverse transcription, subsequent RT-PCR analysis, amplification products separated by gel electrophoresis, and qPCR. Additionally, an example assesses expression of *COCH* mRNA.

[0410] **Materials and Methods for Examples 1-8**

[0411] **Isolation of Corneal Tissue**

[0412] The study was conducted in compliance with the tenets of the Declaration of Helsinki and with the approval of the institutional review board of the University of Texas Southwestern Medical Center (UTSW). Subjects underwent a complete eye examination including slit lamp biomicroscopy by a cornea fellowship-trained ophthalmologist. Patients underwent endothelial keratoplasty for FECD severity Krachmer grade 5 (≥5 mm central confluent guttae without stromal edema) or 6 (≥5 mm central confluent guttae with stromal edema) assessed by slit lamp microscopy. After surgery, surgically explanted endothelium-Descemet's membrane monolayers were preserved in Optisol GS corneal storage media (Bausch & Lomb, Rochester, NY) prior to storage at -80 Celsius. Genomic DNA was extracted from peripheral blood leukocytes of each study subject using Autogen Flexigene (Qiagen, Valencia, CA).

[0413] Corneal endothelial samples from post-mortem donor corneas preserved in Optisol GS corneal storage media (Bausch & Lomb, Rochester, NY) were obtained from the eye bank of Transplant Services at UT Southwestern. Certified eye bank technicians screened the donor corneal endothelium with slit lamp biomicroscopy and Cellchek EB-10 specular microscopy (Konan Medical). Endothelium-Descemet's

membrane monolayers from donor corneas were micro-dissected and stored as previously described (Mootha VV, *et al.*, *Invest. Opthamol. Vis. Sci. (IOVS),* 56(3):2015). DNA from the remaining corneal tissue of each sample was extracted with TRIzol reagent (ThermoScientific).

[0414] **TCF4 CTG18.1 polymorphism genotyping**

[0415] Genomic DNA from subjects' peripheral leukocytes or corneal tissue was used for genotyping. The CTG18.1 trinucleotide repeat polymorphism in the *TCF4* gene was genotyped using a combination of short tandem repeat (STR) and triplet repeat primed polymerase chain reaction (TP-PCR) assays. On samples where STR assay detected only one allele or failed to detect any alleles, repeat primed PCR assay was performed to confirm the presence of an expanded allele(s). For the STR assay, a pair of primers, P1 and P2 (SEQ ID NO: 1 and SEQ ID NO: 2) flanking the CTG18.1 locus was utilized for PCR amplification with one primer labeled with FAM on 5′ end. After PCR, 5 µL of DNA were mixed with 10 µL of Promega Internal Standard 600 (ILS600; Promega, Madison, WI). The TP-PCR assay was performed using the 5' FAM labeled primer specific for the repeat locus paired with repeat sequence targeted primers for PCR amplification. The P1 is a fluorescent primer designed to a region upstream from the CTG18.1 allele. The companion reverse primer P4 on the complementary strand is comprised of 5 units of the CTG repeat and a 5′ tail to serve as an anchor for a second reverse primer P3, which prevents progressive shortening of the PCR products during subsequent cycles. The 5′ tail of primer P4 and the "common" flag primer P3 share no homology with human sequence. For STR, 100ng of genomic DNA was used, together with flanking primer pair 1µM of primer P1 and 1µM of primer P2, 200 µM dNTPs, 1.5 mM $MgCl_2$and 1U/10µl reaction of AmpliTaq Gold™ DNA Polymerase (Applied Biosystems) in 1X Gold Buffer. Thermal cycling conditions were initial denaturation 5 minutes at 95°C, followed by 35 cycles 95°C for 15 seconds, 60°C for 15 seconds, and 72°C for 1 minute and a final extension for 72°C for 7 minutes. For TP-PCR, 200ng of genomic DNA was used. 1µM of primer P1 was added together with 1µM of primer P3 and 0.03µM of primer P4 to GoTaq® Master Mixes (Promega, Madison, WI, USA). Thermal cycling conditions were initial denaturation 9 minutes at 95°C, followed by 10 cycles of 95°C for 30 seconds, 56°C for 30 seconds, and 72°C for 4 minutes, and then 30 cycles of 95°C for 45 seconds, 56°C for 45 seconds, and 72°C for 4 minutes with a 15-second extension at each cycle. The final extension step was 72°C for 10 minutes. PCR amplicons were loaded

on an ABI 3730XL DNA analyzer (Applied Biosystems, Foster City, CA, USA) and the results analyzed with ABI GeneMapper 4.0 (Applied Biosystems). Large triplet repeat expansions were sized by Southern blot analysis using digoxigenin labeled probes.

[0416] Table 5. Primers for STR Analysis and TR-PCR Assay

Primer	Sequence, 5′–3′
P1	AATCCAAACCGCCTTCCAAGT (SEQ ID NO: 1)
P2	CAAAACTTCCGAAAGCCATTTCT (SEQ ID NO: 2)
P3	TACGCATCCCAGTTTGAGACG (SEQ ID NO: 3)
P4	TACGCATCCCAGTTTGAGACGCAGCAGCAGCAGCAG (SEQ ID NO: 4)

[0417] **RNA Isolation and Sequencing**

[0418] Total RNA was isolated from each of 25 tissue samples (6 FECD_REP, 4 FECD_NR, 6 Pre_S and 9 Controls) by homogenization in QIAzol lysis reagent, chloroform extraction and isolation with NucleoSpin RNA XS (Macherey-Nagel GmbH & Co., Germany). RNA quantity and quality were determined by Bioanalyzer 2100. RNA libraries were prepared for each tissue sample with high RIN (> 5.0), using the TruSeq RNA sample Prep kit version 2 (Illumina, San Diego, CA, USA). For TruSeq stranded total RNAseq, ribosomal transcripts were depleted from total RNA, using Ribo-Zero Gold RNA removal kit followed by replacement of deoxythymidine triphosphate (dTTP) with deoxyuridine triphosphate (dUTP) during reverse transcription in the second strand synthesis, using TruSeq stranded total library preparation kit. The resulting libraries were minimally amplified to enrich for fragments using adapters on both ends and then quantified for sequencing at eight samples/flow cell by using a NextSeq 500/550 (Illumina) sequencer (PE 150).

[0419] **Analysis of Differentially Expressed or Spliced Genes**

[0420] Whole transcriptomic sequencing data from each tissue sample was analyzed using an analysis pipeline which includes STAR for initial mapping and Cufflinks (v2.21) for gene and isoform differential analysis, among other publicly available programs. For gene/isoform differential analysis, the minimum expression level of 1.5 FPKM and an FDR < 0.05 were chosen as the threshold. The meta gene pathway analysis was carried out with IPA (Qiagene). The binary alignment map files from STAR were analyzed using rMATS (v.4.0) that quantitates the expression level

of alternatively spliced genes between groups. To find the most significant events, we used stringent filtering criteria within rMATS to perform pairwise comparisons among 4 groups: percentage of spliced in (PSI) changes > 0.15; FDR < 0.001. For PSI, rMATS calculates a value for every differential splicing event, providing a range from 0 to 1, with 0 being completely excluded and 1 being uniformly included in the splicing products. Alternative splicing events were also compared to those obtained in tibialis anterior muscle of myotonic dystrophy type one patients (DM1). DM1 raw data was obtained from Gene Expression Omnibus (GSE86356, 6 Control and 6 DM1 tissue samples were used) and analyzed similarly as the FECD data (visit DMseq.org for more information).

[0421] **Measurement of TCF4 RNA half-life**

[0422] FECD corneal endothelial cell lines (F35T and F45SV) and a control corneal endothelial cells (W4056–17-001579) were cultured as described (Hu J *et al., Hum Mol Genet.* 27(6): 2018). The C9 and VVM84 skin fibroblasts were maintained at 37°C and 5% CO2 in Minimal Essential Media Eagle (MEM) (Sigma, M4655) supplemented with 15% heat inactivated fetal bovine serum (Sigma) and 0.5% MEM nonessential amino acids (Sigma).

[0423] Endothelial or fibroblast cells were seeded in 6-well plate at 90% confluence. At the next day, actinomycin D was added into the wells at 5 µg/mL final concentration. Cells were harvest using Trizol agent (Sigma) at different time point. The *TCF4* RNA levels were analyzed by qPCR.

[0424] **Validation of Differential Gene Expression and Alternative Splicing Patterns**

[0425] Total RNA was extracted from control, Pre_S or FECD corneal endothelial tissues (**Table 6**) by NucleoSpin RNA XS kit (Macherey-Nagel). cDNAs were prepared by reverse transcription. RT-PCR was performed using ChoiceTaq Blue Mastermix (Denville). PCR amplification was as follow: 94 °C for 3 minutes (1 cycle), 94 °C denaturation for 30 sec, 60 °C annealing for 30 sec, and 72 °C extension for 1 min (38 cycles), and a 7 minute 72 °C extension. The PCR primers were used as reported (Wieben *et al., Invest Ophthalmol Vis Sci. (IOVS)*, 58:2017) (**Table 7**). The amplification products were separated by 1.5% agarose gel electrophoresis. *q*PCR experiments were performed on a 7500 real-time PCR system (Applied Biosystems) using iTaq SYBR Green Supermix (Bio-Rad). Data was normalized relative to levels of *RPL19* mRNA.

[0426] Table 6. Characteristics of cornea endothelial tissues used in the experimental validation.

ID	Age	Phenotype	*TCF4* CUG repeat
W4056-17-001398	54	Healthy control	12, 27
W4056-17-001518	64	Healthy control	14, 26
W4056-17-001449	64	Healthy control	13, 19
2015-1477	71	Healthy control	16, 16
W4056-17-001831	59	Healthy control	13, 27
W4056-18-002160	69	Healthy control	15, 15
W4056-17-001754	73	Healthy control	12, 12
W4056-17-001844	66	Healthy control	13, 16
W4056-17-002127	65	Healthy control	12, 18
W4056-17-001239	51	Pre_S	13, 84
W4056-17-001810	57	Pre_S	15, 77
W4056-18-002874	41	Pre_S	17, 86
W4056-19-003507	38	Pre_S	12, 66
2015-1615	41	Pre_S	12, >100
CA208	65	FECD	18, 60
CA179	77	FECD	18, 73
CA213	67	FECD	12, >100
CA219	87	FECD	18, 76
CA103	72	FECD	15, 87
CA099	70	FECD	18, 78
CA072	60	FECD	16, 84
CA083	68	FECD	12, 84
CA095	91	FECD	28, >100
CA209	88	FECD	15, 53
VVM669	66	FECD	17, 84

[0427] Table 7. Primer sequences for qPCR or RT-PCR

Primer	Sequence (5'-3')
TCF4 mRNA	F: TGACGATGAGGACCTGACAC (SEQ ID NO: 5) R: GTCTGGGGCTTGTCACTCTT (SEQ ID NO: 6)
TCF4 intron-upstream	F: GTAGTCGTAGGATCAGCACAAAG (SEQ ID NO: 7) R: GGAAGCAAAGGGATGGAGAA (SEQ ID NO: 8)
TCF4 intron-downstream	F: GAGAGAGGGAGTGAAAGAGAGA (SEQ ID NO: 9) R: GGCAATGTCCATTTCCATCT (SEQ ID NO: 10)

CTGF	F: GCTGACCTGGAAGAGAACATTA (SEQ ID NO: 11) R: GTCGGTACATACTCCACAGAAT (SEQ ID NO: 12)
COCH	F: GATGGGCAGTCCTATGATGATG (SEQ ID NO: 13) R: GCATGAGACTCCTTCGGTTTAG (SEQ ID NO: 14)
MSI1	F: GTTTCGGCTTCGTCACTTTC (SEQ ID NO: 15) R: CTTCGTTCGAGTCACCATCTT (SEQ ID NO: 16)
LUM	F: GGTCTCCCTGTCTCTCTTCTAA (SEQ ID NO: 17) R: AGCCAGTTCGTTGTGAGATAAA (SEQ ID NO: 18)
KDR	F: AGCAGGATGGCAAAGACTAC (SEQ ID NO: 19) R: TACTTCCTCCTCCTCCATACAG (SEQ ID NO: 20)
MBNL2 (RT-PCR)	F: ACACCGTAACCGTTTGTATGG(SEQ ID NO: 21) R: GCATCATGGGTACTGTTGGAATG (SEQ ID NO: 22)

[0428] **Example 1**

[0429] This example describes the experimental design.

[0430] Analyzing the corneal endothelial monolayer presents several advantages as a model for gaining insight into the molecular mechanisms of delayed-onset degenerative disease: 1) corneal tissue is available for analysis because it is routinely removed during surgery (**FIG. 1A-C**); 2) tissue samples are a single near homogeneous layer of cells, facilitating RNAseq and other methods for analyzing gene expression (**FIG. 1D**); 3) donor corneal tissues that are not used for surgery are available from eye bank samples for comparison; 4) because the prevalence of the triplet repeat mutation within the *TCF4* gene is relatively high, donor eyes provide a significant number of pre-symptomatic samples (Pre_S) that possess the CUG expanded repeat; 5) the availability of tissue from four different cohorts (**FIG. 2**), control, Pre_S, FECD_NR, FECD_REP allows multiple cross-comparisons into the different stages and types of FECD. Analysis of the Pre_S cohort has the potential to gain insights into early drivers of disease.

[0431] Here, the analysis of the corneal endothelial monolayer are used to evaluate transcriptomic data from four cohorts of corneal endothelial tissue: control, Pre_S, FECD_REP, and FECD_NR. Tissue samples were collected from 25 individuals [control (9), Pre_S (6), FECD_REP (6), and FECD_NR (4)] between the ages of 38 and 74 (**FIG. 2B**).

[0432] Additionally, among the top ten genes in pre-symptomatic tissue versus control tissue are cochlin (*COCH*) and fibronectin (*FN1*) with >16 and >32 fold change increases respectively (**FIG. 6C**).

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[0433] Samples were homogeneous endothelial cell monolayers surgically removed from patients or dissected from donor tissue (**FIG. 1, FIG. 2A**). The homogenous nature of the tissue samples, in contrast to the more complex mixtures of cells often contained in tissues related to other disease, facilitates subsequent analysis and data interpretation.

[0434] Four groups of human tissue by RNA sequencing (RNAseq) were compared with attention to changes in alternative splicing, differential gene expression, and pathway analysis (**FIG. 2A**). Tissue that was mutant for the CUG expanded repeat within intron 2 of the *TCF4* gene was obtained from pre-symptomatic eye bank donors (Pre_S) and from FECD patients after transplant surgery (FECD_REP). Tissue that was negative for the expanded CUG mutation within *TCF4* was obtained from eye bank donors (Control) and from patients with non-CUG related FECD (FECD_NR). Genotype data indicated that all samples had normal numbers of CTG repeats within the DMPK gene (**FIG. 2B**).

[0435] Control tissues from the eye bank were chosen for analysis that possessed normal endothelial morphology by specular microscopy, were negative for the expanded CUG mutation, and were from donors with ages comparable to our FECD patient cohort (**FIG. 2B**). Obtaining tissue from Pre_S individuals was possible because of the relatively high prevalence, 3%, of the expanded triplet repeat mutation in *TCF4* gene within the general Caucasian population. Pre_S tissue was identified by the presence of the CUG repeat expansion by genotyping. Normal corneal endothelial morphology (absence of central corneal guttae) in Pre_S tissues was confirmed by specular microscopy.

[0436] RNA sequencing (RNAseq) was performed on tissue samples from nine non-FECD/non-expanded repeat donors (Control), six pre-symptomatic donors with the expanded repeat (Pre_S), six patients with the expanded repeat and FECD (FECD_REP), and four patients with FECD who did not have the expanded CUG repeat mutation (FECD_NR) (**FIG. 2B,11,12,13**). Only samples with RNA integrity numbers greater than 5 were used (**FIG. 13**). Gene body coverage analysis suggests that all RNA samples were largely intact (**FIG. 12**). We carried out a paired-end 150 nt RNA-Seq on Illumina NextSeq sequencer. We regularly obtained an output of 50-60 million raw paired reads per sample.

[0437] Clustering analysis of overall gene expression patterns revealed that samples from control and Pre_S donors were closer to one another than to samples

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from patients with FECD_REP or FECD_NR late stage disease (**FIG. 2C-D, 11A-B**). This result is consistent with the clinical observation of large visible differences between diseased and non-diseased tissue and that the clinical manifestations of FECD_REP and FECD_NR are almost identical.

[0438] **Example 2**

[0439] This example describes the stability of TCF4 intron 2 in FECD mutant and non-mutant tissue.

[0440] Analysis of RNAseq data from intron 2 (the intron that contains the CUG repeat) within the *TCF4* gene showed a striking difference between representative samples from individuals with the expanded CUG repeat mutation (FECD_REP and Pre_S) and individuals who lack the mutation (control and FECD_NR) (**FIG. 3A**). Samples from the cohort of control individuals showed similar low numbers of reads upstream or downstream relative to the trinucleotide repeat region. RNA obtained from FECD_NR patients' tissue also showed the same similarity between upstream and downstream reads.

[0441] By contrast, both Pre_S and FECD_REP tissue showed more reads for intronic RNA upstream of the trinucleotide repeat relative to downstream (**FIG. 3A**). The overall expression of mature *TCF4* mRNA from the four cohorts was not significantly different making haploinsufficiency of gene product less likely as the mechanism of disease (**FIG. 14**). These results suggest that an early molecular disease trigger – increased stability the mutant *TCF4* intron 2 upstream of the expanded repeat – occurs at the presymptomatic stage and distinguishes FECD_REP from FECD_NR in late stage disease.

[0442] To investigate factors that might contribute to the prevalence of upstream intronic reads, we examined cultured cells derived from FECD_REP patient corneal endothelium (F35T), FECD_REP patient skin fibroblasts (VVM84), control (without CUG expanded repeat) corneal endothelium (W4056), or control skin fibroblasts (C9) (**FIG. 3B-C**). VVM84 FECD skin fibroblasts and F35T FECD corneal endothelial cells both have the expanded CUG repeat, but the F35T corneal cells have nuclear CUG foci that can be detected by RNA-FISH while VVM84 skin cells lack detectable foci indicating cell-specificity for expanded CUG repeat RNA accumulation. Expression of *TCF4* is similar in F35T, F45SV and VVM84 cells (**FIG. 15**).

[0443] We treated cells with actinomycin D to arrest transcription and examine the half-life of mature *TCF4* mRNA and sequences either upstream our downstream

relative to the intronic *TCF4* CUG repeat using quantitative PCR (qPCR) (**FIG. 3B-C**). Regardless of whether the expanded repeat mutation was present, the half-life of the mature *TCF4* mRNA was similar, >8 hours (**FIG. 3C top**). Likewise, the half-life of the intron 2 downstream region was also similar in each cell line, varying from 10 to 30 minutes (**FIG. 3C middle**). These data suggest that the mutation does not affect stability of the parent mRNA and has only a modest effect on the downstream region of intron 2.

[0444] By contrast, we observe a striking ~20-fold increase in the half-life of the upstream region of intron 2 in FECD corneal cells (F35T and F45SV) that possess the expanded CTG mutation and have detectable foci (**FIG. 3C bottom**). For cell lines that lacked expanded CUG nuclear foci, this region had a half-life of only 10 min. For FECD corneal cells, the half-life was 3–4 h.

[0445] This increased half-life of upstream intronic RNA is consistent with the observation from RNAseq of many more reads covering the upstream region of intron 2 *TCF4* from Pre_S or FECD_REP tissue relative to samples from individuals in the control or FECD_NR cohorts who lack the expanded CUG repeat (**FIG. 3A**). Stabilization of the upstream portion of *TCF4* intron 2 in corneal endothelial tissue and cultured corneal endothelial cells makes more mutant repeat RNA available to perturb gene expression.

[0446] To address the possibility that the 5′ half of intron 2 might be retained in the mature mRNA, we performed PCR using primers complementary to exon 2 and exon 3 in both FECD and control cells. We observed a single PCR product of the predicted length in both FECD and control cells (**FIG. 16**). This data supports the conclusion that the intron is not detectably retained.

[0447] **Example 3**

[0448] This example describes changes in alternative splicing triggered by the expanded repeat within TCF4.

[0449] CUG repeat RNA is known to bind the splicing factors muscleblind-like 1 and 2 (MBNL1 and MNBL2). We used RNAseq to evaluate splicing changes between control tissue and the Pre_S, FECD_REP, and FECD_NR tissue cohorts (**FIG. 4**). To classify changes, we used the FDR (false discovery rate) and delta PSI (the net change of inclusion percentage) as the determinant metrics. Any changes that are less than 0.001 on FDR and more than or equal to 0.15 on PSI were determined to be significant.

[0450] Regardless of which tissue was analyzed, the primary changes in alternative splicing relative to control tissue were increases in the number of skipped exons (SE) events (**FIG. 4A**). FECD_REP or FECD_NR tissues showed more splicing changes than Pre_S tissue (**FIG. 4B**). The greater number of splicing changes is consistent with the extensive cellular degeneration observed in late stage disease. However, while not as many as in tissue from advanced disease, ~450 changes in alternative splicing were observed in Pre_S tissue.

[0451] Three hundred thirteen of the alternative splicing events in Pre_S tissue involved exon skipping (**Table 8**). Heatmap evaluation of 313 skipped exons in Pre_S tissue revealed that the genes hosting the skipped exon events clustered most closely with FECD_REP tissue (**FIG. 4B-C**). 132 skipped exon events were shared between Pre_S and FECD_REP tissue, compared to only 28 were shared between Pre_S and FECD_NR tissue (**FIG. 4B**), consistent with the hypothesis that the changes in Pre_S tissue foreshadow the alterations observed in FECD-REP.

[0452] Table 8. Significant skipped exon events (313) identified in Pre_S. The delta exon inclusion levels for Pre_S, FECD_REP and FECD_NR vs. Control are shown in the last three columns.

Gene_name	SE_locus	Pre_S	FECD_REP	FECD_NR
KIF13A	-:chr6:17787775-17787875:17789871-17789910:17794571-17794704	0.761	0.617	-0.084
TSPOAP1	-:chr17:58307841-58307941:58308540-58309380:58309966-58310158	0.741	0.674	0.051
INF2	+:chr14:104714202-104714856:104715283-104715340:104718794-104719503	0.674	0.48	-0.034
EXOC2	-:chr6:637700-637861:657162-657250:689138-689212	0.672	0.438	0.845
NEBL	-:chr10:20852544-20852649:20858239-20858344:20859712-20859826	0.87	0.199	-0.207
BICRA	+:chr19:47679320-47681276:47681975-47682152:47694114-47694726	0.636	0.52	0.208
CACNA1D	+:chr3:53718300-53718388:53718681-53718741:53719754-53719781	0.626	0.42	-0.062
CLASP1	-:chr2:121430072-121430177:121445448-121445496:121447336-121447507	0.602	0.457	-0.018
VPS39	-:chr15:42191495-42191560:42192065-42192098:42199895-42199961	0.581	0.568	0.137
KIF13A	-:chr6:17787775-17787875:17789871-17789910:17794248-17794395	0.58	0.455	-0.185
TEAD1	+:chr11:12864837-12864900:12878888-12878900:12879707-12879842	0.567	0.524	-0.047
INCENP	+:chr11:62140912-62141044:62141499-62141511:62144981-62145091	0.555	0.493	0.318
MDM1	-:chr12:68316077-68316253:68316580-68316610:68321346-68321446	0.553	0.592	0.033
SORBS1	-:chr10:95346405-95346452:95351215-95351376:95354881-95354967	0.529	0.349	-0.074
CENPBD1P1	+:chr19:58575444-58575588:58591497-58591624:58598966-58599801	0.522	0.487	0.432
SP110	-:chr2:230170620-230170761:230171695-230171767:230172065-230172174	0.522	0.234	0.051
MTA1	+:chr14:105465333-105466578:105466706-105466742:105469466-105469498	0.503	0.19	-0.019
NUMA1	-:chr11:72010785-72010854:72012400-72012442:72012894-72016280	0.5	0.395	-0.041
PLEKHM2	+:chr1:15719733-15719920:15721328-15721388:15725316-15725545	0.497	0.381	-0.036
ITGA6	+:chr2:172497974-172498100:172501771-172501901:172504090-172504534	0.496	0.401	-0.023
SYNE1	-:chr6:152143622-152143765:152145486-152145555:152148044-152148378	0.496	0.305	-0.1

ARHGEF10L	+:chr1:17632320-17632466:17634547-17634562:17634834-17635016	0.489	0.481	0.055
SCARB1	-:chr12:124777632-124778586:124782682-124782811:124786356-124786503	0.482	0.334	-0.053
TMEM177	+:chr2:119679202-119679276:119680831-119681123:119685657-119686507	0.481	0.24	0.14
PPFIBP1	+:chr12:27676427-27676599:27677063-27677096:27679486-27679639	0.468	0.365	-0.127
PLD1	-:chr3:171677565-171677694:171686684-171686798:171687370-171687584	0.462	0.331	-0.095
ZNF248	-:chr10:37856295-37856337:37856434-37856532:37858004-37858084	0.454	0.224	0.143
DESI1	-:chr22:41604043-41604153:41607839-41607861:41620751-41621096	0.45	0.267	0.148
ABI1	-:chr10:26770244-26770345:26771074-26771089:26777064-26777241	0.447	0.218	-0.094
MAP2K7	+:chr19:7903884-7904068:7905807-7905855:7909754-7909896	0.438	0.341	-0.079
ZNF528-AS1	-:chr19:52389018-52389303:52394790-52394847:52395597-52395750	0.436	0.157	0.147
ACOT9	-:chrX:23733171-23733217:23734340-23734367:23735918-23738016	0.43	0.249	-0.005
ZNF75D	-:chrX:135291008-135291135:135292280-135292473:135295767-135296039	0.428	0.021	0.325
ZNF75D	-:chrX:135291008-135291135:135293729-135294258:135295767-135296033	0.426	0.051	0.091
FAM135A	+:chr6:70413424-70413702:70426438-70426532:70452491-70452565	0.424	-0.006	-0.012
NDUFA3	+:chr19:54105933-54106011:54106352-54106446:54106763-54106961	0.42	0.163	-0.03
PHKA2	-:chrX:18897162-18897333:18900669-18900699:18901484-18901603	0.414	0.503	0.145
WASF3	+:chr13:26671871-26671989:26680034-26680201:26681053-26681320	0.412	0.235	-0.04
SMPD4	-:chr2:130157250-130157396:130161185-130161272:130164373-130164445	0.404	0.196	0.005
CATSPERE	+:chr1:244479716-244479784:244490446-244490471:244499001-244499079	0.402	0.461	0.49
NSUN5P2	-:chr7:72950057-72950196:72952151-72952295:72954624-72954717	0.402	0.184	0.222
RBX1	+:chr22:40951356-40951476:40964046-40964117:40972475-40973309	0.402	-0.025	-0.025
PLPP1	-:chr5:55467868-55468149:55475298-55475450:55534571-55535050	0.401	0.402	0.058
SORBS1	-:chr10:95346405-95346452:95351208-95351376:95354881-95354987	0.398	0.258	-0.042
GOLGA2	-:chr9:128268419-128268524:128272784-128272865:128273849-128273972	0.398	0.37	0.027
AC010203.1	-:chr12:100180552-100180716:100198843-100198972:100199519-100199783	0.391	0.495	0.32
ZBED3-AS1	+:chr5:77098654-77098747:77100235-77100391:77118319-77118521	0.388	0.121	0.381
BAZ2B	-:chr2:159395768-159395834:159397073-159397100:159397344-159397389	0.387	-0.002	-0.377
SOS1	-:chr2:38987472-38987591:38989269-38989314:38995122-38995387	0.371	0.438	-0.03
TMEM53B	+:chr6:44135016-44135096:44135327-44135386:44136348-44136439	0.37	0.226	-0.006
RUBCN	-:chr3:197684156-197684217:197691073-197691148:197693714-197693816	0.368	0.365	-0.07
ZNF202	-:chr11:123730509-123730985:123740116-123740232:123740418-123740536	0.363	-0.048	0.037
ZNF202	-:chr11:123730751-123730985:123740116-123740189:123740418-123740536	0.355	-0.027	0.031
LRRFIP2	-:chr3:37083635-37083806:37091466-37091538:37094791-37094908	0.353	0.228	-0.068
MICAL3	-:chr22:17822946-17823060:17826453-17826516:17831853-17831927	0.351	0.17	-0.234
CAPN3	+:chr15:42403740-42403777:42406210-42406324:42409302-42409380	0.342	0.148	-0.084
CACNA1F	-:chrX:49210589-49210686:49210964-49211092:49211321-49211481	0.336	0.508	0.458
CYTH1	-:chr17:78692416-78692493:78696006-78696009:78698268-78698380	0.333	0.098	-0.015
OSBPL3	-:chr7:24842278-24842413:24849068-24849176:24852503-24852634	0.332	0.174	-0.11
PICALM	-:chr11:85976622-85976682:85978069-85978093:85981128-85981228	0.331	0.059	-0.219
ARHGEF40	+:chr14:21087000-21087105:21087319-21087463:21087967-21088098	0.331	0.188	-0.009
GATS	-:chr7:100200652-100202603:100211393-100211994:100213046-100213133	0.331	0.131	0.049
ADAMTS13	+:chr9:133440343-133440525:133442613-133442743:133443375-133443561	0.329	-0.078	-0.078
SEC16A	-:chr9:136443822-136443900:136445051-136445111:136445644-136445719	0.326	0.229	0.073
MACF1	+:chr1:39463611-39463686:39465094-39465112:39468614-39468732	0.324	0.236	-0.041
NFYA	+:chr6:41079028-41079164:41080810-41080897:41084045-41084192	0.324	0.182	-0.152
CSNK1G3	+:chr5:123604723-123604830:123605338-123605362:123614341-123614455	0.322	0.231	-0.081
DCAF6	+:chr1:168004532-168004793:168015780-168015951:168022987-168023047	0.318	0.316	-0.014
TM7SF3	-:chr12:26975495-26975658:26976259-26976357:26980565-26980608	0.316	0.254	0.032

OBSCN	+:chr1:228288824-228288888:228294151-228294415:228305122-228305386	0.312	0.381	0.178
GIT2	-:chr12:109939164-109939247:109945259-109945349:109947255-109947504	0.309	0.175	-0.015
TMEM161B-AS1	+:chr5:88270525-88270585:88410072-88410194:88436272-88436602	0.306	0.266	0.243
CCDC57	-:chr17:82178473-82178605:82179026-82179189:82183773-82183932	0.306	0.3	0.05
MAP2	+:chr2:209709913-209710254:209723594-209723687:209725708-209725790	0.301	0.229	-0.167
PSAP	-:chr10:71821875-71822007:71823687-71823698:71825838-71825893	0.3	0.339	0.1
DEF8	+:chr16:89948774-89948814:89949564-89949638:89954242-89954378	0.299	0.088	0.12
PIGP	-:chr21:37067261-37067380:37072144-37072310:37072433-37072537	0.296	NA	NA
CENPBD1P1	+:chr19:58575444-58575588:58586154-58586356:58598966-58599575	0.292	0.308	0.243
ZBED3	-:chr5:77072071-77077895:77078593-77078728:77087110-77087323	0.29	0.221	0.04
AC109583.3	-:chr3:46756041-46756629:46811105-46811873:46812221-46812558	0.29	0.011	0.079
CD46	+:chr1:207785618-207785682:207790252-207790345:207793518-207793873	0.289	0.303	0.086
NEB	-:chr2:151531791-151531896:151534214-151534319:151535690-151535795	0.289	0.033	-0.126
ZNF202	-:chr11:123730488-123730985:123740116-123740192:123740416-123740536	0.289	-0.027	0.017
FAM47E-STBD1	+:chr4:76263703-76263843:76268659-76268788:76309143-76311120	0.288	NA	NA
NUMA1	-:chr11:72009267-72009367:72012400-72012442:72012694-72016260	0.284	-0.002	-0.005
MYO6	+:chr6:75908495-75908627:75911671-75911698:75914082-75914281	0.281	0.306	0.045
TCF3	-:chr19:1609289-1611849:1612206-1612433:1615284-1615485	0.278	0.174	0.083
EPB41L2	-:chr6:130889562-130870126:130878103-130876250:130885095-130885288	0.276	0.095	-0.068
ARFIP1	+:chr4:152863805-152863714:152870752-152870848:152872451-152872564	0.275	0.175	-0.091
ZNF75D	-:chrX:135291008-135291135:135291471-135291563:135295767-135296039	0.274	NA	NA
FAM228B	+:chr2:24146929-24147086:24161505-24161613:24164197-24164335	0.269	0.072	0.021
HP1BP3	-:chr1:20779811-20779911:20780344-20780540:20787194-20787272	0.268	0.167	-0.045
IQSEC2	-:chrX:53266641-53267064:53279563-53279776:53281495-53281581	0.263	-0.022	-0.031
C1orf43	-:chr1:154214456-154214574:154219835-154219937:154220341-154220533	0.261	0.145	0.029
EPB41L2	-:chr6:130889562-130870126:130880143-130880208:130885095-130885288	0.26	0.117	-0.074
AFDN	+:chr6:167911283-167911489:167913402-167913423:167914167-167914313	0.257	0.174	-0.314
BPTF	+:chr17:67874816-67875020:67875555-67875744:67891843-67892034	0.256	0.167	-0.02
SUN1	+:chr7:843340-843520:849922-850033:851383-851481	0.254	0.251	-0.025
C20orf194	-:chr20:3340503-3340639:3343675-3343731:3359515-3359593	0.253	0.013	-0.061
TNRC6A	+:chr16:24789231-24791817:24793472-24793649:24794543-24794719	0.25	0.207	0.076
SLMAP	+:chr3:57922888-57923023:57925844-57925934:57927295-57927486	0.249	-0.023	-0.098
KIFC3	-:chr16:57758216-57758909:57759124-57759153:57759727-57759836	0.248	0.189	-0.01
AKAP13	+:chr15:85658536-85658590:85662387-85662453:85664562-85664755	0.247	0.231	0.07
SH3YL1	-:chr2:253004-253115:262630-262786:263210-263368	0.247	0.023	0.479
IZUMO4	+:chr19:2098435-2098450:2098786-2098804:2099254-2099560	0.244	0.162	-0.166
MFF	+:chr2:227340291-227340380:227347225-227347384:227355676-227355761	0.241	0.257	0.077
FAM47E-STBD1	+:chr4:76263703-76263843:76268659-76268813:76309143-76310044	0.239	-0.002	0.095
AKAP13	+:chr15:85655418-85655787:85658536-85658590:85664562-85664755	0.237	0.048	-0.125
APBB2	-:chr4:40934613-40934699:40935076-40935139:40944864-40945070	0.237	-0.051	-0.287
FNBP1	-:chr9:129908889-129908999:129915965-129915980:129923843-129923939	0.237	0.194	0.092
CLEC2D	+:chr12:9693033-9693115:9693415-9693948:9694759-9695138	0.236	-0.116	-0.092
ZNF2	+:chr2:95165437-95165860:95176187-95176259:95177482-95177609	0.234	0.14	0.016
OBSCN	+:chr1:228288080-228288324:228305122-228305386:228306371-228306638	0.233	0.164	0.011
CLASP2	-:chr3:33560807-33560971:33563963-33563966:33570726-33570790	0.233	0.045	-0.012
CDH23	+:chr10:71617204-71617393:71643660-71643866:71645830-71645980	0.231	0.245	-0.072
FAM208B	+:chr10:5684837-5685175:5712822-5712918:5720543-5720611	0.231	0.238	0.156

BNIP2	-:chr15:59663378-59664120:59668102-59668138:59668891-59668949	0.231	0.182	-0.048
DIP2C	-:chr10:310030-310092:311536-311566:327005-327176	0.229	0.191	-0.074
MRPS6	+:chr21:34102834-34102908:34103496-34103519:34125340-34125480	0.226	-0.007	0.051
GOLGA4	+:chr3:37251394-37251484:37266841-37266940:37273535-37273801	0.226	0.205	-0.022
TTC8	+:chr14:88841036-88841196:88841424-88841557:88852970-88853058	0.225	-0.074	0.029
ZNF613	+:chr19:51927219-51927540:51929731-51929896:51936027-51936235	0.224	0.1	0.038
COL6A3	-:chr2:237387581-237388184:237394586-237395204:237396726-237396847	0.223	0.228	0.056
CAD	+:chr2:27240264-27240361:27240565-27240617:27240910-27240955	0.222	0.247	0.218
NF2	+:chr22:29681438-29681601:29683019-29683079:29694751-29694811	0.221	0.227	-0.024
FBXL12	-:chr19:9810266-9811717:9813230-9813274:9818727-9819079	0.221	0.165	-0.049
PPHLN1	+:chr12:42374862-42375074:42384939-42384996:42387455-42387535	0.221	0.148	-0.015
NDUFAF7	+:chr2:37241577-37241791:37242634-37242693:37243862-37243973	0.218	0.05	0.087
SPTAN1	+:chr9:128609121-128609284:128609650-128609865:128611713-128611845	0.217	0.221	0.097
MACF1	+:chr1:39463611-39463686:39465094-39465112:39468614-39468732	0.324	0.236	-0.041
NFYA	+:chr6:41079028-41079164:41080810-41080897:41084045-41084192	0.324	0.182	-0.152
CSNK1G3	+:chr5:123604723-123604830:123605338-123605362:123614341-123614455	0.322	0.231	-0.081
DCAF6	+:chr1:168004532-168004793:168015780-168015951:168022987-168023047	0.318	0.316	-0.014
TM7SF3	-:chr12:26975495-26975656:26976259-26978357:26980565-26980808	0.316	0.254	0.032
OBSCN	+:chr1:228288624-228288888:228294151-228294415:228305122-228305386	0.312	0.381	0.178
GIT2	-:chr12:109939164-109939247:109945259-109945349:109947255-109947504	0.309	0.175	-0.015
TMEM161B-AS1	+:chr5:88270525-88270585:88410072-88410194:88436272-88436602	0.306	0.266	0.243
CCDC57	-:chr17:82178473-82178605:82179026-82179189:82183773-82183932	0.306	0.3	0.05
MAP2	+:chr2:209709913-209710254:209723594-209723687:209725708-209725790	0.301	0.229	-0.167
PSAP	-:chr10:71821875-71822007:71823887-71823896:71825836-71825893	0.3	0.339	0.1
DEF8	+:chr18:89948774-89948814:89949564-89949638:89954242-89954378	0.299	0.088	0.12
PIGP	-:chr21:37067261-37067380:37072144-37072310:37072433-37072537	0.296	NA	NA
CENPBD1P1	+:chr19:58575444-58575588:58586154-58586356:58598966-58599575	0.292	0.308	0.243
ZBED3	-:chr5:77072071-77077895:77078593-77078728:77087110-77087323	0.29	0.221	0.04
AC109583.3	-:chr3:46756041-46756629:46811105-46811873:46812221-46812558	0.29	0.011	0.079
CD46	+:chr1:207785618-207785682:207790252-207790345:207793518-207793873	0.289	0.303	0.086
NEB	-:chr2:151531791-151531896:151534214-151534319:151535690-151535795	0.289	0.033	-0.126
ZNF202	-:chr11:123730486-123730985:123740116-123740192:123740418-123740536	0.289	-0.027	0.017
FAM47E-STBD1	+:chr4:76283703-76283843:76288659-76288788:76309143-76311120	0.288	NA	NA
NUMA1	-:chr11:72009267-72009387:72012400-72012442:72012894-72016260	0.284	-0.002	-0.005
MYO6	+:chr6:75908495-75908627:75911671-75911698:75914062-75914281	0.281	0.306	0.045
TCF3	-:chr19:1609289-1611849:1612206-1612433:1615284-1615485	0.278	0.174	0.083
EPB41L2	-:chr6:130869562-130870126:130878103-130878250:130885095-130885268	0.276	0.095	-0.088
ARFIP1	+:chr4:152863805-152863714:152870752-152870848:152872451-152872564	0.275	0.175	-0.091
ZNF75D	-:chrX:135291008-135291135:135291471-135291563:135295767-135296039	0.274	NA	NA
FAM228B	+:chr2:24146929-24147086:24161505-24161613:24164197-24164335	0.269	0.072	0.021
HP1BP3	-:chr1:20779811-20779911:20780344-20780540:20787194-20787272	0.268	0.167	-0.045
IQSEC2	-:chrX:53266641-53267064:53279563-53279776:53281495-53281581	0.263	-0.022	-0.031
C1orf43	-:chr1:154214456-154214574:154219835-154219937:154220341-154220533	0.261	0.145	0.029
EPB41L2	-:chr6:130869562-130870126:130880143-130880206:130885095-130885268	0.26	0.117	-0.074
AFDN	+:chr6:167911283-167911489:167913402-167913423:167914167-167914313	0.257	0.174	-0.314
BPTF	+:chr17:67874816-67875020:67875555-67875744:67891843-67892034	0.256	0.167	-0.02
SUN1	+:chr7:843340-843520:849922-850033:851383-851481	0.254	0.251	-0.025

C20orf194	-:chr20:3340503-3340639:3343675-3343731:3359515-3359593	0.253	0.013	-0.061
TNRC6A	+:chr16:24789231-24791817:24793472-24793649:24794543-24794719	0.25	0.207	0.076
SLMAP	+:chr3:57922888-57923023:57925844-57925934:57927295-57927486	0.249	-0.023	-0.096
KIFC3	-:chr16:57758218-57758909:57759124-57759153:57759727-57759836	0.248	0.189	-0.01
AKAP13	+:chr15:85658536-85658590:85662387-85662453:85664562-85664755	0.247	0.231	0.07
SH3YL1	-:chr2:253004-253115:262630-262786:263210-263368	0.247	0.023	0.479
IZUMO4	+:chr19:2098435-2098450:2098786-2098804:2099254-2099580	0.244	0.162	-0.166
MFF	+:chr2:227340291-227340380:227347225-227347384:227355676-227355761	0.241	0.257	0.077
FAM47E-STBD1	+:chr4:76263703-76263843:76268659-76268813:76309143-76310044	0.239	-0.002	0.095
AKAP13	+:chr15:85655416-85655787:85658536-85658590:85664562-85664755	0.237	0.048	-0.125
APBB2	-:chr4:40934613-40934699:40935076-40935139:40944864-40945070	0.237	-0.051	-0.287
FNBP1	-:chr9:129908889-129908999:129915965-129915980:129923843-129923939	0.237	0.194	0.092
CLEC2D	+:chr12:9693033-9693115:9693415-9693948:9694759-9695138	0.236	-0.116	-0.092
ZNF2	+:chr2:95165437-95165860:95176187-95176259:95177482-95177609	0.234	0.14	0.016
OBSCN	+:chr1:228288080-228288324:228305122-228305386:228306371-228306638	0.233	0.164	0.011
CLASP2	-:chr3:33560807-33560971:33563963-33563966:33570726-33570790	0.233	0.045	-0.012
CDH23	+:chr10:71617204-71617393:71643860-71643866:71645830-71645980	0.231	0.245	-0.072
FAM208B	+:chr10:5684837-5685175:5712822-5712918:5720543-5720611	0.231	0.238	0.156
BNIP2	-:chr15:59663378-59664120:59668102-59668138:59668891-59668949	0.231	0.182	-0.048
DIP2C	-:chr10:310030-310092:311536-311566:327005-327176	0.229	0.191	-0.074
MRPS6	+:chr21:34102834-34102908:34103496-34103519:34125340-34125480	0.226	-0.007	0.051
GOLGA4	+:chr3:37251394-37251484:37266841-37266940:37273535-37273601	0.226	0.205	-0.022
TTC8	+:chr14:88841036-88841196:88841424-88841557:88852970-88853056	0.225	-0.074	0.029
ZNF613	+:chr19:51927219-51927540:51929731-51929896:51936027-51936235	0.224	0.1	0.038
COL6A3	-:chr2:237387581-237388184:237394586-237395204:237396726-237396847	0.223	0.228	0.056
CAD	+:chr2:27240264-27240361:27240566-27240617:27240910-27240955	0.222	0.247	0.218
NF2	+:chr22:29681438-29681601:29683019-29683079:29694751-29694811	0.221	0.227	-0.024
FBXL12	-:chr19:9810266-9811717:9813230-9813274:9818727-9819079	0.221	0.165	-0.049
PPHLN1	+:chr12:42374862-42375074:42384939-42384996:42387455-42387535	0.221	0.148	-0.015
NDUFAF7	+:chr2:37241577-37241791:37242834-37242893:37243882-37243973	0.218	0.05	0.087
SPTAN1	+:chr9:128609121-128609284:128609650-128609665:128611713-128611845	0.217	0.221	0.097
PPIL3	-:chr2:200876941-200877037:200877496-200877604:200881420-200881488	0.156	0.12	0.136
SULF1	+:chr8:69486623-69486950:69495784-69495926:69501873-69501968	0.156	0.142	0.075
ITGB1BP1	-:chr2:9418625-9418732:9419989-9420100:9423372-9423480	0.155	0.096	0.089
SORCS3	+:chr10:105255701-105255801:105256818-105256924:105282330-105282491	0.155	0.059	0.018
SCARB1	-:chr12:124777632-124778586:124782682-124782811:124786440-124786503	0.154	0.024	-0.015
DESI1	-:chr22:41604043-41604153:41607261-41607331:41620751-41621096	0.153	0.111	0.045
BPTF	+:chr17:67874818-67875020:67875555-67875744:67886127-67886318	0.153	0.167	0.029
PC	-:chr11:66952295-66952468:66954248-66954436:66958321-66958370	0.152	0.063	0.12
SUGP2	-:chr19:18990887-18991149:18993637-18993740:18994365-18994486	0.152	-0.003	-0.129
TEAD3	-:chr6:35479304-35479316:35480311-35480374:35484559-35484624	0.152	-0.02	-0.019
MYH10	-:chr17:8569719-8569812:8576642-8576672:8577235-8577338	0.152	0.204	0.056
TFAP2B	+:chr6:50818722-50818972:50822133-50822160:50823406-50823865	0.151	0.126	-0.048
DNM3	+:chr1:172092823-172092875:172093695-172093725:172131174-172131288	0.151	0.074	0.09
ERC1	+:chr12:1110191-1110347:1112214-1112307:1115865-1116033	0.151	0.017	-0.055
SPAG9	-:chr17:50974770-50974947:50975862-50975901:50977107-50977221	0.151	-0.003	-0.31
NSF	+:chr17:46626612-46626712:46630410-46630450:46637375-46637542	0.15	0.146	0.039

ARHGEF12	+:chr11:120407737-120407823:120409393-120409450:120420752-120420851	0.15	0.269	0.098
TUFT1	+:chr1:151540304-151540426:151562090-151562165:151562584-151562686	0.15	0.064	-0.097
USP28	-:chr11:113841662-113841768:113854257-113854335:113875444-113875528	-0.15	0.049	-0.229
FAM126A	-:chr7:22941268-22946163:22946951-22947247:22960255-22960415	-0.15	-0.318	-0.207
PAK1	-:chr11:77392442-77392541:77397026-77397093:77411773-77411944	-0.15	0.006	-0.031
CD47	-:chr3:108047078-108047292:108050577-108050802:108051938-108051970	-0.16	-0.044	0.015
DVL1	-:chr1:1336411-1336515:1337017-1337055:1337976-1338183	-0.16	-0.056	-0.002
ENAH	-:chr1:225514595-225514900:225517195-225517990:225519197-225519565	-0.16	-0.083	0.099
HPS5	-:chr11:18297558-18297717:18300827-18300916:18306134-18306347	-0.17	-0.156	-0.258
TJAP1	+:chr6:43477568-43477628:43478136-43478232:43497880-43497977	-0.17	-0.124	-0.203
LIAS	+:chr4:39465284-39465342:39467517-39467846:39470018-39470164	-0.17	-0.114	-0.18
PLD3	+:chr19:40365552-40365585:40365717-40365930:40366418-40366464	-0.17	-0.171	-0.088
DNM1L	+:chr12:32737104-32737161:32737864-32737942:32740063-32740240	-0.17	-0.291	-0.055
GPRC5D-AS1	+:chr12:12927725-12927803:12978940-12979021:12979523-12979622	-0.17	0.037	-0.028
CDKL3	-:chr5:134304404-134304567:134306608-134306702:134308137-134308466	-0.17	-0.075	0.083
AL772307.1	-:chr9:39983792-39984410:39988443-39988564:40106357-40106611	-0.18	-0.066	0.115
AC091901.1	-:chr5:162561784-162561944:162591609-162591685:162623334-162623461	-0.18	0.031	0.003
AGBL3	+:chr7:134987874-134987996:134989249-134989310:134993492-134993678	-0.18	-0.106	0.047
NCOR2	-:chr12:124326190-124326370:124327408-124327633:124330844-124330898	-0.18	-0.125	0.093
MARK2	+:chr11:63903060-63903158:63903985-63904147:63904785-63905043	-0.18	-0.056	0.195
PLCD4	+:chr2:218615706-218615761:218615903-218615959:218618578-218618807	-0.18	-0.138	-0.126
TSNARE1	-:chr8:142270474-142271691:142274780-142274863:142279859-142279997	-0.18	-0.203	-0.249
HERPUD1	+:chr16:56939248-56939359:56940176-56940245:56943125-56943297	-0.18	0.066	-0.23
REPS1	-:chr6:138921036-138921124:138926400-138926481:138929976-138930098	-0.19	0.013	0.08
PLK5	+:chr19:1531737-1531883:1533930-1534041:1535064-1535365	-0.19	-0.068	-0.056
LIAS	+:chr4:39465284-39465342:39467517-39468427:39470018-39470164	-0.19	-0.115	-0.222
AHSA2	+:chr2:61185501-61185618:61185979-61186081:61186445-61186497	-0.2	-0.142	-0.128
TTC28	-:chr22:27989877-27990007:27990788-27990812:27992586-27992663	-0.2	-0.197	0.141
NRXN3	+:chr14:78243036-78243802:78278644-78278662:78297830-78297860	-0.2	-0.136	0.142
ZNF527	+:chr19:37379119-37379246:37380047-37380372:37388305-37393066	-0.2	-0.211	-0.236
SPIN1	+:chr9:88415606-88415699:88416643-88416766:88418777-88418951	-0.2	-0.037	0.208
ERBIN	+:chr5:68068876-68069020:68072168-68072291:68075023-68075230	-0.2	0.199	0.12
ABI3BP	-:chr3:100789453-100789516:100792690-100792768:100794922-100795003	-0.2	-0.243	-0.104
CDC42BPA	-:chr1:227213135-227213219:227219262-227219420:227254063-227254155	-0.2	-0.17	-0.012
EIF5	+:chr14:103334001-103334260:103334388-103334597:103335652-103335844	-0.2	-0.351	-0.349
WNK1	+:chr12:878211-878361:879572-880031:881691-881789	-0.21	0.039	0.079
SORBS1	-:chr10:95410832-95410777:95414493-95414655:95421960-95422073	-0.21	-0.271	-0.033
CADM1	-:chr11:115178643-115178775:115198405-115198438:115209573-115209657	-0.21	-0.121	0.036
BCS1L	+:chr2:218659759-218659800:218660306-218660421:218660938-218661217	-0.21	-0.125	-0.142
SRCAP	+:chr16:30722121-30722286:30722562-30722748:30722962-30723229	-0.22	-0.093	0.055
CLCN3	+:chr4:169713078-169713295:169717791-169717867:169719906-169720545	-0.22	-0.117	-0.049
CD46	+:chr1:207767012-207767195:207767778-207767823:207783291-207783330	-0.22	-0.189	-0.123
NCOR2	-:chr12:124326179-124326370:124327546-124327633:124330844-124330898	-0.22	-0.098	0.087
PRKD1	-:chr14:29638693-29638904:29656475-29656499:29663698-29663859	-0.22	-0.227	0.006
NFIX	+:chr19:13075534-13075871:13078612-13078735:13081679-13081835	-0.22	-0.195	0.049
IGSF3	-:chr1:116603623-116604025:116606491-116606551:116607941-116608331	-0.23	-0.343	-0.052
AC004980.1	+:chr7:76551463-76551522:76615493-76615683:76621115-76621388	-0.23	-0.148	-0.162

DONSON	-:chr21:33581950-33582055:33582164-33582246:33584589-33584768	-0.23	-0.12	0.089
FGFR2	-:chr10:121503789-121503941:121515116-121515319:121519978-121520189	-0.23	-0.268	-0.335
MED15	+:chr22:20508058-20508444:20518877-20518995:20537116-20537183	-0.23	-0.072	0.227
RAB11FIP5	-:chr2:73075992-73076182:73079650-73081663:73088049-73088749	-0.24	-0.081	0.053
AL392172.1	+:chr1:222815058-222815078:222823855-222823945:222835118-222835215	-0.25	0.05	-0.079
LIAS	+:chr4:39465284-39465342:39468118-39468427:39470018-39470164	-0.25	-0.149	-0.298
FAM114A1	+:chr4:38867815-38867834:38868397-38868546:38891742-38891830	-0.25	0.145	0.037
PLK5	+:chr19:1531737-1531883:1533718-1533848:1535064-1535365	-0.26	-0.219	-0.139
KIF13A	-:chr6:17763692-17764948:17771113-17771218:17771907-17772059	-0.26	-0.233	-0.015
CD46	+:chr1:207767012-207767195:207767778-207767823:207770320-207770362	-0.27	-0.343	-0.3
TCF7L2	+:chr10:113158020-113158069:113158666-113158717:113160618-113160891	-0.27	-0.282	-0.201
AKAP11	+:chr13:42308453-42308809:42313046-42313130:42313893-42313940	-0.27	-0.409	-0.106
TCF7L2	+:chr10:113158020-113158069:113159919-113159992:113160618-113160891	-0.28	-0.427	-0.248
SORBS2	-:chr4:185678795-185678822:185684753-185684846:185775226-185775366	-0.28	-0.081	0.159
CCDC18-AS1	-:chr1:93309714-93309790:93318167-93318228:93324634-93324691	-0.29	-0.047	-0.574
ZFYVE21	+:chr14:103729090-103729182:103729792-103729846:103732619-103732762	-0.29	-0.203	-0.004
ENAH	-:chr1:225500991-225501070:225504990-225505053:225507950-225508017	-0.3	-0.08	0.025
ZEB1	+:chr10:31319215-31319292:31373017-31373173:31387123-31387268	-0.3	0.122	-0.18
DEPDC5	+:chr22:31857444-31857553:31861367-31861433:31870589-31870744	-0.31	-0.04	0.097
TCF4	-:chr18:55585279-55585352:55586920-55587136:55589296-55589778	-0.31	-0.259	0.026
TMEM50B	-:chr21:33455726-33455784:33456003-33458097:33465341-33465409	-0.31	NA	NA
ZCCHC11	-:chr1:52526019-52526373:52529767-52529885:52534986-52535122	-0.32	-0.315	-0.315
ANKRD36	+:chr2:97207810-97207839:97209680-97209709:97209799-97209872	-0.32	-0.211	-0.3
SORBS2	-:chr4:185678795-185678822:185684753-185684846:185690561-185690599	-0.32	-0.157	0.132
CCDC18-AS1	-:chr1:93305387-93305470:93318167-93318228:93324634-93324691	-0.32	-0.002	-0.309
STX2	-:chr12:130790833-130791977:130795994-130796120:130798524-130798635	-0.32	-0.298	-0.054
SORBS1	-:chr10:95410832-95410777:95414493-95414862:95421960-95422073	-0.32	-0.332	-0.057
RAPGEF6	-:chr5:131446482-131446703:131450022-131450048:131453053-131453177	-0.33	-0.213	-0.025
CAMKK2	-:chr12:121245139-121245240:121248605-121248734:121249788-121249874	-0.33	-0.271	-0.018
HIVEP3	-:chr1:41518401-41518488:41524734-41524910:41575543-41575689	-0.33	-0.034	-0.251
MSH5	+:chr6:31758164-31758293:31758532-31758620:31758785-31758875	-0.34	-0.295	-0.335
HOOK3	+:chr8:42997589-42997637:43000270-43000276:43002106-43002141	-0.34	-0.167	0.041
MROH7-TTC4	+:chr1:54678741-54678854:54679262-54679439:54682655-54682794	-0.34	-0.314	-0.211
SOCS7	+:chr17:38361710-38361775:38364751-38364856:38366286-38366417	-0.35	-0.403	-0.074
SSBP3	-:chr1:54257126-54257186:54258068-54258149:54281437-54281527	-0.35	-0.282	0.001
FGFR1	-:chr8:38428345-38428435:38429681-38429948:38457355-38457446	-0.36	-0.264	0.157
SORBS2	-:chr4:185678795-185678822:185684753-185684842:185690561-185690611	-0.36	-0.145	0.123
NHSL1	-:chr6:138430392-138433680:138441982-138442114:138447000-138447193	-0.38	-0.345	-0.039
ARVCF	-:chr22:19969895-19970743:19971215-19971335:19971885-19971971	-0.38	-0.237	0.077
MBD1	-:chr18:50275128-50275245:50275369-50275444:50275599-50275728	-0.39	-0.125	0.014
ZMAT1	-:chrX:101886631-101886731:101887197-101887304:101894453-101894904	-0.39	-0.133	-0.141
WNK1	+:chr12:878211-878361:880720-880999:881591-881789	-0.39	-0.231	0.071
MBNL1	+:chr3:152445281-152445539:152446703-152446757:152447819-152447773	-0.39	-0.143	0.142
TTN	-:chr2:178640540-178640630:178641240-178641315:178644547-178644616	-0.43	-0.507	-0.086
TTN	-:chr2:178640540-178640630:178642236-178642317:178644547-178644616	-0.43	-0.524	-0.181
AC139713.2	+:chr4:143738974-143739117:143808313-143808370:143859015-143859115	-0.43	-0.225	0.095

ADD3	+:chr10:110130362-110130486:110132304-110132400:110133325-110134211	-0.46	-0.305	0.053
CLINT1	-:chr5:157787601-157787992:157790599-157790651:157791702-157791841	-0.46	-0.168	-0.406
MICAL2	+:chr11:12249940-12250273:12255642-12255750:12256784-12256909	-0.47	-0.474	-0.461
AC138409.2	-:chr5:34218294-34218450:34239374-34239448:34244615-34244796	-0.48	-0.234	-0.004
IZUMO4	+:chr19:2098786-2098804:2098975-2099029:2099254-2099590	-0.5	-0.32	-0.108
COPZ2	-:chr17:48026166-48026475:48027675-48027789:48028471-48028510	-0.5	-0.353	0.094
EXOC1	+:chr4:55882726-55883928:55888887-55888932:55890222-55890386	-0.54	-0.405	0.037
CD47	-:chr3:108047078-108047292:108049618-108049651:108050577-108050602	-0.55	-0.57	-0.019
TMEM184A	-:chr7:1548648-1548668:1549546-1549604:1549853-1549945	-0.58	-0.103	-0.006
MBNL2	+:chr13:97347040-97347067:97356795-97356849:97357481-97357635	-0.66	-0.448	0.051

[0453] While not nearly as frequent, other forms of alternative splicing events, alternative 5' splice site (A5SS), alternative 3'-splice site (A3SS), mutually exclusive exon (MXE) and retained intron (RI), also showed that the Pre_S cohort was more similar to the FECD_REP group than the FECD_NR cohort (**FIGS. 17A-D**). Taken together, these data demonstrate that splicing changes in Pre_S tissue are precursors to the changes in FECD_REP - but not FECD_NR - late stage disease.

[0454] We then separated the top 24 skipped exon events in Pre_S tissue, which are shared with FECD_REP for evaluation. As with the overall group of 313 events, the splicing of these genes was much more like FECD_REP tissue than to control or FECD_NR tissue (**FIG. 4D**). Of the top 24 skipped exon events shared by FECD_REP and Pre_S tissue, approximately half are also seen in tibialis anterior muscle of myotonic dystrophy type 1 (DM1) subjects (**FIGS. 4D-E, 17E-G**). This similarity, in spite of the comparison being made between samples from different tissues, suggests that the expanded CUG repeats in DM1 and FECD_REP have a common mechanism for producing splicing changes and that this mechanism is activated in Pre_S tissue.

[0455] Notable genes that show changes in splicing include the splicing factors *MBNL1* and *MBNL2*. Changes in *MBNL1* and *MBNL2* splicing in Pre_S (**Table 8**) cells may trigger other splicing changes and eventually lead to the larger scale change that characterizes late stage disease (Table 8).

[0456] **Example 4**

[0457] This example describes changes in alternative splicing are quantitatively similar in Pre_S and FECD_REP tissue.

[0458] We experimentally validated changes in splicing and levels of gene expression for Pre_S relative to control tissues (**FIG. 5; FIG. 18**). Genes were chosen for validation based on the significance of altered expression and the potential biological role of the gene expression suggested by pathway analysis (**FIG. 8**).

[0459] We used reverse-transcription PCR to evaluate changes of splicing for six genes, *INF2*, *NUMA1*, *SORBS1*, *SYNE1*, *MBNL1*, and *MBNL2* (**FIG. 5**). INF2 protein associates with microtubules, and may affect cell shape. NUMA1 protein is component of the nuclear matrix and may affect mitotic spindle organization and proper cell division. *SORBS1* was chosen for its protein product's involvement in cell adhesion and extracellular matrix. *SYNE1* encodes nesprin-1 which links the nuclear membrane to the actin cytoskeleton and may also affect cell morphology. *MBNL1* and *MBNL2* were chosen because potential alterations in their expression might feed back into even greater changes in splicing.

[0460] The changes in splicing predicted by global RNAseq analysis were confirmed by visual inspection of genes using Sashimi plots (**FIG. 5A**) and validated by semi-quantitative analysis using reverse-transcriptase PCR (RT-PCR) (**FIG. 5B**) using monolayer human corneal endothelial tissue. Pre_S tissue showed the changes in splicing predicted by our RNAseq data (**FIG. 5**). Both Sashimi plots and semi-quantitative reverse transcriptase PCR (RT-PCR) analysis reveal that the absolute magnitude of splicing changes are similar in FECD_REP late stage disease tissues. The amount of change in splicing in Pre_S tissue is substantial, similar to that observed in late stage tissue.

[0461] We also carried out a differential alternative splicing analysis between Pre_S and FECD_REP tissues directly, rather than using the Control as the reference as described above. Although there are hundreds of significant skipped exon events identified between Pre_S and FECD_REP, out of 132 skipped exon events shared between Pre_S/Control and FECD_REP/Control comparison, only five of them are significantly different between Pre_S and FECD_REP (Table 9). This means that majority of shared skipped exon events identified between Pre_S/Control and FECD_REP/Control have similar magnitude in inclusion of exon level changes, This observation suggests that missplicing of key genes does not gradually increase as disease symptoms progress, rather substantial missplicing is a leading indicator of disease.

[0462] Table 9. Overlapped significant differential skipped exon events between Pre_S/FECD_REP and 132 shared SE events between Pre_S/Control and FECD_REP/Control. (FDR < 0.001, |IncLevel Difference| >= 0.15)

Gene Symbol	locus	FDR	IncLevel1	IncLevel2	IncLevel Difference

MTA1	+:chr14:105465333-105466578:105466706-105466742:105469466-105469498	8.6149E-07	0.674,0.322,0.487,0.388,0.523,0.474	0.797,0.841,0.652,0.752,0.783,0.924	**-0.313**
ABI1	-:chr10:26770244-26770345:26771074-26771089:26777064-26777241	0.000412057	0.348,0.391,0.197,0.531,0.256,0.114	0.543,0.513,0.425,0.521,0.598,0.612	**-0.229**
INF2	+:chr14:104714202-104714856:104715283-104715340:104718794-104719603	0.000481285	0.274,0.138,0.133,0.16,0.137,0.434	0.571,0.546,0.4,0.303,0.348,0.272	**-0.194**
EIF5	+:chr14:103334001-103334260:103334388-103334597:103335652-103335844	6.60555E-13	0.568,0.899,0.887,0.786,0.959,0.921	0.984,0.976,1.0,0.988,0.971,1.0	**-0.15**
SYNE1	-:chr6:152143622-152143765:152145486-152145555:152148044-152148378	0.000142873	0.147,0.125,0.082,0.134,0.15,0.388	0.486,0.471,0.199,0.25,0.408,0.359	**-0.191**

[0463] **Example 5**

[0464] This example describes differential gene expression.

[0465] We compared gene expression level changes in Pre_S, FECD_REP, and FECD_NR tissue cohorts relative to control tissue. To classify changes as significant, we used the adjusted *p*-value generated by Cuffdiff, one of the programs within Cufflinks suite, as the determining metric. Changes with a *p*-value less than 0.05 were deemed significant and included in our analysis. Analysis by DeSeq2, an alternate program for evaluating RNAseq data, produced similar results when compared with the output of CuffDiff (**FIG. 19** and Table 10).

[0466] Table 10. Differential expression level analysis results for 8 selected genes by CuffDiff and DeSeq2.

CuffDiff						
gene_name	log2FoldChange_Pre_S/Con	q_value_Pre_S/Con	log2FoldChange_FECD_REP/Con	q_value_FECD_REP/Con	log2FoldChange_FECD_NR/Con	q_value_FECD_NR/Con
FN1	5.08031	0.00226223	7.2246	0.00226223	6.69992	0.00226223
COL4A2	1.68119	0.00226223	3.04457	0.00226223	4.33504	0.00226223
MSI1	3.41382	0.00226223	3.44233	0.00226223	2.70827	0.00226223
CTGF	1.22263	0.00226223	2.72282	0.00226223	2.65112	0.00226223
COCH	4.34706	0.00226223	4.73065	0.00226223	3.90575	0.00738683
LUM	-1.13075	0.045657	-1.69472	0.00226223	0.773072	0.347028
KDR	-1.30521	0.00226223	-2.927	0.00226223	-0.56167	0.378425
SOD3	-1.63529	0.0103752	-3.48636	0.00226223	-1.75043	0.00738683
De Seq2						
gene_name	log2FoldChange_Pre_S/Con	padj_Pre_S/Con	log2FoldChange_FECD_REP/Con	padj_FECD_REP/Con	log2FoldChange_FECD_NR/Con	padj_FECD_NR/Con
FN1	5.055555154	0.000769717	7.282987556	1.17E-09	6.760739221	2.11E-06
COL4A2	1.795732091	0.16084414	3.341905792	4.15E-05	4.634801232	7.80E-07

MSI1	3.737811696	1.24E-10	3.823524012	9.62E-13	3.382481453	9.23E-08
CTGF	1.09560732	0.342783282	2.701641399	3.08E-05	2.636468101	0.00083336
COCH	4.189351978	5.77E-09	4.675618865	6.27E-13	3.881906815	5.48E-07
LUM	-1.22262908	0.258691241	-1.911846973	0.004338117	0.722945995	0.484968174
KDR	-1.356276847	0.105249236	-3.06676426	1.95E-08	-0.667292478	0.4512983
SOD3	-1.646170275	0.004935301	-3.550948801	4.45E-15	-1.638591521	0.004506258

[0467] All sample cohorts showed expression changes relative to control tissue (Pre_S: 215, FECD_REP: 1330; FECD_NR: 696) (**FIG. 6A-B**). The greater number of gene expression changes in the FECD_REP and FECD_NR tissues is consistent with the severe cellular phenotype observed in late stage disease. 602 out of the 696 genes differentially expressed in the FECD_NR tissues were also found in the FECD_REP group suggesting significant overlap of the common final molecular genetic mechanisms in the two forms of late-stage disease.

[0468] Pre_S tissue had 215 genes with significantly altered expression levels relative to control tissue. Only five changes in gene expression were uniquely shared between Pre_S and FECD_NR tissue, compared to 73 shared changes with FECD_REP. (**FIG. 6A**). The closer relationship between Pre-S and FECD_REP is consistent with our splicing data (**FIGS. 4-5**) and supports the conclusion that patterns of gene expression in mutant expanded repeat cells are established long before symptoms or disease findings are observable.

[0469] Volcano plots allow a global overview of individual gene expression changes. They are useful for visualizing patterns of changes and identifying "outlier" genes that combine highly significant changes in gene expression with higher fold changes. The fold change among top genes are less in Pre_S than in FECD_REP or FECD_NR and the identity of top genes differ (**FIGS. 6B-C, 20, 22**). This finding is consistent with the severity of late stage disease and the disruption of many gene expression programs.

[0470] Evaluation of Pre_S tissue may provide a window to identify early gene drivers before symptom-driven secondary changes in gene expression overwhelm analysis. The top twenty differentially over-expressed genes identified in Pre_S tissue (**FIG. 6C**) include genes involved in the extracellular matrix and its assembly, cochlin (*COCH*), fibronectin (*FN1*), and thrombospondin (*THBS2*).

[0471] We found 279 statistically significant up regulated genes that are common to Pre-S and FECD_REP of which the top 50 are shown in Table 11.

[0472] Table 11. Top 50 up regulated genes common to Pre-S and FECD_REP.

FEATURE_NAME	Control-VS-Pre_S.logFC	Control-VS-Pre_S.LR	Control-VS-Pre_S.PValue	Control-VS-FECD_REP.logFC	Control-VS-FECD_REP.Pvalue
ROR2	6.524075	43.41713	4.42E-11	7.198885	8.82E-13
ACKR1	5.839108	34.54291	4.17E-09	7.615229	8.47E-13
CADM3	5.578438	20.98525	4.63E-06	7.107443	4.32E-08
ABCB1	5.459433	48.71004	2.97E-12	8.276607	8.4E-22
CNN1	5.117924	45.30649	1.68E-11	4.418321	2.89E-09
VIPR2	5.082804	19.28708	1.12E-05	6.334537	1.42E-07
FN1	5.080174	29.43764	5.77E-08	7.26223	1.4E-12
ADAM33	5.048453	24.75297	6.52E-07	5.918941	1.57E-08
CADM3-AS1	5.030838	23.8002	1.07E-06	6.795826	2.6E-10
TSHR	4.901685	31.98023	1.56E-08	10.49244	3.3E-27
COCH	4.403612	61.33316	4.82E-15	4.90102	1.17E-17
PCP4	4.357451	16.39757	5.14E-05	5.995339	1.82E-07
KCNA1	4.352557	51.10559	8.75E-13	4.478258	2.41E-13
DPP10	4.304371	23.64629	1.16E-06	7.820025	1.4E-16
VSIG2	4.073351	67.82251	1.79E-16	4.976104	1.82E-23
CLIC6	4.072688	37.32171	1E-09	6.315357	6.76E-19
TMEM30B	3.818031	42.12119	8.58E-11	3.883178	4.15E-11
MARVELD3	3.81801	49.05871	2.48E-12	2.798854	2.01E-07
LGR6	3.660003	23.71591	1.12E-06	3.351386	7.12E-06
CST4	3.652591	13.24441	0.000273	5.927597	6.12E-08
THBS2	3.644255	31.45097	2.05E-08	4.491004	2E-11
ICA1	3.64345	27.63457	1.47E-07	5.191539	6.53E-13
ALPK2	3.614404	11.37385	0.000745	10.3664	7.87E-16
RARRES2	3.590468	23.52695	1.23E-06	1.910993	0.007297
MMP19	3.583226	26.33872	2.86E-07	5.252943	4.61E-13
FRZB	3.567747	31.43543	2.06E-08	3.340459	1.23E-07
DCDC2C	3.552476	28.69988	8.45E-08	5.752764	1.25E-18
CST1	3.518193	11.74597	0.00061	7.105067	1.89E-09
MSI1	3.512031	62.99815	2.07E-15	3.424204	8.93E-15
ITPRIPL1	3.507736	41.89734	9.62E-11	3.000683	2.92E-08
WNT3	3.451001	32.10989	1.46E-08	3.821713	4.39E-10
HPGD	3.43778	32.01004	1.53E-08	3.370523	2.74E-08
SLC5A1	3.40064	49.65363	1.83E-12	3.170105	4.5E-11
ARSJ	3.368825	16.85727	4.03E-05	4.257335	4.15E-07
TPBG	3.350721	29.45705	5.72E-08	4.952642	2.23E-14
GREB1L	3.297108	15.28293	9.25E-05	5.382995	1.55E-09
SLC16A9	3.278027	25.65742	4.08E-07	4.385272	5.22E-11
EPHB6	3.272468	12.02168	0.000526	6.79661	6.39E-11
MROH9	3.264793	37.8166	7.77E-10	4.571302	1.48E-18
ENOX1	3.263818	75.75422	3.21E-18	2.699152	4.02E-13
ECEL1P2	3.225493	24.59929	7.06E-07	3.032914	2.82E-06
PLAC9	3.220549	12.43297	0.000422	6.410981	9.79E-11
KIF21B	3.2063	18.13876	2.05E-05	6.318319	1.62E-16

F5	3.174819	23.69059	1.13E-06	4.601282	2.05E-11
ADAMTS12	3.164387	26.30854	2.91E-07	4.291849	1.72E-11
ITIH5	3.155392	16.01146	6.3E-05	7.171555	5.44E-15
ANXA3	3.119277	11.12734	0.000851	6.788408	1.06E-10
PROS1	3.107313	27.84953	1.31E-07	4.800437	1.42E-14
PTPN3	3.090466	28.54363	9.16E-08	3.693209	3.56E-10
DCLK1	3.073859	22.09089	2.6E-06	5.060074	5.74E-13

[0473] **Example 6**

[0474] This example describes quantitative analysis of gene expression changes

[0475] We used quantitative PCR (qPCR) to confirm the changes in the level of gene expression detected by RNAseq in both Pre_S and FECD tissue (**FIG. 7**). qPCR measurements of corneal endothelial tissues were challenging because of the limited amount of material available, but we could compare expression of eight genes identified in our RNAseq data, *FN1*, *COL4A2*, *COCH*, *CTGF*, *MSI1*, *LUM*, *KDR*, and *SOD3*. Four of these genes, *FN1*, *COL4A2*, *CTGF*, *KDR*, were within the fibrosis pathway. *COCH* and *LUM* encode extracellular matrix proteins, *MSI1* encodes an RNA binding protein/splicing factor, and SOD3 protein is related to oxidative stress. The observed changes in gene expression confirm our RNAseq results (**FIGS. 6B, 23**).

[0476] **Example 7**

[0477] This example describes pathway analysis.

[0478] To elucidate the potential impact of changes in the expression of individual genes on physiologic processes, we applied Ingenuity Pathway Analysis (IPA) to our RNAseq data. Overwhelmingly, the top common canonical pathway was hepatic fibrosis/hepatic stellate cell activation (**FIGS. 8A, 23)**. Involvement of the hepatic fibrosis pathway genes in FECD_REP and FECD_NR is consistent with the observed accumulation of extracellular matrix (ECM) in advanced FECD with thickening of Descemet's membrane with focal excrescences (guttae) and with RNA measurements using tissue from late stage disease. Our FECD transcriptome data indicates robust ECM production in late-stage disease possibly regulated by transforming growth factor-β (TGF-β), the most potent fibrogenic cytokine released by a number of cell populations in the body including the liver (**FIG. 21A-B**).

[0479] Activation of the fibrosis pathway was also observed in Pre_S tissue (**FIGS. 8A-B, 9**). Genes that showed statistically significant increases in expression include fibronectin *FN1*, one of the highest differentially expressed genes in Pre_S tissue (**FIG.**

7). Other genes include connective tissue growth factor (*CTGF*) and four members of the collagen alpha chain family including *COL1A2* which is also abundant in liver fibrosis (**FIG. 20**). Kinase insert domain receptor (KDR, also known as vascular endothelial growth factor receptor-2) showed decreased expression. Relevant in the fibrosis pathway, KDR protein interacts with VEGF to mediate vascular endothelial cell proliferation. These genes are also disturbed in advanced disease - another indication that gene expression programs associated with fibrosis are activated in presymptomatic carriers prior to observable symptoms of disease.

[0480] The pathways underlying FECD_REP and FECD_NR advanced stage disease had significant overlap. There were numerous shared pathways implicating the immune system related to helper T cell activation, signaling, and neuroinflammation. (**FIGS. 8A,C**). Marked overexpression of genes encoding proteins on the surface of antigen-presenting cells including the B7 protein, *CD86* (> 2,000 fold increase), and class II major histocompatibility proteins (> 250 fold) both required for these cells to activate helper T cells implicate the immune system in both FECD groups in late-stage disease (**FIGS. 8C, 21C-E**).

[0481] A few molecular pathways were changed in FECD_REP but not FECD_NR (**FIG. 8D**). The canonical pathway related to mitochondrial dysfunction showed the large difference with p values of 10^{-5} and zero respectively for FECD_REP and FECD_NR (**FIGS. 8A, 21F-H**). Decreased expression of oxidative phosphorylation genes was more pronounced in FECD_REP compared to the FECD_NR (**FIG. 8D)**.

[0482] **Example 8**

[0483] This example provides a discussion of examples 1-7.

[0484] Identifying the early drivers of late-onset disease is important for understanding disease progression and developing therapeutics. Studying early drivers, however, is often not practical because pre-symptomatic tissue is difficult to obtain. Because the expanded CUG repeat mutation within *TCF4* intron 2 that causes FECD_REP is so prevalent (3% of the Caucasian population), significant numbers of pre-symptomatic samples can be obtained from individual donors positive for the CUG expansion. These tissues, together with FECD_REP, FECD_NR, and control tissues (**FIGS. 1-2**) provide an advantageous model for better investigating the early links between expanded trinucleotide repeat mutations and disease.

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[0485] The goal of this study was to understand whether the expanded CUG repeat was changing gene expression in Pre_S tissue and how such changes might relate to the gene expression and phenotypic changes known to occur in late-stage FECD.

[0486] **FECD is a disease of mutant RNA**

[0487] FECD_REP is caused by an expanded CUG trinucleotide repeat within mutant *TCF4* intronic RNA (**FIG. 10**). Remarkably, FECD is also caused by the mutant CUG expanded repeat within the 3'-untranslated region of the *DMPK* gene is also associated with myotonic dystrophy. Unlike other trinucleotide repeat diseases where the contribution of mutant RNA is debated, data demonstrating that CUG RNAs expressed from two different genes are both responsible for FECD offers strong support for RNA playing a central role in the molecular origins of the disease.

[0488] The expanded CUG RNA can be detected by fluorescent in situ hybridization (FISH) as RNA foci. These RNA foci are a hallmark of both Pre_S and FECD_REP corneal endothelium (**FIG. 10**). While Pre_S and FECD_REP tissue both possess the RNA trigger for FECD, Pre_S tissue is visually indistinguishable from control tissue upon specular imaging. By contrast, FECD_REP tissue is dramatically different from control tissue, with reduced cell density and the formation of focal collagen accumulations known as guttae.

[0489] The FECD CUG repeat RNA is present at only a few (<10) copies per cell in disease tissue. It is likely that each "foci" detected by FISH is a single RNA molecule. A low copy number for a disease-causing RNA has also been observed for myotonic dystrophy type 1(DM1) and *C9orf72* ALS/FTD. We find that the CUG repeat expansion stabilizes *TCF4* intronic RNA in a corneal cell-specific manner (**FIG. 3**). This enhanced stability may contribute to an ability of a small number of RNA molecules to bind protein sufficiently to affect overall function in cells and eventually produce observable symptoms that characterize a delayed onset disease like FECD.

[0490] The CUG repeat within intronic *TCF4* and other microsatellite expansions may be associated with intron retention. Our detection of nuclear CUG RNA foci by FISH and upstream intronic RNA due to its increased half-life may be compatible with a disease model where the *TCF4* intron with the expanded repeat is spliced out, forms a linear stable intronic sequence RNA, and undergoes preferential 3' to 5' exonuclease degradation in the nucleus.

[0491] There is no definitive mechanistic insight into how the relatively rare expanded CUG repeat RNA can cause FECD. How one or a few copies of RNA

triggers widespread changes in gene expression and late onset disease remains a major unanswered question. However, the mutant RNA may act by binding to MBNL and affecting splicing (**FIG. 10**).

[0492] There is relatively little MBNL protein is in the nuclei of FECD_REP cells and human tissue. Using quantitative protein titrations against a known standard, we calculated that there were 65,000 copies of MBNL1 and MBNL2 per cell and less than 2000 copies were present in cell nuclei. Low copy numbers for MNBL in the nuclei of affected tissue are consistent with the hypothesis that even a small amount of mutant expanded CUG repeat RNA may be sufficient to affect the available pool of MNBL protein. A reduction in available MBNL protein would produce the alterations of splicing that are a hallmark of FECD_REP disease (**FIGS. 4-5**). It is also possible that the MNBL:mutant RNA interaction may nucleate additional protein or RNA interactions to amplify disruptive effects on gene expression and changes in alternative splicing.

[0493] **Expanded CUG mutant RNA causes splicing changes in presymptomatic tissue**

[0494] Many of the alterations in splicing observed in FECD_REP tissue also define gene expression in presymptomatic tissue, Pre_S (**FIGS. 4-5**). The splicing factors MBNL1 and MBNL2 are among the genes showing altered splicing in Pre_S samples and these changes may amplify other splicing changes to push corneal endothelial cells towards full blown FECD.

[0495] The similarity of alternative splicing changes between symptomatic FECD_REP and presymptomatic Pre_S tissue is much greater than that between Pre_S and FECD_NR samples. The data suggest that there are fundamental differences in the origins of the two forms of FECD. While their origins differ, late-stage FECD_REP and FECD_NR converge at a common set of clinical findings.

[0496] The data also suggest that splicing changes and perturbation of extracellular matrix (ECM) genes seen in FECD_REP late stage disease tissue begin to be observed long before symptoms are observed during standard clinical evaluation. The molecular trigger, mutant RNA, and early molecular changes, altered splicing and observable RNA foci, co-exist in cells that appear to have a normal phenotype. The changes in the magnitude of RNA splicing between control tissue and either Pre_S or late stage FECD_REP samples are similar. This observation suggests that the mutant RNA triggers the splicing changes in key genes independent of the progression of disease.

[0497] The finding that splicing is an early trigger has important implications for the development of agents to treat FECD. It is reasonable to expect that such agents would be most effective when administered early in disease progression prior to exuberant production of ECM with degeneration of the corneal endothelium and activation of the immune system. During drug development it should be possible to monitor the changes in alternative splicing and expression of ECM biomarkers caused by expression of the mutant trinucleotide repeat and rank drug candidates by their ability to return splicing to a more normal state – agents that reverse the splicing defect would be promising development candidates. Monitoring splicing of key genes would offer a rapid and definitive assay for screening compounds.

[0498] Some individuals without previously noted guttae who possessed the expanded repeat but developed "non-FECD corneal edema" do not show changes in alternative splicing. These results might appear to be in conflict with our observation that all CUG expanded repeat individuals exhibited substantial changes in alternative splicing, including many shared between Pre_S and FECD_REP individuals (**FIG. 4**). We note that the expanded repeat positive individuals with corneal decompensation without findings of FECD were between 67 and 83 years old, much older than any individual in our Pre_S cohort. It is possible that these individuals possessed protective mutations that might prevent splicing changes and block the molecular events leading to symptomatic FECD.

[0499] **The fibrosis pathway is activated in Pre_S tissue**

[0500] In the clinic, late stage FECD is a disease of cellular degeneration and aberrant extracellular matrix deposition (**FIG. 10**). Previous studies of FECD_REP tissue have supported activation of the fibrosis pathway as a primary cause for late stage disease pathology. We confirmed fibrosis as the highest ranked canonical pathway in both late stage FECD_REP and FECD_NR (**FIG. 8A**). The fibrosis pathway is also activated in Pre_S tissue (**FIGS. 8A-B**). These results demonstrate that changes in splicing, changes in gene expression, and changes in a key disease pathway begin years before symptoms are observed.

[0501] Among the top ten genes in pre-symptomatic tissue versus control tissue are cochlin (*COCH*) and fibronectin (*FN1*) with >16 and >32 fold change increases respectively (**FIG. 6C**). Cochlin is a secretory extracellular matrix protein originally identified in the cochlear cells of the inner ear. *COCH* is also expressed by the endothelial cells the trabecular meshwork of subjects with primary open-angle

glaucoma (POAG), another common age-related degenerative disorder. There appears to be a convergence of two age-related disorders of the anterior segment of the eye mediated by *COCH*. Primary open-angle glaucoma may be more prevalent in patients with advanced FECD. Primary open angle glaucoma is also a disease mediated by transforming growth factor-β which increases aqueous humor outflow resistance by dysregulation of ECM genes in the endothelial cells lining the trabecular meshwork.

[0502] **Late stage FECD tissue is characterized by changes in immune cell-related and mitochondrial dysfunction pathways**

[0503] Both FECD_REP and FECD_NR tissues show activation of genes related to immune system required for helper T cell activation, signaling, and neuroinflammation (**FIGS. 8A-C, 15C-E, 10**). In both groups, we detected a 2000-fold increase in *CD86* and marked upregulation of major histocompatibility genes (MHC) required by antigen presenting cells to activate helper T cells. This gene expression data along with the observation of cells with a dendritic morphology and positive for the hematopoietic marker CD45 in the endothelial tissue keratoplasty specimens of patients suggest an important role for antigen presenting cells in late-stage disease in both forms of FECD.

[0504] The mitochondrial dysfunction pathway is activated in FECD_REP tissue with the expression of over twenty genes changed, little change was seen in FECD_NR tissue (**FIG. 8D**).

[0505] **Conclusion**

[0506] FECD has many advantages as a model for understanding the origins of trinucleotide repeat disease because pre-symptomatic tissue is relatively accessible. Examination of Pre_S tissue reveals changes in gene expression that preview the more extensive changes in late stage disease. In particular, there is early activation of key genes associated with the fibrosis pathway, the pathway that defines the primary phenotype observe during advanced disease. Splicing patterns and levels of expression for key genes change decades prior to observation of the clinical manifestations of FECD_REP. Surprisingly, many changes in alternative splicing are similar in magnitude in Pre_S and advanced stage FECD_REP tissue. Many altered alternative splicing changes are shared with myotonic dystrophy, another disease caused by expanded CUG trinucleotide repeats, and it is possible that our findings will

also be applicable to the genesis and temporal progression of other trinucleotide repeat diseases.

[0507] **Example 9**

[0508] This example describes methods for example 10.

[0509] Cell culture, qPCR and western blot

[0510] FECD(F35T) or control(HCN19) corneal endothelial cell lines were cultured Cells were grown in modified Eagle's minimal essential media (OptiMEM) (ThermoFisher) supplemented with 8% fetal bovine serum, 5 ng/mL human epidermal growth factor (ThermoFisher), 20 ng/mL nerve growth factor (Fisher Scientific), 100 µg/mL bovine pituitary extract (ThermoFisher), 20 µg/mL ascorbic acid (Sigma-Aldrich), 200 mg/L calcium chloride (Sigma-Aldrich), 0.08% chondroitin sulfate (Sigma-Aldrich), 50 µg/mL gentamicin (ThermoFisher), and antibiotic/antimycotic solution (diluted 1/100) (Sigma-Aldrich). Cultures were incubated at 37°C in 5% CO2 and passed when confluent.

[0511] Endothelial cells were seeded in 6-well plate at 50% confluence. At the next day, TGFβ was added into the wells at indicated concentrations. Cells were harvest after 24 hr using TRIzol agent (Sigma). The *COCH* mRNA levels were analyzed by qPCR. Primers for *COCH* are: F: GATGGGCAGTCCTATGATGATG (SEQ ID NO:13); R: GCATGAGACTCCTTCGGTTTAG (SEQ ID NO:14).

[0512] F35T or HCN19 cells were seeded in 6-well plate at 90% confluence. At the next day, culture media was replaced with OptiMEM. After one or two days, the media was collected for western blot. Equal amount of total proteins was loaded and separated using 4~20% acrylamide pre-cast gels (Bio-Rad). Monoclonal rat cochlin antibody (Millipore, MABF267) was used for detection of cochlin protein.

[0513] ELISA assay

[0514] ELISA assay was performed using DuoSet ELISA kit (R&D Systems) according to the manufacture's protocol. In brief, 96-well plate was coated with anti-cochlin capture antibody overnight. Then blotted with Reagent Diluent. 7 Cochlin standard solutions, which was prepared by 2-fold serial dilution in PBS, were added into the wells. 10-15 uL of AH samples were also added into wells, then filled with PBS to 200 uL total volumes. After incubation for 2 hrs, anti-cochlin detection antibody was added. Next, the wells were treated with Streptavidin-HRP B, Substrate Solution, and Stop Solution. The plate was read using a microplate reader set to 450 nm. All

the standards and samples were tested in duplicate. A cochlin standard curve was generated by a four-parameter logistic (4-PL) curve-fit.

[0515] Immunofluorescence for cochlin

[0516] The paraffin-embedded cornea cross sections were deparaffinated with xylene and rehydrated with 100%, 70%, 50% ethanol, and then water. The slides were blotted with 10% serum in PBS, then incubate with anti-cochlin antibody (Millipore, MABF267; 1:50 dilution) overnight. After PBS wash, the slides were incubated with secondary antibody: Alexa Fluor 488 Goat Anti-rat IgG (H+L) Antibody (Invitrogen A11008), diluted 1:200 in 1% NGS in PBS for 1hr at room temperature. After PBS wash and DAPI staining, the slides were imaged at 20X or 60X magnification using a Widefield Deltavision microscope. Images were processed using ImageJ.

[0517] **Example 10**

[0518] **Cochlin**

[0519] Cochlin is a secretory extracellular matrix protein originally identified in the cochlear cells of the inner ear. The cochlin protein has also been detected in the trabecular meshwork (TM) of subjects with primary open-angle glaucoma (POAG), another common age-related degenerative disorder. Here, we analyzed cochlin as a diagnostic marker and therapeutic target for FECD and glaucoma.

[0520] The cochlin protein has two van Willebrand factor A (vWFA) domains on the C-terminal end, which enables its multimerization and adhesion with other ECM components, especially those containing vWFA domains such as collagen proteins. Importantly, the LCCL domain on the N-terminal end can be cleaved off to recruit innate immune cells in the inner ear in response to infection. Mutations in *COCH* result in deafness, resulting from distinct aggregative extracellular histopathology in the inner ear similar to protein aggregates seen in neurodegenerative disorders such as Huntington's disease, which we note are also reminiscent of FECD guttae histopathology.

[0521] The cellular origin of cochlin protein is unclear as evidenced by conflicting published results on the levels of cochlin mRNA levels in trabecular meshwork cells. In POAG, the cochlin deposition is thought to retard the outflow of aqueous humor through the trabecular meshwork resulting in increased intraocular pressure.

[0522] We investigated *COCH* mRNA expression in FECD samples. We found that *COCH* expression is up-regulated in corneal endothelial cells from FECD/REP, FECD/NR or Pre_Sym corneal tissues analyzed by RNA-seq (**FIG. 24A**). Higher

COCH expressions are verified in endothelial cells from FECD/REP or Pre_Sym corneal tissues by qPCR analysis (**FIG. 24B**). *COCH* expression is up-regulated in FECD endothelial cell line (**FIG. 24C**).

[0523] **FIGS. 25A-B** show TGFβ induces up-regulation of *COCH*. (**A**) *COCH* expression is up-regulated by adding increased concentration of TGFβ in HCN19 healthy control corneal endothelial cells. (**B**) TGFβ activated *COCH* in control corneal tissue.

[0524] **FIGS. 26A-B** show cochlin is a secreted protein. (**A**) Western blot image of cochlin detected in FECD (F35T) corneal endothelial cell culture media. HCN19, healthy control endothelial cell line. (**B**) The full length cochlin band is confirmed by siRNA knocking down in F35T culture media. si173, anti-cochlin siRNA; siCM, non-complementary control siRNA.

[0525] **FIG. 27** shows secreted cochlin proteins were detected in FECD patient aqueous humor by ELISA assay.

[0526] **FIGS. 28A-B** show cochlin deposits in FECD patient corneal tissue by immunofluorescence. (**A**) Cochlin may deposit in Descemet's membrane of FECD patient cornea tissue. (**B**) Cochlin deposits in trabecular meshwork of FECD donor cornea samples. Cross sections 4056-19-4596, 4056-19-4540 are FECD samples without repeat expansion; 4056-19-4463 is considered pre-symptomatic, which has no guttae, but with expanded CTG repeat (CTG repeat number: 18,73).

[0527] Therefore, an embodiment provides methods of detecting glaucoma in a subject comprising detecting an increase in expression of *COCH* in a corneal endothelial sample obtained from the subject. The subject can be treated with one or more therapeutic agents that decrease the amount of expression of *COCH*, prescription eyedrops, oral medications, laser trabeculoplasty, trabeculectomy, drainage tubes, or combinations thereof. Therapeutic agents can be, for example, small molecule inhibitors, oligonucleotides, siRNAs, antibodies, RNAi, shRNA, miRNA, and CRISPR-Cas system, zinc finger nucleases, and TALENs. The therapeutic agents can be delivered to the anterior segment of the eye, posterior segment of the eye, corneal endothelial cells, or other cells of the anterior segment of a glaucoma patient.

CLAIMS

1. A method of detecting Fuchs' endothelial corneal dystrophy (FECD) in a subject comprising:

(a) detecting an increase of expression of one or more of *ADGRG7, FN1, KCNA1, VSIG2, CNN1, ABCB1,ABCB4, COCH, MAGED4, IGSF5,PCP4, MARVELD3, MIR5188, FRZB, ELMOD1, MSI1, HPGD, TPBG, F5, THBS2, ECEL1P1/2, CPVL,LINC02258, CD86, DLK1, FOXF2, GMNC, GPR34, IGKV3-20, IGKV6D-21, TMEM255A, CDKN2A, CLEC5A, MARCH1, GPC3, HLA-DQA1, HLA-DRA, CYBB, GRM5,NOX4, IGKC,IGKJ1,IGKJ2, C3AR1, DCX, MMP2-AS1, LYVE1, FAM198B, FCGR1B, FOLR2, FCGR3A, TNFRSF11B, PSG4, KRT7, COL4A2, CTGF, COL9A3, COL1A2, FGFR2, NOTCH2, TGFBR1, IFNGR1, TGFBR2, NOTCH1, HLA-DPB1, IL18, JAG1, CD4, SPI1, PIK3R5, ITGB2, NFATC2, HLA-DPA1, HLA-DOA, IKZF1, IL10RA, MAPK10, BCL2, COL5A2, ROR2, ACKR1, CADM3, VIPR2, ADAM33, CADM3-AS1, TSHR, DPP10, CLIC6, TMEM30B, LGR6, CST4, ICA1, ALPK2, RARRES2, MMP19, DCDC2C, CST1, ITPRIPL1, WNT3, SLC5A1, ARSJ, GREB1L, SLC16A9, EPHB6, MROH9, ENOX1, PLAC9, KIF21B, ADAMTS12, ITIH5, ANXA3, PROS1, PTPN3,* and *DCLK1*;

(b) detecting a decrease of expression of one or more of *SAA2/4, NPBWR1, GFAP, DNER, INPP5D, SYNDIG1, CSF3, SPATA18, CLEC4GP1, OVCH1, LINC01811, CLIC5, FAM107A, PNMT, CYTL1, SERPINA3/4/5, TMOD1, HMGN2P17, GPRC5B, DRD2, PSPHP1, CDH12, IL17REL, ARC, UBE2W, RNU5E-1, CXCL8, LINC00881,LINC02029, CXCL3, RNU2-63P, CXCL2, RASD1, RNU6-1208P, UTY, CD24P4, RNU6-255P,TTTY14, KDM5DP1,TTTY10, NLGN4Y, RNU1-59P, ZFY, STK40, RNU5B-1, LINC01783,RNU1-6P, RNU1-5P, EPS8L1, LUM, KDR, SOD3, IRF1, JUN, SOCS3, NFIL3, FGFR4, NFKB1, SOD2, MAOA, CYCS, SNCA, PDHA1, UQCRH, COX7B, COX5B, NDUFV1, UQCRC2, NDUFA1, CYC1, UQCRB, VDAC2, COX4I1, SDHB, COX6B1*, and *MAOB*; or

(c) detecting one or more skipped exon events as shown in Table 8

in a sample obtained from the subject.

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2. The method of claim 1, wherein the sample is corneal tissue, aqueous humor, plasma, serum, blood, tear film, trabecular meshwork, or a combination thereof.

3. The method of claim 1, further comprising treating the subject with steroidal eye drops, sodium chloride eye drops, keratoprosthesis implantation, therapeutic contacts, corneal transplant, endothelial keratoplasty, penetrating keratoplasty, prostaglandins, beta blockers, alpha-adrenergic agonists, carbonic anhydrase inhibitors, rho kinase inhibitors, miotic or cholinergic agents, or combinations thereof.

4. The method of claim 1, further comprising treating the subject with one or more therapeutic agents that decrease the amount of expression of one or more of *ADGRG7, FN1, KCNA1, VSIG2, CNN1, ABCB1,ABCB4, COCH, MAGED4, IGSF5,PCP4, MARVELD3, MIR5188, FRZB, ELMOD1, MSI1, HPGD, TPBG, F5, THBS2, ECEL1P1/2, CPVL,LINC02258, CD86, DLK1, FOXF2, GMNC, GPR34, IGKV3-20, IGKV6D-21, TMEM255A, CDKN2A, CLEC5A, MARCH1, GPC3, HLA-DQA1, HLA-DRA, CYBB, GRM5,NOX4, IGKC,IGKJ1,IGKJ2, C3AR1, DCX, MMP2-AS1, LYVE1, FAM198B, FCGR1B, FOLR2, FCGR3A, TNFRSF11B, PSG4, KRT7, COL4A2, CTGF, COL9A3, COL1A2, FGFR2, NOTCH2, TGFBR1, IFNGR1, TGFBR2, NOTCH1, HLA-DPB1, IL18, JAG1, CD4, SPI1, PIK3R5, ITGB2, NFATC2, HLA-DPA1, HLA-DOA, IKZF1, IL10RA, MAPK10, BCL2, COL5A2, ROR2, ACKR1, CADM3, VIPR2, ADAM33, CADM3-AS1, TSHR, DPP10, CLIC6, TMEM30B, LGR6, CST4, ICA1, ALPK2, RARRES2, MMP19, DCDC2C, CST1, ITPRIPL1, WNT3, SLC5A1, ARSJ, GREB1L, SLC16A9, EPHB6, MROH9, ENOX1, PLAC9, KIF21B, ADAMTS12, ITIH5, ANXA3, PROS1, PTPN3*, and *DCLK1*.

5. The method of claim 4, wherein the therapeutic agents are small molecule inhibitors, oligonucleotides, siRNAs, antibodies, RNAi, shRNA, miRNA, viral vectors, non-viral delivery, and CRISPR-Cas system, zinc finger nucleases, and TALENs.

6. The method of claim 1, further comprising treating the subject with one or more therapeutic agents that increase the amount of expression of one or more of *SAA2/4, NPBWR1, GFAP, DNER, INPP5D, SYNDIG1, CSF3, SPATA18, CLEC4GP1, OVCH1, LINC01811, CLIC5, FAM107A, PNMT, CYTL1, SERPINA3/4/5, TMOD1, HMGN2P17, GPRC5B, DRD2, PSPHP1, CDH12, IL17REL, ARC, UBE2W, RNU5E-1, CXCL8, LINC00881,LINC02029, CXCL3, RNU2-63P, CXCL2, RASD1, RNU6-1208P, UTY, CD24P4,RNU6-255P,TTTY14, KDM5DP1,TTTY10, NLGN4Y, RNU1-59P, ZFY, STK40, RNU5B-1, LINC01783,RNU1-6P, RNU1-5P, EPS8L1, LUM, KDR, SOD3, IRF1, JUN, SOCS3, NFIL3, FGFR4, NFKB1, SOD2, MAOA, CYCS, SNCA, PDHA1, UQCRH, COX7B, COX5B, NDUFV1, UQCRC2, NDUFA1, CYC1, UQCRB, VDAC2, COX4I1, SDHB, COX6B1*, and *MAOB*.

7. The method of claim 6, wherein therapeutic agents comprise gene replacement therapy, saRNA, RNAa, CRISPR-Cas system, increasing RNA transcription or translation, and cell-based therapies.

8. A method of monitoring treatment of Fuchs' endothelial corneal dystrophy (FECD) comprising:
   (a) obtaining a first sample from a subject;
   (b) detecting gene expression levels of one or more of *ADGRG7, FN1, KCNA1, VSIG2, CNN1, ABCB1,ABCB4, COCH, MAGED4, IGSF5,PCP4, MARVELD3, MIR5188, FRZB, ELMOD1, MSI1, HPGD, TPBG, F5, THBS2, ECEL1P1/2, CPVL,LINC02258, CD86, DLK1, FOXF2, GMNC, GPR34, IGKV3-20, IGKV6D-21, TMEM255A, CDKN2A, CLEC5A, MARCH1, GPC3, HLA-DQA1, HLA-DRA, CYBB, GRM5,NOX4, IGKC,IGKJ1,IGKJ2, C3AR1, DCX, MMP2-AS1, LYVE1, FAM198B, FCGR1B, FOLR2, FCGR3A, TNFRSF11B, PSG4, KRT7, COL4A2, CTGF, COL9A3, COL1A2, FGFR2, NOTCH2, TGFBR1, IFNGR1, TGFBR2, NOTCH1, HLA-DPB1, IL18, JAG1, CD4, SPI1, PIK3R5, ITGB2, NFATC2, HLA-DPA1, HLA-DOA, IKZF1, IL10RA, MAPK10, BCL2, COL5A2, ROR2, ACKR1, CADM3, VIPR2, ADAM33, CADM3-AS1, TSHR, DPP10, CLIC6, TMEM30B, LGR6, CST4, ICA1, ALPK2, RARRES2, MMP19, DCDC2C, CST1, ITPRIPL1, WNT3, SLC5A1, ARSJ, GREB1L, SLC16A9, EPHB6,*

MROH9, ENOX1, PLAC9, KIF21B, ADAMTS12, ITIH5, ANXA3, PROS1, PTPN3, DCLK1, SAA2/4, NPBWR1, GFAP, DNER, INPP5D, SYNDIG1, CSF3, SPATA18, CLEC4GP1, OVCH1, LINC01811, CLIC5, FAM107A, PNMT, CYTL1, SERPINA3/4/5, TMOD1, HMGN2P17, GPRC5B, DRD2, PSPHP1, CDH12, IL17REL, ARC, UBE2W, RNU5E-1, CXCL8, LINC00881,LINC02029, CXCL3, RNU2-63P, CXCL2, RASD1, RNU6-1208P, UTY, CD24P4,RNU6-255P,TTTY14, KDM5DP1,TTTY10, NLGN4Y, RNU1-59P, ZFY, STK40, RNU5B-1, LINC01783,RNU1-6P, RNU1-5P, EPS8L1, LUM, KDR, SOD3, IRF1, JUN, SOCS3, NFIL3, FGFR4, NFKB1, SOD2, MAOA, CYCS, SNCA, PDHA1, UQCRH, COX7B, COX5B, NDUFV1, UQCRC2, NDUFA1, CYC1, UQCRB, VDAC2, COX4I1, SDHB, COX6B1, and MAOB; or detecting one or more skipped exon events as shown in Table 8 in the first sample obtained from the subject;

(c) administering a treatment to the subject;

(d) obtaining a second sample from the subject at a later time and detecting gene expression levels or skipped exon events of (b) in the second sample; and

(e) comparing the first sample gene expression levels or skipped exon events with the second sample gene expression levels or skipped exon events.

9. The method of claim 8, wherein the first sample and second sample is corneal tissue, aqueous humor, plasma, serum, blood, tear film, trabecular meshwork, or a combination thereof.

10. The method of claim 8, wherein the treatment can comprise therapeutic agents that increase gene expression, therapeutic agents that decrease gene expression, steroidal eye drops, sodium chloride eye drops, keratoprosthesis implantation, therapeutic contacts, corneal transplant, endothelial keratoplasty, penetrating keratoplasty, prostaglandins, beta blockers, alpha-adrenergic agonists, carbonic anhydrase inhibitors, rho kinase inhibitors, miotic or cholinergic agents, or combinations thereof.

11. The method of claim 8, further comprising repeating steps (a)-(e) one, two, three, or more times.

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12. A method of monitoring progression of Fuchs' endothelial corneal dystrophy (FECD) comprising:

(a) obtaining a first sample from a subject;

(b) detecting gene expression levels of one or more of *ADGRG7, FN1, KCNA1, VSIG2, CNN1, ABCB1,ABCB4, COCH, MAGED4, IGSF5,PCP4, MARVELD3, MIR5188, FRZB, ELMOD1, MSI1, HPGD, TPBG, F5, THBS2, ECEL1P1/2, CPVL,LINC02258, CD86, DLK1, FOXF2, GMNC, GPR34, IGKV3-20, IGKV6D-21, TMEM255A, CDKN2A, CLEC5A, MARCH1, GPC3, HLA-DQA1, HLA-DRA, CYBB, GRM5,NOX4, IGKC,IGKJ1,IGKJ2, C3AR1, DCX, MMP2-AS1, LYVE1, FAM198B, FCGR1B, FOLR2, FCGR3A, TNFRSF11B, PSG4, KRT7, COL4A2, CTGF, COL9A3, COL1A2, FGFR2, NOTCH2, TGFBR1, IFNGR1, TGFBR2, NOTCH1, HLA-DPB1, IL18, JAG1, CD4, SPI1, PIK3R5, ITGB2, NFATC2, HLA-DPA1, HLA-DOA, IKZF1, IL10RA, MAPK10, BCL2, COL5A2, ROR2, ACKR1, CADM3, VIPR2, ADAM33, CADM3-AS1, TSHR, DPP10, CLIC6, TMEM30B, LGR6, CST4, ICA1, ALPK2, RARRES2, MMP19, DCDC2C, CST1, ITPRIPL1, WNT3, SLC5A1, ARSJ, GREB1L, SLC16A9, EPHB6, MROH9, ENOX1, PLAC9, KIF21B, ADAMTS12, ITIH5, ANXA3, PROS1, PTPN3, DCLK1, SAA2/4, NPBWR1, GFAP, DNER, INPP5D, SYNDIG1, CSF3, SPATA18, CLEC4GP1, OVCH1, LINC01811, CLIC5, FAM107A, PNMT, CYTL1,,SERPINA3/4/5, TMOD1, HMGN2P17, GPRC5B, DRD2, PSPHP1, CDH12, IL17REL, ARC, UBE2W, RNU5E-1, CXCL8, LINC00881,LINC02029, CXCL3, RNU2-63P, CXCL2, RASD1, RNU6-1208P, UTY, CD24P4,RNU6-255P,TTTY14, KDM5DP1,TTTY10, NLGN4Y, RNU1-59P, ZFY, STK40, RNU5B-1, LINC01783,RNU1-6P, RNU1-5P, EPS8L1, LUM, KDR, SOD3, IRF1, JUN, SOCS3, NFIL3, FGFR4, NFKB1, SOD2, MAOA, CYCS, SNCA, PDHA1, UQCRH, COX7B, COX5B, NDUFV1, UQCRC2, NDUFA1, CYC1, UQCRB, VDAC2, COX4I1, SDHB, COX6B1,* and *MAOB*; or detecting one or more skipped exon events as shown in Table 8 in the first sample obtained from the subject;

(c) obtaining a second sample from the subject at a later time and detecting gene expression levels or skipped exon events of (b) in the second sample; and

(d) comparing the first sample gene expression levels or skipped exon events with the second sample gene expression levels or skipped exon events.

13. The method of claim 12, wherein the first sample and second sample is corneal tissue, aqueous humor, plasma, serum, blood, tear film, trabecular meshwork, or a combination thereof.

14. The method of claim 12, further comprising repeating steps (a)-(d) one, two, three, or more times.

15. A method of detecting glaucoma in a subject comprising detecting an increase in expression of *COCH* in a sample obtained from the subject.

16. The method of claim 15, wherein the sample is corneal endothelial cells, corneal tissue, aqueous humor, plasma, serum, blood, tear film, trabecular meshwork, or a combination thereof.

17. The method of claim 15, further comprising treating the subject with one or more therapeutic agents that decrease *COCH* expression, prescription eyedrops, oral medications, prostaglandins, beta blockers, alpha-adrenergic agonists, carbonic anhydrase inhibitors, rho kinase inhibitors, miotic or cholinergic agents, laser trabeculoplasty, trabeculectomy, drainage tubes, minimally invasive glaucoma surgery (MIGS), peripheral iridotomy, aqueous shunts, or combinations thereof.

18. The method of claim 17, wherein the treatment is delivered to the anterior segment of the eye, posterior segment of the eye, corneal endothelial cells, or other cells of the anterior segment of an eye.

19. The method of claim 17, wherein the therapeutic agents are small molecule inhibitors, oligonucleotides, siRNAs, antibodies, RNAi, shRNA, miRNA, and CRISPR-Cas system, zinc finger nucleases, and TALENs.

20. A method of monitoring treatment of glaucoma comprising:

(a) obtaining a first sample from a subject;
(b) detecting gene expression levels of *COCH* in the first sample obtained from the subject;
(c) administering a treatment to the subject;
(d) obtaining a second sample from the subject at a later time and detecting gene expression levels of *COCH* in the second sample; and
(e) comparing the first sample gene expression levels with the second sample gene expression levels.

21. The method of claim 20, wherein the sample is corneal tissue, aqueous humor, plasma, serum, blood, tear film, trabecular meshwork, or a combination thereof.

22. The method of claim 20, wherein the treatment can comprise therapeutic agents that decrease *COCH* expression, prescription eyedrops, oral medications, prostaglandins, beta blockers, alpha-adrenergic agonists, carbonic anhydrase inhibitors, rho kinase inhibitors, miotic or cholinergic agents, laser trabeculoplasty, trabeculectomy, drainage tubes, minimally invasive glaucoma surgery (MIGS), peripheral iridotomy, aqueous shunts, or combinations thereof.

23. The method of claim 20, wherein the therapeutic agents are small molecule inhibitors, oligonucleotides, siRNAs, antibodies, RNAi, shRNA, miRNA, viral vectors, non-viral delivery, CRISPR-Cas system, zinc finger nucleases, and TALENs.

24. The method of claim 20, further comprising repeating steps (a)-(e) one, two, three, or more times.

25. A method of monitoring progression of glaucoma comprising:
(a) obtaining a first sample from a subject;
(b) detecting gene expression levels of *COCH* in the first sample obtained from the subject;

(c) obtaining a second sample from the subject at a later time and detecting gene expression levels of *COCH* in the second sample; and

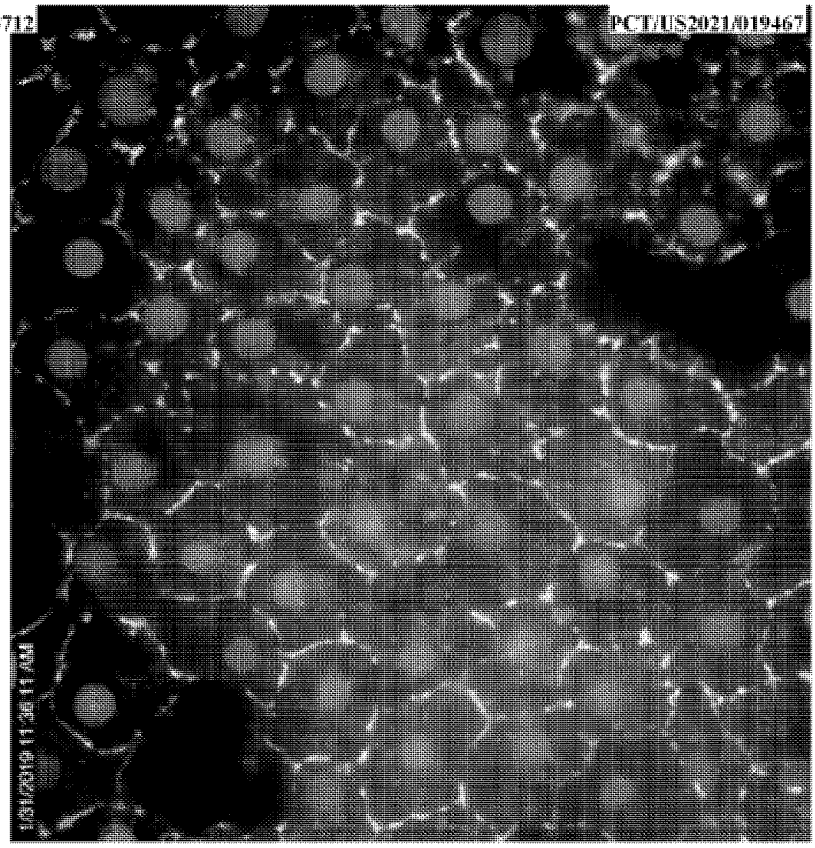
(d) comparing the first sample gene expression levels with the second sample gene expression levels.

26. The method of claim 25, wherein the sample is corneal tissue, aqueous humor, plasma, serum, blood, tear film, trabecular meshwork, or a combination thereof.

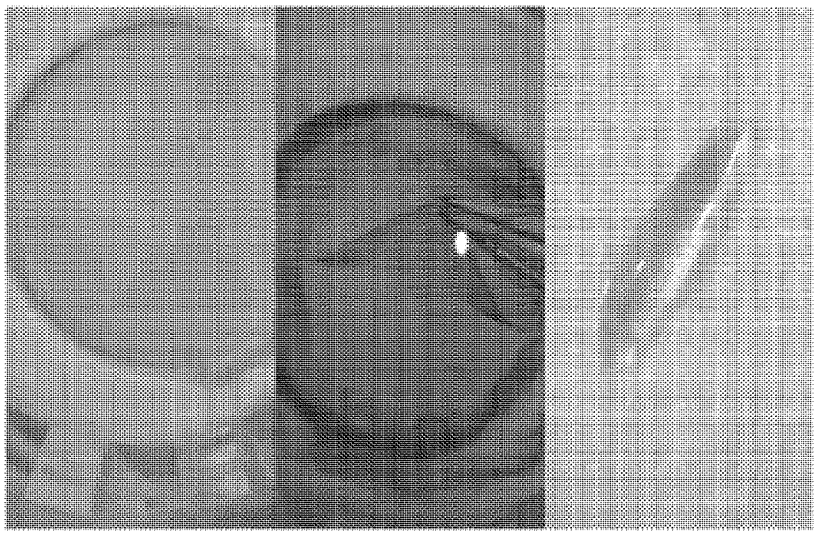
27. The method of claim 25, further comprising repeating steps (a)-(d) one, two, three, or more times.

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FIG. 1



D



A B C

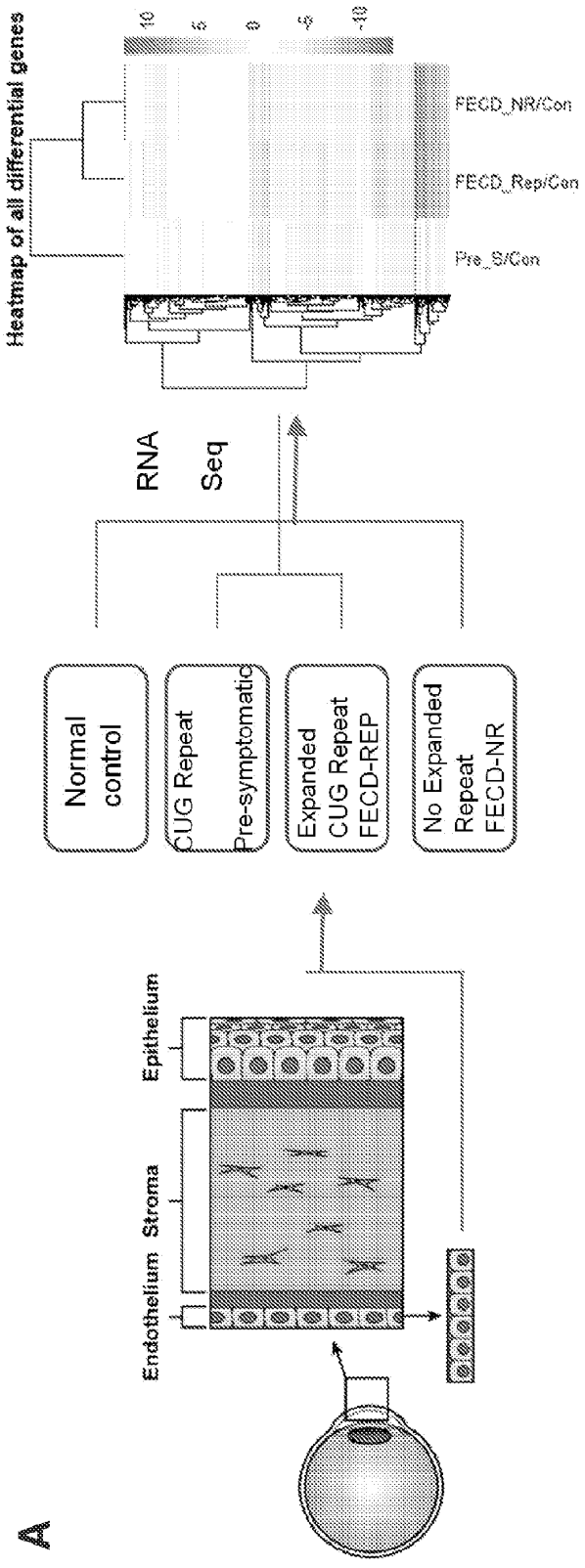

A
Epithelium
Stroma
Endothelium
Normal control
CUG Repeat Pre-symptomatic
Expanded CUG Repeat FECD-REP
No Expanded Repeat FECD-NR
RNA Seq
Heatmap of all differential genes
10
5
0
-5
-10
FECD_NR/Con
FECD_Rep/Con
Pre_S/Con

FIG. 2

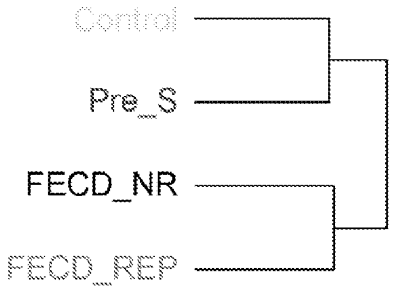
FIG. 2 Cont.

B

Sample_ID	Gender	Age	CTG18.1	RIN
Control_0	F	74	16, 39	7.4
Control_1	F	72	16, 25	7.6
Control_2	M	51	16, 17	8
Control_3	M	68	18, 25	5.2
Control_4	M	68	18,25	7.4
Control_5	M	71	12, 18	5.6
Control_6	F	61	13,19	5.2
Control_7	M	74	13,18	6.4
Control_8	F	43	12,18	6.3
Pre_S_0	M	51	13, 84	7.6
Pre_S_1	M	57	15, 77	5.4
Pre_S_2	M	41	17, 86	6.4
Pre_S_3	M	41	12, >100	6
Pre_S_4	F	53	12, >100	7.8
Pre_S_5	F	38	12, 66	6.9
FECD_REP_0	F	67	14,87	6.3
FECD_REP_1	M	66	15, 150	5.8
FECD_REP_2	F	68	15, 77	8.0
FECD_REP_3	F	58	16, >100	7.3
FECD_REP_4	F	69	15, >100	7
FECD_REP_5	F	71	19, 130	6.4
FECD-NR_0	F	71	15, 18	6.5
FECD-NR_1	F	72	12, 26	5.6
FECD-NR_2	F	61	12, 38	6.2
FECD-NR_3	F	71	15, 18	6.6

FIG. 2 Cont.

C


0 200 400
Control
Pre_S
FECD_NR
FECD_REP

D

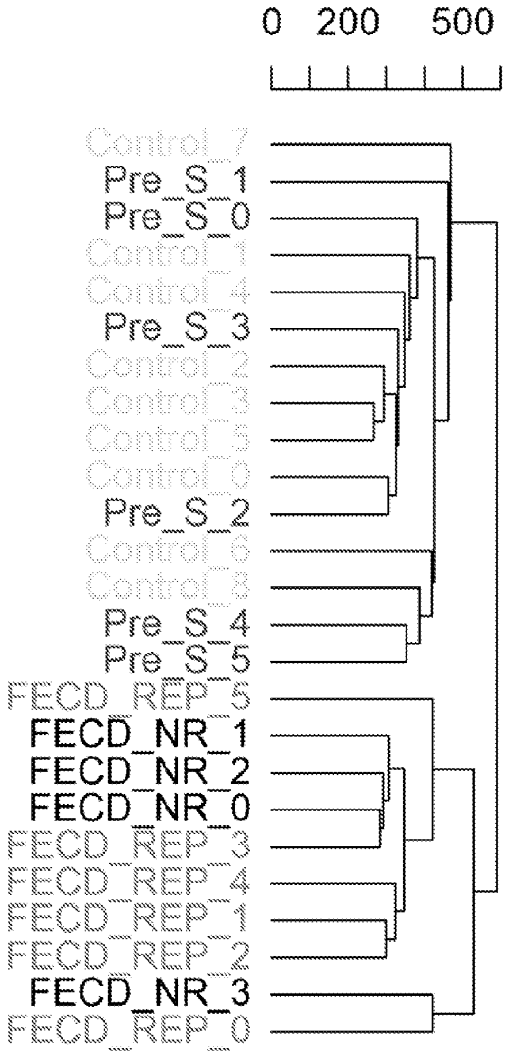

0 200 500
Control_7
Pre_S_1
Pre_S_0
Control_1
Control_4
Pre_S_3
Control_2
Control_3
Control_5
Control_0
Pre_S_2
Control_6
Control_8
Pre_S_4
Pre_S_5
FECD_REP_5
FECD_NR_1
FECD_NR_2
FECD_NR_0
FECD_REP_3
FECD_REP_4
FECD_REP_1
FECD_REP_2
FECD_NR_3
FECD_REP_0

FIG. 3

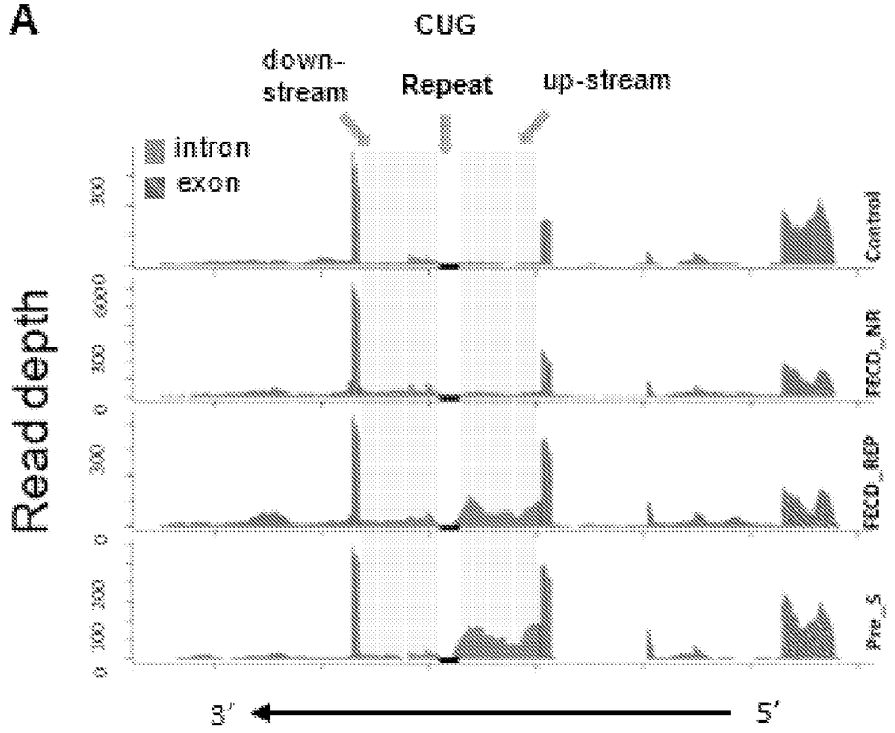

A
CUG
down-stream
Repeat
up-stream
intron
exon
Read depth
Control
RECO_NR
RECO_RIP
Pre_S
3'
5'

FIG. 3 Cont.

B

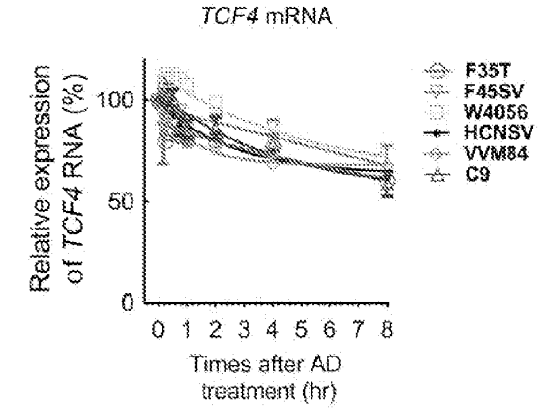
Cell line	Phenotype	*TCF4* CUG repeat	CUG RNA foci	RNA half life	
				mRNA	Intron 2 upstream	Intron 2 downstream
F35T	**FECD** endothelium	1500	Yes	> 8 hr	*~3hr*	30 min
F45SV	**FECD** endothelium	1500	Yes	> 8 hr	*~4hr*	30 min
W4056	Control endothelium	<25	No	> 8 hr	**10 min**	20 min
HCNSV	Control endothelium	<25	No	> 8 hr	**15 min**	20 min
WM84	**FECD** skin fibroblast	1000	No	> 8 hr	**10 min**	10 min
C9	Control skin fibroblast	<25	No	> 8 hr	**10 min**	15 min

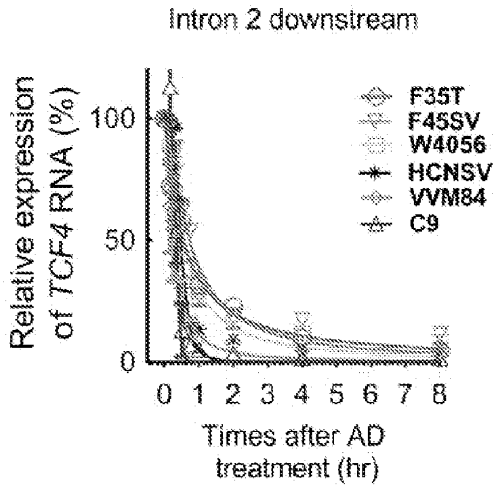
*Longest repeat number

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FIG. 3 Cont.

C


TCF4 mRNA
Relative expression of TCF4 RNA (%)
100
50
0
0 1 2 3 4 5 6 7 8
Times after AD treatment (hr)
F35T
F45SV
W4056
HCNSV
VVM84
C9


Intron 2 downstream
Relative expression of TCF4 RNA (%)
100
50
0
0 1 2 3 4 5 6 7 8
Times after AD treatment (hr)
F35T
F45SV
W4056
HCNSV
VVM84
C9

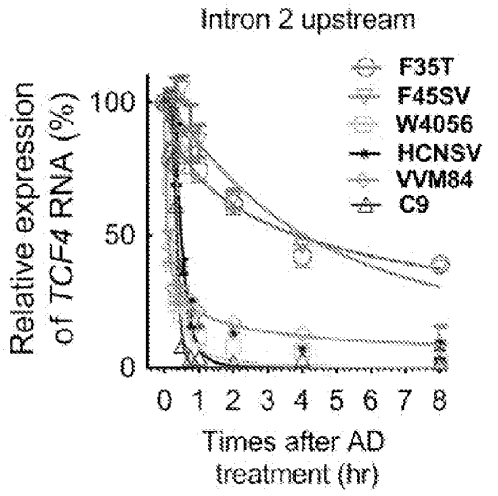

Intron 2 upstream
Relative expression of TCF4 RNA (%)
100
50
0
0 1 2 3 4 5 6 7 8
Times after AD treatment (hr)
F35T
F45SV
W4056
HCNSV
VVM84
C9

FIG. 4

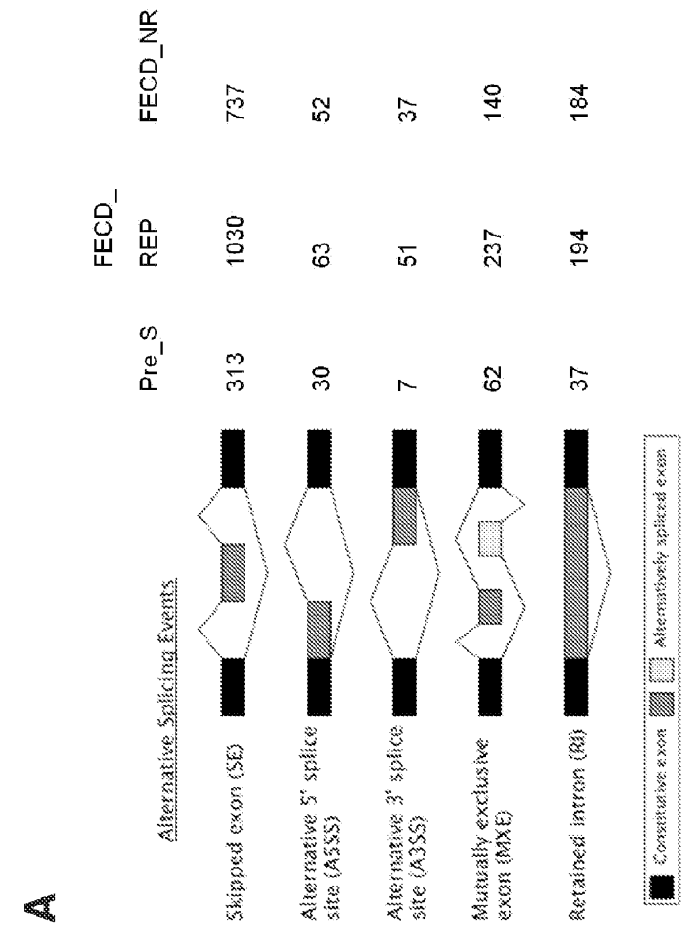
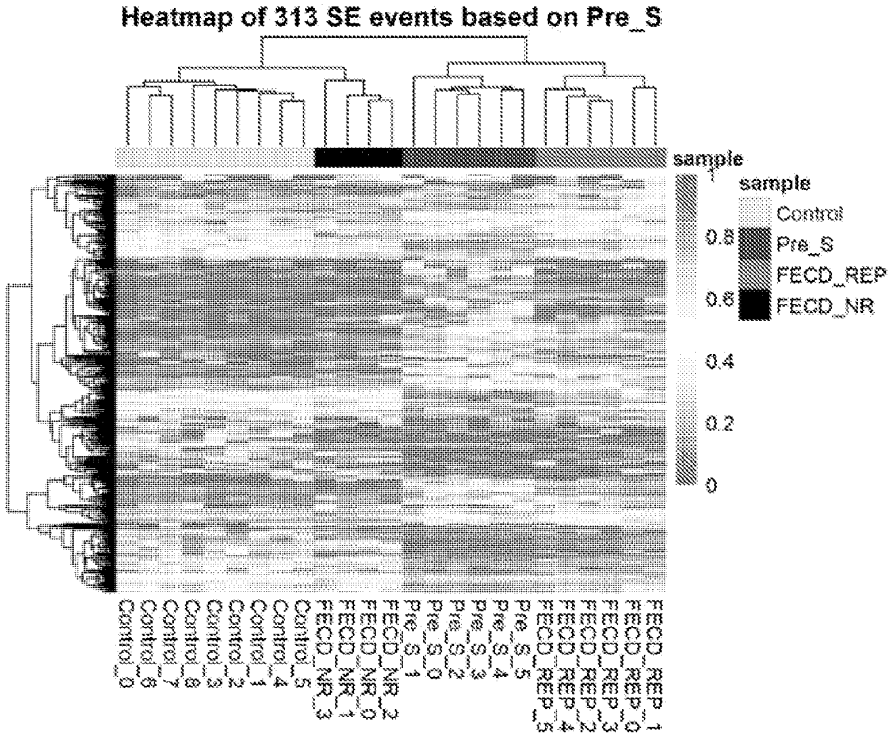

A
Alternative Splicing Events
Pre_S
FECD_REP
FECD_NR
Skipped exon (SE)
313
1030
737
Alternative 5' splice site (A5SS)
30
63
52
Alternative 3' splice site (A3SS)
7
51
37
Mutually exclusive exon (MXE)
62
237
140
Retained intron (RI)
37
194
184
Constitutive exon
Alternatively spliced exon
B
Pre_S vs. Control (313)
FECD_REP vs. Control (1030)
FECD_NR vs. Control (737)
167
118
14
456
14
442
267

FIG. 4 Cont.

C


Heatmap of 313 SE events based on Pre_S
sample
sample
Control
Pre_S
FECD_REP
FECD_NR
1
0.8
0.6
0.4
0.2
0
Control_0
Control_6
Control_7
Control_8
Control_3
Control_2
Control_1
Control_4
Control_5
FECD_NR_3
FECD_NR_1
FECD_NR_0
FECD_NR_2
Pre_S_1
Pre_S_0
Pre_S_2
Pre_S_3
Pre_S_4
Pre_S_5
FECD_REP_5
FECD_REP_4
FECD_REP_2
FECD_REP_3
FECD_REP_0
FECD_REP_1

D

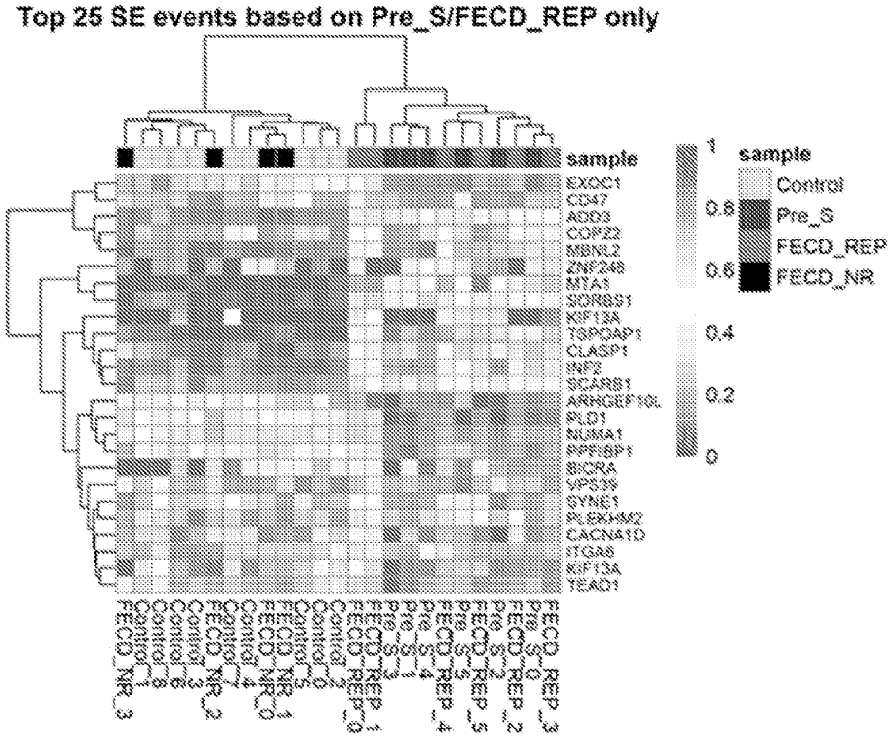

Top 25 SE events based on Pre_S/FECD_REP only
sample
sample
Control
Pre_S
FECD_REP
FECD_NR
1
0.8
0.6
0.4
0.2
0
EXOC1
CD47
ADD3
COPZ2
MBNL2
ZNF346
MTA1
SORBS1
KIF13A
TSPOAP1
CLASP1
RIF1
SCARB1
ARHGEF10L
PLD1
NUMA1
RPTOR
BICRA
VPS39
GYNE1
PLEKHM2
CACNA1D
ITGA6
KIF13A
TEAD1
FECD_NR_3
Control_1
Control_8
Control_3
Control_2
FECD_NR_2
Control_4
FECD_NR_1
FECD_NR_0
Control_5
Control_0
FECD_REP_1
FECD_REP_0
Pre_S_1
Pre_S_0
Pre_S_4
FECD_REP_4
Pre_S_2
FECD_REP_5
Pre_S_3
FECD_REP_2
Pre_S_5
FECD_REP_3

FIG. 4 Cont.

E

Gene name	Basic function	Gene name	Basic function
EXOC1	Exocyst complex	*SCARB1*	Scavenger receptor
CD47	Cell signalling/adhesion	*ARHGEF10L*	Nucleotide exchange factor
ADD3	Assembly of the spectrin-actin network	*PLD1*	Hydrolysis of phosphatidylcholine
COPZ2	Coatamer protein complex	*MLMA1*	Mitototic apparatus
MBML2	Splicing regulator	*PPFIBP1*	Liprin family
ZNF248	Transcription regulator	*BICRA*	Chromatin remodeling
MTA1	Metastasis associate	*VPS39*	Endosome fusion
SORBS1	SH3 domain containing	*SYNE1*	Nuclear envelope
KIF13A	Kinesin family	*PLEKHM2*	Microtubule localization
TSPOAP1	Neurotransmitter Release Cycle	*CACNA1D*	Calcium channel subunit
CLASP1	Cytoplasmic linker	*ITGA6*	Integrin subunit
IMF2	Actin polymerization	*TEAD1*	Transcription factor

FIG. 5

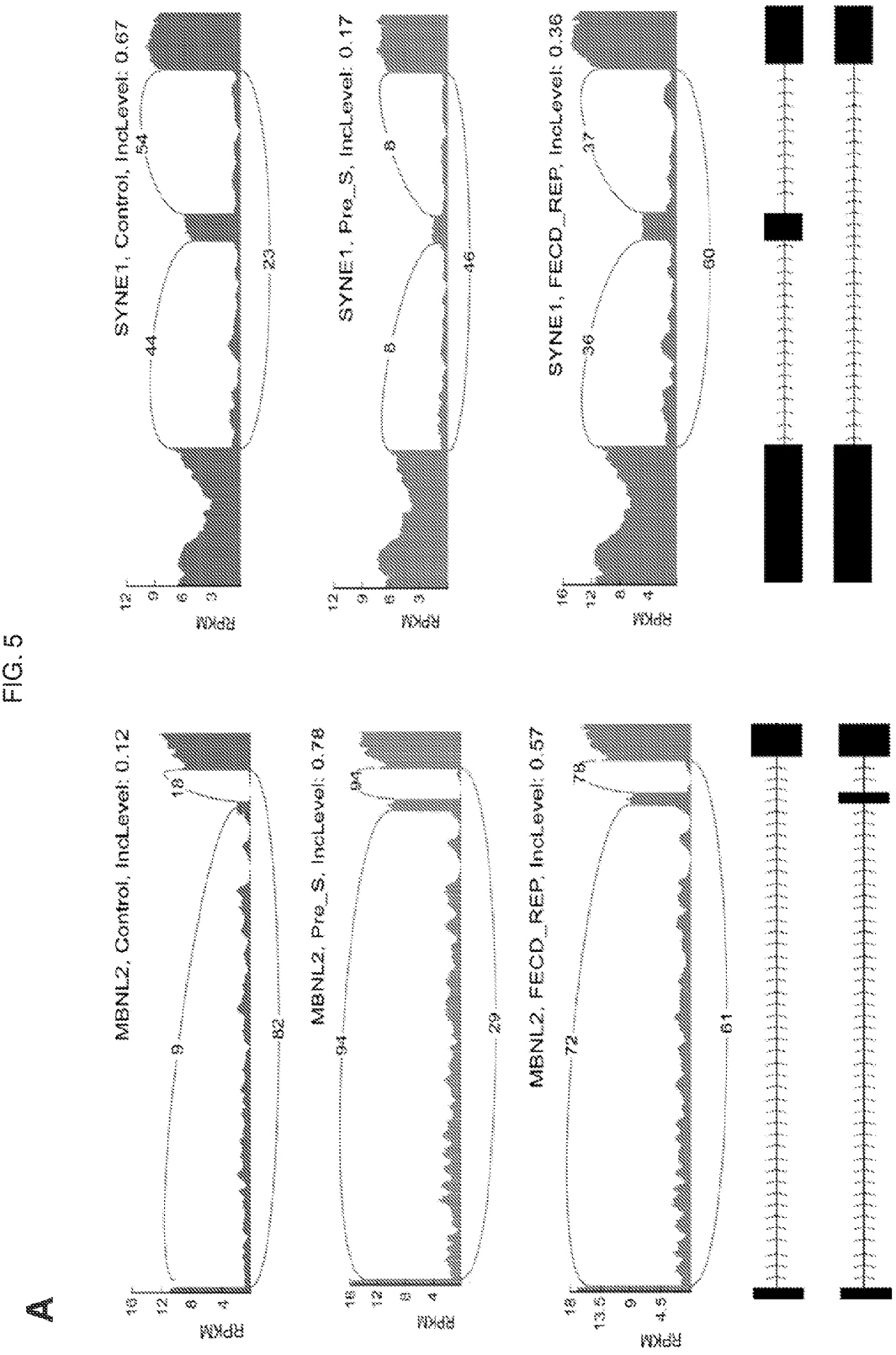

A
MBNL2, Control, IncLevel: 0.12
MBNL2, Pre_S, IncLevel: 0.78
MBNL2, FECD_REP, IncLevel: 0.57
SYNE1, Control, IncLevel: 0.67
SYNE1, Pre_S, IncLevel: 0.17
SYNE1, FECD_REP, IncLevel: 0.36
RPKM

FIG. 5 Cont.

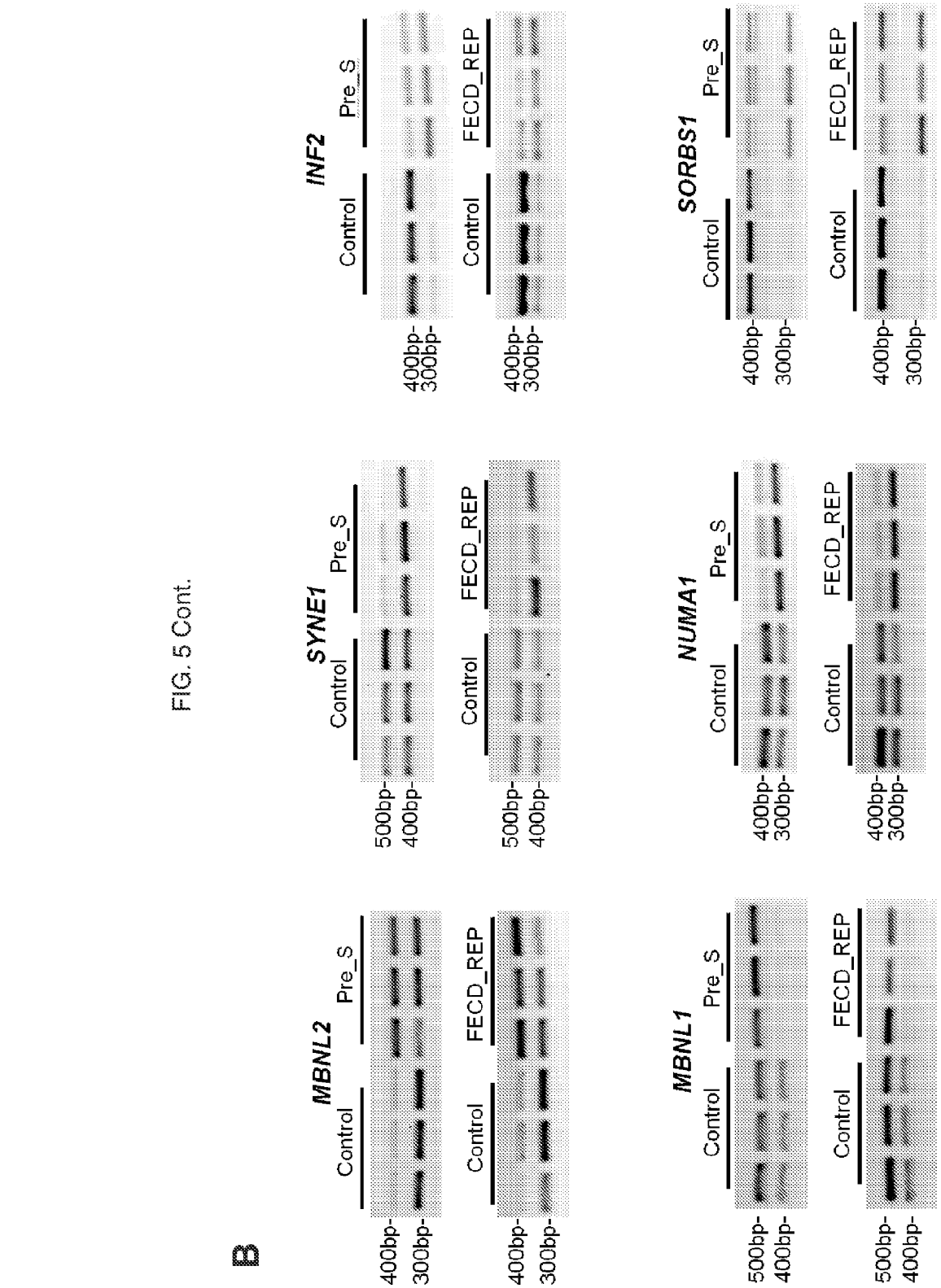
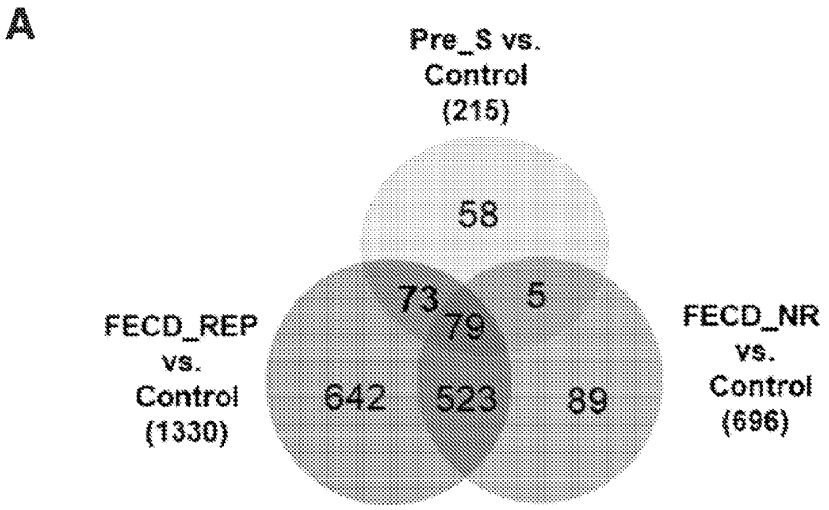

B
MBNL2
Control
Pre_S
FECD_REP
400bp-
300bp-
SYNE1
500bp-
400bp-
INF2
SORBS1
NUMA1
MBNL1

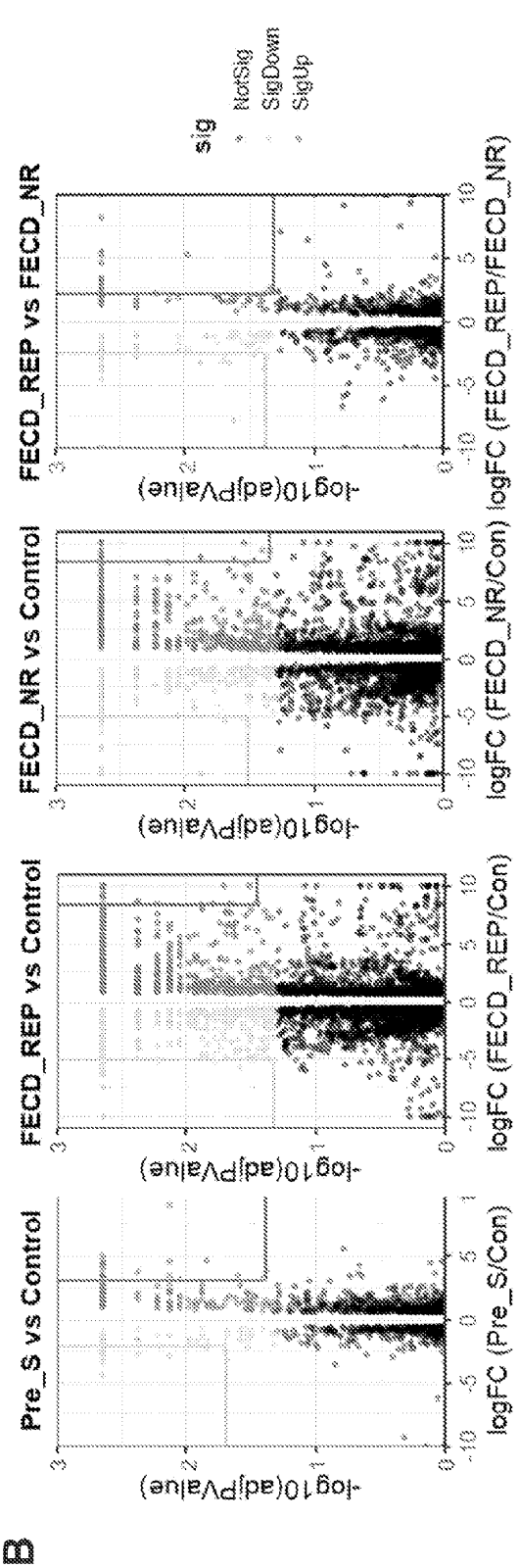
FIG. 6



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FIG. 6 Cont.

B



C

Gene	Log2FC	Gene	Log2FC	Gene	Log2FC	Gene	Log2FC
ADGRG7	9.08357	*MIR5188*	3.74264	*SAA2/4*	-4.3858	*AC018359.1,AC120023.1,LINC01811*	-2.58298
FN1	5.08031	*FRZB*	3.68431	*NPBWR1*	-3.34526	*CLIC5*	-2.56201
KCNA1	4.69413	*ELMOD1*	3.44356	*GFAP*	-3.14885	*FAM107A*	-2.52755
VSIG2	4.66212	*MSI1*	3.41382	*DNER*	-3.11011	*PNMT*	-2.51727
CNN1	4.55628	*HPGD*	3.37914	*INPP5D*	-2.94229	*CYTL1*	-2.31167
ABCB1,ABCB4	4.38883	*TPBG*	3.37536	*SYNDIG1*	-2.85106	*AL049839.2,SERPINA3/4/5*	-2.27301
COCH	4.34706	*F5*	3.32153	*CSF3*	-2.81788	*TMOD1*	-2.26172
MAGED4	4.23649	*THBS2*	3.31266	*SPATA18*	-2.8052	*HMGN2P17*	-2.20506
IGSF5,PCP4	4.14065	*AC068134.1 ECEL1P1/2*	3.18144	*CLEC4GP1*	-2.78093	*GPRC5B*	-2.11762
MARVELD3	3.78917	*CPVL*	3.14501	*OVCH1*	-2.83921	*DRD2*	-2.0636

FIG. 7

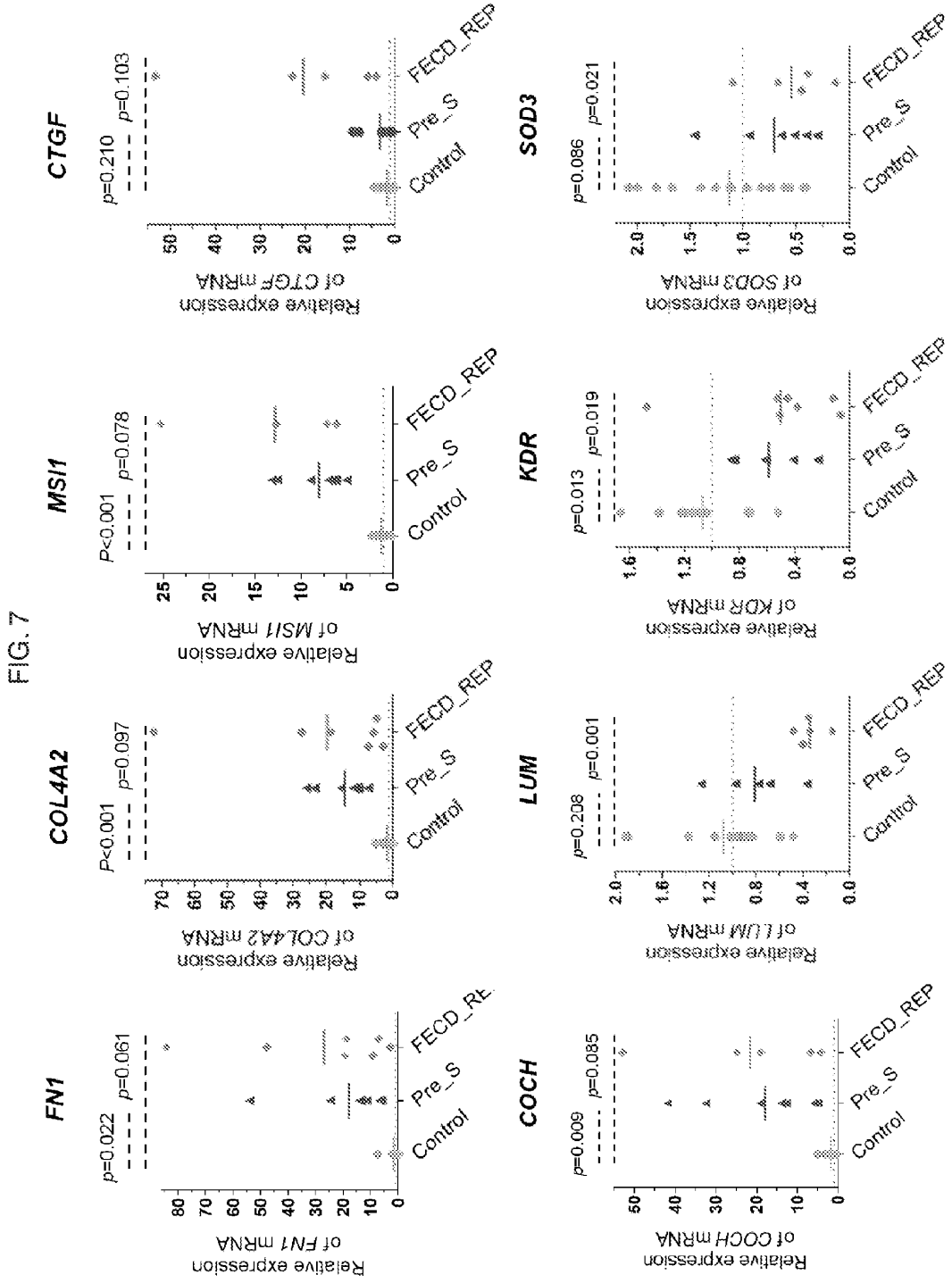
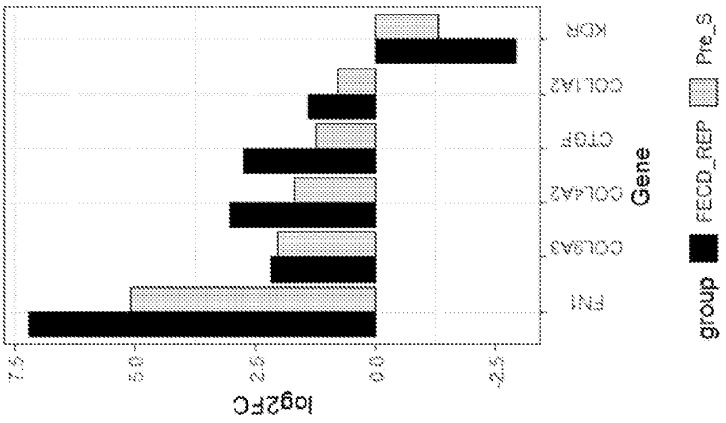

FN1
p=0.022
p=0.061
Relative expression of FN1 mRNA
FECD_RE
Pre_S
Control
COL4A2
P<0.001
p=0.097
Relative expression of COL4A2 mRNA
FECD_REP
Pre_S
Control
MSI1
P<0.001
p=0.078
Relative expression of MSI1 mRNA
FECD_REP
Pre_S
Control
CTGF
p=0.210
p=0.103
Relative expression of CTGF mRNA
FECD_REP
Pre_S
Control
COCH
p=0.009
p=0.085
Relative expression of COCH mRNA
FECD_REP
Pre_S
Control
LUM
p=0.208
p=0.001
Relative expression of LUM mRNA
FECD_REP
Pre_S
Control
KDR
p=0.013
p=0.019
Relative expression of KDR mRNA
FECD_REP
Pre_S
Control
SOD3
p=0.086
p=0.021
Relative expression of SOD3 mRNA
FECD_REP
Pre_S
Control

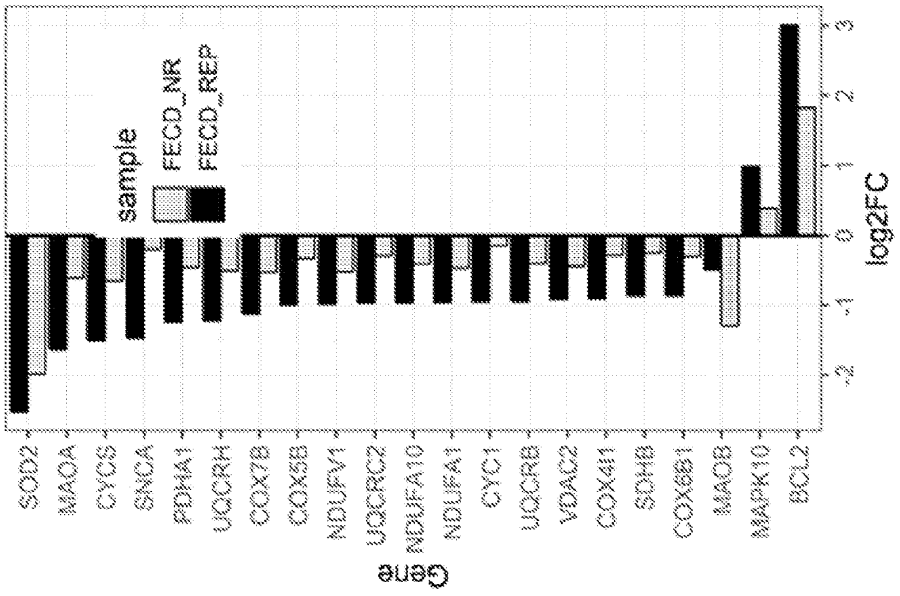
FIG. 8

A

Canonical Pathways	FECD_NR	FECD_REP	Pre_S
Hepatic Fibrosis	20.81	16.30	3.03
Neuroinflammation Signaling	5.72	7.05	0.00
GP6 Signaling	5.71	6.78	2.27
IL-8 Signaling	4.39	6.62	0.98
Th1 and Th2 Activation	7.83	6.33	0.00
Osteoblasts/Osteoclasts/ Chondrocytes in Rheumatoid Arthritis	2.94	6.23	0.88
Axonal Guidance Signaling	3.62	5.80	1.24
Macrophages/Fibroblasts/Endothelial Cells in Rheumatoid Arthritis	3.95	5.69	0.87
Apelin Liver Signaling	4.40	5.64	1.71
Th1	5.63	5.46	0.00
NFAT Regulation/Immune Response	7.47	5.41	0.00
Th2	6.43	5.29	0.00
Osteoarthritis	6.24	5.26	2.70
CD28 Signaling in T Helper Cells	5.06	5.07	0.00
STAT3 Pathway	3.15	5.02	0.00
Mitochondrial Dysfunction	0.00	4.96	0.38
Dendritic Cell Maturation	3.79	4.93	1.09
PTEN Signaling	1.81	4.91	1.06
Inhibition of Angiogenesis by TSP1	2.79	4.56	0.61
Inflammasome	2.83	4.53	0.00
PKCθ Signaling in T Lymphocytes	4.49	4.51	0.00
Molecular Mechanisms of Cancer	4.80	4.39	0.37
IGF-1 Signaling	5.80	4.30	1.80
Phagosome Formation	2.00	4.26	1.53
T Cell Exhaustion Signaling	2.01	4.22	0.00

B





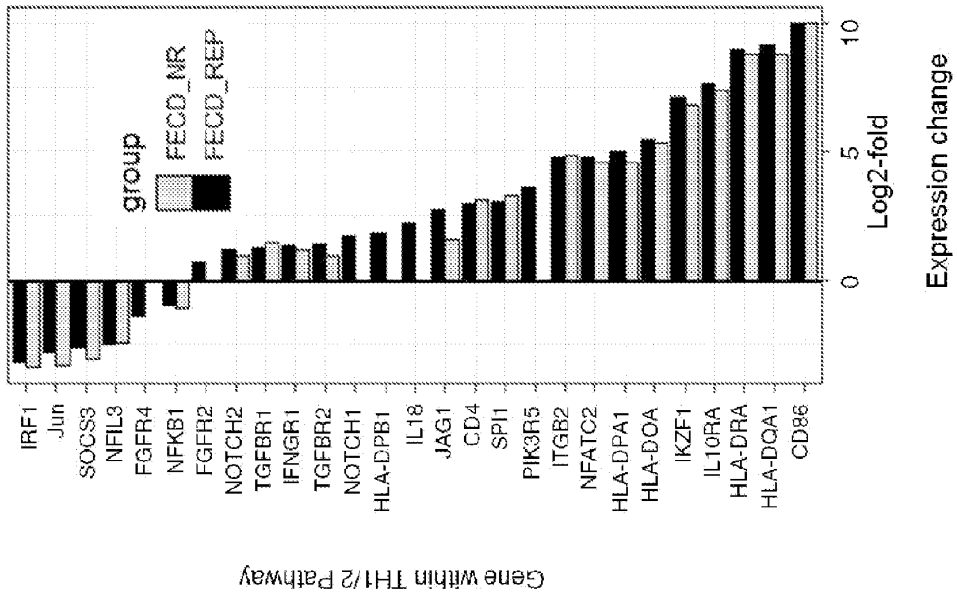


FIG. 8 Cont.

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FIG. 9

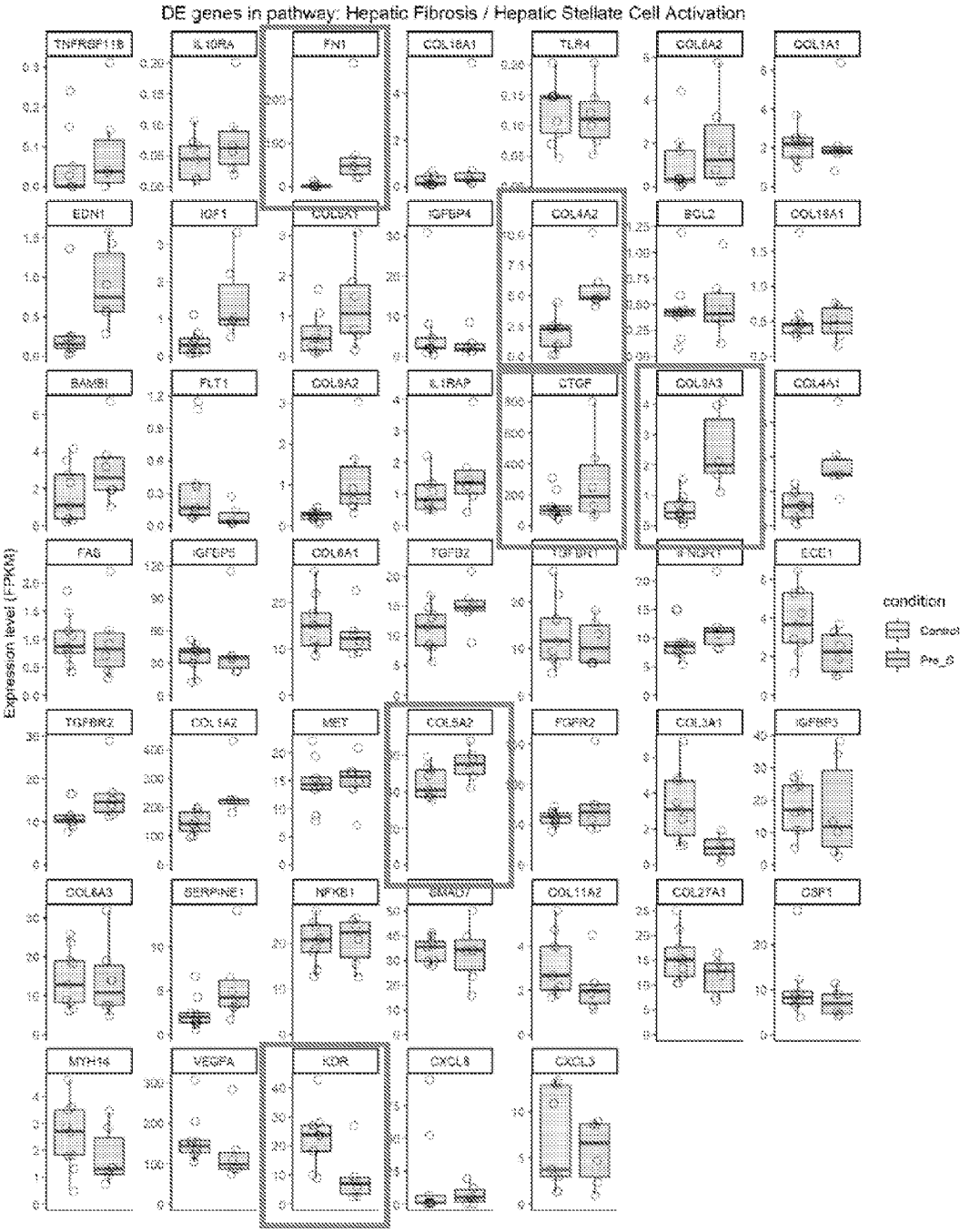

DE genes in pathway: Hepatic Fibrosis / Hepatic Stellate Cell Activation
Expression level (FPKM)
condition
Control
Pre_D
TNFRSF11B
IL10RA
FN1
COL18A1
TLR4
COL6A2
COL1A1
EDN1
IGF1
COL3A1
IGFBP4
COL4A2
BCL2
COL19A1
BAMBI
FLT1
COL3A2
IL1RAP
CTGF
COL3A3
COL4A1
FAS
IGFBP5
COL6A1
TGFB2
ECE1
TGFBR2
COL1A2
MET
COL5A2
FGFR2
COL3A1
IGFBP3
COL6A3
SERPINE1
NFKB1
GRAO1
COL11A2
COL27A1
CSF1
MYH11
VEGFA
KDR
CXCL8
CXCL3

FIG. 10

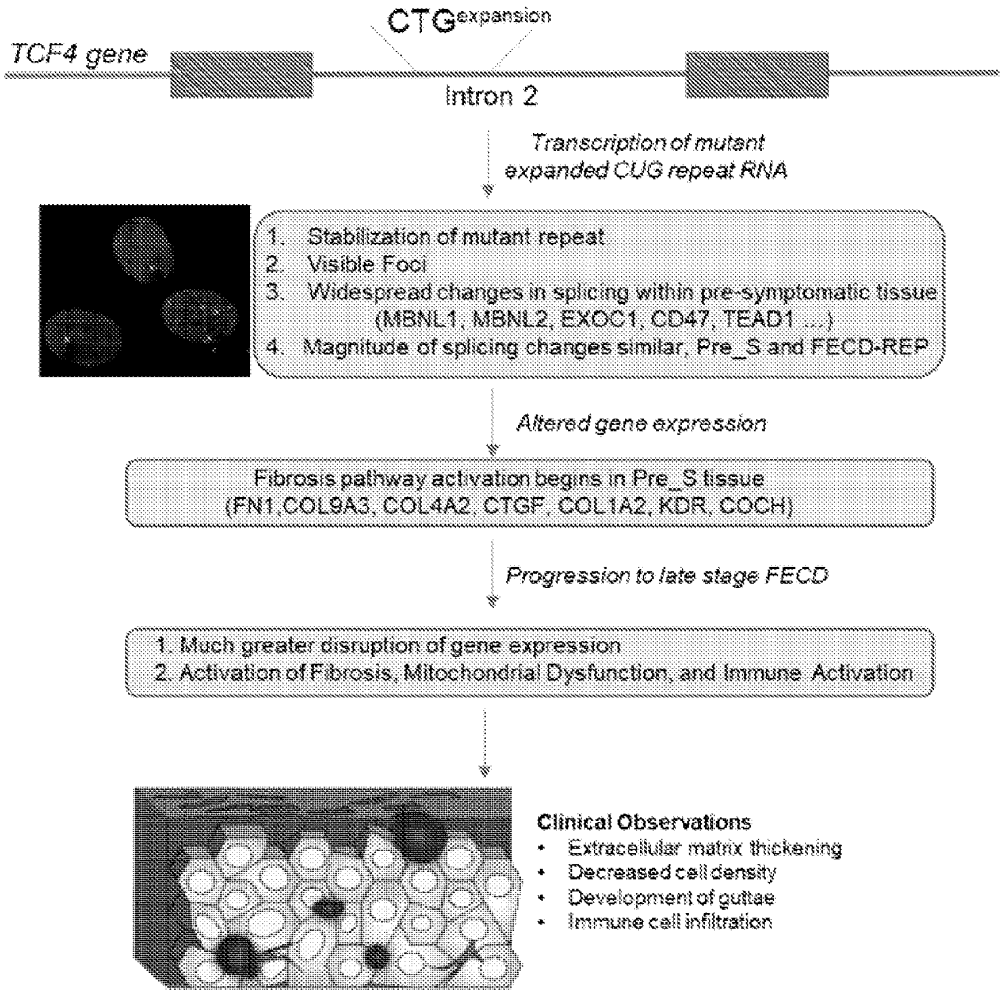
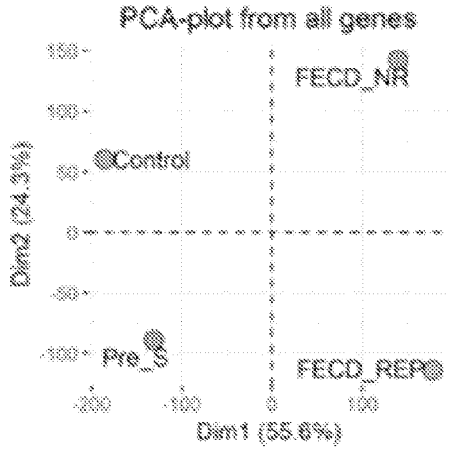

TCF4 gene
CTG expansion
Intron 2
Transcription of mutant expanded CUG repeat RNA
1. Stabilization of mutant repeat
2. Visible Foci
3. Widespread changes in splicing within pre-symptomatic tissue (MBNL1, MBNL2, EXOC1, CD47, TEAD1 ...)
4. Magnitude of splicing changes similar, Pre_S and FECD-REP
Altered gene expression
Fibrosis pathway activation begins in Pre_S tissue (FN1,COL9A3, COL4A2, CTGF, COL1A2, KDR, COCH)
Progression to late stage FECD
1. Much greater disruption of gene expression
2. Activation of Fibrosis, Mitochondrial Dysfunction, and Immune Activation
Clinical Observations
• Extracellular matrix thickening
• Decreased cell density
• Development of guttae
• Immune cell infiltration

FIG. 11

A


PCA-plot from all genes
FECD_NR
Control
Pre_S
FECD_REP
Dim2 (24.3%)
Dim1 (55.6%)

B

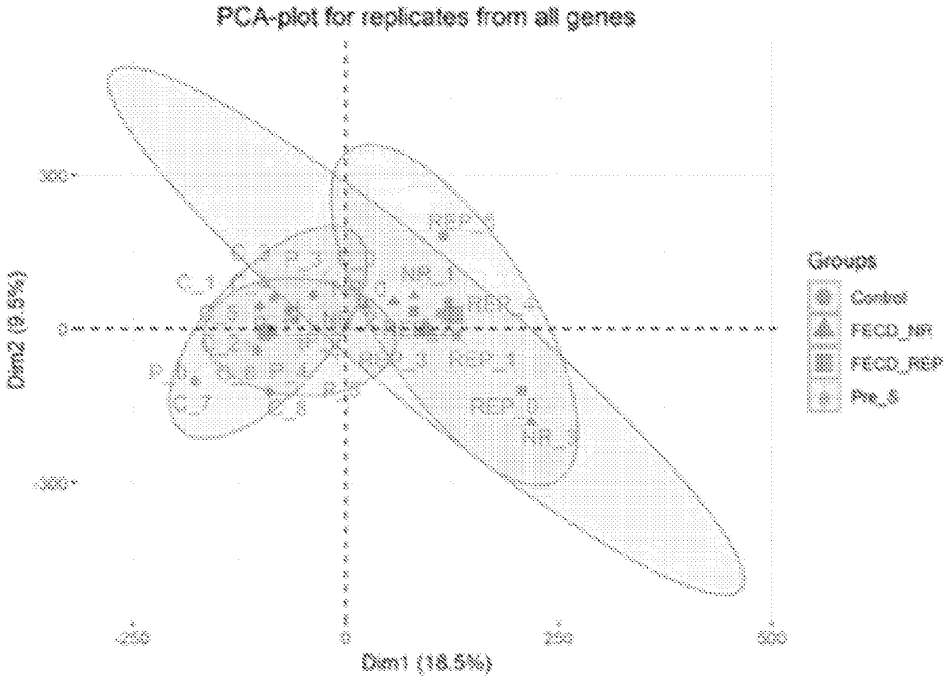

PCA-plot for replicates from all genes
Groups
Control
FECD_NR
FECD_REP
Pre_S
Dim2 (9.5%)
Dim1 (18.5%)

FIG. 12

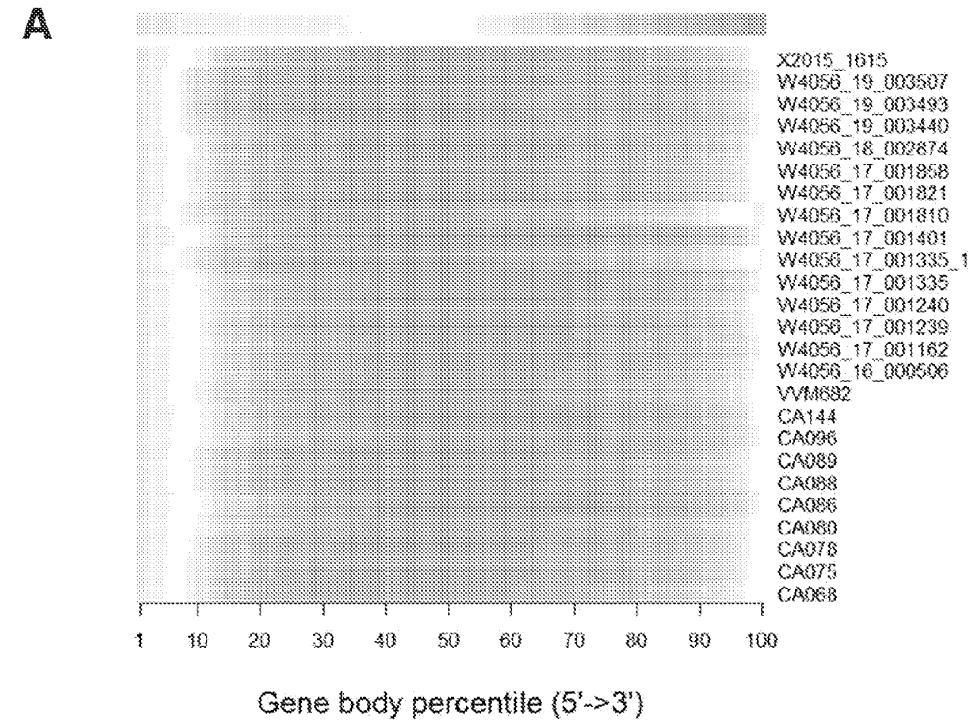

A
X2015_1615
W4056_19_003507
W4056_19_003493
W4056_19_003440
W4056_18_002874
W4056_17_001858
W4056_17_001821
W4056_17_001810
W4056_17_001401
W4056_17_001335_1
W4056_17_001335
W4056_17_001240
W4056_17_001239
W4056_17_001162
W4056_16_000506
VVM682
CA144
CA096
CA089
CA088
CA086
CA080
CA078
CA075
CA068
1 10 20 30 40 50 60 70 80 90 100
Gene body percentile (5'->3')
B
Coverage
0.0 0.2 0.4 0.6 0.8 1.0
0 20 40 60 80 100
Gene body percentile (5'->3')
CA068
CA075
CA078
CA080
CA086
CA088
CA089
CA096
CA144
VVM682
W4056_16_000506
W4056_17_001162
W4056_17_001239
W4056_17_001240
W4056_17_001335
W4056_17_001335_1
W4056_17_001401
W4056_17_001810
W4056_17_001821
W4056_17_001858
W4056_18_002874
W4056_19_003440
W4056_19_003493
W4056_19_003507
X2015_1615

FIG. 13

A

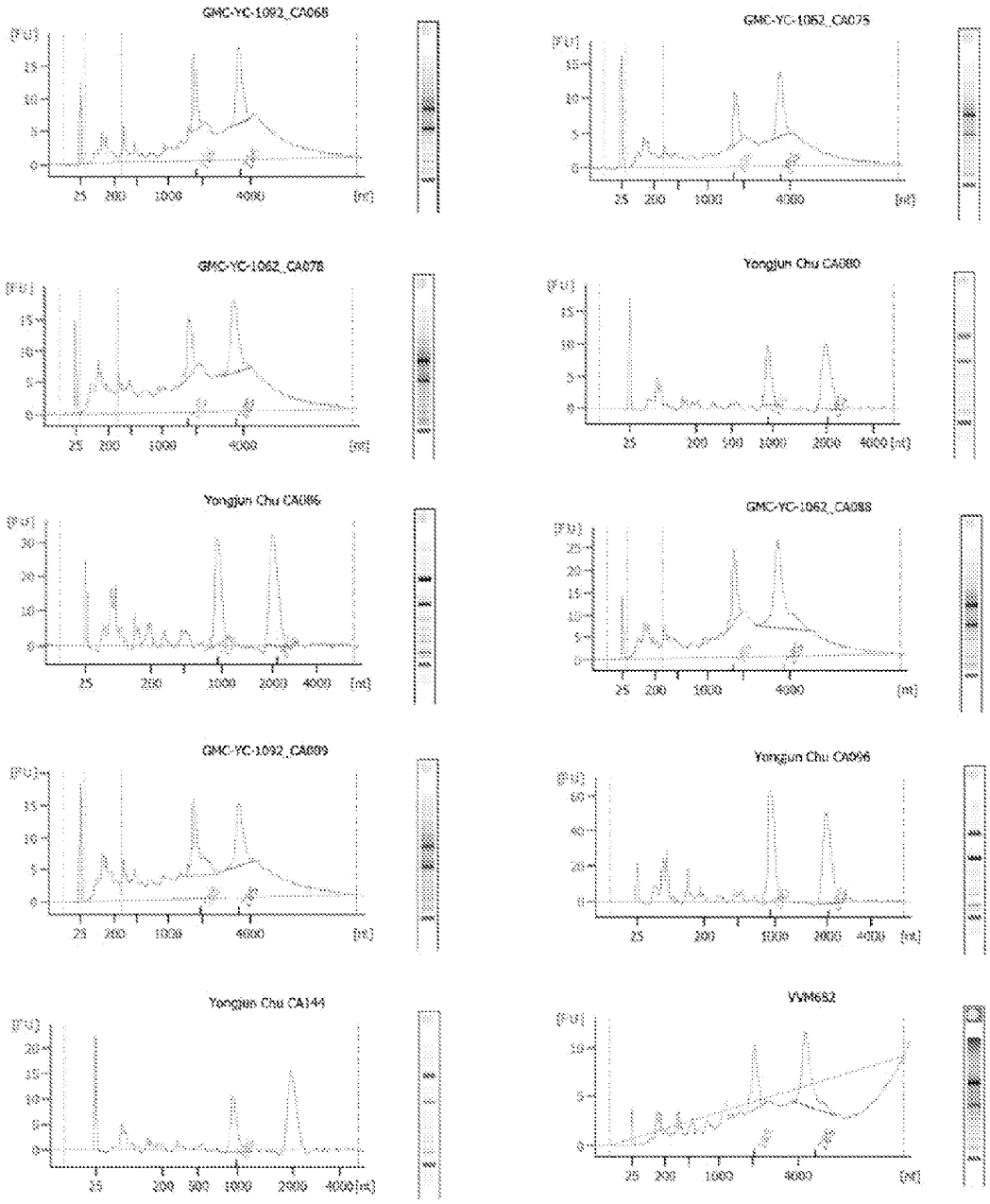

GMC-YC-1092_CA068
GMC-YC-1092_CA075
GMC-YC-1092_CA078
Yongjun Chu CA080
Yongjun Chu CA086
GMC-YC-1092_CA088
GMC-YC-1092_CA089
Yongjun Chu CA096
Yongjun Chu CA144
VVM652

FIG. 13 Cont.

B

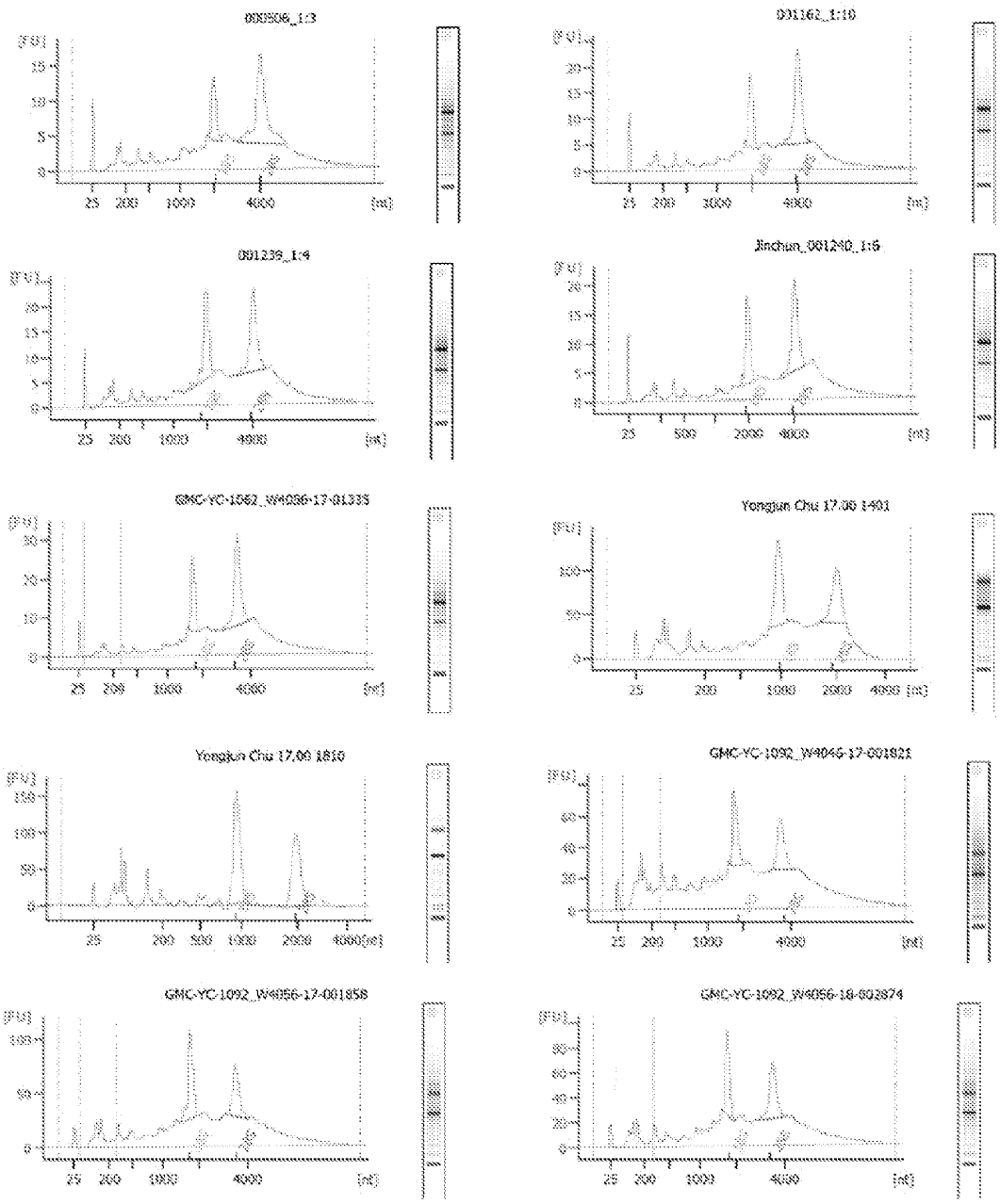

003506_1:3
001162_1:10
001239_1:4
Jinchun_001240_1:6
GMC-YC-1062_W4086-17-001335
Yongjun Chu 17.00 1401
Yongjun Chu 17.00 1810
GMC-YC-1092_W4046-17-001821
GMC-YC-1092_W4056-17-001858
GMC-YC-1092_W4056-18-002874

FIG. 14

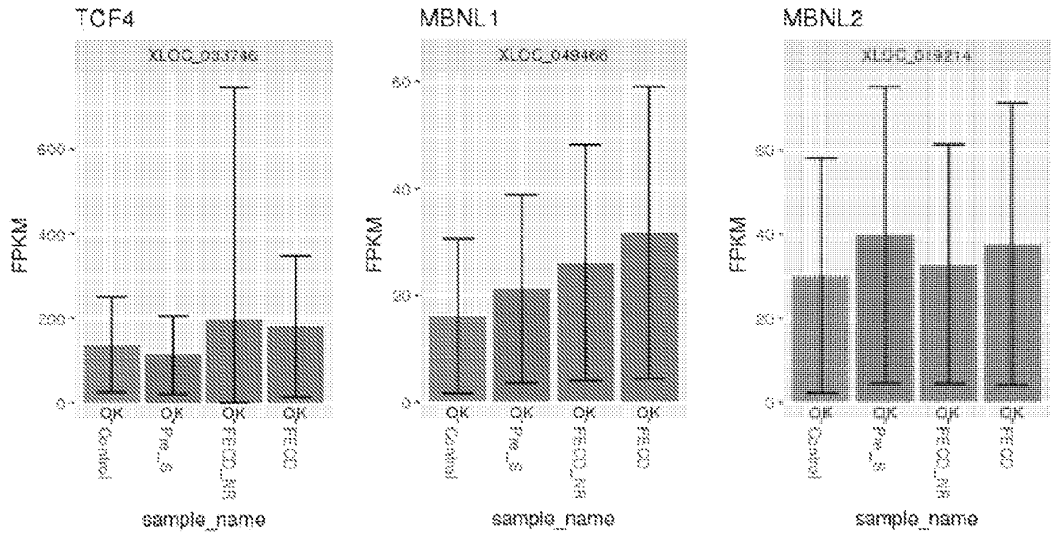

TCF4
MBNL1
MBNL2
FPKM
sample_name
OK
Control
Pre_S
FECD_adv
FECD

FIG. 15

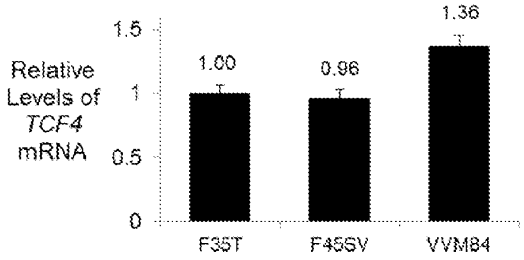

Relative Levels of TCF4 mRNA
1.5
1
0.5
0
1.00
0.96
1.36
F35T
F45SV
VVM84

FIG. 16

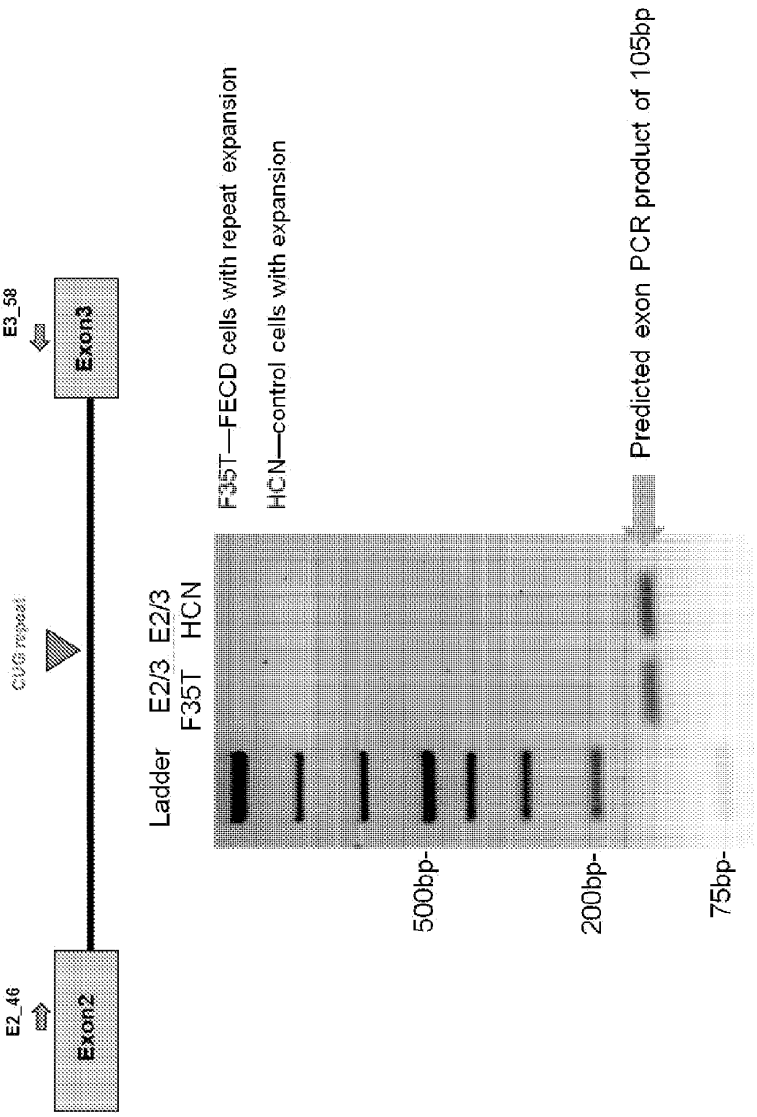

E3_58
Exon3
CUG repeat
E2_46
Exon2
Ladder
E2/3 F35T
E2/3 HCN
F35T—FECD cells with repeat expansion
HCN—control cells with expansion
Predicted exon PCR product of 105bp
500bp-
200bp-
75bp-

FIG. 17

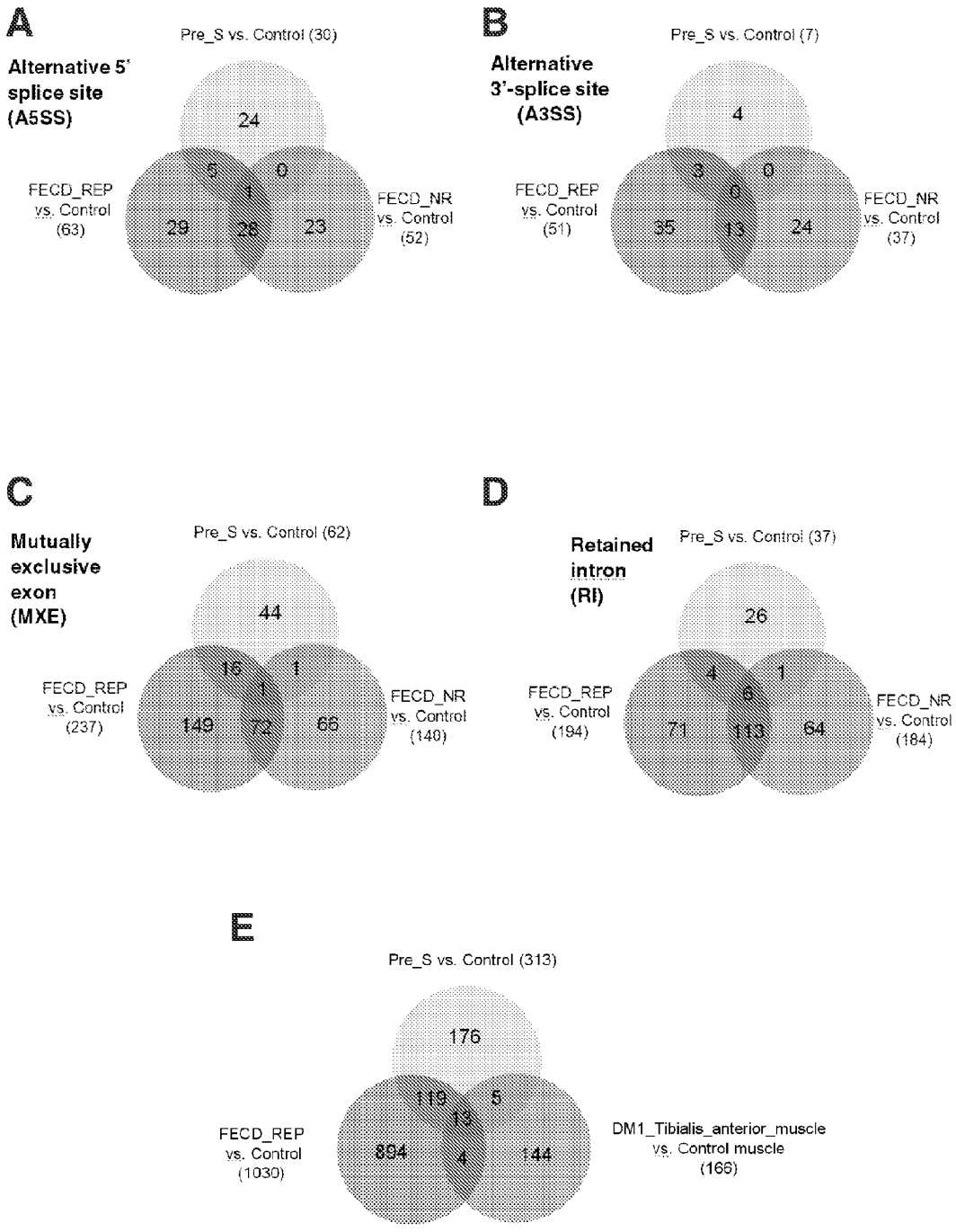

A
Alternative 5' splice site (A5SS)
Pre_S vs. Control (30)
24
5
1
0
29
28
23
FECD_REP vs. Control (63)
FECD_NR vs. Control (52)
B
Alternative 3'-splice site (A3SS)
Pre_S vs. Control (7)
4
3
0
35
13
24
FECD_REP vs. Control (51)
FECD_NR vs. Control (37)
C
Mutually exclusive exon (MXE)
Pre_S vs. Control (62)
44
16
1
1
149
72
66
FECD_REP vs. Control (237)
FECD_NR vs. Control (140)
D
Retained intron (RI)
Pre_S vs. Control (37)
26
4
1
6
71
113
64
FECD_REP vs. Control (194)
FECD_NR vs. Control (184)
E
Pre_S vs. Control (313)
176
119
5
13
894
4
144
FECD_REP vs. Control (1030)
DM1_Tibialis_anterior_muscle vs. Control muscle (166)

FIG. 17 Cont.

F

Gene	Location	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
NUMA1	-:chr11:72010785-72010854:72012400-72012442:72012894-72016260	0.62	0.12	0.23	0.94	0.58
COPZ2	-:chr17:48026166-48026475:48027675-48027789:48028471-48028510	0.23	0.73	0.58	0.14	0.51
HOOK3	+:chr8:42997589-42997637:43000270-43000276:43002106-43002141	0.19	0.53	0.36	0.00	0.28
KIF13A	-:chr6:17787775-17787875:17789871-17789910:17794248-17794395	0.69	0.11	0.25	0.96	0.83
SOS1	-:chr2:38987472-38987591:38989269-38989314:38995132-38995387	0.94	0.57	0.50	0.91	0.45
MBNL2	+:chr13:97347040-97347087:97356795-97356849:97357481-97357635	0.12	0.78	0.37	0.05	0.25
SORBS1	-:chr10:95346405-95346452:95351215-95351376:95354881-95354967	0.92	0.39	0.57	0.99	0.83
DNM1L	+:chr12:32737104-32737161:32737864-32737942:32740063-32740240	0.23	0.40	0.52	0.10	0.37
VPS39	-:chr15:42191495-42191560:42192065-42192098:42199895-42199961	0.78	0.20	0.21	0.82	0.35
TCF4	-:chr18:55585279-55585352:55586920-55587136:55589296-55589778	0.30	0.60	0.55	0.88	0.37
ARHGEF10L	+:chr1:17632320-17632466:17634547-17634562:17634834-17635016	0.59	0.10	0.11	0.97	0.64
CLASP1	-:chr2:121430072-121430177:121445448-121445496:121447335-121447507	0.86	0.26	0.41	0.90	0.41
MYH10	-:chr17:8569719-8569812:8576642-8576672:8577335-8577338	0.46	0.31	0.36	0.04	0.67

G

NUMA1: Nuclear matrix component
COPZ2: Adaptor protein/intracellular transport
HOOK3: Microtubule tethering
KIF13A: Kinesin family member.
SOS1: Rac guanine nucleotide exchange factor
MBNL2: Alternative splicing
SORBS1: Sortilin related VPS10 domain containing receptor
DNM1L: Mitochondrial and peroxisomal division
VPS39: Promote clustering and fusion of late endosomes and lysosomes
TCF4: Transcription factor
ARHGEF10L: Rho guanine nucleotide exchange factor
CLASP1: microtubule-associated protein
MYH10: Regulation of cytokinesis, cell motility, and cell polarity

FIG. 18

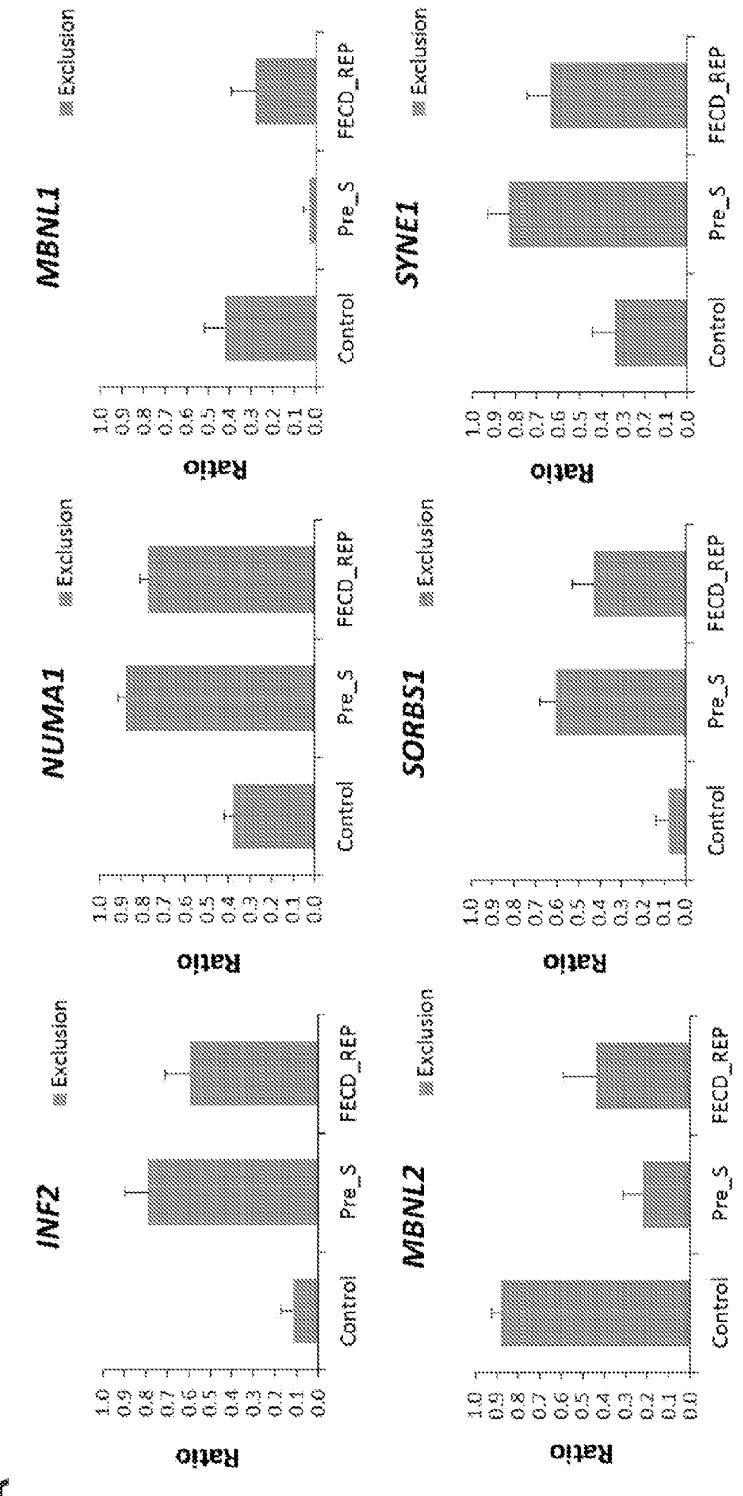

A
INF2
NUMA1
MBNL1
MBNL2
SORBS1
SYNE1
Exclusion
Ratio
Control
Pre_S
FECD_REP

FIG. 18 Cont.

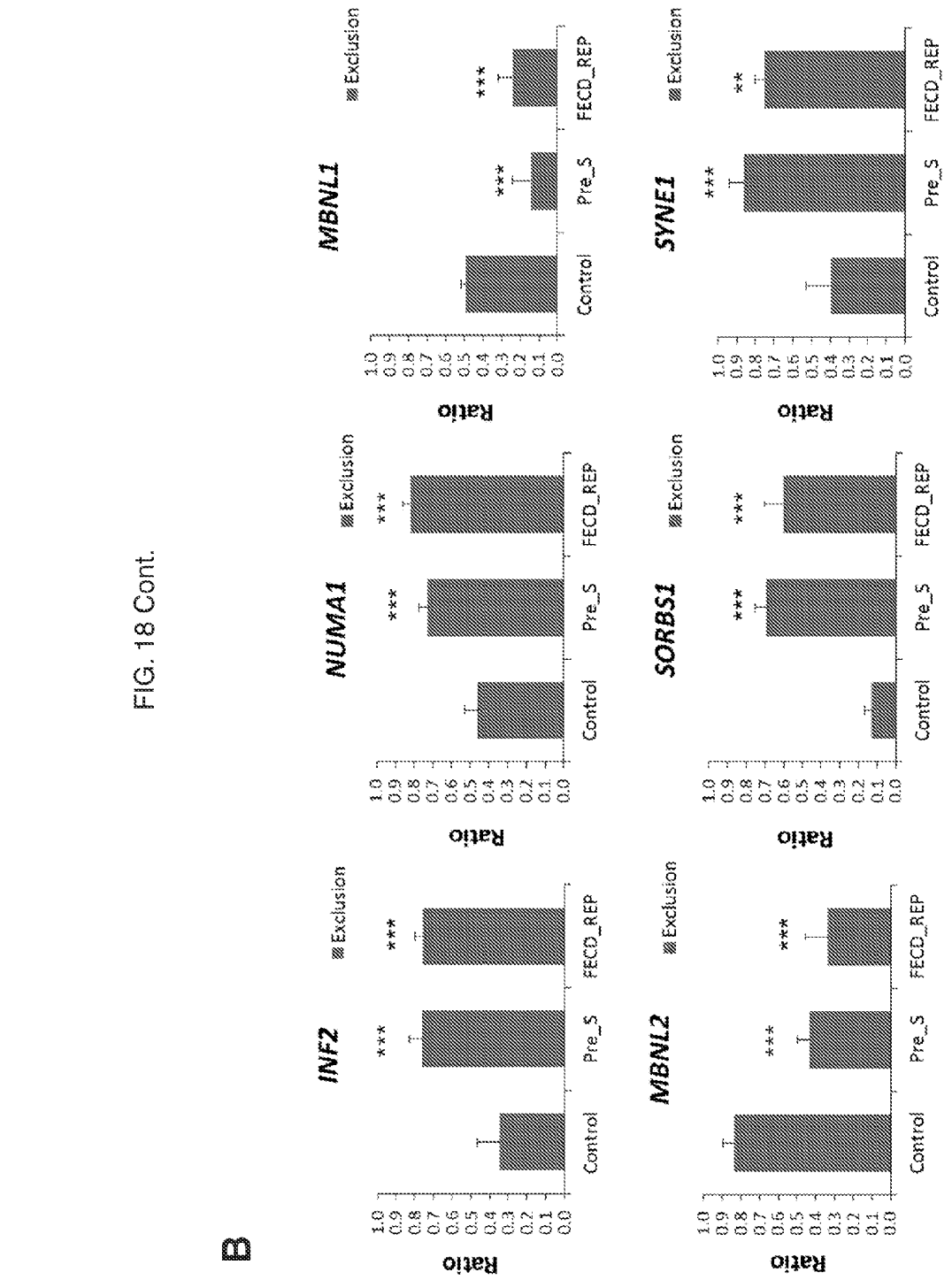

B
INF2
NUMA1
MBNL1
MBNL2
SORBS1
SYNE1
Exclusion
Ratio
Control
Pre_S
FECD_REP
***
**

FIG. 19

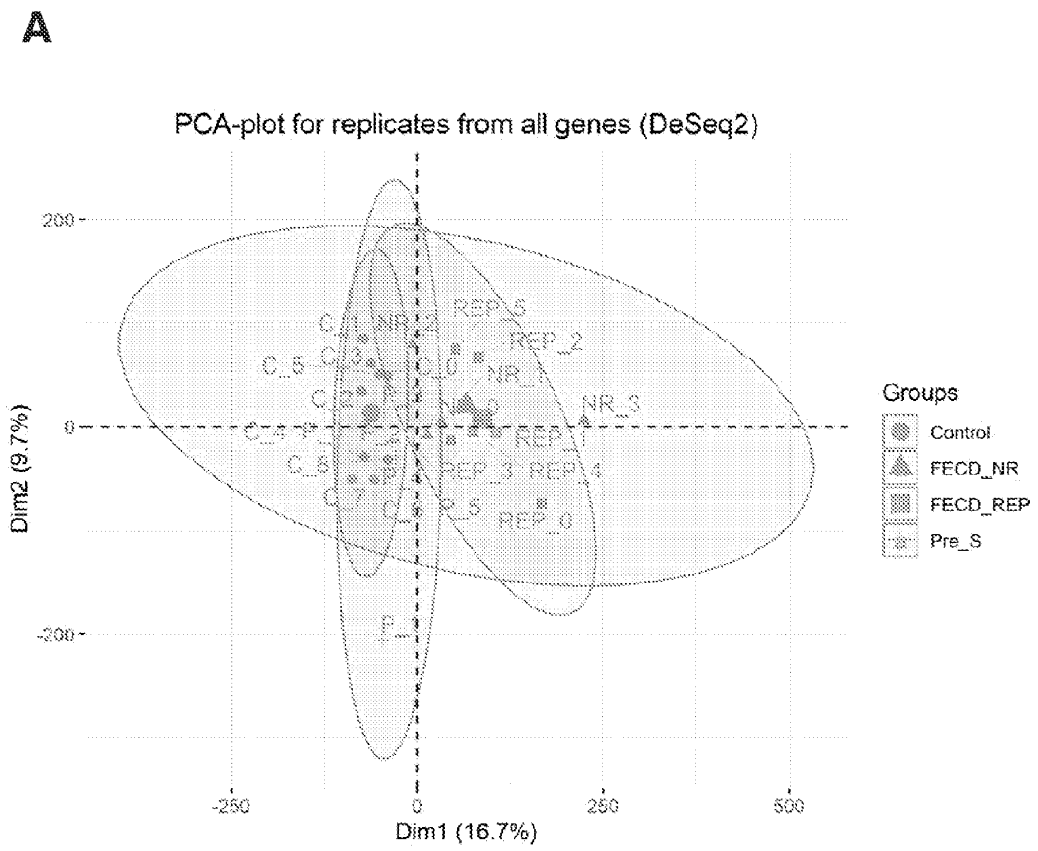

A
PCA-plot for replicates from all genes (DeSeq2)
Dim2 (9.7%)
Dim1 (16.7%)
200
0
-200
-250
0
250
500
Groups
Control
FECD_NR
FECD_REP
Pre_S

FIG. 19 Cont.

B

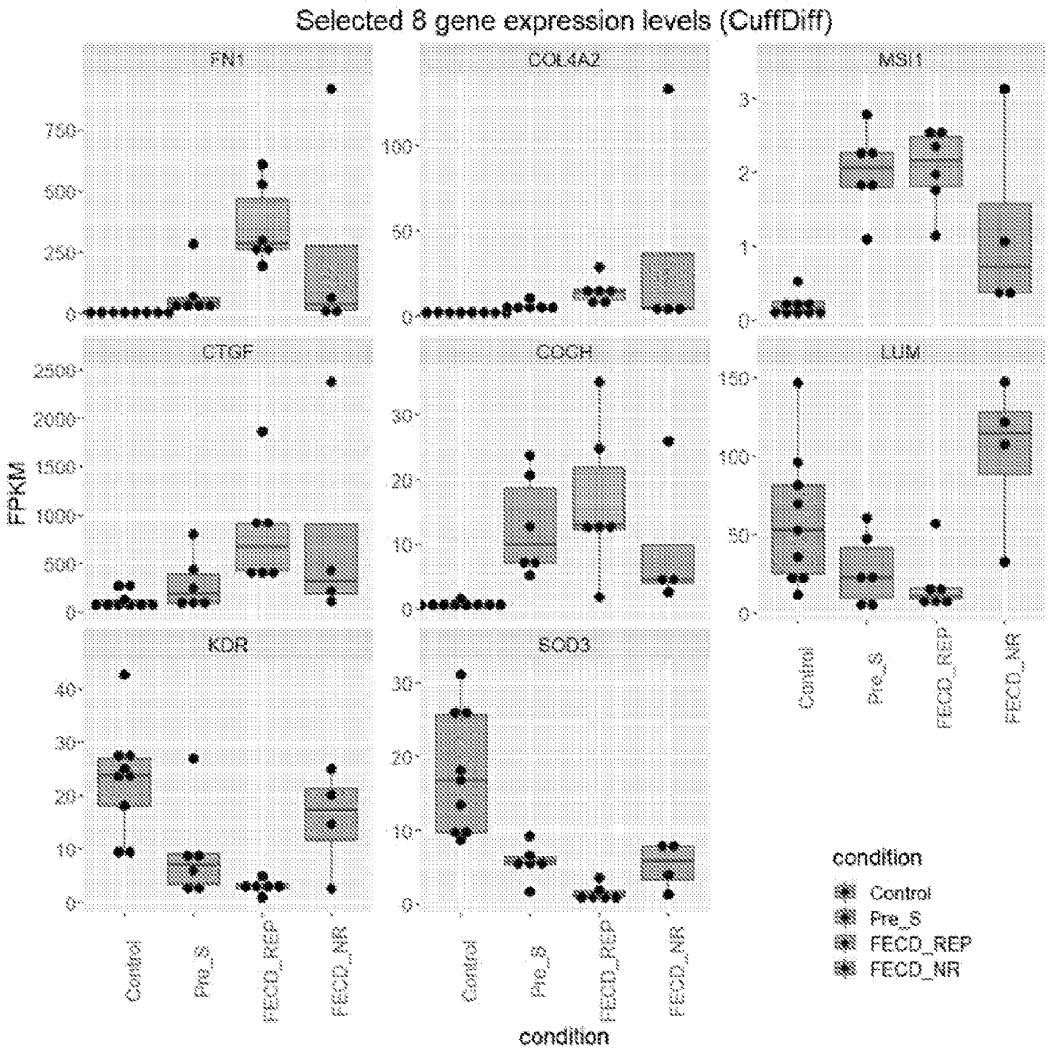

Selected 8 gene expression levels (CuffDiff)
FN1
COL4A2
MSI1
CTGF
GDCH
LUM
KOR
SOD3
FPKM
Control
Pre_S
FECD_REP
FECD_NR
condition

FIG. 19 Cont.

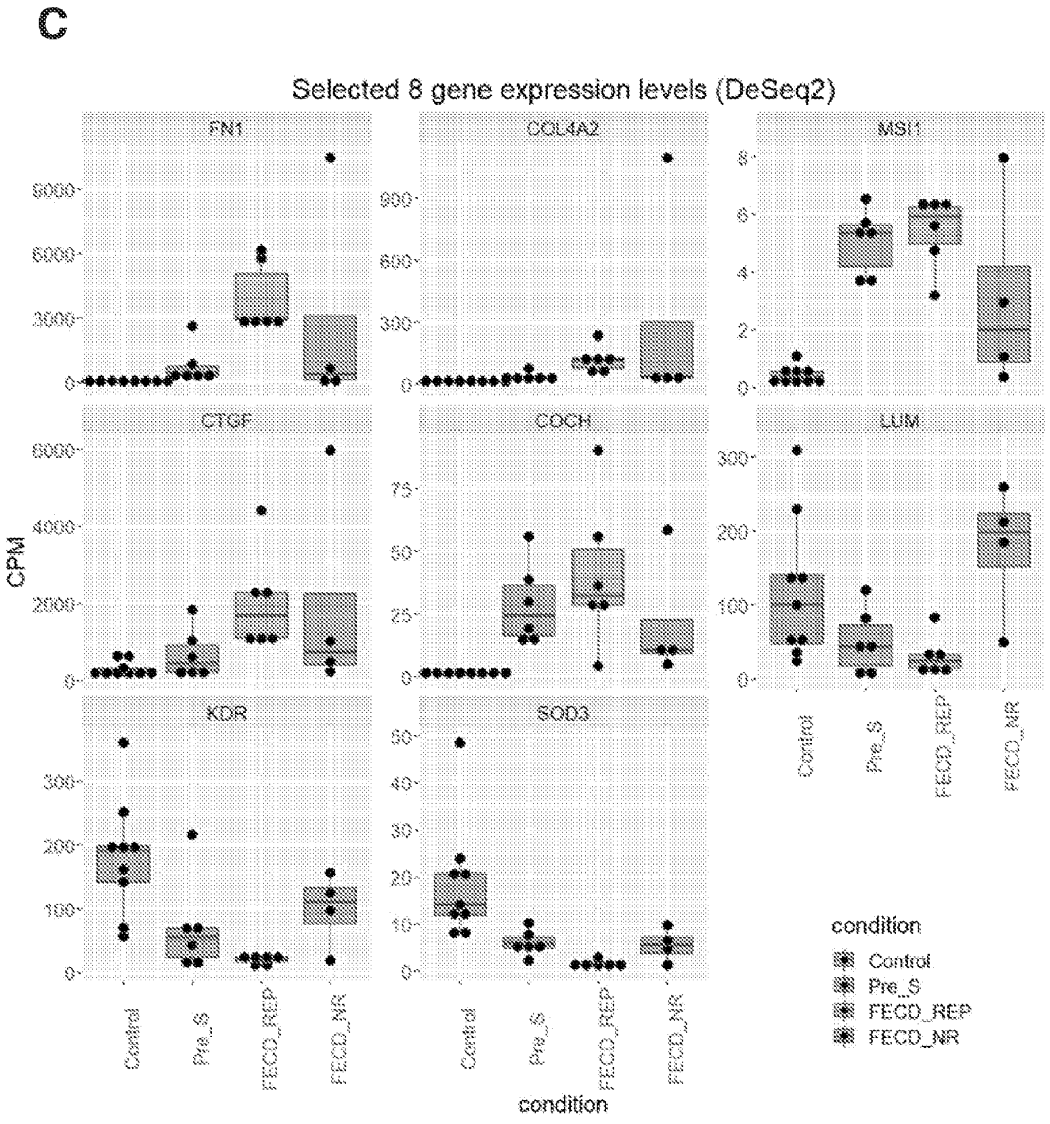
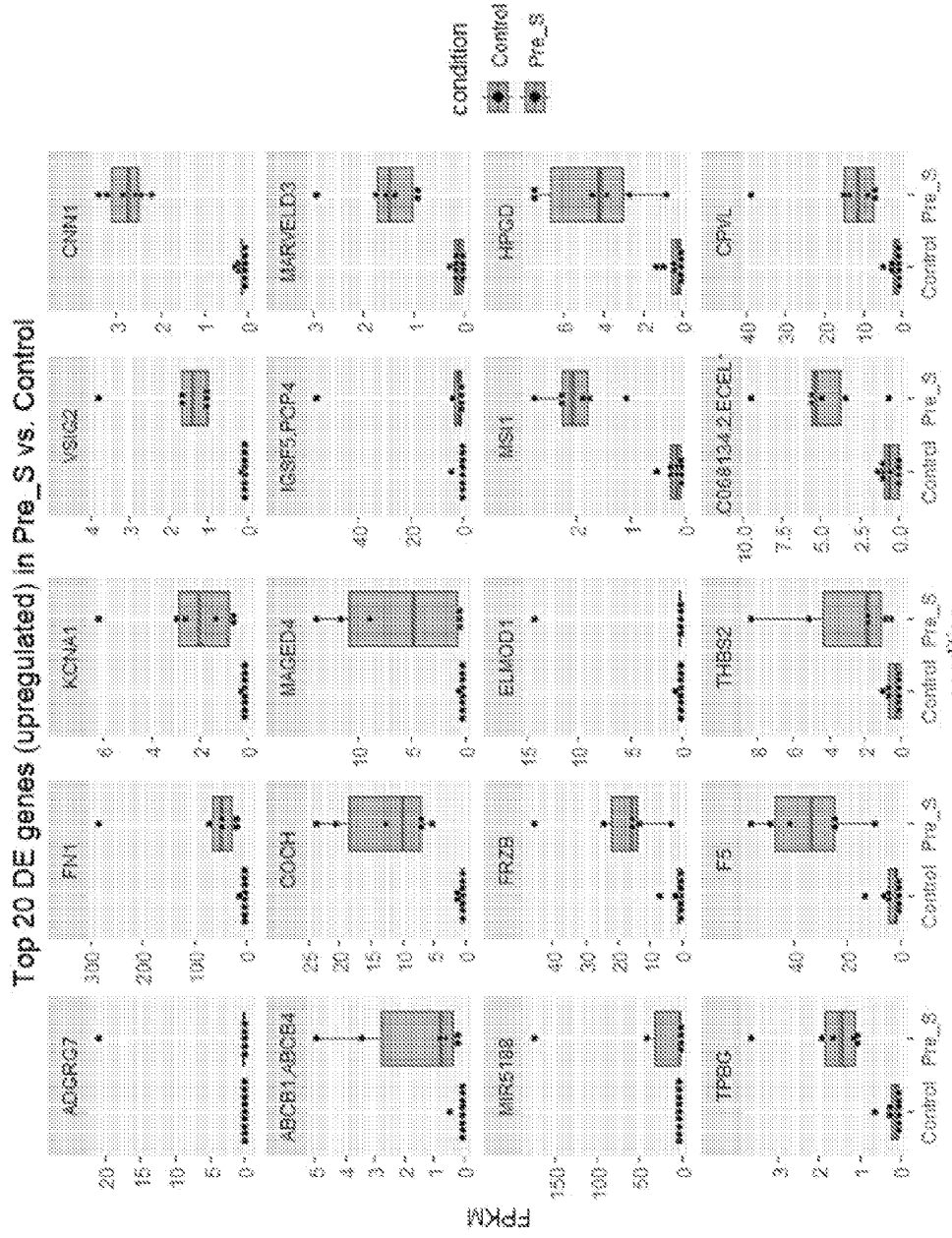
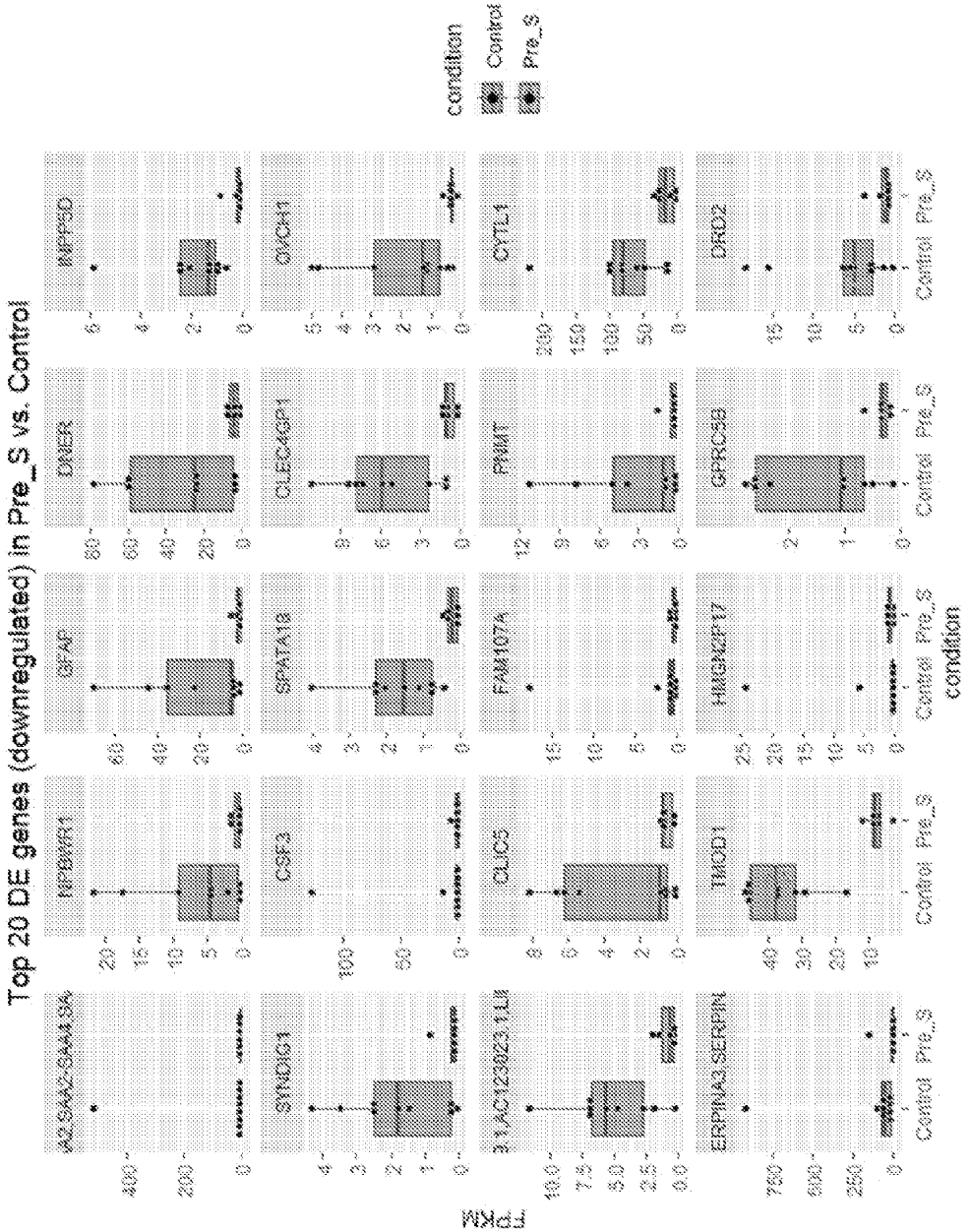

C
Selected 8 gene expression levels (DeSeq2)
FN1
COL4A2
MSI1
CTGF
COCH
LUM
KDR
SOD3
CPM
condition
Control
Pre_S
FECD_REP
FECD_NR

FIG. 20



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FIG. 20 Cont.



MS&D Exhibit 1008, Page 2267 of 4223

FIG. 21

A

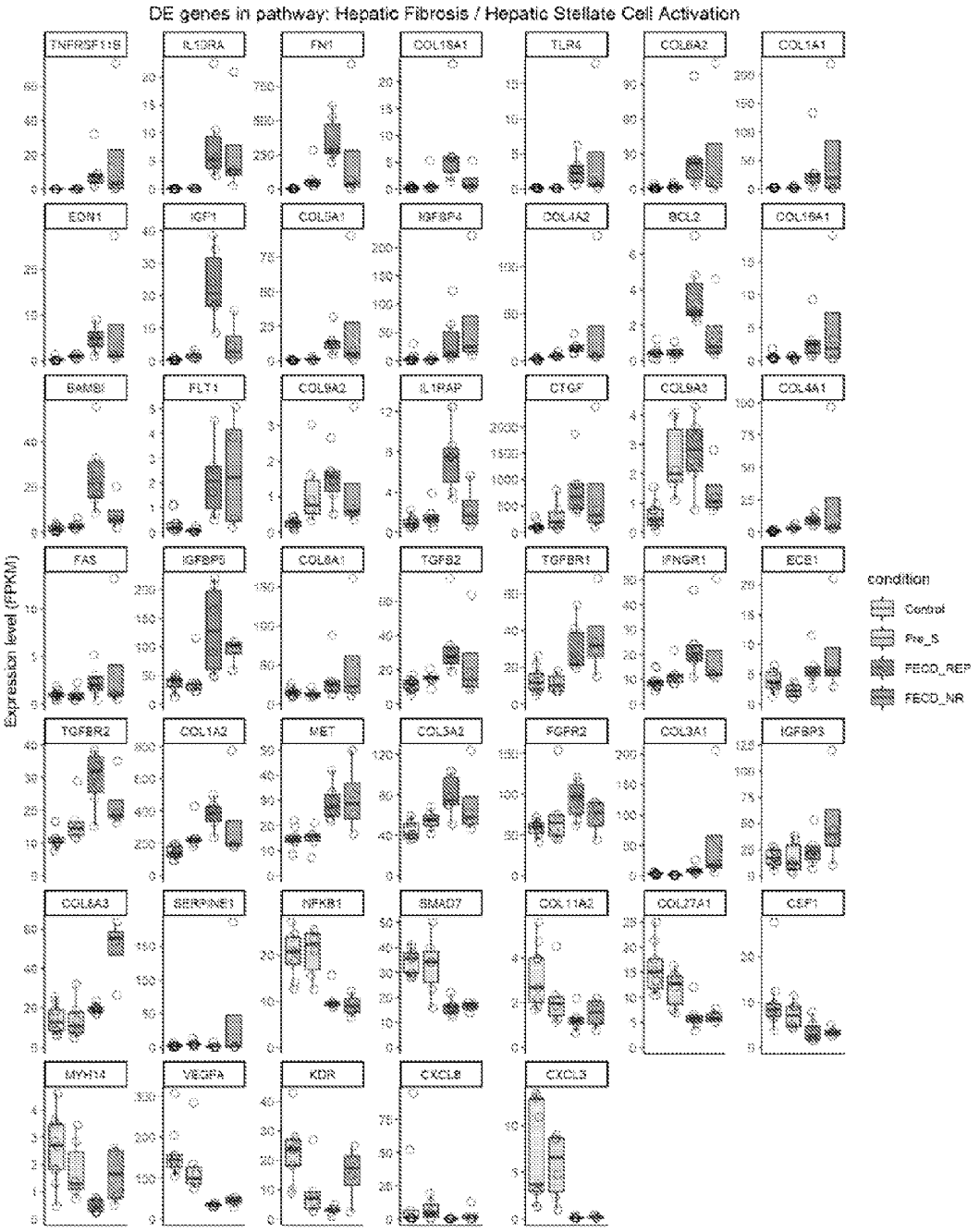

DE genes in pathway: Hepatic Fibrosis / Hepatic Stellate Cell Activation
Expression level (FPKM)
TNFRSF11B
IL13RA
FN1
COL18A1
TLR4
COL8A2
COL1A1
EDN1
IGF1
COL3A1
MFBP4
COL4A2
BCL2
COL19A1
BAMBI
FLT1
COL9A2
IL1RAP
CTGF
COL9A3
COL4A1
FAS
IGFBP3
COL6A1
TGFB2
TGFBR1
IFNGR1
ECE1
TGFBR2
COL1A2
MET
COL5A2
FGFR2
COL3A1
IGFBP5
COL6A3
SERPINE1
NFKB1
SMAD7
COL11A2
COL27A1
CEP1
MYH14
VEGFA
KDR
CXCL8
CXCL3
condition
Control
Pre_IS
FECD_REP
FECD_NR

FIG. 21 Cont.

B

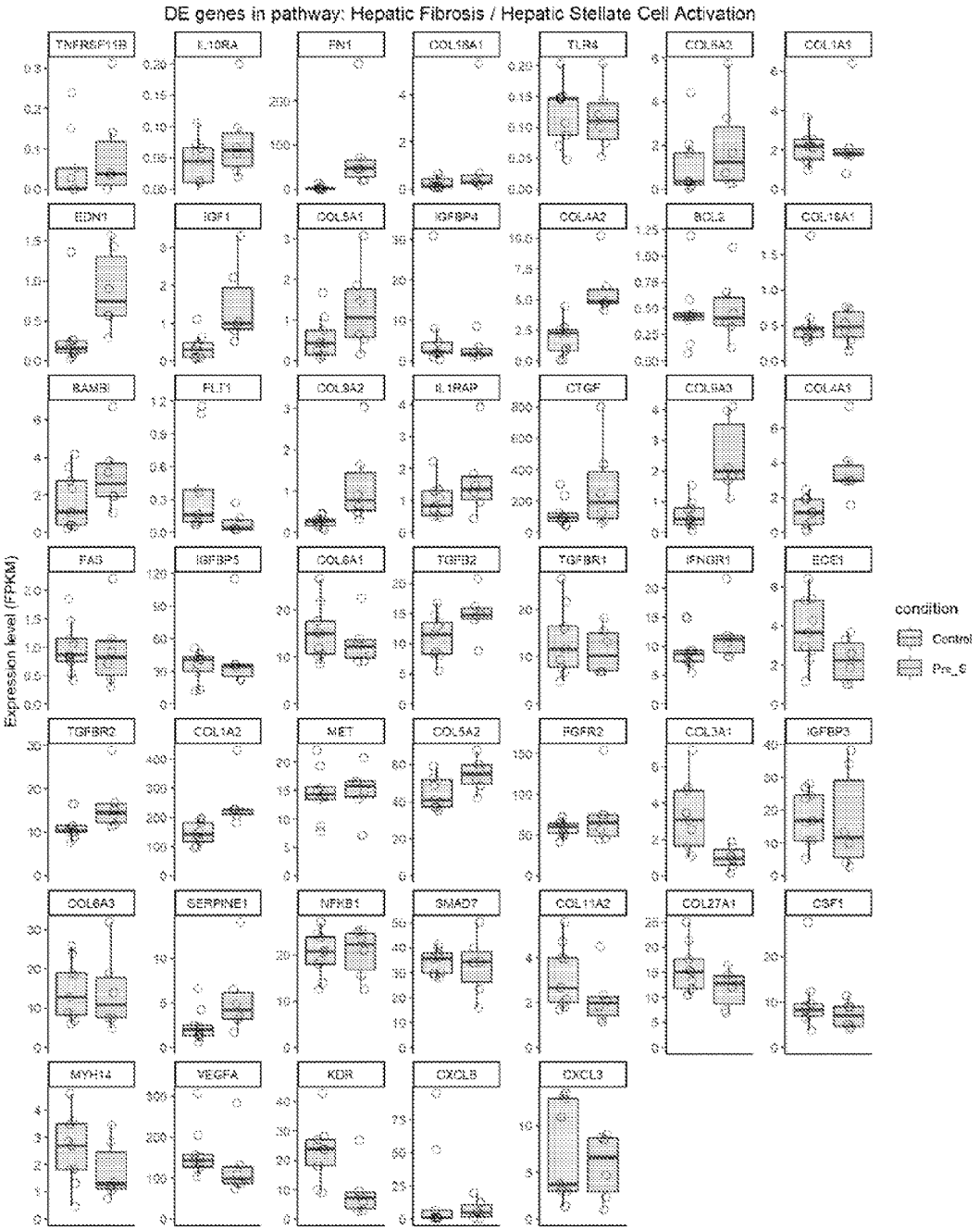

DE genes in pathway: Hepatic Fibrosis / Hepatic Stellate Cell Activation
Expression level (FPKM)
TNFRSF11B
IL10RA
FN1
COL18A1
TLR4
COL6A3
COL1A1
EDN1
IGF1
COL5A1
IGFBP4
COL4A2
BCL2
COL16A1
BAMBI
PLT1
COL9A2
IL1RAP
CTGF
COL8A3
COL4A1
FAS
IGFBP5
COL6A1
TGFB2
TGFBR1
IFNGR1
EGF1
TGFBR2
COL1A2
MET
COL5A2
FGFR2
COL3A1
IGFBP3
COL6A3
SERPINE1
NFKB1
SMAD7
COL11A2
COL27A1
CSF1
MYH14
VEGFA
KDR
CXCL8
CXCL3
condition
Control
Pre_S

FIG. 21 Cont.

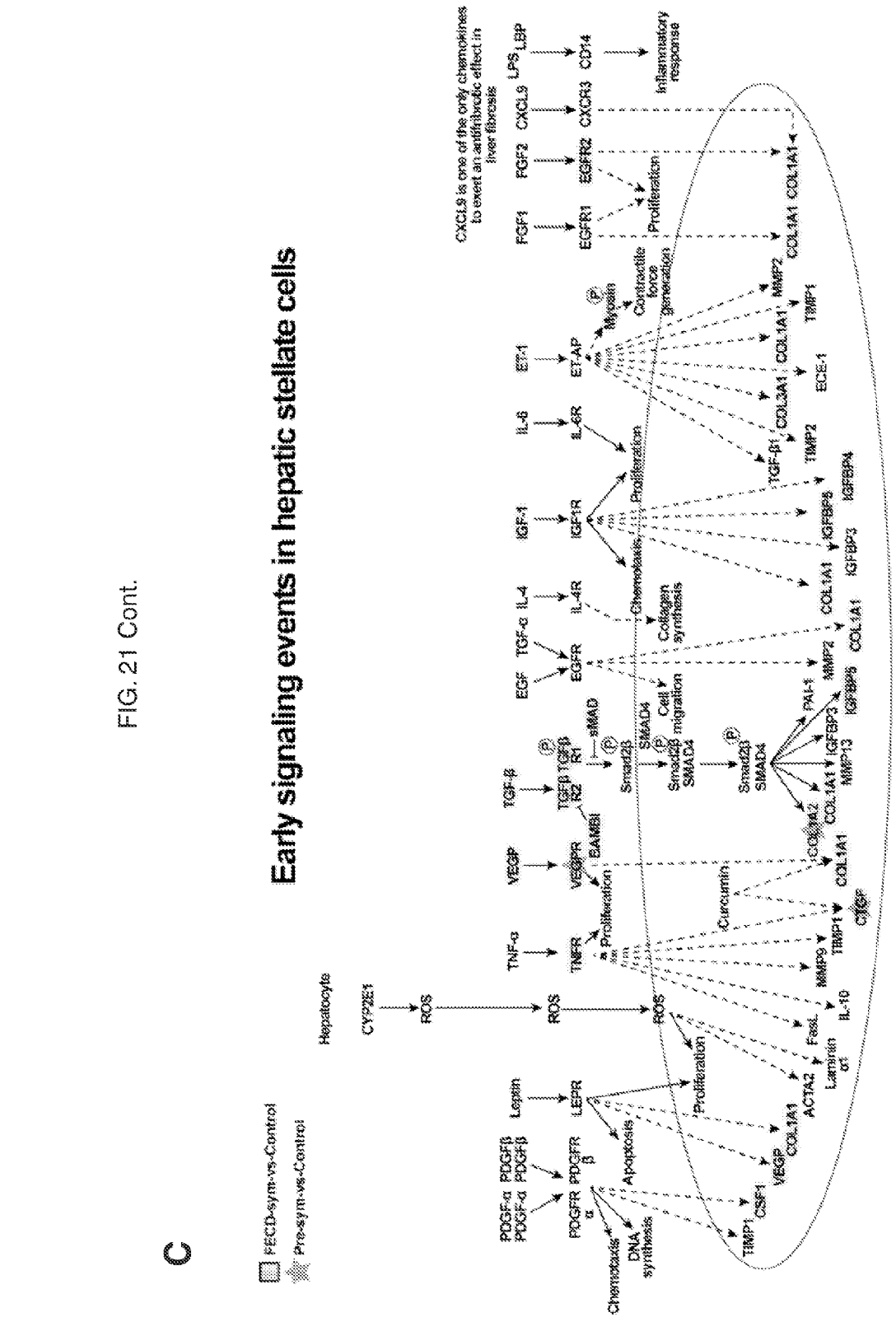

C
FECD-sym-vs-Control
Pre-sym-vs-Control
Early signaling events in hepatic stellate cells
Hepatocyte
CYP2E1
ROS
TNF-α
TNFR
VEGF
VEGFR
TGF-β
TGFβ R2
TGFβ R1
BAMBI
sMAD
Smad2/3
SMAD4
Smad2/3 SMAD4
Cell migration
Proliferation
Curcumin
EGF
EGFR
TGF-α
IL-4
IL-4R
Chemotaxis
Collagen synthesis
IGF-1
IGF1R
IL-6
IL-6R
ET-1
ET-AP
Myosin
Contractile force generation
FGF1
EGFR1
FGF2
EGFR2
CXCL9
CXCR3
LPS
LBP
CD14
Inflammatory response
CXCL9 is one of the only chemokines to exert an antifibrotic effect in liver fibrosis
PDGF-α PDGFβ
PDGFR α
PDGFR β
Leptin
LEPR
Apoptosis
Chemotaxis
DNA synthesis
TIMP1
CSF1
VEGF
COL1A1
ACTA2
FasL
Laminin α1
IL-10
MMP9
TIMP1
CTGF
COL3A1
COL1A1
MMP2
TIMP1
ECE-1
TGF-β1
TIMP2
IGFBP5
IGFBP4
IGFBP3
PAI-1
MMP13

FIG. 21 Cont.

D

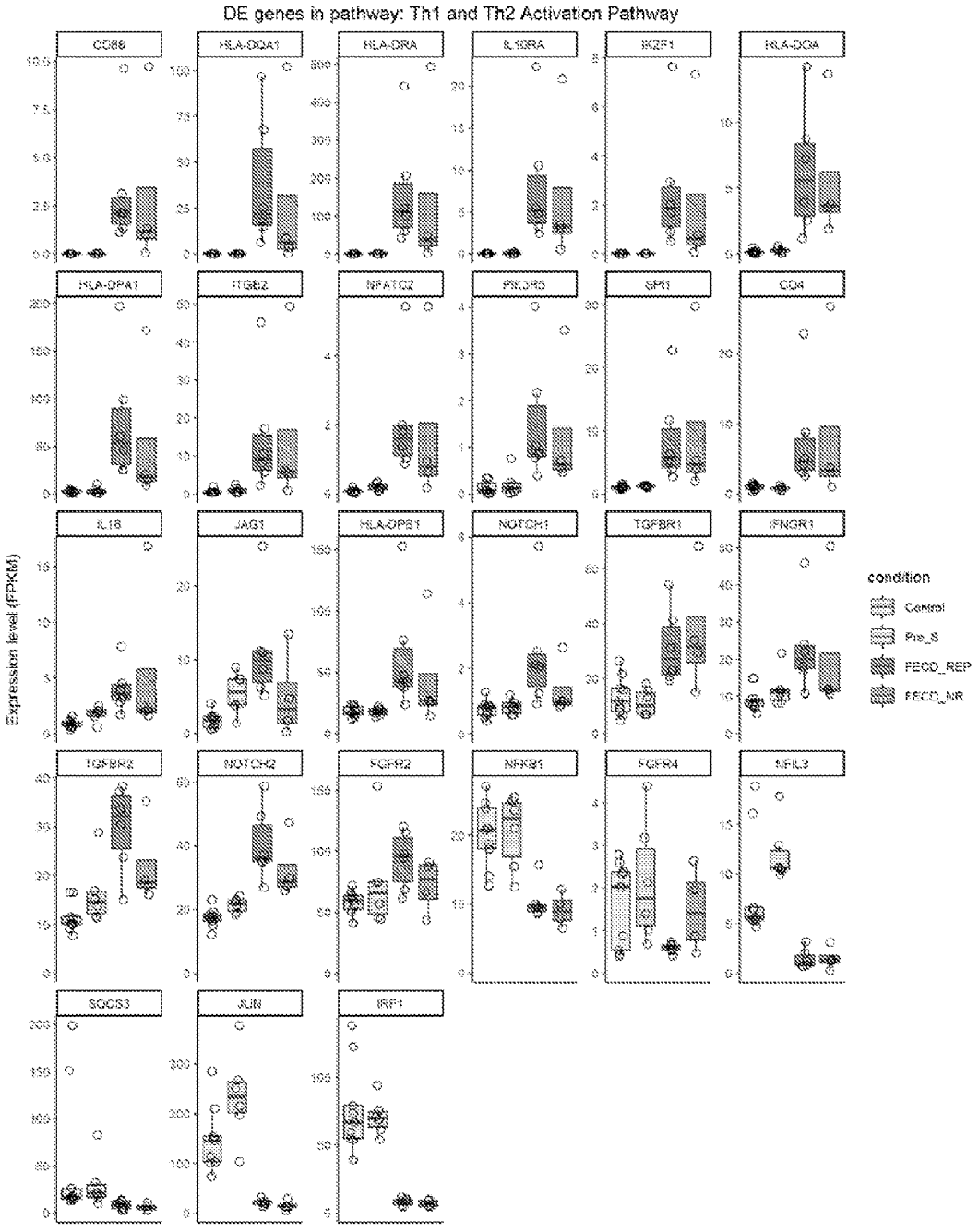

DE genes in pathway: Th1 and Th2 Activation Pathway
CD86
HLA-DQA1
HLA-DRA
IL10RA
IKZF1
HLA-DQA
HLA-DPA1
ITGB2
NFATC2
PRDM1
GPI
CD4
IL18
JAG1
HLA-DPB1
NOTCH1
TGFBR1
IFNGR1
TGFBR2
NOTCH2
FGFR2
NFKB1
FGFR4
NFIL3
SOCS1
JUN
IRF1
Expression level (FPKM)
condition
Control
Pre_IS
FECD_REP
FECD_NR

FIG. 21 Cont.

E

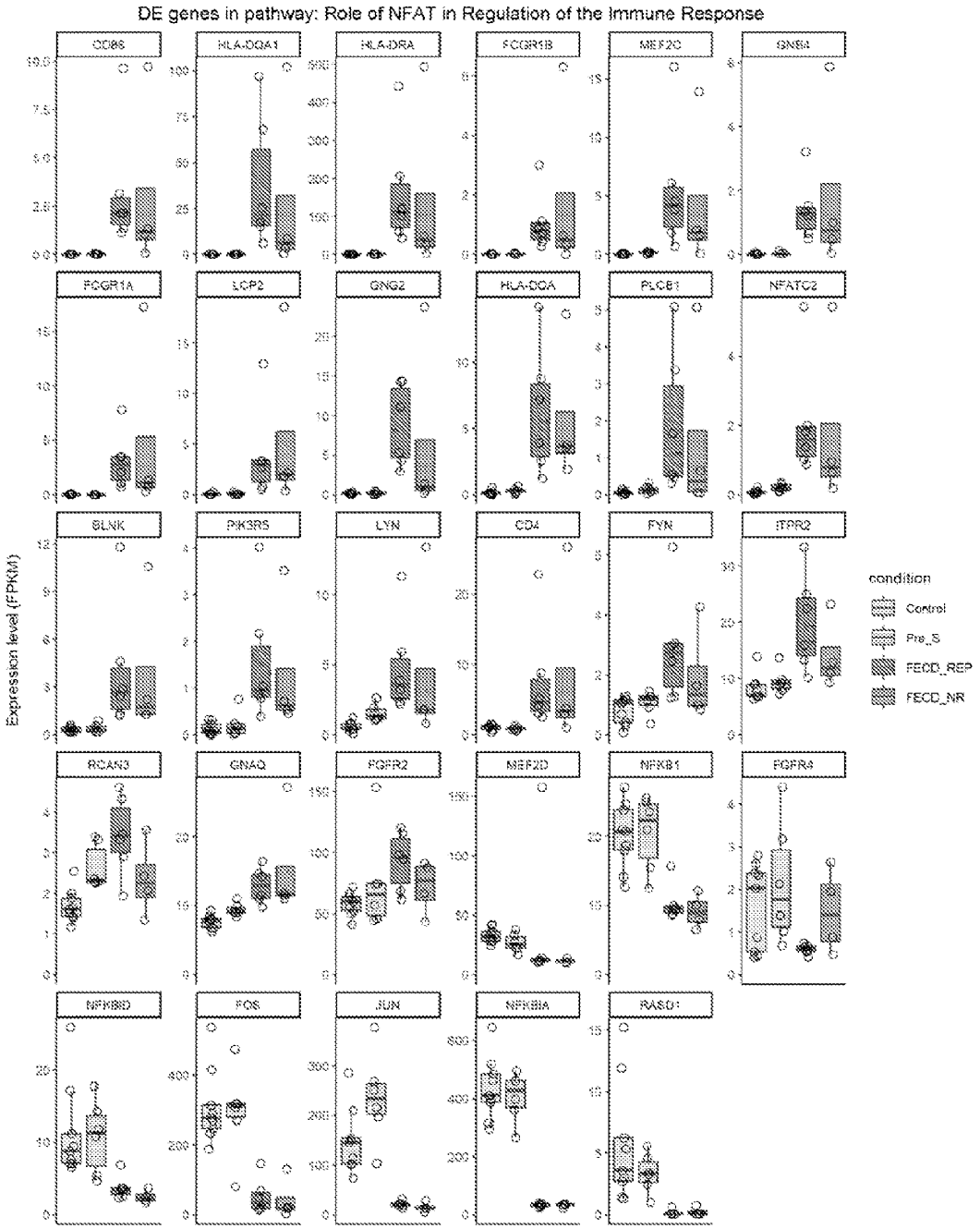

DE genes in pathway: Role of NFAT in Regulation of the Immune Response
CD86
HLA-DQA1
HLA-DRA
FCGR1B
MEF2C
GNB4
FCGR1A
LCP2
GNG2
HLA-DOA
PLCB1
NFATC2
BLNK
PIK3R5
LYN
CD4
FYN
ITPR2
RCAN3
GNAQ
FGFR2
MEF2D
NFKB1
FGFR4
NFKBID
FOS
JUN
NFKBIA
RASD1
Expression level (FPKM)
condition
Control
Pre_S
FECD_REP
FECD_NR

FIG. 21 Cont.

F

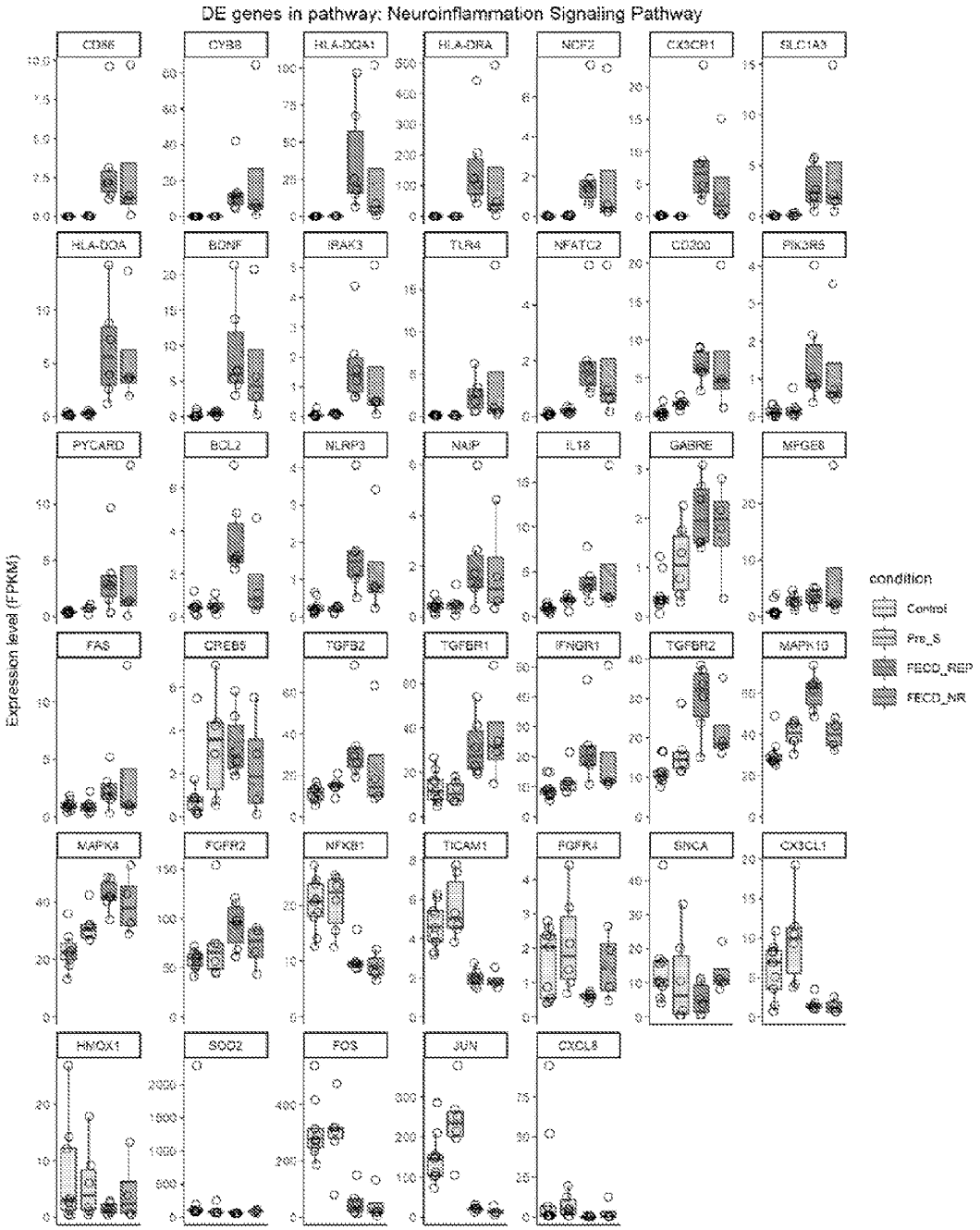
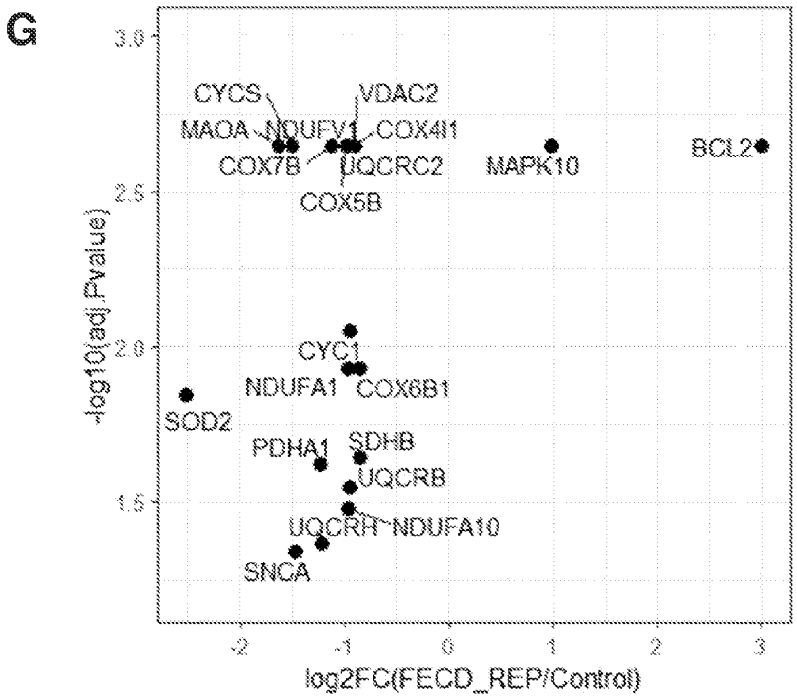

DE genes in pathway: Neuroinflammation Signaling Pathway
Expression level (FPKM)
CD86
CYBB
HLA-DQA1
HLA-DRA
NCF2
CX3CR1
SLC1A3
HLA-DQA
BDNF
IRAK3
TLR4
NFATC2
CD300
PIK3R5
PYCARD
BCL2
NLRP3
NAIP
IL18
GABRE
MPGES
FAS
CREB5
TGFB2
TGFBR1
IFNGR1
TGFBR2
MAPK13
MAPK8
FGFR2
NFKB1
TICAM1
FGFR4
SIVCA
CX3CL1
HMOX1
SOD2
FOS
JUN
CXCL8
condition
Control
Pre_S
FECD_REP
FECD_NR

FIG. 21 Cont.


G
CYCS
VDAC2
MAOA
NDUFV1
COX4I1
COX7B
UQCRC2
MAPK10
BCL2
COX5B
CYC1
NDUFA1
COX6B1
SOD2
PDHA1
SDHB
UQCRB
UQCRH
NDUFA10
SNCA
-log10(adj.Pvalue)
log2FC(FECD_REP/Control)

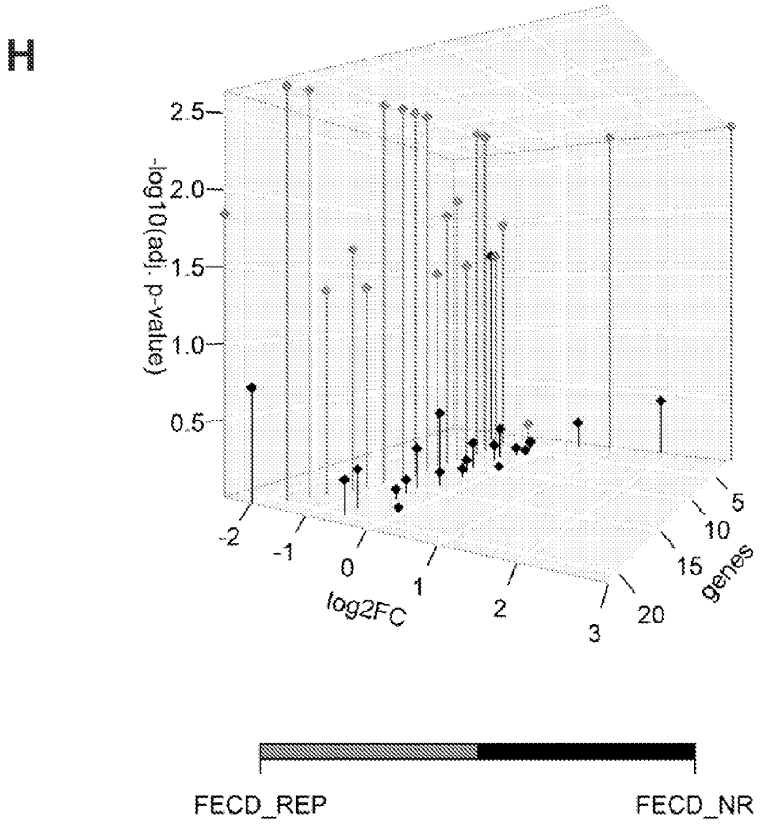

H
-log10(adj. p-value)
log2FC
genes
FECD_REP
FECD_NR

FIG. 22

A

Gene	Log2FC	Gene	Log2FC	Gene	Log2FC	Gene	Log2FC
AC079598.2,LI NC02258	>11	CLEC5A	10.5263	PSPHP1	<-11	CXCL3	-5.39144
CD86	>11	MARCH1	9.64843	CDH12	-10.1984	RNU2-63P	-5.30508
DLK1	>11	GPC3	9.27756	IL17REL	-7.36808	CXCL2	-5.24128
FOXF2	>11	HLA-DQA1	9.18926	SAA2,SAA2-SAA4,SAA4	-6.40902	HMGN2P17	-5.23317
GMNC	>11	HLA-DRA	9.0188	CSF3	-6.13122	RASD1	-5.22904
GPR34	>11	CYBB	8.64696	ARC	-6.12911	AC005920.2	-5.19689
IGKV3-20	>11	AC105383.1,AC 110751.1	8.5003	UBE2W	-5.79138	AL049839.2,SER PINA3,SERPINA 4,SERPINA5	-5.18164
IGKV6D-21	>11	GRM5,NOX4	8.43459	RNU5E-1	-5.7127	AC083899.2	-5.15117
TMEM255A	>11	IGKC,IGKJ1,IG KJ2	8.42556	CXCL8	-5.68791	AC011511.2	-5.12969
CDKN2A	10.6305	C3AR1	8.42367	LINC00881,LI NC02029	-5.63529	RNU6-1208P	-5.11613

FIG. 22

B

Gene	Log2FC	Gene	Log2FC	Gene	Log2FC	Gene	Log2FC
CD86	>12	FAM198B	9.0256	UTY	-13.4226	RNU5E-1	-5.4933
GPR34	>12	FCGR1B	8.9323	CD24P4,RNU6-255P,TTTY14	-11.1463	STK40	-5.44692
DCX	>12	HLA-DRA	8.83383	KDM5DP1,TTTY10	-9.66062	AC105129.2,RNU5B-1	-5.39899
AC007336.2,MIP2-AS1	11.9088	HLA-DQA1	8.78128	NLGN4Y	-9.51863	LINC01783,RNU1-6P	-5.26866
CDKN2A	11.1265	FOLR2	8.77685	SAA2,SAA2-SAA4,SAA4	-7.91267	AC005920.2	-5.20258
CLEC5A	10.8412	FCGR3A	8.67225	IL17REL	-7.61487	LINC00881,LINC02029	-5.15433
CYBB	9.39057	TNFRSF11B	8.58545	CSF3	-6.43948	BX284668.2,RNU1-5P	-5.14755
MARCH1	9.38128	PSG4	8.52816	AC015813.4	-5.81436	CXCL2	-5.05523
ADGRG7	9.366	AC105383.1,AC110751.1	8.44715	RNU1-59P	-5.74863	EPS8L1	-5.02175
LYVE1	9.29724	KRT7	8.43267	ZFY	-5.54493	AL096677.1,AL390037.1	-4.97445

FIG. 23

Symbol	log2 fold change	p-value	log2 fold change	p-value
COL1A2	1.378	0.00226	0.773581	0.00738683
COL3A1	1.63	0.00226	-1.73016	0.00414755
COL4A2	3.045	0.00226	1.68119	0.00226223
COL5A3	2.182	0.00226	2.04259	0.00226223
CTGF	2.723	0.00226	1.27763	0.00226223
FN1	7.225	0.00226	5.08031	0.00226223
KDR	-2.927	0.00226	-1.30521	0.00226223
BAMBI	3.936	0.00226	0.880549	0.703482
COL11A2	-1.337	0.0363	-0.534815	0.824853
COL1A1	4.067	0.00226	0.17908	0.999784
COL27A1	-1.302	0.00226	-0.406276	0.549341
COL4A1	3.112	0.00226	1.70879	0.149814
COL5A2	0.829	0.00226	0.294152	0.70792
COL6A1	1.075	0.00891	-0.215987	0.999784
COL6A2	4.794	0.00226	0.90887	0.750228
CSF1	-1.53	0.00226	-0.496574	0.51737
CXCL3	-5.391	0.00226	-0.288417	0.999784
CXCL8	-5.688	0.00226	-1.30287	0.156507
FGFR2	0.881	0.0457	0.369273	0.658643
IFNGR1	1.289	0.00226	0.355356	0.868174
IGFBP4	2.646	0.00226	-1.01873	0.542776
IGFBP5	1.89	0.00226	0.336968	0.756909
IL1RAP	2.861	0.00226	0.716579	0.486386
MET	1.009	0.00226	0.0417758	0.999784
MYH14	-2.326	0.00226	-0.504027	0.802993
NFKB1	-0.957	0.0457	0.0288995	0.999784
SMAD7	-1.079	0.0169	-0.048409	0.999784
TGFB2	1.616	0.00226	0.418369	0.658669
TGFBR1	1.235	0.00415	-0.249032	0.999784
TGFBR2	1.378	0.00226	0.50825	0.396355
VEGFA	2.232	0.00226	-0.326395	0.74898
BCL2	3.004	0.00226	NA	NA
COL16A1	2.454	0.00226	NA	NA
COL18A1	4.992	0.00226	NA	NA
COL5A1	4.67	0.00226	NA	NA
COL9A2	2.557	0.00226	NA	NA
EDN1	4.109	0.00226	NA	NA
FLT1	2.443	0.00415	NA	NA
IGF1	6.021	0.00226	NA	NA
IL10RA	7.616	0.00226	NA	NA
TLR4	4.397	0.00226	NA	NA
TNFRSF11B	7.586	0.00226	NA	NA

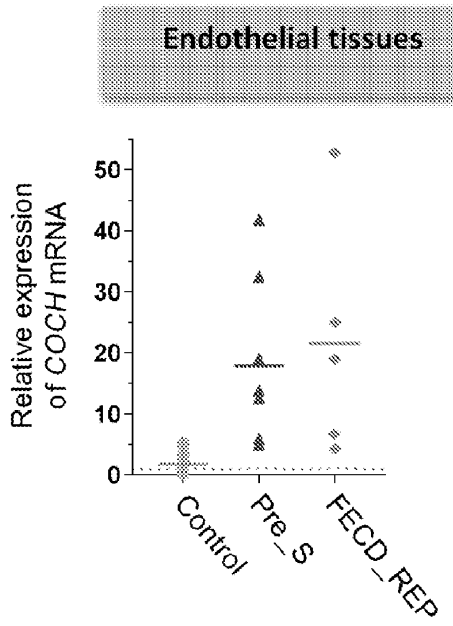
FIG. 24

A

COCH expression by RNA_Seq

Gene	Pre-S/Con	FECD-REP/Con	FECD-NR/Con
	Fold change		
COCH	18.9	22.4	15.3

B



C

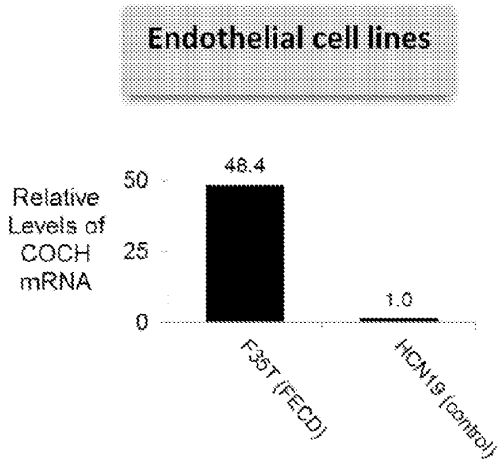
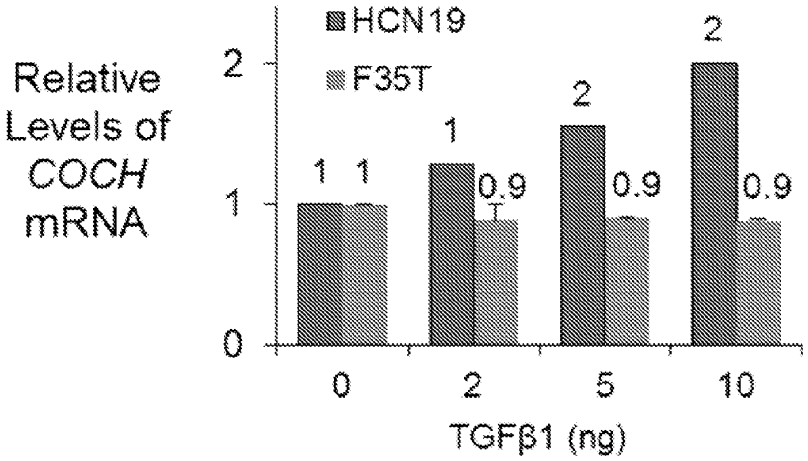


FIG. 25

A


Relative Levels of *COCH* mRNA
HCN19
F35T
2
1
0
1 1
1
0.9
2
0.9
2
0.9
0 2 5 10
TGFβ1 (ng)

B

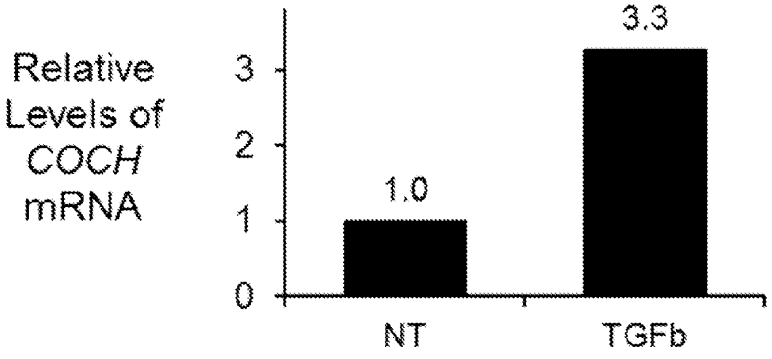
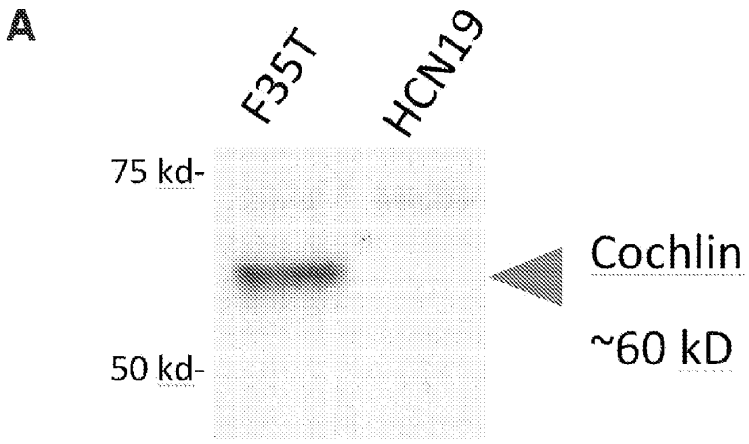

Relative Levels of *COCH* mRNA
3
2
1
0
1.0
3.3
NT
TGFb

FIG. 26


A
F35T
HCN19
75 kd-
50 kd-
Cochlin
~60 kD

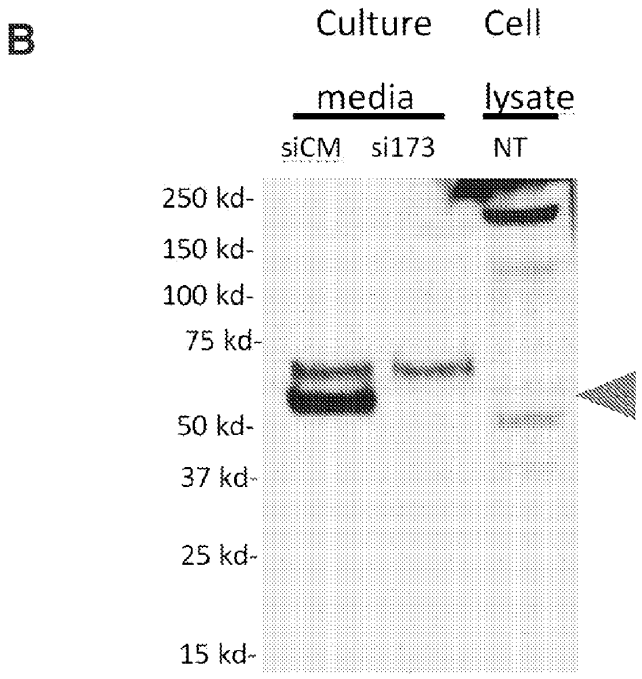

B
Culture media
Cell lysate
siCM
si173
NT
250 kd-
150 kd-
100 kd-
75 kd-
50 kd-
37 kd-
25 kd-
15 kd-

FIG. 27

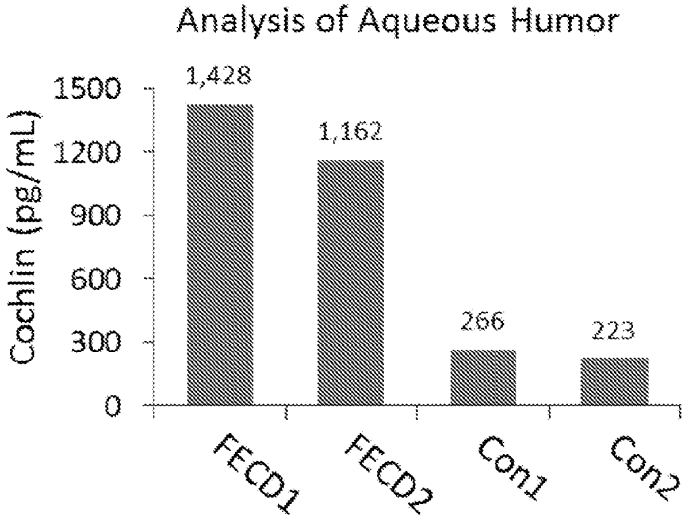
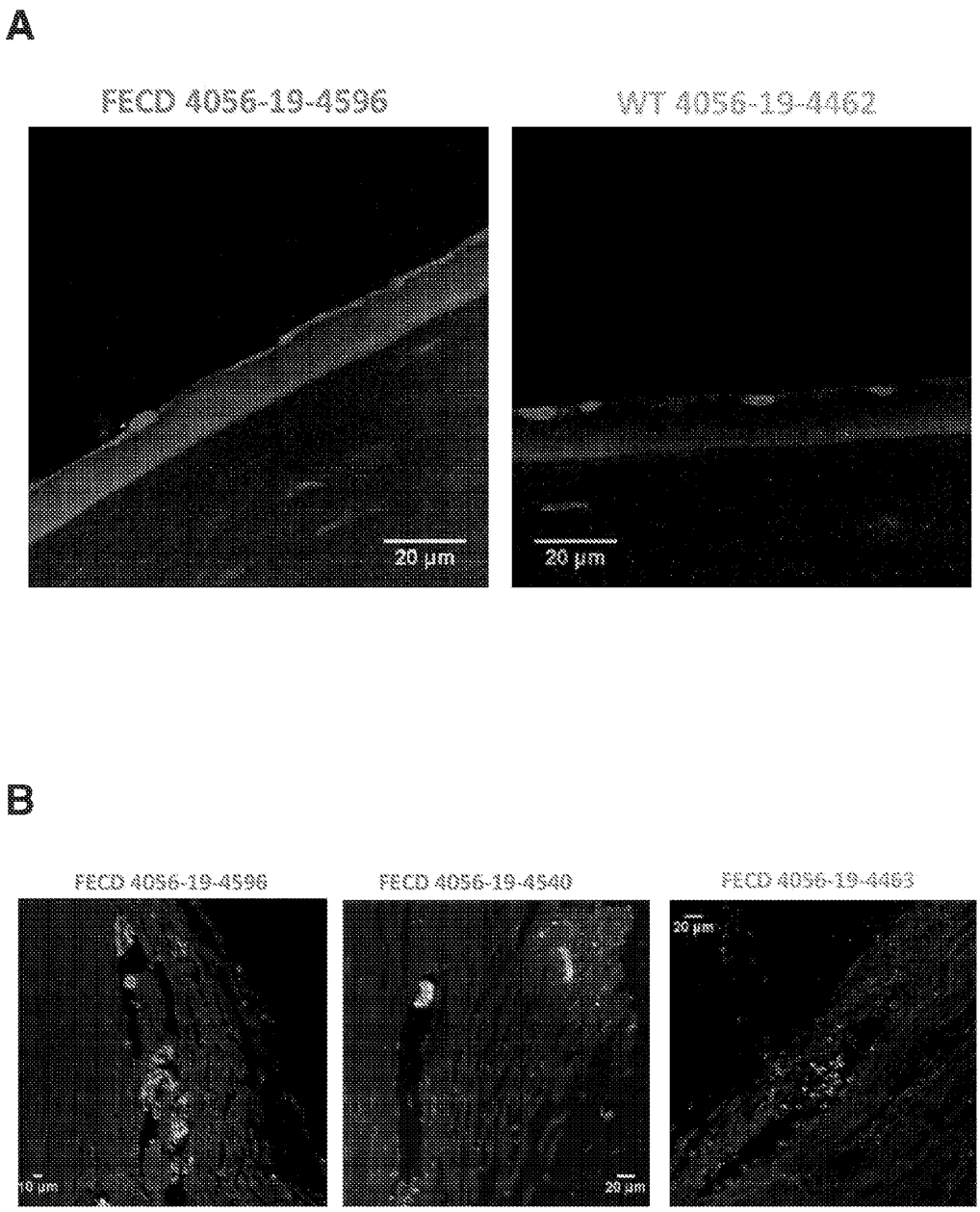

Analysis of Aqueous Humor
Cochlin (pg/mL)
1500
1200
900
600
300
0
1,428
1,162
266
223
FECD1
FECD2
Con1
Con2

FIG. 28


A
FECD 4056-19-4596
WT 4056-19-4462
20 µm
20 µm
B
FECD 4056-19-4596
FECD 4056-19-4640
FECD 4056-19-4463
20 µm

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/019467

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61P 27/02; C12Q 1/6851 (2021.01)
CPC - A61P 27/02; C12Q 1/6851; C12Q 2600/112; C12Q 2600/118; C12Q 2600/158 (2021.05)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
see Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
see Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
see Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2016/0266114 A1 (KYOTO PREFECTURAL PUBLIC UNIVERSITY CORPORATION et al) 15 September 2016 (15.09.2016) entire document	1-3 --- 4-14
X -- Y	BHATTACHARYA et al. "Cochlin as a Glaucoma Molecular Biomarker," Glaucoma Today, 31 October 2015 (31.10.2015), Pgs. 12-16. entire document	15, 16 --- 17-27
Y	US 2010/0184824 A1 (MCSWIGGEN et al) 22 July 2010 (22.07.2010) entire document	4, 5
Y	US 2019/0008985 A1 (FACTOR BIOSCIENCE INC.) 10 January 2019 (10.01.2019) entire document	6, 7
Y	WO 2019/109026 A1 (MIRAGEN THERAPEUTICS, INC.) 06 June 2019 (06.06.2019) entire document	8-14
Y	US 2014/0018527 A1 (SYLENTIS S.A.U) 16 January 2014 (16.01.2014) entire document	17-19
Y	US 2009/0035279 A1 (THORLEIFSSON et al) 05 February 2009 (05.02.2009) entire document	20-24
Y	US 2008/0305103 A1 (SARAGOVI) 11 December 2008 (11.12.2008) entire document	25-27
A	US 2016/0175380 A1 (THE SCHEPENS EYE RESEARCH INSTITUTE, INC.) 23 June 2016 (23.06.2016) entire document	1-27

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 May 2021	JUN 22 2021
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Harry Kim Telephone No. PCT Helpdesk: 571-272-4300

Form PCT/ISA/210 (second sheet) (July 2019)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/019467

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☒ furnished subsequent to the international filing date for the purposes of international search only:

      ☒ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(54) Title: MODULATION OF WNT SIGNALLING IN CORNEAL DISORDERS

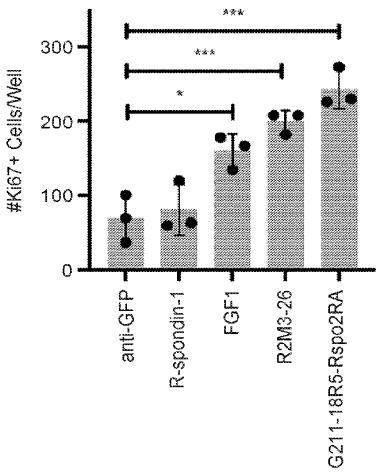


FIG. 2A

(57) Abstract: The present disclosure provides methods of treating corneal disorders with modulators of the WNT signalling pathway. More particularly, provided are treatments for cornea epithelial and/or endothelial injuries, defects, deficiencies, and dystrophies. Further provided are methods of dosing and pharmaceutical compositions for the treatment of corneal disorders.

[Continued on next page]

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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

— *with sequence listing part of description (Rule 5.2(a))*

MODULATION OF WNT SIGNALLING IN CORNEAL DISORDERS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application Serial No. 63/353,968, filed June 21, 2022, and U.S. Provisional Patent Application Serial No. 63/469,499, filed May 29, 2023, the entire contents of which are incorporated herein by reference.

SEQUENCE LISTINGS

[0002] The Sequence Listing XML associated with this application is provided in XML file format and is hereby incorporated by reference into the specification. The name of the XML file containing the Sequence Listing XML is SRZN_021_03WO_ST26.xml. The XML file is 21,937 bytes, and created on June 10, 2023, and is being submitted electronically via USPTO Patent Center.

FIELD OF THE INVENTION

[0003] The disclosure provides WNT signal modulators to treat various corneal disorders. More particularly, provided are treatments for cornea epithelial and/or endothelial injuries, defects, deficiencies, and dystrophies.

BACKGROUND

[0004] The vertebrate cornea is an optically clear layered tissue representing the first and strongest refractive medium of the eye's anatomy. (Patel & Tutchenko, *Contact Lens & Ant. Eye*, 2019 Oct 42(5), 575–80.) The cornea must remain sturdy to contain and protect the eye; transparent to allow visible light to pass into the eye; and appropriately shaped, symmetrical, and smoothed to properly refract and direct a sharp image to the image-forming retina tissue at the back of the eye.

[0005] Unfortunately, the cornea is susceptible to injury and disease that cause scarring, discoloration, or worse, which can severely impair vision and quality of life. Current treatments for corneal disorders, also called keratopathies, depend on the stage of the keratopathy. For mild keratopathies, supportive treatments such as saline eyedrops may be sufficient to ameliorate symptoms. For severe keratopathies, cornea transplant or cellular transplant may be necessary because currently there are no non-surgical treatment options

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available. Cornea and cellular transplants, i.e., keratoplasties, are costly, invasive, and risk tissue rejection. Further, available supply of donor cornea and cells is often lacking.

[0006] There may be a promising treatment avenue: signaling of the WNT developmental pathway has been implicated as important in the stratification and layering of mammalian cornea. (Zhang et al., *Development*, 2015 142:3383–93.) WNT signaling proteins are among the most important developmental signaling molecules in the animal kingdom. In animals ranging from fruit fly to mouse to frog to nematode worm to flatworm, involvement of WNT proteins has been demonstrated in body segmentation, central nervous system (CNS) patterning, dorsal/ventral axis formation, and much more. (*See, e.g.*, Wodarz & Nusse, *Annu. Rev. Cell Dev. Biol.*, 1998 14:59–88.)

[0007] Mutations and modulations of WNT proteins are also thought to play significant roles in numerous cancers and dystrophies. (Nusse, *Cell Res.*, 2005 (15), 28–32.) In the context of the cornea, it is unknown whether WNT modulation post-developmentally may lead to improvement in keratopathies (disorders of the cornea) and injuries. WNT signaling promotes growth and stemness of cornea endothelial and epithelial cells in vitro (Maurizi et al. *Sci. Rep.*, 2020; Nakatsu et al *Invest. Opthalm. Vis. Sci. 2011),* indicating that activating Wnt signaling may have a therapeutic effect in keratopathies where cornea cells are deficient. Wnt signaling is also central to fibrosis and elevated in corneal scarring (Chawla & Ghosh, *J. Cell Physiol.* 2017), indicating that antagonizing Wnt signaling may have a therapeutic effect in keratopathies involving scarring, fibrosis, EMT, and EnMT. (Kawashima et al. *Mol. Vis.*, 2013). Understanding the keratopathy disease progression and the WNT signal involvement extends to the possibilities of new treatments.

[0008] Furthermore, cornea tissue is one of several rare and valuable organ donor tissues. Cornea transplants may be used to treat numerous keratopathies. However, donated corneas may not grow or heal properly in the recipient subject. Accordingly, it would be desirable to have a treatment that would promote *ex vivo* cell growth in donated cornea tissue. Additionally, treatment could also occur post-transplant to increase the survival of transplanted tissue in the recipient.

[0009] Understanding keratopathy disease progression and the involvement of WNT signaling in this progression could extend possibilities of new treatments. The present disclosure provides methods of modulating WNT signaling to treat corneal epithelial and

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and endothelial tissues and cells.

BRIEF SUMMARY

[0010] The present disclosure is directed to WNT signaling modulators to treat various corneal disorders. More particularly, the present disclosure provides treatments for various keratopathic indications, including, e.g., cornea epithelial and/or endothelial injuries, defects, deficiencies, and dystrophies.

[0011] In some embodiments, the present disclosure provides a method of treating a subject suffering from a keratopathy or corneal injury comprising administering the subject, an engineered WNT signaling modulator. In certain embodiments, the WNT signaling modulator is an engineered WNT agonist or an engineered WNT antagonist. In further embodiments the engineered WNT agonist and WNT antagonist comprise binding compositions (or regions) that bind to one or more Fzd receptors and binding compositions (or regions) that bind to one or more LRP receptors. In further embodiments, the binding compositions of the engineered WNT agonist are selected from the group consisting of: a Fzd binding composition, a Lrp5 binding composition, a Lrp6 binding composition, or a LRP5/6 binding composition. In particular embodiments, the FZD binding composition of the engineered WNT agonist binds to one or more Fzd receptor selected from the group consisting of Fzd1, Fzd2, and Fzd7.

[0012] In some embodiments, the engineered WNT agonist or WNT antagonist are administered independently at early and/or late stages of keratopathy. In alternative embodiments, the WNT agonist and WNT antagonist are administered sequentially at early and/or late stages of keratopathy, or the WNT agonist and WNT antagonist are co-administered at early and/or late stages of keratopathy. In further embodiments, the WNT agonist is administered before or after the WNT antagonist.

[0013] In an aspect, the present disclosure provides a method of treating a keratopathy in a subject, comprising administering a WNT signaling modulator to the subject. In another embodiment, the present disclosure provides a method comprising administering the isolated polynucleotide encoding a polypeptide of the molecule, wherein the polynucleotide is optionally an mRNA, optionally a modified mRNA, or administering an expression vector comprising the isolated polynucleotide.

[0014] In preferred embodiments, the subject is a human patient. In some embodiments, the WNT signaling modulator may be an engineered WNT signaling modulator. In some

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embodiments, the WNT signaling modulator may be an engineered WNT agonist or an engineered WNT antagonist.

[0015] In a preferred embodiment, the engineered WNT agonist is selected from: (*i*) a WNT3a; (*ii*) a WNT mimetic; or (*iii*) an R-spondin mimetic or (iv) a WNT mimetic fused to a mutant R-spondin mimetic, referred to as a superSWAP or superagonist. See, e.g., PCT Application Publication No. WO 2021173726, which discloses non-limiting examples of superSWAP molecules. In a still preferred embodiment, the WNT mimetic is a SWAP™ compound, and the R-spondin mimetic is a SWEETS™ compound; and the molecule that encompasses the SWAP and the SWEETs in one combined molecule is referred to as superSWAP or superagonist. Particularly, the WNT signaling modulator may be a canonical WNT modulator or a non-canonical WNT modulator (see, e.g., Ackers and Malgor (2017) Diabetes & Vascular Res., 15:3-13).

[0016] In any embodiment of the method, the WNT signaling modulator may be co-administered with R-spondin, or any R-spondin homologue, mutant, fragment, mimic, or any combination thereof.

[0017] In any embodiment of the method, the wnt signaling modulator may be a WNT mimetic fused to a mutant Rspodin mimetic referred to here as superSWAP or superagonist.

[0018] In preferred embodiments, the WNT signaling modulator is administered to the subject in a therapeutically effective dose. In some embodiments, the WNT signaling modulator may be administered via eye drop, hydrogel, depot, or intraocular injection.

[0019] In any embodiment described herein, the WNT signaling modulator may be suspended in aqueous solution. The WNT signaling modulator may be suspended in aqueous solution at a concentration of about 0.01 pM, 0.1 pM, 1 pM, 0.01 nM, 0.1 nM, 1 nM, 10 nM, 100 nM, 1 μM, 10 μM, 100 μM, 1 mM, 10 mM, 100 mM, up to about 1 M. In preferred embodiments, the WNT signaling modulator is suspended in aqueous solution at a concentration ranging from about 0.1 nM to 1 μM. In still preferred embodiments, the WNT signaling modulator is suspended in aqueous solution at a concentration ranging from about 1 nM to 100 nM.

[0020] In any embodiment described herein, the subject's keratopathy may be a corneal dystrophy. More particularly, in any embodiment of the instant method, the keratopathy may be selected from the group consisting of: bacterial infections, viral infections, fungal infections, protozoan infections, archaeal infections, genetic disorders, brittle cornea syndrome (BCS),

corneal endothelial-mesenchymal transition (EnMT), corneal epithelial-mesenchymal transition (EMT), corneal fibrosis, Cogan syndrome, corneal ulcer, epithelial basement membrane dystrophy (EBMD), Fleck corneal dystrophy, Fuchs' dystrophy, gelatinous droplike corneal dystrophy, granular corneal dystrophy type I, granular corneal dystrophy type II, interstitial keratitis, iridocorneal endothelial syndrome (ICE), keratoconjunctivitis sicca, keratoconus, keratomalacia, lattice dystrophy type I, lattice dystrophy type II, Lisch corneal dystrophy, macular corneal dystrophy, Meesmann corneal dystrophy, bullous keratopathy, aniridia, peripheral ulcerative keratitis, phlyctenular keratoconjunctivitis, posterior polymorphous corneal dystrophy, pterygium, Reis-Bückler corneal dystrophy, Schnyder crystalline corneal dystrophy, Stevens-Johnson syndrome, superficial punctate keratitis, neurotrophic keratitis, herpetic keratitis, Thiel-Behnke corneal dystrophy, scarring, limbal stem cell deficiency, and any combination thereof. In preferred embodiments of the instant method, the keratopathy is selected from: limbal stem cell deficiency (LSCD), epithelial-mesenchymal transition; endothelial-mesenchymal transition; corneal fibrosis; corneal scarring, including post-transplant corneal scarring; or any combination thereof. In a still preferred embodiment of the instant method, the keratopathy is Fuchs' dystrophy.

[0021] Also described herein is a method of increasing cell yield of mammalian cornea epithelium and/or endothelium cells grown *ex vivo* prior to or post cornea transplant, comprising treating a mammalian donor cornea or isolated corneal cells with WNT signaling modulator. In preferred embodiments, the mammalian donor cornea is a human cornea. In other embodiments the isolated corneal cells are limbal cells or corneal endothelial cells. In some embodiments, the WNT signaling modulator may be an engineered WNT signaling modulator. In some embodiments, the WNT signaling modulator may be an engineered WNT agonist.

[0022] In a preferred embodiment of the method of increasing cell yield, the engineered WNT agonist is selected from: (*i*) WNT3a; (*ii*) a WNT mimetic; (*iii*) an R-spondin mimetic, or (iv) a WNT mimetic is fused to a mutant Rspondin mimetic, referred to as a superSWAP or superagonist. In a still preferred embodiment, the WNT mimetic is a SWAP^{TM} compound, the R-spondin mimetic is a SWEETS^{TM} compound, or a SuperSWAP or superagonist.

[0023] In some embodiments, the disclosure provides methods, wherein the WNT signaling modulator is any of:

a. WNT3a or any homologue, mutant, fragment, mimic of WNT3a;

b. G211-18R5;

c. R2M3-26;

d. 1SH1-03;

e. hp1SH1-03

f. 17SB9-03;

g. any of the above alone or in combination with one or more Rspondin, or another growth factor such as a fibroblast growth factor (FGF);

h. G211-18R5-Rspo2RA or G211-R2H1-Rspo2RA or other SuperSWAPs or Superagonists;

i. or a combination thereof of any of the aforementioned.

[0024] In certain embodiments, the engineered WNT agonist comprises a sequence having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in any of SEQ ID NOs:1-16. In particular embodiments, the engineered WNT agonist comprises one or more, e.g., two, sequence having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:1, and one or more, e.g., two, sequence having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:2. In particular embodiments, the engineered WNT agonist comprises one or more, e.g., two, sequence having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:3, and one or more, e.g., two, sequence having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:4. In particular embodiments, the engineered WNT agonist comprises one or more, e.g., two, sequence having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:5, and one or more, e.g., two, sequence having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:6. In particular embodiments, the engineered WNT agonist comprises two sequences having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:1, and two sequences having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:2. In particular embodiments, the engineered WNT agonist comprises two sequences having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:3, and two sequences having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:4. In particular embodiments, the engineered WNT agonist comprises two sequences having at least 90%, at

least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:5, and two sequences having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:6.

[0025] In some embodiments, the engineered WNT agonist comprises two sequences having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:7, and two sequences having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:8.

[0026] In particular embodiments, the engineered WNT agonist comprises one or more, e.g., two, sequence having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:9, and one or more, e.g., two, sequence having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:10. In particular embodiments, the engineered WNT agonist comprises one or more, e.g., two, sequence having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:11, and one or more, e.g., two, sequence having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:12. In particular embodiments, the engineered WNT agonist comprises one or more, e.g., two, sequence having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:13, and one or more, e.g., two, sequence having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:14. In particular embodiments, the engineered WNT agonist comprises one or more, e.g., two, sequence having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:15, and one or more, e.g., two, sequence having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:16.

[0027] In any embodiment of the method of increasing cell yield, the WNT signaling modulator may be administered or co-administered with R-spondin, or any R-spondin homologue, mutant, fragment, mimic, or any combination thereof.

[0028] In preferred embodiments, the WNT signaling modulator is administered to the subject in a therapeutically effective dose. In any embodiment described herein, the WNT signaling modulator may be suspended in aqueous solution. The WNT signaling modulator may be suspended in aqueous solution at a concentration of about 0.01 pM, 0.1 pM, 1 pM, 0.01 nM, 0.1 nM, 1 nM, 10 nM, 100 nM, 1 μM, 10 μM, 100 μM, 1 mM, 10 mM, 100 mM, up to

about 1 M. In preferred embodiments, the WNT signaling modulator is suspended in aqueous solution at a concentration ranging from about 0.1 nM to 1 μM. In still preferred embodiments, the WNT signaling modulator is suspended in aqueous solution at a concentration ranging from about 1 nM to 100 nM.

[0029] In preferred embodiments of the method of increasing cell yield, the WNT signaling modulator is administered to the mammalian donor cornea by bathing the mammalian donor cornea in vitro in an aqueous bath solution containing a dose of WNT signaling modulator. In other embodiments, the WNT signaling modulator is applied to limbal stem cells or corneal endothelial cells prior or post transplantation.

[0030] In preferred embodiments, the engineered WNT agonist and engineered WNT antagonist comprise binding compositions that bind to one or more Fzd receptors and binding compositions that bind to one or more LRP receptors. In still preferred embodiments of the method of increasing cell yield, the binding compositions of the engineered WNT agonist are selected from the group consisting of a Fzd binding composition, a Lrp5 binding composition, a Lrp6 binding composition, and a LRP5/6 binding composition.

BRIEF DESCRIPTION OF THE DRAWINGS

[0031] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0032] Fig. 1A depicts micrographs of fluorescent stained donor corneal endothelial tissue in healthy "normal" eye donors that have been stained for Fzd receptors, Fzd 1, 2, 4, 5, 7, 8, 9, and 10, using in situ hybridization, rendered here in green. Since Fzds1, 2, and 7 were the most prominently expressed, Fzds 1, 2, 7 expression in FECD patients has been the focus.

[0033] Fig. 1B depicts micrographs in additional healthy "normal" patients and in patients diagnosed with Fuchs' dystrophy, a keratopathic disorder. WNT and R-spondin receptors Lrp5/6; Fzd1/2/7; and ZNRF3, an E3 ubiquitin ligase, were stained using in situ hybridization, rendered here in green. The corneal endothelium marker Na+K+ ATPase was stained using immunofluorescence, rendered here in red. DNA is stained with 4′,6-diamidino-2-phenylindole (DAPI), rendered here in grey-white.

[0034] Fig. 2A depicts a graph of #Ki67+ (proliferation marker) cells per well in human corneal endothelial cells treated with FGF1, R-spondin-1, the WNT-mimetic compound

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R2M3-26, or the WNT superagonist or SuperSWAP G211-18R5-Rspo2RA. The results indicate that WNT mimetic and WNT superagonist or superSWAP increase proliferation of human corneal endothelial cells. * $p \leq 0.05$. ** $p \leq 0.01$. *** $p \leq 0.001$. Statistical analysis was performed using an unpaired two-tailed t test.

[0035] Fig. 2B depicts a graph of %Ki67+ cells in human corneal endothelial cells treated with FZD1/2/5/7/8 + LRP6-binding WNT mimetic R2M3-26 or FZD1/2/7 + LRP6-binding WNT mimetic 1RC07-26. The results indicate that WNT mimetics binding to FZD1/2/5/7/8 and LRP6 increase proliferation of human corneal endothelial cells. * $p \leq 0.05$. ** $p \leq 0.01$. Statistical analysis was performed using an unpaired two-tailed t test.

[0036] Fig. 2C depicts a graph of %Ki67+ cells in human corneal endothelial cells treated with the WNT superagonists or superSWAPs, G211-18R5-Rspo2RA or G211-R2H1-Rspo2RA. The results indicate that WNT superagonist or superSWAP binding to FZD1,2,7 and LRP6 is as effective as WNT superagonist or superSWAP G211-18R5-Rspo2RA (which binds to FZD1/2/5/7/8 + LRP6-binding) in increasing proliferation of human corneal endothelial cells. * $p \leq 0.05$. ** $p \leq 0.01$. Statistical analysis was performed using an unpaired two-tailed t test.

[0037] Fig. 2D depicts fluorescence micrographs of untreated primary human corneal endothelial cells and primary human corneal endothelial cells treated with WNT mimetic G211-18R5 + R-spondin-1. The images indicate that WNT agonists increase proliferation of cultured human corneal endothelial cells.

[0038] Fig. 2E depicts fluorescent micrographs of cornea from a human organ donor with Fuchs' dystrophy, both untreated and treated with WNT mimetic G211-18R5 + R-spondin-1. The images indicate that WNT agonists increase proliferation of human corneal endothelial cells in cornea organ culture.

[0039] Fig. 3A depicts the change in Axin2 RNA transcript levels in corneas from mice injected intracamerally with anti-GFP isotype control antibody or wnt mimetic R2M3-26 (61 pmol each).

[0040] Fig. 3B depicts micrographs of fluorescent stained corneal endothelium from mice injected intracamerally with anti-GFP or SWAP, R2M3-26 (61 pmol each). WNT target gene Axin2 was stained using in situ hybridization, rendered here in green. DNA is stained with 4′,6-diamidino-2-phenylindole (DAPI), rendered here in blue.

[0041] Fig. 3C depicts the change in Axin2 RNA transcript levels in corneas from mice injected intracamerally (IC) or intravitreally (IVT) with anti-GFP or wnt superagonist or superSWAP, G211-18R5-Rspo2RA (2.6 mg each).

[0042] Fig. 3D depicts micrographs of fluorescent stained corneal endothelium from mice injected intracamerally with anti-GFP or G211-18R5-Rspo2RA (7 pmol each). WNT target gene Axin2 was stained using in situ hybridization, rendered here in green. DNA is stained with 4′,6-diamidino-2-phenylindole (DAPI), rendered here in blue.

[0043] Figs. 3E-3F depict central corneal thickness measurements (Fig. 3E) and endothelial lesion size measurements (Fig. 3F) from rabbits 3 days after resection of the central 10 mm of the corneal endothelium. Rabbits were injected intracamerally on day 0 with anti-GFP or R2M3-26.

[0044] Figs. 3G-3I, from a separate study, depict central corneal thickness measurements (Fig. 3H), endothelial lesion size (Fig. 3G) and corneal opacity (Fig. 3I) measurements from rabbits 3 days after resection of central 10 mm of the corneal endothelium. Rabbits were injected intracamerally on day 0 with anti-GFP or wnt superagonist or superSWAP, G211-18R5-Rspo2RA. The data in Figs. 3G-3I show a significant improvement in the corneal opacity score with the high dose of wnt superagonist or superSWAP, while there appears to be a trend of decrease in corneal thickness in Fig. 3H.

[0045] Figs. 4A-4C illustrate that the wnt superagonist or superSWAP, G211-18R5-Rspo2RA, reduces corneal thickness (Fig. 4A), improves clarity (Fig. 4B) and shows pharmacodynamic response (PD) (Fig. 4C) in a corneal cryoinjury mouse model. Relative to Anti-GFP isotype control, 5 ug of intravitreally (IVT) injected wnt superagonist or superSWAP, G211-18R5-Rspo2RA showed a significant reduction in central corneal thickness (compilation of 6 independent studies), as measured by optical coherence tomography (OCT) (Fig. 4A) and an improvement in corneal clarity in response to the cryoinjury (representative images from one such study) as measured by brightfield imaging of the anterior chamber of the eye (Fig. 4B). Wnt superagonist or superSWAP showed significant induction of Axin2 mRNA (Wnt target gene) on day 4 in corneal homogenates from one such study where G211-18R5-Rspo2RA or Anti-GFP antibody were administered intravitreally in the mice after cryoinjury (Fig. 4C).

[0046] Figs. 5A-5B show that 1SH1-03 reduces % corneal thickness and improves corneal clarity in a corneal cryoinjury mouse model. Fig. 5A is a graph showing that relative to anti-

GFP isotype control and 5 ug of 1SH1-03, 25 ug of intravitreally (IVT) injected 1SH1-03 showed a significant reduction in central corneal thickness (compilation of 2 independent studies) as measured by optical coherence tomography (OCT). At the 2 day timepoint, the lines from top to bottom correlate to: GFP, 1SH1-03 5ug, and 1SH1-03 25ug, respectively. Fig. 5B shows brightfield images showing that 1SH1-03 showed an improvement in corneal clarity in response to the cryoinjury as measured by brightfield imaging of the anterior chamber of the eye (representative images from one such study).

[0047] Fig. 6 are images showing that the Wnt mimetic, hp1SH1-03, shows a reduction in corneal endothelial lesion size in mice after corneal cryoinjury. In eyes after cryoinjury, intravitreally (IVT) injected hp1SH1-03 showed a reduction in lesion size relative to Anti-GFP isotype control. The figure depicts a corneal flat mount from eyes from the above treatment groups, which has been subjected to immunofluorescence and stained with Ki67 (rendered in red) and Dapi (in blue) and imaged on confocal microscope. While there is a lesion in the central region in the Anti-GFP isotype treated group which is devoid of proliferating Ki67 cells, there appears to be no detectable lesion in the hp1SH1-03-treated eyes and the region is marked by proliferating corneal endothelial cells.

[0048] Figs. 7A-7B show that hp1SH1-03 induces robust proliferation in injured and uninjured human corneal endothelial cells (HCEC). Whole human corneas obtained from eye banks were cut into quarters, and treated with 5nM of hp1SH1-03for 2 days. Fig. 7A shows corneal endothelial cells were detected by ZO-1, and the proliferation rate was measured by counting the proportion of CECs expressing a proliferation marker, Ki67. Fig. 7B is the quantitative analysis, and reveals that hp1SH1-03 dramatically promotes HCEC proliferation, and this proliferation is more pronounced in the wound area; ~6 times higher in the edge and ~3 times higher in the mid-zone compared to anti-GFP treated eyes.

[0049] Figs. 8A-8B show that the Wnt superagonist or superSWAP G211-18R5Rspo2RA shows increased PD response in the UV-A damage-induced FECD rodent model. Fig. 8A depicts the change in Axin2 RNA transcript levels in corneas from mice injected intravitreally (IVT) with anti-GFP or G211-18R5-Rspo2RA (2.6 ug each) in naïve mice or mice whose right eye was treated with 500 J/cm2 of UV-A light. Fig 8B depicts central corneal thickness (CCT) in UV-A treated mice described in Fig. 8A and subjected to optical coherence tomography for the measurement of CCT as a measure of corneal swelling. There is a trend of decreased CCT in response to Wnt superagonist or superSWAP G211-18R5-Rspo2RA on day 2 post treatment.

[0050] Figs. 9A-9B show expression levels of various markers. Fig. 9A depicts fluorescence micrographs of human cornea samples stained for various WNT receptors, cornea and limbal zonal markers, and DNA. Images are of cornea and limbal epithelium. Fig. 9B is a table indicating the expression levels of various WNT and R-spondin receptors in cornea epithelium and limbal epithelium.

[0051] Figs. 10A-10B show expression of Axin2 and p63. Fig. 10A depicts the change in Axin2 RNA transcript levels in rabbit limbal epithelial organoids after 1 week of treatment with 5 nM WNT mimetic R2M3-26 or 1 μg/mL R-spondin-1. * $p \leq 0.05$. *** $p \leq 0.001$. Statistical analysis was performed using an unpaired two-tailed t test. Fig. 10B depicts the change in p63 RNA transcript levels in rabbit limbal epithelial organoids after 1 week of treatment with 5 nM WNT mimetic R2M3-26 or 1 μg/mL R-spondin-1. * $p \leq 0.05$. Statistical analysis was performed using an unpaired two-tailed t test.

[0052] Figs. 11A-11C depict data indicating increased cell growth and proliferation in human corneal epithelium. Fig. 11A depicts cell growth data in cells treated for two days with WNT mimetic G211-18R5. Cell numbers were measured using CellTiter-Glo® assay. Fig. 11B depicts Ki67+ cell proliferation data after treatment with WNT mimetic R2M3-26. Proliferation was measured analyzing immunofluorescence micrographs. Fig. 11C depicts cell growth data in cells treated for two days with R-spondin-1. In each of Figs., statistical analysis was performed using an unpaired two-tailed t test.

[0053] Figs. 12A-12B depict micrographs of an in vitro wound healing assay. Human corneal epithelial cells were plated around a physical barrier. The physical barrier was removed, leaving a gap. Cells were cultured were two days in a medium without (Fig. 12A) and with (Fig. 12B) WNT mimetic R2M3-26. Cells were then stained with DAPI and imaged, and the size of the gap was measured.

[0054] Fig 13 shows that topical Fc-Rspo2 eye drops reduce corneal epithelial defects in corneal epithelial debridement mouse model. Fig.13 depicts fluorescent and brightfield micrographs of central cornea epithelium from eyes of naïve mice, and mice 7 days after limbus-to-limbus debridement either treated with anti-GFP eyedrops (5 mg/mL, 3 uL, 4x a day) or Fc-Rspondin-2 eyedrops (5 mg/mL, 3 uL, 4x a day). WNT target gene Axin2 was stained using in situ hybridization, rendered here in red. DNA is stained with 4′,6-diamidino-2-phenylindole (DAPI), rendered here in blue. Progenitor marker p63 was stained using immunofluorescence, rendered here in green. Hematoxylin and eosin (H&E) staining is also

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depicted. The data illustrate that R-spondin eyedrops activate Wnt signaling, expand progenitor cells, thicken cornea epithelium and reduce conjunctivalization.

[0055] Fig. 14 depicts fluorescent micrographs of cornea from a human organ donor staining for THBD (Thrombomodulin/CD141/BDCA-3, a high affinity thrombin receptor present on endothelial cell membrane) showing specific staining in the membrane in the central cornea and the limbus but not in the conjunctiva), rendered here in green. DNA is stained with 4′,6-diamidino-2-phenylindole (DAPI), rendered here in blue. The data in Fig. 14 suggests that THBD can be employed for generating a limbal-targeted Rspo mimetic/ SWEETs™ molecule for corneal regeneration.

[0056] Fig. 15A depicts a schematic representation of murine conjunctival and cornea epithelial organoids derived from primary tissue. Expanded cultures maintain markers such as keratin 12 (Ck12) or keratin 19 (Ck19).

[0057] Fig. 15B depicts the change in Axin2 mRNA transcript levels in conjunctival or cornea epithelium organoids treated with different WNT mimetics. R2M3-26 is a FZD12578 targeting WNT mimetic. 17SB9 is a FZD8 biased WNT mimetic. Data is normalized to untreated control per tissue. The data in Fig. 15B suggests that 17SB9-03-Rspo-mimetic can be for employed for generating a corneal epithelial-targeted Fzd8-Rspo mimetic/ SWEETs™ molecule for corneal regeneration.

DETAILED DESCRIPTION

[0058] As used herein, including the appended claims, the singular forms of words such as "a," "an," and "the," include their corresponding plural references unless the context clearly dictates otherwise.

[0059] All references cited herein are incorporated by reference to the same extent as if each individual publication, patent application, or patent, was specifically and individually indicated to be incorporated by reference.

I. Definitions.

[0060] "Activity" of a molecule may describe or refer to the binding of the molecule to a ligand or to a receptor, to catalytic activity, to the ability to stimulate gene expression, to antigenic activity, to the modulation of activities of other molecules, and the like. "Activity" of a molecule may also refer to activity in modulating or maintaining cell-to-cell interactions, e.g., adhesion, or activity in maintaining a structure of a cell, e.g., cell membranes or

cytoskeleton. "Activity" may also mean specific activity, e.g., [catalytic activity]/[mg protein], or [immunological activity]/[mg protein], or the like.

[0061] The terms "administering" or "introducing" or "providing", as used herein, refer to delivery of a composition to a cell, to cells, tissues and/or organs of a subject, or to a subject. Such administering or introducing may take place *in vivo*, *in vitro* or *ex vivo*.

[0062] As used herein, the term "antibody" means an isolated or recombinant binding agent that comprises the necessary variable region sequences to specifically bind an antigenic epitope. Therefore, an antibody is any form of antibody or fragment thereof that exhibits the desired biological activity, e.g., binding the specific target antigen. Thus, it is used in the broadest sense and specifically covers monoclonal antibodies (including full-length monoclonal antibodies), polyclonal antibodies, human antibodies, humanized antibodies, chimeric antibodies, nanobodies, diabodies, multispecific antibodies (e.g., bispecific antibodies), and antibody fragments including, but not limited to, scFv, Fab, and Fab2, so long as they exhibit the desired biological activity.

[0063] "Antibody fragments" comprise a portion of an intact antibody, for example, the antigen-binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', F(ab')2, and Fv fragments; diabodies; linear antibodies (e.g., Zapata et al., *Protein Eng*. 8(10): 1057-1062 (1995)); single-chain antibody molecules (e.g., scFv); and multispecific antibodies formed from antibody fragments. Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment, a designation reflecting the ability to crystallize readily. Pepsin treatment yields an F(ab')2 fragment that has two antigen combining sites and is still capable of cross-linking antigen.

[0064] The term "antigen" refers to a molecule or a portion of a molecule capable of being bound by a selective binding agent, such as an antibody, and additionally capable of being used in an animal to produce antibodies capable of binding to an epitope of that antigen. In certain embodiments, a binding agent (e.g., a WNT surrogate molecule or binding region thereof, or a WNT antagonist) is said to specifically bind an antigen when it preferentially recognizes its target antigen in a complex mixture of proteins and/or macromolecules.

[0065] The term "antigen-binding fragment" as used herein refers to a polypeptide fragment that contains at least one complementarity-determining region (CDR) of an immunoglobulin heavy and/or light chain, or of a VHH/sdAb (single domain antibody) or

Nanobody® (Nab), that binds to the antigen of interest, in particular to one or more Fzd receptors, or to LRP5 and/or LRP6. In this regard, an antigen-binding fragment of the herein described antibodies may comprise 1, 2, 3, 4, 5, or all 6 CDRs of a VH and VL from antibodies that bind one or more Fzd receptors or LRP5 and/or LRP6.

[0066] As used herein, the terms "biological activity" and "biologically active" refer to the activity attributed to a particular biological element in a cell. For example, the "biological activity" of a WNT agonist, or fragment or variant thereof refers to the ability to mimic or enhance WNT signals. As another example, the biological activity of a polypeptide or functional fragment or variant thereof refers to the ability of the polypeptide or functional fragment or variant thereof to carry out its native functions of, e.g., binding, enzymatic activity, etc. As a third example, the biological activity of a gene regulatory element, e.g., promoter, enhancer, Kozak sequence, and the like, refers to the ability of the regulatory element or functional fragment or variant thereof to regulate, i.e., promote, enhance, or activate the translation of, respectively, the expression of the gene to which it is operably linked.

[0067] The term "bifunctional antibody," as used herein, refers to an antibody that comprises a first arm having a specificity for one antigenic site and a second arm having a specificity for a different antigenic site, i.e., the bifunctional antibodies have a dual specificity.

[0068] "Bispecific antibody" refers to a full-length antibody that is generated by quadroma technology (*see* Milstein et al., *Nature*, 305(5934): 537-540 (1983)), by chemical conjugation of two different monoclonal antibodies (*see* Staerz et al., *Nature*, 314(6012): 628-631 (1985)), or by knob-into-hole or similar approaches, which introduce mutations in the Fc region (*see* Holliger et al., *Proc. Natl. Acad. Sci. USA*, 90(14): 6444–6448 (1993)), resulting in multiple different immunoglobulin species of which only one is the functional bispecific antibody. A bispecific antibody binds one antigen (or epitope) on one of its two binding arms (one pair of HC/LC), and binds a different antigen (or epitope) on its second arm (a different pair of HC/LC). By this definition, a bispecific antibody has two distinct antigen-binding arms (in both specificity and CDR sequences) and is monovalent for each antigen to which it binds.

[0069] By "comprising," it is meant that the recited elements are required in, for example, the composition, method, kit, etc., but other elements may be included to form the, for example, composition, method, kit etc. within the scope of the claim. For example, an expression cassette "comprising" a gene encoding a therapeutic polypeptide operably linked to a promoter is an

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expression cassette that may include other elements in addition to the gene and promoter, e.g., poly-adenylation sequence, enhancer elements, other genes, linker domains, etc.

[0070] By "consisting essentially of," it is meant a limitation of the scope of the, for example, composition, method, kit, etc., described to the specified materials or steps that do not materially affect the basic and novel characteristic(s) of the, for example, composition, method, kit, etc. For example, an expression cassette "consisting essentially of" a gene encoding a therapeutic polypeptide operably linked to a promoter and a polyadenylation sequence may include additional sequences, e.g., linker sequences, so long as they do not materially affect the transcription or translation of the gene. As another example, a variant, or mutant, polypeptide fragment "consisting essentially of" a recited sequence has the amino acid sequence of the recited sequence plus or minus about 10 amino acid residues at the boundaries of the sequence based upon the full length naïve polypeptide from which it was derived, e.g., 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 residue less than the recited bounding amino acid residue, or 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 residues more than the recited bounding amino acid residue.

[0071] By "consisting of," it is meant the exclusion from the composition, method, or kit of any element, step, or ingredient not specified in the claim. For example, a polypeptide or polypeptide domain "consisting of" a recited sequence contains only the recited sequence.

[0072] A "control element" or "control sequence" is a nucleotide sequence involved in an interaction of molecules that contributes to the functional regulation of a polynucleotide, including replication, duplication, transcription, splicing, translation, or degradation of the polynucleotide. The regulation may affect the frequency, speed, or specificity of the process, and may be enhancing or inhibitory in nature. Control elements known in the art include, for example, transcriptional regulatory sequences such as promoters and enhancers. A promoter is a DNA region capable under certain conditions of binding RNA polymerase and initiating transcription of a coding region usually located downstream (in the 3' direction) from the promoter.

[0073] As used herein, "cornea" and "corneal" refers to the optically clear layered tissue which covers the iris, pupil, and anterior chamber of the eye. The "corneal limbus" or "limbus" refers to the more-or-less-circular border where the cornea meets the sclera of the eye. It should be readily understood to persons having ordinary skill in the art that the border between cornea tissue and limbus tissue is imprecise, and that reference to the "cornea" should be understood to encompass an approximate margin. The cornea comprises five cell layers: (1) epithelium

(the external-most layer, a smooth optical surface and a barrier to chemicals, water, and microbes); (2) Bowman's layer (helps maintain the precise convex shape); (3) stroma (the main mechanical structure and refractive medium of the cornea); (4) Descemet's membrane (the resting layer for the endothelium); and (5) endothelium (maintains clarity by removing water from the stroma).

[0074] As used herein "Limbal cell deficiency" or "Limbal stem cell deficiency" is a genetic, acquired or idiopathic deficiency or complete loss of the stem cells in the limbus that are vital for re-population of the corneal epithelium. Loss or deficiency of Limbal stem cells leaves the corneal epithelium unable to repair or renew, leading to corneal conjunctivalization, neovascularization, corneal scarring, and chronic inflammation.

[0075] As used herein, "corneal dystrophy" refers generally to a disorder characterized by abnormal discoloration, clouding, and/or opacity of any layer or combination of layers of the cornea. Corneal dystrophies may be heritable or non-heritable. They may be caused by abnormal cell growth and/or by deposition and accumulation of collagens, lipids, cholesterols, and/or other extraneous material.

[0076] "Fuchs' dystrophy" (also called Fuchs' endothelial cell dystrophy (FECD), Fuchs' corneal dystrophy (FCD)) is a class of degenerative diseases of the cornea endothelium monolayer, characterized by a decline in endothelial cell density, corneal guttata, and an accumulation of corneal edema, leading to opacity of the cornea and a decline in vision.

[0077] As used herein, the term "engineered" indicates that a molecule, e.g., a Wnt signaling modulator, is non-naturally occurring, e.g., is the result of genetic engineering.

[0078] An "expression vector" is a vector, e.g., plasmid, minicircle, viral vector, liposome, and the like as discussed herein or as known in the art, comprising a region which encodes a gene product of interest, and is used for effecting the expression of the gene product in an intended target cell. An expression vector also comprises control elements, e.g., promoters, enhancers, untranslated regions (UTRs), miRNA targeting sequences, etc., operatively linked to the encoding region to facilitate expression of the gene product in the target. The combination of control elements and a gene or genes to which they are operably linked for expression is sometimes referred to as an "expression cassette," a large number of which are known and available in the art or can be readily constructed from components that are available in the art.

[0079] As used herein, the term "FR set" refers to the four flanking amino acid sequences which frame the CDRs of a CDR set of a heavy or light chain V region. Some FR residues may contact bound antigen; however, FRs are primarily responsible for folding the V region into the antigen-binding site, particularly the FR residues directly adjacent to the CDRs. Within FRs, certain amino residues and certain structural features are very highly conserved. In this regard, all V region sequences contain an internal disulfide loop of around 90 amino acid residues. When the V regions fold into a binding-site, the CDRs are displayed as projecting loop motifs which form an antigen-binding surface. It is generally recognized that there are conserved structural regions of FRs which influence the folded shape of the CDR loops into certain "canonical" structures—regardless of the precise CDR amino acid sequence. Further, certain FR residues are known to participate in non-covalent interdomain contacts which stabilize the interaction of the antibody heavy and light chains.

[0080] The terms "individual," "host," "subject," and "patient" are used interchangeably herein, and refer to a mammal, including, but not limited to, human and non-human primates, including simians and humans; mammalian sport animals (e.g., horses); mammalian farm animals (e.g., sheep, goats, etc.); mammalian pets (dogs, cats, etc.); and rodents (e.g., mice, rats, etc.).

[0081] As used herein, the term "isolated" indicates the molecule, e.g., a naturally-occurring molecule, is not in its native environment or has been separated from one or more component present in its native environment or from one or more component present during manufacturing of the molecule.

[0082] As used herein, the terms "keratopathy" and "keratopathic" refer to disease or disorder of the eye, in particular of the cornea and/or limbus of the eye. Keratopathies include, but are not necessarily limited to, bacterial infections, viral infections (e.g., herpes simplex keratitis and herpes zoster ophthalmicus (i.e., shingles)), fungal infections, protozoan infections, archaeal infections, genetic disorders, brittle cornea syndrome (BCS), corneal endothelial-mesenchymal transition (EnMT), corneal epithelial-mesenchymal transition (EMT), corneal fibrosis, Cogan syndrome, corneal ulcer, epithelial basement membrane dystrophy (EBMD, ABMD, Map Dot), Fleck corneal dystrophy, Fuchs' dystrophy (also called Fuchs' corneal endothelial dystrophy (FCED) or Fuchs' endothelial dystrophy (FED)), gelatinous droplike corneal dystrophy, granular corneal dystrophy type I, granular corneal dystrophy type II, interstitial keratitis, iridocorneal endothelial syndrome (ICE), keratoconjunctivitis sicca, keratoconus, keratomalacia, lattice dystrophy type I, lattice

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dystrophy type II, Lisch corneal dystrophy, macular corneal dystrophy, Meesmann corneal dystrophy, bullous keratopathy, aniridia, peripheral ulcerative keratitis, phlyctenular keratoconjunctivitis, posterior polymorphous corneal dystrophy, pterygium, Reis-Bückler corneal dystrophy, Schnyder crystalline corneal dystrophy, Stevens-Johnson syndrome, superficial punctate keratitis, Thiel-Behnke corneal dystrophy, neurotrophic keratitis, herpetic keratitis, scarring, and limbal stem cell deficiency.

[0083] A "monoclonal antibody" refers to a homogeneous antibody population wherein the monoclonal antibody is comprised of amino acids (naturally occurring and non-naturally occurring) that are involved in the selective binding of an epitope. Monoclonal antibodies are highly specific, being directed against a single epitope. The term "monoclonal antibody" encompasses not only intact monoclonal antibodies and full-length monoclonal antibodies, but also fragments thereof (such as Fab, Fab', F(ab')2, Fv), single chain (scFv), Nanobodies®, variants thereof, fusion proteins comprising an antigen-binding fragment of a monoclonal antibody, humanized monoclonal antibodies, chimeric monoclonal antibodies, and any other modified configuration of the immunoglobulin molecule that comprises an antigen- binding fragment (epitope recognition site) of the required specificity and the ability to bind to an epitope, including WNT surrogate molecules disclosed herein. It is not intended to be limited as regards the source of the antibody or the manner in which it is made (e.g., by hybridoma, phage selection, recombinant expression, transgenic animals, etc.). The term includes whole immunoglobulins as well as the fragments etc. described above under the definition of "antibody".

[0084] The term "native" or "wild-type" as used herein refers to a nucleotide sequence, e.g., gene, or gene product, e.g., RNA or protein, that is present in a wild-type cell, tissue, organ, or organism. The term "variant" as used herein refers to a mutant of a reference polynucleotide or polypeptide sequence, for example a native polynucleotide or polypeptide sequence, i.e., having less than 100% sequence identity with the reference polynucleotide or polypeptide sequence. Put another way, a variant comprises at least one amino acid difference (e.g., amino acid substitution, amino acid insertion, amino acid deletion) relative to a reference polynucleotide sequence, e.g., a native polynucleotide or polypeptide sequence. For example, a variant may be a polynucleotide having a sequence identity of 50% or more, 60% or more, or 70% or more with a full-length native polynucleotide sequence, e.g., an identity of 75% or 80% or more, such as 85%, 90%, or 95% or more, for example, 98% or 99% identity with the full length native polynucleotide sequence. As another example, a variant may be a polypeptide

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having a sequence identity of 70% or more with a full-length native polypeptide sequence, e.g., an identity of 75% or 80% or more, such as 85%, 90%, or 95% or more, for example, 98% or 99% identity with the full-length native polypeptide sequence. Variants may also include variant fragments of a reference, e.g., native, sequence sharing a sequence identity of 70% or more with a fragment of the reference, e.g., native, sequence, e.g., an identity of 75% or 80% or more, such as 85%, 90%, or 95% or more, for example, 98% or 99% identity with the native sequence.

[0085] "Operatively linked" or "operably linked" refers to a juxtaposition of genetic elements, wherein the elements are in a relationship permitting them to operate in the expected manner. For instance, a promoter is operatively linked to a coding region if the promoter helps initiate transcription of the coding sequence. There may be intervening residues between the promoter and coding region so long as this functional relationship is maintained.

[0086] As used herein, the terms "polypeptide," "peptide," and "protein" refer to polymers of amino acids of any length. The terms also encompass an amino acid polymer that has been modified; for example, to include disulfide bond formation, glycosylation, lipidation, phosphorylation, or conjugation with a labeling component.

[0087] The term "polynucleotide" refers to a polymeric form of nucleotides of any length, including deoxyribonucleotides or ribonucleotides, or analogs thereof. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and nucleotide analogs, and may be interrupted by non-nucleotide components. If present, modifications to the nucleotide structure may be imparted before or after assembly of the polymer. The term polynucleotide, as used herein, refers interchangeably to double-stranded and single-stranded molecules. Unless otherwise specified or required, any embodiment of described herein that is a polynucleotide encompasses both the double-stranded form and each of two complementary single-stranded forms known or predicted to make up the double-stranded form.

[0088] A polynucleotide or polypeptide has a certain percent "sequence identity" to another polynucleotide or polypeptide, meaning that, when aligned, that percentage of bases or amino acids are the same when comparing the two sequences. As used herein, the terms "identity" and "identical" refer, with respect to a polypeptide or polynucleotide sequence, to the percentage of exact matching residues in an alignment of that "query" sequence to a "subject" sequence, such as an alignment generated by the BLAST algorithm. Identity is calculated, unless specified otherwise, across the full length of the subject sequence. Thus, a query

sequence "shares at least x% identity to" a subject sequence if, when the query sequence is aligned to the subject sequence, at least x% (rounded down) of the residues in the subject sequence are aligned as an exact match to a corresponding residue in the query sequence. Where the subject sequence has variable positions (*e.g.,* residues denoted X), an alignment to any residue in the query sequence is counted as a match. Sequence alignments are performed using the NCBI Blast service (BLAST+ version 2.12.0) unless otherwise indicated. To determine sequence identity, sequences can be aligned using the methods and computer programs, including BLAST, available over the worldwide web at ncbi.nlm.nih.gov/BLAST/. Another alignment algorithm is FASTA, available in the Genetics Computing Group (GCG) package, from Madison, Wis., USA, a wholly owned subsidiary of Oxford Molecular Group, Inc. Other techniques for alignment are described in METHODS IN ENZYMOLOGY, VOL. 266: COMPUTER METHODS FOR MACROMOLECULAR SEQUENCE ANALYSIS (1996), ed. Doolittle, Academic Press, Inc., a division of Harcourt Brace & Co., San Diego, Calif., USA. Of particular interest are alignment programs that permit gaps in the sequence. The Smith-Waterman is one type of algorithm that permits gaps in sequence alignments. *See Meth. Mol. Biol.* 70: 173-187 (1997). Also, the GAP program using the Needleman and Wunsch alignment method can be utilized to align sequences. *See J. Mol. Biol.* 48: 443-453 (1970).

[0089] Of interest is the BestFit program using the local homology algorithm of Smith and Waterman (*Adv. Appl. Math.* 2: 482-489 (1981) to determine sequence identity. The gap generation penalty will generally range from 1 to 5, usually 2 to 4 and in many embodiments will be 3. The gap extension penalty will generally range from about 0.01 to 0.20 and in many instances will be 0.10. The program has default parameters determined by the sequences input to be compared. Preferably, the sequence identity is determined using the default parameters determined by the program. This program is available also from Genetics Computing Group (GCG) package, from Madison, Wis., USA. Another program of interest is the FastDB algorithm. FastDB is described in CURRENT METHODS IN SEQUENCE COMPARISON AND ANALYSIS, MACROMOLECULE SEQUENCING AND SYNTHESIS, SELECTED METHODS AND APPLICATIONS, pp. 127-149, 1988, Alan R. Liss, Inc. Percent sequence identity is calculated by FastDB based upon the following parameters: Mismatch Penalty: 1.00; Gap Penalty: 1.00; Gap Size Penalty: 0.33; and Joining Penalty: 30.0.

[0090] A "promoter" as used herein encompasses a DNA sequence that directs the binding of RNA polymerase and thereby promotes RNA synthesis, i.e., a minimal sequence sufficient to direct transcription. Promoters and corresponding protein or polypeptide expression may be

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ubiquitous, meaning strongly active in a wide range of cells, tissues and species or cell-type specific, tissue-specific, or species specific. Promoters may be "constitutive," meaning continually active, or "inducible," meaning the promoter can be activated or deactivated by the presence or absence of biotic or abiotic factors. Also included in the disclosed nucleic acid constructs or vectors are enhancer sequences that may or may not be contiguous with the promoter sequence. Enhancer sequences influence promoter-dependent gene expression and may be located in the 5' or 3' regions of the native gene.

[0091] "Recombinant," as applied to a polynucleotide means that the polynucleotide is the product of various combinations of cloning, restriction or ligation steps, and other procedures that result in a construct that is distinct from a polynucleotide found in nature.

[0092] As used herein, "SWAP™" (Surrozen WNT-signal activating proteins) refers to WNT mimetic compounds comprising engineered bi-specific full-length immunoglobulin-G (IgG) antibodies that, like WNT proteins, directly activate the canonical WNT-signaling pathway in a target tissue, e.g., cornea tissues.

[0093] As used herein, "SWEETS™" (Surrozen WNT-signal enhancer engineered for tissue specificity) refers to antibody-based R-spondin mimetic compounds.

[0094] The terms "treatment", "treating" and the like are used herein to generally mean obtaining a desired pharmacologic and/or physiologic effect. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof, e.g., reducing the likelihood that the disease or symptom thereof occurs in the subject, and/or may be therapeutic in terms of a partial or complete cure for a disease and/or adverse effect attributable to the disease.

[0095] "Treatment" as used herein covers any treatment of a disease in a mammal, and includes: (a) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it; (b) inhibiting the disease, i.e., arresting its development; or (c) relieving the disease, i.e., causing regression of the disease. The therapeutic agent may be administered before, during or after the onset of disease or injury. The treatment of ongoing disease, where the treatment stabilizes or reduces the undesirable clinical symptoms of the patient, is of particular interest. Such treatment is desirably performed prior to complete loss of function in the affected tissues. The subject therapy will desirably be administered during the symptomatic stage of the disease, and in some cases after the symptomatic stage of the disease.

[0096] The practice of the present disclosure will employ, unless otherwise indicated, conventional techniques of cell biology, molecular biology techniques, microbiology, biochemistry and immunology, which are within the scope of those of skill in the art. Such techniques are explained fully in the literature, such as, "Molecular Cloning: A Laboratory Manual", second edition (Sambrook et al., 1989); "Oligonucleotide Synthesis" (M. J. Gait, ed., 1984); "Animal Cell Culture" (R. I. Freshney, ed., 1987); "Methods in Enzymology" (Academic Press, Inc.); "Handbook of Experimental Immunology" (D. M. Weir & C. C. Blackwell, eds.); "Gene Transfer Vectors for Mammalian Cells" (J. M. Miller & M. P. Calos, eds., 1987); "Current Protocols in Molecular Biology" (F. M. Ausubel et al., eds., 1987); "PCR: The Polymerase Chain Reaction", (Mullis et al., eds., 1994); and "Current Protocols in Immunology" (J. E. Coligan et al., eds., 1991), each of which is expressly incorporated by reference herein.

[0097] Several aspects of the disclosure are described below with reference to example applications for illustration. It should be understood that numerous specific details, relationships, and methods are set forth to provide a full understanding of the disclosure. One having ordinary skill in the relevant art, however, will readily recognize that the disclosure can be practiced without one or more of the specific details or with other methods. The present disclosure is not limited by the illustrated ordering of acts or events, as some acts may occur in different orders and/or concurrently with other acts or events. Furthermore, not all illustrated acts or events are required to implement a methodology in accordance with the present disclosure.

[0098] The terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the disclosure. As used herein, the singular forms "a", "an" and "the" are intended to include the plural forms as well, unless the context clearly indicates otherwise. Furthermore, to the extent that the terms "including", "includes", "having", "has", "with", or variants thereof are used in either the detailed description and/or the claims, such terms are intended to be inclusive in a manner similar to the term "comprising".

[0099] The term "about" or "approximately" means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system. For example, "about" can mean within 1 or more than 1 standard deviation, per the practice in the art. Alternatively, "about" can mean a range of up to 20%, preferably up to 10%, more

preferably up to 5%, and more preferably still up to 1% of a given value. Alternatively, particularly with respect to biological systems or processes, the term can mean within an order of magnitude, preferably within 5-fold, and more preferably within 2-fold, of a value. Where particular values are described in the application and claims, unless otherwise stated the term "about" meaning within an acceptable error range for the particular value should be assumed.

[0100] All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. It is understood that the present disclosure supersedes any disclosure of an incorporated publication to the extent there is a contradiction.

[0101] It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as "solely", "only" and the like in connection with the recitation of claim elements, or the use of a "negative" limitation.

[0102] Unless otherwise indicated, all terms used herein have the same meaning as they would to one skilled in the art and the practice of the present disclosure will employ, conventional techniques of microbiology and recombinant DNA technology, which are within the knowledge of those of skill of the art.

II. General.

[0103] The present disclosure provides methods of modulating WNT signals to treat cornea disorders, including but not limited to, scarring, and corneal epithelial and endothelial dystrophies. In particular, the present disclosure provides a WNT/β-catenin agonist and/or antagonist to stimulate corneal tissue regeneration and/or prevent corneal fibrosis.

[0104] WNT ("Wingless-related integration site" or "Wingless and Int-1" or "Wingless-Int") ligands and their signals play key roles in the control of development, homeostasis and regeneration of many essential organs and tissues, including bone, liver, skin, stomach, intestine, kidney, central nervous system, mammary gland, taste bud, ovary, cochlea, lung, and many other tissues (reviewed, e.g., by Clevers, Loh, and Nusse, 2014; 346:1248012). Modulation of WNT signaling pathways has potential for treatment of degenerative diseases and tissue injuries.

[0105] One of the challenges for modulating WNT signaling as a therapeutic is the existence of multiple WNT ligands and WNT receptors, Frizzled 1-10 (Fzd1-10), with many

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tissues expressing multiple and overlapping Fzds. Canonical WNT signals also involve Low-density lipoprotein (LDL) receptor-related protein 5 (LRP5) or Low-density lipoprotein (LDL) receptor-related protein 6 (LRP6) as co-receptors, which are broadly expressed in various tissues, in addition to Fzds.

[0106] R-spondins 1–4 are a family of ligands that amplify WNT signals. Each of the R-spondins work through a receptor complex that contains Zinc and Ring Finger 3 (ZNRF3) or Ring Finger Protein 43 (RNF43) on one end and a Leucine-rich repeat-containing G-protein coupled receptor 4-6 (LGR4-6) on the other (reviewed, e.g., by Knight & Hankenson 2014, *Matrix Biol.*; 37: 157-161). R-spondins might also work through additional mechanisms of action. ZNRF3 and RNF43 are two membrane-bound E3 ligases specifically targeting WNT receptors (Fzd1-10 and LRP5 or LRP6) for degradation. Binding of an R-spondin to ZNRF3/RNF43 and LGR4-6 causes clearance or sequestration of the ternary complex, which removes E3 ligases from WNT receptors and stabilizes WNT receptors, resulting in enhanced WNT signals. Each R-spondin contains two Furin domains (1 and 2), with Furin domain 1 binding to ZNRF3/RNF43, and Furin domain 2 binding to LGR4-6. Fragments of R-spondins containing Furin domains 1 and 2 are sufficient for amplifying WNT signaling. While R-spondin effects depend on WNT signals, since both LGR4-6 and ZNRF3/RNF43 are widely expressed in various tissues, the effects of R-spondins are not tissue-specific.

[0107] In some embodiments, the WNT/β-catenin signaling antagonist or agonist can include binding agents or epitope binding domains that bind one or more Fzd receptors and inhibit or enhance WNT signaling. In certain embodiments, the agent or antibody specifically binds to the cysteine-rich domain (CRD) within the human frizzled receptor(s) to which it binds. Additionally, antagonistic binding agents containing epitope binding domains against LRP can also be used. In some embodiments, the WNT/β-catenin antagonist possesses binding agents or epitope binding domains that bind E3 ligases ZNRF3/RNF43 and one or more FZD receptors or one or more LRP co-receptors to promote the degradation of FZD or LRP receptors, and this molecule can also contain a binding domain that binds a cell type specific epitope for targeting. The E3 ligase agonist antibodies or fragments thereof can be single molecules or combined with other WNT antagonists, e.g., Fzd receptor antagonists, LRP receptor antagonists, etc.

[0108] As is well known in the art, an antibody is an immunoglobulin molecule capable of specific binding to a target such as a carbohydrate, polynucleotide, lipid, polypeptide, etc., through at least on epitope binding domain, located on the variable region of the

immunoglobulin molecule. As used herein, the term encompasses not only intact polyclonal or monoclonal antibodies, but also fragments thereof containing epitope binding domains (e.g., dAb, Fab, Fab', $(F(ab')_2$, Fv, single chain (scFv), VHH (i.e., Nanobodies®) or single domain antibodies (sdAb), DVD-Igs, synthetic variants thereof, naturally occurring variants, fusion proteins comprising and epitope binding domain, humanized antibodies, chimeric antibodies, and any other modified configuration of the immunoglobulin molecule that comprises an antigen-binding site or fragment (epitope recognition site) of the required specificity. "Diabodies," multivalent or multispecific fragments constructed by gene fusion (WO94/13804; P. Holliger et al., *Proc. Natl. Acad. Sci. USA* 90 6444-6448, 1993) are also a particular form of antibody contemplated herein. Minibodies comprising a scFv joined to a CH3 domain are also included herein (S. Hu et al., *Cancer Res.*, 56, 3055-3061, 1996). *See e.g.*, Ward, E. S. et al., *Nature* 341, 544-546 (1989); Bird et al., *Science*, 242, 423-426, 1988; Huston et al., *Proc. Natl. Acad. Sci. USA*, 85, 5879-5883, 1988); PCT/US92/09965; WO94/13804; P. Holliger et al., *Proc. Natl. Acad. Sci. USA* 90 6444–6448, 1993; Y. Reiter et al., *Nature Biotech*, 14, 1239-1245, 1996; S. Hu et al., *Cancer Res.*, 56, 3055-3061, 1996; C. Bever et al., *Anal Bioanal Chem.* 2016 Sept; 408(22); 5985–6002.

[0109] The proteolytic enzyme papain preferentially cleaves IgG molecules to yield several fragments, two of which (the F(ab) fragments) each comprise a covalent heterodimer that includes an intact antigen-binding site. The enzyme pepsin is able to cleave IgG molecules to provide several fragments, including the F(ab')2 fragment which comprises both antigen-binding sites. An Fv fragment for use according to certain embodiments of the present disclosure can be produced by preferential proteolytic cleavage of an IgM, and on rare occasions of an IgG or IgA immunoglobulin molecule. Fv fragments are, however, more commonly derived using recombinant techniques known in the art. The Fv fragment includes a non-covalent VH:VL heterodimer including an antigen-binding site which retains much of the antigen recognition and binding capabilities of the native antibody molecule. Inbar et al. (1972) *Proc. Nat. Acad. Sci. USA* 69:2659-2662; Hochman et al. (1976) *Biochem* 15:2706-2710; and Ehrlich et al. (1980) *Biochem* 19:4091-4096.

[0110] In certain embodiments, single chain Fv (scFV) antibodies are contemplated. For example, Kappa bodies (Ill et al., *Prot. Eng.* 10: 949-57 (1997)); minibodies (Martin et al., *EMBO J* 13: 5305-9 (1994)); diabodies (Holliger et al., *Proc. Nat. Acad. Sci.* 90: 6444-8 (1993)); or Janusins (Traunecker et al., *EMBO J* 10: 3655-59 (1991) and Traunecker et al., *Int. J. Cancer Suppl.* 7: 51-52 (1992)), may be prepared using standard molecular biology

techniques following the teachings of the present application with regard to selecting antibodies having the desired specificity. In still other embodiments, bispecific or chimeric antibodies may be made that encompass the ligands of the present disclosure. For example, a chimeric antibody may comprise CDRs and framework regions from different antibodies, while bispecific antibodies may be generated that bind specifically to one or more Fzd receptors through one binding domain and to a second molecule through a second binding domain. These antibodies may be produced through recombinant molecular biological techniques or may be physically conjugated together.

[0111] A single chain Fv (scFv) polypeptide is a covalently linked VH:VL heterodimer which is expressed from a gene fusion including VH- and VL-encoding genes linked by a peptide-encoding linker. Huston et al. (1988) *Proc. Nat. Acad. Sci. USA* 85(16):5879-5883. A number of methods have been described to discern chemical structures for converting the naturally aggregated—but chemically separated—light and heavy polypeptide chains from an antibody V region into an scFv molecule which will fold into a three dimensional structure substantially similar to the structure of an antigen-binding site. *See, e.g.*, U.S. Pat. Nos. 5,091,513 and 5,132,405, to Huston et al.; and U.S. Pat. No. 4,946,778, to Ladner et al.

[0112] In certain embodiments, an antibody as described herein is in the form of a diabody. Diabodies are multimers of polypeptides, each polypeptide comprising a first domain comprising a binding region of an immunoglobulin light chain and a second domain comprising a binding region of an immunoglobulin heavy chain, the two domains being linked (e.g., by a peptide linker) but unable to associate with each other to form an antigen binding site: antigen binding sites are formed by the association of the first domain of one polypeptide within the multimer with the second domain of another polypeptide within the multimer (WO94/13804).

[0113] A dAb fragment of an antibody consists of a VH domain (Ward, E. S. et al., *Nature* 341, 544-546 (1989)).

[0114] Where bispecific antibodies are to be used, these may be conventional bispecific antibodies, which can be manufactured in a variety of ways (Holliger, P. & Winter G., *Curr. Opin. Biotech.* 4, 446-449 (1993)), e.g., prepared chemically or from hybrid hybridomas, or may be any of the bispecific antibody fragments mentioned above. Diabodies and scFv can be constructed without an Fc region, using only variable domains, potentially reducing the effects of anti-idiotypic reaction.

[0115] Bispecific diabodies, as opposed to bispecific whole antibodies, may also be particularly useful because they can be readily constructed and expressed in E. coli. Diabodies (and many other polypeptides such as antibody fragments) of appropriate binding specificities can be readily selected using phage display (WO94/13804) from libraries. If one arm of the diabody is to be kept constant, for instance, with a specificity directed against antigen X, then a library can be made where the other arm is varied, and an antibody of appropriate specificity selected. Bispecific whole antibodies may be made by knobs-into-holes engineering (J. B. B. Ridgeway et al., *Protein Eng.*, 9, 616-621 (1996)).

[0116] In certain embodiments, the antibodies described herein may be provided in the form of a UniBody®. A UniBody® is an IgG4 antibody with the hinge region removed (see GenMab Utrecht, The Netherlands; see also, e.g., US2009/0226421). This proprietary antibody technology creates a stable, smaller antibody format with an anticipated longer therapeutic window than current small antibody formats. IgG4 antibodies are considered inert and thus do not interact with the immune system. Fully human IgG4 antibodies may be modified by eliminating the hinge region of the antibody to obtain half-molecule fragments having distinct stability properties relative to the corresponding intact IgG4 (GenMab, Utrecht). Halving the IgG4 molecule leaves only one area on the UniBody® that can bind to cognate antigens (e.g., disease targets) and the UniBody® therefore binds univalently to only one site on target cells.

[0117] In certain embodiments, antibodies and antigen-binding fragments thereof as described herein include a heavy chain and a light chain CDR set, respectively interposed between a heavy chain and a light chain framework region (FR) set which provide support to the CDRs and define the spatial relationship of the CDRs relative to each other. As used herein, the term "CDR set" refers to the three hypervariable regions of a heavy or light chain V region. Proceeding from the N-terminus of a heavy or light chain, these regions are denoted as "CDR1," "CDR2," and "CDR3" respectively. An antigen-binding site, therefore, includes six CDRs, comprising the CDR set from each of a heavy and a light chain V region. A polypeptide comprising a single CDR, (e.g., a CDR1, CDR2 or CDR3) is referred to herein as a "molecular recognition unit." Crystallographic analysis of a number of antigen-antibody complexes has demonstrated that the amino acid residues of CDRs form extensive contact with bound antigen, wherein the most extensive antigen contact is with the heavy chain CDR3. Thus, the molecular recognition units are primarily responsible for the specificity of an antigen-binding site.

[0118] As used herein, the term "FR set" refers to the four flanking amino acid sequences which frame the CDRs of a CDR set of a heavy or light chain V region. Some FR residues may

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contact bound antigen; however, FRs are primarily responsible for folding the V region into the antigen-binding site, particularly the FR residues directly adjacent to the CDRs. Within FRs, certain amino residues and certain structural features are very highly conserved. In this regard, all V region sequences contain an internal disulfide loop of around 90 amino acid residues. When the V regions fold into a binding-site, the CDRs are displayed as projecting loop motifs which form an antigen-binding surface. It is generally recognized that there are conserved structural regions of FRs which influence the folded shape of the CDR loops into certain "canonical" structures—regardless of the precise CDR amino acid sequence. Further, certain FR residues are known to participate in non-covalent interdomain contacts which stabilize the interaction of the antibody heavy and light chains.

[0119] A "monoclonal antibody" refers to a homogeneous antibody population wherein the monoclonal antibody is comprised of amino acids (naturally occurring and non-naturally occurring) that are involved in the selective binding of an epitope. Monoclonal antibodies are highly specific, being directed against a single epitope. The term "monoclonal antibody" encompasses not only intact monoclonal antibodies and full-length monoclonal antibodies, but also fragments thereof (such as Fab, Fab', F(ab')2, Fv), single chain (scFv), Nanobodies®, variants thereof, fusion proteins comprising an antigen-binding fragment of a monoclonal antibody, humanized monoclonal antibodies, chimeric monoclonal antibodies, and any other modified configuration of the immunoglobulin molecule that comprises an antigen- binding fragment (epitope recognition site) of the required specificity and the ability to bind to an epitope, including WNT surrogate molecules disclosed herein. It is not intended to be limited as regards the source of the antibody or the manner in which it is made (e.g., by hybridoma, phage selection, recombinant expression, transgenic animals, etc.). The term includes whole immunoglobulins as well as the fragments etc. described above under the definition of "antibody".

[0120] In certain embodiments, the antibodies of the present disclosure may take the form of a Nanobody®. Nanobody® technology was originally developed following the discovery and identification that camelidae (e.g., camels, alpacas, and llamas) possess fully functional antibodies that consist of heavy chains only and therefore lack light chains. These heavy-chain only antibodies contain a single variable domain (VHH) and two constant domains (CH2, CH3). The cloned and isolated single variable domains have full antigen binding capacity and are very stable. These single variable domains, with their unique structural and functional properties, form the basis of "Nanobodies®". Nanobodies® are encoded by single genes and

are efficiently produced in almost all prokaryotic and eukaryotic hosts, e.g., E. coli (see, e.g., U.S. Pat. No. 6,765,087), molds (for example Aspergillus or Trichoderma) and yeast (for example Saccharomyces, Kluyvermyces, Hansenula, or Pichia (see, e.g., U.S. Pat. No. 6,838,254). The production process is scalable and multi-kilogram quantities of Nanobodies® have been produced. Nanobodies® may be formulated as a ready-to-use solution having a long shelf life. The Nanoclone® method (see, e.g., WO 06/079372) is a proprietary method for generating Nanobodies® against a desired target, based on automated high-throughput selection of B-cells. Nanobodies® are single-domain antigen-binding fragments of camelid-specific heavy-chain only antibodies. Nanobodies®, also referred to as VHH antibodies, typically have a small size of around 15 kDa. *See* C. Bever et al., *Anal Bioanal Chem.* 2016 Sept; 408(22); 5985–6002.

[0121] Another antibody fragment contemplated is a dual-variable domain-immunoglobulin (DVD-Ig) is an engineered protein that combines the function and specificity of two monoclonal antibodies in one molecular entity. A DVD-Ig is designed as an IgG-like molecule, except that each light chain and heavy chain contains two variable domains in tandem through a short peptide linkage, instead of one variable domain in IgG. The fusion orientation of the two variable domains and the choice of linker sequence are critical to functional activity and efficient expression of the molecule. A DVD-Ig can be produced by conventional mammalian expression systems as a single species for manufacturing and purification. A DVD-Ig has the specificity of the parental antibodies, is stable in vivo, and exhibits IgG-like physicochemical and pharmacokinetic properties. DVD-Igs and methods for making them are described in Wu, C., et al., *Nat Biotech*, 25:1290–1297 (2007).

[0122] In certain embodiments, the antibodies or antigen-binding fragments thereof as disclosed herein are humanized. This refers to a chimeric molecule, generally prepared using recombinant techniques, having an antigen- binding site derived from an immunoglobulin from a non-human species and the remaining immunoglobulin structure of the molecule based upon the structure and/or sequence of a human immunoglobulin. The antigen-binding site may comprise either complete variable domains fused onto constant domains or only the CDRs grafted onto appropriate framework regions in the variable domains. Epitope binding sites may be wild type or modified by one or more amino acid substitutions. This eliminates the constant region as an immunogen in human individuals, but the possibility of an immune response to the foreign variable region remains (LoBuglio, A. F. et al., (1989) *Proc Natl Acad Sci USA* 86:4220–4224; Queen et al., *PNAS* (1988) 86:10029–10033; Riechmann et al., *Nature* (1988)

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332:323–327). Illustrative methods for humanization of the anti-Fzd or LRP antibodies disclosed herein include the methods described in U.S. Pat. No. 7,462,697.

[0123] Another approach focuses not only on providing human-derived constant regions but modifying the variable regions as well so as to reshape them as closely as possible to human form. It is known that the variable regions of both heavy and light chains contain three complementarity-determining regions (CDRs) which vary in response to the epitopes in question and determine binding capability, flanked by four framework regions (FRs) which are relatively conserved in a given species and which putatively provide a scaffolding for the CDRs. When nonhuman antibodies are prepared with respect to a particular epitope, the variable regions can be "reshaped" or "humanized" by grafting CDRs derived from nonhuman antibody on the FRs present in the human antibody to be modified. Application of this approach to various antibodies has been reported by Sato, K., et al., (1993) *Cancer Res* 53:851-856; Riechmann, L., et al., (1988) *Nature* 332:323-327; Verhoeyen, M., et al., (1988) *Science* 239:1534-1536; Kettleborough, C. A., et al., (1991) *Protein Engineering* 4:773-3783; Maeda, H., et al., (1991) Human Antibodies Hybridoma 2:124-134; Gorman, S. D., et al., (1991) *Proc Natl Acad Sci USA* 88:4181-4185; Tempest, P. R., et al., (1991) *Bio/Technology* 9:266-271; Co, M. S., et al., (1991) *Proc Natl Acad Sci USA* 88:2869-2873; Carter, P., et al., (1992) *Proc Natl Acad Sci USA* 89:4285-4289; and Co, M. S. et al., (1992) *J Immunol* 148:1149-1154. In some embodiments, humanized antibodies preserve all CDR sequences (for example, a humanized mouse antibody which contains all six CDRs from the mouse antibodies). In other embodiments, humanized antibodies have one or more CDRs (one, two, three, four, five, six) which are altered with respect to the original antibody, which are also termed one or more CDRs "derived from" one or more CDRs from the original antibody.

[0124] In certain embodiments, the antibodies of the present disclosure may be chimeric antibodies. In this regard, a chimeric antibody is comprised of an antigen-binding fragment of an antibody operably linked or otherwise fused to a heterologous Fc portion of a different antibody. In certain embodiments, the heterologous Fc domain is of human origin. In other embodiments, the heterologous Fc domain may be from a different Ig class from the parent antibody, including IgA (including subclasses IgA1 and IgA2), IgD, IgE, IgG (including subclasses IgG1, IgG2, IgG3, and IgG4), and IgM. In further embodiments, the heterologous Fc domain may be comprised of CH2 and CH3 domains from one or more of the different Ig classes. As noted above with regard to humanized antibodies, the antigen-binding fragment of a chimeric antibody may comprise only one or more of the CDRs of the antibodies described

herein (e.g., 1, 2, 3, 4, 5, or 6 CDRs of the antibodies described herein), or may comprise an entire variable domain (VL, VH or both).

[0125] The structures and locations of immunoglobulin CDRs and variable domains may be determined by reference to Kabat, E. A. et al., SEQUENCES OF PROTEINS OF IMMUNOLOGICAL INTEREST, 4th Edition, US Department of Health and Human Services. 1987, and updates thereof, now available on the Internet (immuno.bme.nwu.edu).

[0126] In certain embodiments, the antagonist or agonist binding agent binds with a dissociation constant (K_D) of about 1 μM or less, about 100 nM or less, about 40 nM or less, about 20 nM or less, or about 10 nM or less. For example, in certain embodiments, a FZD binding agent or antibody described herein that binds to more than one FZD, binds to those FZDs with a K_D of about l00nM or less, about 20 nM or less, or about 10 nM or less. In certain embodiments, the binding agent binds to one or more its target antigen with an EC50 of about 1 μM or less, about 100 nM or less, about 40 nM or less, about 20 nM or less, about 10 nM or less, or about 1 nM 20 or less.

[0127] The antibodies or other agents of the present disclosure can be assayed for specific binding by any method known in the art. The immunoassays which can be used include, but are not limited to, competitive and non-competitive assay systems using techniques such as biolayer interferometry (BLI) analysis, FACS analysis, immunofluorescence, immunocytochemistry, Western blots, radioimmunoassays, ELISA, "sandwich" immunoassays, immunoprecipitation assays, precipitation reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, and protein A immunoassays. Such assays are routine and well known in the art (*see, e.g.*, Ausubel et al, eds, 1994, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety).

[0128] For example, the specific binding of an antibody to a target antigen may be determined using ELISA. An ELISA assay comprises preparing antigen, coating wells of a 96 well microtiter plate with antigen, adding the antibody or other binding agent conjugated to a detectable compound such as an enzymatic substrate (e.g., horse-radish peroxidase or alkaline phosphatase) to the well, incubating for a period of time and detecting the presence of the antigen. In some embodiments, the antibody or agent is not conjugated to a detectable compound, but instead a second conjugated antibody that recognizes the first antibody or agent

is added to the well. In some embodiments, instead of coating the well with the antigen, the antibody or agent can be coated to the well and a second antibody conjugated to a detectable compound can be added following the addition of the antigen to the coated well. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art (*see, e.g.*, Ausubel et al, eds, 1994, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, Vol. 1, John Wiley & Sons, Inc., New York at 11.2.1).

[0129] The binding affinity of an antibody or other agent to a target antigen and the off-rate of the antibody-antigen interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (e.g., Fzd, LRP), or fragment or variant thereof, with the antibody of interest in the presence of increasing amounts of unlabeled antigen followed by the detection of the antibody bound to the labeled antigen. The affinity of the antibody and the binding off-rates can be determined from the data by scattered plot analysis. In some embodiments, BLI analysis is used to determine the binding on and off rates of antibodies or agents. BLI kinetic analysis comprises analyzing the binding and dissociation of antibodies from chips with immobilized antigens on their surface.

[0130] In certain embodiments, the WNT agonist is selected from those disclosed in PCT Publication No. WO 2019/126398, which is incorporated herein in its entirety. G211 (also known as YW211.31.57) is disclosed in US Patent No. 8,846,041.

[0131] In some embodiments, a WNT agonist comprises a sequence having at least 90% identity (e.g., 95%, 98%, 99% or 100% identity) to a sequence disclosed in any of the sequences depicted in Table 1. In some embodiments, a WNT agonist comprises two sequences, each having at least 90% identity (e.g., 95%, 98%, 99% or 100% identity) to a sequence disclosed in any of the sequences depicted in Table 1. In some embodiments, a WNT agonist comprises four sequences, each having at least 90% identity (e.g., 95%, 98%, 99% or 100% identity) to a sequence disclosed in any of the sequences depicted in Table 1, and in particular embodiments, two of the sequences are light chain sequences, and two of the sequences are heavy chain sequences. In some embodiments, a WNT agonist comprises two heavy chain sequences. In certain embodiments, the WNT agonist comprises a light chain sequence and/or a heavy chain sequence, each independently comprising at least one, at least two, or all three CDR sequences disclosed in any of SEQ ID NOs: 1-16, or variants thereof wherein the sequence comprises zero, less than two, less than three, less than four, less than five, less than six, less than seven,

or less than eight amino acid modifications, e.g., substitutions, within the CDRs. G211-18R5, R2M3-26, 1RCO7-26, 1SH1-03 and hp1SH1-03 comprise two of the indicated heavy chains (HC) and two of the indicated light chains (LC) disclosed in Table 1. In certain embodiments, the WNT agonist comprises two light chain sequences and two heavy chain sequence, each independently comprising at least one, at least two, or all three CDR sequences disclosed in any of SEQ ID NOs: 1-16, or variants thereof. In certain embodiments, the Wnt agonist has an Ig format, and in certain embodiments, the Wnt agonist comprises two heavy chains bound to each other, and two light chains, each bound to a different one of the two heavy chains. Wnt superagonists or superSWAPs G211-18R5-Rspo2RA and G211-R2H1-Rspo2RA are also listed in Table 1; they each comprises two of the indicated heavy chains (HC) and two of the indicated light chains (LC) disclosed in Table 1. 17SB9-03 comprise two of the indicated heavy chains (HC) disclosed in Table 1, i.e., one HC of SEQ ID NO: 15 and one heavy chain of SEQ ID NO:16. In various embodiments, the molecules do not include the tag sequences.

[0132] Table 1: Sequences of SWAPTM and Wnt superagonists or superSWAP molecules; the variable chains are provided in plain text in the order indicated by the format; when present, the VHH is in BOLD (not italics); and the constant chain is in italics. The VL is in italics and underlined; the VH is in italics and BOLD. The constant region of the lambda light chain is highlighted in light gray. The constant region of the kappa light chain is underlined, BOLD, and highlighted in light gray. The CH1 is in italics. The Fc is in italics, BOLD, and highlighted in light gray. The Rspo region is highlighted and BOLD (not italics or underline). The linker is in smaller font. The bold, underlined and italicized AA and G represent substitutions of the wild-type LL and P amino acids at these positions with AA and G, respectively. Tag sequences are underlined with a dotted line.

G211-18R5_LC (SEQ ID NO:1)
Format: G211.VK-**GS linker**-18R5.VL-*hCL (constant lambda light chain)*
*DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYTTPPTFGQGTKVEIK*GGGGSGGGGSGGGGS*DIE LTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQAPVLVIYDKSNRPSGIPERFSGS NSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVL*GQPKAAPSVTLFPPSSEE LQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSL TPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
G211-18R5_HC (SEQ ID NO:2)
Format: G211.VH- **GS linker**-18R5.VH-*hIgG1 CH1-CH3* ***LALAPG*** *(constant heavy chain)*
EVQLVESGGGLVQPGGSLRLSCAASGFTFTSYYISWVRQAPGKGLEWVAEISPYSGST YYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCALRARPPIRLHPRGSVMDY

WGQGTLVTVSSGGGGSGGGGSGGGGS***EVQLVESGGGLVQPGGSLRLSCAASGFTFSHY TLSWVRQAPGKGLEWVSVISGDGSYTYYADSVKGRFTISSDNSKNTLYLQMNSLRAE DTAVYYCARNFIKYVFANWGQGTLVTVSS****ASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSC**DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK***

R2M3-26_LC (SEQ ID NO: 3)

Format: VHH26-**GS linker**-R2M3.VL-*hCL (constant lambda light chain)*

DVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQRELVAMIRP VVTEIDYADSVKGRFTISRNNAMKTVYLQMNNLKPEDTAVYYCNAKRPWGSRD EYWGQGTQVTVSSGSGSG*QAVVLQEPSLSVSPGGTVTLTCGLSSGSVSTNYYPSWYQQTP GQAPRTLIYYTNTRSSDVPERFSGSIVGNKAALTITGAQPDDESVYFCLLYLGRGIWVFGGG TKLTVL*GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKA GVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

R2M3-26_HC (SEQ ID NO: 4)

Format: R2M3.VH-*hIgG1 CH1-CH3* ***LALAPG*** *(constant heavy chain)*

EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMGWISAYNG NTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCASSKEKATYYYGMDVW GQGTTVTVSS*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC**DKTHTCPPC PAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQ PREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK***

1RC07-26_LC (SEQ ID NO: 5)

Format: VHH26-**GS linker**-1RC07.VL-*hCL (constant lambda light chain)*

DVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQRELVAMIRP VVTEIDYADSVKGRFTISRNNAMKTVYLQMNNLKPEDTAVYYCNAKRPWGSRD EYWGQGTQVTVSSGSGSG*SYVLTQPPSVSVSPGQTASITCSGDKVGHKYASWYQQKPGQ SPVLVIYEDSQRPSGIPVRFSGSNSGNTATLTISGTQAMDEADYYCQAWDSSTDVVFGGGT KLTVL*GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAG VETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

1RC07-26_HC (SEQ ID NO: 6)

Format: 1RC07.VH-*hIgG1 CH1-CH3* ***LALAPG*** *(constant heavy chain)*

QVQLQQWGAGLLKPSETLSLTCAVSGASFSGHYWTWIRQPPGKGLEWIGEIDHTGS TNYEPSLRSRVTISVDTSKNQFSLNLKSVTAADTAVYYCARGGQGGYDWGHYHGLD VWGQGTTVTVSS*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC**DKTHTC PPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKA KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK***

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hp-1SH1-03_LC (SEQ ID NO: 7) **Format**: VHH03-**GS linker**-hp-1SH1 VL-hCK (constant kappa light chain)
EVQLVESGGGLVQPGGSLRLSCASSANIQSIETLGWYRQAPGKQRELIANMRG GGYMKYADSLKGRFTMSTDNSKNTMYLQMNSLRAEDTAVYYCYVKLRDEDY VYRGQGTQVTVSSGGGGS*DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSGGYTYLDWYL QKPGQSPQLLIYLGSKRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQIPPTF GQGTKVEIK***RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTK SFNRGEC***
hp-1SH1-03_HC (SEQ ID NO: 8) **Format:** hp-1SH1.VH- *hIgG1 CH1-CH3* ***LALAPG*** *(constant heavy chain)*
EVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQHPGKGLEWIGYIYYSGS TYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARHAGFYGLADYFDYWGQ GTLVTVSS*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC****DKTHTCPPCPA PEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPR EPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK***
1SH1-03_LC (SEQ ID NO:9) **Format:** VHH3-**GS linker**-1SH1 VL-*hCK (constant kappa light chain)*
DVQLVESGGGLVQPGGSLRLSCTSSANINSIETLGWYRQAPGKQRELIANMRGG GYMKYAGSLKGRFTMSTESAKNTMYLQMNSLKPEDTAVYYCYVKLRDDDYV YRGQGTQVTVSSGGSGS*DVVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQ KPGQSPQLLIYLGSKRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQIPPTFG QGTKVEIK***RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNAL QSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGEC***
1SH1-03_HC (SEQ ID NO: 10) **Format:** 1SH1.VH- *hIgG1 CH1-CH3* ***LALAPG*** *(constant heavy chain)*
EVQLVESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQHPGKGLEWIGYIYYSGS TYYNPSLKSRVTISVDTSKNQFSLKLNSVTAADTAVYYCARHAGFYGLADYFDYWGQ GTLVTVSS*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC****DKTHTCPPCPA PEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPR EPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK***
G211-18R5-LC (SEQ ID NO: 11) **Format:** G211.VL-**GS linker**-18R5.VL-*hCL (constant lambda light chain)*
*DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYTTPPTFGQGTKVEIK*GGGGSGGGGSGGGGS*DIE LTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQAPVLVIYDKSNRPSGIPERFSGS NSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVL*GQPKAAPSVTLFPPSSEE

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LQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSL TPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
G211-18R5-Rspo2RA_HC (SEQ ID NO: 12) **Format:** G211.VH-**GS linker**-18R5.VH-*hIgG1 CH1-CH3* ***LALAPG*** *(constant heavy chain)*-**GS linker**-Rspo2RA
EVQLVESGGGLVQPGGSLRLSCAASGFTFTSYYISWVRQAPGKGLEWVAEISPYSGST YYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCALRARPPIRLHPRGSVMDY WGQGTLVTVSSGGGGSGGGGSGGGGS***EVQLVESGGGLVQPGGSLRLSCAASGFTFSHY TLSWVRQAPGKGLEWVSVISGDGSYTYYADSVKGRFTISSDNSKNTLYLQMNSLRAE DTAVYYCARNFIKYVFANWGQGTLVTVSS****ASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSC****DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK***GGGGSGSGGSGGGGS**NPICKGCLSCSKDNGCSRCQQKLFFFLRREG MRQYGECLHSCPSGYYGHRAPDMNRCARCRIENCDSCRSKDACTKCKVGFYL HRGRCFDECPDGFAPLEETMECVE****
G211-R2H1-LC (SEQ ID NO: 13) **Format:** G211.VL-**GS linker**-R2H1.VL-*hCK (constant kappa light chain)*
*DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYTTPPTFGQGTKVEIK*GGGGSGGGGSGGGGS*DIQ MTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIYSASSLYSGVPSRFSGSR SGTDFTLTISSLQPEDFATYYCQQYWYGVAPITFGQGTKVEIK***RTVAAPSVFIFPPSDEQ LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC**
G211-R2H1-Rspo2RA-HC (SEQ ID NO: 14) **Format:** G211.VH-**GS linker**-R2H1.VH-*hIgG1 CH1-CH3* ***LALAPG*** *(constant heavy chain)*-**GS linker**- Rspo2RA
RAEVQLVESGGGLVQPGGSLRLSCAASGFTFTSYYISWVRQAPGKGLEWVAEISPYS GSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCALRARPPIRLHPRGSV MDYWGQGTLVTVSSGGGGSGGGGSGGGGS***EVQLVESGGGLVQPGGSLRLSCAASGFNI SSSYIHWVRQAPGKGLEWVAYIYSSYGSTYYADSVKGRFTISADTSKNTAYLQMNSLR AEDTAVYYCARASWYALDYWGQGTLVTVSS****ASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSC****DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC KVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN HYTQKSLSLSPGK***GGGGSGSGGSGGGGS**NPICKGCLSCSKDNGCSRCQQKLFFFLRRE GMRQYGECLHSCPSGYYGHRAPDMNRCARCRIENCDSCRSKDACTKCKVGFY LHRGRCFDECPDGFAPLEETMECVE****
17SB9-03-HC1 (SEQ ID NO: 15) **Format:** VHH03*hIgG1 Fc* ***LALAPG(Hole)*** **-GS linker**-17SB9-**GS linker**-6xHis
DVQLVESGGGLVQPGGSLRLSCTSSANINSIETLGWYRQAPGKQRELIANMRGG GYMKYAGSLKGRFTMSTESAKNTMYLQMNSLKPEDTAVYYCYVKLRDDDYV

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YRGQGTQVTVSS*DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLSCAVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK*GGSGSAVQQVESGGGLVQPGGSLRLSCAASGFTLDYYAIS WFRQAPGKKRELVADITSGGSTNYADSVKGRFTISRDNAKNTIYLQMNSLKPED TAVYFCNAVTYNGYTIWGQGTQVTVSS**GSGSGHHHHHH**
17SB9-03-HC2 (SEQ ID NO:16) **Format:** 17SB9_hIgG1_Fc **LALAPG(Knob) -GS linker-**VHH03-**GS linker-**Flag
AVQQVESGGGLVQPGGSLRLSCAASGFTLDYYAISWFRQAPGKKRELVADITSG GSTNYADSVKGRFTISRDNAKNTIYLQMNSLKPEDTAVYFCNAVTYNGYTIWG QGTQVTVSS*DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLWCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK*GGSGSDVQLVESGGGLVQPGGSLRLSCTSSANINSIETLGWYRQ APGKQRELIANMRGGGYMKYAGSLKGRFTMSTESAKNTMYLQMNSLKPEDTA VYYCYVKLRDDDYVYRGQGTQVTVSS**GSGSGDYKDDDDK**

[0133] In particular embodiments, the engineered WNT agonist comprises one or more, e.g., two, sequence having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:1, and one or more, e.g., two, sequence having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:2. In particular embodiments, the engineered WNT agonist comprises one or more, e.g., two, sequence having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:3, and one or more, e.g., two, sequence having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:4. In particular embodiments, the engineered WNT agonist comprises one or more, e.g., two, sequence having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:5, and one or more, e.g., two, sequence having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:6. In particular embodiments, the engineered WNT agonist comprises two sequences having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:1, and two sequences having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:2. In particular embodiments, the engineered WNT agonist comprises two sequences having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:3, and two sequences having at least 90%, at least 95%, at least 98%, at least 99%, or 100%

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identity to a sequence set forth in SEQ ID NO:4. In particular embodiments, the engineered WNT agonist comprises two sequences having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:5, and two sequences having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:6. In particular embodiments, each sequence comprises less than one (i.e., zero), less than two, less than three, less than four, less than five, less than six, less than seven, less than eight, less than nine, less than ten, less than eleven, or less than twelve modifications, e.g., substitutions, of amino acids present within CDRs of the WNT agonist. In particular embodiments, the engineered WNT agonist comprises less than one (i.e., zero), less than two, less than three, less than four, less than five, less than six, less than seven, less than eight, less than nine, less than ten, less than eleven, or less than twelve modifications of amino acids present within CDRs of the WNT agonist. In certain embodiments, the engineered Wnt agonist comprises an antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises at least two, at least three, at least four, at least five, or at least six CDRs of any of the sequences of SEQ ID NOs: 1-16.

[0134] In some embodiments, the engineered WNT agonist comprises two sequences having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:7, and two sequences having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:8. In particular embodiments, each sequence comprises less than one (i.e., zero), less than two, less than three, less than four, less than five, less than six, less than seven, less than eight, less than nine, less than ten, less than eleven, or less than twelve modifications, e.g., substitutions, of amino acids present within CDRs of the WNT agonist. In particular embodiments, the engineered WNT agonist comprises less than one (i.e., zero), less than two, less than three, less than four, less than five, less than six, less than seven, less than eight, less than nine, less than ten, less than eleven, or less than twelve modifications of amino acids present within CDRs of the WNT agonist, e.g., less than two, less than three, less than four, less than five, less than six, less than seven, less than eight, less than nine, less than ten, less than eleven, or less than twelve amino acid substitutions within CDRs of the WNT agonist. In certain embodiments, the engineered Wnt agonist comprises an antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises at least two, at least three, at least four, at least five, or at least six CDRs of any of the sequences of SEQ ID NOs: 1-16.

[0135] In particular embodiments, the engineered WNT agonist comprises one or more, e.g., two, sequence having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:9, and one or more, e.g., two, sequence having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:10. In particular embodiments, the engineered WNT agonist comprises one or more, e.g., two, sequence having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:11, and one or more, e.g., two, sequence having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:12. In particular embodiments, the engineered WNT agonist comprises one or more, e.g., two, sequence having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:13, and one or more, e.g., two, sequence having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:14. In particular embodiments, the engineered WNT agonist comprises one or more, e.g., two, sequence having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:15, and one or more, e.g., two, sequence having at least 90%, at least 95%, at least 98%, at least 99%, or 100% identity to a sequence set forth in SEQ ID NO:16. In particular embodiments, each sequence comprises less than one (i.e., zero), less than two, less than three, less than four, less than five, less than six, less than seven, less than eight, less than nine, less than ten, less than eleven, or less than twelve modifications of amino acids present within CDRs of the WNT agonist. In particular embodiments, the engineered WNT agonist comprises less than one (i.e., zero), less than two, less than three, less than four, less than five, less than six, less than seven, less than eight, less than nine, less than ten, less than eleven, or less than twelve modifications of amino acids present within CDRs of the WNT agonist, e.g., less than two, less than three, less than four, less than five, less than six, less than seven, less than eight, less than nine, less than ten, less than eleven, or less than twelve amino acid substitutions within CDRs of the WNT agonist. In certain embodiments, the engineered Wnt agonist comprises an antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises at least two, at least three, at least four, at least five, or at least six CDRs of any of the sequences of SEQ ID NOs: 1-16.

III. Pharmaceutical Compositions

[0136] Pharmaceutical compositions comprising a WNT antagonist molecule or WNT agonist molecule (a WNT antagonist/agonist molecule) described herein and one or more pharmaceutically acceptable diluent, carrier, or excipient are also disclosed. The term “WNT

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antagonist/agonist molecule" refers collectively to both WNT agonist molecules and WNT agonist molecules.

[0137] In further embodiments, pharmaceutical compositions comprising a polynucleotide comprising a nucleic acid sequence encoding a WNT antagonist/agonist molecule described herein and one or more pharmaceutically acceptable diluent, carrier, or excipient are also disclosed. In certain embodiments, the polynucleotides are DNA or mRNA, e.g., a modified mRNA. In particular embodiments, the polynucleotides are modified mRNAs further comprising a 5′ cap sequence and/or a 3′ tailing sequence, e.g., a polyA tail. In other embodiments, the polynucleotides are expression cassettes comprising a promoter operatively linked to the coding sequences.

[0138] In some embodiments the WNT antagonist/agonist is an engineered recombinant polypeptide incorporating various epitope binding fragments that bind to various molecules in the WNT signaling pathway. For example, a WNT antagonist can be an antibody or fragment thereof that binds to a FZD receptor and/or an LRP receptor and inhibits WNT signaling. The FZD and LRP antibody fragments (e.g., Fab, scFv, VHH/sdAbs, etc.) may be joined together directly or with various size linkers, on one molecule.

[0139] Conversely, engineered WNT agonists/antagonists can also be recombinant polypeptides incorporating epitope binding fragments that bind to various molecules in the WNT signaling pathway and enhance WNT signaling. For example, a WNT agonist can be an antibody or fragment thereof that binds to Fzd receptor and/or an LRP receptor and enhances WNT signaling. The Fzd and LRP antibody fragments (e.g., Fab, scFv, VHH/sdAbs, etc.) may be joined together directly or with various size linkers, on one molecule.

[0140] In further embodiments, pharmaceutical compositions comprising an expression vector, e.g., a viral vector, comprising a polynucleotide comprising a nucleic acid sequence encoding a WNT antagonist/agonist molecule described herein and one or more pharmaceutically acceptable diluent, carrier, or excipient are also disclosed. In certain embodiments, the nucleic acid sequence encoding the WNT antagonist molecule and the nucleic acid sequence encoding the WNT agonist are in the same polynucleotide, e.g., expression cassette.

[0141] The present disclosure further contemplates a pharmaceutical composition comprising a cell comprising an expression vector comprising a polynucleotide comprising a promoter operatively linked to a nucleic acid encoding a WNT antagonist/agonist molecule and

one or more pharmaceutically acceptable diluent, carrier, or excipient. In particular embodiments, the pharmaceutical composition further comprises a cell comprising an expression vector comprising a polynucleotide comprising a promoter operatively linked to a nucleic acid sequence encoding a WNT antagonist and a WNT agonist. In certain embodiments, the nucleic acid sequence encoding the WNT antagonist molecule and the nucleic acid sequence encoding the WNT agonist molecule are present in the same polynucleotide, e.g., expression cassette and/or in the same cell. In particular embodiments, the cell is a heterologous cell, or an autologous cell obtained from the subject to be treated.

[0142] In particular embodiments, the cell is a stem cell, e.g., an adipose-derived stem cell or a hematopoietic stem cell. The present disclosure contemplates pharmaceutical compositions comprising a first molecule for delivery of a WNT antagonist molecule as a first active agent, and a WNT agonist as a second molecule. The first and second molecule may be the same type of molecule or different types of molecules. For example, in certain embodiments, the first and second molecule may each be independently selected from the following types of molecules: polypeptides, small organic molecules, nucleic acids encoding the first or second active agent (optionally DNA or mRNA, optionally modified RNA), vectors comprising a nucleic acid sequence encoding the first or second active agent (optionally expression vectors or viral vectors), and cells comprising a nucleic acid sequence encoding the first or second active agent (optionally an expression cassette).

[0143] The subject molecules, alone or in combination, can be combined with pharmaceutically acceptable carriers, diluents, excipients and reagents useful in preparing a formulation that is generally safe, non-toxic, and desirable, and includes excipients that are acceptable for mammalian, e.g., human or primate, use. Such excipients can be solid, liquid, semisolid, or, in the case of an aerosol composition, gaseous. Examples of such carriers, diluents and excipients include, but are not limited to, water, saline, Ringer's solutions, dextrose solution, and 5% human serum albumin. Supplementary active compounds can also be incorporated into the formulations. Solutions or suspensions used for the formulations can include a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial compounds such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating compounds such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates or phosphates; detergents such as Tween 20 to prevent aggregation; penetration-enhancing agents such as sodium caprate, viscosity-enhancing agents such as

hydroxypropyl methylcellulose, in particular for eyedrop formulations, and compounds for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. In particular embodiments, the pharmaceutical compositions are sterile.

[0144] Pharmaceutical compositions may further include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, or phosphate buffered saline (PBS). In some cases, the composition is sterile and should be fluid such that it can be drawn into a syringe or delivered to a subject from a syringe. In certain embodiments, it is stable under the conditions of manufacture and storage and is preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be, e.g., a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the internal compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0145] Sterile solutions can be prepared by incorporating the WNT antagonist/agonist antibody or antigen-binding fragment thereof (or encoding polynucleotide or cell comprising the same) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile- filtered solution thereof.

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[0146] In one embodiment, the pharmaceutical compositions are prepared with carriers that will protect the antibody or antigen-binding fragment thereof against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially. Liposomal suspensions can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art.

[0147] It may be advantageous to formulate the pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active antibody or antigen-binding fragment thereof calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms are dictated by and directly dependent on the unique characteristics of the antibody or antigen-binding fragment thereof and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active antibody or antigen-binding fragment thereof for the treatment of individuals.

[0148] The pharmaceutical compositions can be included in a container, pack, or dispenser, e.g., syringe or eye dropper, e.g., a prefilled syringe or eye dropper, together with instructions for administration.

[0149] The pharmaceutical compositions of the present disclosure may be delivered to a subject in the form of a pill, capsule, cream, salve, syrup, dermal patch, suppository, intravenous drip, aqueous solution, non-aqueous solution, eye wash solution, or any combination of thereof.

[0150] The pharmaceutical compositions of the present disclosure may be delivered to a subject by direct ophthalmic application, muscular injection, intravenous injection, peritoneal injection, nasally, orally, rectally, or any combination thereof.

[0151] The pharmaceutical compositions of the present disclosure encompass any pharmaceutically acceptable salts, esters, or salts of such esters, or any other compound which,

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upon administration to an animal comprising a human, is capable of providing (directly or indirectly) the biologically active antibody or antigen-binding fragment thereof.

[0152] The present disclosure includes pharmaceutically acceptable salts of a WNT antagonist/agonist molecule described herein. The term "pharmaceutically acceptable salt" refers to physiologically and pharmaceutically acceptable salts of the compounds of the present disclosure: i.e., salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto. A variety of pharmaceutically acceptable salts are known in the art and described, e.g., in "Remington's Pharmaceutical Sciences", 17th edition, Alfonso R. Gennaro (Ed.), Mark Publishing Company, Easton, PA, USA, 1985 (and more recent editions thereof), in the "Encyclopedia of Pharmaceutical Technology", 3rd edition, James Swarbrick (Ed.), Informa Healthcare USA (Inc.), NY, USA, 2007, and in *J. Pharm. Sci.* 66:2 (1977). Also, for a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, 2002). Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines.

[0153] Metals used as cations comprise sodium, potassium, magnesium, calcium, and the like. Amines comprise N-N′-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N- methylglucamine, and procaine (see, for example, Berge et al., "Pharmaceutical Salts," *J. Pharma Sci.*, 1977, 66, 119). The base addition salts of said acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid in the conventional manner. The free acid forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid for purposes of the present disclosure.

[0154] In some embodiments, the pharmaceutical composition provided herein comprise a therapeutically effective amount of a WNT antagonist/agonist molecule or pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier, diluent and/or excipient, for example saline, phosphate buffered saline, phosphate and amino acids, polymers, polyols, sugar, buffers, preservatives and other proteins. Exemplary amino acids, polymers and sugars and the like are octylphenoxy polyethoxy ethanol compounds, polyethylene glycol monostearate compounds, polyoxyethylene sorbitan fatty acid esters, sucrose, fructose, dextrose, maltose, glucose, mannitol, dextran, sorbitol, inositol, galactitol, xylitol, lactose,

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trehalose, bovine or human serum albumin, citrate, acetate, Ringer's and Hank's solutions, cysteine, arginine, carnitine, alanine, glycine, lysine, valine, leucine, polyvinylpyrrolidone, polyethylene and glycol. Preferably, this formulation is stable for at least six months at 4° C.

[0155] In some embodiments, the pharmaceutical composition provided herein comprises a buffer, such as phosphate buffered saline (PBS) or sodium phosphate/sodium sulfate, tris buffer, glycine buffer, sterile water and other buffers known to the ordinarily skilled artisan such as those described by Good et al. (1966) *Biochemistry* 5:467. The pH of the buffer may be in the range of 6.5 to 7.75, preferably 7 to 7.5, and most preferably 7.2 to 7.4.

IV. Methods of Use

[0156] The present disclosure also provides methods for using the WNT antagonist/agonist molecules, e.g., to modulate a WNT signaling pathway, e.g., to increase or decrease WNT signaling, and the administration of a WNT antagonist/agonist molecule in a variety of therapeutic settings. Provided herein are methods of treatment using a WNT antagonist/agonist molecule. In one embodiment, a WNT antagonist/agonist molecule is provided to a subject having a disease involving inappropriate or deregulated WNT signaling.

[0157] In certain embodiments, a WNT antagonist/agonist molecule may be used to block or enhance a WNT signaling pathway in a tissue or a cell. Antagonizing the WNT signaling pathway may include decreasing or inhibiting WNT signaling in a cell or tissue. Agonizing the WNT signaling pathway may include, for example, increasing WNT signaling or enhancing WNT signaling in a tissue or cell. Thus, in some aspects, the present disclosure provides a method for antagonizing/agonizing a WNT signaling pathway in a cell, comprising contacting the tissue or cell with an effective amount of a WNT antagonist/agonist molecule or pharmaceutically acceptable salt thereof disclosed herein, wherein the WNT antagonist/agonist molecule is a WNT signaling pathway antagonist/agonist. In some embodiments, contacting occurs *in vitro*, *ex vivo*, or *in vivo*. In particular embodiments, the cell is a cultured cell, and the contacting occurs *in vitro*.

[0158] The WNT antagonist/agonist molecules may be used for the treatment of keratopathy. In particular, experiments have indicated that activation of WNT signaling regulates cornea cell growth and layer patterning. (Zhang et al., *Development*, 2015 142:3383–93.) Conditional knockout of either β-catenin or Lrp5/6 results in mis-stratification, particularly of epithelium. Recent *in vitro* experimentation indicates that WNT agonists promote cell growth in homogenized cornea cell culture. See, e.g., Figs. 2A-E and 7A-B**.** Therefore,

controlled administrations of WNT agonist or/and antagonist are proposed to promote epithelial and endothelial cell growth, and reverse pathology of various keratopathies, including dystrophies and scarring. In the particular embodiments, WNT agonist/antagonist will be administered in either earlier or later phase of keratopathy disease progression in the subjects.

[0159] Both WNT agonists and antagonists may be administered alone as a monotherapy or sequentially. In certain embodiments, the method comprises administration of a WNT agonist in earlier phase of disease development, followed by administration of a WNT antagonist at late stages of the disease where there is significant scarring or fibrosis.

[0160] The present disclosure also provides for combination treatment with known treatments for keratopathies. Examples of therapies that could be administered with a WNT agonist or antagonist include, but are not limited to, Rho kinase inhibitors (e.g., Ripasudil or Fasudil), anti-inflammatories (e.g., steroidal and non-steroidal), and immunosuppressants.

[0161] Keratopathies that may be treated include, but are not necessarily limited to, bacterial infections, viral infections (e.g., herpes simplex keratitis and herpes zoster ophthalmicus (i.e., shingles)), fungal infections, protozoan infections, archaeal infections, genetic disorders, brittle cornea syndrome (BCS), corneal endothelial-mesenchymal transition (EnMT), corneal epithelial-mesenchymal transition (EMT), corneal fibrosis, Cogan syndrome, corneal ulcer, epithelial basement membrane dystrophy (EBMD, ABMD, Map Dot), Fleck corneal dystrophy, Fuchs' dystrophy (also called Fuchs' corneal endothelial dystrophy (FCED) or Fuchs' endothelial dystrophy (FED) or Fuchs' endothelial cell dystrophy (FECD)), gelatinous droplike corneal dystrophy, granular corneal dystrophy type I, granular corneal dystrophy type II, interstitial keratitis, iridocorneal endothelial syndrome (ICE), keratoconjunctivitis sicca, keratoconus, keratomalacia, lattice dystrophy type I, lattice dystrophy type II, Lisch corneal dystrophy, macular corneal dystrophy, Meesmann corneal dystrophy, peripheral ulcerative keratitis, phlyctenular keratoconjunctivitis, posterior polymorphous corneal dystrophy, pterygium, Reis-Bückler corneal dystrophy, Schnyder crystalline corneal dystrophy, Stevens-Johnson syndrome, superficial punctate keratitis, Thiel-Behnke corneal dystrophy, neurotrophic keratitis, herpetic keratitis and scarring.

[0162] In a further embodiment, the WNT antagonist and/or WNT agonist molecule may also incorporate a tissue targeting moiety, e.g., an antibody or fragment thereof that recognizes a cornea tissue or cell type specific receptor or cell surface molecule.

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[0163] The dose and dosage regimen may depend upon a variety of factors readily determined by a physician, such as the nature of the disease or disorder, the characteristics of the subject, and the subject's history. In particular embodiments, the amount of a Wnt signaling molecule administered or provided to the subject is in the range of about 0.01 mg/kg to about 50 mg/kg, 0.1 mg/kg to about 500 mg/kg, or about 0.1 mg/kg to about 50 mg/kg of the subject's body weight. In particular embodiments, the amount of an engineered WNT signaling modulator administered or provided to the subject is in the range of about 0.01 mg/kg to about 50 mg/kg, about 0.1 mg/kg to about 500 mg/kg, or about 0.1 mg/kg to about 50 mg/kg of the subject's body weight. In certain embodiments of any of the methods disclosed herein, the WNT signaling modulator is administered to a subject, *e.g.*, a mammal, intravenously, *e.g.*, as a bolus injection, or subcutaneously. In particular embodiments, the WNT signaling modulator is administered at least once per week. In particular embodiments, the subject is administered about 0.5 to about 100 mg/kg body weight of the WNT signaling modulator, or about 2 to about 50 mg/kg body weight of the WNT agonist, *e.g.*, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, or about 50 mg/kg. In particular embodiments, the subject is administered about 25 mg, about 75 mg, about 250 mg, about 750 mg, about 1500 mg or about 2250 mg of the WNT signaling modulator. In particular embodiments, the subject is administered about 3 to about 30 mg/kg body weight intravenously or subcutaneously at least once per week.

[0164] The therapeutic agent (e.g., a WNT antagonist/agonist) may be administered before, during or after the onset of disease or injury. The treatment of ongoing disease, where the treatment stabilizes or reduces the undesirable clinical symptoms of the patient, is of particular interest. Such treatment is desirably performed prior to complete loss of function in the affected tissues. The subject therapy will desirably be administered during the symptomatic stage of the disease, and in some cases after the symptomatic stage of the disease. In some embodiments, the subject method results in a therapeutic benefit, e.g., preventing the development of a disorder, halting the progression of a disorder, reversing the progression of a disorder, etc. In some embodiments, the subject method comprises the step of detecting that a therapeutic benefit has been achieved. The ordinarily skilled artisan will appreciate that such measures of therapeutic efficacy will be applicable to the particular disease being modified and will recognize the appropriate detection methods to use to measure therapeutic efficacy.

[0165] All of the above U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non- patent publications referred to in this specification and/or listed in the Application Data Sheet, are incorporated herein by reference, in their entirety.

[0166] From the foregoing it will be appreciated that, although specific embodiments of the present disclosure have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the present disclosure. Accordingly, the present disclosure is not limited except as by the appended claims.

[0167] The broad scope of this disclosure is best understood with reference to the following example, which is not intended to limit the disclosure to a specific embodiment.

EXAMPLES

Example I. General methods

[0168] Standard methods in molecular biology are described. Maniatis et al. (1982) *Molecular Cloning, A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.; Sambrook and Russell (2001) *Molecular Cloning*, 3rd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.; Wu (1993) *Recombinant DNA*, Vol. 217, Academic Press, San Diego, Calif. Standard methods also appear in Ausbel et al. (2001) *Current Protocols in Molecular Biology, Vols.* 1-4, John Wiley and Sons, Inc. New York, N.Y., which describes cloning in bacterial cells and DNA mutagenesis (Vol. 1), cloning in mammalian cells and yeast (Vol. 2), glycoconjugates and protein expression (Vol. 3), and bioinformatics (Vol. 4).

[0169] Methods for protein purification including immunoprecipitation, chromatography, electrophoresis, centrifugation, and crystallization are described. Coligan et al. (2000) *Current Protocols in Protein Science, Vol.* 1, John Wiley and Sons, Inc., New York. Chemical analysis, chemical modification, post-translational modification, production of fusion proteins, glycosylation of proteins are described. See, e.g., Coligan et al. (2000) *Current Protocols in Protein Science, Vol.* 2, John Wiley and Sons, Inc., New York; Ausubel et al. (2001) *Current Protocols in Molecular Biology, Vol.* 3, John Wiley and Sons, Inc., NY, N.Y., pp. 16.0.5-16.22.17; Sigma-Aldrich, Co. (2001) *Products for Life Science Research*, St. Louis, Mo.; pp. 45-89; Amersham Pharmacia Biotech (2001) *BioDirectory*, Piscataway, N.J., pp. 384-391. Production, purification, and fragmentation of polyclonal and monoclonal antibodies are

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described. Coligan et al. (2001) *Current Protocols in Immunology, Vol.* 1, John Wiley and Sons, Inc., New York; Harlow and Lane (1999) *Using Antibodies*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.; Harlow and Lane, supra. Standard techniques for characterizing ligand/receptor interactions are available. See, e.g., Coligan et al. (2001) *Current Protocols in Immunology, Vol.* 4, John Wiley, Inc., New York.

[0170] Methods for flow cytometry, including fluorescence activated cell sorting detection systems (FACS®), are available. See, e.g., Owens et al. (1994) *Flow Cytometry Principles for Clinical Laboratory Practice*, John Wiley and Sons, Hoboken, N.J.; Givan (2001) *Flow Cytometry*, 2nd ed.; Wiley-Liss, Hoboken, N.J.; Shapiro (2003) *Practical Flow Cytometry*, John Wiley and Sons, Hoboken, N.J. Fluorescent reagents suitable for modifying nucleic acids, including nucleic acid primers and probes, polypeptides, and antibodies, for use, e.g., as diagnostic reagents, are available. Molecular Probes (2003) *Catalogue*, Molecular Probes, Inc., Eugene, Oreg.; Sigma-Aldrich (2003) *Catalogue*, St. Louis, Mo.

[0171] Standard methods of histology of the immune system are described. See, e.g., Muller-Harmelink (ed.) (1986) *Human Thymus: Histopathology and Pathology*, Springer Verlag, New York, N.Y.; Hiatt, et al. (2000) *Color Atlas of Histology*, Lippincott, Williams, and Wilkins, Phila, Pa.; Louis, et al. (2002) *Basic Histology: Text and Atlas*, McGraw-Hill, New York, N.Y.

[0172] Software packages and databases for determining, e.g., antigenic fragments, leader sequences, protein folding, functional domains, glycosylation sites, and sequence alignments, are available. See, e.g., GenBank, Vector NTI® Suite (Informax, Inc, Bethesda, Md.); GCG Wisconsin Package (Accelrys, Inc., San Diego, Calif.); DeCypher® (TimeLogic Corp., Crystal Bay, Nev.); Menne et al. (2000) *Bioinformatics* 16: 741-742; Menne et al. (2000) *Bioinformatics Applications Note* 16:741-742; Wren et al. (2002) *Comput. Methods Programs Biomed.* 68:177-181; von Heijne (1983) *Eur. J. Biochem.* 133:17-21; von Heijne (1986) *Nucleic Acids Res.* 14:4683-4690.

Example II. Construction of WNT mimetics

[0173] WNT mimetics R2M3-26, G211-18R5, 1RC07-26, 1SH1-03, and hp1SH1-03 were constructed as described in WO 2019/126398 A1, WO 2020/010308 A1, and WO 2020132365 A1, WO 2021173726, which are incorporated by reference in their entirety herein. All molecules are presented in Table 1. All recombinant proteins were produced in Expi293F™ cells (Thermo Fisher Scientific) by transient transfection unless otherwise specified. All IgG-

based and Fc-containing constructs were first purified with Protein-A resin and eluted with 0.1 M glycine pH 3.5. All proteins were then polished by a size exclusion column in 2x HBS buffer (40 mM HEPES pH 7.4, 300 mM NaCl).

Example III. WNT agonist treatment in primary human corneal endothelium cell culture

[0174] Human corneal endothelial cells with attached Descemet membrane were received from Eversight (Ann Arbor, MI). Multiple donor samples were pooled and digested in 2 mg/mL collagenase A in MEM-alpha + 15% FBS + 20 μg/mL gentamicin sulfate for 3 hours at 37°C with occasional trituration. Samples were then washed with MEM-alpha + 15% FBS + 20 μg/mL gentamicin before resuspension and plating in Human Endothelial SFM + 5% FBS + 2 ng/mL EGF + 20 μg/mL gentamicin sulfate.

[0175] Endothelial cells were treated with test proteins (5 nM R2M3-26, 1 μg/mL hR-spondin-1, 5 ng/mL FGF1, 5 nM G211-18R5-Rspo2RA, 5nM G211-R2H1-Rspo2RA, or 5 nM 1RC07-26) or left untreated in Human Endothelial SFM + 5% FBS + 2ng/mL EGF + 20 μg/mL gentamicin sulfate. After 2 days, cells were fixed and immunofluorescence performed for Ki67 (Abcam #ab16667, 1:100) and Na+K+ ATPase (Sigma #05-369, 1:100) prior to nuclear staining with DAPI. Ki67 is a well-known marker for cell proliferation. See discussion in, e.g., Aung TN et al., Mod Pathol (2021), https://doi.org/10.1038/s41379-021-00745-6. Samples were imaged on a Leica Dmi8 microscope. The percentage of Ki67+ cells (# of Ki67+ cells / total # of cells) in the resulting images were quantified using a custom Python script. The results are depicted in FIGs. 2A, 2B, 2C, 2D, 2E.

Example IV. WNT agonist treatments in human cornea organ culture

[0176] Human donor cornea with Fuchs' dystrophy was obtained from Eversight Eye Bank. Tissue was cut into pieces and cultured in Human Endothelial SFM + 5% FBS + anti-mycotic/anti-biotic for 3 days, with no treatment or Wnt agonist (5 nM G211-18R5 + 1 μg/mL R-spondin-1) treatment. Corneas were then fixed and immunofluorescence performed for proliferation marker Ki67 (Cell Signaling Technology #9449S, 1:400) and corneal endothelium marker ZO1 (Abcam #ab216880, 1:100). The results are depicted in FIG. 2D.

Example V. WNT agonist treatments in primary human corneal epithelium cell culture

[0177] Primary human corneal epithelial cells (PCS-700-010™, lot #80915170) were received from American Type Culture Collection (ATCC®). (Cell product information sheet available at the time of filing at https://www.atcc.org/products/all/PCS-700-010.aspx, incorporated by reference in its entirety herein.) Cells were cultured according to ATCC® recommendations. (Available as of the time of filing at https://www.atcc.org/products/all/PCS-700-010.aspx#culturecconditions, incorporated by reference in its entirety herein.)

[0178] Cells were treated with WNT agonist (1 nM of R2M3-26) or left as untreated negative control for 2 days. Next, the cells were fixed, and immunofluorescence performed for Ki67 cell proliferation marker (Abcam #ab16667, 1:100) prior to nuclear staining with DAPI. Samples were imaged on a Leica Dmi8 microscope. #$Ki67^+$ cells per field of view in the resulting images were quantified using a custom Python script. FIG11B.

[0179] Cells were treated with Wnt agonist (5 nM G211-18R5 or 1 μg/mL R-spondin-1) or left untreated for 2 days. After this, cell numbers were measured using a CellTiter-Glo® Viability Assay (Promega) according to the manufacturer's instructions. (Available as of the time of filing at https://www.promega.com/products/cell-health-assays/cell-viability-and-cytotoxicity-assays/celltiter glo-luminescent-cell-viability-assay/?catNum=G7570 , incorporated by reference in its entirety herein.). Results are depicted in FIG. 11A and FIG. 11C.

[0180] A wound healing assay kit was used (Abcam, ab242285) according to the manufacturer's instructions. Cells were left untreated or treated with Wnt agonist (1 nM R2M3-26). Results are depicted in FIG. 12A and FIG. 12B.

Example VI. WNT agonist treatments in rabbit limbal epithelial organoid culture.

[0181] Rabbit eyes were received from Innovative Research. The limbal region was dissected and epithelial cells dissociated by incubation in 2.5 U/mL Dispase II in Organoid Basal Medium (Advanced DMEM/F12 + 1x N-2 + 1x B-27 + 2 mM GlutaMAX + 10 mM HEPES + 1 mM N-acetylcysteine + 1x penicillin-streptomycin + 1x normocin). Epithelial cells were embedded in Matrigel and incubated with Organoid Basal Medium containing WNT agonist (5 nM R2M3-26) or 1 ug/mL R-spondin-1.

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[0182] RNA was harvested from individual wells using an RNEasy Kit including RNeasy Plus Mini Kit (Qiagen) and cDNA synthesized using a SuperScript™ IV VILO™ cDNA Synthesis Kit (ThermoFisher). (Product information sheet available at the time of filing at https://www.thermofisher.com/document-connect/document-connect.html?url=https%3A%2F%2Fassets.thermofisher.com%2FTFS-Assets%2FLSG%2Fmanuals%2FsuperscriptIV_VILO_master_mix_UG.pdf&title=VXNlciBHdWlkZTogU3VwZXJTY3JpcHQgSVYgVklMTyBNYXN0ZXIgTWl4, incorporated by reference herein in its entirety.) qPCR for Wnt target gene Axin2 and progenitor marker p63 was carried out using TaqMan™ Gene Expression Assay reagents (ThermoFisher) on a CFX96™ thermocycler (BioRad). β-actin was used for normalization. Results are depicted in FIG. 10A and FIG. 10B.

Example VII. Lrp5/6, Fzd, and Znrf3/Rnf43 RNA expression in human corneal epithelium and endothelium tissue

[0183] A whole eye globe from a 47-year-old Caucasian female donor with no history of ocular disorders was received from Eversight (Ann Arbor, MI). The cornea was dissected, fixed in 10% formalin, and embedded in paraffin.

[0184] Fuchs' dystrophy tissue sample corneas were obtained from 73-year-old (Fuchs #1) and a 96-year-old (Fuchs #2), delivered from Eversight (Ann Arbor, MI). Fuchs #1 received a post-mortem diagnosis of Fuchs' dystrophy based on low endothelial cell counts and presence of severe guttate. Fuchs #2 received an in-life diagnosis of Fuchs' dystrophy. The corneas were dissected, fixed in 10% formalin, and embedded in paraffin.

[0185] Sections of paraffin-embedded tissue were made and Lrp5/6, Fzd, and Znrf3/Rnf43 RNA levels measured using an RNAscope® kit including RNAscope Multiplex Fluorescent Reagent Kit v2 (ACDBio) according to the manufacturer's instructions. Immunofluorescence for the corneal epithelium marker CK12 (Abcam #ab185627, 1:100), limbal progenitor marker p63 (Biocare #4A4, 1:100) and corneal endothelium marker Na^+K^+ ATPase (ThermoFisher #05-369-MI, 1:100) was subsequently performed to confirm tissue identity. Stained sections were mounted in VECTASHIELD® mounting media with DAPI and imaged on a Leica DMi8A epifluorescence microscope. Results are depicted in FIG. 1 and FIG. 9.

Example VIII. WNT agonist treatment in a murine limbus-to-limbus debridement model

[0186] Mechanical debridement model: 6 to 12-week-old female C57Bl/6 mice were anesthetized by placing the animal in an induction chamber connected to an oxygen source and isoflurane vaporizer, and adjusting oxygen flow to 0.9 liters/min and the isoflurane vaporizer to 3-4%. As soon as the mouse became unresponsive and had shallow breathing, it was transferred to the anesthesia platform with the nose cone and placed on a heating pad. The head was positioned so that the eye to be injured is facing up towards the microscope objective. Only one eye per mouse was injured, the contralateral used as control. 1 drop of Proparacaine was placed on the cornea for 30 seconds. A weck-cel™ cellulose eye spear was used to dry off the cornea by gently sweeping across cornea once and dabbing both corners of the eye. Periocular pressure was applied with one hand to proptose the mouse eye. The right cornea was marked with a 3 mm Trephine and scraped with a Algerbrush (Algerbrush II with 0.5 mm Burr (Katena, catalog number: K 2-4900) to remove the corneal epithelium, with care taken to avoid limbal blood vessels. After scraping, eyes were treated with erythromycin ophthalmic ointment to minimize inflammation and to keep the ocular surface moist while the mice were under anesthesia. Post surgery, the affected eye of the mice was treated with topical Fc-R-spondin-2 or Anti GFP antibody (5mg/ml, 3ul, 4X/day/ 7 days). At day 7, the mice were humanely euthanized and the eyes were entirely removed from each animal, and collected in Davidson's fixative, followed by 10% phosphate-buffered formalin and processed for histological analysis of Axin2, p63 and H&E as described in Fig. 13. The data indicate that R-spondin-2 eyedrops activate Wnt signaling, expand progenitor cells, thicken cornea epithelium and reduce conjunctivalization.

Example IX. WNT agonist treatments in naïve mice by intracameral and intravitreal injection

[0187] 6 to 12-week-old female Balb/C mice were anesthetized by placing the animal in an induction chamber connected to an oxygen source and isoflurane vaporizer and adjusting oxygen flow to 0.9 liters/min and the isoflurane vaporizer to 3-4%. As soon as the mouse became unresponsive and had shallow breathing, it was transferred to the anesthesia platform with the nose cone. The head was positioned so that the eye to be injected is facing up towards the microscope objective. Only one eye per mouse was injected, the contralateral used as control. 1 drop of Proparacaine was placed on the cornea for 30 seconds. The cornea was punctured closely anterior to the iridocorneal angle. The fluid that emanates from the anterior

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chamber was wiped off with a weck-cell before 1 microliter of wnt agonist R2M3-26 or superagonist G211-18R5-Rspo2RA or anti-GFP antibody (2.6 ug) was injected into the anterior chamber (intracamerally) or posterior chamber (intravitreally) using a 33 gauge needle attached to Hamilton syringe. The mice were allowed to recover from the anesthesia. The mice were taken down the next day, the eyes harvested, and the corneas were dissected, fixed in 10% formalin, and embedded in paraffin. For half of the eye samples, sections of paraffin-embedded tissue were made and Axin2 levels measured using an RNAscope® kit including RNAscope Multiplex Fluorescent Reagent Kit v2 (ACDBio) according to the manufacturer's instructions. For the remaining eye samples, RT- qPCR for Wnt target gene Axin2 was carried out using TaqMan™ Gene Expression Assay reagents (ThermoFisher) on a CFX96™ thermocycler (BioRad). β-actin was used for normalization. Results from such studies are described in Figs. 3A-3D.

Example X. WNT agonist treatment in a rabbit endothelial resection model

[0188] The objective of these studies was to evaluate recovery of corneal endothelial cells (CECs) in the central cornea following removal by surgical scraping of endogenous CECs. The wnt agonists or control were injected intracamerally after resection surgery. Two separate studies were conducted to evaluate the ability of the WNT-mimetic R2M3-26, and the WNT superagonist G211-18R5-Rspo2RA in the rabbit endothelial resection model. In the first study, R2M3-26 at two different doses (1 and 8.3 uM) or anti-GFP antibody (8.3 uM) was administered on Day 0 after endothelial cell scraping to create a 10 mm lesion. The rabbits' eyes were examined at various timepoints including baseline and Day 3 post surgery for corneal thickness by optical coherence tomography, ocular exam to assess corneal opacity, and lesion size by performing corneal flat mounts and histologic staining for corneal endothelial markers. At day 3, lower dose R2M3-26 treatment trended towards decreased corneal thickness, lesion size and increased cell density (Fig. 3E and FIG. 3F). A second study was performed with the WNT superagonist G211-18R5-Rspo2RA at two concentrations (1 and 5 uM) and anti GFP (5 uM). A significant decrease in corneal opacity was observed in response to 5 uM wnt superagonist, whereas there was a trend of decreased corneal swelling/thickness and a reduction in lesion size in response to wnt superagonist at Day 3 (Figs. 3G-3I).

Example XI. UV-A burn model for Corneal endothelial damage (Liu et al., 2019, PNAS)

[0189] C57BL/6 wild-type mice (7 to 15 wk old; The Jackson Laboratory) were used for this study. Mice were anesthetized with isoflurane. A UVA LED light source (M365LP1;

Thorlabs) with an emission peak of 365 nm light, 9 nm bandwidth (FWHM) and irradiance of 398 mW/cm^2 was focused to illuminate a 4-mm-diameter spot onto the mouse cornea. The energy was measured using a laser sensor (model L49 [150A]; Ophir), and the time of UVA exposure was adjusted to deliver the appropriate fluence (20 min 57 s for 500 J/cm^2). The right eye (OD) was irradiated while the contralateral eye (OS) was covered with heat retention drapes (SpaceDrapes, Inc.) to serve as untreated control. The drug was injected IVT a couple of hours before UV A burn. The cornea were imaged daily and photographed daily, and by OCT and at day 2, CCT was measured (Fig. 8A and Fig. 8B).

Example XII. Cryoinjury Model

[0190] Mice were randomly divided into two groups, and 2 cycles of cryoinjury were applied to the right eye of each mouse (Han et al., 2013). Under Isoflurane anesthesia, transcorneal freezing was initiated by gently placing a cryoprobe made of stainless steel (2.5 mm indiameter; flat tip; ERBE Elektromedizin GmbH, Tübingen, Germany), precooled in liquid nitrogen for a minute on the central cornea. A cryoprobe with a diameter of 2.5 mm was be chosen, as it is similar to the corneal diameter (2.6 mm) of C57BL/6 mice. No pressure was applied to avoid damage to adjacent tissue including the lens and the trabecular meshwork. The cryoprobe was kept on the corneal surface until an ice ball formed on the cornea and covered the entire corneal surface, which corresponded to the duration of 3 s, as the defect on the endothelium was shown to be the same size as the ice ball. This injury was repeated after a 1min interval. Immediately after freezing, the cryoprobe was freed from the corneal surface with irrigation with a balanced salt solution, and the cornea was allowed to thaw spontaneously. Only the right eye was treated with the cryoprobe, and the left eye served as an untreated control. Recovery of the cornea was followed over 4-5 days typically by following corneal thickness via OCT and corneal clarity via bright field imaging (both Phoenix micron IV) (Figs. 4 and 5A and 5B).

Example XIII. Methods for cornea and conjunctival organoids

[0191] An average of three mice (6 eyeballs) were used per experiment. Eyes were enucleated and cornea and conjunctiva separated under a dissection scope as diagrammed in Fig. 15A. Cornea epithelium was digested to a single cell suspension in 1x TrypLE Express. The conjunctiva was digested in 2.5 mg/mL collagenase A in HBSS for one hour. Near single cell suspensions were resuspended in Matrigel and plated in 40 uL droplets to solidify. Basal medium contained Advanced DMEM, 10mM HEPES, 1x pen/strep, 100mg/mL Normocin,

2mM GlutaMAX, 1x B27, 1mM N-acetylcysteine, 100ng/mL KGF and 10uM Y-27632. Cells were expanded for 5-7 days prior to 48h treatment with the indicated WNT mimetics. Results are shown in Fig. 15B.

[0192] The various embodiments described above can be combined to provide further embodiments. All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet are incorporated herein by reference, in their entirety. Aspects of the embodiments can be modified, if necessary, to employ concepts of the various patents, applications and publications to provide yet further embodiments. These and other changes can be made to the embodiments in light of the above-detailed description. In general, in the following claims, the terms used should not be construed to limit the claims to the specific embodiments disclosed in the specification and the claims, but should be construed to include all possible embodiments along with the full scope of equivalents to which such claims are entitled. Accordingly, the claims are not limited by the disclosure.

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WHAT IS CLAIMED IS:

1. A method of treating a keratopathy in a subject, comprising administering a WNT signaling modulator to the subject.

2. The method of claim 1, wherein the WNT signaling modulator is an engineered WNT signaling modulator.

3. The method of claim 1, wherein the WNT signaling modulator is an engineered WNT agonist or an engineered WNT antagonist.

4. The method of claim 3, wherein the engineered WNT agonist is selected from: (*i*) a WNT mimetic; or (*ii*) an R-spondin mimetic; or (iii) a super SWAP/super agonist.

5. The method of claim 4, wherein the WNT mimetic is a SWAP™ compound and wherein the R-spondin mimetic is a SWEETS™ compound or a WNT enhancer superSWAP compound.

6. The method of claim 1, wherein the WNT signaling modulator is any of WNT3a or any homologue, mutant, fragment, mimic of WNT3a, or a combination thereof.

7. The method of any of claims 1 – 6, wherein the WNT signaling modulator is co-administered with R-spondin-1, or any R-spondin-1 homologue, mutant, fragment, mimic, or any combination thereof.

8. The method of claim 1, wherein the WNT signaling modulator is administered to the subject in a therapeutically effective dose.

9. The method of claim 1, wherein the subject is a human patient.

10. The method of claim 1, wherein the WNT signaling modulator is administered via eye drop, intracameral injection, intravitreal injection, intrastromal or subconjunctival injection.

11. The method of claim 1, wherein the WNT signaling modulator is suspended in aqueous solution.

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12. The method of claim 11, wherein the WNT signaling modulator is suspended in aqueous solution at a concentration between 0.1 nM and 10 mM.

13. The method of claim 11, wherein the WNT signaling modulator is suspended in aqueous solution at a concentration between 1 nM and 100 nM.

14. The method of claim 3, wherein the engineered WNT agonist and engineered WNT antagonist comprise binding compositions that bind to one or more Fzd receptors and/or binding compositions that bind to one or more LRP receptors.

15. The method of claim 14, wherein the binding compositions of the engineered WNT agonist are selected from the group consisting of a Fzd binding composition, a Lrp5 binding composition, a Lrp6 binding composition, and a LRP5/6 binding composition.

16. The method of claim 14, wherein the FZD binding composition of the engineered WNT agonist are selected from the group consisting of Fzd1, Fzd2, and Fzd7.

17. The method of claim 1, comprising administering an engineered WNT agonist and an engineered WNT antagonist, wherein the engineered WNT agonist and engineered WNT antagonist are administered independently at early and/or late stages of the keratopathy.

18. The method of claim 1, comprising administering an engineered WNT agonist and an engineered WNT antagonist, wherein the engineered WNT agonist and the engineered WNT antagonist are administered sequentially at early and/or late stages of the keratopathy.

19. The method of claim 1, comprising administering an engineered WNT agonist and an engineered WNT antagonist, wherein the engineered WNT agonist and the engineered WNT antagonist are co-administered at early and/or late stages of the keratopathy.

20. The method of any one of claims 1-19, comprising administering an isolated polynucleotide encoding a polypeptide of the Wnt signaling modulator, optionally wherein the polynucleotide is an mRNA, optionally a modified mRNA.

21. The method of claim 20, comprising administering an expression vector comprising the isolated polynucleotide.

22. The method of any one of claims 1-21, wherein the keratopathy is a corneal dystrophy.

23. The method of any one of claims 1-21, wherein the keratopathy is selected from the group consisting of: bacterial infections, viral infections, fungal infections, protozoan infections, archaeal infections, genetic disorders, brittle cornea syndrome (BCS), corneal endothelial-mesenchymal transition (EnMT), corneal epithelial-mesenchymal transition (EMT), corneal fibrosis, Cogan syndrome, corneal ulcer, epithelial basement membrane dystrophy (EBMD), Fleck corneal dystrophy, Fuchs' dystrophy, post-cornea transplant scarring, gelatinous droplike corneal dystrophy, granular corneal dystrophy type I, granular corneal dystrophy type II, interstitial keratitis, iridocorneal endothelial syndrome (ICE), keratoconjunctivitis sicca, keratoconus, keratomalacia, lattice dystrophy type I, lattice dystrophy type II, Lisch corneal dystrophy, macular corneal dystrophy, Meesmann corneal dystrophy, bullous keratopathy, aniridia, peripheral ulcerative keratitis, phlyctenular keratoconjunctivitis, posterior polymorphous corneal dystrophy, pterygium, Reis-Bückler corneal dystrophy, Schnyder crystalline corneal dystrophy, Stevens-Johnson syndrome, superficial punctate keratitis, Thiel-Behnke corneal dystrophy, neurotrophic keratitis, herpetic keratitis, scarring, limbal stem cell deficiency and any combination thereof.

24. The method of claim 23, wherein the keratopathy is selected from:
epithelial-mesenchymal transition;
endothelial-mesenchymal transition;
corneal fibrosis;
corneal scarring; or
any combination thereof.

25. The method of claim 23, wherein the keratopathy is Fuchs' dystrophy or limbal stem cell deficiency.

26. The method of claim 23, wherein the keratopathy is post-cornea transplant scarring.

27. A method of increasing cell yield of mammalian cornea epithelium and/or endothelium cells grown *ex vivo* prior or post cornea or corneal cell transplant, comprising: treating a mammalian donor cornea or isolated mammalian cornea cells with WNT signaling modulator.

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28. The method of claim 27, wherein the WNT signaling modulator is an engineered WNT signaling modulator.

29. The method of claim 27, wherein the WNT signaling modulator is an engineered WNT agonist or an engineered WNT antagonist.

30. The method of claim 29, wherein the engineered WNT agonist is selected from: (*i*) WNT3a; (*ii*) a WNT mimetic; (*iii*) an R-spondin mimetic; or (*iv*) a WNT mimetic fused to a mutant Rspondin mimetic, refered to as a superSWAP or superagonist.

31. The method of claim 30, wherein the WNT mimetic is a SWAP™ compound and wherein the R-spondin mimetic is a SWEETS™ compound.

32. The method of claim 27, wherein the WNT signaling modulator is any of:
WNT3a or any homologue, mutant, fragment, mimic of WNT3a;
G211-18R5;
R2M3-26;
1SH1-03;
hp1SH1-03
17SB9-03;
SuperSWAP or Superagonist; or
a combination thereof.

33. The method of any of claims 27-32 wherein the WNT signaling modulator is co-administered with R-spondin-1, or any R-spondin-1 homologue, mutant, fragment, mimic, or any combination thereof.

34. The method of claim 27, wherein the WNT signaling modulator is administered to the subject in a therapeutically effective dose.

35. The method of claim 27, wherein the subject is a human patient.

36. The method of claim 27, wherein the WNT signaling modulator is administered via eye drop, intracameral injection, subconjunctival injection, intrastromal,or intravitreal injection.

37. The method of claim 27, wherein the WNT signaling modulator is suspended in aqueous solution.

38. The method of claim 37, wherein the WNT signaling modulator is administered to the mammalian donor cornea by bathing the mammalian donor cornea *in vitro* in an aqueous bath solution containing a dose of WNT signaling modulator, or a polynucleotide encoding the polypeptide wherein the polynucleotide is an mRNA or optionally modified mRNA; or an expression vector comprising the isolated polynucleotide.

39. The method of claim 37, wherein the WNT signaling modulator is suspended in aqueous solution at a concentration between 0.1 nM and 10 mM.

40. The method of claim 39, wherein the WNT signaling modulator is suspended in aqueous solution at a concentration between 1 nM and 100 nM.

41. The method of claim 27, wherein the engineered WNT agonist and engineered WNT antagonist comprise binding compositions that bind to one or more Fzd receptors and binding compositions that bind to one or more LRP receptors.

42. The method of claim 41, wherein the binding compositions of the engineered WNT agonist are selected from the group consisting of a Fzd binding composition, a Lrp5 binding composition, a Lrp6 binding composition, and a LRP5/6 binding composition.

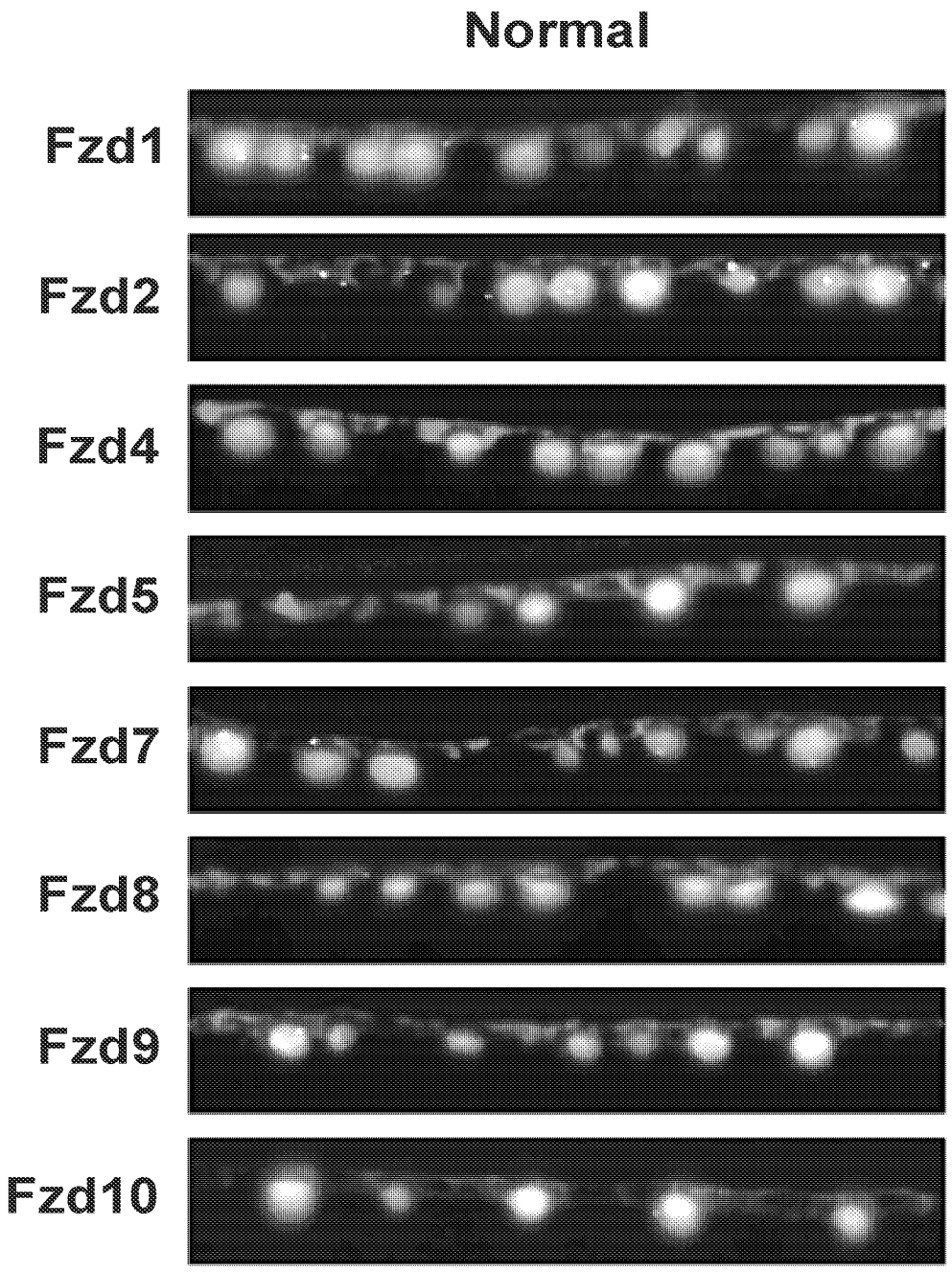


FIG. 1A

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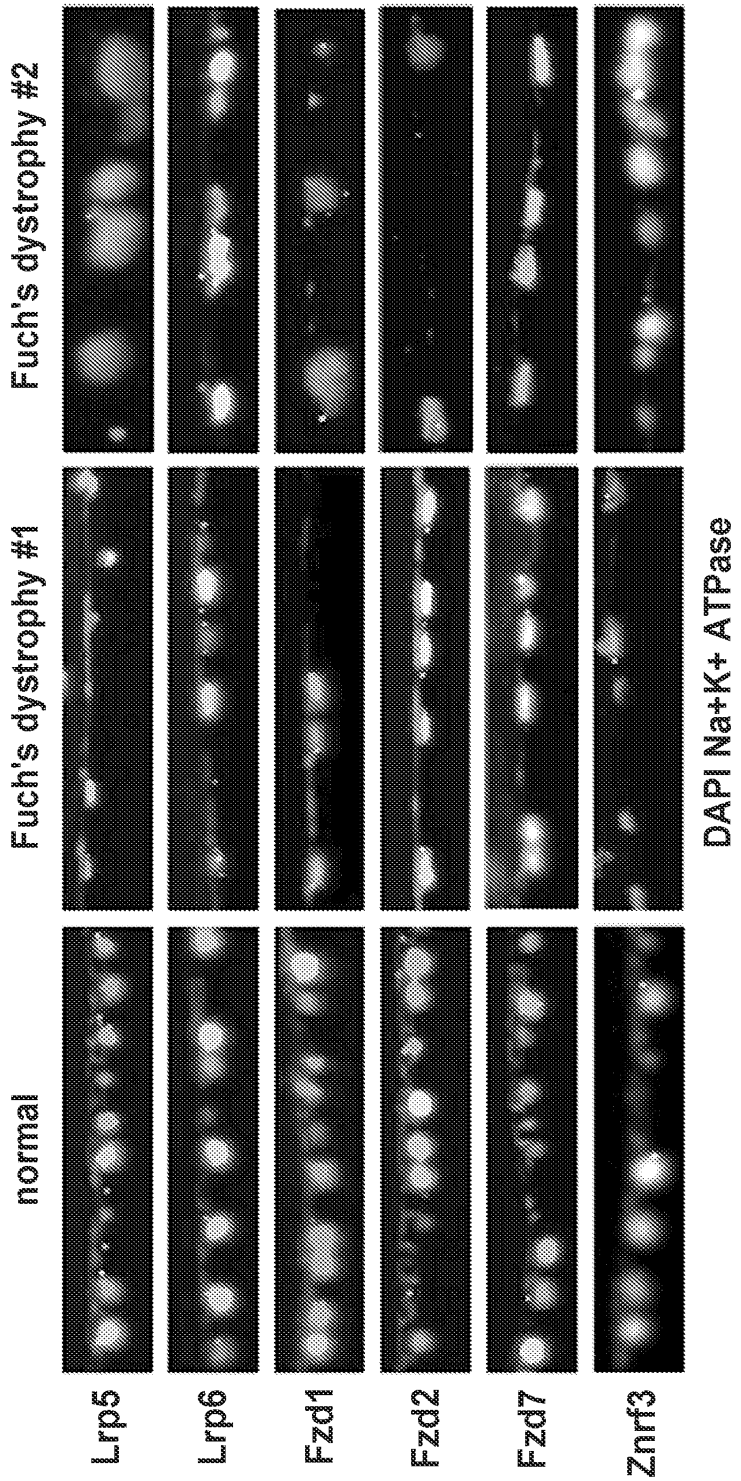


FIG. 1B

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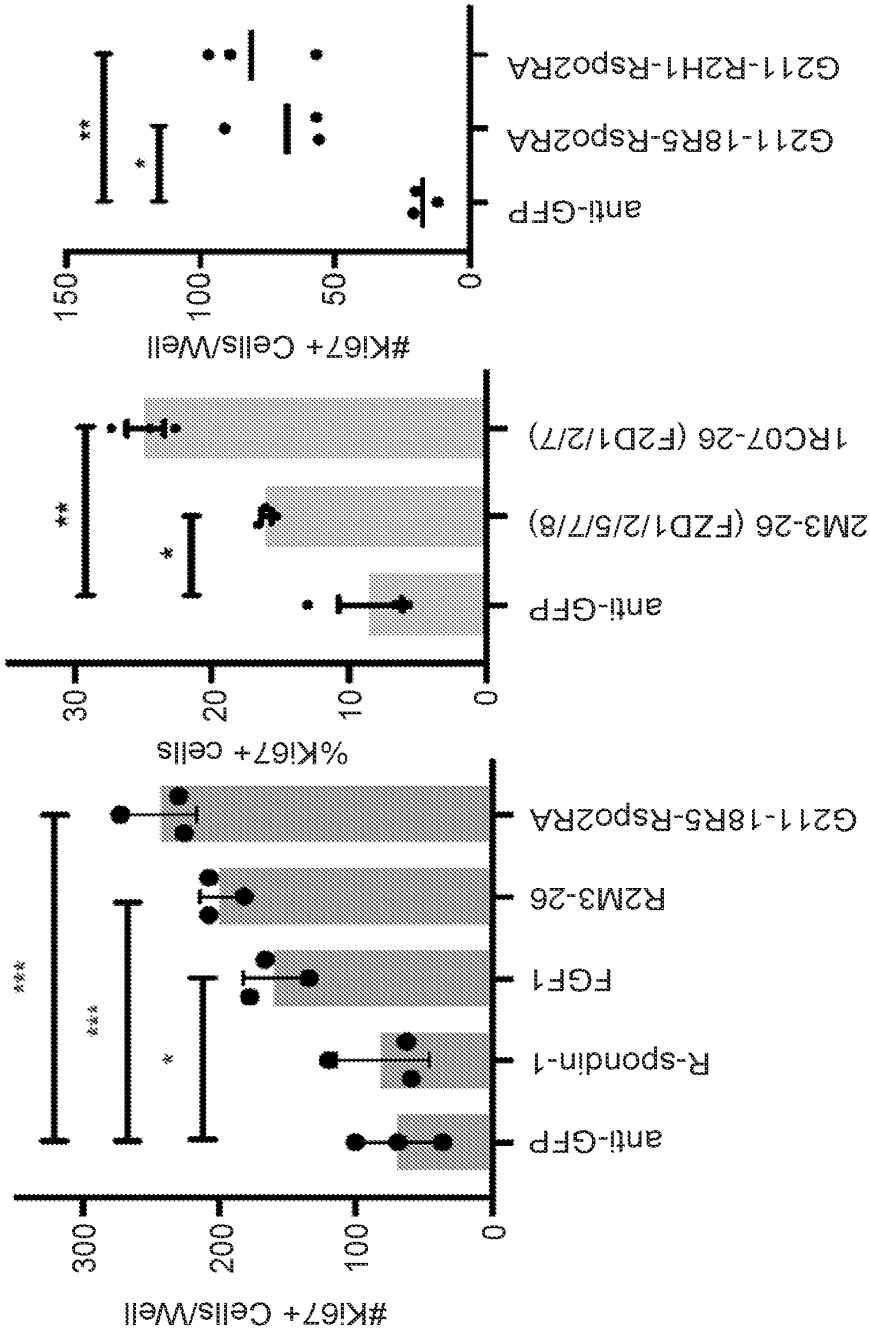


FIG. 2A

FIG. 2B

FIG. 2C

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FIG. 2D

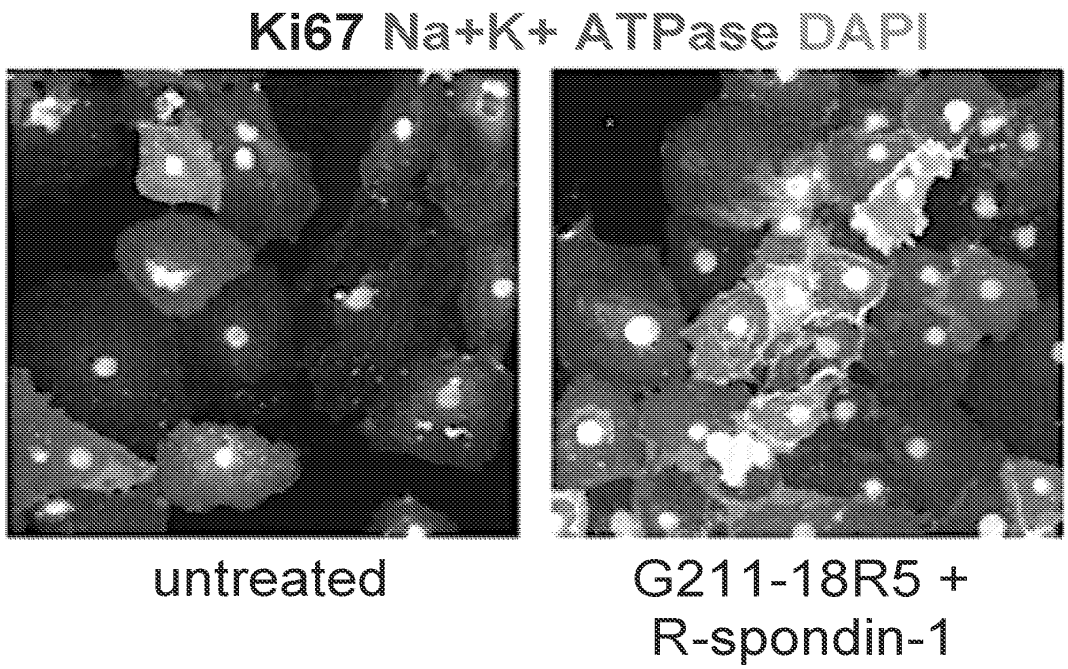
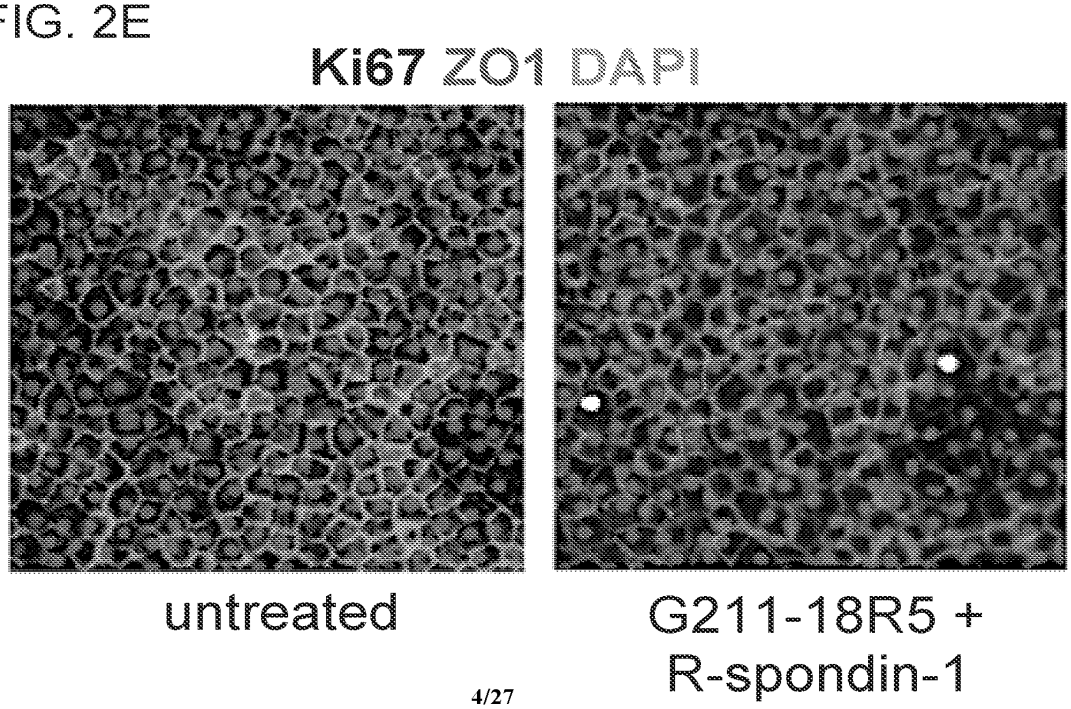

Ki67 Na+K+ ATPase DAPI
untreated
G211-18R5 +
R-spondin-1

FIG. 2E


Ki67 ZO1 DAPI
untreated
G211-18R5 +
R-spondin-1

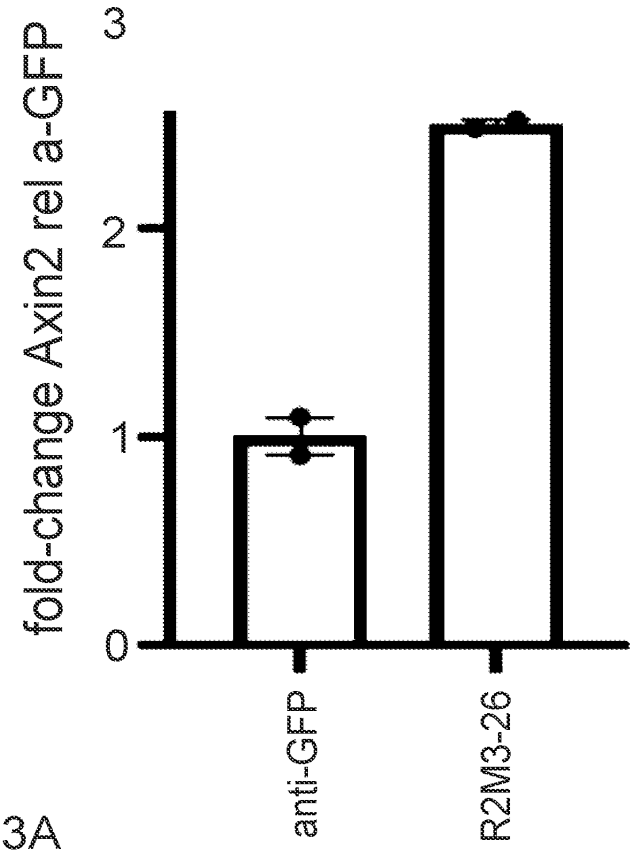

fold-change Axin2 rel a-GFP
3
2
1
0
anti-GFP
R2M3-26

FIG. 3A

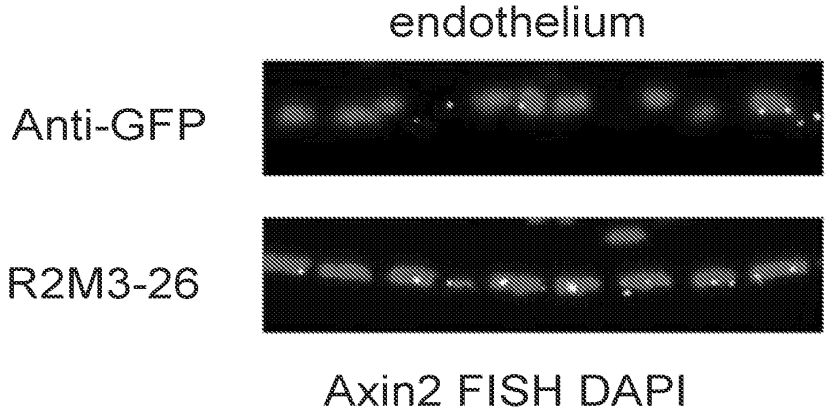

endothelium
Anti-GFP
R2M3-26
Axin2 FISH DAPI

FIG. 3B

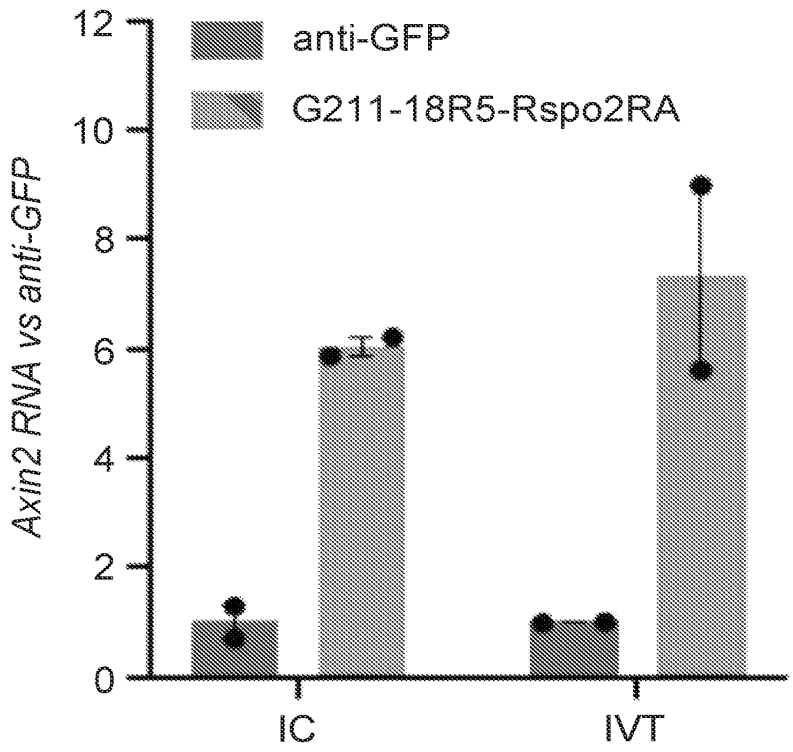

12
10
8
6
4
2
0
anti-GFP
G211-18R5-Rspo2RA
Axin2 RNA vs anti-GFP
IC
IVT

FIG. 3C

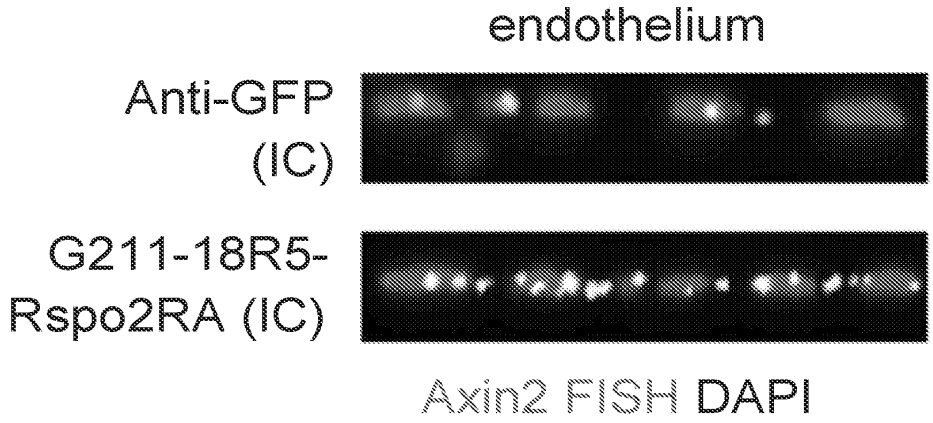

endothelium
Anti-GFP (IC)
G211-18R5-Rspo2RA (IC)
Axin2 FISH DAPI

FIG. 3D

FIG. 3F

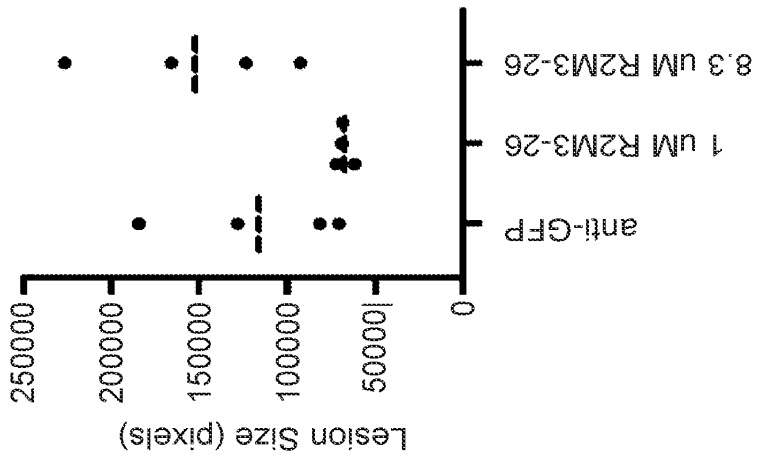

Lesion Size (pixels)
250000
200000
150000
100000
50000
0
anti-GFP
1 uM R2M3-26
8.3 uM R2M3-26

FIG. 3E

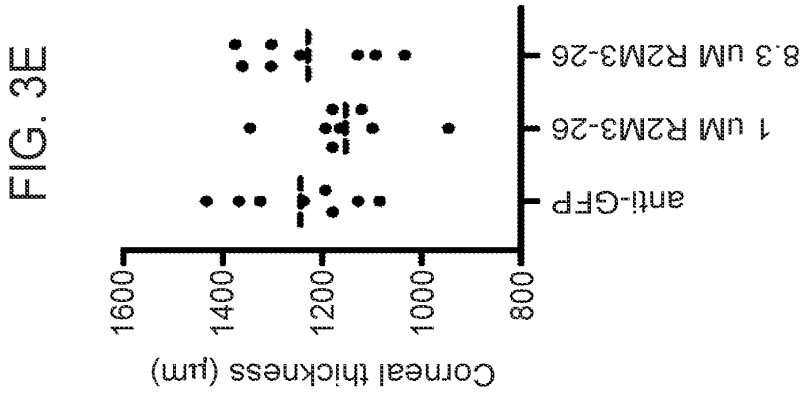

Corneal thickness (µm)
1600
1400
1200
1000
800
anti-GFP
1 uM R2M3-26
8.3 uM R2M3-26

FIG. 3I

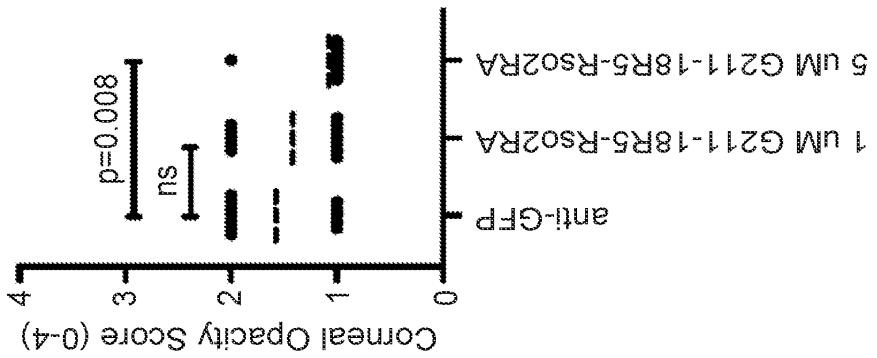


FIG. 3H

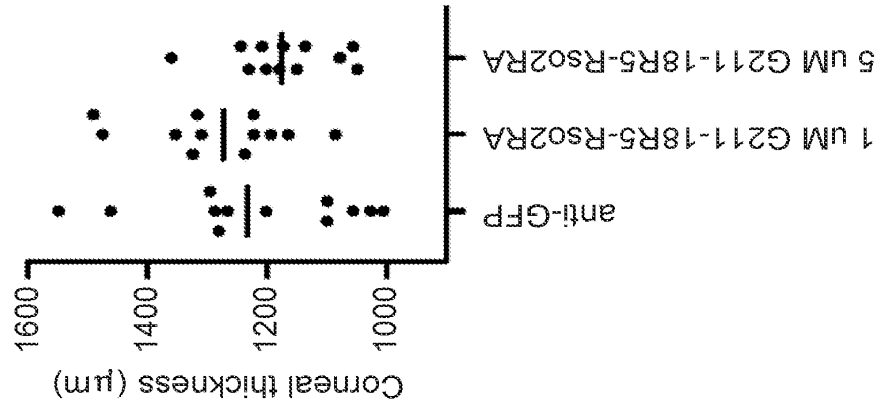
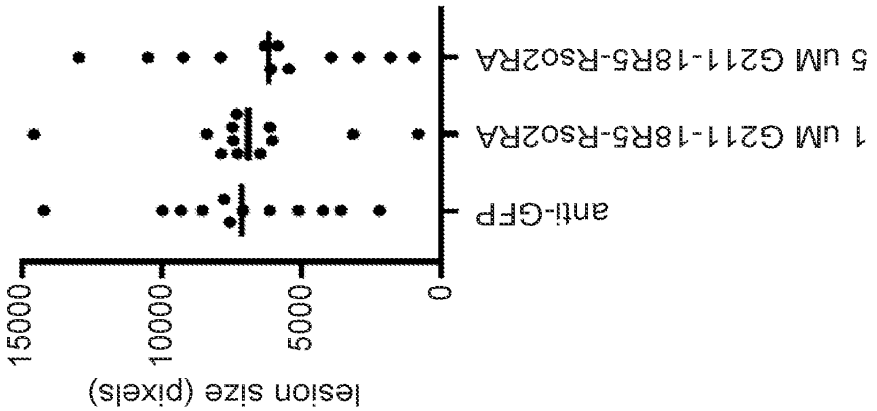


FIG. 3G



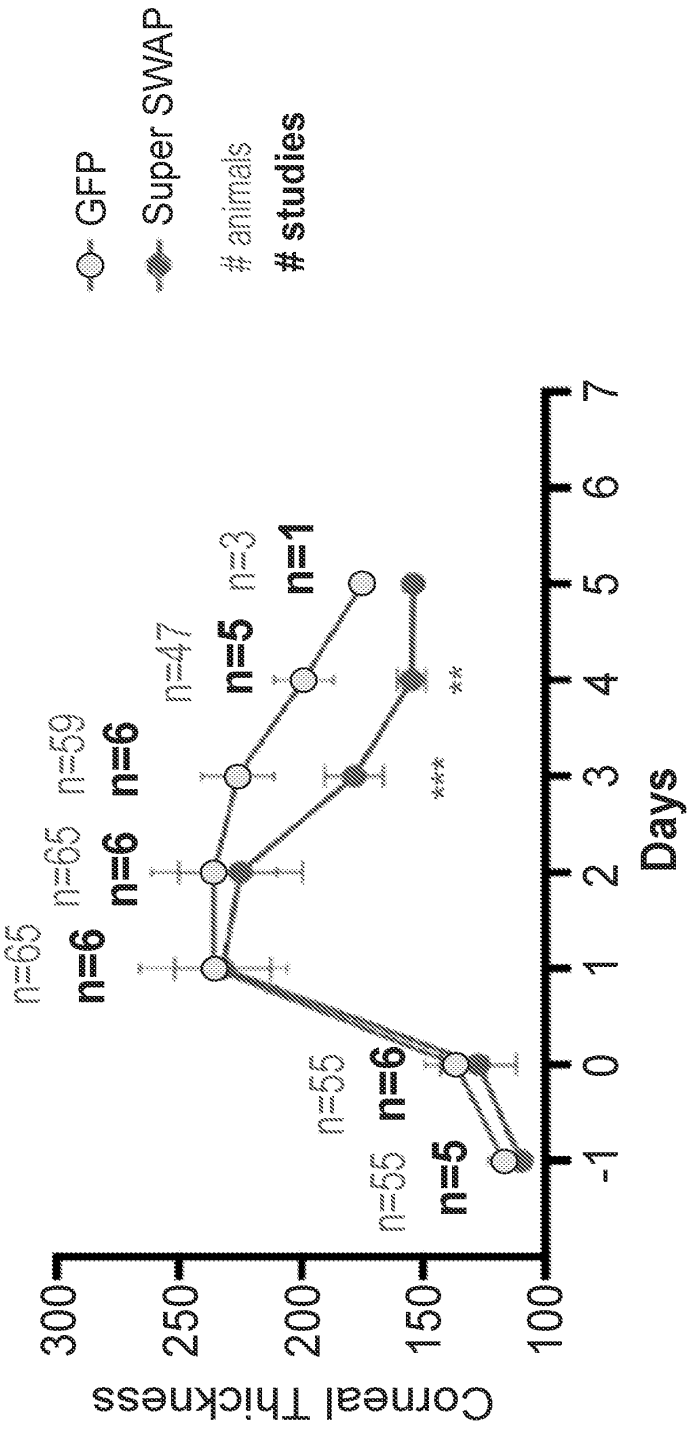


FIG. 4A

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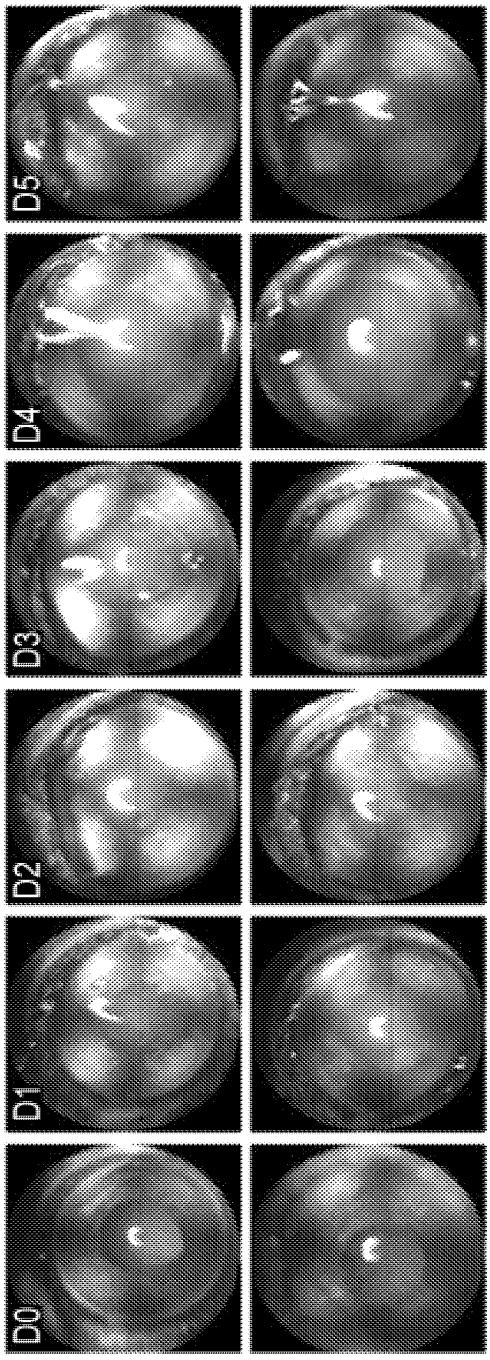


FIG. 4B

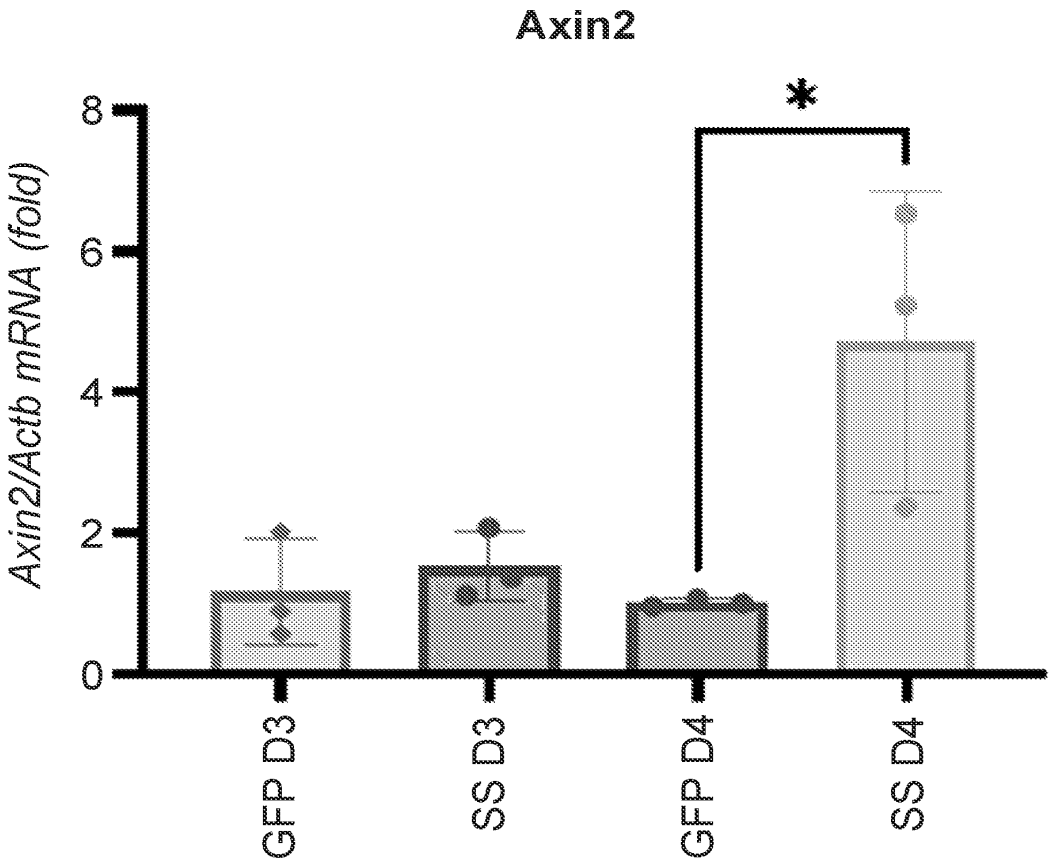


FIG. 4C

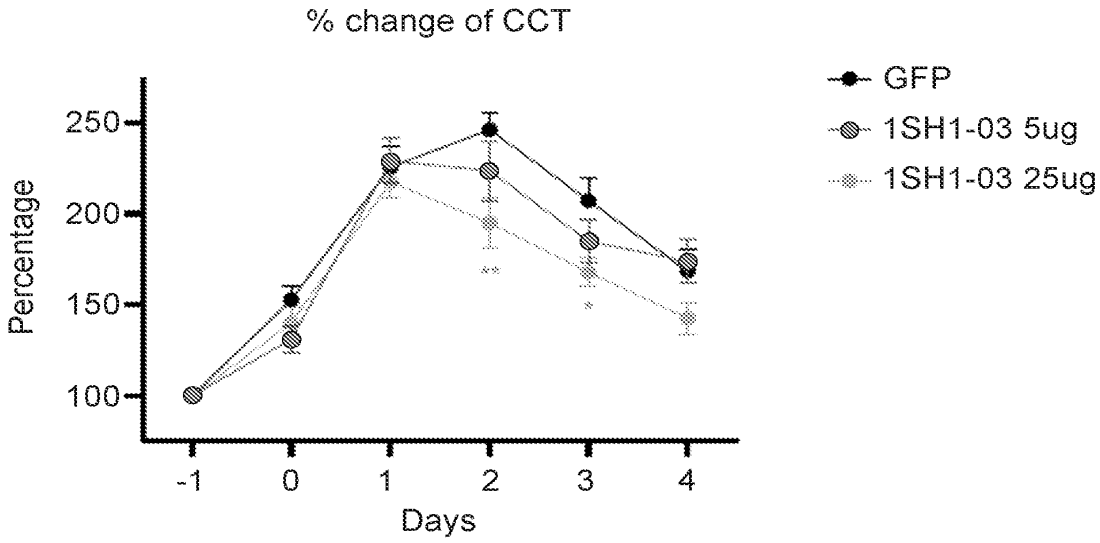

% change of CCT
Percentage
250
200
150
100
-1
0
1
2
3
4
Days
GFP
1SH1-03 5ug
1SH1-03 25ug

FIG. 5A

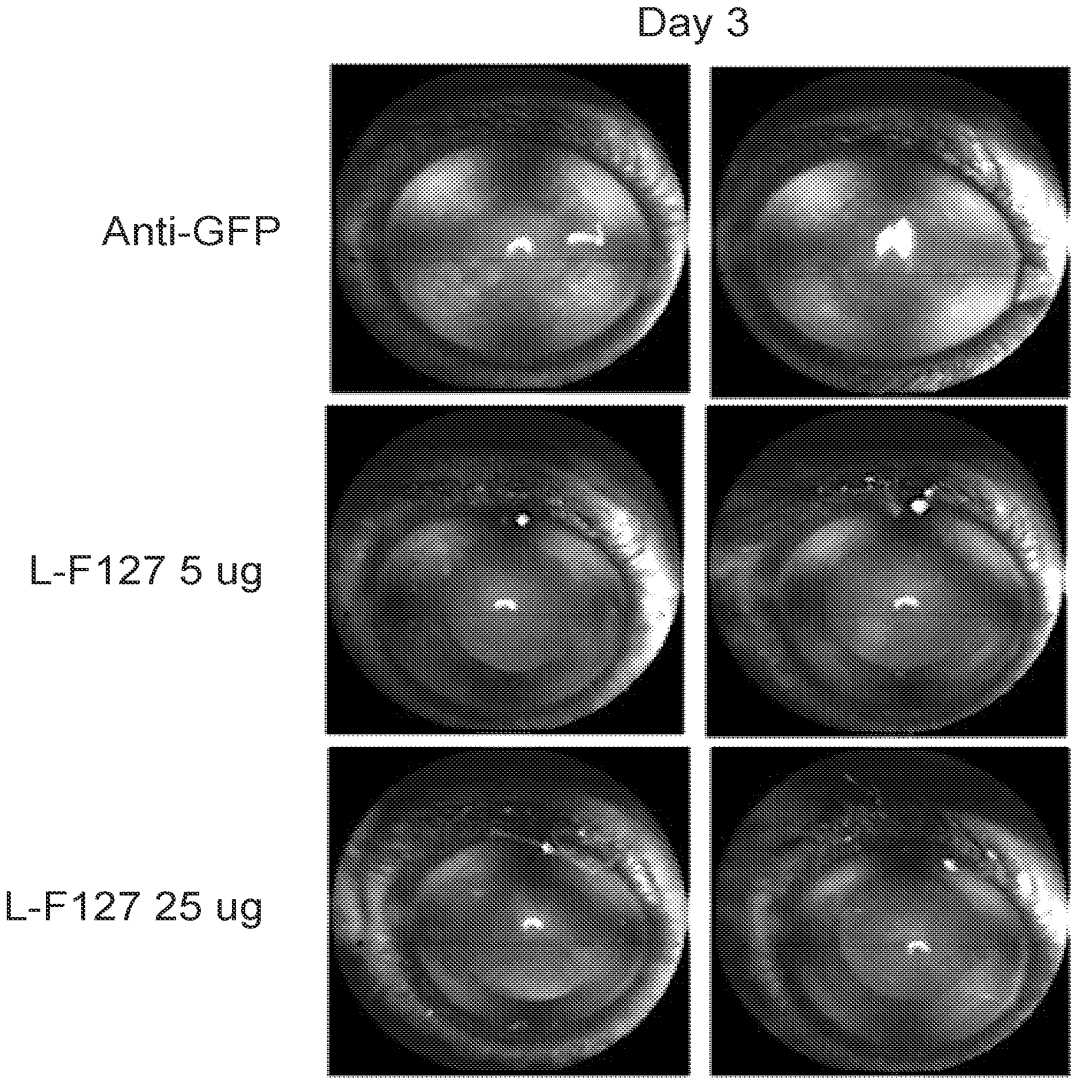


FIG. 5B

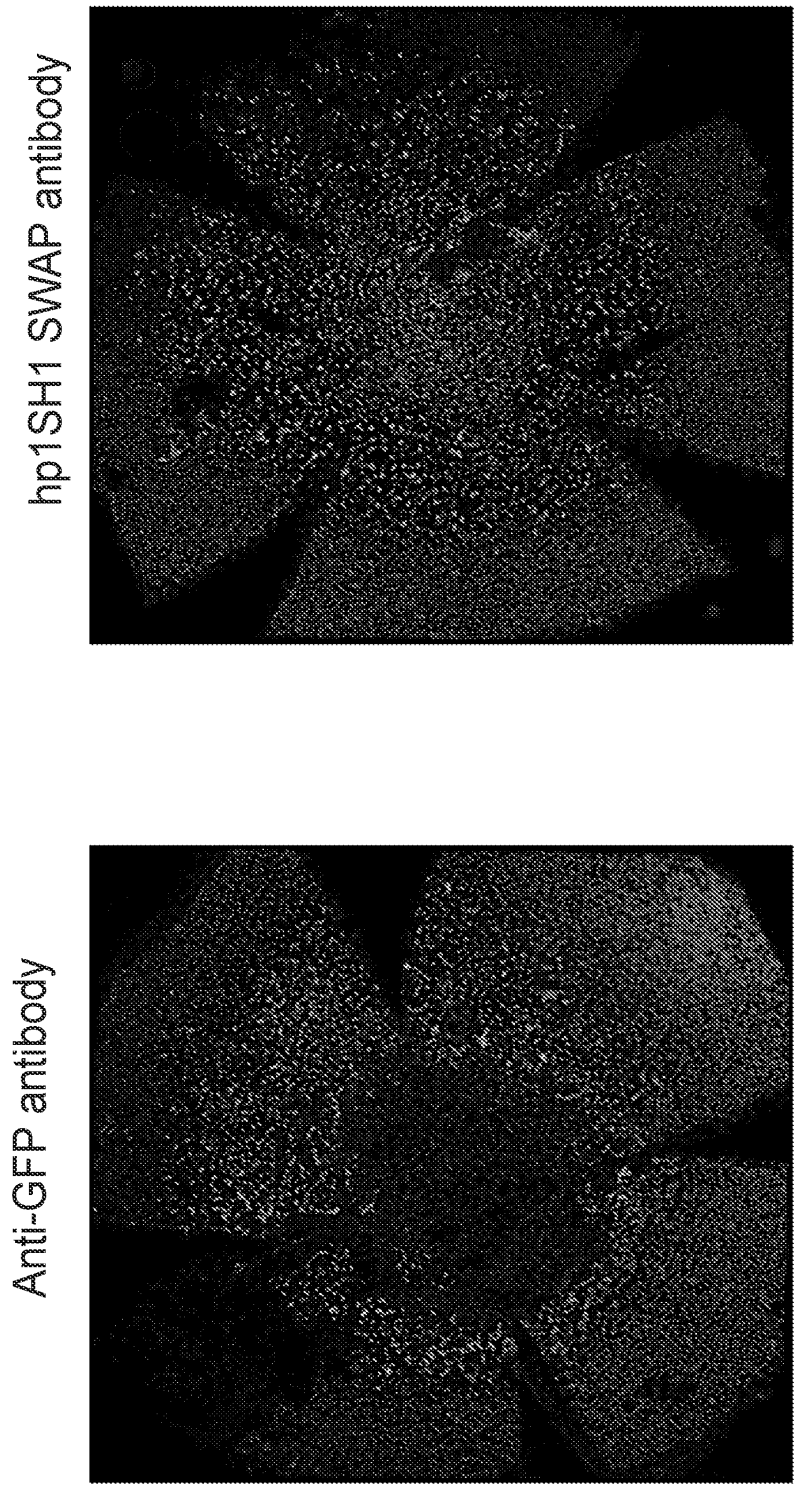


FIG. 6

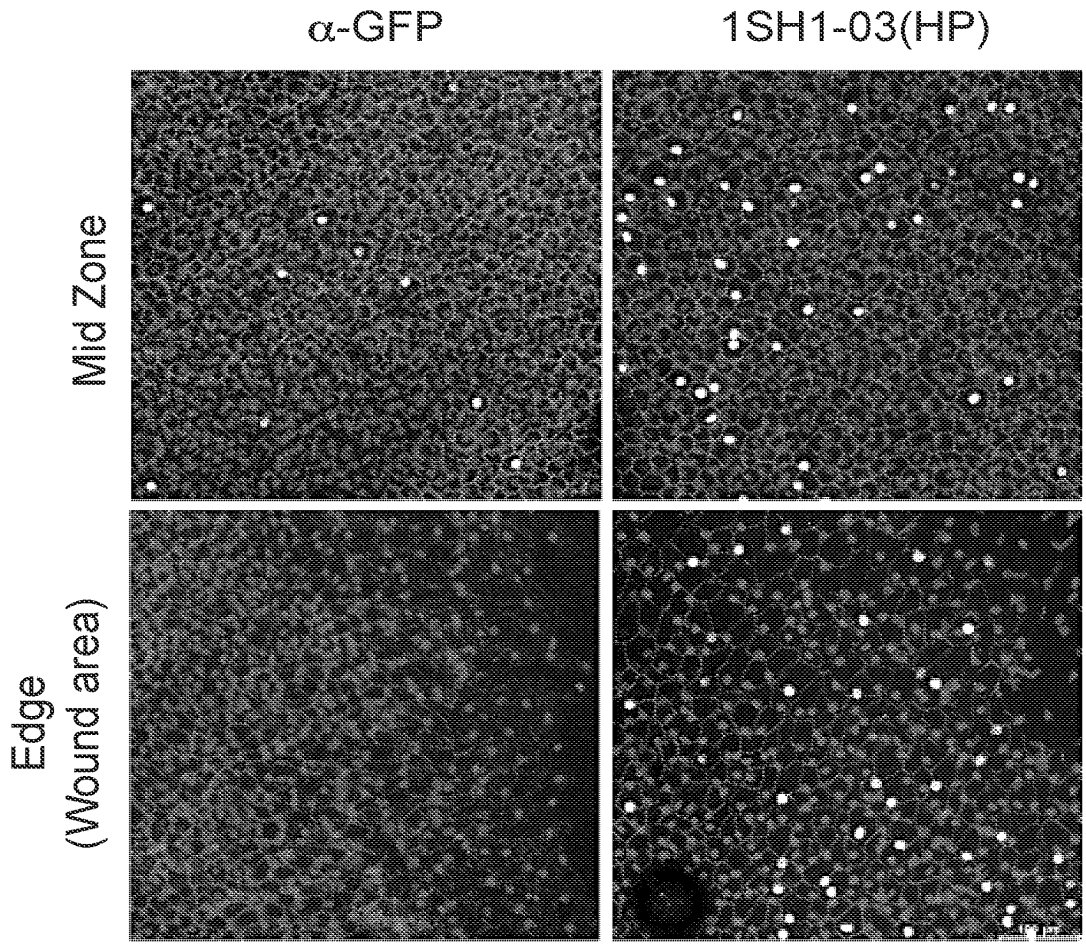


FIG. 7A

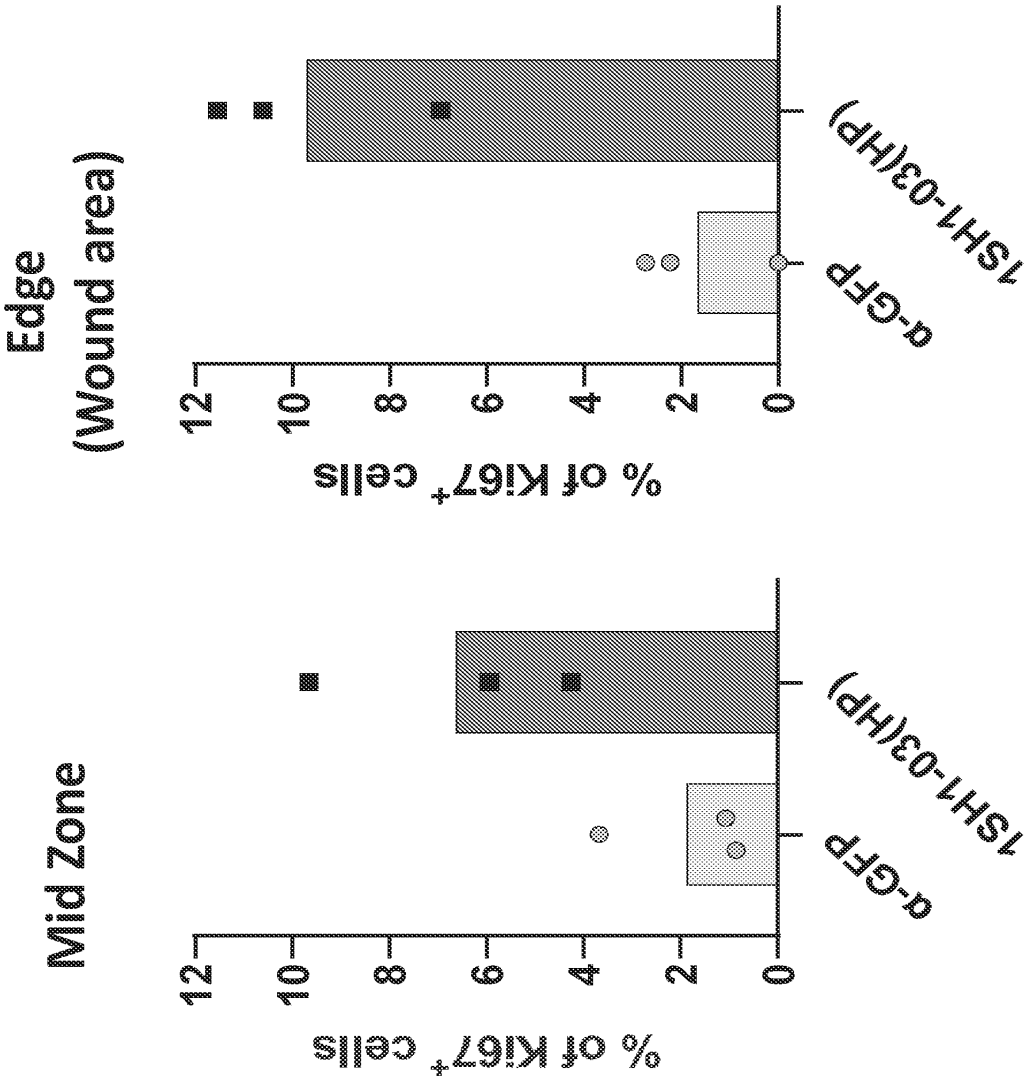

Edge
(Wound area)
% of Ki67+ cells
0
2
4
6
8
10
12
α-GFP
7SH1-03(HP)
Mid Zone
% of Ki67+ cells
0
2
4
6
8
10
12
α-GFP
7SH1-03(HP)

FIG. 7B

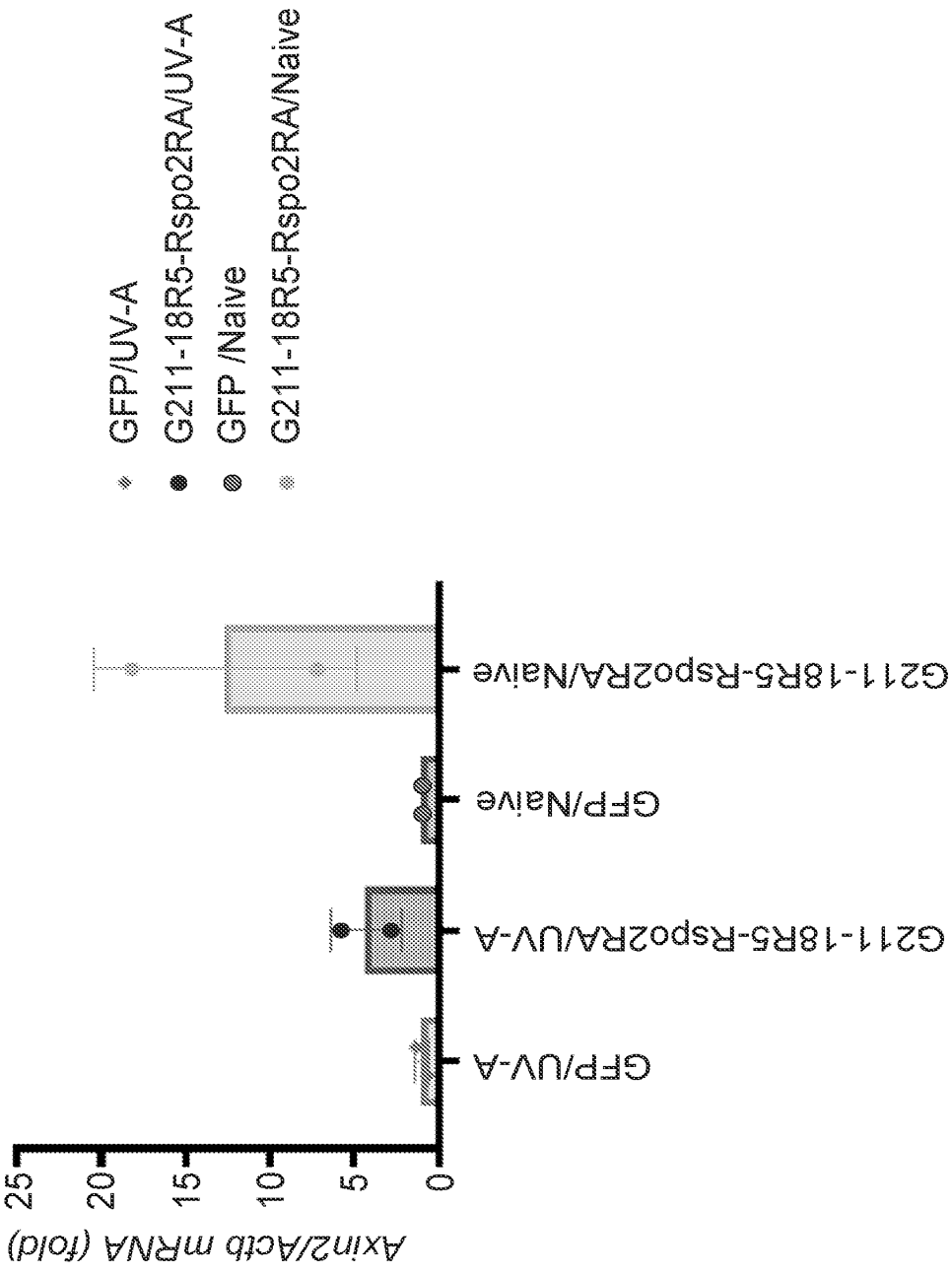

GFP/UV-A
G211-18R5-Rspo2RA/UV-A
GFP /Naive
G211-18R5-Rspo2RA/Naive
Axin 2
Axin2/Actb mRNA (fold)
0
5
10
15
20
25
GFP/UV-A
G211-18R5-Rspo2RA/UV-A
GFP/Naive
G211-18R5-Rspo2RA/Naive

FIG. 8A

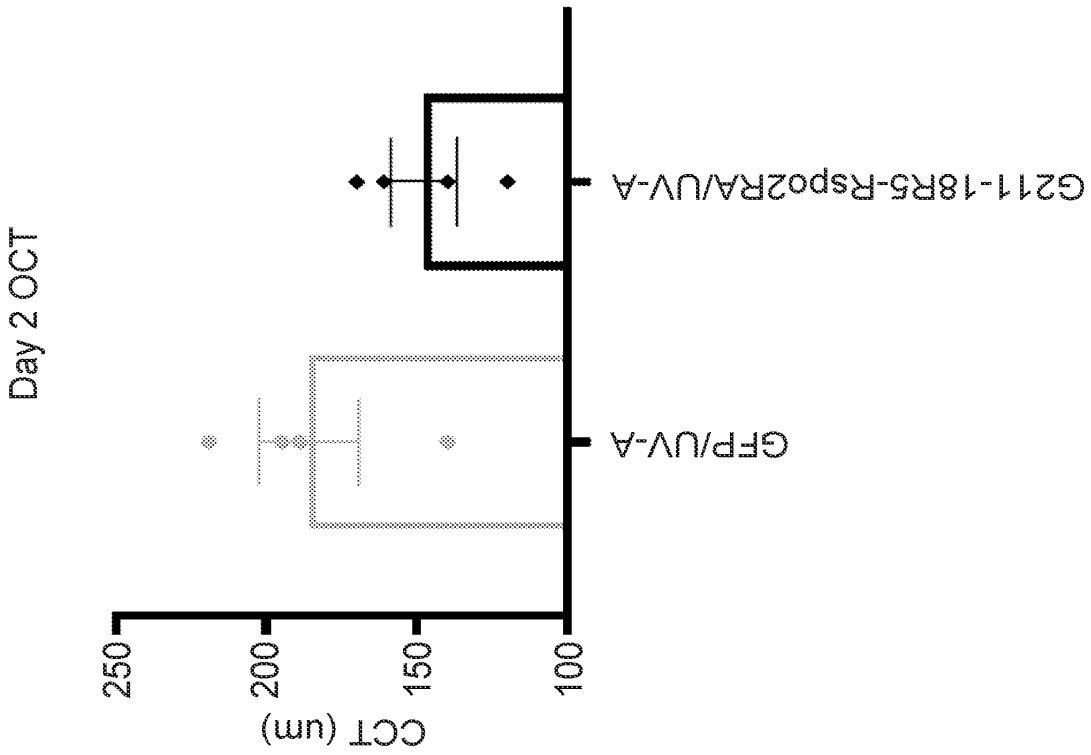


FIG. 8B

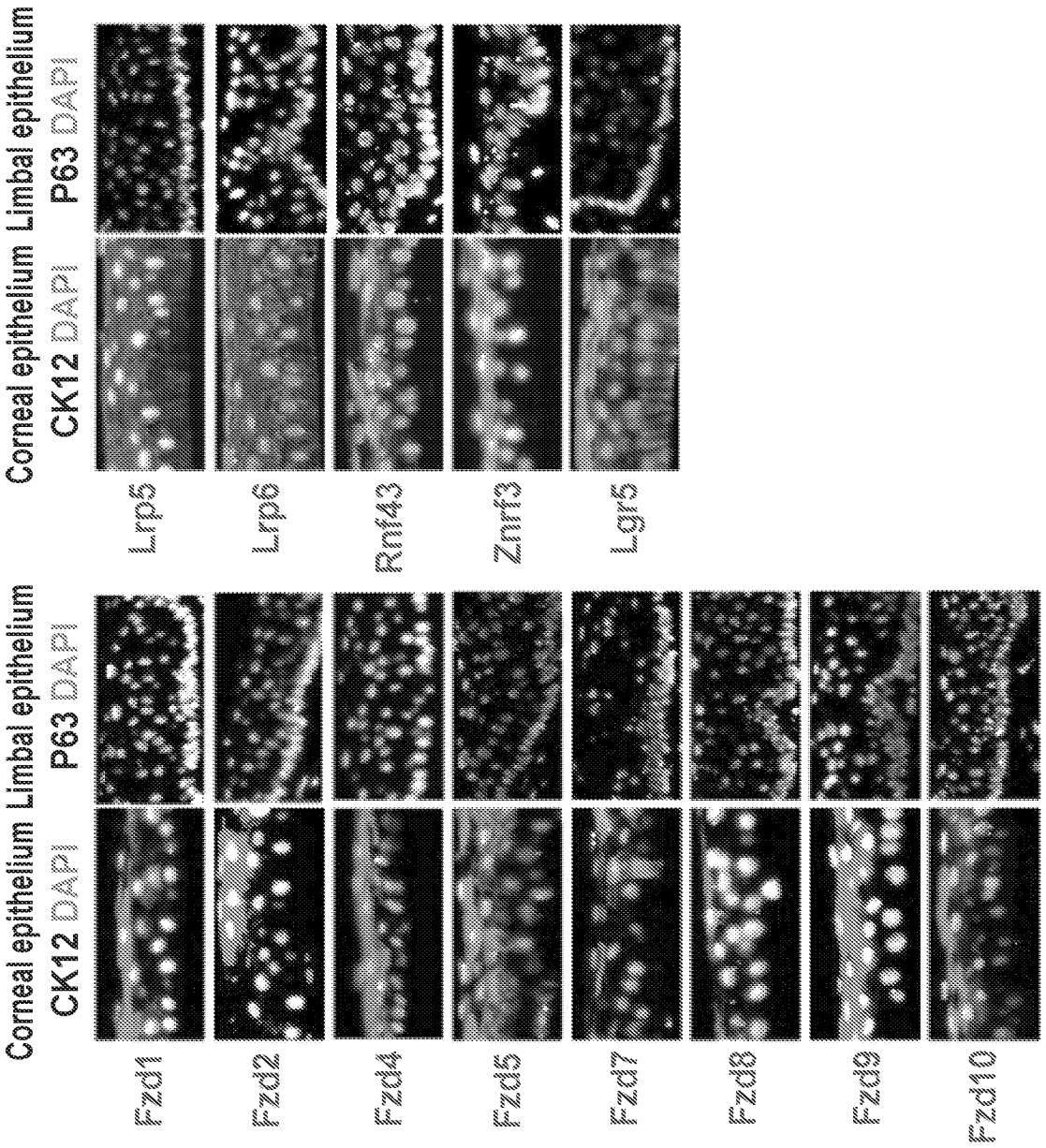


FIG. 9A

MS&D Exhibit 1008, Page 2368 of 4223

FIG. 9B

Gene	Corneal Epithelium	Limbal Epithelium
Fzd1	+	++
Fzd2	+	+
Fzd4	+	+
Fzd5	++	++
Fzd7	+	++
Fzd8	++	++
Fzd9	+	+
Fzd10	+	++
Lrp5	+	++
Lrp6	++	+
Rnf43	++	++
Znrf3	++	++
Lgr5	-	+

MS&D Exhibit 1008, Page 2369 of 4223

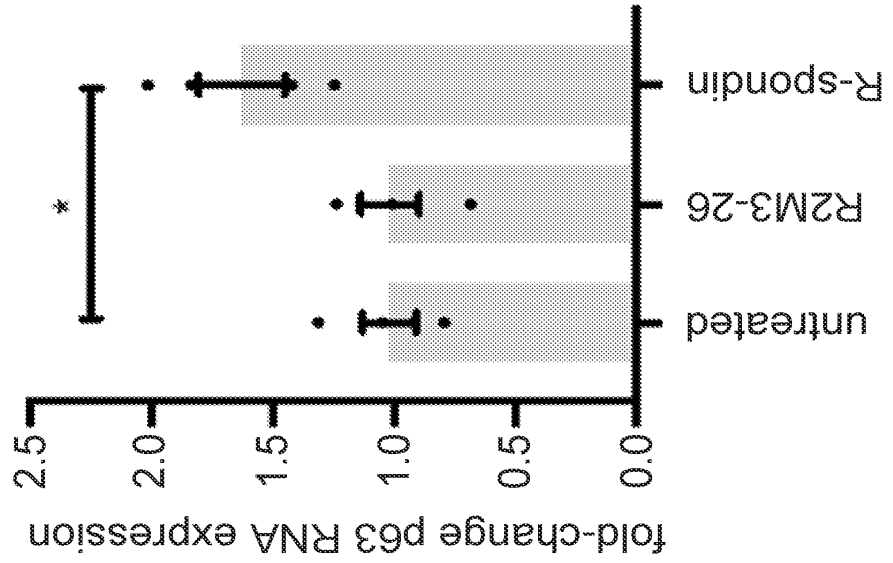


FIG. 10B

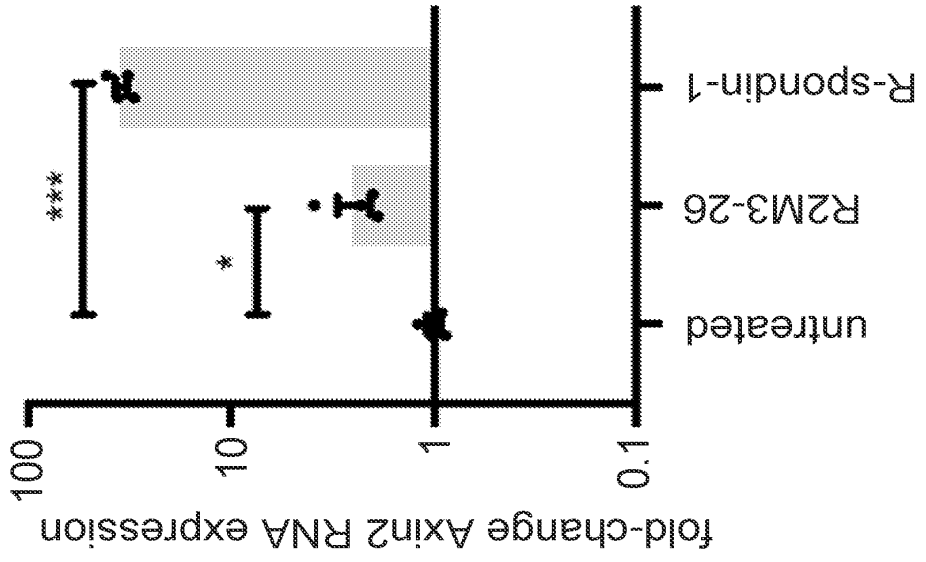


FIG. 10A

SUBSTITUTE SHEET (RULE 26)

FIG. 11A

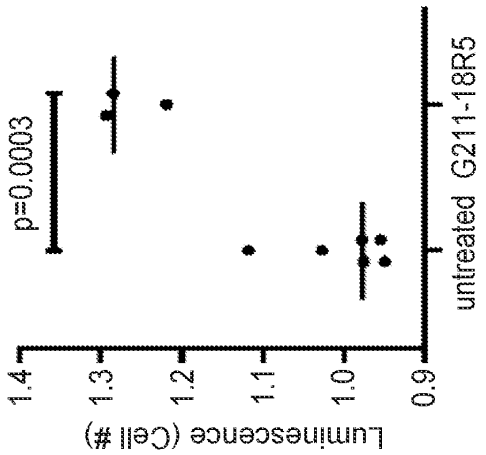


FIG. 11B

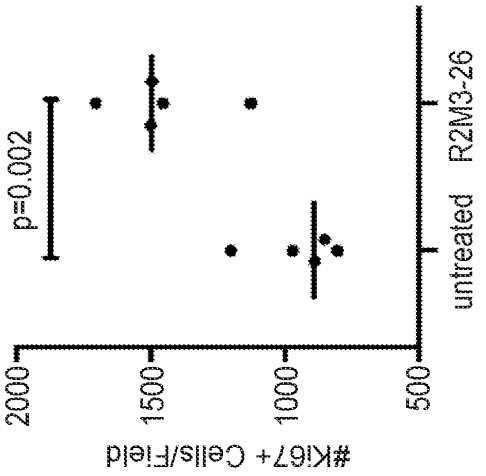
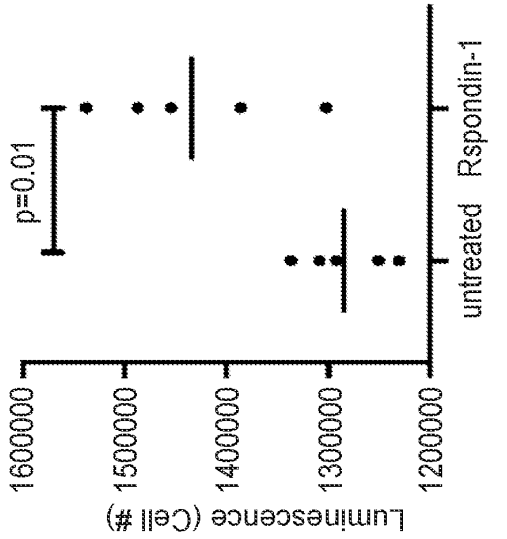


FIG. 11C



SUBSTITUTE SHEET (RULE 26)

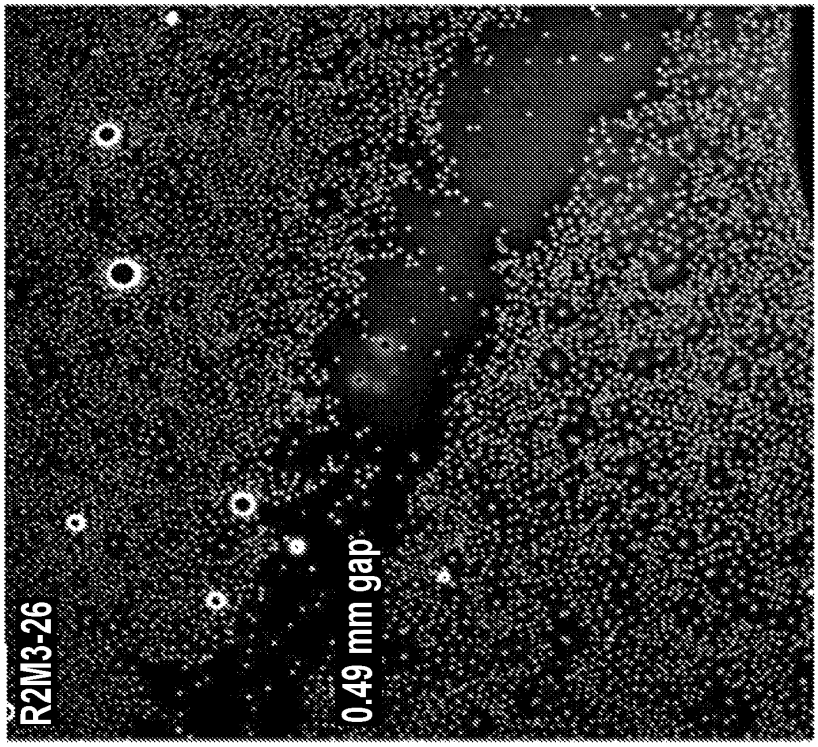


FIG. 12B

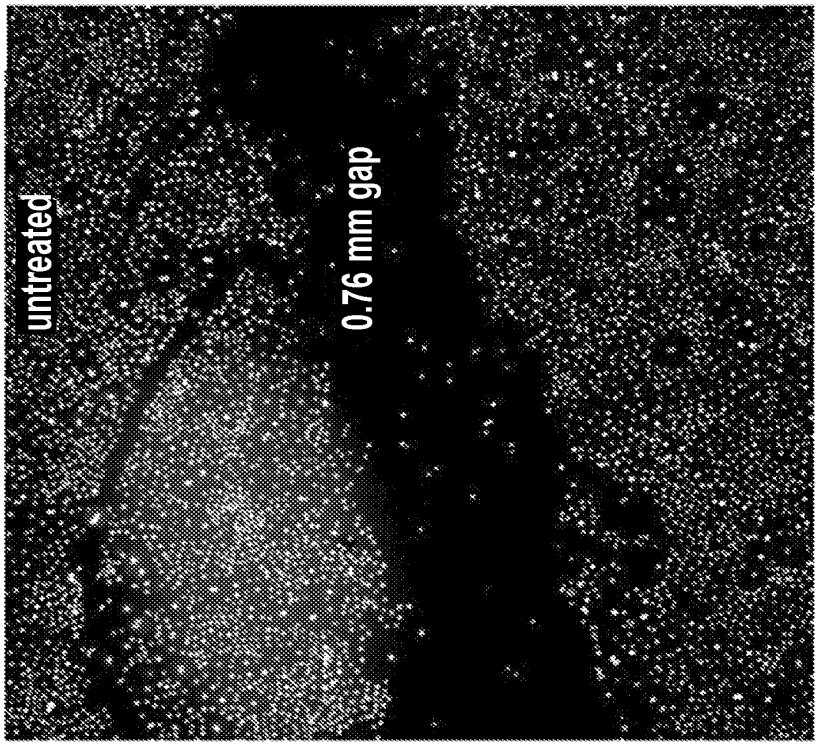


FIG. 12A

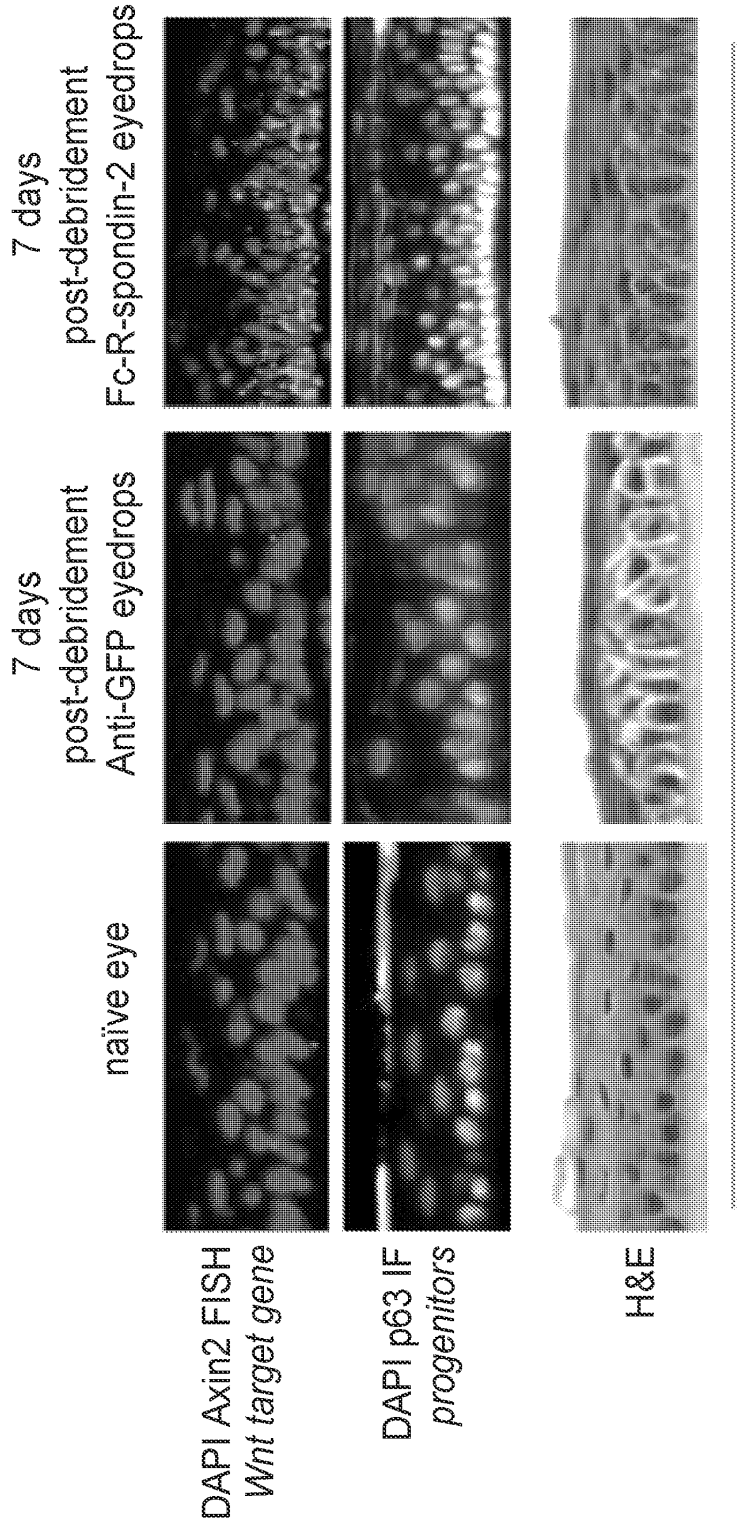


FIG. 13

SUBSTITUTE SHEET (RULE 26)

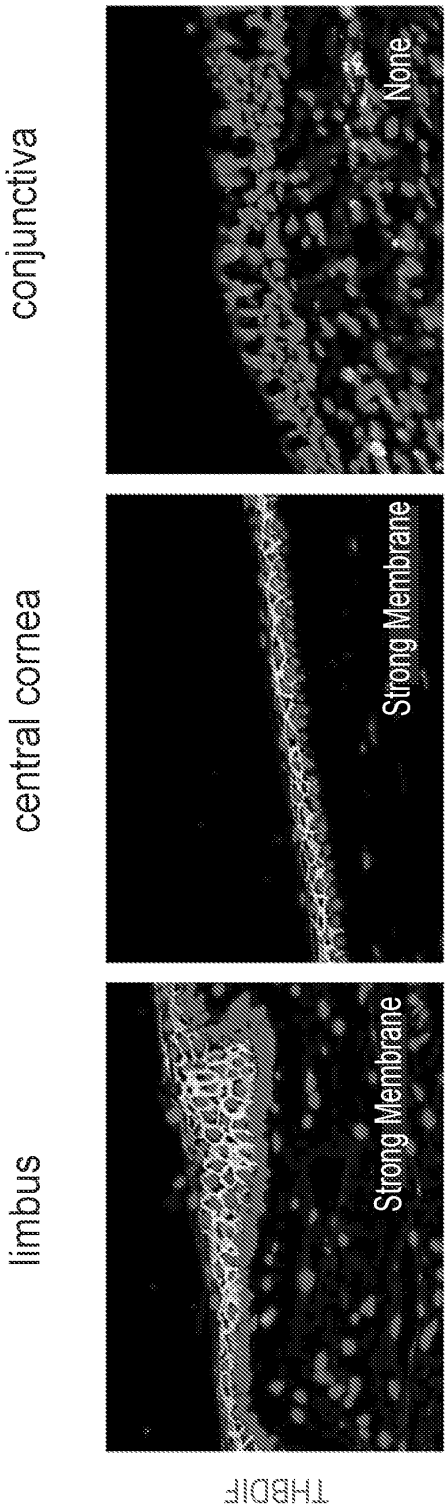


FIG. 14

SUBSTITUTE SHEET (RULE 26)

MS&D Exhibit 1008, Page 2374 of 4223

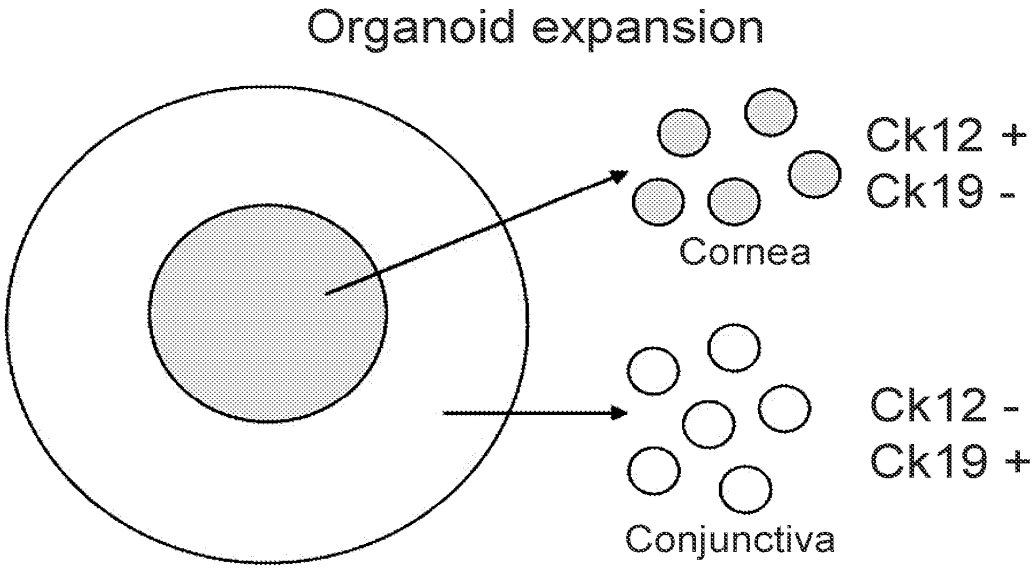

Organoid expansion
Ck12 +
Ck19 -
Cornea
Ck12 -
Ck19 +
Conjunctiva

FIG. 15A

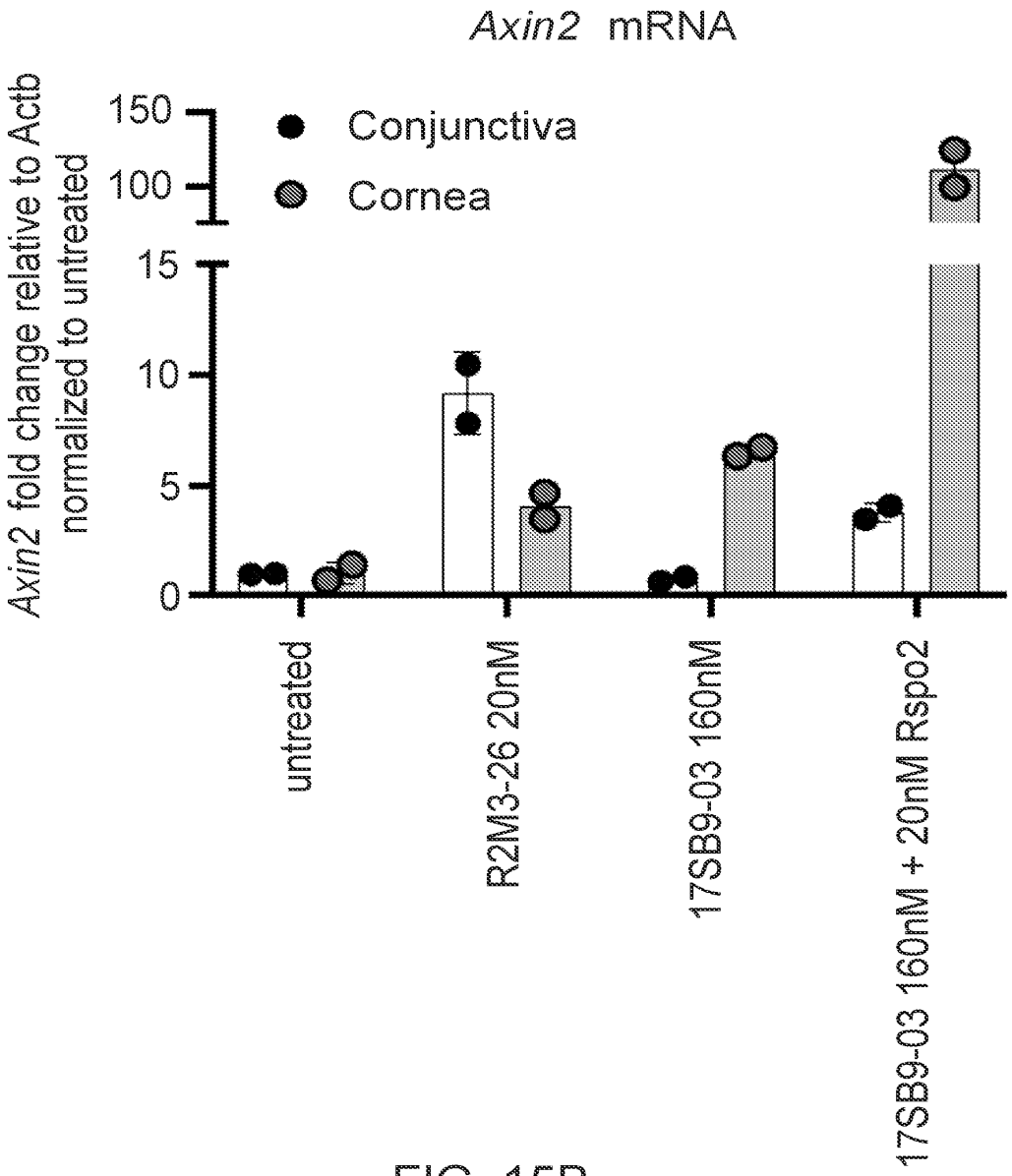


FIG. 15B

SUBSTITUTE SHEET (RULE 26)

Docket No.: SRZN-006/04US 328202-2203
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor:	Yang LI	Confirmation No.:	9001
Application No.:	18/361,782	Group Art Unit:	Not Yet Assigned
Filed:	July 28, 2023	Examiner:	Not Yet Assigned

For: WNT SURROGATE MOLECULES AND USES THEREOF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT
UNDER 37 C.F.R. §§ 1.56, 1.97, AND 1.98

In accordance with the duty of disclosure set forth in 37 C.F.R. §1.56, Applicant hereby submits the following information in conformance with 37 C.F.R. §§1.97 and 1.98. It is respectfully requested that the information be expressly considered during the prosecution of this application, and the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

[X] Pursuant to 37 C.F.R. §1.98, a copy of each non-US patent document cited on the attached Form used in lieu of PTO/SB/08 is enclosed.

[] No copies of the foreign patent, foreign patent application, or non-patent literature publications listed on the attached Form used in lieu of PTO/SB/08 are being provided pursuant to 37 C.F.R. §1.98(d) because the publications were previously cited by or submitted to the Office in prior Application No(s). ____ to which the above-identified application claims priority under 35 U.S.C. §120.

[X] No copies of any U.S. patents or U.S. patent application publications listed on the attached Form used in lieu of PTO/SB/08 are being provided pursuant to 37 C.F.R. §1.98.

[] Publication(s) listed on the attached Form used in lieu of PTO/SB/08 were cited in a foreign search or examination report corresponding to Application No. and mailed on .

[] Enclosed is a copy of a non-English publication(s) _____ Pursuant to §609 of the M.P.E.P., Applicant submits the attached foreign search or examination report, which cites such non-English language publication(s).

[] Enclosed is a copy of a non-English publication(s) _____ English language publication _____ (copy enclosed) claims priority from this non-English publication.

[] Enclosed is an explanation of non-English publication(s) _____ for which an English translation is not available.

[] Enclosed is an English translation of non-English publication(s) _____ cited on the attached Form used in lieu of PTO/SB/08.

[] Enclosed is an English language Abstract of non-English publication(s) _____ cited on the attached Form used in lieu of PTO/SB/08.

[] A copy of pending patent Application No. _____, at cite no. _____, is not submitted pursuant to the Waiver of the Copy Requirement in 37 CFR 1.98 for Cited Pending U.S. Patent Applications, issued October 19, 2004.

[X] In accordance with **37 C.F.R. §1.97(b)**, no additional fee for submission of this Information Disclosure Statement is required, as it is filed within any one of the following time periods:

[] within three months from the filing date of this national application other than a CPA under 37 C.F.R. § 1.53(d);

[] within three months from the date of entry of the national stage as set forth in 37 C.F.R. §1.491 in this international application;

[X] before the mailing date of a first Office action on the merits; or

[] before the mailing of a first Office action after the filing of a request for continued examination under 37 C.F.R. § 1.114.

[] In accordance with **37 C.F.R. §1.97(c)**, this Information Disclosure Statement is filed after the period specified in 37 C.F.R. § 1.97(b), but before the mailing of any of the following: a final action under 37 C.F.R. §1.113; a notice of allowance under 37 C.F.R. §1.311; or an action that otherwise closes prosecution in this application.

In accordance with 37 C.F.R. §1.97(c) also enclosed is:

[] Fee under 37 C.F.R. §1.17(p) in the amount of $260.00;

[] Fee under 37 C.F.R. §1.17(p) in the amount of $104.00;

[] Fee under 37 C.F.R. §1.17(p) in the amount of $52.00; or

[] Statement as specified in 37 C.F.R. §1.97(e):

[] Each item of information contained in the Information Disclosure Statement cited herein was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing date of the Information Disclosure Statement; or

[] No item of information contained in the Information Disclosure Statement submitted herewith was cited in any communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the undersigned, having made a reasonable inquiry, no item of information contained in the Information Disclosure Statement was known to any individual designated in 37 C.F.R. §1.56(c) more than three months prior to the filing date of the Information Disclosure Statement.

[] This Information Disclosure Statement is filed after payment of the issue fee, but before issuance of the patent under the Quick Path Information Disclosure Statement pilot program.

In accordance with the Quick Path Information Disclosure Statement pilot program also enclosed is:

[] Fee under 37 C.F.R. §1.17(p) in the amount of $260.00;

[] Fee under 37 C.F.R. §1.17(p) in the amount of $104.00;

[] Fee under 37 C.F.R. §1.17(p) in the amount of $52.00;

and

[] Statement as specified in 37 C.F.R. §1.97(e):

[] Each item of information contained in the Information Disclosure Statement cited herein was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing date of the Information Disclosure Statement; or

[] No item of information contained in the Information Disclosure Statement submitted herewith was cited in any communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the undersigned, having made a reasonable inquiry, no item of information contained in the Information Disclosure Statement was known to any individual designated in 37 C.F.R. §1.56(c) more than three months prior to the filing date of the Information Disclosure Statement.

[] In accordance with **37 C.F.R. §1.97(d)**, this Information Disclosure Statement is filed after the period specified in 37 C.F.R. § 1.97(c), but with or before the payment of the issue fee.

In accordance with 37 C.F.R. §1.97(d) also enclosed is:

[] Fee under 37 C.F.R. §1.17(p) in the amount of $260.00;

[] Fee under 37 C.F.R. §1.17(p) in the amount of $104.00; or

[] Fee under 37 C.F.R. §1.17(p) in the amount of $52.00;

and

[] Statement as specified in 37 C.F.R. §1.97(e):

[] Each item of information contained in the Information Disclosure Statement cited herein was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing date of the Information Disclosure Statement; or

[] No item of information contained in the Information Disclosure Statement submitted herewith was cited in any communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the undersigned, having made a reasonable inquiry, no item of information contained in the Information Disclosure Statement was known to any individual designated in 37 C.F.R. §1.56(c) more than three months prior to the filing date of the Information Disclosure Statement.

[] In accordance with **37 C.F.R. § 1.704(d)**, Applicant notes that to our knowledge each item of information contained in the information disclosure statement:

[] was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § **1.56(c)** more than thirty days prior to the filing of the information disclosure statement.

[] is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by any individual designated in § **1.56(c)** more than thirty days prior to the filing of the information disclosure statement.

In accordance with 37 C.F.R. § 1.97(g), this Information Disclosure Statement shall not be construed as to mean that a search has been made.

In accordance with 37 C.F.R. § 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that the information cited in the statement is, or is considered to be material to patentability as defined by 37 C.F.R § 1.56(b).

REMARKS

It is respectfully requested that the Examiner consider the above-noted information and return an initialed copy of the attached Form used in lieu of PTO/SB/08 to the undersigned.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Dated: January 18, 2024

Respectfully submitted,
COOLEY LLP

Electronic signature: /Ashley M. Sherrid/
Carol D. Laherty
Reg. No. 51,909
Ashley M. Sherrid
Reg. No. 81,446

USPTO CUSTOMER NO. 157070

COOLEY LLP
ATTN: IP Docketing Department
1299 Pennsylvania Avenue NW, Suite 700
Washington, DC 20004

Tel: (206) 452-8700
Fax: (202) 842-7899

Bibliographic data

Title:	TISSUE-SPECIFIC WNT SIGNAL ENHANCING MOLECULES AND USES
Pub/Pat no:	CN112654363A
Pub/Issue Date:	2021-04-13
Inventor(s):	ZHANG ZHENGJIAN| LI YANG| YEH WEN-CHEN| YUAN TOM ZHIYE| BARIBAULT HELENE| LAI KUO-PAU (JIMMY)| ||||· |
Applicant(s):	SURROZEN INC
Classification:	A61K38/17AI; C07K16/18AI; C07K16/28AI
Application number:	CN20198052962 2019-07-09
Priority number:	US201862695509P 20180709; US201862770026P 20181120; US201962822731P 20190322; WO2019US41067 20190709;

Abstract of CN112654363A

The present disclosure provides tissue-specific Wnt signal enhancing molecules, and related methods of using these molecules to increase Wnt signaling in liver tissues.

(19)中华人民共和国国家知识产权局

(12)发明专利申请

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(43)申请公布日 2021.04.13

(21)申请号 201980052962.2
(22)申请日 2019.07.09
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62/822,731 2019.03.22 US
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WO2020/014271 EN 2020.01.16
(71)申请人 瑟罗泽恩公司
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(74)专利代理机构 北京英赛嘉华知识产权代理有限责任公司 11204
代理人 王达佐 洪欣
(51)Int.Cl.
A61K 38/17(2006.01)
C07K 16/18(2006.01)
C07K 16/28(2006.01)

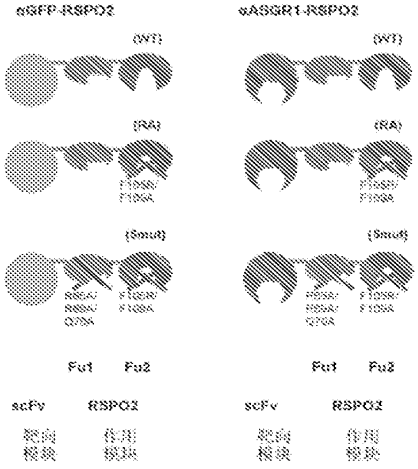
权利要求书5页 说明书86页
序列表341页 附图101页

(54)发明名称

组织特异性WNT信号增强分子和其用途

(57)摘要

本公开提供了组织特异性Wnt信号增强分子和使用这些分子增加肝组织中的Wnt信号传导的相关方法。



CN 112654363 A

1.一种组织特异性Wnt(“无翅相关整合位点”或“无翅和Int-1”或“无翅-Int”)信号增强分子或其药学上可接受的盐,其包括第一结构域和第二结构域,所述第一结构域特异性地结合选自锌指和环指3(ZNRF3)和环指蛋白43(RNF43)的一种或多种跨膜E3泛素连接酶,所述第二结构域特异性地结合脱唾液酸糖蛋白受体1(ASGR1)和/或脱唾液酸糖蛋白受体2(ASGR2),其中:

(a)所述第一结构域包括抗体或其抗原结合片段,所述抗体或其抗原结合片段包括:

(i)针对表2A的抗体中的任何抗体所示的CDRH1、CDRH2和CDRH3序列;和/或

(ii)针对表2A的抗体中的任何抗体所示的CDRL1、CDRL2和CDRL3序列,

或所述抗体或其抗原结合片段的变体,所述变体包括一个或多个氨基酸修饰,其中所述变体在所述CDR序列中包括少于8个氨基酸取代;和/或

(b)所述第二结构域包括抗体或其抗原结合片段,所述抗体或其抗原结合片段包括:

(i)针对表3A的抗体中的任何抗体所示的CDRH1、CDRH2和CDRH3序列;和/或

(ii)针对表3A的抗体中的任何抗体所示的CDRL1、CDRL2和CDRL3序列,

或所述抗体或其抗原结合片段的变体,所述变体包括一个或多个氨基酸修饰,其中所述变体在所述CDR序列中包括少于8个氨基酸取代。

2.根据权利要求1所述的分子,其中所述分子是肝特异性Wnt信号增强分子,并且所述第二结构域包括抗体或其抗原结合片段,所述抗体或其抗原结合片段包括:

(i)针对表3A的抗体中的任何抗体所示的CDRH1、CDRH2和CDRH3序列;和/或

(ii)针对表3A的抗体中的任何抗体所示的CDRL1、CDRL2和CDRL3序列,

或所述抗体或其抗原结合片段的变体,所述变体包括一个或多个氨基酸修饰,其中所述变体在所述CDR序列中包括少于8个氨基酸取代。

3.根据权利要求1所述的分子,其中所述第一结构域包括抗体或其抗原结合片段,所述抗体或其抗原结合片段包括:

(i)针对表2A的抗体中的任何抗体所示的CDRH1、CDRH2和CDRH3序列;和/或

(ii)针对表2A的抗体中的任何抗体所示的CDRL1、CDRL2和CDRL3序列,

或所述抗体或其抗原结合片段的变体,所述变体包括一个或多个氨基酸修饰,其中所述变体在所述CDR序列中包括少于8个氨基酸取代。

4.根据权利要求1或权利要求2所述的分子,其中所述第一结构域包括R-脊椎蛋白多肽序列或其片段或者变体,其中R-脊椎蛋白任选地为R-脊椎蛋白-1、R-脊椎蛋白-2、R-脊椎蛋白-3或R-脊椎蛋白-4。

5.根据权利要求4所述的分子,其中所述第一结构域包括R-脊椎蛋白弗林蛋白酶结构域1序列和任选地野生型或突变的弗林蛋白酶结构域2或其片段或者变体,其中第一多肽序列与含富亮氨酸重复的G蛋白偶联受体4-6(LGR4-6)的结合相比于全长R-脊椎蛋白任选地有所降低。

6.根据权利要求4或权利要求5所述的分子,其中R-脊椎蛋白弗林蛋白酶结构域1与存在于SEQ ID NO:1-4中的弗林蛋白酶1结构域中的任何一个弗林蛋白酶1结构域具有至少90%的同一性。

7.根据权利要求1到6中任一项所述的分子,其中所述分子是融合蛋白,其中所述第一结构域和所述第二结构域是任选地通过接头部分连接的多肽。

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8.根据权利要求7所述的分子，其中所述接头部分是肽基接头序列。

9.根据权利要求8所述的分子，其中所述接头序列包括选自由以下组成的组的一个或多个氨基酸：甘氨酸、天冬酰胺、丝氨酸、苏氨酸和丙氨酸。

10.一种核酸序列，其针对根据权利要求1到9中任一项所述的分子的至少所述第一结构域或所述第二结构域进行编码。

11.根据权利要求10所述的核酸序列，其中所述核酸序列是DNA或mRNA。

12.一种载体，其包括根据权利要求11所述的核酸序列。

13.根据权利要求12所述的载体，其中所述载体是表达载体，所述表达载体包括操作性地连接到所述核酸序列的启动子序列。

14.根据权利要求13所述的载体，其中所述载体是病毒，所述病毒包括操作性地连接到所述核酸序列的启动子序列。

15.一种宿主细胞，其包括根据权利要求14所述的载体。

16.一种用于产生根据权利要求7到9中任一项所述的融合多肽的方法，所述方法包括：在所述融合多肽由所述表达载体表达的条件下培养根据权利要求15所述的宿主细胞。

17.根据权利要求16所述的方法，其进一步包括分离产生的所述融合多肽的步骤。

18.一种药物组合物，其包括：

a)有效量的根据权利要求1到9中任一项所述的分子、根据权利要求10到11中任一项所述的核酸序列、根据权利要求12到14中任一项所述的载体或根据权利要求15所述的宿主细胞；以及

b)药学上可接受的稀释剂、佐剂或载体。

19.根据权利要求18所述的药物组合物，其包括所述有效量的根据权利要求1到9中任一项所述的分子和有效量的Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子。

20.根据权利要求18所述的药物组合物，其包括所述有效量的根据权利要求10到11中任一项所述的核酸序列和有效量的对Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的核酸序列，其中对所述Wnt多肽、所述Norrin多肽或所述Wnt信号传导激动剂分子进行编码的所述核酸序列任选地为DNA或mRNA。

21.根据权利要求20所述的药物组合物，其中根据权利要求13到14中任一项所述的核酸序列和/或对所述Wnt多肽、所述Norrin多肽或所述Wnt信号传导激动剂分子进行编码的所述核酸序列是经过修饰的mRNA。

22.根据权利要求18所述的药物组合物，其包括所述有效量的根据权利要求12到14中任一项所述的载体和有效量的包括对Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的核酸序列的载体，其中包括对所述Wnt多肽、所述Norrin多肽或所述Wnt信号传导激动剂分子进行编码的所述核酸序列的所述载体任选地为表达载体。

23.根据权利要求19到22中任一项所述的药物组合物，其中所述Wnt多肽是选自以下的哺乳动物Wnt多肽：Wnt1、Wnt2、Wnt2B、Wnt3、Wnt3A、Wnt4、Wnt5A、Wnt5B、Wnt6、Wnt7A、Wnt7B、Wnt8A、Wnt8B、Wnt9A、Wnt9B、Ant10A、Wnt10B、Wnt11和Wnt16以及前述Wnt多肽中的任何一个Wnt多肽的功能性变体和片段。

24.根据权利要求19到22中任一项所述的药物组合物，其中所述Norrin多肽是哺乳动物Norrin多肽或其功能性变体或片段。

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25.根据权利要求19到22中任一项所述的药物组合物，其中所述Wnt信号传导激动剂分子是使卷曲蛋白(Fz)受体与Lrp5/6二聚化的水溶性Wnt信号传导激动剂。

26.根据权利要求25所述的药物组合物，其中所述Wnt信号传导激动剂分子包括多肽。

27.根据权利要求26所述的药物组合物，其中所述多肽包括对一种或多种Fzd蛋白具有亲和力的结合结构域和对Lrp5/Lrp6蛋白具有亲和力的结合结构域，并且其中所述结合结构域任选地直接连接或通过接头连接。

28.一种用于增加靶组织中的Wnt(“无翅相关整合位点”或“无翅和Int-1”或“无翅-Int”)信号传导的方法，所述方法包括使所述靶组织与以下接触：

a)根据权利要求1到9中任一项所述的分子；根据权利要求10到11中任一项所述的核酸；根据权利要求12到14中任一项所述的载体；或根据权利要求15所述的宿主细胞，其中所述第二结构域特异性地结合所述靶组织上的细胞特异性表面分子，并且其中根据权利要求1到12中任一项所述的分子结合所述靶组织并且螯合选自锌指和环指3(ZNRF3)和环指蛋白43(RNF43)的一种或多种跨膜E3泛素连接酶或增加其在所述靶组织中的内吞作用；和/或

b)Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子；对Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的核酸序列；包括对Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的核酸序列的载体；或包括表达载体的宿主细胞，所述表达载体包括对Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的核酸序列；其中对所述Wnt多肽、所述Norrin多肽或所述Wnt信号传导激动剂分子进行编码的所述核酸序列任选地为DNA或mRNA，任选地经过修饰的mRNA。

29.根据权利要求28所述的方法，其包括使所述靶组织与根据权利要求1到9中任一项所述的分子接触。

30.根据权利要求28所述的方法，其包括使所述靶组织与根据权利要求10到11中任一项所述的核酸接触。

31.根据权利要求28所述的方法，其包括使所述靶组织与根据权利要求12到14中任一项所述的载体接触。

32.根据权利要求28所述的方法，其包括使所述靶组织与对所述Wnt多肽、所述Norrin多肽或所述Wnt信号传导激动剂分子进行编码的所述核酸序列接触。

33.一种用于治疗或预防有需要的受试者的肝疾病或肝病状的方法，其中所述肝疾病或肝病症与减少的Wnt(“无翅相关整合位点”或“无翅和Int-1”或“无翅-Int”)信号传导相关或者将受益于增加的Wnt信号传导，所述方法包括向所述受试者提供有效量的根据权利要求18到27中任一项所述的药物组合物，任选地其中所述分子是根据权利要求2所述的分子。

34.根据权利要求33所述的方法，其进一步包括向所述受试者提供药物组合物，所述药物组合物包括：药学上可接受的稀释剂、佐剂或载体；以及有效量的：

a)Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子；

b)对Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的核酸序列，其中对所述Wnt多肽、所述Norrin多肽或所述Wnt信号传导激动剂分子进行编码的所述核酸序列任选地为DNA或mRNA；

c)包括对Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的核酸序列的载

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体，其中包括对所述Wnt多肽、所述Norrin多肽或所述Wnt信号传导激动剂分子进行编码的所述核酸序列的所述载体任选地为表达载体；或者

d)包括表达载体的宿主细胞，所述表达载体包括对Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的核酸。

35.根据权利要求34所述的方法，其包括向所述受试者提供包括有效量的根据权利要求1到9中任一项所述的分子的药物组合物和包括有效量的Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子的药物组合物。

36.根据权利要求34所述的方法，其包括向所述受试者提供包括有效量的根据权利要求10到11中任一项所述的核酸序列的药物组合物和包括有效量的对Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的核酸序列的药物组合物，其中所述核酸序列中的一个或两个核酸序列任选地为DNA或mRNA，任选地经过修饰的mRNA。

37.根据权利要求34所述的方法，其包括向所述受试者提供包括有效量的根据权利要求12到14中任一项所述的载体的药物组合物和包括有效量的载体的药物组合物，所述载体包括对Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的核酸序列，其中所述载体中的一个或两个载体任选地为表达载体或病毒载体。

38.根据权利要求34到37中任一项所述的方法，其中所述Wnt多肽是选自以下的哺乳动物Wnt多肽：Wnt1、Wnt2、Wnt2B、Wnt3、Wnt3A、Wnt4、Wnt5A、Wnt5B、Wnt6、Wnt7A、Wnt7B、Wnt8A、Wnt8B、Wnt9A、Wnt9B、Wnt10A、Wnt10B、Wnt11和Wnt16以及前述Wnt多肽中的任何一种Wnt多肽的功能性变体和片段。

39.根据权利要求34到37中任一项所述的方法，其中所述Norrin多肽是哺乳动物Norrin多肽或其功能性变体或片段。

40.根据权利要求34到37中任一项所述的方法，其中所述Wnt信号传导激动剂分子是使卷曲蛋白(Fzd)受体与Lrp5/6二聚化的水溶性Wnt信号传导激动剂。

41.根据权利要求40所述的方法，其中所述Wnt信号传导激动剂分子包括多肽。

42.根据权利要求41所述的方法，其中所述多肽包括对一种或多种Fzd蛋白具有亲和力的结合结构域和对Lrp5/Lrp6蛋白具有亲和力的结合结构域，并且其中所述结合结构域任选地直接连接或通过接头连接。

43.根据权利要求33到42中任一项所述的方法，其中所述肝疾病或肝病状选自由以下组成的组：所有原因的急性肝衰竭、药物诱导的急性肝衰竭、酒精性肝病、所有原因的慢性肝衰竭、肝硬化、所有原因的肝纤维化、门脉高压、所有原因的慢性肝功能不全、终末期肝病(ESLD)、非酒精性脂肪性肝炎(NASH)、非酒精性脂肪肝病(NAFLD)(脂肪肝)、酒精性肝炎、丙型肝炎病毒诱导的肝病(HCV)、乙型肝炎病毒诱导的肝病(HBV)、其它病毒性肝炎(例如，甲型肝炎病毒诱导的肝病(HAV)和丁型肝炎病毒诱导的肝病(HDV))、原发性胆汁性肝硬化、自身免疫性肝炎、肝脏外科手术、肝损伤、肝移植、肝脏外科手术和移植中的“小肝(small for size)”综合征、先天性肝疾病和病症、由遗传性疾病、变性、老化、药物或损伤引起的任何其它肝病症或缺陷。

44.根据权利要求33到43中任一项所述的方法，其中所述药物组合物被肠胃外地、口服地、肌内地或局部地提供给肝。

45.根据权利要求33到44中任一项所述的方法，其中所述受试者是哺乳动物，任选地

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人。

46.一种分离的抗体或其抗原结合片段，其与RNF43或ZNRF3多肽结合、包括包含以下的序列：(i)针对表2A的抗体中的任何抗体所示的CDRH1、CDRH2和CDRH3序列；和/或(ii)针对表2A的抗体中的任何抗体所示的CDRL1、CDRL2和CDRL3序列，或所述抗体或其抗原结合片段的变体，所述变体包括一个或多个氨基酸修饰，其中所述变体在所述CDR序列中包括少于8个氨基酸取代。

47.根据权利要求46所述的抗体或其抗原结合片段，其包括重链可变区和/或轻链可变区，所述重链可变区和/或轻链可变区包括与表2B或SEQ ID NO:78-150或165-170中所示的氨基酸序列具有至少90％同一性的氨基酸序列。

48.根据权利要求47所述的抗体或其抗原结合片段，其包括重链可变区和/或轻链可变区，所述重链可变区和/或轻链可变区包括表2B或SEQ ID NO:78-150或165-170中所示的氨基酸序列。

49.一种分离的抗体或其抗原结合片段，其与ASGR1或ASGR2多肽结合、包括包含以下的序列：(i)针对表3A的抗体中的任何抗体所示的CDRH1、CDRH2和CDRH3序列；和/或(ii)针对表3A的抗体中的任何抗体所示的CDRL1、CDRL2和CDRL3序列，或所述抗体或其抗原结合片段的变体，所述变体包括一个或多个氨基酸修饰，其中所述变体在所述CDR序列中包括少于8个氨基酸取代。

50.根据权利要求49所述的抗体或其抗原结合片段，其包括重链可变区和/或轻链可变区，所述重链可变区和/或轻链可变区包括与表3B或SEQ ID NO:47-77、151-154、171-179或274-305中所示的氨基酸序列具有至少90％同一性的氨基酸序列。

51.根据权利要求50所述的抗体或其抗原结合片段，其包括重链可变区和/或轻链可变区，所述重链可变区和/或轻链可变区包括表3B或SEQ ID NO:47-77、151-154、171-179或274-305中所示的氨基酸序列。

52.一种抗体，其包括重链可变区和/或轻链可变区，所述重链可变区和/或轻链可变区包括与表3C或SEQ ID NO:180-185中所示的氨基酸序列或其片段或者变体具有至少90％同一性的氨基酸序列。

53.一种抗体或其抗原结合片段，其与根据权利要求46到52中任一项所述的抗体或其抗原结合片段竞争结合。

54.一种药物组合物，其包括根据权利要求46到53中任一项所述的抗体。

55.一种用于增加肝与体重之比、促进肝再生、增加肝细胞增殖或有丝分裂、任选地在慢性肝损伤后减少肝纤维化、增加肝细胞功能或减少肝中的凝血时间的方法，所述方法包括向受试者提供有效量的根据权利要求53所述的药物组合物，其中与ASGR1或ASGR2多肽结合的所述抗体或其抗原结合片段。

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组织特异性WNT信号增强分子和其用途

[0001] 相关申请的交叉引用

[0002] 本申请要求于2018年7月9日提交的美国临时申请第62/695,509号、于2018年11月20日提交的美国临时申请第62/770,026号和于2019年3月22日提交的美国临时申请第62/822,731号的优先权，所述美国临时申请中的每个美国临时申请通过全文引用的方式并入本文。

[0003] 关于序列表的声明

[0004] 与本申请相关的序列表以文本格式提供以代替纸质副本并且在此通过引用并入本说明书中。含有序列表的文本文件的名称为SRZN_010_03WO_ST25.txt。文本文件为661KB、创建于2019年7月9日并且通过EFS-Web以电子方式提交。

技术领域

[0005] 本公开涉及组织特异性Wnt信号增强分子(例如，融合蛋白)以及使用组织特异性Wnt信号增强分子介导E3连接酶、ZNRF3/RNF43的组织特异性内化或螯合从而以组织特异性方式稳定Wnt受体并增强Wnt信号传导并治疗和预防各种疾病和病症的相关方法，所述组织特异性Wnt信号增强分子包括结合E3泛素连接酶、ZNRF3或RNF43的结构域和组织特异性细胞表面受体结合结构域。

背景技术

[0006] Wnt(“无翅相关整合位点”或“无翅和Int-1”或“无翅-Int”)配体和其信号在控制许多基本器官和组织(包含骨、肝、皮肤、胃、肠、肾、中枢神经系统、乳腺、口腔粘膜、味蕾、卵巢、耳蜗和许多其它组织)的发育、内稳态和再生中发挥了关键作用(例如，由Clevers、Loh和Nusse,2014;346:1248012综述)。对Wnt信号传导通路的调节具有治疗变性疾病和组织损伤的潜力。为了实现此目标，期望开发以组织特异性或细胞类型特异性的方式调节Wnt信号传导活性的策略以避免不希望的效果。将调节Wnt信号传导作为治疗的挑战之一是存在多种Wnt配体和Wnt受体、卷曲蛋白1-10(Fzd1-10)，其中许多组织表达多种Fzd和重叠的Fzd。典型Wnt信号还涉及作为共受体的低密度脂蛋白(LDL)受体相关蛋白5(LRP5)或低密度脂蛋白(LDL)受体相关蛋白6(LRP6)，所述共受体在除了Fzd之外的各种组织中广泛表达。

[0007] R-脊椎蛋白1-4是扩增Wnt信号的配体家族。R-脊椎蛋白中的每一个通过受体复合物起作用，所述受体复合物在一端含有锌指和环指3(ZNRF3)或环指蛋白43(RNF43)并且在另一端含有含富亮氨酸重复的G蛋白偶联受体4-6(LGR4-6)(例如，由Knight和Hankenson,2014,《基质生物学(Matrix Biology)》;37:157-161综述)。R-脊椎蛋白也可能通过另外的作用机制发挥作用。ZNRF3和RNF43是两种膜结合的E3连接酶，其特异性地靶向Wnt受体(Fzd1-10和LRP5或LRP6)以进行降解。R-脊椎蛋白与ZNRF3/RNF43和LGR4-6的结合使三元复合物清除或螯合，所述三元复合物从Wnt受体中移除E3连接酶并稳定Wnt受体，从而导致Wnt信号增强。每个R-脊椎蛋白含有两个弗林蛋白酶结构域(1和2)，其中弗林蛋白酶结构域1与ZNRF3/RNF43结合，并且弗林蛋白酶结构域2与LGR4-6结合。含有弗林蛋白酶结构域1和2的

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R-脊椎蛋白的片段足以使Wnt信号传导扩增。虽然R-脊椎蛋白效果依赖于Wnt信号，但由于LGR4-6和ZNRF3/RNF43两者在各种组织中广泛表达，因此R-脊椎蛋白的效果是非组织特异性的。

[0008] 本领域明显需要用于治疗和预防具体疾病和病症的组织特异性Wnt信号增强分子。本发明通过提供可用于以组织特异性方式增强Wnt活性的组合物和方法来解决此需要。

发明内容

[0009] 本发明涉及组织特异性Wnt信号增强分子以及其例如在增加靶组织中的Wnt信号传导并治疗将会受益于增加的Wnt信号传导的疾病和病状方面的用途。在特定实施例中，所述组织为肝。

[0010] 在一个实施例中，本发明提供了一种组织特异性Wnt信号增强分子或其药学上可接受的盐，所述组织特异性Wnt信号增强分子或其药学上可接受的盐包括第一结构域和第二结构域，所述第一结构域特异性地结合选自ZNRF3和RNF43的一种或多种跨膜E3泛素连接酶，所述第二结构域特异性地结合组织特异性细胞表面分子，其中所述分子增加组织中的Wnt信号传导。在某些实施例中，所述Wnt信号增强分子是肝特异性的，并且所述第二结构域特异性地结合肝特异性细胞表面分子并增加肝或肝细胞中的Wnt信号传导。在各种实施例中，所述第一结构域和所述第二结构域中的任一者或两者是多肽、抗体、小分子、天然配体、非天然配体或其变体。

[0011] 在Wnt信号增强分子的特定实施例中，所述第一结构域包括第一多肽序列和/或所述第二结构域包括第二多肽序列。在特定实施例中，所述分子是包括所述第一多肽序列和所述第二多肽序列的融合蛋白。在某些实施例中，所述第一多肽序列包括R-脊椎蛋白序列或其片段或者变体。在特定实施例中，所述R-脊椎蛋白是R-脊椎蛋白-1、R-脊椎蛋白-2、R-脊椎蛋白-3或R-脊椎蛋白-4，例如，人R-脊椎蛋白-1-4。在某些实施例中，所述第一多肽序列包括R-脊椎蛋白弗林蛋白酶结构域1或其片段或者变体。在特定实施例中，所述第一多肽序列是野生型R-脊椎蛋白衍生的序列或经过修饰的序列。另外，所述第一多肽序列与LGR4-6的结合相比于对应的天然全长R-脊椎蛋白可以有所增加、类似或有所降低。在一些实施例中，所述R-脊椎蛋白或所述R-脊椎蛋白弗林蛋白酶结构域1与存在于SEQ ID NO:1-4中的R-脊椎蛋白或R-脊椎蛋白弗林蛋白酶1结构域中的任何一个具有至少50％、至少60％、至少70％、至少80％、至少90％或至少95％的同一性。在某些实施例中，所述第一多肽是特异性地结合ZNRF3和/或RNF43的抗体或其抗原结合片段。在特定实施例中，所述第一多肽是抗体或其抗原结合片段，所述抗体或其抗原结合片段包括：a)针对表2A的抗体中的任何抗体所示的CDRH1、CDRH2和CDRH3序列；和/或b)针对表2A的抗体中的任何抗体所示的CDRL1、CDRL2和CDRL3序列，或所述抗体或其抗原结合片段的变体，所述变体包括一个或多个氨基酸修饰，其中所述变体在所述CDR序列中包括少于8个氨基酸取代。在特定实施例中，所述第一多肽是抗体或其抗原结合片段，所述抗体或其抗原结合片段包括表2B或SEQ ID NO:78-150或165-170中所示的纳米抗体、VH或VL序列或其片段或者变体。

[0012] 在某些实施例中，所述第二多肽序列是多肽、抗体或其片段或者变体或配体或其片段或者变体。在某些实施例中，第二多肽是特异性地结合ASGR1和/或ASGR2的抗体或其抗原结合片段。在特定实施例中，第二多肽是抗体或其抗原结合片段，所述抗体或其抗原结合

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片段包括:a)针对表3A的抗体中的任何抗体所示的CDRH1、CDRH2和CDRH3序列;和/或b)针对表3A的抗体中的任何抗体所示的CDRL1、CDRL2和CDRL3序列,或所述抗体或其抗原结合片段的变体,所述变体包括一个或多个氨基酸修饰,其中所述变体在所述CDR序列中包括少于8个氨基酸取代。在特定实施例中,所述第一多肽是抗体或其抗原结合片段,所述抗体或其抗原结合片段包括表3B或SEQ ID NO:47-77、151-154、171-179或274-305中所示的纳米抗体、VH或VL序列或其片段或者变体。

[0013] 在本文公开的组织特异性Wnt信号增强分子的某些说明性实施例中:组织是骨组织,并且细胞表面受体是甲状旁腺激素受体1(PTH1R);组织是肝组织,并且细胞表面受体是脱唾液酸糖蛋白受体1(ASGR1)、脱唾液酸糖蛋白受体2(ASGR2)、转铁蛋白受体2(TFR2)或溶质载体家族10成员1(SLC10A1);或者组织是口腔粘膜组织,并且细胞表面受体是含LY6/PLAUR结构域的蛋白3(LYPD3)或桥粒芯糖蛋白3(DSG3)。在特定实施例中,所述第二多肽是抗体或其抗原结合片段,所述抗体或其抗原结合片段包括表3C或SEQ ID NO:180-186中所示的纳米抗体、VH或VL序列或其片段或者变体。

[0014] 在本文公开的组织特异性Wnt信号增强分子的某些说明性实施例中:细胞表面分子是PTH1,并且所述第二多肽序列特异性地结合PTH1R;细胞表面分子是ASGR1,并且所述第二多肽序列特异性地结合ASGR1;细胞表面分子是ASGR2,并且所述第二多肽序列特异性地结合ASGR2;细胞表面分子是SLC10A1,并且所述第二多肽序列特异性地结合SLC10A1;细胞表面分子是TFR2,并且所述第二多肽序列特异性地结合TFR2;细胞表面分子是LYPD3,并且所述第二多肽序列特异性地结合LYPD3;或者细胞表面分子是DSG3,并且所述第二多肽序列特异性地结合DSG3,其中所述第二多肽是细胞表面分子的抗体或其片段、小分子或配体或其片段或者变体。

[0015] 在本文描述的组织特异性Wnt信号增强分子的特定实施例中,所述第一结构域和所述第二结构域通过接头部分连接。在某些实施例中,所述接头部分是肽基接头序列。在特定实施例中,所述肽基接头序列包括选自由以下组成的组的一个或多个氨基酸:甘氨酸、天冬酰胺、丝氨酸、苏氨酸和丙氨酸。

[0016] 在特定实施例中,本文描述的组织特异性Wnt信号增强分子由单一多肽(例如,包括第一结构域和第二结构域的融合蛋白)组成。在某些实施例中,本文描述的组织特异性Wnt信号增强分子包括两种或更多种多肽,如包括两种或更多种融合蛋白的二聚体或多聚体,所述两种或更多种融合蛋白各自包括第一结构域和第二结构域,其中所述两种或更多种多肽例如通过接头部分或经由所述两种或更多种多肽中的每种多肽的氨基酸残基之间的键例如半胱氨酸残基之间的分子间二硫键来连接。在特定实施例中,本文描述的组织特异性Wnt信号增强分子包括两个或更多个多肽序列。例如,组织特异性Wnt信号增强分子可以包括构成第一结构域或第二结构域的抗体重链和抗体轻链(或其抗原结合片段),其中另一个结构域(即,第二结构域或第一结构域)作为融合蛋白或通过接头部分与所述抗体重链或所述抗体轻链连接。在特定实施例中,另一个结构域与重链的N端、重链的C端、轻链的N端或轻链的C端连接。这种结构在本文中可以称为附加IgG支架或格式。

[0017] 在相关实施例中,本发明包含一种核酸序列,所述核酸序列针对本文公开的组织特异性Wnt信号增强融合蛋白或其亚单位,例如具有附加的或融合的第一结构域或第二结构域的抗体重链或抗体轻链进行编码。在进一步相关的实施例中,本发明包含一种载体,所

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述载体包括所述核酸序列。在一些实施例中，所述载体是表达载体，所述表达载体包括例如以适合于在细菌细胞或真核细胞中表达的方式操作性地连接到所述核酸序列的启动子序列。在另一个实施例中，所述载体被工程化成用于体外翻译和修饰功能性mRNA。在进一步相关的实施例中，本发明包含一种宿主细胞，所述宿主细胞包括所述载体。在又另一个进一步相关的实施例中，本发明包含一种用于产生本文描述的组织特异性Wnt信号增强融合蛋白的方法，所述方法包括在融合多肽由所述表达载体表达的条件下培养所述宿主细胞。在一些实施例中，所述方法进一步包括分离产生的融合多肽的步骤。

[0018] 在另一个实施例中，本发明提供了一种药物组合物，所述药物组合物包括：本文描述的组织特异性Wnt信号增强分子或其药学上可接受的盐；以及药学上可接受的稀释剂、佐剂或载体。

[0019] 在另一个实施例中，本发明提供了一种药物组合物，所述药物组合物包括：多核苷酸，所述多核苷酸包括对本文描述的组织特异性Wnt信号增强分子或其药学上可接受的盐进行编码的核酸序列；以及药学上可接受的稀释剂、佐剂或载体。在特定实施例中，所述核酸序列包括DNA或mRNA，任选地经过修饰的mRNA。

[0020] 在另一个实施例中，本发明提供了一种药物组合物，所述药物组合物包括：载体，所述载体包括对组织特异性Wnt信号增强分子或其药学上可接受的盐进行编码的核酸序列；以及药学上可接受的稀释剂、佐剂或载体。在特定实施例中，所述载体包括操作性地连接到所述核酸序列的启动子，所述启动子驱动所述组织特异性Wnt信号增强分子的表达。在某些实施例中，所述载体是表达载体或病毒载体。

[0021] 在另一个实施例中，本发明提供了一种药物组合物，所述药物组合物包括：本文描述的组织特异性Wnt信号增强分子或其药学上可接受的盐；Wnt多肽、Norrin多肽或Wnt信号传导激动剂或其药学上可接受的盐；以及药学上可接受的稀释剂、佐剂或载体。

[0022] 在另一个实施例中，本发明提供了一种药物组合物，所述药物组合物包括：多核苷酸，所述多核苷酸包括对本文描述的组织特异性Wnt信号增强分子或其药学上可接受的盐进行编码的核酸序列；多核苷酸，所述多核苷酸包括对Wnt多肽、Norrin多肽或Wnt信号传导激动剂或其药学上可接受的盐进行编码的核酸序列；以及药学上可接受的稀释剂、佐剂或载体。在特定实施例中，所述核酸序列包括DNA或mRNA，任选地经过修饰的mRNA。

[0023] 在另一个实施例中，本发明提供了一种药物组合物，所述药物组合物包括：载体，所述载体包括对组织特异性Wnt信号增强分子或其药学上可接受的盐进行编码的核酸序列；载体，所述载体包括对Wnt多肽、Norrin多肽或Wnt信号传导激动剂或其药学上可接受的盐进行编码的核酸序列；以及药学上可接受的稀释剂、佐剂或载体。在特定实施例中，所述载体包括操作性地连接到所述核酸序列的启动子，所述启动子驱动所述组织特异性Wnt信号增强分子的表达。在某些实施例中，所述载体是表达载体或病毒载体。

[0024] 在另外的实施例中，本发明包含一种用于增加靶组织中的Wnt信号传导的方法，所述方法包括使所述靶组织与本文描述的组织特异性Wnt信号增强分子接触，其中所述第二结构域特异性地结合所述靶组织上的细胞特异性表面分子，并且其中所述组织特异性Wnt信号增强分子结合所述靶组织并螯合选自ZNRF3和RNF43的一种或多种跨膜E3泛素连接酶或增加其在所述靶组织中的内吞作用。

[0025] 在本文描述的方法中的任何一种方法的某些实施例中：所述组织是骨组织，并且

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细胞表面分子是PTH1R;所述组织是肝组织,并且细胞表面分子是ASGR1、ASGR2、TFR2或SLC10A1;或者所述组织是口腔粘膜组织,并且细胞表面受体是LYPD3或DSG3。在特定实施例中,使所述靶组织或所述靶细胞与包括对所述组织特异性Wnt信号增强分子进行编码的核酸序列的多核苷酸或包括对所述组织特异性Wnt信号增强分子进行编码的核酸序列的载体(例如,表达载体或病毒载体)接触。

[0026] 在另外的实施例中,本发明包含一种用于增加靶组织中的Wnt信号传导的方法,所述方法包括使所述靶组织与以下接触:本文描述的组织特异性Wnt信号增强分子,其中所述第二结构域特异性地结合所述靶组织上的细胞特异性表面分子,并且其中所述组织特异性Wnt信号增强分子结合所述靶组织并螯合选自ZNRF3和RNF43的一种或多种跨膜E3泛素连接酶或增加其在所述靶组织中的内吞作用;以及Wnt多肽、Norrin多肽或Wnt信号传导激动剂或其药学上可接受的盐。在特定实施例中,使所述靶组织或所述靶细胞与包括对所述组织特异性Wnt信号增强分子进行编码的核酸序列的多核苷酸和对所述Wnt多肽、Norrin多肽或Wnt信号传导激动剂进行编码的核酸接触。在其它实施例中,使所述靶组织或所述靶细胞与包括对所述组织特异性Wnt信号增强分子进行编码的核酸序列的载体和对所述Wnt多肽、Norrin多肽或Wnt信号传导激动剂进行编码的载体接触。

[0027] 在又另一个相关的实施例中,本发明包含一种用于治疗或预防有需要的受试者的疾病或病状的方法,其中所述疾病或病状与减少的Wnt信号传导相关或者将受益于增加的Wnt信号传导,所述方法包括向所述受试者提供有效量的药物组合物,所述药物组合物单独地或与Wnt、Norrin或Wnt活化/模拟分子组合地包括所述组织特异性Wnt信号增强分子或其药学上可接受的盐。在特定实施例中,单独地或与包括包含对所述Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的核酸序列的多核苷酸(例如,DNA或mRNA)或包含对所述Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的核酸序列的载体(例如,表达载体或病毒载体)的药物组合物组合地,使用包括包含对所述组织特异性Wnt信号增强分子进行编码的核酸序列的多核苷酸(例如,DNA或mRNA)或包含对所述组织特异性Wnt信号增强分子进行编码的核酸序列的载体(例如,表达载体或病毒载体)的药物组合物执行所述方法。

[0028] 在本文描述的治疗方法中的任何一种治疗方法的特定实施例中,所述疾病或病症是肝疾病或组织的病症,所述肝疾病或组织的病症选自由以下组成的组:所有原因的急性肝衰竭、药物诱导的急性肝衰竭、酒精性肝病、所有原因的慢性肝衰竭、肝硬化、所有原因的肝纤维化、门脉高压、所有原因的慢性肝功能不全、终末期肝病(ESLD)、非酒精性脂肪性肝炎(NASH)、非酒精性脂肪肝病(NAFLD)(脂肪肝)、酒精性肝炎、丙型肝炎病毒诱导的肝病(HCV)、乙型肝炎病毒诱导的肝病(HBV)、其它病毒性肝炎(例如,甲型肝炎病毒诱导的肝病(HAV)和丁型肝炎病毒诱导的肝病(HDV))、原发性胆汁性肝硬化、自身免疫性肝炎、肝脏外科手术、肝损伤、肝移植、肝脏外科手术和移植中的“小肝(small for size)”综合征、先天性肝疾病和病症、由遗传性疾病、变性、老化、药物或损伤引起的任何其它肝病症或缺陷。在本文描述的治疗或预防方法中的任何一种治疗或预防方法的特定实施例中,所述药物组合物全身性地、肠胃外地、口服地、肌内地、局部地(locally)或局部地(topically)被提供。在特定实施例中,所述受试者是哺乳动物,任选地人。

[0029] 在另一个实施例中,本公开提供了一种分离的抗体或其抗原结合片段,所述分离的抗体或其抗原结合片段与RNF43多肽或ZNRF3多肽结合、包括包含以下的序列:(i)针对表

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2A的抗体中的任何抗体所示的CDRH1、CDRH2和CDRH3序列；和/或(ii)针对表2A的抗体中的任何抗体所示的CDRL1、CDRL2和CDRL3序列，或所述抗体或其抗原结合片段的变体，所述变体包括一个或多个氨基酸修饰，其中所述变体在所述CDR序列中包括少于8个氨基酸取代。在某些实施例中，所述抗体或其抗原结合片段包括：包括与表2B或SEQ ID NO:78-150或165-170中所示的氨基酸序列具有至少90％同一性的氨基酸序列的重链可变区；或包括表2B或SEQ ID NO:78-150或165-170中所示的氨基酸序列的重链可变区。在特定实施例中，所述抗体或其抗原结合片段包括：包括与表2B或SEQ ID NO:78-150或165-170中所示的氨基酸序列具有至少90％同一性的氨基酸序列的轻链可变区；或包括表2B或SEQ ID NO:78-150或165-170中所示的氨基酸序列的轻链可变区。

[0030] 在另一个实施例中，本公开提供了一种分离的抗体或其抗原结合片段，所述分离的抗体或其抗原结合片段与ASGR1多肽或ASGR2多肽结合、包括包含以下的序列：(i)针对表3A的抗体中的任何抗体所示的CDRH1、CDRH2和CDRH3序列；和/或(ii)针对表3A的抗体中的任何抗体所示的CDRL1、CDRL2和CDRL3序列，或所述抗体或其抗原结合片段的变体，所述变体包括一个或多个氨基酸修饰，其中所述变体在所述CDR序列中包括少于8个氨基酸取代。在某些实施例中，所述抗体或其抗原结合片段包括：包括与表3B或SEQ ID NO 47-77、151-154、171-179或274-305中所示的氨基酸序列具有至少90％同一性的氨基酸序列的重链可变区；或包括表3B或SEQ ID NO 47-77、151-154、171-179或274-305中所示的氨基酸序列的重链可变区。在某些实施例中，所述抗体或其抗原结合片段包括：包括与表3B或SEQ ID NO:47-77、151-154、171-179或274-305中所示的氨基酸序列具有至少90％同一性的氨基酸序列的轻链可变区；或包括表3B或SEQ ID NO:47-77、151-154、171-179或274-305中所示的氨基酸序列的轻链可变区。

[0031] 在特定实施例中，所述抗体或其抗原结合片段包括重链可变区或轻链可变区，所述重链可变区或轻链可变区包括与表3C或SEQ ID NO:180-185中所示的氨基酸序列或其片段或者变体具有至少90％同一性的氨基酸序列。

[0032] 本公开还提供了与本文所描述的抗体或其抗原结合片段中的任何抗体或其抗原结合片段竞争结合的抗体或其抗原结合片段。

[0033] 在相关实施例中，本公开提供了一种药物组合物，所述药物组合物包括本文所描述的抗体或其抗原结合片段中的任何抗体或其抗原结合片段。

[0034] 在另外的实施例中，本公开提供了一种用于增加肝与体重之比、促进肝再生、增加肝细胞增殖或有丝分裂、任选地在慢性肝损伤后减少肝纤维化、增加肝细胞功能或减少肝中的凝血时间的方法，所述方法包括向有需要的受试者提供有效量的药物组合物，所述药物组合物包括本文公开的与ASGR1多肽或ASGR2多肽结合的抗体或其抗原结合片段。

附图说明

[0035] 本专利或申请文件含有至少一幅彩色附图。在请求并支付必要的费用后，将由专利局提供带有一幅或多幅彩色附图的本专利或专利申请公开物的副本。

[0036] 在所附权利要求中具体阐述了本公开的特征。通过参考阐述了说明性实施例的以下详细描述以及附图，将获得对本发明的这些特征和优势的更好理解，在所述说明性实施例中利用了本发明的原理。

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[0037] 图1A-1D:组织特异性Wnt信号传导增强子分子的设计。(图1A)所有四种人R-脊椎蛋白(Rspo1(SEQ ID NO:1);Rspo2(SEQ ID NO:2);Rspo3(SEQ ID NO:3);和Rspo4(SEQ ID NO:4))的比对,其中弗林蛋白酶结构域1(Fu1)和弗林蛋白酶结构域2(Fu2)分别以浅色和深色阴影阴影化。Fu1结构域通常对应于:SEQ ID NO:1的约氨基酸残基38-94;SEQ ID NO:2的约氨基酸残基37-93;SEQ ID NO:3的约氨基酸残基39-95;以及SEQ ID NO:4的约氨基酸残基32-88。Fu2结构域通常对应于:SEQ ID NO:1的约氨基酸残基97-144;SEQ ID NO:2的约氨基酸残基96-143;SEQ ID NO:3的约氨基酸残基98-144;以及SEQ ID NO:4的约氨基酸残基91-137。(图1B)说明性设计分子的方案。将跨越Fu1结构域和Fu2结构域(作用模块)的RSPO2的片段与scFv抗体(靶向模块)的C端融合以生成图1B中示出的构建体,所述构建体对应于SEQ ID NO:5-16中所示的多核苷酸和多肽序列。指示了Fu1结构域和Fu2结构域中的特异性突变。(图1C)对LGR5与抗GFP系列和抗ASGR1系列融合蛋白的结合的生物层干涉法分析,如所指示的。在顶部示出了用111nM RSPO2衍生的融合蛋白进行的结合测定的全部步骤。插入框中单独示出了由缔合相和解离相构成的结合反应。通过稳态分析,分析了来自7个不同浓度的缔合相介于140到145秒之间的平均反应,以确定K_D值(底部)。(图1D)对指示的构建体与RNF43和ZNRF3的结合的分析,如所指示的(SEQ ID NO:43-46)。

[0038] 图2A-2C:肝细胞特异性Wnt信号传导增强子分子的体外活性。(图2A)对HEK293、Huh-7和A431细胞中的ASGR1和ASGR2(顶部)以及TFRC(底部)基因表达水平的半定量PCR分析(针对每个基因从左往右示出)。信号相对于ACTB标准化。(图2B)在外源性Wnt源(30%Wnt3a条件培养基)存在(左图)或不存在(右图)的情况下HEK293(上图)或Huh-7(下图)中的指定蛋白(SEQ ID NO:5-16)的SuperTop Flash(STF)报告基因活性。(图2C)对Huh-7细胞中的LRP6受体和DVL2磷酸化的蛋白质印迹分析。星号指示通过所使用的抗体在Huh-7中检测到的非特异性带。由箭头指示的下方的带对应于具有或不具有磷酸化的DVL2。微管蛋白(TUB)用作上样对照。

[0039] 图3A-3C:特异性Wnt信号增强子活性对靶向受体的依赖性。(图3A)在外源性Wnt源(30%Wnt3a条件培养基)存在(左图)或不存在(右图)的情况下,用TFRC(编码转铁蛋白受体TFR1作为对照,顶部)、ASGR1(中部)以及ASGR1和ASGR2(下部)瞬时转染的HEK293细胞的STF活性。(图3B)具有如所指定的TFRC或ASGR1过表达的A431细胞中的STF的活性。(图3C)对Fzd蛋白的细胞表面水平的流式细胞术分析。将HEK293细胞用仅ZNRF3(顶部)或ASGR1和ZNRF3(底部)转染、用10nM指定融合蛋白处理、然后用pan-Fzd抗体18R5染色。

[0040] 图4A-4E:用靶向不同受体TFR1的另一个分子对机制的验证。(图4A)通过生物层干涉法分析抗TFR1系列融合构建体(SEQ ID NO:17-22)的LGR5结合。在顶部示出了用111nM RSPO2衍生的融合蛋白进行的结合测定的全部步骤。插入框中单独示出了由缔合相和解离相构成的结合反应。通过稳态分析,分析了来自7个不同浓度的缔合相介于140到145秒之间的平均反应,以确定K_D值(底部)。(图4B)对抗TFR1系列融合构建体与RNF43(左)和ZNRF3(右)的结合的分析,其中下图中从左往右为αTFR-RSPO2、αTFR-RSPO2-RA和αTFR-RPOS-5mut的稳态拟合分析。(图4C)在存在(左)或不存在(右)外源性Wnt源(30%Wnt3a条件培养基)时HEK293(顶部)或Huh-7(底部)上的指定蛋白的STF活性。(图4D)对HEK293细胞中的LRP6受体和DVL2磷酸化的蛋白质印迹分析。微管蛋白(TUB)用作上样对照。(图4E)对Fzd蛋白在用融合蛋白或对照处理之后的细胞表面水平的流式细胞术分析。将HEK293细胞用ZNRF3瞬时转

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染、用10nM指定融合蛋白处理并且然后用pan-Fzd抗体18R5染色。

[0041] 图5A-5D:通过肝细胞特异性Wnt信号增强分子进行的Wnt反应基因Axin2诱导。(图5A)在外源性Wnt源(30%Wnt3a条件培养基)存在(左)或不存在(右)的情况下,IgG格式的靶向Wnt信号增强分子(SEQ ID NO:23-34)在HEK293(顶部)或Huh-7(底部)中的STF活性。(图5B)研究设计。在腹膜内注射α-GFP-IgG(SEQ ID NO:25-26和33-34)、Fc-RSPO2-WT(SEQ ID NO:23-24)、αGFP-RSPO2-RA-IgG(SEQ ID NO:25-28)或αASGR1-RSPO2-RA-IgG(SEQ ID NO:29-31)后8小时Axin2的(图5C)肝和(图5D)小肠表达(n=8只小鼠/组)。使用单向ANOVA执行统计分析:(ns)不显著,(*)p<0.05,(**)p<0.01,(***)p<0.001。

[0042] 图6A-6E:肝细胞特异性Wnt信号增强分子(SEQ ID NO:25-34)对增殖标志物Ki-67的肝特异性诱导。(图6A)研究设计。(图6B)对在如所指定的处理后48小时Mki67的肝表达的半定量PCR分析(n=10只小鼠/组)。(图6C)处理后在10倍物镜下的每个视场中肝中的Ki-67+薄壁组织的细胞核的平均数量。使用单向ANOVA执行统计分析:(**)P<0.01,(****)p<0.0001。(图6D)Ki67蛋白的经过染色的肝切片的代表性图像。(图6E)对小肠中的Mki67表达的半定量PCR分析。

[0043] 图7A-7C:针对hASGR1/2的结合剂的表征的实例。(图7A)对通过噬菌体展示鉴别的三种Fab抗体(024S-D03、-E03和-A04;SEQ ID NO:47-52)与hASGR1的结合的生物层干涉法分析。在顶部为传感图,并且在底部为用于确定K_D的稳态拟合分析。(图7B)两种Fab(ABV-3D11和-10B8;SEQ ID NO:151-154)针对来自杂交瘤发展的hASGR2的结合。(图7C)两种Fab(LP1-2I13和LP1-8M24;SEQ ID NO:284-285和298-299)针对来自杂交瘤发展的hASGR1的结合。

[0044] 图8:说明性肝特异性Wnt信号传导增强子的方案。在某些实施例中,靶向模块可以是针对hASGR1或hASGR2的IgG抗体,和/或作用模块可以是具有野生型或突变活性的RSPO衍生物。RSPO衍生物可以附加到IgG的不同位置(轻链或重链的N端或C端)。在某些配置中,活化结构域可以是与人ZNRF3/RNF43结合的抗体或其抗原结合片段,例如呈纳米抗体(nAb)、单链可变区(scFv)、Fab片段或全IgG形式。与nAb和scFv不同,Fab含有两条多肽链,这两条多肽链都可以例如以共价方式连接到靶向模块。混合IgG是另一种任选的配置,其含有一个Fab作为靶向模块和另一个Fab作为作用模块。另外,在某些配置中,靶向模块可以呈nAb/scFv/Fab形式,而作用模块呈IgG形式(未示出)。

[0045] 图9A-9D:原初健康小鼠中肝特异性Wnt信号传导增强子的剂量滴定。(图9A)对用于构建αASGR1-RSPO2-RA-IgG(表达为Fab,SEQ ID NO:29-30和161-162)的ASGR1抗体的跨物种反应性的生物层干涉法分析。使用了人和小鼠ASGR1 ECD(SEQ ID NO:35-36和163-164)。指示了通过曲线模型拟合确定的Kd。在腹膜内注射指定蛋白后48小时通过半定量PCR分析了肝(上图)和小肠(下图)中的(图9B)Axin2和(图9C)Ki67表达(n=8只小鼠/组)。使用单向ANOVA执行统计分析:(ns)不显著,(*)p<0.05,(**)p<0.01,(***)p<0.001。(图9D)来自10mg/kg处理组的肝样品的免疫组织化学染色。抗β-半乳糖苷酶(α-β-Gal-IgG、SEQ ID NO:155-158)是用作对照的中和抗体。其它被测试蛋白的SEQ ID NO如图5的图例所描述的。

[0046] 图10A-10D:靶向RSPO模拟物在TAA小鼠慢性肝病模型中的功效。(图10A)对正常小鼠和经过TAA处理的小鼠的Wnt配体和Rspo基因的半定量PCR分析。(图10B)研究设计。(图10C)对肝(上)和小肠(底部)中的Axin2(左)和Ki67(右)基因表达的半定量PCR分析。(n=10

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只小鼠/组)。(图10D)处理期间凝血酶原时间的国际标准化比率(INR)。使用单向ANOVA执行统计分析:(**)p<0.01,(****)p<0.0001(n=10只小鼠/组)。抗β-半乳糖苷酶(α-β-Gal-IgG,SEQ ID NO:155-156和159-160)是用作对照的中和抗体。其它被测试蛋白的SEQ ID NO如图5的图例所描述的。

[0047] 图11A-11BR:Wnt信号增强子组分的序列。

[0048] 图12:说明性CCl4诱导的肝纤维化小鼠模型的方案和处理方案。在首个10天内用CCl4(在第1天、第4天、第7天、第10天时0.5mL/kg,蓝色箭头)加上烯丙醇(在第2天、第5天、第8天时0.0125mL/kg,黄色箭头)间歇地处理8-9周大的C57BL/6雄性小鼠(杰克逊实验室(Jackson Laboratories)),然后进行每周两次为期8周的CCl4处理(0.5mL/kg,蓝色箭头)。在CCl4处理之后,用蛋白质向小鼠给药2周。处理组如下:无蛋白对照,n=8;10mpk抗βGal,n=8(每周两次给药);4.6mpk RSPO2,n=7(每周两次给药);10mpk抗eGFP-mutRspo2,n=8(每天给药);10mpkαASGR1-RSPO2-RA-IgG2,n=8(每天给药)。另外的对照组包含:无CCl4处理(橄榄油载体,0.5mL/kg),n=8;原初对照,n=7。在第69天、第72天、第76天取小鼠血液进行INR(国际标准化比率)测试。所有小鼠均于第83天被终结。

[0049] 图13:CCl4诱导的纤维化模型的各个治疗组的天狼星红染色百分比。图13为示出在两周的蛋白质处理后小鼠肝中的胶原蛋白的天狼星红染色的图,如所指示的。*表示αASGR-1-RSPO2-RA-IgG相对于αeGFP-mutRSPO2的统计显著性(p<0.05);**表示Fc-RSPO2-WT相对于αeGFP-mutRSPO2的统计显著性;***表示αASGR-1-RSPO2-RA-IgG相对于αβgal的统计显著性;****表示Fc-RSPO2-WT相对于αβgal的统计显著性。

[0050] 图14A-14D:用内部杂交瘤衍生的ASGR1结合剂构建的RSPO模拟分子的体外肝细胞特异性活性。通过将突变RSPO2连接到IgG2重链的C端(图14A和图14B)或ASGR1结合剂的IgG1(N297G)重链的N端(图14C和图14D)来构建融合蛋白(SEQ ID NO:190-271)。在外源性Wnt替代物分子(100pM R2M3-26,描述于WO 2019126398中)存在的情况下,测试经过纯化的蛋白在HEK293(上图)或Huh-7(下图)中的SuperTop Flash(STF)报告基因活性。使用的对照为:Fc-RSPO2-WT(SEQ ID NO:23-24)、αGFP-RSPO2-RA-IgG(附加到重链的N端的RSPO2,SEQ ID NO:25-28;或附加到重链的C端的RSPO2,SEQ ID NO:25-26和188-189)或α-β-Gal-RSPO2-RA-IgG(附加到重链的C端的RSPO2,SEQ ID NO:155-156和186-187)。在每幅图中提供了总结与Fc-RSPO阳性对照比较的EC50和Emax的表。

[0051] 图15:通过衍生自内部杂交瘤结合剂的RSPO模拟分子进行的Wnt反应基因肝Axin2诱导。在蛋白质给药前五天分别向小鼠注射1×10^{11}个基因组颗粒的AAV-TBG-hASGR1和AAV-TBG-hASGR2。蛋白质给药后24小时收集肝样品并对其进行处理以便进行半定量PCR分析。(A)研究中使用的序列ID编号、名称、剂量和小鼠数量。(B)腹膜内注射后Axin2的肝表达。使用单向ANOVA执行统计分析:(**)p<0.01,(***)p<0.001

具体实施方式

[0052] 本公开提供了组织特异性Wnt信号增强分子,其中在某些实施例中,所述分子:1)与组织特异性或细胞特异性细胞表面受体选择性地结合;2)在靶向组织或细胞类型中介导ZNRF3/RNF43的内化或螯合;和/或3)以组织特异性方式增强Wnt信号传导。在某些实施例中,分子是融合蛋白。在某些实施例中,分子是具有另外的附加结合结构域的抗体。还提供

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了药物组合物和用于使用本文所公开的组合物中的任何组合物增强即增加靶向组织或细胞类型中的Wnt信号传导例如以治疗或预防疾病或病症的方法。在特定实施例中，分子结合肝组织并且可以用于增加肝组织或肝细胞中的Wnt信号传导。在阅读如下文更全面地描述的组合物和方法的细节后，本发明的这些和其它目的、优势和特征对本领域技术人员而言将变得显而易见。

[0053] 定义

[0054] 本文所使用的“载体”是指包括多核苷酸或与多核苷酸缔合并且可以用于介导多核苷酸到细胞的递送的大分子或大分子缔合物。说明性载体包含例如质粒、病毒载体、脂质体和其它基因递送媒剂。

[0055] 术语“多核苷酸”是指任何长度的核苷酸的聚合形式，包含脱氧核糖核苷酸或核糖核苷酸或者其类似物。多核苷酸可以包括经过修饰的核苷酸如甲基化核苷酸和核苷酸类似物并且可以被非核苷酸组分打断。如果存在，则对核苷酸结构的修饰可以在组装聚合物之前或之后进行。如本文所使用的，术语多核苷酸可互换地指双链分子和单链分子。除非另外指定或需要，否则是多核苷酸的本文所描述的本发明的任何实施例既涵盖双链形式，也涵盖已知或预测构成双链形式的两种互补的单链形式中的每种单链形式。

[0056] 多核苷酸或多肽与另一种多核苷酸或多肽具有一定比例的“序列同一性”，这意味着，当比对时，所述比例的碱基或氨基酸在对这两个序列进行比较时是相同的。序列相似性可以通过多种不同的方式来确定。为了确定序列同一性，可以使用包含可通过万维网ncbi.nlm.nih.gov/BLAST/获得的BLAST在内的方法和计算机程序来比对序列。另一种比对算法是FASTA，可从牛津分子集团有限公司(Oxford Molecular Group,Inc.)的全资子公司、来自美国威斯康星州麦迪逊市(Madison,Wis.,USA)的遗传学计算机集团(Genetics Computing Group)(GCG)的软件包中获得。以下中描述了用于比对的其它技术：《酶学方法(Methods in Enzymology)》，第266卷：用于大分子序列分析的计算机方法(Computer Methods for Macromolecular Sequence Analysis)(1996)，Doolittle编，学术出版社有限公司(Academic Press,Inc.)，美国加利福尼亚州圣地亚哥哈考特布瑞斯公司(Harcourt Brace&Co.,San Diego,Calif.,USA)的分公司。特别关注了允许序列中有空位的比对程序。Smith-Waterman是允许序列比对中有空位的一种类型的算法。参见《分子生物学方法(Meth.Mol.Biol.)》70:173-187(1997)。而且，可以利用使用Needleman和Wunsch比对方法的GAP程序来比对序列。参见《分子生物学期刊(J.Mol.Biol.)》48:443-453(1970)

[0057] 关注了使用Smith和Waterman的局部同源性算法(《应用数学进展(Advances in Applied Mathematics)》2:482-489(1981))来确定序列同一性的BestFit程序。空位生成罚分的范围通常将为1到5、经常为2到4并且在许多实施例中将为3。空位生成罚分的范围通常将为0.01到0.20并且在许多情况下将为0.10。程序具有由被输入以进行比较的序列确定的默认参数。优选地，序列同一性是使用由程序确定的默认参数来确定的。此程序也可从来自美国威斯康星州麦迪逊市的遗传学计算集团(GCG)的软件包获得。

[0058] 关注的另一个程序是FastDB算法。以下中描述了FastDB：序列比较和分析的当前方法(Current Methods in Sequence Comparison and Analysis)，《大分子测序与合成所选方法与应用(Macromolecule Sequencing and Synthesis,Selected Methods and Applications)》，第127-149页，1988,Alan R.Liss有限公司(Alan R.Liss,Inc.)。基于以

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下参数通过FastDB来计算序列同一性百分比:不匹配罚分:1.00;空位罚分:1.00;空位大小罚分:0.33;以及连接罚分:30.0。

[0059] 如应用于多核苷酸的"重组"意味着,多核苷酸是克隆、限制或连接步骤和产生不同于天然存在的多核苷酸的构建体的其它程序的各种组合的产物。

[0060] "控制元件"或"控制序列"是参与分子相互作用的核苷酸序列,所述相互作用有助于多核苷酸的功能调节,包含多核苷酸的重复、复制、转录、剪接、翻译或降解。调节会影响过程的频率、速度或特异性并且在本质上会具有增强或抑制性。本领域中已知的控制元件包含例如转录调节序列,如启动子和增强子。启动子是在某些条件下能够结合RNA聚合酶并且启动对通常位于启动子下游(沿3'方向)的编码区进行转录的DNA区域。

[0061] "操作性地连接"或"可操作地连接"是指遗传元件的并置,其中所述元件处于允许所述元件以预期方式操作的关系中。例如,如果启动子帮助启动对编码序列的转录,则启动子与编码区域操作性地连接。只要维持这一功能关系,启动子与编码区域之间就会存在插入残基。

[0062] "表达载体"是包括对关注的基因产物进行编码的区域的载体并且被用于引发基因产物在预期靶细胞中的表达。表达载体还包括与编码区域操作性地连接以促进基因产物在靶标中表达的控制元件。控制元件和其所可操作地连接以用于表达的一个或多个基因的组合有时被称为"表达盒",所述控制元件中的许多控制元件在本领域是已知且可获得的或者可以由本领域中可获得的组分容易地构建。

[0063] 如本文所使用的,术语"多肽"、"肽"和"蛋白质"是指任何长度的氨基酸的聚合物。所述术语还涵盖已被修饰的氨基酸聚合物;例如,以包含二硫键形成、糖基化、脂化、磷酸化或与标记组分缀合。

[0064] 如本文所使用的,术语"抗体"意指包括特异性地结合抗原表位所必需的可变区序列的分离结合剂或重组结合剂。因此,抗体是展现出期望的生物活性(例如,结合特异性靶抗原)的抗体或其片段的任何形式。因此,抗体最广义地使用并且具体覆盖单克隆抗体(包含全长单克隆抗体)、多克隆抗体、人抗体、人源化抗体、嵌合抗体、纳米抗体、双抗体、多特异性抗体(例如,双特异性抗体)和抗体片段,所述抗体片段包含但不限于scFv、Fab和Fab_2,只要所述抗体和抗体片段展现出期望的生物活性即可。

[0065] "抗体片段"包括完整抗体的一部分,例如完整抗体的抗原结合区或可变区。抗体片段的实例包含:Fab片段、Fab'片段、$F(ab')_2$片段和Fv片段;双抗体;线性抗体(例如,Zapata等人,《蛋白质工程(Protein Eng.)》,8(10):1057-1062(1995));单链抗体分子(例如,scFv);以及由抗体片段形成的多特异性抗体。木瓜蛋白酶消化抗体产生了:两个相同的抗原结合片段,被称为"Fab"片段,每个抗原结合片段具有单个抗原结合位点;以及残留的"Fc"片段,这一名称反映了容易结晶的能力。胃蛋白酶处理得到具有两个抗原组合位点并且仍然能够交联抗原的$F(ab')_2$片段。

[0066] "包括"意味着,所列举要素在例如组合物、方法、试剂盒等中是必需的,但是其它元素也可以包含在内以在权利要求的范围内形成例如组合物、方法、试剂盒等。例如,"包括"对与启动子可操作地连接的治疗性多肽进行编码的基因的表达盒是除基因和启动子以外还可以包含其它元件(例如,聚腺苷酸化序列、增强子元件、其它基因、接头结构域等)的表达盒。

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[0067] “基本上由……组成”意指对例如针对不实质影响例如组合物、方法、试剂盒等的一种或多种基本和新颖特性的指定材料或步骤所描述的组合物、方法、试剂盒等的范围的限制。例如“基本上由对与启动子可操作地连接的治疗性多肽进行编码的基因以及多腺苷酸化序列组成”的表达盒可以包含另外的序列，例如接头序列，只要所述另外的序列不实质影响基因的转录或翻译即可。作为另一个实例，“基本上由列举的序列组成”的变体或突变多肽片段具有列举的序列的、基于全长初始多肽在序列的边界处加上或减去约10个氨基酸残基的氨基酸序列，例如比列举的结合氨基酸残基少10个、9个、8个、7个、6个、5个、4个、3个、2个或1个残基或者比列举的结合氨基酸残基多1个、2个、3个、4个、5个、6个、7个、8个、9个或10个残基，所述氨基酸序列源自所述全长初始多肽。

[0068] “由……组成”意指从组合物、方法或试剂盒中排除权利要求中未指定的任何要素、步骤或成分。例如，“由列举的序列组成”的多肽或多肽结构域仅含有列举的序列。

[0069] 如本文所使用的，“表达载体”涵盖载体(例如，如本文所讨论或如本领域中已知的质粒、微环、病毒载体、脂质体等，包括对关注的基因产物进行编码的多核苷酸)并且被用于引发基因产物在预期靶细胞中的表达。表达载体还包括与编码区域操作性地连接以促进基因产物在靶标中表达的控制元件。控制元件例如促进子、增强子、UTR、miRNA靶向序列等和其所可操作地连接以用于表达的一个或多个基因的组合有时被称为“表达盒”。许多这种控制元件在本领域是已知且可获得的或者可以由本领域中可获得的组分容易地构建。

[0070] 如本文所使用的，“启动子”涵盖引导RNA聚合酶的结合并且由此促进RNA合成的DNA序列，即，足以引导转录的最小序列。启动子和对应的蛋白质或多肽表达可以是普遍存在的，这意味着在广泛范围的细胞、组织和物种中具有强活性或者细胞类型特异性、组织特异性或物种特异性。启动子可以是“组成型”(意指持续活性)或“诱导型”(意指启动子可以通过生物因子或非生物因子的存在或不存在而活化或失活)。本发明的核酸构建体或载体中还包含增强子序列，所述增强子序列可以或可以不与启动子序列邻接。增强子序列影响启动子依赖性基因表达并且可以位于天然基因的5’区或3’区。

[0071] 如本文所使用的，术语“天然”或“野生型”是指存在于野生型细胞、组织、器官或生物体中的核苷酸序列(例如，基因)或基因产物(例如，RNA或蛋白质)。如本文所使用的，术语“变体”是指参考多核苷酸或多肽序列的突变体，例如天然多核苷酸或多肽序列，即，与参考多核苷酸或多肽序列具有小于100％的序列同一性。换句话说，变体相对于参考多核苷酸序列包括至少一个氨基酸差异(例如，氨基酸取代、氨基酸插入、氨基酸缺失)，例如天然多核苷酸或多肽序列。例如，变体可以是与全长天然多核苷酸序列具有50％或更多、60％或更多或者70％或更多序列同一性的多核苷酸，例如与全长天然多核苷酸序列具有75％或80％或更多同一性，如85％、90％或95％或更多，例如98％或99％同一性。作为另一个实例，变体可以是与全长天然多肽序列有70％或更多序列同一性的多肽，例如与全长天然多肽序列有75％、80％或更多同一性，如85％、90％、95％或更多，例如98％或99％同一性。变体还可以包含参考例如天然序列的与参考例如天然序列的片段共享70％或更多序列同一性的变体片段，例如与天然序列有75％、80％或更多同一性，如85％、90％、95％或更多，例如98％或99％同一性。

[0072] 如本文所使用的，术语“生物活性(biological activity)”和“生物活性(biologically active)”是指归因于细胞中的特定生物元素的活性。例如，R-脊椎蛋白或

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其片段或者变体的“生物活性”是指增强Wnt信号的能力。作为另一个实例，多肽或其功能性片段或者变体的生物活性是指多肽或其功能性片段或者变体实施其天然功能例如结合的能力、酶活性等。作为第三实例，基因调节元件例如启动子、增强子、Kozak序列等的生物活性是指调节元件或其功能性片段或者变体分别对其可操作地连接的基因的表达的翻译进行调节即促进、增强或活化的能力。

[0073] 如本文所使用的，术语“施用”或“引入”或“提供”是指向细胞、向受试者的细胞、组织和/或器官或者向受试者递送组合物。这种施用或引入可以在体内、在体外或离体地发生。

[0074] 术语“治疗(treatment)”、“治疗(treating)”等在本文中用于通常意指获得期望的药理学和/或生理学效应。效果在完全或部分地预防疾病或其症状方面可以是预防性的，例如降低受试者体内发生疾病或其症状的可能性，和/或在部分或完全治愈疾病和/或由疾病引起的不良反应方面可以是治疗性的。如本文所使用的，“治疗”覆盖了对哺乳动物的疾病的任何治疗并且包含：(a)防止疾病在可能倾向于患有疾病但尚未被诊断为患有疾病的受试者身上发生；(b)抑制疾病，即，中止疾病发展；或者(c)缓解疾病，即，使疾病消退。可以在疾病或损伤发作之前、期间或之后施用治疗剂。特别关注了对发展中的疾病的治疗，其中所述治疗稳定或减少了患者的不期望的临床症状。理想的是，在受影响组织的功能完全丧失之前执行这种治疗。理想的是，将在疾病的症状期期间并且在一些情况下在疾病的症状期之后施用主题疗法。

[0075] 术语“个体”、“宿主”、“受试者”和“患者”在本文中可互换使用并且是指哺乳动物，包含但不限于：人和非人灵长类动物，包含猿猴和人类；哺乳类运动动物(例如，马)；哺乳类农场动物(例如，绵羊、山羊等)；哺乳类宠物(狗、猫等)；以及啮齿动物(例如，小鼠、大鼠等)。

[0076] 下面描述了本发明的各种组合物和方法。尽管本文例示了特定的组合物和方法，但是应当理解，多个替代性组合物和方法中的任何替代性组合物和方法均是适用的并且适于用于实践本发明。还应当理解，可以使用本领域中标准的程序对本发明的表达构建体和方法进行评估。

[0077] 除非另有指示，否则本发明的实践将采用细胞生物学、分子生物学(包含重组技术)、微生物学、生物化学和免疫学的常规技术，所述技术在本领域技术人员的范围内。文献中充分解释了这种技术，如《分子克隆：实验室手册(Molecular Cloning:A Laboratory Manual)》，第二版(Sambrook等人，1989)；《寡核苷酸合成(Oligonucleotide Synthesis)》(M.J.Gait编，1984)；《动物细胞培养(Animal Cell Culture)》(R.I.Freshney编，1987)；《酶学方法(Methods in Enzymology)》(学术出版社有限公司)；《实验免疫学手册(Handbook of Experimental Immunology)》(D.M.Weir和C.C.Blackwell编)；《哺乳动物细胞用基因转移载体(Gene Transfer Vectors for Mammalian Cells)》(J.M.Miller和M.P.Calos编，1987)；《当代分子生物学方法(Current Protocols in Molecular Biology)》(F.M.Ausubel等人编，1987)；《PCR:聚合酶链反应(PCR:The Polymerase Chain Reaction)》(Mullis等人编，1994)；以及《当代免疫学方法(Current Protocols in Immunology)》(J.E.Coligan等人编，1991)，所述文献中的每个文献均通过引用明确并入本文。

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[0078] 下文参考用于说明的示例应用说明了本发明的若干方面。应理解，阐述了许多具体细节、关系和方法以提供对本发明的充分理解。然而，相关领域普通技术人员将很容易认识到，可以在没有所述具体细节中的一个或多个具体细节的情况下或者用其它方法来实践本发明。本发明不受所展示的活动或事件的顺序的限制，因为一些活动可以按不同的顺序和/或与其它活动或事件同时地发生。此外，实施根据本发明的方法并不需要所有展示的活动或事件。

[0079] 本文所使用的术语是出于仅描述特定实施例的目的并且不旨在限制本发明。如本文所使用的，除非上下文另外清楚地指示，否则单数形式“一个/一种(a、an)”和“所述(the)”旨在也包含复数形式。此外，在详细描述和/或权利要求中使用术语“包含(including)”、“包含(include)”、“具有(having)”、“具有(has)”、“具有(with)”或其变体的情况下，这种术语旨在以类似于术语“包括(comprising)”的方式是包含性的。

[0080] 术语“约(about)”或“大约(approximately)”意指在如由本领域普通技术人员确定的特定值的可接受误差范围内，这将部分地取决于所述值是如何测量或确定的，即，测量系统的局限性。例如，根据本领域的实践，“约”可以意指在1个或大于1个标准偏差内。可替代地，“约”可以意指给定值的至多20％、优选地至多10％、更优选地至多5％并且还更优选地至多1％的范围。可替代地，特别是对于生物系统或过程，所述术语可以意指在值的数量级内，优选地在5倍内并且更优选地在2倍内。当在本申请和权利要求中描述特定值时，除非另外指出，否则应当假设术语“约”意指在特定值的可接受误差范围内。

[0081] 本文所提及的所有公开均通过引用并入本文，以披露和描述引用公开所结合的方法和/或材料。应当理解，在存在矛盾的情况下，本公开代替所并入公开的任何公开内容。

[0082] 另外应注意，权利要求可以被撰写成不包括任何任选的要素。因此，本声明旨在充当结合所列权利要求要素使用如“仅(solely)”、“仅(only)”等排他性术语或使用“否定型”限制的前提基础。

[0083] 除非另有指示，否则本文所使用的所有术语具有与本领域技术人员所知的含义相同的含义，并且本发明的实践将采用在本领域技术人员的知识范围内的微生物学常规技术和重组DNA技术。

[0084] 组织特异性Wnt信号增强分子

[0085] 在某些方面，本公开提供了能够以组织特异性或细胞特异性方式增强Wnt活性的新颖的组织特异性Wnt信号增强分子。在某些实施例中，组织特异性Wnt信号增强分子是双功能分子，所述双功能分子包括与一个或多个ZNRF3和/或RNF43连接酶结合的第一结构域和以组织特异性或细胞特异性方式与一种或多种靶向组织或细胞类型结合的第二结构域。第一结构域和第二结构域中的每个结构域分别可以是能够与连接酶复合物或者靶向组织或靶向细胞结合的任何部分。例如，第一结构域和第二结构域中的每个结构域可以是但不限于选自以下的部分：多肽(例如，抗体或其抗原结合片段或者不同于抗体的肽或多肽)、小分子和天然配体或其变体、片段或者衍生物。在某些实施例中，天然配体是多肽、小分子、离子、氨基酸、脂质或糖分子。第一结构域和第二结构域可以是彼此相同的类型的部分，或者第一结构域和第二结构域可以是不同类型的部分。在某些实施例中，组织特异性Wnt信号增强分子与组织特异性或细胞特异性细胞表面受体结合。在特定实施例中，组织特异性Wnt信号增强分子，例如与阴性对照相比，使Wnt信号传导增加或增强至少50％、至少两倍、至少三

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倍、至少五倍、至少十倍、至少二十倍、至少三十倍、至少四十倍或至少五十倍。

[0086] 组织特异性Wnt信号增强分子可以具有不同的格式。图1A和图8中描绘了说明性格式。在特定实施例中，组织特异性Wnt信号增强分子是融合蛋白，所述融合蛋白包括与ZNRF3/RNF43结合的第一多肽序列和以组织特异性或细胞特异性方式与一种或多种靶向组织或细胞类型结合的第二多肽序列(参见例如图1A)。在某些实施例中，所述两个多肽序列可以直接融合或通过接头融合。在某些实施例中，组织特异性Wnt信号增强分子包括两种或更多种多肽，如包括两种或更多种融合蛋白的二聚体或多聚体，所述两种或更多种融合蛋白各自包括第一结构域和第二结构域，其中所述两种或更多种多肽例如通过接头部分或经由所述两种或更多种多肽中的每种多肽的氨基酸残基之间的键(例如，半胱氨酸残基之间的分子间二硫键)来连接。在特定实施例中，组织特异性Wnt信号增强分子是包括构成第一结构域或第二结构域的抗体重链和轻链的抗体(或其抗原结合片段)，其中另一个结构域(即，第二结构域或第一结构域)与抗体重链或轻链连接成融合蛋白或经由接头部分与抗体重链或轻链连接。在特定实施例中，另一个结构域与重链的N端、重链的C端、轻链的N端或轻链的C端连接。这种结构在本文中可以称为附加IgG支架或格式。例如，组织特异性Wnt信号增强分子可以是结合ZNRF3/RNF43的抗体，其中结合组织特异性或细胞特异性受体的结合结构域融合或附加到结合ZNRF3/RNF43的抗体的重链或轻链。在另一个实例中，组织特异性Wnt信号增强分子可以是结合组织特异性或细胞特异性受体的抗体，其中结合ZNRF3/RNF43的结合结构域融合或附加到结合组织特异性或细胞特异性受体的抗体的重链或轻链。在特定实施例中，肝特异性Wnt信号增强分子是结合ASGR1或ASGR2的抗体或其抗原结合片段，其中结合ZNRF3/RNF43的结合结构域融合或附加到抗体或其抗原结合片段的重链或轻链(参见例如图8)。在特定实施例中，结合ZNRF3/RNF43的结合结构域包括Fu1结构域和Fu2结构域，其中Fu1结构域和Fu2结构域任选地包括一个或多个氨基酸修饰，包含本文公开的氨基酸修饰中的任何氨基酸修饰，例如F105R和/或F109A。

[0087] 在某些实施例中，组织特异性Wnt信号增强分子包括结合ZNRF3/RNF43的第一结构域(“作用模块”)和例如以高亲和力结合组织特异性或细胞特异性受体的第二结构域(“靶向模块”)。在某些实施例中，这两个结构域中的每个结构域具有大幅降低的活性或者在自身增强Wnt信号时无活性。然而，当组织特异性Wnt信号增强分子与表达组织特异性受体的靶组织接合时，E3连接酶ZNRF3/RNF43被募集到与组织特异性受体的三元复合物，从而使E3连接酶ZNRF3/RNF43被螯合和/或经由受体介导的内吞作用从细胞表面清除。最终结果是以组织特异性方式增强Wnt信号。

[0088] 在某些实施例中，作用模块是与ZNRF3/RNF43 E3连接酶的结合剂并且可以基于R-脊椎蛋白(例如，R-脊椎蛋白-1-4，包含但不限于人R-脊椎蛋白-1-4)进行设计。在某些实施例中，作用模块是R-脊椎蛋白(例如，野生型R-脊椎蛋白-1-4，任选地人R-脊椎蛋白-1-4)或其变体或者片段。在特定实施例中，作用结构域是R-脊椎蛋白-1-4中的任何R-脊椎蛋白的变体，所述变体与对应的野生型R-脊椎蛋白-1-4序列具有至少80％、至少85％、至少90％、至少95％、至少98％或至少99％的序列同一性。在某些实施例中，作用模块包括R-脊椎蛋白的弗林蛋白酶结构域1(例如，结合ZNRF3/RNF43的R-脊椎蛋白1-4中的任何R-脊椎蛋白)或由其组成。也可以使用弗林蛋白酶结构域1的延伸版本(包含但不限于具有与LGR4-6不再结合或已经降低了与LGR4-6的结合的突变弗林蛋白酶结构域2的那些)或工程化抗体或任何

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其它衍生物或与能够与ZNRF3/RNF43特异性地结合的抗体不同的任何工程化多肽。在某些实施例中，作用模块包括R-脊椎蛋白的一个或多个弗林蛋白酶结构域1。在某些实施例中，作用结构域不包括R-脊椎蛋白的弗林蛋白酶结构域2，或者作用结构域包括R-脊椎蛋白的经过修饰的或变体弗林蛋白酶结构域2，例如与野生型弗林蛋白酶结构域2相比具有降低的活性的弗林蛋白酶结构域2。在某些实施例中，作用模块包括R-脊椎蛋白的弗林蛋白酶结构域1但不包括弗林蛋白酶结构域2。在某些实施例中，作用模块包括两个或更多个弗林蛋白酶结构域1或者弗林蛋白酶结构域1的多聚体。作用模块可以包括R-脊椎蛋白的一个或多个野生型弗林蛋白酶结构域1。在特定实施例中，作用模块包括R-脊椎蛋白的经过修饰的或变体弗林蛋白酶结构域1，所述经过修饰的或变体弗林蛋白酶结构域1与野生型弗林蛋白酶结构域1相比具有增加的活性，例如与ZNRF3/RNF43的结合。可以例如通过筛选包括R-脊椎蛋白弗林蛋白酶结构域1的变体的噬菌体或酵母展示文库来鉴别出与ZNRF3/RNF43具有增加的结合的变体。还可以通过筛选鉴别出与R-脊椎蛋白弗林蛋白酶结构域1不相关但与ZNRF3/RNF43具有增加的结合的肽或多肽。作用模块可以进一步包括另外的部分或多肽序列例如的另外的氨基酸残基以稳定作用模块的或作用模块所存在于的组织特异性Wnt信号增强分子的结构。

[0089] 在某些实施例中，作用模块包括特异性地结合ZNRF3和/或RNF43的抗体或其抗原结合片段。在特定实施例中，作用模块是抗体或其抗原结合片段，所述抗体或其抗原结合片段包括：a)针对表2A的抗体中的任何抗体所示的CDRH1、CDRH2和CDRH3序列；和/或b)针对表2A的抗体中的任何抗体所示的CDRL1、CDRL2和CDRL3序列，或所述抗体或其抗原结合片段的变体，所述变体包括一个或多个氨基酸修饰，其中所述变体在所述CDR序列中包括少于8个氨基酸取代。在特定实施例中，作用模块是包括纳米抗体、表2B中所示的VH或VL序列或SEQ ID NO:78-150或者其片段或变体的抗体或其抗原结合片段。

[0090] 在另外的实施例中，作用模块包括降低或阻止ZNRF3/RNF43活性或表达的另一个抑制部分，如核酸分子，例如反义寡核苷酸；小干扰RNA(siRNA)；短发夹RNA(shRNA)；微RNA(miRNA)；或核酶。如本文所使用的，“反义”是指与核酸序列互补的核酸序列，无论其长度如何。在某些实施例中，反义RNA是指单链RNA分子，所述单链RNA分子可以被引入到单独的细胞、组织或受试者中并通过不一定依赖于内源性基因沉默通路的机制使靶基因的表达减少。反义核酸可以含有经过修饰的主链例如硫代磷酸酯、二硫代磷酸酯或本领域已知的其它物质或者可以含有非天然核苷间键。反义核酸可以包括例如锁核酸(LNA)。在特定实施例中，另一个抑制剂部分抑制ZNRF3/RNF43中的一者或两者的活性或抑制ZNRF3/RNF43中的一者或两者的基因、mRNA或蛋白质表达。在某些实施例中，抑制部分是与ZNRF3/RNF43基因或mRNA结合的核酸分子或其补体。

[0091] 如本文所使用的，“RNA干扰”是指使用通过内源性基因沉默通路(例如，Dicer和RNA诱导的沉默复合物(RISC))降解靶mRNA来减少靶基因的表达的药剂。RNA干扰可以使用各种药剂来实现，包含shRNA和siRNA。“短发夹RNA”或“shRNA”是指可以用于通过RNA干扰(RNAi)使靶基因表达沉默的具有发夹弯的双链的人工RNA分子。细胞中的shRNA的表达通常通过质粒的递送或通过病毒或细菌载体来完成。shRNA是RNAi的有利介体，因为其具有相对低的降解和转换率。小干扰RNA(siRNA)是通常长度为20-25个碱基对、类似于miRNA并在RNA干扰(RNAi)通路内操作的一类双链RNA分子。siRNA通过在转录后降解mRNA来干扰具有互补

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核苷酸序列的特定基因的表达，从而阻止翻译。在某些实施例中，siRNA的长度为18个、19个、20个、21个、22个、23个或24个核苷酸并且在其3'端处具有2个碱基的突出端。siRNA可以被引入到单独细胞和/或培养系统中并导致靶mRNA序列降解。如本文所使用的，"吗啉代"是指经过修饰的核酸寡聚体，其中标准核酸碱基与吗啉环结合并通过磷酸二酰胺酯(phosphorodiamidate)键连接。类似于siRNA和shRNA，吗啉代与互补mRNA序列结合。然而，吗啉代通过立体抑制mRNA翻译和改变mRNA剪接而非靶向互补mRNA序列进行降解来发挥作用。

[0092] 在某些实施例中，靶向模块与细胞特异性表面分子例如细胞特异性表面受体特异性地结合并且可以是例如天然配体、抗体或合成化学品。在特定实施例中，细胞特异性表面分子优先表达在靶器官、组织或细胞类型上，例如期望增强Wnt信号传导例如以治疗或预防疾病或病症的器官、组织或细胞类型。在特定实施例中，细胞特异性表面分子例如与一个或多个其它非靶向器官、组织或细胞类型相比，在靶器官、组织或细胞类型上的表达增加或增强，例如期望增强Wnt信号传导例如以治疗或预防疾病或病症的器官、组织或细胞类型。在某些实施例中，分别与一种或多种其它器官、组织或细胞类型相比，细胞特异性表面分子优先表达在靶器官、组织或细胞类型的表面上。例如，在特定实施例中，与分别在一种或多种、五种或更多种所有其它器官、组织或细胞中或者在平均的所有其它器官、组织或细胞中表达相比，如果在靶器官、组织或细胞中表达细胞表面受体的水平高至少两倍、至少五倍、至少10倍、至少20倍、至少30倍、至少40倍、至少50倍、至少100倍、至少500倍或至少1000倍，则细胞表面受体被认为是组织特异性或细胞特异性细胞表面分子。在某些实施例中，组织特异性或细胞特异性细胞表面分子是细胞表面受体，例如包括位于细胞表面膜内的区域和靶向模块可以结合的细胞外区域的多肽受体。在各种实施例中，本文所描述的方法可以通过以下来实践：特异性地靶向仅表达在靶组织或包含靶组织的组织子集上的细胞表面分子；或特异性地靶向与所有、大多数或大量其它组织相比在靶组织上具有更高表达水平的细胞表面分子，例如，与在至少两个、至少五个、至少十个或至少二十个其它组织上相比在靶组织上具有更高的表达。

[0093] 组织特异性和细胞特异性细胞表面受体在本领域中是已知的。组织特异性和细胞特异性表面受体的实例包含但不限于ASGR1(用于肝特异性)、ASGR2(用于肝特异性)、TFR2(用于肝特异性)、SLC10A1(用于肝特异性)、PTH1R(用于骨和肾特异性)、LYPD3(用于口腔粘膜特异性)、DSG3(用于口腔粘膜特异性)等。例如Yan等人，《肿瘤生物学(Tumor Biology)》，2015;36:55-67描述了针对肝递送的另外的受体。

[0094] 在某些实施例中，靶向模块包括特异性地结合ASGR1和/或ASGR2的抗体或其抗原结合片段。在特定实施例中，第二多肽是抗体或其抗原结合片段，所述抗体或其抗原结合片段包括：a)针对表3A的抗体中的任何抗体所示的CDRH1、CDRH2和CDRH3序列；和/或b)针对表3A的抗体中的任何抗体所示的CDRL1、CDRL2和CDRL3序列，或所述抗体或其抗原结合片段的变体，所述变体包括一个或多个氨基酸修饰，其中所述变体在所述CDR序列中包括少于8个氨基酸取代。在特定实施例中，作用模块是纳米抗体、表3B中所示的VH或VL序列或SEQ ID NO:47-77或151-154或者其片段或变体的抗体或其抗原结合片段。

[0095] 在特定实施例中，组织特异性Wnt信号增强分子或其药学上可接受的盐包括特异性地结合选自锌指和环指3(ZNRF3)和环指蛋白43(RNF43)的一种或多种跨膜E3泛素连接酶

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的第一结构域和特异性地结合脱唾液酸糖蛋白受体1(ASGR1)和/或脱唾液酸糖蛋白受体2(ASGR2)的第二结构域,其中(a)所述第一结构域包括抗体或其抗原结合片段,所述抗体或其抗原结合片段包括:(i)针对表2A的抗体中的任何抗体所示的CDRH1、CDRH2和CDRH3序列;和/或(ii)针对表2A的抗体中的任何抗体所示的CDRL1、CDRL2和CDRL3序列,或所述抗体或其抗原结合片段的变体,所述变体包括一个或多个氨基酸修饰,其中所述变体在所述CDR序列中包括少于8个氨基酸取代;和/或(b)所述第二结构域包括抗体或其抗原结合片段,所述抗体或其抗原结合片段包括:(i)针对表3A的抗体中的任何抗体所示的CDRH1、CDRH2和CDRH3序列;和/或(ii)针对表3A的抗体中的任何抗体所示的CDRL1、CDRL2和CDRL3序列,或所述抗体或其抗原结合片段的变体,所述变体包括一个或多个氨基酸修饰,其中所述变体在所述CDR序列中包括少于8个氨基酸取代。在特定实施例中,组织特异性Wnt信号增强分子或其药学上可接受的盐包括与SEQ ID NO:47-77或151-154中的任何一个具有至少90%同一性的多肽。在特定实施例中,组织特异性Wnt信号增强分子或其药学上可接受的盐是包括抗体或其抗原结合片段的肝特异性Wnt信号增强分子,所述抗体或其抗原结合片段包括:(i)针对表3A的抗体中的任何抗体所示的CDRH1、CDRH2和CDRH3序列;和/或(ii)针对表3A的抗体中的任何抗体所示的CDRL1、CDRL2和CDRL3序列,或所述抗体或其抗原结合片段的变体,所述变体包括一个或多个氨基酸修饰,其中所述变体在所述CDR序列中包括少于8个氨基酸取代。

[0096] “与特定细胞表面多肽或受体特异性地结合”或“针对特定细胞表面多肽或受体具有特异性”的作用模块或靶向模块例如抗体或其抗原结合片段是在基本上不与任何其它多肽或多肽表位结合的情况下与所述特定多肽或受体结合的模块。在一些实施例中,本公开的作用模块和靶向模块分别与ZNRF3/RNF43或组织特异性细胞表面分子(例如,受体)特异性地结合,其中当在约4℃、25℃、37℃或42℃的温度下测量时,解离常数(K_d)等于或小于1000nM、等于或小于100nM、等于或小于10nM、等于或小于1nM、等于或小于0.5nM、等于或小于0.1nM、等于或小于0.01nM、等于或小于0.005nM、等于或小于0.001nM或者等于或小于0.0005nM。使用常规技术,可以容易地确定结合剂例如抗体的亲和力,常规技术例如由Scatchard等人所描述的那些(《美国纽约科学院年刊(Ann.N.Y.Acad.Sci.USA)》51:660(1949),ELISA测定、生物层干涉法(BLI)测定和表面等离子体共振(SPR)测定)。通常可以使用免疫检测法来确定和估计抗体与其抗原、细胞或组织的结合性质,所述免疫检测法包含例如基于免疫荧光的测定,如免疫组织化学(IHC)和/或荧光活化细胞分选(FACS)。

[0097] 在某些实施例中,组织特异性Wnt信号增强分子的作用模块和/或靶向模块是多肽,而在其它实施例中,组织特异性Wnt信号传导分子的作用模块和/或靶向模块是有机小分子。在某些实施例中,作用模块和靶向模块两者都是多肽,例如抗体或其抗原结合片段。在某些实施例中,组织特异性Wnt信号增强分子的作用模块和靶向模块彼此共价结合。在某些实施例中,组织特异性Wnt信号增强融合分子的作用模块和靶向模块彼此非共价结合。在某些实施例中,组织特异性Wnt信号增强分子的作用模块和靶向模块存在于相同的融合蛋白内。在其它实施例中,作用模块存在于进一步包括第一结合结构域的第一多肽内,并且靶向模块存在于进一步包括第二结合结构域的第二多肽内,其中所述第一结合结构域和所述第二结合结构域彼此结合。在一些实施例中,第一结合结构域和第二结合结构域是相同的或者是其变体,例如Fc多肽。在一些实施例中,第一结合结构域和第二结合结构域不同于彼

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此。在特定实施例中，本发明包含使用本文所描述的靶向模块或作用模块中的任何模块的片段或变体，包含参考分子的功能性片段或变体。

[0098] 在某些实施例中，组织特异性Wnt信号增强分子（例如，融合蛋白）具有选自以下的式：R_1-L-R_2和R_2-L-R_1，其中R_1是结合ZNRF3/RNF43的作用模块，R_2是结合组织特异性细胞表面受体的靶向模块并且L是接头，并且其中L可以不存在或存在。R_1和R_2各自分别可以是本文所描述的各个作用模块和靶向模块中的任何模块。R_1和R_2各自分别可以是能够与E3连接酶（ZNRF3或RNF43）或者靶向组织或细胞中的一个或多个结合的任何部分。例如，R_1和R_2各自可以是但不限于选自以下的部分：多肽（例如，抗体或其抗原结合片段或者不同于抗体的肽或多肽）、小分子和天然配体或其变体、片段或者衍生物。在某些实施例中，天然配体是多肽、小分子、离子、氨基酸、脂质或糖分子。作用模块和靶向模块（即，R_1和R_2）可以是彼此相同类型的部分，或者作用模块和靶向模块可以是不同类型的部分。在特定实施例中，R_2是其抗原结合片段的抗体，并且在某些实施例中，R_2包括Fc蛋白或其类似物。

[0099] 在某些实施例中，组织特异性Wnt信号增强分子包括单个分子（例如，多肽），而在其它实施例中，Wnt信号增强融合分子包括彼此结合（例如，彼此非共价结合）的两个或更多个分子（例如，多肽）。例如，在一个实施例中，组织特异性Wnt信号增强融合物包括分别具有式R_3-L_1和R_4-L_2的两个分子，其中R_3是作用模块，R_4是靶向模块，并且其中L_1基团和L_2基团彼此结合例如以形成二聚体。在各种实施例中，L_1基团和L_2基团彼此相同或彼此不同。L_1基团或L_2基团的一个实例是Fc序列，例如鼠类Fc2b或人Fc1，鼠类Fc2b或人Fc1中的每一个在本领域中是已知的。R_3和R_4各自分别可以是本文所描述的各个作用模块和靶向模块中的任何模块。R_3和R_4各自分别可以是能够与E3连接酶（ZNRF3和/或RNF43）或者靶向组织或细胞中的一个或多个结合的任何部分。在特定实施例中，组织特异性Wnt信号增强分子包括结合E3连接酶（ZNRF3和/或RNF43）中的一个或多个连接酶的抗体或其结合片段，其中抗体重链和/或抗体轻链包括结合靶向组织或细胞的附加结合结构域。在特定实施例中，组织特异性Wnt信号增强分子包括结合靶向组织或细胞的抗体或其结合片段，其中抗体重链和/或抗体轻链包括结合E3连接酶（ZNRF3和/或RNF43）中的一个或多个连接酶的附加结合结构域。附加结合结构域可以与抗体的N端或C端直接融合，例如作为重链或轻链融合蛋白，或者附加结合结构域可以经由接头部分附加到重链或轻链，例如到重链或轻链的N端、C端或内部氨基酸。在某些实施例中，抗体是IgG。

[0100] 在某些实施例中，组织特异性Wnt信号增强分子（例如，融合蛋白）增加与融合蛋白接触的肝组织或肝细胞中的Wnt信号传导。在特定实施例中，肝组织或细胞类型中的Wnt信号传导增加了至少50％、至少两倍、至少三倍、至少四倍、至少五倍或至少十倍。

[0101] 组织特异性Wnt信号增强分子可以通过本领域中已知且可获得的有机合成和分子生物学的标准方法来产生。例如，组织特异性Wnt信号增强融合蛋白可以通过融合靶向模块（例如，结合ASGR1或ASGR2的抗体或其抗原结合片段）与作用模块（例如，对应于氨基酸残基N37-R95的单独的人R-脊椎蛋白2弗林蛋白酶结构域1或者人R-脊椎蛋白2弗林蛋白酶结构域1、然后是弗林蛋白酶结构域2，其中弗林蛋白酶结构域2与LGR蛋白的相互作用通过点突变例如F105A和F109A单独地或组合地被消除或受损）来生成。在某些实施例中，靶向模块和作用模块通过接头例如甘氨酸-丝氨酸接头与位于组织特异性Wnt信号增强分子的N端的任一结构域融合。在某些实施例中，靶向模块和作用模块通过蛋白接头（例如，白蛋白）融合。

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“融合”靶向模块与作用模块的另外的方式包含但不限于例如“杵臼结构(knob-in-hole)”或亮氨酸拉链介导的二聚化。可以使对靶向模块、作用模块(和任选地接头)进行编码的DNA序列基因工程化以对期望的融合蛋白进行编码。

[0102] 对于包含抗体重链和轻链的组织特异性Wnt信号增强融合分子,对融合蛋白的不同部分进行编码的DNA序列可以使用标准分子克隆技术插入到细菌或真核表达载体中并且在适合的宿主细胞中进行表达。被表达的融合蛋白可以使用蛋白质科学中的标准技术例如亲和、离子交换和尺寸排阻色谱法纯化到均质。本公开还包含本文所描述的多肽作用模块、靶向模块和融合蛋白中的任何多肽作用模块、靶向模块和融合蛋白的功能性片段和变体,包含与本文所描述的作用模块、靶向模块或融合蛋白具有至少50%、至少60%、至少70%、至少80%、至少85%、至少90%、至少95%、至少98%或至少99%的多肽序列同一性的变体。与本文所公开的序列中的任何序列相比,这种变体可以包括一个或多个氨基酸修饰,例如一个或多个氨基酸缺失、插入或取代。在特定实施例中,组织特异性Wnt信号增强融合蛋白的功能性片段和变体与其源自的组织特异性Wnt信号增强融合蛋白相比,具有至少5%、至少10%、至少20%、至少30%、至少40%、至少50%、至少60%、至少70%、至少80%、至少90%、至少100%或更多的Wnt信号增强活性。在某些实施例中,多肽作用模块的功能性片段和变体与其源自的作用模块相比,具有至少5%、至少10%、至少20%、至少30%、至少40%、至少50%、至少60%、至少70%、至少80%、至少90%、至少100%或更多的Wnt信号增强活性(当在整个组织特异性Wnt信号增强分子的背景下测量时)。在某些实施例中,靶向模块的功能性片段和变体与其源自的靶向模块相比,具有至少5%、至少10%、至少20%、至少30%、至少40%、至少50%、至少60%、至少70%、至少80%、至少90%、至少100%或更多的结合活性。

[0103] 本公开还包含对本文所描述的一个或多个组织特异性Wnt信号增强分子或其组分例如融合蛋白或其变体进行编码的多核苷酸或核酸序列、包括这些多核苷酸的载体以及包括这些载体的细胞,所述载体包含表达载体。在某些实施例中,多核苷酸或核酸序列是DNA或RNA。在特定实施例中,RNA是信使RNA(mRNA)。在某些实施例中,RNA是包括一个或多个经过修饰的核苷的经过修饰的mRNA。包括一个或多个经过修饰的核苷的经过修饰mRNA已经被描述为相比于未经过修饰的mRNA具有优势,所述优势包含稳定性增加、表达水平更高和免疫原性降低。例如,以下中描述了可以根据本发明使用的经过修饰的mRNA的非限制性实例:PCT专利申请公开第WO2011/130624号、第WO2012/138453号、第WO 2013052523号、第WO 2013151666号、第WO2013/071047号、第WO2013/078199号、第WO 2012045075号、第WO 2014081507号、第WO2014093924号、第WO 2014164253号;美国专利申请第US 8,278,036号(描述了包括假尿苷的经过修饰的mRNA)、第US 8,691,966号(描述了包括假尿苷和/或N1-甲基假尿苷的经过修饰的mRNA)、第US 8,835,108号(描述了包括5-甲基胞苷的经过修饰的mRNA)、第US 8,748,089号(描述了包括假尿苷或1-甲基假尿苷的经过修饰的mRNA)。在特定实施例中,与未经过修饰的A、G、U或C核糖核苷相比,对组织特异性Wnt信号增强多肽进行编码的经过修饰的mRNA序列包括至少一个修饰。在特定实施例中,所述至少一个经过修饰的核苷包含N1-甲基假尿苷和/或5-甲基胞苷。在特定实施例中,经过修饰的mRNA包括5’端帽序列、接着是对组织特异性Wnt信号增强多肽进行编码的序列、接着是3’拖尾序列,如polyA或polyA-G序列。

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[0104] 在特定实施例中，多核苷酸是载体，例如表达载体，并且表达载体包括对与启动子序列可操作地连接的本文所描述的组织特异性Wnt信号增强融合分子(例如，融合蛋白或者附加的抗体的一条链或两条链)进行编码的多核苷酸序列，所述启动子序列例如驱动多核苷酸在细胞中的表达的启动子序列。在某些实施例中，载体是病毒载体，例如包括多核苷酸的病毒，所述多核苷酸包括表达盒，所述表达盒包括与对组织特异性Wnt信号增强多肽进行编码的DNA或RNA序列可操作地连接的启动子。在特定实施例中，表达盒包括5'和/或3'细胞或病毒UTR或其衍生物。

[0105] 本公开还包含本文所描述的多核苷酸的功能性片段和变体，包含与本文所描述的多核苷酸具有至少50％、至少60％、至少70％、至少80％、至少85％、至少90％、至少95％、至少98％或至少99％的多核苷酸序列同一性的变体。与本文所公开的序列中的任何序列相比，这种变体可以包括一个或多个核苷酸或核苷修饰，例如一个或多个核苷酸缺失、插入或取代。在特定实施例中，本文所描述的多核苷酸被密码子优化，例如以增强经过编码的多肽在宿主细胞中的表达。在特定实施例中，多核苷酸变体包括一个或多个经过修饰的核苷酸或核苷。

[0106] 本公开还包含包括对本文所描述的组织特异性Wnt信号增强分子例如融合蛋白进行编码的多核苷酸或载体的细胞。在某些实施例中，细胞是宿主细胞，例如可以用于产生组织特异性Wnt信号增强融合蛋白的HEK293细胞。在制备主题组合物时，可以采用任何宿主细胞，包含但不限于例如哺乳动物细胞(例如，293细胞)、昆虫细胞(例如，SF9细胞)、微生物和酵母。在某些实施例中，细胞对用本文所描述的组织特异性Wnt信号增强多肽治疗的受试者而言是异源或自体的。在特定实施例中，细胞从受试者获得并且用本文所描述的病毒载体进行转导。在特定实施例中，经过转导的细胞被递送到受试者以用于治疗。

[0107] 本公开还包含包括一种或多种组织特异性Wnt信号增强分子(例如，融合蛋白)或者一种或多种多核苷酸或载体的药物组合物，所述一种或多种多核苷酸或载体包括对组织特异性Wnt信号增强分子进行编码的序列。

[0108] 可以使用本领域中已知且可获得的技术和测定来测量Wnt信号传导。在某些实施例中，使用对应于靶组织或细胞类型的细胞系来确定Wnt信号传导的增加。在特定实施例中，在Wnt信号反应性启动子的控制下，细胞系含有具有标志物基因(例如，荧光素酶基因)的报告基因质粒。通过单独添加弗林蛋白酶结构域1(或与弗林蛋白酶结构域2、F105A点突变和/或F109A点突变一起)作为阴性对照或添加功能性R-脊椎蛋白(全长或弗林蛋白酶结构域1和2)作为阳性对照，可以确定细胞响应于Wnt3a、Wnt3a条件培养基或Wnt3a重组源的增强的报告基因活性。响应于组织特异性Wnt信号增强分子的报告基因活性还可以通过使报告基因细胞系与组织特异性Wnt信号增强分子接触来确定。阴性对照的报告基因活性可以是基本上、显著地或完全阴性的，并且在报告基因活性增加时，组织特异性Wnt信号增强分子和阳性对照应当示出增加的Wnt信号传导反应。另外的对照可以包含单独的抗ASGR1抗体(阴性)、使用抗GFP抗体代替抗ASGR1抗体的融合蛋白(阴性)以及完整的弗林蛋白酶结构域1-弗林蛋白酶结构域2蛋白(阳性)。可以通过类似地测量响应于用除靶向细胞类型或组织之外的细胞类型或组织中的组织特异性Wnt信号增强分子进行的治疗的报告基因活性来确定组织特异性Wnt信号增强分子的组织特异性。在某些实施例中，通过组织特异性Wnt信号增强分子结合的靶向组织中的报告基因活性比非靶向组织高，例如高至少50％、至少两

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倍、至少三倍、至少四倍、至少五倍或至少十倍。

[0109] 在特定实施例中，组织特异性Wnt信号增强多肽包括作用模块和靶向模块的任何组合，所述组合包含本文所描述的作用模块和靶向模块中的任何模块的任何组合。在特定实施例中，作用模块和靶向模块通过接头例如白蛋白(例如，人血清白蛋白)、肽基接头或非肽基接头连接，其中所述靶向模块和所述作用模块处于接头例如Fc或白蛋白、肽基接头或非肽基接头的N端和C端。

[0110] 组织特异性Wnt信号增强分子还可以如本领域中已知的与如聚乙二醇(PEG)、Fc、白蛋白等部分连接，以增强体内稳定性。

[0111] 组织特异性Wnt信号增强分子的说明性非限制性实例包含以下：

[0112] a)骨组织特异性Wnt信号增强多肽，所述骨组织特异性Wnt信号增强多肽包括：作用模块，所述作用模块包括增强Wnt信号传导的能力降低的R-脊椎蛋白(例如，人R-脊椎蛋白2)的变体或片段；以及靶向模块，所述靶向模块与PTH1R特异性地结合，其中所述组织特异性Wnt信号增强多肽增加了骨组织中的Wnt信号传导并且可以用于治疗骨组织疾病或病状；

[0113] b)肝组织特异性Wnt信号增强多肽，所述肝组织特异性Wnt信号增强多肽包括：作用模块，所述作用模块包括增强Wnt信号传导的能力降低的R-脊椎蛋白(例如，人R-脊椎蛋白2)的变体或片段；以及靶向模块，所述靶向模块与ASGR1、ASGR2、TFR2或SLC10A1特异性地结合，其中所述组织特异性Wnt信号增强多肽增加了肝组织中的Wnt信号传导并且可以用于治疗肝组织疾病或病状；或者

[0114] c)口腔粘膜组织特异性Wnt信号增强多肽，所述口腔粘膜组织特异性Wnt信号增强多肽包括：作用模块，所述作用模块包括增强Wnt信号传导的能力降低的R-脊椎蛋白(例如，人R-脊椎蛋白2)的变体或片段；以及靶向模块，所述靶向模块与LYPDS3或DSG3特异性地结合，其中所述组织特异性Wnt信号增强多肽增加了口腔粘膜组织中的Wnt信号传导并且可以用于治疗口腔粘膜组织疾病或病状。

[0115] 组织特异性Wnt信号增强分子的说明性非限制性实例包含随附的实例和序列中描述的那些，包含但不限于表1中描述的那些。在特定实施例中，组织特异性Wnt信号增强分子包括本文所公开的两个或更多个多肽序列，例如呈附加IgG或抗体格式。本文公开的多肽包含但不限于包括与表1所示的序列中的任何序列以及其片段和变体具有至少80％、至少85％、至少90％、至少95％、至少98％或至少99％的同一性的序列或由其组成的多肽。在特定实施例中，多肽包括表1所示的序列(例如，所述序列可能缺乏标签(例如，His标签或Flag标签)或其它另外的序列)中的任何序列以及其片段和变体内存在的作用模块或靶向模块。在某些实施例中，多肽具有作为作用模块和/或靶向模块的活性。

[0116] 本文所公开的多核苷酸的说明性非限制性实例包含对本文所描述的多肽、变体和片段中的任何多肽、变体和片段进行编码的任何多核苷酸，包含上文所描述的那些。在某些实施例中，多核苷酸对具有作为功能性结构域和/或靶向模块的活性的多肽进行编码。

[0117] 表1.序列标识符的描述

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[0118]

图	SEQ ID NO:	简要描述
1	1	全长人 RSPO1（PP）
1	2	全长人 RSPO2（PP）
1	3	全长人 RSPO3（PP）
1	4	全长人 RSPO4（PP）
1、2、3	5 和 6	抗 GFP RSPO2 野生型（PN 和 PP）
1、2、3	7 和 8	抗 GFP RSPO2（F105R/F109A）（PN 和 PP）
1、2、3	9 和 10	抗 GFP RSPO2（R65A/R69A/Q70A/F105A/F109A）（PN 和 PP）
1、2、3	11 和 12	抗 ASGR1 RSPO2 野生型（PN 和 PP）
1、2、3	13 和 14	抗 ASGR1 RSPO2（F105R/F109A）（PN 和 PP）
1、2、3	15 和 16	抗 ASGR1 RSPO2（R65A/R69A/Q70A/F105A/F109A）（PN 和 PP）
4	17 和 18	抗 TFR1 RSPO2 野生型（PN 和 PP）
4	19 和 20	抗 TFR1 RSPO2（F105R/F109A）（PN 和 PP）
4	21 和 22	抗 TFR1 RSPO2（R65A/R69A/Q70A/F105A/F109A）（PN 和 PP）
5、9-15	23 和 24	Fc-RSPO2（PN 和 PP）
		αGFP-RSPO2-RA-IgG
5、6、9、13-15	25 和 26	抗 GFP 轻链（PN 和 PP）
5、6、9、13 和 15	27 和 28	RSPO2（F105R/F109A）、抗 GFP 重链 IgG2（PN 和 PP）
		αASGR1-RSPO2-RA-IgG
5、6、9、13 和 15	29 和 30	抗 ASGR1 轻链（PN 和 PP）
5、6、9、13 和 15	31 和 32	RSPO2（F105R/F109A）、抗 ASGR1 重链 IgG2（PN 和 PP）
		αGFP-IgG
5 和 6	25 和 26	抗 GFP 轻链（PN 和 PP）
5 和 6	33 和 34	抗 GFP 重链 IgG1（PN 和 PP）
		ASGR ECD
7 和 9	35 和 36	hASGR1 ECD
9	163 和 164	mASGR1 ECD
7	37 和 38	hASGR2 ECD
	39 和 40	cynoASGR1 ECD
	41 和 42	cynoASGR2 ECD
		E3 连接酶 ECD
1 和 4	43 和 44	hRNF43 ECD

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[0119]

1 和 4	45 和 46	hZNRF3 ECD
		抗 β-Gal
9、10、13 和 15	155 和 156	抗 β-Gal 轻链（PN 和 PP）
9	157 和 158	抗 β-Gal 重链 IgG1-LALAPG（PN 和 PP）
10、13 和 15	159 和 160	抗 β-Gal 重链 IgG2（PN 和 PP）
		抗 ASGR1 Fab
9	29 和 30	抗 ASGR1 轻链（PN 和 PP）
9	161 和 162	抗 ASGR1 VH-CH1（PN 和 PP）
		α-β-Gal-RSPO2-RA-IgG（附加 C-HC）
14	155 和 156	抗 β-Gal 轻链（PN 和 PP）
14	186 和 187	抗 β-Gal 重链 IgG2、RSPO2（F105R/F109A）（PN 和 PP）
		α-GFP-RSPO2-RA-IgG（附加 C-HC）
14	25 和 26	抗 GFP 轻链（PN 和 PP）
14	188 和 189	抗 GFP 重链 IgG2、RSPO2（F105R/F109A）（PN 和 PP）
		LP1-1F8-RSPO2-RA-IgG（附加 C-HC）
14	190 和 191	LP1-1F8 轻链（PN 和 PP）
14	192 和 193	LP1-1F8 重链 IgG2、RSPO2（F105R/F109A）（PN 和 PP）
		LP1-1N15-RSPO2-RA-IgG（附加 C-HC）
14	194 和 195	LP1-1N15 轻链（PN 和 PP）
14	196 和 197	LP1-1N15 重链 IgG2、RSPO2（F105R/F109A）（PN 和 PP）
		LP1-1P13-RSPO2-RA-IgG（附加 C-HC）
14	198 和 199	LP1-1P13 轻链（PN 和 PP）
14	200 和 201	LP1-1P13 重链 IgG2、RSPO2（F105R/F109A）（PN 和 PP）
		LP1-1P5-RSPO2-RA-IgG（附加 C-HC）
14	202 和 203	LP1-1P5 轻链（PN 和 PP）
14	204 和 205	LP1-1P5 重链 IgG2、RSPO2（F105R/F109A）（PN 和 PP）
		LP1-2E12-RSPO2-RA-IgG（附加 C-HC）
14	206 和 207	LP1-2E12 轻链（PN 和 PP）
14	208 和 209	LP1-2E12 重链 IgG2、RSPO2（F105R/F109A）（PN 和 PP）
		LP1-2I13-RSPO2-RA-IgG（附加 C-HC）
14	210 和 211	LP1-2I13 轻链（PN 和 PP）
14	212 和 213	LP1-2I13 重链 IgG2、RSPO2（F105R/F109A）（PN 和 PP）
		LP1-2I22-RSPO2-RA-IgG（附加 C-HC）
14	214 和 215	LP1-2I22 轻链（PN 和 PP）

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[0120]

14	216 和 217	LP1-2I22 重链 IgG2、RSPO2（F105R/F109A）（PN 和 PP）
		LP1-3A24-RSPO2-RA-IgG（附加 C-HC）
14	218 和 219	LP1-3A24 轻链（PN 和 PP）
14	220 和 221	LP1-3A24 重链 IgG2、RSPO2（F105R/F109A）（PN 和 PP）
		LP1-3E20-RSPO2-RA-IgG（附加 C-HC）
14	222 和 223	LP1-3E20 轻链（PN 和 PP）
14	224 和 225	LP1-3E20 重链 IgG2、RSPO2（F105R/F109A）（PN 和 PP）
		LP1-6H3-RSPO2-RA-IgG（附加 C-HC）
14	226 和 227	LP1-6H3 轻链（PN 和 PP）
14	228 和 229	LP1-6H3 重链 IgG2、RSPO2（F105R/F109A）（PN 和 PP）
		LP1-7B13-RSPO2-RA-IgG（附加 C-HC）
14	230 和 231	LP1-7B13 轻链（PN 和 PP）
14	232 和 233	LP1-7B13 重链 IgG2、RSPO2（F105R/F109A）（PN 和 PP）
		LP1-7I20-RSPO2-RA-IgG（附加 C-HC）
14	234 和 235	LP1-7I20 轻链（PN 和 PP）
14	236 和 237	LP1-7I20 重链 IgG2、RSPO2（F105R/F109A）（PN 和 PP）
		LP1-8M24-RSPO2-RA-IgG（附加 C-HC）
14	238 和 239	LP1-8M24 轻链（PN 和 PP）
14	240 和 241	LP1-8M24 重链 IgG2、RSPO2（F105R/F109A）（PN 和 PP）
		LP1-9C3-RSPO2-RA-IgG（附加 C-HC）
14	242 和 243	LP1-9C3 轻链（PN 和 PP）
14	244 和 245	LP1-9C3 重链 IgG2、RSPO2（F105R/F109A）（PN 和 PP）
		LP1-9M16-RSPO2-RA-IgG（附加 C-HC）
14	246 和 247	LP1-9M16 轻链（PN 和 PP）
14	248 和 249	LP1-9M16 重链 IgG2、RSPO2（F105R/F109A）（PN 和 PP）
		LP1-10C22-RSPO2-RA-IgG（附加 C-HC）
14	250 和 251	LP1-10C22 轻链（PN 和 PP）
14	252 和 253	LP1-10C22 重链 IgG2、RSPO2（F105R/F109A）（PN 和 PP）
		LP1-1N15-RSPO2-RA、IgG1 N297G（附加 N-HC）
14-15	194 和 195	LP1-1N15 轻链（PN 和 PP）
14-15	254 和 255	RSPO2（F105R/F109A）、LP1-1N15 重链 IgG1 N297G（PN 和 PP）
		LP1-1P13-RSPO2-RA-IgG1 N297G（附加 N-HC）
14-15	198 和 199	LP1-1P13 轻链（PN 和 PP）
14-15	256 和 257	RSPO2（F105R/F109A）、LP1-1P13 重链 IgG1 N297G（PN 和 PP）
		LP1-2I13-RSPO2-RA-IgG1 N297G（附加 N-HC）

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[0121]

14-15	210 和 211	LP1-2I13 轻链（PN 和 PP）
14-15	258 和 259	RSPO2（F105R/F109A）、LP1-2I13 重链 IgG1 N297G（PN 和 PP）
		LP1-2I22-RSPO2-RA-IgG1 N297G（附加 N-HC）
14-15	214 和 215	LP1-2I22 轻链（PN 和 PP）
14-15	260 和 261	RSPO2（F105R/F109A）、LP1-2I22 重链 IgG1 N297G（PN 和 PP）
		LP1-3A24-RSPO2-RA-IgG1 N297G（附加 N-HC）
14-15	230 和 231	LP1-7B13 轻链（PN 和 PP）
14-15	266 和 267	RSPO2（F105R/F109A）、LP1-7B13 重链 IgG1 N297G（PN 和 PP）
		LP1-8M24-RSPO2-RA-IgG1 N297G（附加 N-HC）
14-15	238 和 239	LP1-8M24 轻链（PN 和 PP）
14-15	268 和 269	RSPO2（F105R/F109A）、LP1-8M24 重链 IgG1 N297G（PN 和 PP）
		LP1-9M16-RSPO2-RA-IgG1 N297G（附加 N-HC）
14-15	246 和 247	LP1-9M16 轻链（PN 和 PP）
14-15	270 和 271	RSPO2（F105R/F109A）、LP1-9M16 重链 IgG1 N297G（PN 和 PP）
15	29 和 30	抗 ASGR1 轻链（PN 和 PP）
15	272 和 273	抗 ASGR1 重链 IgG2（PN 和 PP）

[0122] 作用模块

[0123] R-脊椎蛋白能够放大Wnt信号。R-脊椎蛋白的最小功能性单元由两个弗林蛋白酶结构域即与ZNRF3/RNF43 E3连接酶结合的弗林蛋白酶结构域1和与LGR4-6结合的弗林蛋白酶结构域2构成，从而使R-脊椎蛋白、LGR和E3连接酶在一起形成三元复合物。这导致整个复合物内化并且ZNRF3/RNF43从ZNRF3/RNF43的破坏靶标中移除。单独的弗林蛋白酶结构域1不具有功能性，但是能够与ZNRF3和RNF43两者结合。

[0124] 本文所描述的组织特异性Wnt信号增强分子的作用模块可以是但不限于可以与ZNRF3/RNF43连接酶结合的任何功能性部分，例如多肽或有机化学品。在特定实施例中，作用模块例如包括R-脊椎蛋白的弗林蛋白酶结构域1的多肽单独地或与靶向模块一起在非靶组织中基本上无活性，以便使潜在的脱靶效应最小化。在组织特异性Wnt信号增强分子的背景下，作用模块与靶向模块融合或结合，并且当组织特异性Wnt信号增强分子与表达组织特异性受体的靶组织接合时，E3连接酶ZNRF3/RNF43被募集到与组织特异性受体的第三复合物，从而使E3连接酶ZNRF3/RNF43重定位在细胞表面上、被螯合和/或从细胞表面清除。

[0125] 在某些实施例中，作用模块包括R-脊椎蛋白多肽(例如，R-脊椎蛋白1-4中的任何R-脊椎蛋白)的片段或变体或者R-脊椎蛋白多肽的功能性片段或变体。在特定实施例中，作用模块包括野生型R-脊椎蛋白的片段，并且在其它实施例中，作用模块包括R-脊椎蛋白的片段，所述片段包括一个或多个氨基酸修饰。R-脊椎蛋白可以是本领域中已知的任何R-脊椎蛋白或其同源物，包含来自任何动物物种的R-脊椎蛋白，所述动物物种包含但不限于哺乳动物物种，如人R-脊椎蛋白。已经鉴别和描述了R-脊椎蛋白，并且其多肽和编码多核苷酸序列在本领域中是已知且可获得的。在特定实施例中，R-脊椎蛋白多肽是人R-脊椎蛋白或在其它脊椎动物或非脊椎动物中发现的同源物，例如小鼠R-脊椎蛋白。图1和SEQ ID NO:1-4中分别提供了人R-脊椎蛋白1、人R-脊椎蛋白2、人R-脊椎蛋白3和人R-脊椎蛋白4以及其弗林蛋白酶结构域1的氨基酸序列。其同源物和变体可从通用数据库搜索中获得，如https://

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www.dot.ncbi.dot.nlm.dot.nih.dot.gov/protein/。本发明包含(但不限于)作用模块,所述作用模块包括这些或其它R-脊椎蛋白中的任何R-脊椎蛋白的片段和变体或由其组成。在各种实施例中,与野生型R-脊椎蛋白多肽相比,R-脊椎蛋白多肽中的任何R-脊椎蛋白多肽的变体和其片段包括一个或多个氨基酸修饰,例如缺失、添加或取代。所述一个或多个修饰可以存在于R-脊椎蛋白的变体或其片段的任何区域中,所述区域包含但不限于弗林蛋白酶结构域1和/或弗林蛋白酶结构域2。应当理解,弗林蛋白酶结构域1或弗林蛋白酶结构域2外部的氨基酸修饰可以改变所得变体,从而使得所得变体与野生型R-脊椎蛋白或其片段相比具有降低的LGR4-6结合活性。

[0126] 在某些实施例中,作用模块包括R-脊椎蛋白序列或其变体或者片段或由其组成,例如全长或野生型R-脊椎蛋白-1、全长或野生型R-脊椎蛋白-2、全长或野生型R-脊椎蛋白-3或者全长或野生型R-脊椎蛋白-4,任选地人R-脊椎蛋白-1、人R-脊椎蛋白-2、人R-脊椎蛋白-3或人R-脊椎蛋白-4。在特定实施例中,作用结构域是R-脊椎蛋白-1-4中的任何R-脊椎蛋白的变体,所述变体与对应的野生型R-脊椎蛋白-1-4序列具有至少80%、至少85%、至少90%、至少95%、至少98%或至少99%的序列同一性。在某些实施例中,作用模块包括包含一个或多个氨基酸修饰的全长R-脊椎蛋白(例如,R-脊椎蛋白-1-4中的任何R-脊椎蛋白)或由其组成,所述一个或多个氨基酸修饰包含但不限于本文所公开的那些氨基酸修饰中的任何氨基酸修饰。在某些实施例中,作用模块包括野生型或经过修饰的R-脊椎蛋白(例如,R-脊椎蛋白-1-4中的任何R-脊椎蛋白)的片段或由其组成。在特定实施例中,片段能够与ZNRF3和/或RNF43结合。在某些实施例中,作用模块包括R-脊椎蛋白的弗林蛋白酶结构域1或者R-脊椎蛋白蛋白的片段或变体。在某些实施例中,作用模块包括R-脊椎蛋白(例如,R-脊椎蛋白-1-4)的一个或多个(例如,一个、两个、三个或更多个)弗林蛋白酶结构域1或其变体,所述变体与R-脊椎蛋白弗林蛋白酶结构域1具有至少85%、至少90%、至少95%、至少98%或至少99%的序列同一性。在某些实施例中,作用模块包括R-脊椎蛋白弗林蛋白酶1结构域或其变体或者片段以及R-脊椎蛋白弗林蛋白酶2结构域或其变体或者片段。在某些实施例中,作用模块包括结合ZNRF3/RNF43的抗体或其抗原结合片段。在特定实施例中,作用模块与ZNRF3或RNF43特异性地结合。

[0127] 在某些实施例中,作用模块包括R-脊椎蛋白例如人R-脊椎蛋白1或人R-脊椎蛋白2的一个或多个弗林蛋白酶结构域1或其变体。在某些实施例中,作用模块包括R-脊椎蛋白的一个或多个弗林蛋白酶结构域1,但不包括R-脊椎蛋白的弗林蛋白酶结构域2。在某些实施例中,作用模块包括R-脊椎蛋白的一个或多个弗林蛋白酶结构域1,并且作用模块包括R-脊椎蛋白的经过修饰的或变体弗林蛋白酶结构域2,例如与野生型弗林蛋白酶结构域2相比具有降低的活性的弗林蛋白酶结构域2。在某些实施例中,作用模块包括R-脊椎蛋白,所述R-脊椎蛋白具有R-脊椎蛋白的经过修饰的或变体弗林蛋白酶结构域2,例如与野生型弗林蛋白酶结构域2相比具有降低的活性的弗林蛋白酶结构域2。在某些实施例中,作用模块包括两个或更多个弗林蛋白酶结构域1或其变体或者弗林蛋白酶结构域1或其变体的多聚体。在某些实施例中,作用模块包括变体R-脊椎蛋白弗林蛋白酶1结构域,所述变体R-脊椎蛋白弗林蛋白酶1结构域包括例如在对应于人R-脊椎蛋白2的K58、H76、S77、R86和/或N91的氨基酸残基处的一个或多个点突变。在某些实施例中,作用模块包括变体R-脊椎蛋白弗林蛋白酶2结构域,所述变体R-脊椎蛋白弗林蛋白酶2结构域包括例如在对应于人R-脊椎蛋白2的

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F105、F109和/或K121的氨基酸残基处的一个或多个点突变。在特定实施例中，作用模块包括R-脊椎蛋白的经过修饰的或变体弗林蛋白酶结构域1，所述经过修饰的或变体弗林蛋白酶结构域1与野生型弗林蛋白酶结构域1相比具有增加的活性，例如与ZNRF3/RNF43的结合。作用模块可以进一步包括另外的部分或多肽序列例如的另外的氨基酸残基以稳定作用模块的或作用模块所存在于的组织特异性Wnt信号增强分子的结构。在某些实施例中，作用模块在与R-脊椎蛋白不具有明显的/强烈的序列同源性的情况下包括肽或多肽，但是与ZNRF3/RNF43的结合亲和力与R-脊椎蛋白与ZNRF3/RNF43的亲和力相当或比其更高。

[0128] 在某些实施例中，作用模块包括R-脊椎蛋白多肽(例如，人R-脊椎蛋白)的弗林蛋白酶结构域1或者其功能性片段或变体以及R-脊椎蛋白多肽(例如，人R-脊椎蛋白)的经过修饰的或变体弗林蛋白酶结构域2，其中所述经过修饰的弗林蛋白酶结构域2与对应的野生型弗林蛋白酶结构域2相比，与LGR4-6具有降低的结合亲和力(参见图1和4)。在某些实施例中，弗林蛋白酶结构域2包括例如在对应于人R-脊椎蛋白2的F105和/或F109的氨基酸残基处的一个或多个点突变。通过比较其它R-脊椎蛋白多肽的氨基酸序列与人R-脊椎蛋白2，技术人员可以容易地确定其它R-脊椎蛋白多肽中的对应的氨基端残基。在某些实施例中，作用模块包括弗林蛋白酶结构域1或其变体和弗林蛋白酶结构域2或其变体，其中所述弗林蛋白酶结构域1和/或所述弗林蛋白酶结构域2包括一个或多个点突变。作用模块内的所述一个或多个点突变(相比于对应的野生型R-脊椎蛋白序列)可以发生在弗林蛋白酶结构域1和/或弗林蛋白酶结构域2内的任何氨基酸残基处，所述氨基酸残基包含但不限于例如氨基酸残基K58、H76、S77、R86、N91、F105、F109或K121以及可以被修饰以降低与LGR4-6的结合亲和力的其它残基。已经鉴别出对人R-脊椎蛋白1的功能活性重要的人R-脊椎蛋白1的弗林蛋白酶结构域1和弗林蛋白酶结构域2的区域，所述区域包含保守的亲水残基S48、N51、R66、R70和Q71以及保守性较低的疏水残基L46、L54、I62和L64，所述残基对与E3连接酶的结合而言具有重要性。另外，在人R-脊椎蛋白1弗林蛋白酶结构域1中，氨基酸残基K59、S78、D85、R87、N88和N92与LGR5形成亲水相互作用表面，并且FSHNF氨基酸序列已经被鉴别为对疏水表面而言具有重要性的环。在特定实施例中，包括R-脊椎蛋白弗林蛋白酶结构域1和/或弗林蛋白酶结构域2的作用模块可以包括在这些区域、表面或氨基酸残基中的任何区域、表面或氨基酸残基内的一个或多个突变。在特定实施例中，包括R-脊椎蛋白弗林蛋白酶结构域1和/或弗林蛋白酶结构域2的作用模块可以包括在这些区域、表面或氨基酸残基外的一个或多个突变或其它改变，所述一个或多个突变或其它改变通过影响结合表面的结构和/或稳定性间接损害了LGR4-6结合。在某些实施例中，包括R-脊椎蛋白弗林蛋白酶结构域1和/或弗林蛋白酶结构域2的作用模块可以包括任何氨基酸残基处的一个或多个突变，所述一个或多个突变包含但不限于随附的实例中描绘的那些突变中的任何突变。在特定实施例中，作用模块包括经过修饰的弗林蛋白酶结构域2，所述弗林蛋白酶结构域2包括氨基酸残基F105和/或F109处的氨基酸取代。在特定实施例中，作用模块包括弗林蛋白酶1结构域和经过修饰的弗林蛋白酶结构域2，所述弗林蛋白酶1结构域和经过修饰的弗林蛋白酶结构域2包括氨基酸残基F105和/或F109处的氨基酸取代。在特定实施例中，作用模块包括经过修饰的弗林蛋白酶1结构域和经过修饰的弗林蛋白酶2结构域，其中在某些实施例中，所述经过修饰的弗林蛋白酶1结构域在氨基酸R65、R69和/或Q70处包括一个或多个氨基酸修饰，并且所述经过修饰的弗林蛋白酶结构域在氨基酸F105和/或F109处包括一个或多个氨基酸修

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饰。在特定实施例中，经过修饰的弗林蛋白酶结构域2与LGR4-6的结合亲和力比对应的野生型弗林蛋白酶结构域2的结合低80％、50％、20％或10％，例如在全长R-脊椎蛋白的背景下。

[0129] 在某些实施例中，作用模块包括R-脊椎蛋白多肽(例如，人R-脊椎蛋白)的弗林蛋白酶结构域1或其功能性片段或者变体和R-脊椎蛋白多肽(例如，人R-脊椎蛋白)的未经过修饰的弗林蛋白酶结构域2。虽然在某些实施例中，更期望与对应的野生型弗林蛋白酶结构域2相比与LGR4-6具有降低的结合亲和力的经过修饰的弗林蛋白酶结构域2来增加组织靶向特异性，但是在特定实施例中，与靶向模块组合的未经过修饰的弗林蛋白酶结构域2与没有靶向模块的野生型R-脊椎蛋白相比具有经过改进的组织靶向性并且在某些背景下具有实用性。

[0130] 在某些实施例中，作用模块包括例如来自R-脊椎蛋白-1、R-脊椎蛋白-2、R-脊椎蛋白-3、R-脊椎蛋白-4中的任何R-脊椎蛋白，任选地人R-脊椎蛋白-1、人R-脊椎蛋白-2、人R-脊椎蛋白-3或人R-脊椎蛋白-4的野生型或经过修饰的R-脊椎蛋白弗林蛋白酶结构域1。在特定实施例中，作用模块包括例如来自R-脊椎蛋白-1、R-脊椎蛋白-2、R-脊椎蛋白-3、R-脊椎蛋白-4中的任何R-脊椎蛋白，任选地人R-脊椎蛋白-1、人R-脊椎蛋白-2、人R-脊椎蛋白-3或人R-脊椎蛋白-4的R-脊椎蛋白弗林蛋白酶1结构域和野生型或经过修饰的R-脊椎蛋白弗林蛋白酶2结构域。在特定实施例中，作用模块包括例如来自R-脊椎蛋白-1、R-脊椎蛋白-2、R-脊椎蛋白-3、R-脊椎蛋白-4中的任何R-脊椎蛋白，任选地人R-脊椎蛋白-1、人R-脊椎蛋白-2、人R-脊椎蛋白-3或人R-脊椎蛋白-4的第一R-脊椎蛋白弗林蛋白酶1结构域和第二野生型或经过修饰的R-脊椎蛋白弗林蛋白酶1结构域。在特定实施例中，相比于对应的野生型弗林蛋白酶结构域2的结合，经过修饰的弗林蛋白酶结构域2与LGR4-6具有相当的结合亲和力或与LGR4-6具有小于80％、小于50％、小于20％或小于10％的结合亲和力，例如在全长R-脊椎蛋白的背景下。

[0131] 在某些实施例中，作用模块包括特异性地结合ZNRF3和/或RNF43的抗体或其抗原结合片段。在特定实施例中，作用模块包括与人RNF43(hRNF43，NCBI参考序列XP_011523257.1，残基44-198；SEQ ID NO:43-44)或人ZNRF3(hZNRF3；NCBI参考序列NP_001193927.1，残基56-219；SEQ ID NO:45-46)结合的抗体或其抗原结合片段。在特定实施例中，作用模块是抗体或其抗原结合片段，所述抗体或其抗原结合片段包括：a)针对表2A的抗体中的任何抗体所示的CDRH1、CDRH2和CDRH3序列；和/或b)针对表2A的抗体中的任何抗体所示的CDRL1、CDRL2和CDRL3序列，或所述抗体或其抗原结合片段的变体，所述变体包括一个或多个氨基酸修饰，其中所述变体在所述CDR序列中包括少于8个氨基酸取代。在特定实施例中，分离的抗体或其抗原结合片段包括重链可变区、轻链、纳米抗体或scFv序列，所述重链可变区、轻链、纳米抗体或scFv序列包括与这些抗体中的任何抗体的重链可变区、轻链、纳米抗体或scFv具有至少90％同一性的氨基酸序列，例如，SEQ ID NO:78-154或165-170中的任何氨基酸序列。VL指示可变轻链，并且VH指示可变重链序列。

[0132] 表2A：针对hRNF43/ZNRF3的结合剂的克隆ID和CDR序列

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[0133]

克隆ID	特异性	CDRH1	SID NO.	CDRH2	SID NO.	CDRH3	SID NO.
020S-E06	RNF43	YTFTGYYMH	329	GIINPSGGSTSYA	349	CARGRQGVWDYW	393
020S-F06	RNF43	YTFTSYYLH	338	GWMNPNSGNTGYA	366	CARGDFWSGYYPYYYYYYGMDVW	388
028S-B01	RNF43	YTFTAYYMH	327	GIINPNGGRTTYA	345	CARSFGVAGTLDYW	404
028S-E01	RNF43	YTFTSYDIN	336	GVINPGGSDTTYA	354	CARDGYYYGMDVW	379
028S-G01	RNF43	YTFTNYYMH	332	GWINPHSGGTNYA	356	CAREDYNWNDGWFDPW	386
028S-H01	RNF43	GTFSNYAIS	318	GWINPNSGGTNYA	358	CAKDSGYCSSTSCYDGGYFDLW	376
028S-B02	RNF43	FTFSSYAMH	312	SAISGSGTYYA	372	CARDQGHDYGDYEIDYW	383
028S-C02	RNF43	YTFTNYYMH	332	GIINPSGGSANYA	348	CARDPVRGISAFDYW	382
024S-A02	RNF43、ZRNF3	YTFTSYAMH	335	GWINAGNGNTKYS	355	CARDLMVRGGPPFDYW	381
028S-D02	ZNRF3	DSVSSNSAAWY	306	GRTYYRSKWYHDYA	353	CARVVRAVDAFDIW	407
020S-H06	ZNRF3	YTFTSYYMH	339	GWMNPNSGNTGYA	366	CARGRVVRGVIISYGMDVW	397
020S-A07	ZNRF3	DTFTGYYIH	307	GGIIPIFDAATYA	342	CTRARGQRSGYSYFDLW	409
020S-B07	ZNRF3	GTFSTSGIT	321	GWMNPNTGGIKYS	367	CAKSRALKGSYTSW	377
020S-D07	RNF43、ZNRF3	GTFSNTDIN	317	GGIIPIFGTANYA	344	CVGGRSGWIWYFDLW	410
020S-E07	ZNRF3	GTFSNYSLS	319	GIINPRRGSTRYA	347	CARDGLGVDAFDIW	378
020S-F07	RNF43、ZNRF3	FTFSNYAMG	311	SYISRSSSTIYYA	697	CARRRDGYNWGYW	402
028S-H02	ZNRF3	YTFTNYYMH	332	GRIKPNSGNTGYA	351	CARGRRSRGSSSLGYYYYMDVW	395
028S-C03	ZNRF3	YTFSRYFMH	326	GWINPNSGGTRYA	359	CARDQKGKSSSWFRFDPW	384
028S-A04	ZNRF3	YTFTNYKMH	331	GKINPSSGSTSYA	350	CARSGAGMWYFDLW	405
028S-B04	ZNRF3	YTFRRYPMH	325	GIINPSGGSTSYA	349	CARDKVGAIDYW	380
028S-C04	ZNRF3	YTFTRYYMH	334	GIINPSGGSTSYA	349	CARGGSGWLDYW	391
028S-	ZNRF3	GTFSSYAIS	320	GRISPNRGGTKY	352	CARDSWLRGAWGY	385

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[0134]

D04				A		W	
028S-E04	ZNRF3	FTFNNFGMS	310	SGISASGRNTYYA	373	CARETRHGSDYW	387
028S-H04	ZNRF3	YTFIGYYMH	324	GWVNPKNGHTGYA	368	CAKDLEHTGYSSGWAGFDYW	375
028S-B06	ZNRF3	YRFTNYYMH	322	GWISPNSGATNYA	363	CARGGRTTVTTMAYW	390
028S-G06	ZNRF3	FAFSNFAMI	308	SAISGSGGSTYYA	370	CARLRANYGMDVW	400
028S-B07	ZNRF3	YTFTEYYMH	328	GWMNPNSGHAGSA	365	CARGRRSGLSPPAYW	394
028S-H07	ZNRF3	YTFTNYGIS	330	GWISADNGNTNYA	362	CARGRSGNWKFW	396
028S-D08	ZNRF3	YTFTSYYMH	339	GWINPNSGNTKYA	360	CARGSNGMDVW	399
028S-E08	ZNRF3	FSFSNYAMS	309	SAISGSGRTTYYA	371	CARRTSSFSLW	403
028S-F08	ZNRF3	GTFSNYAIS	318	GGIIPIFDATNYA	343	CARRQYSGYDTHFDYW	401
028S-A09	ZNRF3	YRFTSYYLH	323	GWMNPKSGGTNYA	364	CARGGRSYGYWYFDLW	389
028S-D09	ZNRF3	YTFTRHYMH	333	GIINPSGGSTSYA	349	CARGSLGYFDLW	398
028S-E10	ZNRF3	YTFTSYYMH	339	GWINPNTGGTKSA	361	CARVLRGSLGFDYW	406
028S-G10	ZNRF3	YTFTSYGVS	337	GIINPRGGSTSYA	346	CARYSSSWSWPFDYW	408
028S-A11	ZNRF3	GTFSGYYMH	316	GWINPNRGGTSYA	357	CARGMYSSSWLRYW	392
SC-01	RNF43	GFNIKDT	314	DPANGK	340	GGGYYGMDY	411
SC-02	RNF43	GFNIKDD	313	DPENGD	341	SRTTALDY	412
NV-01	ZNRF3	GFTFSDY	315	KSKTDGGI	369	AIYYLEAFDV	374

[0135] 表2A (续)

[0136]

克隆ID	特异性	CDRL1	SID NO.	CDRL2	SID NO.	CDRL3	SID NO.
020S-E06	RNF43	RSSQSIRTYLN	439	AASTLQS	448	CQQANSFPITF	473
020S-F06	RNF43	RVSQGISSYLN	441	AASTLQS	448	CQQSYGAPLTF	479
028S-B01	RNF43	RSSQSLLHSNGYNYLD	440	DASNLET	451	CMQTLHTPYTF	472
028S-E01	RNF43	KSSQSVLYSSNNKNYLA	414	WASTRES	465	CQQYYSDPITF	498
028S-G01	RNF43	RASENIHKYLN	417	AASSLQS	447	CQQGYSTPYTF	477
028S-H01	RNF43	RASQNIYDWLA	426	DASNLET	451	CQQTYSTPFTF	492

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028S-B02	RNF43	RSSQSLLHSNGYNYLD	440	LGSYRAS	462	CMQALQTPLTF	468
028S-C02	RNF43	RASQSIRSYLN	428	AASSLQS	447	CLQDYDYPLTF	467
024S-A02	RNF43、ZRNF3	RASQSVSSSYLA	437	GASSRAT	456	CQQYGSSPRTF	494
028S-D02	ZNRF3	RASQSVNSRYLA	434	GASSRAT	456	CQQYGSSRLTF	495
020S-H06	ZNRF3	RASQSVSSSNLA	436	ATSTRAT	450	CQQYGSSPITF	493
020S-A07	ZNRF3	RASQNIRSWLA	425	DASSLQR	454	CQQSYSTPPTF	487
020S-B07	ZNRF3	RAGQSISRFLN	416	AASSLQS	447	CQQSYSTPYTF	489
020S-D07	RNF43、ZNRF3	RASQSISRWLA	429	DASSLET	452	CQQAYSFPWTF	475
020S-E07	ZNRF3	QASQDISRYLN	415	AASSLQS	447	CQQSYSRPFTF	484
020S-F07	RNF43、ZNRF3	RASQDISNSLN	419	AASTLQS	448	CQQSYSPPHTF	483
028S-H02	ZNRF3	RASQFISTYLN	422	DASSLPS	453	CQQSYSTSWTF	490
028S-C03	ZNRF3	RSSQSLLHSNGYNYLD	440	LGSNRAS	461	CMQSLEAPLAF	471
028S-A04	ZNRF3	RASQDIYRYLN	421	AASSLHS	445	CQQSYTTPITF	491
028S-B04	ZNRF3	RASQGISNYLA	424	AASSLQR	446	CQQSYSTPLTF	486
028S-C04	ZNRF3	RASQSISTWLA	432	AASTLQS	448	CQQSYSSPLTF	485
028S-D04	ZNRF3	RASQSISRWLA	429	AASTLQS	448	CQQSFSTPYTF	478
028S-E04	ZNRF3	TSSQSVLHSSNKKNYLA	443	WASTRAS	464	CQQYHSTPYTF	496
028S-H04	ZNRF3	KSSQSVLYSSNNKNYLA	414	WASTRES	465	CQQYYSTPLTF	499
028S-B06	ZNRF3	RSSQSLLHSNGYNYLD	440	GASSLQS	455	CMQGTHWPRTF	469
028S-G06	ZNRF3	RASQSISSYLN	431	AASSLQS	447	CQQSYRTPYTF	481
028S-B07	ZNRF3	RASQSVSASLA	435	GASTRAT	457	CHQYFSPPMTF	466
028S-H07	ZNRF3	RASQYIGSYLN	438	AASTLQS	448	CQQSYSPPFTF	482
028S-D08	ZNRF3	RSSQSLLHSNGYNYLD	440	KASSLES	458	CMQGTHWPYAF	470
028S-E08	ZNRF3	RASQSINNWLA	427	KASSLES	458	CQQANTFPITF	474
028S-F08	ZNRF3	KSSQSVLYSSNNKNYLA	414	WASTRES	465	CQQYYSTPPTF	500

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028S-A09	ZNRF3	RASQSVDSSYLA	433	AASARAA	444	CQQYYRSPPTF	497
028S-D09	ZNRF3	RASQSISSWLA	430	AASSLQS	447	CQQSYSTPLTF	486
028S-E10	ZNRF3	RASQDISRYLA	420	AASTVES	449	CQQSYRSPYTF	480
028S-G10	ZNRF3	RASQGISNNLN	423	AASTLQS	448	CQQSYSTPTF	488
028S-A11	ZNRF3	RASQGISNYLA	424	AASSLQS	447	CQQGSSFPLTF	476
SC-01	RNF43	RASESVDSYGNSFMH	418	LASNLES	459	QQNNEDPLT	502
SC-02	RNF43	KASQSVRPAVA	413	LASNRHT	460	LQHWNYPYT	501
NV-01	ZNRF3	SGDSLGSYYVH	442	RNKQRPS	463	QTYDWMYSSRV	503

[0139] 表2B.序列标识符的描述

[0140]

SID NO:	简要描述	序列
78	020S-E06 VL	DIQMTQSPSSLSASVGDRVTITCRSSQSIRTYLNWYQQKPGKAPKLLIYAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPITFGGGTKVEIK
79	020S-E06 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGRQGVWDYWGRGTLVTVSS
80	020S-F06 VL	DIQMTQSPSSLSASVGDRVTITCRVSQGISSYLNWYQQKPGKAPKLLIYAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYGAPLTFGQGTKVEIK
81	020S-F06 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYLHWVRQAPGQGLEWMGWMNPNSGNTGYAQNFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGDFWSGYYPYYYYYYGMDVWGQGTTVTVSS
82	028S-B01 VL	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYDASNLETGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQTLHTPYTFGQGTKLEIK
83	028S-B01 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTAYYMHWVRQAPGQGLEWMGIINPNGGRTTYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARSFGVAGTLDYWGQGTLVTVSS
84	028S-E01 VL	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYSDPITFGQGTRLEIK
85	028S-E01 VH	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYDINWVRQAPGQGLEWMGVINPGGSDTTYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDGYYYGMDVWGQGTTVTVSS
86	028S-G01 VL	DIQMTQSPSSLSASVGDRVTITCRASENIHKYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQGYSTPYTFGQGTKLEIK
87	028S-G01 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYYMHWVRQAPGQGLEWMGWINPHSGGTNYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAREDYNWNDGWFDPWGQGTLVTVSS
88	028S-H01 VL	DIQMTQSPSSLSASVGDRVTITCRASQNIYDWLAWYQQKPGKAPKLLIYDASNLETGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQTYSTP

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[0141]

		FTFGPGTKVDIK
89	**028S-H01 VH**	QVQLVQSGAEVKKPGASVKVSCKASGGTFSNYAISWVRQAPGQGL EWMGWINPNSGGTNYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDT AVYYCAKDSGYCSSTSCYDGGYFDLWGRGTLVTVSS
90	**028S-B02 VL**	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQ SPQLLIYLGSYRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCM QALQTPLTFGGGTKVEIK
91	**028S-B02 VH**	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYAMHWVRQAPGKGLE WVSAISGSGTYYADSVKGRFTISRDDSKNTLYLQMNSLKTEDTAVY YCARDQGHDYGDYEIDYWGQGTLVTVSS
92	**028S-C02 VL**	DIQMTQSPSSLSASVGDRVTITCRASQSIRSYLNWYQQKPGKAPKLLI YAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCLQDYDYPL TFGGGTKVEIK
93	**028S-C02 VH**	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYYMHWVRQAPGQG LEWMGIINPSGGSANYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDT AVYYCARDPVRGISAFDYWGQGTLVTVSS
94	**024S-D04 VHH**	DVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLE WVSVINSGGGSTSYAESVKGRFIISRDNAKNTLYLQMNSLKPEDTAV YYCARGTYYSGSYYYPALYYGMDYWGKGTQVTVSS
95	**024S-A02 VL**	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLL IYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPR TFGQGTKVEIK
96	**024S-A02 VH**	EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYAMHWVRQAPGQRL EWMGWINAGNGNTKYSQTFQGRVTITRDTSASTAYMELSSLRSEDT AVYYCARDLMVRGGPPFDYWGQGTLVTVSS
97	**028S-D02 VL**	ETTLTQSPGTLSLSPGERATLSCRASQSVNSRYLAWYQQKPGQAPRL LIYGASSRATGIPDRLTGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSR LTFGGGTKVEIK
98	**028S-D02 VH**	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWYWIRQSPSRGL EWLGRTYYRSKWYHDYAVSVKSRITINADTSKNQFSLQLNSVTPEDT AVYYCARVVRAVDAFDIWGQGTMVTVSS
99	**020S-H06 VL**	EIVMTQSPATLSVSPGERATLSCRASQSVSSSNLAWYQQKPGQAPRL LIYATSTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYGSSPI TFGGGTKVEIK
100	**020S-H06 VH**	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQG LEWMGWMNPNSGNTGYAQKFQGRVTMTRDTSTSTVYMELSSLRSE DTAVYYCARGRVVRGVIISYGMDVWGQGTTVTVSS
101	**020S-A07 VL**	DIQMTQSPSSLSASVGDRVTITCRASQNIRSWLAWYQQKPGKAPKLL IYDASSLQRGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPP TFGQGTKLEIK
102	**020S-A07 VH**	QVQLVQSGAEVKKPGSSVKVSCKASGDTFTGYYIHWVRQAPGQGL EWMGGIIPIFDAATYAQKFQGRVTITADESTSTAYMELSSLRSEDTAV YYCTRARGQRSGYSYFDLWGRGTLVTVSS
103	**020S-B07 VL**	DIQMTQSPSSLSASVGDRVTITCRAGQSISRFLNWYQQKPGKAPKLLI YAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPYT FGQGTKLEIK
104	**020S-B07 VH**	QVQLVQSGAEVKKPGASVKVSCKASGGTFSTSGITWVRQAPGQGLE WMGWMNPNTGGIKYSQKFQGRVTMTRDTSTSTVYMELSSLRSEDT AVYYCAKSRALKGSYTSWGQGTLVTVSS
105	**020S-D07 VL**	DIQMTQSPSSLSASVGDRVTITCRASQSISRWLAWYQQKPGKAPKLLI YDASSLETGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQAYSFPW

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[0142]

		TFGQGTKVEIK
106	020S-D07 VH	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSNTDINWVRQAPGQGL EWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAV YYCVGGRSGWIWYFDLWGRGTLVTVSS
107	020S-E07 VL	DIQMTQSPSSLSASVGDRVTITCQASQDISRYLNWYQQKPGKAPKLL IYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSRPF TFGPGTKVDIK
108	020S-E07 VH	QVQLVQSGAEVKKPGASVKVSCKASGGTFSNYSLSWVRQAPGQGL EWMGIINPRRGSTRYAQNFQGRVTMTRDTSTSTVYMELSSLRSEDTA VYYCARDGLGVDAFDIWGQGTMVTVSS
109	020S-F07 VL	DIQMTQSPSSLSASVGDRVTITCRASQDISNSLNWYQQKPGKAPKLLI YAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSPPHT FGGGTKVEIK
110	020S-F07 VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMGWVRQAPGKGLE WVSYISRSSSTIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCARRRDGYNWGYWGQGTLVTVSS
111	028S-H02 VL	DIQMTQSPSSLSASVGDRVTITCRASQFISTYLNWYQQKPGKAPKLLI YDASSLPSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTSW TFGQGTKVEIK
112	028S-H02 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYYMHWVRQAPGQG LEWMGRIKPNSGNTGYAQKFQGRVTMTRDTSTSTVYMELSSLRSED TAVYYCARGRRSRGSSSLGYYYYYMDVWGKGTTVTVSS
113	028S-C03 VL	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQ SPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCM QSLEAPLAFGQGTKLEIK
114	028S-C03 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFSRYFMHWVRQAPGQGL EWMGWINPNSGGTRYAQNLQGRVTMTRDTSTSTVYMELSSLRSEDT AVYYCARDQKGKSSSWFRFDPWGQGTLVTVSS
115	028S-A04 VL	DIQMTQSPSSLSASVGDRVTITCRASQDIYRYLNWYQQKPGKAPKLL IFAASSLHSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYTTPIT FGQGTKVEIK
116	028S-A04 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYKMHWVRQAPGQG LEWMGKINPSSGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDT AVYYCARSGAGMWYFDLWGRGTLVTVSS
117	028S-B04 VL	DIQMTQSPSSLSASVGDRVTITCRASQGISNYLAWYQQKPGKAPKLL IYAASSLQRGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPL TFGGGTKVEIK
118	028S-B04 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFRRYPMHWVRQAPGQG LEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDT AVYYCARDKVGAIDYWGQGTLVTVSS
119	028S-C04 VL	DIQMTQSPSSLSASVGDRVTITCRASQSISTWLAWYQQKPGKAPKLLI YAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSSPLT FGGGTKVEIK
120	028S-C04 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTRYYMHWVRQAPGQG LEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDT AVYYCARGGSGWLDYWGQGTLVTVSS
121	028S-D04 VL	DIQMTQSPSSLSASVGDRVTITCRASQSISRWLAWYQQKPGKAPKLLI YAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSFSTPYT FGQGTKVEIK
122	028S-D04 VH	QVQLVQSGAEVKKPGASVKVSCKASGGTFSSYAISWVRQAPGQGLE WMGRISPNRGGTKYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTA

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		VYYCARDSWLRGAWGYWGQGTLVTVSS
123	028S-E04 VL	DIVMTQSPDSLAVSLGERATINCTSSQSVLHSSNKKNYLAWYQQKPG QPPKLLIYWASTRASGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQ QYHSTPYTFGQGTKVEIK
124	028S-E04 VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFNNFGMSWVRQAPGKGLE WVSGISASGRNTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDRA VYYCARETRHGSDYWGQGTLVTVSS
125	028S-H04 VL	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPG QPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQ QYYSTPLTFGGGTKVEIK
126	028S-H04 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFIGYYMHWVRQAPGQG LEWLGWVNPKNGHTGYAQKFQGRVTMTRDTSTSTVYMELSSLRSE DTAVYYCAKDLEHTGYSSGWAGFDYWGQGTLVTVSS
127	028S-B06 VL	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQ SPQLLIYGASSLQSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCM QGTHWPRTFGQGTKVDIK
128	028S-B06 VH	QVQLVQSGAEVKKPGASVKVSCKASGYRFTNYYMHWVRQAPGQG LEWMGWISPNSGATNYAQNFQGRVTMTRDTSTSTVYMELSSLRSED TAVYYCARGGRTTVTTMAYWGQGTLVTVSS
129	028S-G06 VL	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLI YAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYRTPYT FGQGTKLEIK
130	028S-G06 VH	EVQLLESGGGLVQPGGSLRLSCAASGFAFSNFAMIWVRQAPGKGLE WVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCARLRANYGMDVWGQGTTVTVSS
131	028S-B07 VL	EIVMTQSPATLSVSPGERATLSCRASQSVSASLAWYQQKPGQAPRLLI YGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCHQYFSPPMT FGQGTRLEIK
132	028S-B07 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYYMHWVRQAPGQG LEWMGWMNPNSGHAGSAQKFQGRVTMTRDTSTSTVYMELSSLRSE DTAVYYCARGRRSGLSPPAYWGQGTLVTVSS
133	028S-H07 VL	DIQMTQSPSSLSASVGDRVTITCRASQYIGSYLNWYQQKPGKAPKLL IYAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSPPF TFGQGTKVEIK
134	028S-H07 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYGISWVRQAPGQGL EWMGWISADNGNTNYAQKFQGRVTMTRDTSTSTVYMELSSLRSED TAVYYCARGRSGNWKFWGQGTLVTVSS
135	028S-D08 VL	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQ SPQLLIYKASSLESGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCM QGTHWPYAFGQGTRLEIK
136	028S-D08 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQG LELMGWINPNSGNTKYAQKFQGRVTMTRDTSTSTVYMELSSLRSED TAVYYCARGSNGMDVWGQGTTVTVSS
137	028S-E08 VL	DIQMTQSPSSLSASVGDRVTITCRASQSINNWLAWYQQKPGKAPKLL IYKASSLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANTFPIT FGQGTRLEIK
138	028S-E08 VH	EVQLLESGGGLVQPGGSLRLSCAASGFSFSNYAMSWVRQAPGKGLE WVSAISGSGRTTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCARRTSSFSLWGQGTLVTVSS
139	028S-F08 VL	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPG QPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQ

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		QYYSTPPTFGQGTKLEIK
140	028S-F08 VH	QVQLVQSGAEVKKPGSSVKVSCKASAGTFSNYAISWVRQAPGQGLE WMGGIIPIFDATNYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVY YCARRQYSGYDTHFDYWGQGTLVTVSS
141	028S-A09 VL	EIVMTQSPATLSVSPGERATLSCRASQSVDSSYLAWYQQKPGQAPRL LIYAASARAAGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYYRSP PTFGQGTRLEIK
142	028S-A09 VH	QVQLVQSGAEVKKPGASVKVSCKASGYRFTSYYLHWVRQAPGQGL EWMGWMNPKSGGTNYAQKFQGRVTMTRDTSTSTVYMELSSLRSE DTAVYYCARGGRSYGYWYFDLWGRGTLVTVSS
143	028S-D09 VL	DIQMTQSPSSLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLI YAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLT FGGGTKVEIK
144	028S-D09 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTRHYMHWVRQAPGQG LEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDT AVYYCARGSLGYFDLWGRGTLVTVSS
145	028S-E10 VL	DIQMTQSPSSLSASVGDRVTITCRASQDISRYLAWYQQKPGKAPKLLI YAASTVESGVPSRFSGSGSGTDFTLTI?SLQPEDFATYYCQQSYRSPYT FGQGTKLEIK
146	028S-E10 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQG LEWMGWINPNTGGTKSAQKFQGRVTMTRDTSTSTVYMELSSLRSE DTAVYYCARVLRGSLGFDYWGQGTLVTVSS
147	028S-G10 VL	DIQMTQSPSSLSASVGDRVTITCRASQGISNNLNWYQQKPGKAPKLL IYAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPT FGQGTKVEIK
148	028S-G10 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGVSWVRQAPGQGL EWMGIINPRGGSTSYAQNFQGRVTMTRDTSTSTVYMELSSLRSEDTA VYYCARYSSSWSWPFDYWGQGTLVTVSS
149	028S-A11 VL	DIQMTQSPSSLSASVGDRVTITCRASQGISNYLAWYQQKPGKAPKLL IYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQGSSFPLT FGQGTKVDIK
150	028S-A11 VH	QVQLVQSGAEVKKPGASVKVSCKASGGTFSGYYMHWVRQAPGQG LEWMGWINPNRGGTSYAQNFQGRVTMTRDTSTSTVYMELSSLRSE DTAVYYCARGMYSSSWLRYWGQGTLVTVSS
165	SC-01 VL	DIVMTQSPDSLAVSLGERATINCRASESVDSYGNSFMHWYQQKPGQ PPKLLIYLASNLESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQ NNEDPLTFGQGTKVEIK
166	SC-01 VH	QVQLVQSGAEVKKPGASVKVSCKASGFNIKDTYIHWVRQAPGQGL EWMGRIDPANGKANYDPKFQGRVTMTRDTSTSTFYMELSSLRSEDT AVYYCALGGGYYGMDYWGQGTLVTVSS
167	SC-02 VL	DIVMTQSQKFMSTSVGDRVSITCKASQSVRPAVAWYQQKPGQSPKA LIYLASNRHTGVPDRFTGSGSGTDFTLTISNVQSEDLADYFCLQHWN YPYTFGGGTKLEIK
168	SC-02 VH	EVQLQQSGAELVRPGASVKLSCTASGFNIKDDYIHWVKQRPEQGLE WIGWIDPENGDTKYASKFPGKATMTADTSSNTAYLQLSSLTSEDTAV YYCTASRTTALDYWGPGTTLTVSS
169	NV-01 VL	DIELTQPPSVSVSPGQTASITCSGDSLGSYYVHWYQQKPGQAPVLVIY RNKQRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQTYDWMYS SRVFGGGTKLTVL
170	NV-01 VH	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGIHWVRQAPGKGLE WVGRIKSKTDGGTTEYAAPVKGRFTISRDDSKNTLYLQMNSLKTEDT
		AVYYCARAIYYLEAFDVWGQGTLVTVSS

[0144]

[0145]

[0146] 表2C:E3连接酶结合剂的结合数据

[0147]

克隆ID	特异性	Octet KD(M)	Octet KD(M)
020S-E06	RNF43	未测试	未测试

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020S-F06	RNF43	未测试	未测试
028S-B01	RNF43	未测试	未测试
028S-E01	RNF43	NB	NB
028S-G01	RNF43	未测试	未测试
028S-H01	RNF43	NB	NB
028S-B02	RNF43	NB	NB
028S-C02	RNF43	NB	NB
024S-A02	RNF43、ZRNF3	1.01E-05	*
028S-D02	ZNRF3	3.32E-06	*
020S-H06	ZNRF3	NB	NB
020S-A07	ZNRF3	NB	NB
020S-B07	ZNRF3	NB	NB
020S-D07	RNF43、ZNRF3	NB	NB
020S-E07	ZNRF3	NB	NB
020S-F07	RNF43、ZNRF3	NB	NB
028S-H02	ZNRF3	2.63E-06	*
028S-C03	ZNRF3	2.51E-08	***
028S-A04	ZNRF3	3.62E-08	***
028S-B04	ZNRF3	2.56E-07	**
028S-C04	ZNRF3	1.64E-07	**
028S-D04	ZNRF3	8.74E-07	**
028S-E04	ZNRF3	9.53E-08	***
028S-H04	ZNRF3	4.80E-08	***
028S-B06	ZNRF3	7.64E-07	**
028S-G06	ZNRF3	1.09E-07	**
028S-B07	ZNRF3	6.54E-08	***
028S-H07	ZNRF3	NB	NB
028S-D08	ZNRF3	1.39E-06	*
028S-E08	ZNRF3	3.90E-06	*
028S-F08	ZNRF3	1.04E-06	*
028S-A09	ZNRF3	1.25E-05	*
028S-D09	ZNRF3	3.54E-07	**
028S-E10	ZNRF3	4.16E-06	*
028S-G10	ZNRF3	6.84E-07	**
028S-A11	ZNRF3	2.03E-07	**
SC-01	RNF43	未测试	未测试
SC-02	RNF43	未测试	未测试
NV-01	ZNRF3	未测试	未测试

[0148] *指示KD≥1uM,**指示1uM>KD≥100nM,***指示100nM>KD,

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[0149] NB指示无结合

[0150] 结合特异性通过ELISA确定

[0151] 靶向模块

[0152] 特异性组织内的特异性细胞类型和细胞可以包括一个或多个细胞特异性或组织特异性表面分子，如细胞表面受体。如本文所使用的，如果与一种或多种其它细胞或组织类型或者任何其它细胞或组织类型相比，特异性细胞或组织类型中存在更大数量的分子，则所述分子被认为具有细胞特异性或组织特异性。在某些实施例中，与所述一种或多种其它细胞或组织类型或者任何其它细胞或组织类型中的数量相比，所述更大数量为至少两倍、至少五倍、至少10倍、至少20倍、至少50倍或至少100倍。在特定实施例中，细胞特异性表面分子例如与一个或多个其它非靶向器官、组织或细胞类型相比，在靶器官、组织或细胞类型上的表达增加或增强，例如期望增强Wnt信号传导例如以治疗或预防疾病或病症的器官、组织或细胞类型。在某些实施例中，分别与一种或多种其它器官、组织或细胞类型相比，细胞特异性表面分子优先表达在靶器官、组织或细胞类型的表面上。例如，在特定实施例中，与分别在一种或多种、五种或更多种所有其它器官、组织或细胞中或者在平均的所有其它器官、组织或细胞中表达相比，如果在靶器官、组织或细胞中表达细胞表面受体的水平高至少两倍、至少五倍、至少10倍、至少20倍、至少30倍、至少40倍、至少50倍、至少100倍、至少500倍或至少1000倍，则细胞表面受体被认为是组织特异性或细胞特异性细胞表面分子。在某些实施例中，组织特异性或细胞特异性细胞表面分子是细胞表面受体，例如包括位于细胞表面膜内的区域和靶向模块可以结合的细胞外区域的多肽受体。在各种实施例中，本文所描述的方法可以通过以下来实践：特异性地靶向仅表达在靶组织或包含靶组织的组织子集上的细胞表面分子；或特异性地靶向与所有、大多数或大量其它组织相比在靶组织上具有更高表达水平的细胞表面分子，例如，与在至少两个、至少五个、至少十个或至少二十个其它组织上相比在靶组织上具有更高的表达。

[0153] 在特定实施例中，靶向模块与表达在关注的靶细胞或组织类型上的组织特异性表面分子结合，即期望增强或增加Wnt信号传导活性的细胞或组织类型。与每个组织特异性表面分子结合的靶向模块可以是但不限于抗体或其抗原结合片段、肽、组织特异性或细胞特异性受体的天然配体或其衍生物以及合成的小分子等。

[0154] 通过靶向模块结合的靶向组织可以是任何组织，例如任何哺乳动物组织或细胞类型。在某些实施例中，靶向组织可以存在于任何器官中。在某些实施例中，靶组织是骨组织、肝组织、皮组织、胃组织、肠组织、口腔粘膜组织、肾组织、中枢神经系统组织、乳腺组织、味蕾组织、卵巢组织、内耳组织(包含耳蜗组织和前庭组织)、毛囊、胰腺组织、视网膜组织、角膜组织、心脏组织或肺组织，并且靶向模块分别与优先表达在以下组织上的组织特异性细胞表面分子(例如，细胞表面受体)结合：骨组织、肝组织、皮组织、胃组织、肠组织、口腔粘膜组织、肾组织、中枢神经系统组织、乳腺组织、味蕾组织、卵巢组织、内耳组织(包含耳蜗组织和前庭组织)、毛囊、胰腺组织、视网膜组织、角膜组织、心脏组织或肺组织。

[0155] 靶向模块可以与任何细胞类型结合，例如任何组织、器官或动物内的任何细胞，所述动物包含但不限于哺乳动物，如人。在某些实施例中，组织特异性Wnt信号增强分子与特异性细胞类型结合，例如与靶组织相关的特异性细胞类型。例如，在肝组织中，靶向模块可以与肝细胞、肝细胞的前体和干细胞、胆道细胞和/或内皮细胞或其它血管细胞结合。例如，

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在骨组织中，靶向模块可以结合产生骨组织中存在的骨细胞、软骨细胞和/或其它细胞的成骨细胞、成骨细胞的前体、间充质干细胞、干细胞和前体细胞。包含但不限于本文所描述的组织的各个组织中存在的细胞类型在本领域中是已知的，并且在各种实施例中，本文所描述的组织特异性Wnt信号增强分子可以结合所述组织类型中的任何组织类型。在某些实施例中，靶向模块与肝组织或肝细胞结合。

[0156] 脱唾液酸糖蛋白受体(ASGPR)包含ASGR1和ASGR2(例如Stockert、Morell和Ashwell,1991,《靶向诊断和疗法(Targeted Diagnostics and Therapy)》4:41-64所综述的)。这个受体是跨膜蛋白，所述跨膜蛋白通过介导具有暴露的末端半乳糖或N-乙酰半乳糖胺残基的糖蛋白的内吞作用和溶酶体降解而在血清糖蛋白稳态中发挥关键作用。因此，AGPR的天然配体和合成配体包含但不限于半乳糖化胆碱酯酶、半乳糖(Gal)和N-乙酰半乳糖胺(GalNAc)、含有GalNAc的分子如GalNAc封端的糖蛋白以及含有的单糖、寡糖或聚糖的分子或纳米颗粒(例如D'Souza和Devarajan,2015,《控释期刊(Journal of Controlled Release)》,203:126-139所综述的)。

[0157] SLC10家族以钠依赖性方式运输胆汁酸、硫酸化溶质和其它异生物质。创始成员SLC10A1(NTCP)和SLC10A2(ASBT)用于维持胆汁酸的肠肝循环。SLC10A的天然配体和合成配体的实例包含但不限于胆酸盐、Na(+)/胆汁酸、Na(+)/牛磺胆酸盐以及乙型肝炎病毒的preS1结构域以及其片段或变体(例如Yan等人,2012《e生命(eLife)》,1:e00049所报告的)。

[0158] 转铁蛋白受体2(TFR2)是转铁蛋白受体1(TFR1)的同源物，即通过受体介导的二价铁转铁蛋白(Fe_2TF)的内吞作用将铁递送到细胞中的蛋白质。TFR2还结合Fe_2TF，但TFR2似乎主要用于调节系统性铁稳态(例如Worthen和Enns,2014,《药理学前沿(Frontiers in Pharmacology)》5:34所综述的)。TFR2的天然配体和合成配体以及结合配偶体的实例包含但不限于转铁蛋白如二价铁转铁蛋白和血色沉着症(HFE)蛋白以及其片段和变体。

[0159] 甲状旁腺激素(PTH)和PTH相关肽(PTHrP)的1型受体(PTH1R)高度地表达在骨和肾中(例如Mannstadt、Juppner和Gardella,1999,《美国生理学期刊(American Journal of Physiology)》277:F665-F675所综述的)。甲状旁腺激素受体1(PTH1R)的天然配体和合成配体包含但不限于PTH、PTHrP以及其片段和变体。

[0160] 含Ly6/PLAUR结构域的蛋白3(LYPD3)是在于如口腔粘膜、皮肤和食管等组织中发现的复层鳞状上皮中展现出高度特异性表达的GPI锚定蛋白。在伤口愈合期间在迁移的角化细胞中以及在各种癌中也观察到了LYPD3表达上调(例如Jacobsen、Kriegbaum、Santoni-Rugiu和Ploug,2014,《世界临床肿瘤学期刊(World Journal of Clinical Oncology)》,5(4):621-32)所综述的)。尽管已经报道了LYPD3表达，但是其确切功能仍不清楚，因为缺乏LYPD3基因的动物在鳞状上皮的发育中可存活、可繁殖且没有明显的缺陷。各个分子已经被鉴别为LYPD3的结合配偶体。层粘连蛋白1、层粘连蛋白5和半乳凝素-3与LYPD3缔合以促进细胞迁移(Paret、Bourouba、Beer、Miyazaki、Schnölzer、Fiedler和Zöller《国际癌症期刊(International Journal of Cancer)》.2005年7月10日;115(5):724-33)。前梯度2(Anterior gradient 2)AGR2与LYPD3相互作用并且促进胰腺导管腺癌(PDAC)的癌生长、转移和对疗法的抗性(Arumugam、Deng、Bover、Wang、Logsdon和Ramachandran,《分子癌症治疗学(Molecular Cancer Therapeutics)》.2015年4月;14(4):941-51)。在缺氧条件下，LYPD3与α6β4整合素和基质金属蛋白酶14(MMP14)形成复合物，所述复合物通过病灶化层粘连蛋

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白332降解促进了癌细胞的运动性。(Ngora、Galli、Miyazaki和Zöller《肿瘤形成(Neoplasia)》.2012年2月;14(2):95-107)。

[0161] 桥粒芯蛋白3(DSG3)对属于蛋白质的钙粘蛋白细胞粘附分子超家族的成员的钙结合跨膜糖蛋白进行编码。DSG3表达在细胞与细胞粘附的特殊结构桥粒中、在上皮和粘膜中。DSG3具有含有DSG3细胞间相互作用所需的Ca2+结合位点的五个细胞外钙粘蛋白结构域(ECD)(例如Thomason、Scothern、McHarg和Garrod,2010,《生物化学期刊(Biochemical Journal)》,429(3):419-433所综述的)。DSG3细胞间相互作用由其N端附近的反式同嗜性相互作用(trans-homophilic interaction)介导。动物体内DSG3的损耗会导致非常严重的口腔粘膜糜烂和断奶时脱发,这表明了这个基因对这些组织中的上皮细胞的完整性的重要性。单分子原子力显微镜实验已经示出了经由细胞外钙粘蛋白结构域的同嗜性反式DSG3结合(Heupel、Zillikens、Drenckhahn和Waschke《免疫学期刊(Journal of Immunology》2008年8月1日,181(3)1825-1834)。

[0162] 在各种实施例中,组织特异性表面分子是组织特异性细胞表面受体。对于肝脏,组织特异性细胞表面受体包含但不限于ASGR1、ASGR2、TFR2、SLC10A1等。在某些实施例中,靶向模块是结合ASGR1、ASGR2、TFR2、SLC10A1、LYPD3或DSG3的天然配体或其功能性变体或者片段或抗体或者其抗原结合片段。对于骨或肾,这种组织特异性细胞表面受体包含但不限于甲状旁腺激素受体1(PTH1R)等。在某些实施例中,靶向模块是结合PTH1R的天然配体或其功能性变体或者片段或抗体或者其抗原结合片段。对于口腔粘膜,这种组织特异性细胞表面受体包含但不限于LYPD3和DSG3。在某些实施例中,靶向模块是结合LYPD3或DSG3的天然配体或其功能性变体或者片段或抗体或者其抗原结合片段。

[0163] 在特定实施例中,靶向模块与人ASGR1(hASGR1;NCBI参考序列NP_001662.1,残基62-291;SEQ ID NO:35-36)、人ASGR2(hASGR2;NCBI参考序列NP_550436.1,残基66-292;SEQ ID NO:37-38)、猕猴ASGR1(cynoASGR1,序列ID XP_005582755.1,残基62-291;SEQ ID NO:39-40)或猕猴ASGR2(cynoASGR2;SEQ ID NO:41-42)结合。

[0164] 在某些实施例中,靶向模块包括抗体或其抗原结合片段,所述抗体或其抗原结合片段包括:针对表3A中所列抗体中的任何抗体所示的CDRH1、CDRH2和CDRH3序列;和/或针对表3A的抗体中的任何抗体所示的CDRL1、CDRL2和CDRL3序列,或所述抗体或其抗原结合片段的变体,所述变体包括一个或多个氨基酸修饰,其中所述变体在所述CDR序列中包括少于8个氨基酸取代。在特定实施例中,分离的抗体或其抗原结合片段包括重链可变区、轻链、纳米抗体或scFv序列,所述重链可变区、轻链、纳米抗体或scFv序列包括与这些抗体中的任何抗体的重链可变区、轻链、纳米抗体或scFv具有至少90%同一性的氨基酸序列(例如,SEQ ID NO:47-77、151-154、171-179、180-185或274-305中的任何氨基酸序列)(参见例如表3B或3C)。

[0165] 表3A:针对hASGR1/2的结合剂的克隆ID和CDR序列

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[0166]

克隆ID	特异性	CDRH1	SID NO.	CDRH2	SID NO.	CDRH3	SID NO.
024S-D03	ASGR1	DSVSSNSAAWN	505	GRTYYRSKWYNDYA	551	CARWNHEEHYFDYW	589
024S-E03	ASGR1	ASVSSNSAAWN	504	GRTYYRSKWYNDYA	551	CARWNHEEHYFDYW	589
024S-A04	ASGR1	DSVSSNSVAWN	505	GRTYYRSKWYYDYA	552	CASWTRGAFDIW	594
020S-A05	ASGR2	GTFSSYAIS	517	GGIIPIFGTANYA	544	CAVSDGYDLDYW	596
020S-	ASGR2	GTFSSYAIS	517	GGIIPIFGTANYA	544	CASFGVGAPDYW	591

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[0167]

C05							
020S-G06	ASGR2	YTFTSYGIS	533	GWISAYNGNTNYA	561	CASAGGGYW	590
020S-A06	ASGR2	YTFTGYHMH	530	GGIIPVFGAPNYA	546	CARDGGYGMDVW	576
020S-B06	ASGR2	YTFTGYYMH	531	GIINPSGGGTSYA	548	CARDTGATAEYFQHW	580
020S-C06	ASGR2	YSFTGNYMH	520	GGIIPMFGTVKYA	545	CAKDRGYRFDFDLW	570
020S-D06	ASGR2	FTFSSYAMS	508	SYISSYNSHTNDA	568	CARWAVAAGGQYYYMDVW	588
020S-C07	ASGR2	YTFSNYYMH	525	GWINPKSGGTKYA	559	CARDRGITMVRGVMDYW	579
028S-H09	ASGR2	YTFTTYYMH	535	GWINPNGGGTNYA	560	CAKDRTAMAPEGAFDIW	571
028S-C11	ASGR2	YTFSDYYVH	524	GIINPRNGRTSYA	547	CARDHLYGMDVW	577
028S-D11	ASGR2	FTVSSNYMS	514	SAISGSGGSTYYA	565	CAKDSPIVRRGERGRYYGMDVW	572
028S-G11	ASGR2	YTFTDYNMH	527	GWMNPNTGNTAYA	562	CARDKNYYGMDVW	578
020S-H05	ASGR2	HTFSSYAMG	518	AAISQSGYVRYYA	536	CNARWGAGSLFASW	599
Abv-3 D11	ASGR2	GFSFNTY	515	RSKSNNYA	564	PRYDYWYFDV	605
Abv-1 0B8	ASGR2	GFTFSSY	516	SSGGDY	567	EGTGGMDY	604
RO-01	ASGR1	GFTFSSY	516	SGSGGS	566	DFSSRRWYLEY	603
RO-02	ASGR1	FTFSSYAMS	509	AISGSGGSTYYA	538	CAKSWYLPGRGFDYW	575
RO-03	ASGR1	FTFSSYAMS	509	AISGSGGSTYYA	538	CAKSSFTFGRYFDYW	574
RO-04	ASGR1	FTFSSYAMS	509	AISGSGGSTYYA	538	CAKSSFSYLRAFDYW	573
LP1-1F8	ASGR1	FTFSTYTMS	511	ATISSIGVNTYYP	541	CARHVDYYDGISFDYW	583
LP1-1N15	ASGR1	YTFTDYYMN	529	GRVIPSNGGTNYN	554	CARGMDYW	582
LP1-1P13	ASGR1	YSFTDYFMN	519	GRFNPFNGQTFYN	550	CARRGRYDVYYVLDYW	586
LP1-1P5	ASGR1	YTFLTYWMN	523	GQIFPATGITYYS	549	CARRRAYHSNFFDYW	587
LP1-2E12	ASGR1	YSITSGYYWN	522	GSIGYDDTNHYN	557	CAGDYPFAFW	569
LP1-2I13	ASGR1	FTFSDYGMH	507	AYISSGSSTIYYA	542	CSRKGGFGDYEKSYAMDYW	600
LP1-2I22	ASGR1	YSFTGYFMN	521	GRFNPFNGQTFYN	550	CARRGRYDVYYALDYW	585
LP1-3A24	ASGR1	YTFTDYYIN	528	GRVIPSNGGSNYN	553	CATQLGRW	595

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[0168]

LP1-3E20	ASGR1	YTFTSYWIH	534	GYINPSSGYAEYN	563	CARESYYSFDYTMDYW	581
LP1-6H3	ASGR1	YTFSRFDMH	526	GVIYPGNGDTSYN	558	CASSYYGNPW	593
LP1-7B13	ASGR1	FTFTDYYMN	512	GRVNPSNDDTRYN	556	CTRWFYFDYW	601
LP1-7I20	ASGR1	FTFTDYYMS	513	ALIRNKANGYTTEYS	539	CAVTYGAYW	597
LP1-8M24	ASGR1	YTFTNYGIN	532	GEIFPRSDNTFYN	543	CARKGRDYGTSHYFDYW	584
LP1-9C3	ASGR1	FSLSTSYMGVS	506	AHIFWDDDKRYN	537	CGGPYYPFTYW	598
LP1-9M16	ASGR1	YTFTDYYMN	529	GRVNPNNGGSNYN	555	CASRNFDVW	592
LP1-10C22	ASGR1	FTFSSYGMS	510	ASISSGGSYTYYP	540	CVRHEEYGKSGFAYW	602

[0169] 表3A (续)

克隆ID	特异性	CDRL1	SID NO.	CDRL2	SID NO.	CDRL3	SID NO.
024S-D03	ASGR1	RASQSVGSYLA	625	DATNRAT	644	CQHRRTF	679
024S-E03	ASGR1	RASQSVGSYLA	625	DATNRAT	644	CQHRRTF	679
024S-A04	ASGR1	RASQSVGSYLA	625	DATNRAT	644	CQHRRTF	679
020S-A05	ASGR2	RASQSVGSYLA	625	DASNRAT	643	CQQRSNWPLTF	685
020S-C05	ASGR2	RASQSVSSYLA	626	DASNRAT	643	CQQRSNWPVTF	686
020S-G06	ASGR2	RSSQSLLHSDGHNYLQ	630	LGSYRAS	651	CMQATHWPPTF	670
020S-A06	ASGR2	RASQNIYTYLN	618	AASSLQS	638	CQQYYNYPITF	692
020S-B06	ASGR2	RASQGISSWLA	617	AASSLQS	638	CQQAYDFPLTF	682
020S-C06	ASGR2	RASQSISSWLA	623	AATTLQS	640	CQQSYSTPLTF	688
020S-D06	ASGR2	RASQGIATWLA	616	DASNLQS	641	CQQANSFPVTF	681
020S-C07	ASGR2	RASQSISRYLN	622	DASNLRS	642	CQQGYTIPITF	684
028S-H09	ASGR2	RASQSISSYLN	624	QASNKDT	655	CQQGYSTPLTF	683
028S-C11	ASGR2	RASQSINNYLN	619	AASSLQS	638	CQQANSFPLTF	680
028S-D11	ASGR2	RSSQSLLHSNGYNYLD	631	AASNLQS	636	CMQALQTPLTF	669
028S-G11	ASGR2	RASQSISNWLA	620	AASRLQS	637	CQQTYAIPLTF	689

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020S-H05	ASGR2						
Abv-3D11	ASGR2	KSSQSLLDSDGKTYLN	611	LVSKLDS	652	WQGTHFPYT	696
Abv-10B8	ASGR2	SASSSVSSSFLH	634	RTSNLAS	658	QQWSGYPYT	695
RO-01	ASGR1	QGDSLRSYYAS	613	GKNNRPS	648	NSLERIGYLSYV	694
RO-02	ASGR1	QGDSLRSYYAS	613	GKNNRPS	648	CNSRLRSGKMVVF	673
RO-03	ASGR1	QGDSLRSYYAS	613	GKNNRPS	648	CNSRKSSSKNVVF	672
RO-04	ASGR1	QGDSLRSYYAS	613	GRNNRPS	649	CNSRDRRGYSVF	671
LP1-1F8	ASGR1	KSSQSLFNSRTRKNYLA	610	WASTRES	661	CKQSYYLLTF	663
LP1-1N15	ASGR1	KASQDINSHLS	606	RANRLVD	657	CLQYDEFPFTF	667
LP1-1P13	ASGR1	RTSENIYSNLA	632	AATNLAD	639	CQHFWGSTWTF	674
LP1-1P5	ASGR1	KASQNVGTNVA	609	SASYRYS	659	CQQYNSYPLTF	691
LP1-2E12	ASGR1	RSSQSLANSYGNTYLS	629	GISNRFS	647	CLQGTHQPLTF	665
LP1-2I13	ASGR1	RASENIYSYLV	615	NAKTLAE	653	CQHHYGTWTF	678
LP1-2I22	ASGR1	RASENIYSNLA	614	GATNLAD	646	CQHFWGTTWTF	676
LP1-3A24	ASGR1	KASQNVGSNVA	608	SSSYRYS	660	CQQYNSFPLTF	690
LP1-3E20	ASGR1	KASQDINSYLS	607	RANRLVD	657	CLQYDDLWTF	666
LP1-6H3	ASGR1	KSSQSLLDSDGKTYLN	612	LVSKLDS	652	CWQGTHFPHTF	693
LP1-7B13	ASGR1	RASQSISNYLH	621	FASQSIS	645	CQQSNSWPLTF	687
LP1-7I20	ASGR1	RTSENIYSYLA	633	NAKTLAK	654	CQHHYGTPYTF	677
LP1-8M24	ASGR1	RISENIYSNLA	627	AAINLAD	635	CQHFWGTPFTF	675
LP1-9C3	ASGR1	RSSQSLANSYGNTYLS	629	GISNRFS	647	CLQATHQPWTF	664
LP1-9M16	ASGR1	KASQDINSYLS	607	RANRLAD	656	CLQYDEFPLTF	668
LP1-10C22	ASGR1	RSSQGIVHSNGNIYLE	628	KVSNRFS	650	CFQGSHVPPTF	662

[0172] 表3B.序列标识符的描述(ASGR靶向模块)

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[0173]

SID NO:	简要描述	序列
47	024S-D03 VL	EIVLTQSPATLSFSPGERATLSCRASQSVGSYLAWYQQRPGQAPRPLIY DATNRATGIPTRFSGSGSGTDFTLTISSLEPEDFATYY CQHRRTFGRGTKLEIK
48	024S-D03 VH	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWMRQSPSRGL EWLGRTYYRSKWYNDYAVSVKSRMTINPDTSRNQF SLQLNSVTLEDTAVYYCARWNHEEHYFDYWGQGTLVTVSS
49	024S-E03 VL	DVVMTQSPATLSFSPGERATLSCRASQSVGSYLAWYQQRPGQAPRPLI YDATNRATGIPTRFSGSGSGTDFTLTISSLEPEDFAT YYCQHRRTFGRGTKLEIK
50	024S-E03 VH	QVQLQQSGPGLVKPSQTLSLTCAISGASVSSNSAAWNWIRQSPSRGLE WLGRTYYRSKWYNDYAVSVKSRITINPDTSKN QFSLQLNSVTPGDTAVYYCARWNHEEHYFDYWGQGTLVTVSS
51	024S-A04 VL	DIQLTQSPATLSFSPGERATLSCRASQSVGSYLAWYQQRPGQAPRPLIY DATNRATGIPTRFSGSGSGTDFTLTISSLEPEDF ATYYCQHRRTFGRGTKLEIK
52	024S-A04 VH	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSVAWNWMRQSPSRGL EWLGRTYYRSKWYYDYAVSVKSRITINPDTSKN QFSLQLNSVTPEDTAVYYCASWTRGAFDIWGQGTMVTVSS
53	020S-A05 VL	EIVMTQSPATLSLSPGERATLSCRASQSVGSYLAWYQQKPGLAPRLLIY DASNRATGIPARFSGSGSGTDFTLTISSLEPEDF AVYYCQQRSNWPLTFGGGTKVEIK
54	020S-A05 VH	EVQLVESGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEW MGGIIPIFGTANYAQKFQGRVTITADESTSTAYM ELSSLRSEDTAVYYCAVSDGYDLDYWGQGTLVTVSS
55	020S-C05 VL	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIH DASNRATGIPARFSGSGSGTDFTLIISSLEPEDF AVYYCQQRSNWPVTFGGGTKVEIK
56	020S-C05 VH	EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEW MGGIIPIFGTANYAQKFQGRVTITADESTSTAYM ELSSLRSEDTAVYYCASFGVGAPDYWGQGTLVTVSS
57	020S-G06 VL	DVVMTQSPLSLPVTPGEPASISCRSSQSLLHSDGHNYLQWYLQKPGQS PQLLILLGSYRASGVPDRFSGSGSGTDFTLKISR VEAEDVGVYYCMQATHWPPTFGQGTKVEIK
58	020S-G06 VH	EVQLVQSGAEVKKPGATVKVSCKASGYTFTSYGISWVRQAPGQGLE WMGWISAYNGNTNYAQKLQGRVTMTTDTSTSTAY MELRSLRSDDTAVYYCASAGGGYWGQGTLVTVSS
59	020S-A06 VL	DIQMTQSPSSLSASVGDRVTITCRASQNIYTYLNWYQQKPGKAPKLLI YAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQYYNYPITFGQGTRLEIK
60	020S-A06 VH	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTGYHMHWVRQAPGQGL EWVGGIIPVFGAPNYAQKFQGRVTITADESTSTA YMELSSLRSEDTAVYYCARDGGYGMDVWGQGTMVTVSS
61	020S-B06 VL	DIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLI YAASSLQSGVPSRFSGSGSGTDFTLTISSLQPED FATYYCQQAYDFPLTFGGGTKVEIK
62	020S-B06 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGL EWMGIINPSGGGTSYAQKFQGRVTMTRDTSTSTV

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[0174]

		YMELSSLRSEDTAVYYCARDTGATAEYFQHWGQGTLVTVSS
63	020S-C06 VL	DIQMTQSPSSLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIY AATTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSTPLTFGQGTKLEIK
64	020S-C06 VH	QVQLVQSGAEVKKPGSSVKVSCKASGYSFTGNYMHWVRQAPGQGL EWMGGIIPMFGTVKYAQKFQGRVTITADESTSTAYM ELSSLRSEDTAVYYCAKDRGYRFDFDLWGRGTLVTVSS
65	020S-D06 VL	DIQMTQSPSSLSASVGDRVTITCRASQGIATWLAWYQQKPGKAPKLLI YDASNLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQANSFPVTFGPGTKVDIK
66	020S-D06 VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEW VSYISSYNSHTNDADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARWAVAAGGQYYYMDVWGKGTTVTVSS
67	020S-C07 VL	DIQMTQSPSSLSASVGDRVTITCRASQSISRYLNWYQQKPGKAPKLLIY DASNLRSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQGYTIPITFGQGTKVEIK
68	020S-C07 VH	QVQLVQSGAEVKKTGASVKVSCKASGYTFSNYYMHWVRQAPGQGL EWMGWINPKSGGTKYAQKFQGRVTMTRDTSTSTVY MELSSLRSEDTAVYYCARDRGITMVRGVMDYWGQGTLVTVSS
69	028S-H09 VL	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIY QASNKDTGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQGYSTPLTFGGGTKVEIK
70	028S-H09 VH	QVQLVQSGAEVKKPGATVKVSCKASGYTFTTYYMHWVRQAPGQGL EWMGWINPNGGGTNYAQKFQGRVTMTRDTSTSTVYM ELSSLRSEDTAVYYCAKDRTAMAPEGAFDIWGQGTMVTVSS
71	028S-C11 VL	DIQMTQSPSSLSASVGDRVTITCRASQSINNYLNWYQQKPGKAPKLLI YAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATY YCQQANSFPLTFGGGTKVEIK
72	028S-C11 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFSDYYVHWVRQAPGQGL EWMGIINPRNGRTSYAQRFQGRVTMTRDTSTSTVYME LSSLRSEDTAVYYCARDHLYGMDVWGQGTTVTVSS
73	028S-D11 VL	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQS PQLLIYAASNLQSGVPDRFSGSGSGTDFTLKISRVEAE DVGVYYCMQALQTPLTFGGGTKVEIK
74	028S-D11 VH	EVQLLESGGGLVQPGGSLRLSCAASGFTVSSNYMSWVRQAPGKGLE WVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQM NSLRAEDTAVYYCAKDSPIVRRGERGRYYGMDVWGQGTTVTVSS
75	028S-G11 VL	DIQMTQSPSSLSASVGDRVTITCRASQSISNWLAWYQQKPGKAPKLLI YAASRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATY YCQQTYAIPLTFGGGTKVEIK
76	028S-G11 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYNMHWVRQAPGQGL EWMGWMNPNTGNTAYAQKFQGRVTMTRDTSTSTVYM ELSSLRSEDTAVYYCARDKNYYGMDVWGQGTTVTVSS
77	020S-H05 nAb	EVQLVESGGGLVQAGDSLRLSCTASGHTFSSYAMGWFRQAPGKEREF VAAISQSGYVRYYADSVKGRFTISRDNAKNTVYLQMN SLKPDDTAVYYCNARWGAGSLFASWGQGTQVTVSS
151	Abv-3D11 VL	EVVMTQTPLTLSVTIGQPASISCKSSQSLLDSDGKTYLNWLLQRPGQSP KRLIYLVSKLDSGVPDRFTGSGSGTDFTLKISRVEAEDL GVYYCWQGTHFPYTFGGGTKLEIK
152	Abv-3D11 VH	EVQLVESGGGLVQPKGSLKLSCAASGFSFNTYAMNWVRQAPGKGLE WVARIRSKSNNYATYYADSVKDRFTISRDDSESMLYL

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[0175]

		QMNNLKTEDTAMYYCVRPRYDYWYFDVWGTGTTVTVSS
153	Abv-10B8 VL	ENVLTQSPAIMAASLGQKVTMTCSASSSVSSSFLHWYQQKSGASPKPL IHRTSNLASGVPARFSGSGSGTSYSLTISSVEAED DATYYCQQWSGYPYTFGGGTKLEIK
154	Abv-10B8 VH	DVKLVESGEGLVKPGGSLKLSCAASGFTFSSYAMSWVRQTPEKRLEW VAYISSGGDYIYYVDTVKGRFTISRDNARNTLYL QMSSLKSEDTAVYYCTREGTGGMDYWGQGTSVTVSS
171	RO-01v VL	DIELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIY GKNNRPSGIPDRFSGSSSGNTASLTITGAQAE DEADYYCNSLERIGYLSYVFGGGTKLTVL
172	RO-01 VL	SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIY GKNNRPSGIPDRFSGSSSGNTASLTITGAQAEDE ADYYCNSLERIGYLSYVFGGGTKLTVL
173	RO-01 VH	EVQLLESGGGLVQPGGSLRLSCAAASGFTFSSYAMSWVRQAPGKGLEW VSAISGSGGSTYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCAKDFSSRRWYLEYWGQGTLVTVSS
174	RO-02 VL	SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIY GKNNRPSGIPDRFSGSSSGNTASLTITGAQAE DEADYYCNSRLRSGKMVVFGGGTKLTVL
175	RO-02 VH	EVQLLESGGGLVQPGGSLRLSCAAASGFTFSSYAMSWVRQAPGKGLEW VSAISGSGGSTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAKSWYLPGRGFDYWGQGTLVTVSS
176	RO-03 VL	SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIY GKNNRPSGIPDRFSGSSSGNTASLTITGAQAE DEADYYCNSRKSSSKNVVFGGGTKLTVL
177	RO-03 VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEW VSAISGSGGSTYYADSVKGRFTISRDNSKNT LYLQMNSLRAEDTAVYYCAKSSFTFGRYFDYWGQGTLVTVSS
178	RO-04 VL	SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIY GRNNRPSGIPDRFSGSSSGNTASLTITGAQAE DEADYYCNSRDRRGYSVFGGGTKLTVL
179	RO-04 VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEW VSAISGSGGSTYYADSVKGRFTISRDNSKNTL YLQMNSLRAEDTAVYYCAKSSFSYLRAFDYWGQGTLVTVSS
274	LP1-1F8 VL	DIVMSQSPSSLAVSAGEKVTMSCKSSQSLFNSRTRKNYLAWYQQKPG QSPKLLIYWASTRESGVPDRFTGSGSGTDFTLTI SSVQAEDLAVYYCKQSYYLLTFGAGTKLELK
275	LP1-1F8 VH	EVKLVESGGGLVKPGGSLKLSCAASGFTFSTYTMSWVRQTPAKRLEW VATISSIGVNTYYPDSVKGRFTISRDNARNTLYL QVSSLRSEDTAMYYCARHVDYYDGISFDYWGQGTTLTVSS
276	LP1-1N15 VL	DIKMTQSPSSMYASLGERVTITCKASQDINSHLSWFQQKPGKSPKTLII RANRLVDGVPSRFSGSGSGQDYSLTISSPEYEEM GIYYCLQYDEFPFTFGGGTKLEIK
277	LP1-1N15 VH	EVQLQQSGPELVKPGASVKMSCKASGYTFTDYYMNWVKQSHGESLE WIGRVIPSNGGTNYNQKFKGKATLTVDKSLTTA YMQLNSLTSEDSAVYFCARGMDYWGPGTSVTVSS
278	LP1-1P13 VL	DIQMTQSPASLSASVGQTVIITCRTSENIYSNLAWYQQKQGKSPQLLVY AATNLADGVPSRFSGSGSGTQYYLKINSLQSED FGSYYCQHFWGSTWTFGGGTKLDIK
279	LP1-1P13 VH	EVQLQQSGPELVKPGASVKISCKASGYSFTDYFMNWVKQSHGKSLE WIGRFNPFNGQTFYNQEFKGKATLTVDKSSSTAH

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[0176]

		MELRSLTSEDSAVYYCARRGRYDVYYVLDYWGQGTSVTVSS
280	LP1-1P5 VL	DIVMTQSQKFMSTSVGDRVSVTCKASQNVGTNVAWYQQKPGQSPKA LIYSASYRYSGVPDRFTGSGSGTDFTLTISNVQSE DLAEYFCQQYNSYPLTFGAGTKLELK
281	LP1-1P5 VH	QVQLQQSGPELVRPGTSVKISCKASGYTFLTYWMNWVKQRPGQGLE WIGQIFPATGITYYSEMFKDKATLTEDTSSTTAY MQLSSLTSEATAVYFCARRRAYHSNFFDYWGQGTTLTVSS
282	LP1-2E12 VL	DVVVTQTPLSLPVSFGDRVSISCRSSQSLANSYGNTYLSWYLHKPGQS PQLLIYGISNRFSGVPDRFSGSGSGTDFTLKISTIKP EDLGMYYCLQGTHQPLTFGAGTKLELK
283	LP1-2E12 VH	DVQLQESGPGLVKPSQSLSLTCSVTGYSITSGYYWNWIRQFPGNKLE WMGSIGYDDTNHYNPSLKNRISITRDTSKNQFFLK LNSVTTEDTATYYCAGDYPFAFWGQGTLVTVSA
284	LP1-2I13 VL	DIQMTQSPASLSASVGETVTITCRASENIYSYLVWYQQKQGKSPQLLV YNAKTLAEGVPSRFSGSGSGTQFSLKINSLQPED FGSYYCQHHYGTWTFGGGIKLEIK
285	LP1-2I13 VH	EVQLVESGGGLVKPGGSRKLSCAASGFTFSDYGMHWVRQAPEKGLE WVAYISSGSSTIYYADTVKGRFTISRDNAKNTL FLQMTSLRSEDTAMYYCSRKGGFGDYEKSYAMDYWGQGTSVTVSS
286	LP1-2I22 VL	DIQMTQSPASLSASVGETVTITCRASENIYSNLAWYQQKQGKSPQLLV YGATNLADGVTSRFSGSGSGTQFSLKIDSLQSE DFGSYYCQHFWGTTWTFGGGTKLEIK
287	LP1-2I22 VH	EVQLQQSGPELVKPGASVKISCKASGYSFTGYFMNWVKQSHGKSLE WIGRFNPFNGQTFYNQEFKGKATLTVDKSSDTAH MELRSLTSEDSAVYYCARRGRYDVYYALDYWGQGTSVTVSS
288	LP1-3A24 VL	DIVMTQSQKFMSTSVGDRVSVTCKASQNVGSNVAWFQQKPGQSPKA LIYSSSYRYSGVPDRFTGSGSGTDFTLTITNVQSE DLAEYFCQQYNSFPLTFGAGTKLELK
289	LP1-3A24 VH	EVQLQQSGPELVKPGASVKMSCKASGYTFTDYYINWVRQSHGKSLE WIGRVIPSNGGSNYNQKFKGKATLTVDKSLSTAY MHLNSLTSEDSAVYYCATQLGRWGQGTLVTVSA
290	LP1-3E20 VL	DIKMTQSPSSMYASLGERVTITCKASQDINSYLSWFQQKPGKSPKTLIY RANRLVDGVPSRFSGSGSGQDYSLTISSLEYEDM GIYYCLQYDDLWTFGGGTKLEIK
291	LP1-3E20 VH	QVQLQQSGAELAKPGASVKMSCKASGYTFTSYWIHWVKQRPGQGLE WIGYINPSSGYAEYNQKFKVRATLTADKSSSTAY MQLSSLTSEDSAVYYCARESYYSFDYTMDYWGQGTSVTVSS
292	LP1-6H3 VL	DVVMTQTPLTLSVTIGQPASISCKSSQSLLDSDGKTYLNWLLQRPGQS PKRLIYLVSKLDSGVPDRFTGSGSGTDFTLKISRV EAEDLGVYYCWQGTHFPHTFGSGTKLEIK
293	LP1-6H3 VH	QAYLQQSGAELVRPGASVKMSCKASGYTFSRFDMHWVKQTPRQGLE WIGVIYPGNGDTSYNQKFRDKASLTVDKSSSTAY MQLSSLTSEDSAVYFCASSYYGNPWGQGTTLTVSS
294	LP1-7B13 VL	DIVLTQSPATLSVTPGDRVSLSCRASQSISNYLHWYQQKSHESPRLLIKF ASQSISGIPSRFSGSGSGTDFTLTINSVETEDFG MYFCQQSNSWPLTFGAGTKLELK
295	LP1-7B13 VH	EVQLQQSGPEVVKPGASVKMSCKTSGFTFTDYYMNWVKQGHGKSL EWIGRVNPSNDDTRYNQKFKGKATLTVDKSLST AYMQLNSLTSEDSAVYYCTRWFYFDYWGQGTTLTVSS
296	LP1-7I20 VL	DIQMTQSPASLSASVGETVTITCRTSENIYSYLAWYQQKQGKSPQLLV YNAKTLAKGVPSRFSGSGSGTQFSLKINGLQPED

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		FGNYYCQHHYGTPYTFGGGTKVEIK
297	LP1-7I20 VH	EVKLVESGGGLVQPGGSLSLSCAASGFTFTDYYMSWVRQPPGKALE WLALIRNKANGYTTEYSASVKGRFTISRDNSQSIL YLQMNALRAEDSATYYCAVTYGAYWGQGTLVTVSA
298	LP1-8M24 VL	DIQMTQSPASLSVSVGETVTITCRISENIYSNLAWYQQKQGKSPHLLVY AAINLADGVPSRFSGSGSGTQF SLKINSLQSEDFGSYYCQHFWGTPFTFGSGTKLEIK
299	LP1-8M24 VH	QVQLQQSGAELARPGASVKLSCKASGYTFTNYGINWVKQRTGQGLE WIGEIFPRSDNTFYNEKFKGKATLTADKS STTAYMELRSLTSEDSAVYFCARKGRDYGTSHYFDYWGQGTTLTVSS
300	LP1-9C3 VL	DVVVTQTPLSLPVSFGDQVSISCRSSQSLANSYGNTYLSWYLHKPGQS PQLLIYGISNRFSGVPDRFSGSGSGTDFTL KISTIKPEDLGIYYCLQATHQPWTFGGGTKLEIK
301	LP1-9C3 VH	QVTLKESGPGILQPSQTLSLTCSFSGFSLSTSYMGVSWIRKPSGKGLEW LAHIFWDDDKRYNPSLKSRLTISKDTSSN QVFLMITSVETADTATYYCGGPYYPFTYWGQGTLVTVSA
302	LP1-9M16 VL	DIKMTQSPSSMYASLGERVTITCKASQDINSYLSWFQQKPGKSPKTLIY RANRLADGVPSRFSGSGSGQDYSLTISNL EYEDMGIYYCLQYDEFPLTFGAGTKLELK
303	LP1-9M16 VH	EVQLQQSGPELVKPGASVKMSCKASGYTFTDYYMNWVKQSHGKSLE WIGRVNPNNGGSNYNQKFKGKATLTVDK SLSTAYMQLNSLTSEDSAVYYCASRNFDVWGAGTTVTVSS
304	LP1-10C22 VL	DVLMTQTPLSLPVSLGDQASISCRSSQGIVHSNGNIYLEWYLQKPGQS PKLLIYKVSNRFSGVPDRFSGSGSGTDFTLK ISRVEAEDLGVYYCFQGSHVPPTFGGGTKLEIK
305	LP1-10C22 VH	EVQLVESGGDLVKPGGSLKLSCAASGFTFSSYGMSWVRQTPDKRLEW VASISSGGSYTYYPDSVKGRFTISRDNAQN TLYLQMSSLKSEDTAMYYCVRHEEYGKSGFAYWGQGTLITVSA

[0177]

[0178] 表3C.序列标识符的描述(替代性靶向模块)

SID NO:	简要描述	序列
180	GT-01 (TFR1) VH	QVQLQQSGPELVRPGVSVKISCKGSGYTFTDYAMHWVKQSHAKSLE WIGGISTYFGRTNYNQKFKGRATMTVDKSSSTAYMELARLTSEDSALY YCARGLSGNYVMDYWGQGTSVTVSS
181	GT-01 (TFR1) VL	DIVLFQSPASLAVSLGQRATISCRASESVDDYGNSFMHWYQQKPGQPP KLLIYRASNLESGIPARFSGSGSRTDFTLTINPVEADDVATYYCQQSNE APPTFGGGTKLEIK
182	BA-01 (LYPD3) VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNAWMSWVRQAPGKGLE WVSYISSSGSTIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVY YCAREGLWAFDYWGQGTLVTVTS
183	BA-01 (LYPD3) VL	QSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYVVHWYQQLPGTAPKL LIYDNNKRPSGVPDRFSGSKSGTSASLAISGLASEDEADYYCAAWDD RLNGPVFGGGTKLTVL
184	FR-01 (DSG3) VH	EVQLQQSGTVLARPGASVKMSCKASGYTFASYWIHWVKQRPGQGLE WIGSIYPGNSDTTYNQKFKGKAKLTVVTSASSAYMELSSLTNEDSAVY YCTEPTYYSYDDYYAMDYWGQGTSVTVSS
185	FR-01 (DSG3) VL	EIVLTQSPALMAASPGEKVTITCSVSSSISSSNLHWYQQKSGTSPKPWI YGTSNLASGVPVRFSGSGSGTSYSLTISTMEAEDAATYYCQQWSSYPL

[0179]

		TFGAGTKLELK

[0180]

[0181] 组织特异性Wnt信号增强分子的说明性非限制性实例包含包括以下的融合蛋白:1)包括R-脊椎蛋白弗林蛋白酶结构域1或其变体的第一结构域和包括特异性地结合ASGR1或ASGR2的抗体或其片段的第二结构域;2)包括R-脊椎蛋白弗林蛋白酶结构域1或其变体的第一结构域和包括特异性地结合SLC10A1的抗体或其片段的第二结构域;3)包括R-脊椎蛋

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白弗林蛋白酶结构域1或其变体的第一结构域和包括特异性地结合TFR2的抗体或其片段的第二结构域;4)包括R-脊椎蛋白弗林蛋白酶结构域1或其变体的第一结构域和包括特异性地结合PTH1R的配体衍生物、抗体或其片段的第二结构域;5)包括R-脊椎蛋白弗林蛋白酶结构域1或其变体的第一结构域和包括特异性地结合LYPD3的配体衍生物、抗体或其片段的第二结构域;6)包括R-脊椎蛋白弗林蛋白酶结构域1或其变体的第一结构域和包括特异性地结合DSG3的配体衍生物、抗体或其片段的第二结构域;以及7)包括R-脊椎蛋白弗林蛋白酶结构域1或其变体的第一结构域和包括特异性地结合TFR1的配体衍生物、抗体或其片段的第二结构域。组织特异性Wnt信号增强分子的另外的说明性非限制性实例包含包括以下的融合蛋白:1)包括特异性地结合ZNRF3和/或RNF43的抗体或其片段的第一结构域和包括特异性地结合ASGR1或ASGR2的抗体或其片段的第二结构域;2)包括特异性地结合ZNRF3和/或RNF43的抗体或其片段的第一结构域和包括特异性地结合SLC10A1的抗体或其片段的第二结构域;3)包括特异性地结合ZNRF3和/或RNF43的抗体或其片段的第一结构域和包括特异性地结合TFR2的抗体或其片段的第二结构域;4)包括特异性地结合ZNRF3和/或RNF43的抗体或其片段的第一结构域和包括特异性地结合PTH1R的配体衍生物、抗体或其片段的第二结构域;5)包括特异性地结合ZNRF3和/或RNF43的抗体或其片段的第一结构域和包括特异性地结合LYPD3的配体衍生物、抗体或其片段的第二结构域;6)包括特异性地结合ZNRF3和/或RNF43的抗体或其片段的第一结构域和包括特异性地结合DSG3的配体衍生物、抗体或其片段的第二结构域;以及7)包括特异性地结合ZNRF3和/或RNF43的抗体或其片段的第一结构域和包括特异性地结合TFR1的配体衍生物、抗体或其片段的第二结构域。在特定实施例中,第一结构域包括包含表2中所示的重链或轻链CDR序列的集合中的任何重链或轻链CDR序列的抗体,和/或第二结构域包括包含表3中所示的重链或轻链CDR序列的组中的任何重链或轻链CDR序列的抗体。在特定实施例中,所述两个结构域通过接头例如多肽接头连接。在某些实施例中,接头是白蛋白,例如人血清白蛋白,其中靶向模块和作用模块处于白蛋白的N端和C端。在特定实施例中,组织特异性Wnt信号增强分子具有包括抗体重链和抗体轻链(或任一条链或两条链的片段或其变体)的附加抗体(例如,IgG)格式,其中一条链或两条链进一步包括一个或多个另外的结合结构域。在特定实施例中,组织特异性Wnt信号增强分子具有附加抗体(例如,IgG)格式,其中第二结构域包括抗体重链和抗体轻链(或任一条链或两条链的片段或其变体),并且其中包括R-脊椎蛋白弗林蛋白酶结构域1或变体的第一结构域例如在任一条链或两条链的N端和/或C端处附加到抗体重链和/或轻链中的一条链或两条链。在特定实施例中,第一结构域例如在N端或C端处附加或融合到重链。在特定实施例中,第一结构域例如在N端或C端处附加或融合到轻链。

[0182] 接头

[0183] 在某些实施例中,靶向模块和作用模块彼此直接结合或融合,而在其它实施例中,靶向模块和作用模块通过接头例如多肽接头或非肽基接头等分离。在特定实施例中,接头是Fc接头,例如能够与另一个Fc接头例如经由一个或多个二硫键二聚化的抗体Fc结构域的区域。在另一个特定实施例中,接头是白蛋白,例如人血清白蛋白,其中靶向模块和作用模块处于白蛋白的N端和C端。

[0184] 在某些实施例中,特别是当连接两个多肽时,接头由通过肽键连接在一起的氨基酸构成。在特定实施例中,接头的长度包括1个直到约40个氨基酸残基、1个直到约20个氨基

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酸残基或1个到约10个氨基酸残基。在某些实施例中，接头中的氨基酸残基来自这二十个经典氨基酸，并且在某些实施例中，选自半胱氨酸、甘氨酸、丙氨酸、脯氨酸、天冬酰胺、谷氨酰胺和/或丝氨酸。在某些实施例中，接头包括一个或多个非天然氨基酸。在一些实施例中，肽基接头由无空间位阻的大多数氨基酸构成，如通过肽键连接的甘氨酸、丝氨酸和丙氨酸。某些接头包含聚甘氨酸、聚丝氨酸和聚丙氨酸或这些氨基酸中的任何氨基酸的组合。一些示例性肽基接头是poly(Gly)1-8、尤其是(Gly)3、(Gly)4(SEQ ID NO:698)、(Gly)5(SEQ ID NO:699)和(Gly)7(SEQ ID NO:700)以及poly(Gly)4Ser(SEQ ID NO:701)、poly(Gly-Ala)2-4和poly(Ala)1-8。肽基接头的其它具体实例包含(Gly)5Lys(SEQ ID NO:702)和(Gly)5LysArg(SEQ ID NO:703)。为了解释以上命名法，例如(Gly)3Lys(Gly)4(SEQ ID NO:704)意指Gly-Gly-Gly-Lys-Gly-Gly-Gly-Gly(SEQ ID NO:704)。Gly和Ala的其它组合也是有用的。另外，肽基接头还可以包括非肽基区段，如式--CH2--CH2--CH2--CH2--CH2--CH2--的6碳脂肪族分子。可以改变肽基接头以形成如本文所描述的衍生物。

[0185] 说明性非肽基接头包含例如烷基接头，如--NH--(CH2)s--C(O)--，其中s＝2-20。这些烷基接头可以进一步被任何无空间位阻的基团取代，如低级烷基(例如，C1-C6)、低级酰基、卤素(例如，Cl、Br)、CN、NH2、苯基等。可以通过常规有机化学反应合成本发明的物质组合物的非肽部分，如非肽基接头或非肽半衰期延伸部分。如本领域中已知的，可用于连接结合结构域的化学基团包含：氨基甲酸酯；酰胺(胺加羧酸)；酯(醇加羧酸)、硫醚(卤代烷加巯基；马来酰亚胺加巯基)、席夫碱(Schiff's base)(胺加醛)、尿素(胺加异氰酸酯)、硫脲(胺加异硫氰酸酯)、磺胺(胺加磺酰氯)、二硫化物；脲、脂质等。

[0186] 结构域之间的连接可以包括间隔基(spacer)，例如烷基间隔基，所述间隔基可以是直链的或支链的，通常是直链的，并且可以包含一个或多个不饱和键；通常具有一个到约300个碳原子；更通常具有约一个到25个碳原子；并且可以是约三个到12个碳原子。这种类型的间隔基还可以包括杂原子或官能团，包含胺、醚、磷酸二酯等。关注的具体结构包含：$(CH_2CH_2O)n$，其中n为1到约12；$(CH_2CH_2NH)n$，其中n为1到约12；$[(CH_2)n(C=O)NH(CH_2)_m]_z$，其中n和m为1到约6，并且z为1到约10；$[(CH_2)nOPO_3(CH_2)_m]_z$，其中n和m为1到约6，并且z为1到约10。这种接头可以包含聚乙二醇，聚乙二醇可以是直链的或支链的。

[0187] 在某些实施例中，结构域可以通过同双功能或异双功能接头连接。说明性实体包含：叠氮基苯甲酰基酰肼、N-[4-(对-叠氮基水杨基氨基)丁基]-3'-[2'-吡啶基二硫]丙酰胺)、双-磺基琥珀酰亚胺基辛二酸酯、二亚胺代己二酸二甲酯(dimethyladipimidate)、二琥珀酰亚胺基酒石酸酯(disuccinimidyltartrate)、N-γ-马来酰亚胺基丁酰基氧琥珀酰亚胺酯(N-γmaleimidobutyryloxysuccinimide ester)、N-羟基磺基琥珀酰亚胺基-4-叠氮基苯甲酸酯、N-琥珀酰亚胺基[4-叠氮基苯基]-1,3'-二硫代丙酸酯、N-琥珀酰亚胺基[4-碘代乙酰基]氨基苯甲酸酯、戊二醛、NHS-PEG-MAL；琥珀酰亚胺基4-[N-马来酰亚胺甲基]环己烷-1-甲酸酯；3-(2-吡啶基二硫)丙酸N-羟基琥珀酰亚胺酯(SPDP)；N,N'-(1,3-亚苯基)双马来酰亚胺；N,N'-乙烯-双-(碘代乙酰胺)；或4-(N-马来酰亚胺甲基)-环己烷-1-羧酸N-羟基琥珀酰亚胺酯(SMCC)；间马来酰亚胺基苯甲酰基-N-羟基琥珀酰亚胺酯(MBS)；以及MBS的延伸链类似物琥珀酰亚胺4-(对马来酰亚胺苯基)丁酸酯(SMPB)。在某些实施例中，这些交联剂的琥珀酰亚胺基与伯胺反应，并且硫醇反应性马来酰亚胺与半胱氨酸残基的硫醇形成共价键。

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[0188] 有用的其它试剂包含:包含双马来酰亚胺己烷("BMH")的同双功能交联剂;p,p'-二氟代-m,m'-二硝基二苯砜(与氨基和酚基形成不可逆交联);二甲基胺代己二酸酯(针对氨基具有特异性);苯酚-1,4-二磺酰氯(主要与氨基反应);六亚甲基二异氰酸酯或二异硫氰酸酯或偶氮苯基对二异氰酸酯(主要与氨基反应);双重氮联苯胺(主要与酪氨酸和组氨酸反应);邻苯并三唑基四甲基脲六氟磷酸酯(O-benzotriazolyloxy tetramethuluronium hexafluorophosphate)(HATU)、二环己基碳二酰亚胺、溴代-三(吡咯烷基)溴化磷(PyBroP);N,N-二甲氨基吡啶(DMAP);4-吡咯烷基吡啶;N-羟基苯并三唑;等等。

[0189] 抗体和其用途

[0190] 在各种实施例中,本发明提供了抗RNF43、抗ZNRF3和抗ASGR1/2抗体和其抗原结合片段以及相关使用方法。

[0191] 在一个实施例中,本公开提供了一种分离的抗体或其抗原结合片段,所述分离的抗体或其抗原结合片段与RNF43、ZNRF3、ASGR1或ASGR2(任选地人)结合、包括包含以下的序列:(i)针对表2A或3A的抗体中的任何抗体所示的CDRH1、CDRH2和CDRH3序列;和/或(ii)针对表2A或3A的抗体中的任何抗体所示的CDRL1、CDRL2和CDRL3序列,或所述抗体或其抗原结合片段的变体,所述变体包括一个或多个氨基酸修饰,其中所述变体在所述CDR序列中包括少于8个氨基酸取代。在特定实施例中,抗体或其抗原结合片段包括:包括与表2B或表3B中所示的氨基酸序列具有至少90%同一性的氨基酸序列的重链可变区;或包括表2B或表3B中所示的氨基酸序列的重链可变区。在特定实施例中,抗体或其抗原结合片段包括:包括与表2B或表3B中所示的氨基酸序列具有至少90%同一性的氨基酸序列的轻链可变区;或包括表2B或表3B中所示的氨基酸序列的轻链可变区。

[0192] 在特定实施例中,抗体或其抗原结合片段中的任何一种抗体或其抗原结合片段是人源化的。在某些实施例中,抗体或其抗原结合片段中的任何一种抗体或其抗原结合片段是单链抗体、scFv、缺乏铰链区的单价抗体、纳米抗体或微抗体。在特定实施例中,抗体或其抗原结合片段中的任何一种抗体或其抗原结合片段是VHH纳米抗体。在特定实施例中,抗体或其抗原结合片段中的任何一种抗体或其抗原结合片段是Fab或Fab'片段。

[0193] 在某些实施例中,抗体或其抗原结合片段中的任何一种抗体或其抗原结合片段是融合蛋白。

[0194] 在相关实施例中,本公开提供了一种分离的抗体或其抗原结合片段,所述分离的抗体或其抗原结合片段与本文公开的抗体中的任何一种抗体竞争与其靶标ZNRF3、RNF43或ASGR1/2的结合。在特定实施例中,抗体或其抗原结合片段中的任何一种抗体或其抗原结合片段以50μm或更低的KD与其靶标结合。

[0195] 在一个实施例中,本发明包括一种分离的抗体或其抗原结合片段,所述分离的抗体或其抗原结合片段与人ASGR结合并且抑制ASGR与配体的结合。在另一个实施例中,本发明包括一种分离的抗体或其抗原结合片段,所述分离的抗体或其抗原结合片段与人ASGR-1结合并且抑制ASGR-1与配体的结合和/或ASGR-1与ASGR-2的相互作用。在另一个实施例中,本发明包括一种分离的抗体或其抗原结合片段,所述分离的抗体或其抗原结合片段与人ASGR-2结合并且抑制ASGR-2与配体的结合和/或ASGR-2与ASGR-1的相互作用。在又另一个实施例中,本发明包括一种分离的抗体或其抗原结合片段,所述分离的抗体或其抗原结合片段与人ASGR-1和人ASGR-2结合并且抑制ASGR-1和/或ASGR-2与配体的结合。在一些实施

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例中，分离的抗体或其抗原结合片段与人ASGR、ASGR-1和/或ASGR-2特异性地结合。

[0196] 在特定实施例中，抗体或其抗原结合片段中的任何一种抗体或其抗原结合片段调节细胞，任选地哺乳动物细胞中的Wnt信号传导通路。在特定实施例中，抗体或其抗原结合片段中的任何一种抗体或其抗原结合片段增加通过细胞中的Wnt信号传导通路进行的信号传导。在特定实施例中，抗体或其抗原结合片段中的任何一种抗体或其抗原结合片段减少通过细胞中的Wnt信号传导通路进行的信号传导。在某些实施例中，Wnt信号传导通路是典型的Wnt信号传导通路或非典型的Wnt信号传导通路。

[0197] 在另外的相关实施例中，本公开提供了一种对本文公开的抗体或其抗原结合片段进行编码的分离的多核苷酸。在某些实施例中，本公开提供了一种包括分离的多核苷酸的表达载体和包括所述表达载体的分离的宿主细胞。

[0198] 在另一个实施例中，本公开提供了一种药物组合物，所述药物组合物包括生理学上可接受的赋形剂、稀释剂或载体以及治疗有效量的本文公开的分离的抗体或其抗原结合片段。

[0199] 本公开提供了用于检测例如生物样品(例如，细胞或组织)中的ZNRF3、RNF43或ASGR1/2多肽的存在度或表达水平的方法，所述方法包括使所述生物样品与特异性地结合靶多肽的本文公开的抗体或其抗原结合片段接触。在某些实施例中，抗体或其抗原结合片段例如通过荧光标签进行可检测地标记。因此，抗体可以用于对表达抗体靶多肽的细胞进行染色。例如，抗ASGR1/2抗体和其抗原结合片段可以用于对肝细胞进行检测或染色。

[0200] 本文公开的抗体或其抗原结合片段还可以用于向所述抗体或其抗原结合片段所结合的细胞递送药物。例如，可以将抗ASGR1/2抗体和其抗原结合片段缀合到治疗剂以向肝细胞，例如正常或癌症肝细胞递送治疗剂。

[0201] 在另外的实施例中，本公开提供了一种用于激动细胞中的Wnt信号传导通路的方法，所述方法包括使所述细胞与本文公开的增加Wnt信号传导的分离的抗体或其抗原结合片段接触。在另一个实施例中，本公开提供了一种用于抑制细胞中的Wnt信号传导通路的方法，所述方法包括使所述细胞与本文公开的抑制Wnt信号传导的分离的抗体或其抗原结合片段接触。

[0202] 在另一个实施例中，本公开包含一种用于治疗患有与减少的Wnt信号传导相关的疾病或病症的受试者的方法，所述方法包括向所述受试者施用有效量的药物组合物，所述药物组合物包括本文公开的作为Wnt信号传导通路的激动剂的分离的抗体或其抗原结合片段。在特定实施例中，所述疾病或病症是本文所公开的通过组织特异性Wnt信号增强分子治疗的那些疾病或病症中的任何疾病或病症。

[0203] 在一些实施例中，本公开包含一种减少患上冠状动脉疾病或患有MI的风险的方法，所述方法包括向有需要的受试者施用治疗有效剂量的本文公开的抗ASGR抗体或其抗原结合片段。在一些实施例中，抗体结合ASGR-1，并且在一些实施例中，抗体结合ASGR-2。在一些实施例中，抗体是ASGR-1和/或ASGR-2的抑制剂。在一些实施例中，与未经治疗的受试者相比，经过治疗的受试者的冠状动脉疾病或MI的相对风险降低至少约5%、至少约10%、至少约15%、至少约20%、至少约25%、至少约30%、至少约35%、至少约40%、至少约45%、至少约50%、至少约55%、至少约60%。

[0204] 在一些实施例中，本公开提供了一种降低受试者的血液LDL胆固醇水平的方法，所

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述方法包括向有需要的受试者施用治疗有效剂量的本文公开的抗ASGR抗体或其抗原结合片段。在一些实施例中，抗体结合ASGR-1，并且在一些实施例中，抗体结合ASGR-2。在一些实施例中，抗体是ASGR-1和/或ASGR-2的抑制剂。在一些实施例中，经过治疗的受试者的血液LDL胆固醇水平与受试者的给药前血液LDL胆固醇水平相比降低至少约15％。在本发明的此方面的一些实施例中，所述受试者的血液LDL胆固醇水平与受试者的给药前血液LDL胆固醇水平相比降低至少约5％、至少约10％、至少约15％、至少约20％、至少约25％、至少约30％、至少约35％、至少约40％、至少约45％、至少约50％、至少约55％、至少约60％、至少约65％、至少约70％、至少约75％、至少约80％、至少约85％或至少约90％。

[0205] 在一些实施例中，本公开提供了一种降低受试者的非HDL胆固醇水平的方法，所述方法包括向有需要的受试者施用治疗有效剂量的本文公开的抗ASGR抗体或其抗原结合片段。在一些实施例中，抗体结合ASGR-1，并且在一些实施例中，抗体结合ASGR-2。在一些实施例中，抗体是ASGR-1和/或ASGR-2的抑制剂。在一些实施例中，受试者的非HDL胆固醇水平与受试者的给药前非HDL胆固醇水平相比降低至少约5％。在本发明的此方面的一些实施例中，所述患者的非HDL胆固醇水平与患者的给药前非HDL胆固醇水平相比降低至少约10％、至少约15％、至少约20％、至少约25％、至少约30％、至少约35％、至少约40％、至少约45％、至少约50％、至少约55％、至少约60％、至少约65％、至少约70％、至少约75％、至少约80％、至少约85％或至少约90％。

[0206] 在一些实施例中，本公开提供了一种通过抑制ASGR活性来提高患者的ALP水平的方法，所述方法包括向有需要的受试者施用治疗有效剂量的本文公开的抗ASGR抗体或其抗原结合片段。在一些实施例中，抗体结合ASGR-1，并且在一些实施例中，抗体结合ASGR-2。在一些实施例中，抗体是ASGR-1和/或ASGR-2的抑制剂。在一些实施例中，患者的ALP水平与患者的给药前ALP水平相比提高至少约30％。在本发明的此方面的一些实施例中，所述受试者的ALP水平与受试者的给药前ALP水平相比提高至少约35％、至少约40％、至少约45％、至少约50％、至少约55％、至少约60％、至少约65％、至少约70％、至少约75％、至少约80％、至少约85％或至少约90％。在一些实施例中，ALP水平比治疗前提高至少约1.25倍、1.5倍、2倍、2.5倍、3倍、3.5倍、4倍、4.5倍和5倍。

[0207] 在一些实施例中，本公开提供了一种拮抗受试者的ASGR、ASGR-1和/或ASGR-2的方法，所述方法包括向有需要的受试者施用治疗有效剂量的本文公开的抗ASGR抗体或其抗原结合片段。在一些实施例中，抗体结合ASGR-1，并且在一些实施例中，抗体结合ASGR-2。在一些实施例中，抗体是ASGR-1和/或ASGR-2的抑制剂。

[0208] 在一些实施例中，提供了一种治疗或预防心血管疾病的方法，并且所述方法包括向有需要的受试者施用治疗有效剂量的本文公开的抗ASGR抗体或其抗原结合片段。在一些实施例中，抗体结合ASGR-1，并且在一些实施例中，抗体结合ASGR-2。在一些实施例中，抗体是ASGR-1和/或ASGR-2的抑制剂。在一些实施例中，患者的心血管事件的相对风险降低至少约5％、至少约10％、至少约15％、至少约20％、至少约25％、至少约30％、至少约35％、至少约40％、至少约45％、至少约50％、至少约55％、至少约60％。

[0209] Wnt分子、Norrin分子和Wnt信号增强分子

[0210] 本公开进一步涉及Wnt多肽、Norrin多肽和Wnt信号传导激动剂分子以及其用于增加Wnt信号传导和治疗或预防Wnt相关疾病或病症的用途，包含本文所描述的那些疾病或病

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症。在某些实施例中，单独地或与本文所描述的一种或多种组织特异性Wnt信号增强分子组合地向受试者提供Wnt多肽、Norrin多肽和Wnt信号传导激动剂分子。

[0211] Wnt多肽和Wnt编码多核苷酸序列是本领域中已知的并且包含任何和所有Wnt多肽或多核苷酸，包含属于任何和所有物种的那些Wnt多肽或多核苷酸，包含哺乳动物Wnt多肽和多核苷酸，如人Wnt多肽和多核苷酸。说明性Wnt多肽包含Wnt1、Wnt2、Wnt2B、Wnt3、Wnt3A、Wnt4、Wnt5A、Wnt5B、Wnt6、Wnt7A、Wnt7B、Wnt8A、Wnt8B、Wnt9A、Wnt9B、Wnt10A、Wnt10B、Wnt11和Wnt16以及前述Wnt中的任何Wnt的功能性变体和片段。Wnt多肽涵盖天然Wnt多肽、Wnt多肽变体、Wnt多肽片段和嵌合Wnt多肽。在特定实施例中，Wnt多肽是天然人全长成熟Wnt蛋白。

[0212] 例如，本申请中关注的人天然序列Wnt蛋白包含但不限于以下：Wnt1(GenBank登录号NM_005430)；Wnt-2(GenBank登录号NM_003391)；Wnt2B(Wnt-13)(GenBank登录号NM_004185(同种型1)、NM_024494.2(同种型2))、Wnt3(RefSeq.:NM_030753)、Wnt3A(GenBank登录号NM_033131)、Wnt4(GenBank登录号NM_030761)、Wnt5A(GenBank登录号NM_003392)、Wnt5B(GenBank登录号NM_032642)、Wnt6(GenBank登录号NM_006522)、Wnt7A(GenBank登录号NM_004625)、Wnt7B(GenBank登录号NM_058238)、Wnt8A(GenBank登录号NM_058244)、Wnt8B(GenBank登录号NM_003393)、Wnt9A(Wnt-14)(GenBank登录号NM_003395)、Wnt9B(Wnt15)(GenBank登录号NM_003396)、Wnt1 OA(GenBank登录号NM_025216)、Wnt10B(GenBank登录号NM_003394)、Wnt11(GenBank登录号NM_004626)、Wnt16(GenBank登录号NM_016087)。尽管每个成员与家族具有不同程度的序列同一性，但是所有成员均对含有间距高度保守的23-24个保守半胱氨酸残基的较小(即，39-46kD)、酰化、棕榈酰化、分泌的糖蛋白进行编码(McMahon,A P等人，《遗传学趋势(Trends Genet.)》1992;8:236-242;Miller,J R.,《基因组生物学(Genome Biol.)》2002;3(1):3001.1-3001.15)。关注的其它天然序列Wnt多肽包含来自任何哺乳动物的上述直系同源物，所述哺乳动物包含家养和农场动物以及动物园、实验室或宠物动物，如狗、猫、牛、马、绵羊、猪、山羊、兔、大鼠、小鼠、青蛙、斑马鱼、果蝇、蠕虫等。

[0213] Norrin多肽和Norrin编码多核苷酸序列也是本领域中已知的并且包含任何物种的Norrin多肽或多核苷酸以及其功能性变体和片段，包含哺乳动物Norrin多肽和多核苷酸，如人Norrin多肽和多核苷酸。

[0214] Wnt信号传导激动剂分子包含激动Wnt信号传导的任何类型的分子。在特定实施例中，Wnt信号传导激动剂分子描述于PCT专利申请公开第WO 2016/040895号中。Wnt信号传导激动剂可以是任何分子，例如在某些实施例中具有水溶性的蛋白质或药物(例如，有机小分子)，所述分子通过与一种或多种Fzd蛋白和与Lrp5/6结合来直接活化经典Wnt信号传导。在特定实施例中，Wnt信号传导激动剂分子是小分子，所述小分子可以小于约15Kd。在其它实施例中，Wnt信号传导激动剂分子是多肽。另外，某些Wnt信号传导激动剂可以包括多肽区域或结构域和非多肽区域或结构域两者。

[0215] 在本发明的一些实施例中，Wnt信号传导激动剂分子是多肽，所述多肽可以包括Fzd和Lrp5/6的独立的或连续的结合结构域或元件。多肽Wnt信号传导激动剂可以是单链、二聚体或更高阶多聚体。Fzd结合结构域/元件和Lrp5/6结合结构域/元件可以直接连接，或者可以通过接头例如多肽接头或非肽接头等分离。

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[0216] 在多肽实施例中，Fzd结合结构域可以选自以高亲和力结合Fzd的任何结构域，例如KD为至少约1×10-7M、至少约1×10-8M、至少约1×10-9M或至少约1×10-10M。适合的Fzd结合结构域包含但不限于：重新设计的Fzd结合蛋白、抗体衍生的结合蛋白例如scFv、Fab等以及与一种或多种Fzd蛋白特异性地结合的抗体的其它部分；纳米抗体衍生的结合结构域；基于打结素的工程化支架；Norrin和由其衍生的工程化结合片段、天然存在的Fzd结合结构域等等。

[0217] 在一些实施例中，Fzd结合结构域与一种、两种、三种、四种、五种或更多种不同的卷曲蛋白结合，例如人卷曲蛋白Fz1、Fz2、Fz3、Fz4、Fz5、Fz6、Fz7、Fz8、Fz9、Fz10中的一种或多种人卷曲蛋白。在一些实施例中，基于抗体的信号传导激动剂与Fz1、Fz2、Fz5、Fz7和Fz8结合。在其它实施例中，卷曲蛋白结合部分对关注的一种或多种卷曲蛋白具有选择性，例如相对于其它卷曲蛋白，针对所述一种或多种期望的卷曲蛋白具有至少10倍、25倍、50倍、100倍、200倍或更多倍的特异性。

[0218] 在某些实施例中，卷曲蛋白结合结构域包括泛特异性卷曲蛋白抗体OMP-18R5(泛替妥人单抗(vantictumab))的六个CDR区域。在某些实施例中，卷曲蛋白结合结构域是包括泛特异性卷曲蛋白抗体OMP-18R5(泛替妥人单抗)的六个CDR区域的scFv。参见例如通过引用明确并入本文的美国专利第8507442号。例如，OMP-18R5的CDR序列包含：包括GFTFSHYTLS(SEQ ID NO:705)的重链CDR1、包括VISGDGSYTYYADSVKG(SEQ ID NO:706)的重链CDR2和包括NFIKYVFAN(SEQ ID NO:707)的重链CDR3；以及(ii)包括SGDKLGKKYAS(SEQ ID NO:708)或SGDNIGSFYVH(SEQ ID NO:709)的轻链CDR1、包括EKDNRPSG(SEQ ID NO:710)或DKSNRPSG(SEQ ID NO:711)的轻链CDR2和包括SSFAGNSLE(SEQ ID NO:712)或QSYANTLSL(SEQ ID NO:713)的轻链CDR3。在特定实施例中，卷曲蛋白结合结构域是抗体或其衍生物，包含但不限于ScFv、微抗体、纳米抗体和包括OMP-18R5的CDR序列的各种抗体模拟物。在某些实施例中，与OMP-18R5的CDR序列相比，这些CDR序列包括一个或多个氨基酸修饰。

[0219] 在其它实施例中，Fzd结合结构域包括来自多种卷曲蛋白特异性抗体中的任何一种卷曲蛋白特异性抗体的可变区序列或其CDR，所述多种卷曲蛋白特异性抗体是本领域中已知的并且可商购获得或者可以从头生成。卷曲蛋白多肽中的任何一种卷曲蛋白多肽可以用作免疫原或在筛选测定法中用于开发抗体。“Fz”、“Fz蛋白”和“Fz受体”在本文中用于指代卷曲蛋白受体家族的蛋白质。这些蛋白质是包括CRD结构域的七次跨膜蛋白(Ingham，P.W.(1996)《遗传学趋势(Trends Genet.)》12:382-384；Yang-Snyder，J.等人(1996)《当代生物学(Curr.Biol.)》6:1302-1306；Bhanot，P.等人(1996)《自然(Nature)》382:225-230)。Fz家族中有十个已知成员(Fz1到Fz10)，所述十个成员中的任何成员均可以充当Wnt的受体。人卷曲蛋白参考序列的Genbank登录号如下：FZD1(NM_003505)；FZD2(NM_001466)；FZD3(NM_145866)；FZD4(NM_012193)；FZD5(NM_003468)；FZD6(NM_003506)；FZD7(NM_003507)；FZD8(NM_031866)；FZD9(NM_003508)；FZD10(NM_007197)。[0076]卷曲蛋白结合结构域的非限制性实例包含：可从Biolegend公司获得的抗体，例如，对人卷曲蛋白4具有特异性的克隆CH3A4A7(CD344)、对人Fz9具有特异性的克隆W3C4E11(CD349)；可从Abeam公司获得的抗体，例如，对Fz7具有特异性的ab64636、对人Fz4具有特异性的ab83042、对人Fz7具有特异性的ab77379、对人Fz8具有特异性的ab75235、对人Fz9具有特异性的ab102956；等等。适合的抗体的其它实例尤其描述于以下中：美国专利申请20140105917；美国专利申请20130230521；

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美国专利申请20080267955;美国专利申请20080038272;美国专利申请20030044409。

[0220] 替代物的卷曲蛋白结合部分可以是被选择用于与Wnt蛋白的卷曲蛋白结合区域的结构同源的工程化蛋白。这种蛋白质可以通过筛选结构数据库的同源性来鉴别。由此鉴别出初始蛋白,例如微生物Bh1478蛋白。然后,天然蛋白被工程化以提供增加亲和力的氨基酸取代,并且可以通过亲和力成熟进行进一步的选择以便在与期望的卷曲蛋白结合时具有增加的亲和力和选择性。卷曲蛋白结合部分的非限制性实例包含PCT专利申请公开第WO 2016/040895号的图1中展示的Fz27蛋白和Fz27-B12蛋白。

[0221] 在某些多肽实施例中,Lrp5/6结合结构域或元件可以选自以高亲和力结合Lrp5/6的任何结构域,例如K_D为至少约1×10^{-7}M、至少约1×10^{-8}M、至少约1×10^{-9}M、至少约1×10^{-10}M。适合的Lrp5/6结合结构域包含但不限于:重新设计的Lrp5/6结合蛋白、抗体衍生的结合蛋白例如scFv、Fab等和与一种或多种Fzd蛋白特异性地结合的抗体的其它部分;纳米抗体衍生的结合结构域;基于打结素的工程化支架;天然存在的Lrp5/6结合蛋白或多肽,包含但不限于Norrin、DKK1、DKK2、DKK3、DKK4、骨硬化蛋白;等等。在某些实施例中,Lrp5/6结合结构域是DKK1的C端部分。

[0222] Lrp5/6结合结构域可以选自以高亲和力结合Lrp5或Lrp6的任何结构域,例如其中K_D为至少约1×10^{-7}M、至少约1×10^{-8}M、至少约1×10^{-9}M、至少约1×10^{-10}M1。"LRP"、"LRP蛋白"和"LRP受体"在本文中用于指代低密度脂蛋白受体相关蛋白家族的蛋白质。这些受体是在受体介导的内吞作用过程中结合并且内化配体的单次跨膜蛋白。LRP蛋白LRP5(GenBank登录号NM 002335.2)和LRP6(GenBank登录号NM 002336.2)包含在Wnt受体复合物中。

[0223] 适合的Lrp5/6结合结构域包含但不限于:重新设计的Lrp5/6结合蛋白、抗体衍生的结合蛋白例如scFv、Fab等和与一种或多种Fzd蛋白特异性地结合的抗体的其它部分;纳米抗体衍生的结合结构域;基于打结素的工程化支架;天然存在的Lrp5/6,包含但不限于DKK1、DKK2、DKK3、DKK4、骨硬化蛋白;Wise;包括上述中的任何一种的融合蛋白;上述中的任何一种的衍生物;上述中的任何一种的变体;以及上述中的任何一种的生物活性片段;等等。可以亲和选择Lrp5/6结合结构域以增强结合。

[0224] Dickkopf(Dkk)基因家族的成员(参见Krupnik等人(1999)《基因(Gene)》238(2):301-13)包含Dkk-1、Dkk-2、Dkk-3和Dkk-4,并且Dkk-3相关蛋白Soggy(Sgy.)hDkk 1-4含有两个不同的富含半胱氨酸的结构域,其中10个半胱氨酸残基的位置在家族成员之间高度保守。人Dkk基因和蛋白质的示例性序列是可公开获得的,例如Genbank登录号:NM_014419(soggy-1);NM_014420(DKK4);AF177394(DKK-1);AF177395(DKK-2);NM_015881(DKK3);以及NM_014421(DKK2)。在本发明的一些实施例中,Lrp6结合部分是DKK1肽,包含但不限于人DKK1的C端结构域。如图5所示,C端结构域可以包括序列KMYHTKGQEGSVCLRSSDCASGLCCARHFWSKICKPVLKEGQVCTKHRRKGSHGLEIFQRC YCGEGLSCRIQKDHHQASNSSRLHTCQRH(SEQ ID NO:714)(参见Genbank登录号NP_036374)或其生物活性片段。

[0225] 例如在以下中讨论了DKK蛋白与LRP5/6的结合:Brott和Sokol《分子与细胞生物学(Mol.Cell.Biol.)》22(17),6100-6110(2002);以及Li等人《生物化学期刊(J.Biol.Chem.)》277(8),5977-5981(2002),所述文献各自通过引用明确并入本文。人DKK2(Genbank参考NP_055236)的对应区域可以包括序列KMSHIKGHEGDPCLRSSDCIEGFCCARHFWTKICKPVLHQGEVCTKQRKKGSHGLEIFQRCDCAKGLSCKVWKDATYSSKARLHVCQK(SEQ ID NO:715)或其生

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物活性片段。

[0226] 与Lrp5或Lrp6特异性地结合的抗体是本领域中已知的并且可商购获得或者可以重新生成。Lrp5、Lrp6或其片段可以用作免疫原或用于筛选测定中以开发抗体。已知抗体的实例包含但不限于以下中描述的那些:Gong等人(2010)《PLoS One》5(9):e12682;Marvin等人(2010)《美国国家科学院院刊(Proc Natl Acad Sci U S A.)》107(35):15473-8;以及可从例如以下商购的那些:圣克鲁兹生物技术公司(Santa Cruz biotechnology)抗体克隆1A12,所述抗体克隆是针对人类来源的合成LRP5/6培育的并且与小鼠和人类来源的LRP 6和LRP 5的全长和蛋白水解片段两者结合;单克隆抗体2B11;对目录号为5731的LRP5(D80F2)具有特异性的信号传导技术公司(Cell Signaling Technology)抗体;等。

[0227] 多肽和结合结构域还可以包含上述多肽的衍生物、变体和生物活性片段。“变体”多肽意指如下文所限定的与所提供序列具有小于100%的序列同一性的生物活性多肽。这种变体包含:与所提供序列相比包括一个或多个氨基酸修饰例如插入、缺失或取代的多肽,例如,其中在天然序列的N端或C端处或者在天然序列内添加一个或多个氨基酸残基;约一个到四十个氨基酸残基缺失,并且任选地被一个或多个氨基酸残基取代;以及上述多肽的衍生物,其中氨基酸残基已被共价修饰,使得所得产物具有非天然存在的氨基酸。在某些实施例中,生物活性变体将具有与天然序列多肽有至少约90%、至少约95%或至少约99%的氨基酸序列同一性的氨基酸序列。序列的“功能性变体”是与初始序列一样具有定性生物学性质的化合物。“功能性变体”包含但不限于序列片段和序列的变体,前提条件是其共同具有生物学活性。术语“变体”涵盖多肽的氨基酸序列变体和其共价修饰两者。

[0228] Fzd结合结构域和Lrp5/6结合结构域在一个球状结构域内可以是连续的,或者可以通过接头分离,例如多肽接头或非肽接头等,包含但不限于本文所描述的那些接头中的任何接头。接头的长度以及因此结合结构域之间的间距可以用来调节信号强度并且可以根据Wnt信号传导激动剂的期望用途进行选择。结合结构域之间的加强距离可以有所变化,但在某些实施例中可以小于约100埃、小于约90埃、小于约80埃、小于约70埃、小于约60埃或小于约50埃。

[0229] 在一些实施例中,接头是刚性接头,在其它实施例中,接头是柔性接头。在接头是肽接头的情况下,在某些实施例中,接头在长度上可以为约1个、2个、3个、4个、5个、6个、7个、8个、9个、10个、11个、12个、13个、14个、15个、16个、17个、18个、19个、20个、21个、22个、23个、24个、25个、26个、27个、28个、29个、30个或更多个氨基酸,并且具有足够的长度和氨基酸组成来加强结合结构域之间的距离。在一些实施例中,接头包括一个或多个甘氨酸和/或丝氨酸残基或由其组成。

[0230] 本公开还包含对一种或多种Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的多核苷酸或核酸序列以及包括这些多核苷酸的载体以及包括这些载体的细胞,所述载体包含表达载体。在某些实施例中,多核苷酸或核酸序列是DNA或RNA。在特定实施例中,RNA是信使RNA(mRNA)。在某些实施例中,RNA是包括一个或多个经过修饰的核苷的经过修饰的mRNA。包括一个或多个经过修饰的核苷的经过修饰mRNA已经被描述为相比于未经过修饰的mRNA具有优势,所述优势包含稳定性增加、表达水平更高和免疫原性降低。例如,以下中描述了可以根据本发明使用的经过修饰的mRNA的非限制性实例:PCT专利申请公开第WO2011/130624号、第WO2012/138453号、第WO 2013052523号、第WO 2013151666号、第

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WO2013/071047号、第WO2013/078199号、第WO 2012045075号、第WO 2014081507号、第WO 2014093924号、第WO 2014164253号;美国专利申请第US 8,278,036号(描述了包括假尿苷的经过修饰的mRNA)、第US 8,691,966号(描述了包括假尿苷和/或N1-甲基假尿苷的经过修饰的mRNA)、第US 8,835,108号(描述了包括5-甲基胞苷的经过修饰的mRNA)、第US 8,748,089号(描述了包括假尿苷或1-甲基假尿苷的经过修饰的mRNA)。在特定实施例中,与未经过修饰的A、G、U或C核糖核苷相比,对Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的经过修饰的mRNA序列包括至少一个修饰。在特定实施例中,所述至少一个经过修饰的核苷包含N1-甲基假尿苷和/或5-甲基胞苷。在特定实施例中,经过修饰的mRNA包括5'端帽序列、接着是对Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的序列、接着是3'拖尾序列,如polyA或polyA-G序列。

[0231] 在特定实施例中,多核苷酸是载体,例如表达载体,并且表达载体包括对与启动子序列可操作地连接的本文所描述的Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的多核苷酸序列,所述启动子序列例如驱动多核苷酸在细胞中的表达的启动子序列。在某些实施例中,载体是病毒载体,例如包括多核苷酸的病毒,所述多核苷酸包括表达盒,所述表达盒包括与对Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的DNA或RNA序列可操作地连接的启动子。在特定实施例中,表达盒包括5'和/或3'细胞或病毒UTR。

[0232] 本公开还包含本文所描述的多核苷酸的功能性片段和变体,包含与本文所描述的多核苷酸具有至少50%、至少60%、至少70%、至少80%、至少85%、至少90%、至少95%、至少98%或至少99%的多核苷酸序列同一性的变体。与本文所公开的序列中的任何序列相比,这种变体可以包括一个或多个核苷酸或核苷修饰,例如一个或多个核苷酸缺失、插入或取代。在特定实施例中,本文所描述的多核苷酸被密码子优化,例如以增强经过编码的多肽在宿主细胞中的表达。在特定实施例中,多核苷酸变体包括一个或多个经过修饰的核苷酸或核苷。

[0233] 本公开还包含包括对本文所描述的Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的多核苷酸或载体的细胞。在某些实施例中,细胞是宿主细胞,例如可以用于产生Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子的HEK293细胞。在制备主题组合物时,可以采用任何宿主细胞,包含但不限于例如哺乳动物细胞(例如,293细胞)、昆虫细胞(例如,SF9细胞)、微生物和酵母。在某些实施例中,细胞对用本文所描述的Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子治疗的受试者而言是异源或自体的。在特定实施例中,细胞从受试者获得并且用本文所描述的病毒载体进行转导。在特定实施例中,经过转导的细胞被递送到受试者以用于治疗。本公开还包含包括一种或多种Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子或者一种或多种多核苷酸或载体的药物组合物,所述一种或多种多核苷酸或载体包括对Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的序列。

[0234] 药物组合物

[0235] 还公开了包括本文所描述的组织特异性Wnt信号增强分子或抗体或其抗原结合片段和一种或多种药学上可接受的稀释剂、载体或赋形剂的药物组合物。在特定实施例中,药物组合物进一步包括本文所描述的一种或多种Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子。

[0236] 在另外的实施例中,还公开了包括多核苷酸和一种或多种药学上可接受的稀释

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剂、载体或赋形剂的药物组合物，所述多核苷酸包括对本文所描述的本文所描述的组织特异性Wnt信号增强分子或抗体或其抗原结合片段进行编码的核酸序列。在特定实施例中，药物组合物进一步包括一种或多种多核苷酸，所述一种或多种多核苷酸包括对本文所描述的Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的核酸序列。在某些实施例中，多核苷酸是DNA或mRNA，例如经修饰的mRNA。在特定实施例中，多核苷酸是进一步包括5'帽序列和/或3'拖尾序列(例如polyA尾)的经修饰的mRNA。在其它实施例中，多核苷酸是包括与编码序列操作性地连接的启动子的表达盒。在某些实施例中，对组织特异性Wnt信号增强分子进行编码的核酸序列和对Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的核酸序列存在于相同的多核苷酸中。

[0237] 在另外的实施例中，还公开了包括表达载体例如病毒载体和一种或多种药学上可接受的稀释剂、载体或赋形剂的药物组合物，所述载体包括多核苷酸，所述多核苷酸包括对本文所描述的本文所描述的组织特异性Wnt信号增强分子或抗体或其抗原结合片段进行编码的核酸序列。在特定实施例中，药物组合物进一步包括表达载体，例如病毒载体，所述表达载体包括多核苷酸，所述多核苷酸包括对本文所描述的Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的核酸序列。在某些实施例中，对组织特异性Wnt信号增强分子进行编码的核酸序列和对Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的核酸序列存在于相同的多核苷酸例如表达盒中。

[0238] 本发明进一步设想了包括细胞和一种或多种药学上可接受的稀释剂、载体或赋形剂的药物组合物，所述细胞包括表达载体，所述表达载体包括多核苷酸，所述多核苷酸包括与对本文所描述的本文所描述的组织特异性Wnt信号增强分子或抗体或其抗原结合片段进行编码的核酸操作性地连接的启动子。在特定实施例中，药物组合物进一步包括细胞，所述细胞包括表达载体，所述表达载体包括多核苷酸，所述多核苷酸包括与对本文所描述的Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的核酸序列操作性地连接的启动子。在某些实施例中，对组织特异性Wnt信号增强分子进行编码的核酸序列和对Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的核酸序列存在于相同的多核苷酸例如表达盒中和/或在相同的细胞中。在特定实施例中，细胞是从待治疗受试者获得的异源细胞或自体细胞。在特定实施例中，细胞是干细胞，例如脂肪源干细胞或造血干细胞。

[0239] 本公开设想了包括用于递送组织特异性Wnt信号增强分子作为第一活性剂的第一分子和用于递送Wnt多肽、Norrin多肽或Wnt信号传导激动剂作为第二活性剂的第二分子的药物组合物。第一分子和第二分子可以是相同类型的分子或不同类型的分子。例如，在某些实施例中，第一分子和第二分子可以各自独立地选自以下类型的分子：多肽、有机小分子、对第一活性剂或第二活性剂进行编码的核酸(任选地，DNA或mRNA，任选地，经过修饰的RNA)、包括对第一活性剂或第二活性剂进行编码的核酸序列的载体(任选地，表达载体或病毒载体)以及包括对第一活性剂或第二活性剂进行编码的核酸序列的细胞(任选地，表达盒)。

[0240] 单独的或组合的主题分子可以与可用于制备通常安全、无毒且理想的调配物的药学上可接受的载体、稀释剂和试剂进行组合，并且包含可接受以供哺乳动物例如人或灵长类动物使用的赋形剂。这种赋形剂可以是固体、液体、半固体或在气雾组合物的情况下为气态的。这种载体或稀释剂的实例包含但不限于水、盐水、林格氏溶液、右旋糖溶液和5％人血

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清白蛋白。补充性活性化合物也可以并入调配物中。用于调配物的溶液或悬浮液可以包含：无菌稀释剂，如注射用水、盐水溶液、不挥发性油、聚乙二醇、甘油、丙二醇或其它合成溶剂；抗菌化合物，如苯甲醇或对羟基苯甲酸甲酯；抗氧化剂，如抗坏血酸或亚硫酸氢钠；螯合化合物，如乙二胺四乙酸(EDTA)；缓冲剂，如乙酸盐、柠檬酸盐或磷酸盐；洗涤剂，如用于防止聚合的吐温(Tween)20；以及用于调节张力的化合物，如氯化钠或右旋糖。可以用酸或碱(如盐酸或氢氧化钠)调节pH。在特定实施例中，药物组合物是无菌的。

[0241] 药物组合物可以进一步包含无菌水溶液或分散液和用于临时制备无菌可注射溶液或分散液的无菌粉末。对于静脉内施用，合适的载体包含生理盐水、抑菌水或磷酸盐缓冲盐水(PBS)。在一些情况下，组合物是无菌的并且应当具有易于注射的程度的流动性。在某些实施例中，组合物在制造和储存条件下是稳定的并且抵抗如细菌和真菌等微生物的污染作用进行保存。载体可以是例如含有例如水、乙醇、多元醇(例如，甘油、丙二醇和液体聚乙二醇等)和其适合的混合物的溶剂或分散介质。可以例如通过使用如卵磷脂的包衣、通过在分散情况下保持所需粒度以及通过使用表面活性剂来保持适当的流动性。防止微生物的作用可以通过各种抗细菌剂和抗真菌剂(例如，对羟苯甲酸酯、三氯叔丁醇、苯酚、抗坏血酸、硫柳汞等)来实现。在许多情况下，优选在组合物中包含等渗剂，例如糖、多元醇(如甘露醇、山梨醇)、氯化钠。可以通过在组合物中包括延迟吸收的试剂(例如，单硬脂酸铝和明胶)来实现内服组合物的延长吸收。

[0242] 无菌溶液可以根据需要通过将所需量的组织特异性Wnt信号增强分子并入具有上文所列举成分中的一种成分或其组合的适当溶剂中、之后进行过滤灭菌来制备。通常，通过将活性化合物并入无菌媒剂中来制备分散液，所述无菌媒剂含有基础分散介质和来自以上列举的那些的其它所需成分。在用于制备无菌可注射溶液的无菌粉末的情况下，制备方法为真空干燥和冷冻干燥，这些干燥产生活性成分加来自其先前经无菌过滤溶液的任何另外的所需成分的粉末。

[0243] 在一个实施例中，药物组合物与保护融合蛋白免于从体内快速消除的载体一起制备，如控释调配物，包含植入物和微囊化递送系统。可以使用可生物降解、生物相容的聚合物，如乙烯乙酸乙烯酯、聚酸酐、聚乙醇酸、胶原、聚原酸酯和聚乳酸。用于制备这种调配物的方法对本领域技术人员而言是显而易见的。材料也可以商购获得。脂质体悬浮液也可以用作药学上可接受的载体。这些脂质体悬浮液可以根据本领域技术人员已知的方法制备。

[0244] 以易于施用和实现剂量均匀性的剂量单位形式来配制药物组合物可以是有利的。如本文所用，剂量单位形式是指作为针对有待治疗的受试者的单一剂量适合的物理上离散单位；每单位含有经计算以与所需的药物载体的联合产生所期望的治疗效果的预定量的活性化合物。本发明的单位剂型的规格由如下决定并且直接依赖于：活性化合物的独特特征和待实现的特定治疗效果，和本领域中配制用于治疗个体的这种活性化合物的固有局限性。

[0245] 药物组合物可以与施用说明书一起包含在容器、包装或分配器中，分配器例如注射器，例如载药注射器。

[0246] 本发明的药物组合物涵盖任何药学上可接受的盐、酯或这种酯的盐或在施用于包括人在内的动物时能够(直接地或间接地)提供生物活性组织特异性Wnt信号增强分子的任何其它化合物。

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[0247] 本发明包含本文所描述的组织特异性Wnt信号增强分子的药学上可接受的盐。术语“药学上可接受的盐”是指本发明的化合物的生理学上可接受的盐和药学上可接受的盐：即，保留了亲本化合物的期望生物活性并且不对亲本化合物产生不期望的毒理效果的盐。各种药学上可接受的盐是本领域已知的并且描述于例如以下中：《雷明顿药学大全(Remington's Pharmaceutical Sciences)》，第17版，Alfonso R.Gennaro(编)，美国宾夕法尼亚州伊斯顿Mark出版公司(Mark Publishing Company,Easton,PA,USA)，1985(以及其最近的版本)；《制药技术百科全书(Encyclopaedia of Pharmaceutical Technology)》，第3版，James Swarbrick(编)，美国纽约州美国英富曼卫生保健(有限公司)(Informa Healthcare USA(Inc.)，NY,USA)，2007；以及《药物科学期刊(J.Pharm.Sci.)》66:2(1977)。而且，有关适合的盐的综述，参见Stahl和Wermuth的《“药用盐手册：性质、选择和使用(Handbook of Pharmaceutical Salts:Properties,Selection,and Use)”》(Wiley-VCH,2002)。

[0248] 用如碱金属和碱土金属或有机胺等金属或胺形成药学上可接受的碱加成盐。用作阳离子的金属包括钠、钾、镁、钙等。胺包括N-N'-二苄基乙二胺、氯普鲁卡因、胆碱、二乙醇胺、二环己胺、乙二胺、N-甲基葡糖胺和普鲁卡因(参见例如Berge等人，“药用盐(Pharmaceutical Salts)”，《药物科学期刊(J.Pharma Sci)》，1977,66,119)。酸性化合物的碱加成盐是通过使游离酸形式与足量的期望的碱相接触以常规方式产生盐来制备的。游离酸形式可以通过使盐形式与酸相接触并且以常规方式分离游离酸来再生。游离酸形式在某些物理性质方面如在极性溶剂中的溶解度与其各自的盐形式略有不同，但是出于本发明的目的，盐等同于其各自的游离酸。

[0249] 在一些实施例中，本文所提供的药物组合物包括与药学上可接受的载体、稀释剂和/或赋形剂混合的治疗有效量的本文所描述的组织特异性Wnt信号增强分子，所述药学上可接受的载体、稀释剂和/或赋形剂例如盐水、磷酸盐缓冲盐水、磷酸盐和氨基酸、聚合物、多元醇、糖、缓冲剂、防腐剂和其它蛋白质。示例性氨基酸、聚合物和糖等是辛基苯氧基聚乙氧基乙醇化合物、聚乙二醇单硬脂酸酯化合物、聚氧乙烯山梨醇酐脂肪酸酯、蔗糖、果糖、右旋糖、麦芽糖、葡萄糖、甘露醇、葡聚糖、山梨醇、肌醇、半乳糖醇、木糖醇、乳糖、海藻糖、牛或人血清白蛋白、柠檬酸酯、乙酸酯、林格氏和汉克氏溶液、半胱氨酸、精氨酸、肉碱、丙氨酸、甘氨酸、赖氨酸、缬氨酸、亮氨酸、聚乙烯吡咯烷酮、聚乙烯和二醇。优选地，此调配物在4℃下在至少六个月内是稳定的。

[0250] 在一些实施例中，本文所提供的药物组合物包括缓冲液，如磷酸盐缓冲盐水(PBS)或磷酸钠/硫酸钠、tris缓冲液、甘氨酸缓冲液、无菌水以及本领域普通技术人员已知的其它缓冲液，如Good等人(1966)《生物化学(Biochemistry)》5:467中描述的那些缓冲液。所述缓冲液的pH值可以处于6.5到7.75的范围内，优选地7到7.5并且最优选地7.2到7.4。

[0251] 用于增加Wnt活性或Wnt受体细胞表面表达的方法

[0252] 本文关于融合蛋白所例证的组织特异性Wnt信号增强分子可以用于增加靶向组织或细胞类型中的Wnt信号传导。在特定实施例中，Wnt信号传导是经典Wnt信号传导。因此，在一些方面，本发明提供了一种用于增加或增强靶组织或靶细胞中的Wnt信号传导的方法，所述方法包括使靶组织或靶细胞与有效量的本文所公开的组织特异性Wnt信号增强分子接触，其中所述分子包括以组织特异性或细胞特异性方式与靶组织或靶细胞上的细胞表面受

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体结合的靶向模块。在一些实施例中，接触在体外、离体地或在体内发生，例如向受试者施用或提供主题组织特异性Wnt信号增强分子。在特定实施例中，细胞是培养细胞，并且接触发生在体外。

[0253] 在某些实施例中，所述方法包括进一步使靶组织或靶细胞与本文所描述的一种或多种Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子接触。本公开设想了使靶组织或靶细胞与用于递送组织特异性Wnt信号增强分子作为第一活性剂的第一分子和用于递送Wnt多肽、Norrin多肽或Wnt信号传导激动剂作为第二活性剂的第二分子接触。第一分子和第二分子可以是相同类型的分子或不同类型的分子。例如，在某些实施例中，第一分子和第二分子可以各自独立地选自以下类型的分子：多肽、有机小分子、对第一活性剂或第二活性剂进行编码的核酸(任选地，DNA或mRNA，任选地，经过修饰的RNA)、包括对第一活性剂或第二活性剂进行编码的核酸序列的载体(任选地，表达载体或病毒载体)以及包括对第一活性剂或第二活性剂进行编码的核酸序列的细胞(任选地，表达盒)。

[0254] 在相关方面，本发明提供了一种用于增加靶组织或靶细胞中的Wnt信号传导的方法，所述方法包括使靶组织或靶细胞与有效量的包括对本文所公开的组织特异性Wnt信号增强分子进行编码的核酸序列的多核苷酸接触，其中所述分子包括以组织特异性或细胞特异性方式与靶组织或靶细胞上的细胞表面受体结合的靶向模块。在某些实施例中，还使靶组织或靶细胞与包括对Wnt多肽、Norrin多肽或Wnt信号传导激动剂进行编码的核酸序列的多核苷酸接触。在某些实施例中，多核苷酸是DNA或mRNA，例如经修饰的mRNA。在特定实施例中，多核苷酸是进一步包括5'帽序列和/或3'拖尾序列(例如polyA尾)的经修饰的mRNA。在其它实施例中，多核苷酸是包括与编码序列操作性地连接的启动子的表达盒。在某些实施例中，对组织特异性Wnt信号增强分子进行编码的核酸序列和对Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的核酸序列存在于相同的多核苷酸中。

[0255] 在相关方面，本发明提供了一种用于增加靶组织或靶细胞中的Wnt信号传导的方法，所述方法包括使靶组织或靶细胞与有效量的包括对本发明的组织特异性Wnt信号增强分子进行编码的核酸序列的载体接触，其中所述分子包括以组织特异性或细胞特异性方式与靶组织或靶细胞上的细胞表面受体结合的靶向模块。在某些实施例中，还使靶组织或靶细胞与包括对Wnt多肽、Norrin多肽或Wnt信号传导激动剂进行编码的核酸序列的载体接触。在某些实施例中，载体是表达载体并且可以包括与核酸序列操作性地连接的启动子序列。在特定实施例中，载体是病毒载体。在某些实施例中，对组织特异性Wnt信号增强分子进行编码的核酸序列和对Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的核酸序列存在于相同的载体中，例如在相同的表达盒中。

[0256] 在相关方面，本发明提供了一种用于增加靶组织中的Wnt信号传导的方法，所述方法包括使靶组织与有效量的包括对本发明的组织特异性Wnt信号增强分子进行编码的核酸序列的细胞接触，其中所述分子包括以组织特异性或细胞特异性方式与靶组织或靶细胞上的细胞表面受体结合的靶向模块。在某些实施例中，还使靶组织与包括对Wnt多肽、Norrin多肽或Wnt信号传导激动剂进行编码的核酸序列的细胞接触。在某些实施例中，对组织特异性Wnt信号增强分子进行编码的核酸序列和对Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的核酸序列存在于相同的细胞中。在特定实施例中，细胞是从待治疗受试者获得的异源细胞或自体细胞。在某些实施例中，用包括对组织特异性Wnt信号增强分子或者

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Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的表达盒的载体对细胞进行转导。在特定实施例中，细胞是干细胞，例如脂肪源干细胞或造血干细胞。

[0257] 本文所描述的用于增加Wnt信号传导的方法中的任何方法也可以用于增加靶向细胞，例如肝组织细胞的表面上的卷曲蛋白(Fz)受体的数量。在某些实施例中，靶向细胞的表面的Fz受体的数量增加至少10％、至少20％、至少30％、至少40％、至少50％、至少60％、至少70％、至少80％、至少90％、至少两倍、至少五倍或至少10倍。在特定实施例中，Fz受体包含人卷曲蛋白Fz1、Fz2、Fz3、Fz4、Fz5、Fz6、Fz7、Fz8、Fz9、Fz10中的一种或多种人卷曲蛋白。例如，本公开提供了一种用于增加靶向细胞的表面上的Fz受体的方法，所述方法包括使细胞与有效量的本文所公开的组织特异性或细胞特异性Wnt信号增强分子接触，其中所述分子包括以组织特异性或细胞特异性方式与靶组织或靶细胞上的细胞表面受体结合的靶向模块。在特定实施例中，细胞是肝细胞，并且靶向模块结合ASGR1或ASGR2。在某些实施例中，靶向模块包括本文所公开的抗体或其抗原结合片段。在一些实施例中，接触在体外、离体地或在体内发生，例如向受试者施用或提供组织特异性Wnt信号增强分子。在特定实施例中，细胞是培养细胞，并且接触发生在体外。在某些实施例中，靶向细胞或靶向组织最初直接与Wnt信号增强分子接触，而在其它相关实施例中，细胞最初与对Wnt信号增强分子进行编码的多核苷酸接触，所述多核苷酸例如表达载体，由此，细胞吸收多核苷酸并且表达Wnt信号增强分子。在某些实施例中，所述方法包括进一步使靶向组织或靶向细胞与本文所描述的一种或多种Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子接触。

[0258] 本文所描述的用于增加Wnt信号传导的方法中的任何方法也可以用于增加靶向细胞，例如肝组织细胞上的Ki-67。

[0259] 用于治疗疾病和病症的方法

[0260] 本文关于融合蛋白所例证的组织特异性Wnt信号增强分子可以用于治疗疾病、病症或病状，例如通过增加靶向细胞、组织或器官中的Wnt信号传导。因此，在一些方面，本发明提供了一种用于治疗有需要的受试者的疾病或病状(例如，与Wnt信号传导减少相关的疾病或病症或针对其增加Wnt信号传导将提供治疗益处的疾病或病症)的方法，所述方法包括使受试者与有效量的本公开的组合物接触。在特定实施例中，所述组合物是包括以下中的任何一种的药物组合物：组织特异性Wnt信号增强分子，例如小分子或多肽；多核苷酸，所述多核苷酸包括对组织特异性Wnt信号增强分子进行编码的核酸序列，例如DNA或mRNA，任选地经过修饰的mRNA；载体，所述载体包括对组织特异性Wnt信号增强分子进行编码的核酸序列，例如表达载体或病毒载体；或者细胞，所述细胞包括对组织特异性Wnt信号增强分子进行编码的核酸序列，例如用对组织特异性Wnt信号增强分子进行编码的表达载体或病毒载体转导的细胞。在特定实施例中，疾病或病状是病理性疾病或病症或者损伤，例如由伤口引起的损伤。在某些实施例中，伤口可能是另一种治疗性治疗的结果。在某些实施例中，疾病或病状包括受损组织修复、愈合或再生，或者会受益于增加的组织修复、愈合或再生。在一些实施例中，在体内发生接触，即，向受试者施用主题组合物。

[0261] 在某些实施例中，所述方法包括使受试者进一步接触药物组合物，所述药物组合物包括本文所描述的一种或多种Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子。本公开设想了使受试者接触用于递送组织特异性Wnt信号增强分子作为第一活性剂的第一分子和用于递送Wnt多肽、Norrin多肽或Wnt信号传导激动剂作为第二活性剂的第二分子。第一分

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子和第二分子可以是相同类型的分子或不同类型的分子。例如，在某些实施例中，第一分子和第二分子可以各自独立地选自以下类型的分子：多肽、有机小分子、对第一活性剂或第二活性剂进行编码的核酸（任选地，DNA或mRNA，任选地，经过修饰的RNA）、包括对第一活性剂或第二活性剂进行编码的核酸序列的载体（任选地，表达载体或病毒载体）以及包括对第一活性剂或第二活性剂进行编码的核酸序列的细胞（任选地，表达盒）。

[0262] 在相关方面，本发明提供了一种用于治疗疾病或病状的方法，所述疾病或病状例如与减少的Wnt信号传导相关的疾病或病症或者增加的Wnt信号传导将会提供治疗益处的疾病或病症，所述方法包括使有需要的受试者与包括有效量的多核苷酸的药物组合物接触，所述多核苷酸包括对本发明的组织特异性Wnt信号增强分子进行编码的核酸序列，其中所述分子包括以组织特异性或细胞特异性方式与靶组织或靶细胞上的细胞表面受体结合的靶向模块。在某些实施例中，还使受试者与包括有效量的多核苷酸的药物组合物接触，所述多核苷酸包括对Wnt多肽、诺里病蛋白多肽或Wnt信号传导激动剂进行编码的核酸序列。在某些实施例中，多核苷酸是DNA或mRNA，例如经修饰的mRNA。在特定实施例中，多核苷酸是进一步包括5'帽序列和/或3'拖尾序列（例如polyA尾）的经修饰的mRNA。在其它实施例中，多核苷酸是包括与编码序列操作性地连接的启动子的表达盒。在某些实施例中，对组织特异性Wnt信号增强分子进行编码的核酸序列和对Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的核酸序列存在于相同的多核苷酸中。

[0263] 在相关方面，本发明提供了一种用于治疗疾病或病状的方法，所述疾病或病状例如与减少的Wnt信号传导相关的疾病或病症或者增加的Wnt信号传导将会提供治疗益处的疾病或病症，所述方法包括使有需要的受试者与包括有效量的载体的药物组合物接触，所述载体包括对本发明的组织特异性Wnt信号增强分子进行编码的核酸序列，其中所述分子包括以组织特异性或细胞特异性方式与靶组织或靶细胞上的细胞表面受体结合的靶向模块。在某些实施例中，还使受试者与包括有效量的载体的药物组合物接触，所述载体包括对Wnt多肽、Norrin多肽或Wnt信号传导激动剂进行编码的核酸序列。在某些实施例中，载体是表达载体并且可以包括与核酸序列操作性地连接的启动子序列。在特定实施例中，载体是病毒载体。在某些实施例中，对组织特异性Wnt信号增强分子进行编码的核酸序列和对Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的核酸序列存在于相同的载体中，例如在相同的表达盒中。

[0264] 在相关方面，本发明提供了一种用于治疗疾病或病状的方法，所述疾病或病状例如与减少的Wnt信号传导相关的疾病或病症或者增加的Wnt信号传导将会提供治疗益处的疾病或病症，所述方法包括使有需要的受试者与包括有效量的细胞的药物组合物接触，所述细胞包括对本发明的组织特异性Wnt信号增强分子进行编码的核酸序列，其中所述分子包括以组织特异性或细胞特异性方式与靶组织或靶细胞上的细胞表面受体结合的靶向模块。在某些实施例中，还使受试者与包括对Wnt多肽、Norrin多肽或Wnt信号传导激动剂进行编码的核酸序列的细胞接触。在某些实施例中，对组织特异性Wnt信号增强分子进行编码的核酸序列和对Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的核酸序列存在于相同的细胞中。在特定实施例中，细胞是从待治疗受试者获得的异源细胞或自体细胞。在某些实施例中，用包括对组织特异性Wnt信号增强分子或者Wnt多肽、Norrin多肽或Wnt信号传导激动剂分子进行编码的表达盒的载体对细胞进行转导。在特定实施例中，细胞是干细胞，

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例如脂肪源干细胞或造血干细胞。

[0265] Wnt信号传导在干细胞的发育过程和维持中发挥着关键作用。Wnt信号的重新活化与损伤和疾病后大多数组织的再生和修复相关。组织特异性Wnt信号增强分子可以响应于损伤和疾病提供愈合和组织修复的益处。组织损害和损失的原因包含但不限于老化、变性、遗传性病状、感染和炎症、创伤性损伤、毒素/代谢诱导的毒性或其它病理性病状。已经示出Wnt信号和Wnt信号的增强子使成年组织驻留干细胞活化。在一些实施例中，施用本发明的化合物以用于治疗患病组织或受损组织、用于组织再生以及用于细胞生长和增殖和/或用于组织工程化。

[0266] 与Wnt通路的突变相关的人类疾病针对治疗和预防疾病中Wnt信号的增强提供了有力证据。临床前体内和体外研究提供了许多疾病病状中涉及Wnt信号的另外的证据，并且进一步支持将组织特异性Wnt信号增强分子用于各种人类疾病。例如，本发明的组合物可以用于促进或增加骨生长或再生、骨移植、骨折愈合、骨质疏松症和骨质疏松性骨折的治疗、脊柱融合、矫形装置的骨整合、腱-骨整合、牙齿生长和再生、牙种植、牙周疾病、颌面重建和颌骨坏死。本发明的组合物还可以用于：治疗脱发；增强感觉器官的再生(例如，治疗听力丧失，包含内和外听觉毛细胞的再生)、治疗前庭功能减退、治疗黄斑变性、治疗视网膜病变(包含玻璃体视网膜病变、糖尿病性视网膜病变或其它视网膜变性疾病)、富克斯氏营养不良(Fuchs'dystrophy)、其它角膜疾病等；治疗中风、创伤性脑损伤、阿尔茨海默病、多发性硬化症和影响血脑屏障的变性或完整性的其它病状；治疗脊髓损伤、其它脊髓疾病。本发明的组合物还可以用于治疗口腔粘膜炎、肠粘膜炎；治疗短肠综合征、炎性肠疾病(IBD)，包含但不限于克罗恩氏病(Crohn's disease)(CD)和溃疡性结肠炎(UC)，具体地是伴有瘘管形成的CD和UC、其它胃肠病症；治疗代谢综合征；治疗糖尿病；治疗胰腺炎、其中外分泌或内分泌胰腺组织受损的病状、其中期望增强的表皮再生例如表皮伤口愈合的病状；治疗糖尿病足溃疡、涉及牙齿、指甲或真皮发育不全等的综合征、其中血管生成有益的病状；治疗心肌梗死、冠状动脉疾病、心力衰竭；增强造血细胞的生长，例如增强来自骨髓的造血干细胞移植、动员外周血；治疗免疫缺陷、移植物抗宿主疾病等；治疗急性肾损伤、慢性肾病；治疗肺病、慢性阻塞性肺病(COPD)、特发性肺纤维化、肺组织的增强的再生，具体地是肺干细胞(例如，AT2和AT1细胞)的增殖和分化。本发明的组合物还可以用于增强肝细胞再生，例如肝再生、治疗肝硬化、增强肝移植、治疗急性肝衰竭、治疗经历肝炎(甲型、乙型或丙型)病毒感染或抗病毒后药物疗法的慢性肝病、酒精性肝病(包含酒精性肝炎)、伴有脂肪变性或脂肪性肝炎的非酒精性肝病等。本发明的组合物可以治疗疾病和病症，包含但不限于其中期望再生性细胞生长的病状。

[0267] 涉及Wnt信号传导组分中的功能丧失突变或功能获得突变的人类遗传学示出了支持增强Wnt信号以用于骨生长的有力证据。其中期望增强的骨生长的病状可以包含但不限于骨折、移植、在假体装置周围向内生长、骨质疏松症、骨质疏松性骨折、脊柱融合、颌骨坏死、牙种植、牙周疾病、颌面重建等。组织特异性Wnt信号增强分子增强和促进了对促进骨再生至关重要的Wnt信号。用于使骨组织再生的方法受益于施用本发明的化合物，所述施用可以是全身性的或局部化的。在一些实施例中，使骨髓细胞暴露于本发明的分子，从而使得所述骨髓内的干细胞活化。

[0268] 在一些实施例中，通过使反应性细胞群与有效剂量的本发明的分子接触来增强骨

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再生，所述反应性细胞群例如骨髓、骨祖细胞、骨干细胞等。用于使骨组织再生的方法受益于施用本发明的化合物，所述施用可以是全身性的或局部化的。在一些这种实施例中，在体内执行接触。在其它这种实施例中，离体地执行接触。分子可以例如通过加载到任选地可生物降解的基质上而定位到作用位点，并且任选地提供活性剂的缓释。基质载体包含但不限于可吸收的胶原海绵、陶瓷、水凝胶、高分子微球、纳米颗粒、骨水泥等。

[0269] 包括本发明的分子中的一种或多种分子的组合物可以用于在体内治疗骨骼组织缺陷。“骨骼组织缺陷”意指骨骼或其它骨骼结缔组织在期望恢复骨骼或结缔组织的任何位点处的缺陷，无论缺陷是如何引起的，例如无论是手术干预、肿瘤切除、溃疡、植入、骨折还是其它创伤性或变性病状的结果。本发明的组合物可以用作用于恢复结缔组织的软骨功能、用于修复软骨组织的缺损或损伤的方案的一部分，所述软骨组织的缺损或损伤如变性磨损和关节炎、组织创伤、半月板撕裂移位、半月板切除、由韧带撕裂、关节不齐、骨折或遗传性疾病引起的关节脱位。

[0270] 本发明的组合物还可以用于治疗牙周病。牙周病是牙齿脱落的主要原因并且与多种全身性病状有关。在一些实施例中，通过接触反应性细胞群来增强牙齿或下层骨再生。在一些这种实施例中，在体内执行接触。在其它这种实施例中，离体地执行接触，随后植入活化的干细胞或祖细胞。分子可以例如通过加载到任选地可生物降解的基质上而定位到作用位点，并且任选地提供活性剂的缓释。基质载体包含但不限于可吸收的胶原海绵、陶瓷、水凝胶、骨水泥、聚合物微球、纳米颗粒等。

[0271] 研究已经表明，Wnt信号传导和R-脊椎蛋白的生物学能够在损伤、老化或变性后促进内耳中的感觉毛细胞再生。听力丧失或前庭功能减退所涉及的内耳中感觉毛细胞的损失也可以受益于本发明的组合物。在内耳中，听觉器官容纳将声音振动转化为电脉冲所需的机械敏感毛细胞。包括半规管(SSC)、椭圆囊和球囊的前庭器官还含有感觉毛细胞，以检测头部位置和头部运动。本发明的组合物可以用于例如：输注；基质或其它储库系统；或者到耳朵的其它局部应用以增强听觉再生。

[0272] 本发明的组合物还可以用于视网膜组织再生。在成年哺乳动物视网膜中，穆勒神经胶质细胞(Muller glia cell)能够例如在体内神经毒性损伤后之后使视网膜细胞(包含光感受器)再生。Wnt信号传导和Wnt信号的增强子可以促进穆勒神经胶质源视网膜祖细胞在损害后或在变性期间增殖。本发明的组合物还可以用于使眼中的组织和其它细胞类型再生。例如，年龄相关性黄斑变性(AMD)、其它视网膜变性疾病、角膜病、富克斯氏营养不良、玻璃体视网膜病变、遗传性疾病等可以受益于本发明的组合物。AMD的特征在于渐进性降低的中心视觉和视敏度。富克斯氏营养不良症的特征在于角膜内皮细胞逐渐丧失。Wnt信号和Wnt信号的增强可以促进眼部组织中角膜内皮、视网膜上皮等的再生。在其它实施例中，本发明的组合物可以用于例如：输注；基质或其它储库系统；或者到眼睛的其它局部应用以使视网膜再生并治疗黄斑变性。

[0273] 已经通过谱系示踪研究鉴别出用于肝细胞的稳态更新的特定增殖细胞群，例如中心周围区的Axin2阳性细胞。谱系示踪研究还鉴别出了另外可能的肝脏祖细胞，包含但不限于Lgr阳性细胞。包含Lgr5阳性细胞和Axin2阳性细胞在内的自我更新肝细胞和其它可能祖细胞群被鉴别为能够在损伤后响应于Wnt信号和/或R-脊椎蛋白进行再生。急性肝损伤和衰竭以及慢性肝病的许多临床前模型示出肝细胞的恢复和再生受益于增强Wnt信号。在某些

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实施例中，本发明的组合物可以用于治疗例如(所有原因的)急性肝衰竭、急性酒精性肝损伤、经历丙型肝炎或乙型肝炎病毒感染或抗病毒后药物疗法的慢性肝病、慢性酒精性肝病、非酒精性脂肪肝病(NAFLD)(脂肪肝)、非酒精性脂肪性肝炎(NASH)、肝硬化、所有原因的重度慢性肝病、所有原因的急性肝衰竭、药物诱导的急性肝衰竭、酒精性肝病、(所有原因的)慢性肝衰竭、所有原因的肝纤维化、门脉高压、所有原因的慢性肝功能不全、酒精性肝炎、丙型肝炎病毒诱导的肝病(HCV)、乙型肝炎病毒诱导的肝病(HBV)、其它病毒性肝炎(例如，甲型肝炎病毒诱导的肝病(HAV)和丁型肝炎病毒诱导的肝病(HDV))、原发性胆汁性肝硬化、自身免疫性肝炎、肝脏外科手术、肝损伤、肝移植、肝脏外科手术和移植中的“小肝”综合征、先天性肝疾病和病症、由遗传疾病、变性、老化、药物或损伤引起的任何其它肝病症或缺陷。本发明的组合物还可以用于在体内或在体外增强肝细胞的再生。用于使肝组织再生的方法受益于施用本发明的化合物，所述施用可以是全身性的或局部化的。这些方法包含但不限于全身性施用方法和局部化施用方法，例如通过注射到肝组织中、通过注射到通向肝脏的静脉或血管中、通过植入缓释调配物等。

[0274] 本发明的组合物可以用于治疗终末期肝病(ESLD)。ESLD或慢性肝衰竭通常是重度肝硬化和所产生的肝纤维化的结果。ESLD通过发展有腹水、静脉曲张出血、肝性脑病变和/或肝功能受损(例如，代偿失调的肝病)而表现出来。与ESLD相关的常见疾病或病症包含：酒精性肝炎、慢性丙型肝炎感染、慢性乙型肝炎感染、慢性丁型肝炎感染、非酒精性脂肪肝病(NAFLD)(包含非酒精性脂肪性肝炎(NASH))以及如囊性纤维化、α-1抗胰蛋白酶缺乏、血色沉着病、威尔逊病(Wilson disease)、半乳糖血症和糖原贮积病等遗传性疾病。长期暴露于药物、毒性化学品、寄生虫感染以及伴有肝淤血的重复心力衰竭也可能导致ESLD。

[0275] Wnt信号在各种上皮组织的再生中发挥着重要作用。各种表皮病状受益于用本发明的化合物进行的治疗。当附在胃肠道上的快速分开的上皮细胞破裂从而使粘膜组织易于溃疡和感染时，发生粘膜炎。上皮层(epithelial lining)的覆盖口腔的部分，被称为口腔粘膜，是身体最敏感的部位之一，并且特别容易受到化疗和放射的伤害。口腔粘膜炎可能是癌症治疗特别是化疗和放射中最常见的使人衰弱的并发症。另外，本发明的组合物还可以有益于治疗肠道粘膜炎、短肠综合征、炎性肠病(IBD)或其它胃肠病症。其它表皮病状包含表皮伤口愈合、糖尿病足溃疡、涉及牙齿、指甲或皮肤发育不全的综合征等。本发明的分子可以用于所有这些病状，其中再生性细胞与本发明的化合物接触。用于使上皮组织再生的方法受益于施用本发明的化合物，所述施用可以是全身性的或局部化的。接触可以是例如局部的，包含皮内、皮下，以施加在靶向位点等处的凝胶、洗剂、乳膏等形式。

[0276] 除皮肤和胃肠道外，Wnt信号以及Wnt信号的增强和促进还在临床前模型中在包含胰腺、肾和肺在内的组织的修复和再生中发挥着重要作用。组织特异性Wnt信号增强分子可以有益于涉及外分泌和内分泌胰腺、肾或肺的各种疾病病状。本发明的组合物可以用于：治疗代谢综合征；治疗糖尿病；治疗急性或慢性胰腺炎、外分泌胰腺功能不全；治疗急性肾损伤、慢性肾病；治疗肺病，包含但不限于慢性阻塞性肺病(COPD)、特发性肺纤维化、导致肺上皮组织缺失的其它病状。用于使这些组织再生的方法受益于施用本发明的化合物，所述施用可以是全身性的或局部化的。

[0277] 与经由其它发育因子进行的信号传导协调的表皮Wnt信号传导对成人毛囊再生至关重要。脱发是常见问题，并且雄激素性脱发，通常称为男性型秃发，是男性最常见的脱发

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形式。在一些实施例中，通过使反应性细胞群与本发明的分子接触来增强毛囊再生。在一些这种实施例中，在体内执行接触。在其它这种实施例中，离体地执行接触。分子可以定位到作用位点处，例如外用洗剂、凝胶、乳膏等。

[0278] 可以用本发明的组织特异性Wnt信号增强分子治疗中风、创伤性脑损伤、阿尔茨海默病、多发性硬化和影响血脑屏障(BBB)的其它病状。血管生成对确保向贯穿全身的许多组织供应氧气和营养物至关重要，并且对CNS而言尤其重要，因为神经组织对缺氧和缺血极其敏感。形成BBB的CNS内皮细胞与非神经组织中的内皮细胞的不同之处在于，CNS内皮细胞是通过紧密连接保持在一起的高度极化细胞并且表达特定转运蛋白。Wnt信号传导调节CNS血管形成和/或功能。BBB受损的病状可以受益于施用本发明的化合物，所述施用可以是全身性的或局部化的，例如通过直接注射、鞘内施用、植入缓释配制物等。另外，Wnt信号积极参与神经发生并且在损伤后发挥神经保护的作用。本发明的组合物还可以用于治疗脊髓损伤、其它脊髓疾病、中风、创伤性脑损伤等。

[0279] Wnt信号还在血管生成中发挥作用。组织特异性Wnt信号增强分子可以有益于血管生成有利的病状、治疗心肌梗死、冠状动脉疾病、心力衰竭等以及源自遗传性疾病的病状。用于使这些组织再生的方法受益于施用本发明的化合物，所述施用可以是全身性的或局部化的。

[0280] 在某些实施例中，本发明的方法促进组织再生，例如在经受损害或者组织或细胞减少或损耗的组织中。损耗或损害可以是导致细胞数量减少的任何事物，包含疾病或损伤。例如，事故、自身免疫病症、治疗副作用或疾病状态可能会构成创伤。组织再生增加了组织内的细胞数量，并且优选地使组织的细胞之间能够重新建立连接，并且更优选地使组织能够重新获得功能。

[0281] 在特定实施例中，组合物是肠胃外施用的，例如，静脉内、口服、直肠或通过注射施用。在一些实施例中，局部地，例如局部地或肌内地施用药物组合物。在一些实施例中，组合物施用于靶组织，例如骨、关节、耳组织、眼组织、胃肠道、皮肤、伤口部位或脊髓。可以在体内或离体地实践本发明的方法。在一些实施例中，离体地执行靶细胞或靶组织与组织特异性Wnt信号增强分子的接触，随后将细胞或组织例如活化的干细胞或祖细胞植入到受试者体内。技术人员可以基于正在治疗的疾病或病症确定适合的施用位点和施用途径。

[0282] 剂量和剂量方案可以取决于医师容易确定的各种因素，如疾病或病症的性质、受试者的特性和受试者的病史。在特定实施例中，向受试者施用或提供的组织特异性Wnt信号增强分子例如融合蛋白的量的范围为受试者体重的约0.01mg/kg到约50mg/kg、0.1mg/kg到约500mg/kg或约0.1mg/kg到约50mg/kg。

[0283] 在某些实施例中，受试者可以是任何哺乳动物，例如人、啮齿动物(例如，小鼠、大鼠、沙鼠)、兔、猫科动物、犬科动物、山羊、绵羊、猪、马科动物、牛科动物或灵长类动物。

[0284] 在一些实施例中，主题方法产生了治疗益处，例如预防病症的发展、停止病症的进展、逆转病症的进展等。在一些实施例中，主题方法包括检测到已经达到治疗益处的步骤。本领域内普通技术人员应了解，治疗功效的这种量度将适用于正被修饰的特定疾病，并且应认识到用于测量治疗功效的适当检测方法。

[0285] 在某些实施例中，本公开提供了一种用于治疗或预防与减少的Wnt信号传导相关或者将会受益于骨组织中增加的Wnt信号传导活性的疾病或病症的方法，所述疾病或病症

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例如期望骨生长的本文所公开的病状中的任何病状，所述方法包括向有需要的受试者提供包括Wnt信号增强分子的药物组合物，所述Wnt信号增强分子包括结合骨组织的靶向模块，例如与PTH1R特异性地结合的靶向模块，其中所述Wnt信号增强分子增加或增强了受试者的骨组织中的Wnt信号传导。在某些实施例中，药物组合物口服或全身性地例如肠胃外施用。在特定实施例中，Wnt信号增强分子包括作用模块，所述作用模块包括R-脊椎蛋白弗林蛋白酶结构域1或其片段或者变体以及任选地突变的弗林蛋白酶结构域2或其片段或者变体。

[0286] 在某些实施例中，本公开提供了一种用于治疗或预防与减少的Wnt信号传导相关或者将会受益于肝组织中增加的Wnt信号传导活性的疾病或病症的方法，所述疾病或病症例如将会受益于肝再生的本文所公开的疾病或病症中的任何疾病或病症，所述方法包括向有需要的受试者提供包括Wnt信号增强分子的药物组合物，所述Wnt信号增强分子包括结合肝组织的靶向模块，例如与ASGR1、ASGR2、TFR2或SLC10A1特异性地结合的靶向模块，其中所述Wnt信号增强分子增加或增强了受试者的肝组织中的Wnt信号传导。在某些实施例中，药物组合物口服或全身性地例如肠胃外施用。在特定实施例中，Wnt信号增强分子包括作用模块，所述作用模块包括R-脊椎蛋白弗林蛋白酶结构域1或其片段或者变体以及任选地突变的弗林蛋白酶结构域2或其片段或者变体。

[0287] 在某些实施例中，本公开提供了一种用于治疗或预防与减少的Wnt信号传导相关或者将会受益于口腔粘膜组织中增加的Wnt信号传导活性的疾病或病症例如口腔粘膜炎的方法，所述方法包括向有需要的受试者提供包括Wnt信号增强分子的药物组合物，所述Wnt信号增强分子包括结合口腔粘膜组织的靶向模块，例如与LYPD3或DSG3特异性地结合的靶向模块，其中所述Wnt信号增强分子增加或增强了受试者的口腔粘膜组织中的Wnt信号传导。在某些实施例中，药物组合物口服或全身性地例如肠胃外施用。在特定实施例中，Wnt信号增强分子包括作用模块，所述作用模块包括R-脊椎蛋白弗林蛋白酶结构域1或其片段或者变体以及任选地突变的弗林蛋白酶结构域2或其片段或者变体。

[0288] 本说明书中提及的和/或在申请数据表中列出的所有上述美国专利、美国专利申请公开、美国专利申请、外国专利、外国专利申请和非专利公开均通过全文引用的方式并入本文。

[0289] 从上文应理解的是，虽然出于说明的目的已经在本文中描述了本发明的特定实施例，但可以在不偏离本发明的精神和范围的情况下进行各种修改。因此，除所附的权利要求之外本发明不受限制。

[0290] 实例

[0291] 提出以下实例以便向本领域普通技术人员提供如何形成和使用本发明的完整公开和描述并且不旨在限制诸位发明人考虑作为其发明的范围，所述实例也不旨在表示以下实验是执行的全部或仅有的实验。虽然已尽力确保所用数字(例如，量、温度等)的准确性，但仍应考虑一些实验误差和偏差。除非另有指示，否则份是重量份、分子量是重均分子量、温度是以摄氏度为单位并且压力是处于或接近于大气压。

[0292] 可以在这种标准教科书中找到分子生物学、细胞生物学和生物化学的一般方法，如《分子克隆:实验室手册(Molecular Cloning:A Laboratory Manual)第3版》(Sambrook等人，港口实验室出版社(HaRBor Laboratory Press)2001)；《精编分子生物学实验指南(Short Protocols in Molecular Biology)第4版》(Ausubel等人编，约翰威利父子公司

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(John Wiley&Sons)1999);《蛋白质方法(Protein Methods)》(Bollag等人,约翰威利父子出版公司,1996);《基因疗法的非病毒载体(Nonviral Vectors for Gene Therapy)》(Wagner等人编,学术出版社1999);《病毒载体(Viral Vector)》(Kaplift和Loewy,编辑,学术出版社,1995);《免疫学方法手册(Immunology Methods Manual)》(I.Lefkovits编辑,学术出版社,1997);和《细胞和组织培养:生物技术实验室程序(Cell and Tissue Culture: Laboratory Procedures in Biotechnology)》(Doyle和Griffiths,约翰威利父子出版公司,1998),所述标准教科书的公开内容通过引用并入本文。本公开中提及的用于基因操纵的试剂、克隆载体和试剂盒可从如伯乐公司(BioRad)、斯特拉塔基因公司(Stratagene)、英杰公司(Invitrogen)、西格玛奥德里奇公司(Sigma-Aldrich)和酷龙技术公司(ClonTech)等商业供应商获得。

[0293] 以下实例中所采用的材料与方法包含以下。

[0294] 已发表的ASGR1结合剂:原型抗ASGR1结合剂(RO-01)和几种其它结合剂(RO-02、RO-03和RO-04)选自PCT专利申请公开第WO2014/023709号。抗TFR1序列选自PCT专利申请公开第WO2016/081640号。抗LYPD3序列选自PCT专利申请公开第WO2017/0158775号。抗DSG3序列选自PCT专利申请公开第WO2010/092457号。ZNRF3结合剂SC-01和SC-02选自PCT专利申请公开第WO2015/164392号。RNF43结合剂NV-01选自PCT专利申请公开第WO 2013/054307号。

[0295] 蛋白质产生:除非另外指明,否则所有重组蛋白均通过瞬时转染在Expi293F细胞(赛默飞世尔科技公司(Thermo Fisher Scientific))中产生。所有含有scFv的融合物都含有FLAG-His标签并且首先遵循供应商推荐的程序使用完整的his标签纯化树脂(西格玛奥德里奇公司)进行纯化。将所有基于IgG并且含有Fc的构建体首先用蛋白A树脂纯化并且用pH 3.5的0.1M甘氨酸洗脱。然后将所有蛋白质在HBS缓冲液(10mM HEPES pH 7.2,150mM NaCl)中通过尺寸排阻柱进行抛光。将蛋白质用甘油补充至10%,以便在-80℃下长期储存。对于体外受体结合分析,将人RNF3(Q44-D198)和ZNRF3(K56-M219)以及ASGR1(Q62-L291)在N端处用His-Avi标签表达,并且将小鼠ASGR1(Q61-N284)的的细胞外结构域在C端处用His-Avi标签表达。将所述蛋白质通过His标签树脂纯化、如所描述地生物素化(Janda等人,2017;《自然》545:234)、然后通过尺寸排阻色谱法进一步纯化。对于亲和力测量,将ASGR1结合剂的Fab版本用人IgG1CH1结构域的C端处的(His)6标签、之后是5聚体接头(GSGSG)来形成并且通过His标签树脂、然后通过尺寸排阻色谱法纯化。将所有测试的蛋白质通过SDS-聚丙烯酰胺电泳进行检查并且估计纯度为至少90%。

[0296] SuperTop Flash(STF)测定:使用含有由报告的(Janda等人,2017;《自然》545:234)Wnt反应性启动子(Super Top Flash报告基因测定,STF)控制的荧光素酶基因的细胞系来测量Wnt信号传导活性。简而言之,处理前24小时将细胞以每孔10,000个的密度接种在96孔板中,然后将细胞单独地或与30%Wnt3a条件培养基一起用RSPO或模拟蛋白处理过夜。Wnt3a条件培养基遵循供应商推荐的条件由ATCC-CRL-2647 Wnt3a分泌性L细胞制备。用荧光素酶细胞培养裂解试剂(普洛麦格公司(Promega))来裂解细胞,并且使用供应商建议的程序用荧光素酶测定系统(普洛麦格公司)测量活性。一式三份地将数据绘制成均值-/+标准偏差并且使用Prism(GraphPad软件)通过非线性回归进行拟合。对于外源性受体的过表达,将细胞在真核表达启动子下用含有关注的受体(ASGR1是来自金斯瑞公司(GenScript)的克隆OHU03658D,ASGR2是内部克隆的同种型d/NP_001188281.1,并且TFRC是来自赛诺生

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物技术有限公司(SinoBiologicals)的克隆HG11020-UT)的质粒瞬时转染,然后将细胞分到96孔板(每孔20,000个细胞)中,以在转染后24小时进行STF测定。

[0297] 亲和力测量:通过生物层干涉法(BLI)使用Octet Red 96(加利福尼亚州佛瑞蒙的PALL ForteBio公司(PALL ForteBio,Fremont,CA))仪器在30℃以1000 rpm利用链霉亲和素(SA)生物传感器或抗hIgG Fc捕获(AHC)生物传感器来测定RSPO衍生的蛋白质与LGR5、RNF43或ZNRF3的结合动力学以及抗ASGR Fab与人和/或小鼠ASGR1的结合。在分别捕获到SA生物传感器和AHC生物传感器的运行缓冲液(PBS、0.05%吐温-20、0.5%BSA,pH 7.2)中将RNF43或ZNRF3或ASGR1的生物素化细胞外结构域(ECD)和人IgG1融合的LGR5-ECD(R&D系统公司(R&D systems))的Fc部分稀释到50 nM,直到偶联水平达到约1.0 nm。在捕获RNF43、ZNRF3或LGR5的ECD之后,将生物传感器浸入含有在运行缓冲液中的7种不同浓度下的相关测试分子的孔以及仅将运行缓冲液作为参考通道的孔中。基于缔合相在介于140到145秒之间对与LGR5、RNF43和ZNRF3的结合的平均反应通过稳态分析来测定K_D。对于与ASGR的结合,使用Octet®Red数据分析软件(Fortebio公司)通过曲线模型拟合来测定K_D。

[0298] 细胞流式细胞术:将HEK293细胞单独或与ASGR1一起用过表达ZNRF3(金斯瑞公司OHu22977)的质粒瞬时转染并且然后在10 nM最终浓度下在具有或不具有10%Wnt3a条件培养基的情况下用RSPO衍生分子处理24小时。将细胞使用Gibco公司(Gibco)无酶解离缓冲液解离、洗涤并重悬于FACS缓冲液(具有1%BSA和0.02%叠氮化钠的1X PBS)中。将细胞与1 nM 18R5 IgG(泛卷曲蛋白)温育1小时。洗涤之后,将细胞与山羊抗人IgG Alexa Fluor 647(英杰公司)温育40分钟。将细胞用FACS缓冲液洗涤并且使用BD Accuri C6+流式细胞仪进行多通道分析。用FlowJo软件对数据进行处理,并且以直方绘图显示荧光信号。

[0299] 细胞蛋白的蛋白质印迹分析:用补充有蛋白酶和磷酸酶抑制剂的RIPA缓冲液(50mM Tris-HCl pH 7.4、150 mM NaCl、1%IGEPAL CA630、0.5%脱氧胆酸钠、0.1%SDS和1 mM EDTA)对细胞进行裂解。将细胞裂解物在4℃以15,000 rpm旋转5分钟,并且将上清液通过SDS-PAGE溶解、转移到硝酸纤维素膜并且用一级抗体进行探测、然后是HRP缀合的二级抗体和ECL膜检测。抗LRP6一级抗体、抗磷酸-LRP6一级抗体(Ser1490)和抗DLV2一级抗体来自细胞信号传导科技公司(Cell Signaling Technology)。抗α微管蛋白抗体来自西格玛奥德里奇公司。

[0300] 基因表达的半定量PCR分析:使用Qiagen RNeasy微试剂盒(凯杰公司(Qiagen),74004)从人细胞培养物(HEK293、Huh-7和A431)中提取RNA。使用SuperScript™ VILO™ cDNA合成试剂盒(赛默飞世尔公司(ThermoFisher),11754050)产生cDNA。通过使用TaqMan®快速高级主混合物(Fast Advanced Master Mix)(赛默飞世尔公司,4444963)以及Hs01005019_m1 ASGR1、Hs00154160_m1 ASGR2和Hs00951083_m1 TFRC探针(赛默飞世尔公司,4331182)来测量人ASGR1、ASGR2和TFRC表达。使用Hs01060665_m1探针(赛默飞世尔公司,4331182)将值相对于组成型肌动蛋白B基因的表达标准化。使用MagMAX™ mirVana™总RNA分离试剂盒(赛默飞世尔公司,A27828)从小鼠组织(肝样品和小肠样品)中提取RNA。使用高容量cDNA逆转录试剂盒(赛默飞世尔公司,43-688-14)或SuperScript™ IV VILO™主混合物(赛默飞世尔公司,目录号11756050)产生cDNA。通过使用TaqMan®快速高级主混合物(赛默飞世尔公司,4444963)以及Mm00443610_m1 Axin2、Mm01278617_m1 Ki67、Mm01300555_g1 wnt1、Mm00470018_m1 wnt2、Mm00437336_m1 wnt3、Mm01194003_m1 wnt4、

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Mm00437347_m1 wnt5a、Mm01183986_m1 wnt5b、Mm00437353_m1 wnt6、Mm00437356_m1 wnt7a、Mm01301717_m1 wnt7b、Mm01157914_g1 wnt8a、Mm00457102_m1 wnt9b、Mm00442104_m1 wnt10b、Mm00437327_g1 wnt11、Mm00446420_m1 wnt16、Mm00507077_m1 rspo1、Mm00555790_m1 rspo2、Mm01188251_m1 rspo3和Mm00615419_m1 rspo4探针(赛默飞世尔公司,4331182)来测定小鼠Axin2和Ki67 mRNA表达。使用Mm02619580_g1探针(赛默飞世尔公司,4351368)将值相对于组成型肌动蛋白B基因的表达标准化。

[0301] 动物研究:从杰克逊实验室(美国缅因州巴港)(Bar Harbor,ME,USA)获得六周龄的C57Bl/6J雄性小鼠,并且将其分组饲养。所有动物实验均符合国家科学院(National Academy of Sciences)制定的"实验室动物护理和使用指南(Guide for the Care and Use of Laboratory Animals)"的准则。用于动物实验的方案得到了Surrozen机构动物护理和使用委员会(Surrozen Institutional Animal Care and Use Committee)批准。在开始实验之前至少两天,使小鼠适应环境。使小鼠无限制地饮用纯化的实验室级酸化水并且随意喂养(2018Teklad全球18%蛋白质啮齿动物饮食)。保持小鼠在30%到70%的湿度环境和20℃到26℃范围内的室温下处于12/12小时光照/黑暗循环。

[0302] 在小鼠针对人ASGR基因表达被人源化的情况下,在第0天向每只小鼠静脉内给药1×10^{11}个ssAAV8-CAG-hASGR1基因组拷贝(宾夕法尼亚州马尔文的载体生物实验室(Vector Biolabs,Malvern,PA))。在第7天,向小鼠腹膜内注射(i.p.)αGFP、Fc-RSPO2-WT、αGFP-RSPO2-RA或αASGR1-RSPO2-RA。在蛋白质给药后的指示时间,用异氟醚麻醉小鼠,并且通过心脏穿刺取得血液。收集肝左叶和十二指肠的一部分以供分析。

[0303] 实例1

[0304] 组织特异性WNT信号传导增强分子的表征

[0305] 为了产生组织特异性RSPO样Wnt信号传导增强子分子,靶向脱唾液酸糖蛋白受体(ASGR)。ASGR是由两种多肽ASGR1和ASGR2构成的异源寡聚体,所述两种多肽主要表达在肝细胞上并且经历快速的内吞作用。将ASGR1抗体(例如,RO-01)转换成scFv格式并且将其融合到不同RSPO2变体的N端以产生αASGR1-RSPO2-WT、αASGR1-RSPO2-RA或αASGR1-RSPO2-5mut(SEQ ID NO:11-16,图1B,右图)。在此设计中,融合物的抗体部分充当引导细胞/组织特异性的"靶向模块",而RSPO2组分充当与E3连接酶相互作用的"作用模块"(图1B)。为了消除LGR结合,将点突变引入到RSPO2的Fu2结构域内的据报告对与LGR蛋白的结合至关重要的两个高度保守的疏水残基中,引入了F105R和F109A(图1B,名为αASGR1-RSPO2-RA)。为了验证Fu1结构域在E3连接酶中的参与,还添加了Fu1结构域中的据报告对此相互作用至关重要的另外的点突变(R65A/R69A/Q70A)(图1B,含有Fu1和Fu2两者中所有5个突变F105R/F109A/R65A/R69A/Q70A的αASGR1-RSPO2-5mut)。作为靶向模块的阴性对照,将针对绿色荧光蛋白(GFP)的scFv抗体融合到相同的人Rspo2片段和人Rspo2突变体(α-GFP-Rspo2-WT、α-GFP-Rspo2-RA和α-GFP-Rspo2-5mut;SEQ ID NO:5-10,图1B;左图)。

[0306] 在Octet系统上使用生物层干涉法来验证Fu1和Fu2突变对LGR和E3连接酶结合的影响。测量了野生型(αGFP-RSPO2-WT)或突变体(αGFP-RSPO2-RA或αGFP-RSPO2-5mut)与重组LGR5蛋白的结合,并且观察到了野生型的结合,但未观察到两个Fu2突变RSPO变体的结合(图1C)。由于αGFP-RSPO2-RA与E3连接酶、ZNRF3和RNF3的结合未受影响,所以Fu2突变的效果对LGR相互作用具有特异性(图1D),而在Fu1结构域中含有突变的αGFP-RSPO2-5mut另外

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地影响了与E3连接酶的相互作用(图1D)。

[0307] 在HEK293和Huh-7 Wnt反应性STF细胞中测试Fu1和Fu2突变对RSPO2增强Wnt信号传导的能力的影响。如图2B的右图中示出的,在不存在任何添加的Wnt的情况下,RSPO2蛋白均不活化Wnt信号传导。在存在Wnt3a条件培养基(CM)的情况下,αGFP-RSPO2-WT以剂量反应性方式增强Wnt3a活性,然而Fu1(αGFP-RSPO2-RA)或Fu1+Fu2(αGFP-RSPO2-5mut)中的突变完全无活性,这与RSPO2活性依赖于接合E3连接酶和LGR蛋白两者的能力的预期一致。

[0308] 将靶向模块从抗GFP切换到抗ASGR1对RSPO2与E3连接酶或LGR5蛋白的相互作用没有明显影响。αASGR1-RSPO2-WT与E3连接酶和LGR5两者结合,αASGR1-RSPO2-RA丧失了与LGR5相互作用的能力,并且αASGR1-RSPO2-5mut丧失了与LGR5和E3连接酶两者相互作用的能力(图1C和1D)。

[0309] 还在HEK293 STF Wnt反应性报告基因细胞和Huh-7 STF Wnt反应性报告基因细胞两者中评估这些分子调节Wnt信号传导的能力。在HEK293 STF细胞中,由于这些分子不表达ASGR1(如通过半定量PCR分析验证的,图2A),因此抗ASGR1-RSPO2融合蛋白几乎与其抗GFP对应物相同地表现(图2B)。在不存在添加的Wnt的情况下,αASGR1-RSPO2蛋白均不活化Wnt信号传导(图2B,右图)。在存在Wnt3a条件培养基(CM)的情况下,αASGR1-RSPO2-WT以类似于αGFP-RSPO2-WT的剂量反应性方式增强Wnt3a活性,而αASGR1-RSPO2-RA和αASGR1-RSPO2-5mut无活性(图2B)。相比之下,在表达ASGR1的人肝癌细胞系Huh-7 STF细胞中,αASGR1 scFv的融合显著地挽救了RSPO2-RA突变体增强Wnt3a诱导的信号传导的能力(图2B,左下图)。αASGR1-RSPO2-5mut保持无活性,这证明观察到的αASGR1-RSPO2-RA的活性依赖于其接合E3连接酶的能力。有趣的是,相比于αGFP-RSPO2-WT,αASGR1 scFv与WT RSPO2的融合αASGR1-RSPO2-WT还在剂量反应曲线中示出了显著的约6倍的左移(图2B),这表明新的靶向模块αASGR1 scFv的连接可能已经与LGR协同以进一步增强WT RSPO2功能。

[0310] 除了STF报告基因系统之外,还通过蛋白质印迹分析来直接检查Wnt信号传导活性。如图2C中示出的,虽然用10%Wnt3a CM处理Huh-7细胞未诱导显著的变化,但αGFP-RSPO2-WT的添加除了增加LRP6蛋白的总水平之外还增强了Wnt3a反应并且显著地增加了磷酸化LRP6蛋白和DVL2蛋白两者。如在αGFP-RSPO2-RA处理的细胞中所看到的,Fu2中的突变消除了此增强活性。然而,与αASGR scFv的融合αASGR1-RSPO2-RA挽救了与αGFP-RSPO2-RA的功能表型的损失、略微增加了总LRP6蛋白并且显著增加了磷酸化水平LRP6以及在较小程度上DVL2(图2C)。

[0311] 为了进一步证实抗ASGR1 RSPO2-RA融合蛋白的细胞类型特异性活性依赖于靶向受体ASGR的存在,用对全长人ASGR1 cDNA进行编码的质粒瞬时转染HEK293细胞。由于ASGR1和ASGR2形成复合物,因此除了转染不相关的受体人转铁蛋白受体1(TFR1,由TFRC基因编码)作为阴性对照外,还执行两个ASGR cDNA的共转染。与未转染的亲本HEK293细胞类似,在用TFRC转染的细胞中,仅与αGFP或αASGR1的RSPO2-WT融合蛋白以Wnt依赖性方式增强了Wnt信号传导(比较图2B的顶部图与图3A的顶部图)。相比之下,在单独用ASGR1转染或用ASGR1和ASGR2两者共转染的细胞中,αASGR1 scFv的融合部分地挽救了RSPO2-RA突变体增强Wnt信号传导能力的功能损失。αASGR1的融合也使RSPO2-WT蛋白的剂量反应向左移位,这与在Huh-7细胞中观察到的类似(比较图2B的下图与图3A的中间图和下图)。αASGR1-RSPO融合分子的活性也完全依赖于Wnt配体的存在(图3A,右图)。

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[0312] 在另一种ASGR1阴性细胞系A431中也证实了ASGR1依赖性活性，所述A431衍生自人表皮样癌并且不表达ASGR基因(图2A)。与HEK293转染研究类似，αASGR1-RSPO2-RA仅在表达ASGR1的A431细胞中，但未在表达阴性对照受体TFR1的A431细胞中挽救RSPO2-RA活性(图3B)。此外，αASGR1 scFv也使RSPO2-WT剂量反应曲线向左移位，并且所有RSPO衍生物的活性完全依赖于Wnt配体的存在(图3B，右图)。来自图2和3的所有结果一起证明，RSPO介导的Wnt信号增强活性可以通过靶向不同细胞表面受体ASGR1而不是LGR来置换。所得RSPO模拟分子在Wnt依赖和其通过E3连接酶的作用方面类似于WT RSPO，但不同之处在于其Wnt信号传导增强是细胞类型特异性的。

[0313] 为了进一步验证RSPO衍生分子的作用机制，检查了细胞表面上的卷曲蛋白(FZD)受体水平。为了使系统敏感，在处理前通过瞬时转染来过表达ZNRF3。使用泛卷曲蛋白抗体18R5(基于专利EP2331136A4进行克隆)对细胞进行染色，并且发现与未经处理的细胞相比，αGFP-RSPO2-WT明显增加了信号(如所预期的)，并且在用αGFP-RSPO2-RA或αASGR1-RSPO2-RA处理时未观察到这种位移(图3C，顶部)。这与HEK293细胞中缺乏这两种RSPO-RA构建体的活性一致。另一方面，当细胞用ZNRF3和ASGR1两者共转染时，αASGR1-RSPO2-RA就像αGFP-RSPO2-WT一样增加泛FZD染色，从而使αGFP-RSPO2-RA与未经处理的细胞类似(图3C，底部)。这与通过RSPO或RSPO模拟物来移除ZNRF3/RNF43 E3连接酶一致，所述移除使Wnt受体稳定。

[0314] 为了验证组织特异性Wnt信号增强分子在另外的细胞类型中增强Wnt信号传导的能力，测试靶向不同细胞表面受体转铁蛋白受体1(TFR1)的第二新颖双特异性构建体。TFR1由TFRC基因编码并且在许多细胞类型中广泛表达。据报告，TFR1经历了连续的内吞作用。构建并表征含有与人TFR1的scFv结合剂的融合蛋白RSPO2-WT、RSPO2-RA或RSPO2-5mut(SEQ ID NO:17-22)。除了抗GFP组分或抗ASGR1组分被抗TFR1 scFv置换之外，这些融合蛋白的设计类似于图1B。与抗GFP融合蛋白或抗ASGR1融合蛋白类似，αTFR1-RSPO2-RA蛋白丧失了与LGR5相互作用的能力，并且αTFR1-RSPO2-5mut丧失了与LGR5和E3连接酶两者相互作用的能力(图4A-B)。当在存在Wnt源的情况下在HEK293 STF报告基因测定中检测时，TFR1靶向的RSPO2-RA(αTFR1-RSPO2-RA)刺激Wnt信号传导并且展现出比野生型RSPO(αGFP-RSPO2-WT)大约20倍的效力。(图4C)。抗TFR1 RSPO2-WT融合物αTFR1-RSPO2-WT进一步将EC_{50}又提高了约20倍，这与αGFP-RSPO2-WT相比效力提高了近400倍。在Huh-7 STF细胞中也获得了类似的结果，这与两种细胞系中靶向受体的表达一致(图2A)。与RSPO的机制一致的是，在不存在Wnt配体的情况下，未观察到抗TFR1 RSPO模拟分子的Wnt信号传导(图4C，右图)。观察到抗TFR1 RSPO2融合蛋白有更强有力的活性表明，受体和结合剂的特定结合可以在组织特异性Wnt信号增强分子的活性中发挥作用。

[0315] 如用αGFP-RSPO2-WT看到的，αTFR1-RSPO2-RA而非αASGR1-RSPO2-RA在HEK293 STF细胞中存在Wnt刺激的情况下刺激了LRP6和DVL2的磷酸化并且增加了总LRP6蛋白水平(图4D)。通过流式细胞术分析还检查了RSPO模拟分子对细胞表面上的FZD受体水平的影响。如图4E中示出的，用αGFP-RSPO2-WT处理HEK293细胞，αTFR1-RSPO2-RA而非αGFP-RSPO2-RA增加了这些细胞上的通过泛FZD抗体测量的FZD受体水平。

[0316] 实例2

[0317] 使用原型肝特异性WNT信号传导增强分子的体内肝效果

[0318] 为了证明αASGR1-RSPO2-RA可以在体内以组织特异性方式活化Wnt信号传导通路，

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用αASGR1-RSPO2-RA和对照蛋白对小鼠进行处理。由于scFv-RSPO2融合蛋白的分子量在约40kDa的范围内，因此为了增加其血浆半衰期，将结合剂的scFv切换为IgG格式，其中RSPO2融合到IgG重链的N端。αASGR1-RSPO2-RA-IgG(SEQ ID NO:29-32)在HEK293细胞中具有与αGFP-RSPO2-RA-IgG(SEQ ID NO:25-28)类似的效力，但在Huh-7细胞中远比后者更具效力且有效(图5A)。实际上，在100pM时的活性αASGR1-RSPO2-RA-IgG与10nM时αGFP-RSPO2-RA-IgG的活性相当(图5A，左下图)，这表明以IgG格式保存了强靶向效果。

[0319] 通过IV注射ssAAV8-CAG-hASGR1诱导了人ASGR1在小鼠肝中的表达，在用重组蛋白处理前7天，示出每只小鼠1×10^{11}个基因组颗粒的剂量实现了与内源性肝Asgr1mRNA相当的转基因表达水平(数据未示出)。

[0320] 在第一研究中(图5B)，向小鼠腹膜内注射等摩尔剂量的αGFP-IgG(SEQ ID NO:25-26和33-34)(1mg/kg)、Fc-RSPO2-WT(SEQ ID NO:23-24)(0.46mg/kg)、αGFP-RSPO2-RA-IgG(SEQ ID NO:25-28)(1mg/kg)或αASGR1-RSPO2-RA-IgG(SEQ ID NO:29-32)(1mg/kg)重组蛋白(具有大约匹配的摩尔浓度，n＝8只小鼠/组)。8小时后收集肝和小肠样品，以供表达分析。与用αGFP阴性对照或αGFP-RSPO2-RA-IgG阴性对照处理的小鼠体内的肝Axin2表达相比，用Fc-RSPO2-WT和αASGR1-RSPO2-RA-IgG处理显著地诱导了肝Axin2表达(图5C)。相比之下，用Fc-RSPO2-WT但不用αASGR1-RSPO2-RA-IgG处理显著增加了小肠Axin2表达(图5D)。这些结果表明，αASGR1-RSPO2-RA-IgG可以在体内以组织特异性方式活化Wnt通路。

[0321] 在第二研究中(图6A)，向小鼠腹膜内注射αGFP-IgG(1mg/kg)、αGFP-RSPO2-RA-IgG(1mg/kg)或αASGR1-RSPO2-RA-IgG(1mg/kg)重组蛋白(n＝10只小鼠/组)。48小时后收集肝和小肠样品，以供表达分析和组织免疫化学。用αASGR1-RSPO2-RA-IgG处理诱导了细胞增殖标志物基因Mki67的表达(图6B)，并且与用αGFP-IgG阴性对照或αGFP-RSPO2-RA-IgG阴性对照处理的小鼠相比显著增加了肝中Ki-67阳性细胞的数量(图6C-D)。相比之下，在小肠中未观察到通过αASGR1-RSPO2-RA-IgG诱导的此Mki67表达(图5E)。这些结果表明，αASGR1-RSPO2-RA-IgG可以在肝实质细胞中以组织特异性方式刺激增殖。

[0322] 实例3

[0323] 抗体的生成

[0324] 对针对ASGR、ZNRF3和RNF43多肽序列的抗体进行鉴别。对于用于抗体筛选和免疫的重组蛋白的产生，将以下蛋白质的细胞外结构域(ECD)克隆到具有His/Avi标签的pcDNA真核表达载体中：人ASGR1(hASGR1，NCBI参考序列NP_001662.1，残基62-291；SEQ ID NO:35-36(分别为多核苷酸和多肽))、人ASGR2(hASGR2，NCBI参考序列NP_550436.1，残基66-292；SEQ ID NO:37-38(分别为多核苷酸和多肽))、猕猴ASGR1(cynoASGR1，序列ID XP_005582755.1，残基62-291；SEQ ID NO:39-40(分别为多核苷酸和多肽))、猕猴ASGR2(cynoASGR2，序列克隆自来自Fisher/Zyagen实验室(Fisher/Zyagen Labs)的猕猴肝cDNA样品；SEQ ID NO:41-42(分别为多核苷酸和多肽))、人RNF43(hRNF43，NCBI参考序列XP_011523257.1，残基44-198；SEQ ID NO:43-44(分别为多核苷酸和多肽))、ZNRF3(hZNRF3；NCBI参考序列NP_001193927.1，残基56-219；SEQ ID NO:45-46(分别为多核苷酸和多肽))。将构建体用Expi293F细胞(赛默飞世尔科技公司)表达、通过Ni-NTA树脂、然后通过尺寸排阻色谱法纯化。对于噬菌体展示，将蛋白质根据已发表的方法(Janda等人，《自然》；545:234)生物素化。

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[0325] 将生物素化的抗原固定以便针对噬菌体展示文库进行淘选，并且对阳性克隆进行测序。进行进一步分析，所述进一步分析包含在Expi293F细胞中的表达和对抗原结合的表征。

[0326] 还使用非生物素化的抗原对小鼠进行免疫以生成杂交瘤。通过ELISA针对具有含有相同的纯化标签作为对照的对照蛋白针对免疫原并且通过流式细胞术分析(ASGR表达性Huh-7作为测试系，并且ASGR非表达性HEK293作为对照)对杂交瘤系进行筛选。对所选择的杂交瘤系进行测序，并且因此生成重组Fab或IgG以便进一步结合表征。

[0327] 使用具有链霉亲和素(SA)涂覆的生物传感器(PALL ForteBio公司)的Octet Red96平台(加利福尼亚州佛瑞蒙的PALL ForteBio公司)通过生物层干涉法(BLI)进行重组Fab或IgG的结合表征。将生物素化的抗原稀释到50nM以便固定到传感器上。在固定后，将传感器浸入到含有七种浓度的测试分子的样品中。通过以1:1结合模型对所得数据进行拟合来测定K_D的值。表2C提供了精选克隆的结合数据。

[0328] 图7提供了示出被鉴别为hASGR1(图7A和7C)或hASGR2(图7B)的说明性抗体的结合的数据。

[0329] 实例4

[0330] 原初健康小鼠中抗ASGR1-RSPO2-RA的体内剂量滴定和组织特异性

[0331] 在健康原初小鼠中进一步检查IgG格式的ASGR1靶向分子和对照分子的活性。这些研究中使用的αASGR1抗体(例如，RO-01)与人和鼠类ASGR1受体两者具有类似的亲和力(图9A)。

[0332] 在此研究中，向六周龄C57B1/6J雄性小鼠腹膜内注射(i.p.)指示剂量的α-β-Gal-IgG、Fc-RSPO2-WT、αGFP-RSPO2-RA或αASGR1-RSPO2-RA(n＝8只/组)。在蛋白质给药后48小时，用异氟醚麻醉小鼠，并且通过心脏穿刺取得血液。收集肝左叶和十二指肠的各部分并且将其速冻以进行qPCR分析或固定在福尔马林中24小时，然后转移到70％EtOH以进行免疫组织化学分析。

[0333] 与αGFP-RSPO2-RA-IgG(SEQ ID NO:25-28)和其它对照相比，针对αASGR1-RSPO2-RA-IgG(SEQ ID NO:29-32)执行剂量反应，以检查Wnt靶基因Axin2的诱导。小鼠接受从0.1mg/kg到30mg/kg的范围的被测试蛋白质的腹膜内(i.p.)注射。48小时后收集肝和小肠样品，以进行基因表达分析。以1mg/kg和10mg/kg处理时，Fc-RSPO2-WT(SEQ ID NO:23-24)增加了在肝和小肠两者中的Axin2表达(图9B)。相比之下，10mg/kg和30mg/kg的αASGR1-RSPO2-RA-IgG诱导了仅在肝中的Axin2表达，但在小肠中未诱导。重要的是，此特异性依赖于αASGR1靶向模块，因为未靶向分子αGFP-RSPO2-RA-IgG在高达30mg/kg处理时在任一组织中均未示出对Axin2表达的体内影响(图9B)。用0.01mg/kg和10mg/kg的对照抗体抗β-半乳糖苷酶(α-β-Gal-IgG，SEQ ID NO:155-158)未观察到影响。

[0334] 在增殖标志物Ki67基因的表达中也观察到了αASGR1-RSPO2-RA-IgG的类似组织特异性和对靶向模块的依赖性(图9C)。为了检查肝细胞中是否发生增殖，用针对Ki67蛋白具有特异性的抗体和成熟肝细胞标志物之一HNF4α对肝样品进行共染色。用αASGR1-RSPO2-RA-IgG和Fc-RSPO2-WT处理的肝似乎增加了用HNF4α共定位的Ki67阳性核的数量，而用αGFP-RSPO2-RA-IgG或α-β-Gal-IgG处理的肝似乎具有少得多的Ki67染色(图9D)。这些结果合起来表明，αASGR1-RSPO2-RA-IgG可以在体内以肝特异性方式活化Wnt通路，并且肝细胞

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是响应于此刺激的主要细胞群。

[0335] 实例5

[0336] 组织靶向RSPO模拟物对慢性硫代乙酰胺诱导的小鼠肝纤维化模型中的肝功能的影响

[0337] 用硫代乙酰胺(TAA)对六周龄C57Bl/6J雄性小鼠进行处理。在1号研究(Wnt和Rspo基因表达谱)中,将TAA以200mg/L的浓度添加到饮用水中二十七周以诱导肝纤维化。另外,在TAA条件作用的最后四周期间,每周3次向小鼠腹膜内施用TAA。在2号研究(在第3天和第7天时的肝和小肠Axin2和Ki67表达)中,将TAA以200mg/L的浓度添加到饮用水中二十周以诱导肝纤维化。另外,在TAA条件作用的最后六周期间,每周3次向小鼠腹膜内施用TAA。在3号研究(在第3天、第7天和第14天时的INR分析)中,将TAA添加到饮用水中十八周。在TAA暴露的最后九周期间每周3次还向小鼠腹膜内施用200mg/kg TAA。在用重组蛋白给药前2天中断TAA处理,并且使小鼠恢复饮用经过纯化的实验室级酸化饮用水。向小鼠腹膜内(i.p.)注射重组α-β-gal-IgG(10mpk)或Fc-RSPO2-WT(10mpk)每周两次或者αASGR1-RSPO2-RA-IgG(10mpk)每天一次。在指示的时间,使用Roche CoaguChek——XS+来测量INR。在开始给药后3天、7天或14天,用异氟醚麻醉小鼠,并且通过心脏穿刺取得血液。收集肝左叶和十二指肠的一部分以供分析。将福尔马林固定并且石蜡包埋的肝样品切片并且用抗Ki-67兔抗体(Abcam公司,ab15580)染色。使用Image J对每个随机选择的场(使用10倍物镜的100倍放大率)的Ki-67+阳性核的数量进行计数。

[0338] 在慢性硫代乙酰胺(TAA)模型中检查αASGR1-RSPO2-RA-IgG的活性和功效,其中观察到了广泛的肝纤维化并且肝功能受损。在此模型中,包含对许多Wnt配体进行编码的基因的Wnt信号传导通路组分上调(图10A)。相比之下,四个R-脊椎蛋白的表达保持不变或者甚至在Rspo2的情况下减少。Rspo4在小鼠肝中几乎不可检测到(图10A)。因此,肝特异性RSPO模拟物的施用可以是有益的(图10A)。

[0339] 图10B中概述了实验设计,所述实验设计概述了TAA预处理和随后的蛋白质处理(αASGR1-RSPO2-RA-IgG和对照蛋白SEQ ID NO:23-24、29-32、155-156和159-160)的持续时间。进行了类似设计的两项研究。在一项研究中,在开始蛋白质处理后的0天、3天和7天终结小鼠。在第二研究中,在开始蛋白质处理后的0天和14天终结小鼠(图10B)。收集肝和小肠样品,并且评估其基因表达的变化。如所预期的,αASGR1-RSPO2-RA-IgG在第3天和第7天时使Axin2表达的肝特异性增加,而Fc-RSPO-WT在肝和小肠两者中均诱导了Axin2(图10C)。用α-β-Gal-IgG对照处理时未观察到变化。αASGR1-RSPO2-RA-IgG还以肝特异性方式增加了Ki67表达(图10C)。

[0340] 为了监测肝功能,在处理期间在指示的时间取血液样品,并且将血液样品用于测量凝血酶原时间的国际标准化比率(INR)。正常小鼠具有大约0.9的INR。由于严重的肝损害,TAA处理使INR增加到1.1(图10D)。TAA移除后,已知小鼠展现出肝损害的一些自然消退,这与未经处理的动物体内观察到的INR从第0天的1.1降至第14天的<1.0一致。然而,αASGR1-RSPO2-RA-IgG加速了INR恢复,因为经过100%的αASGR1-RSPO2-RA-IgG处理的小鼠到第3天具有0.9的INR。在第7天,经过Fc-RSPO2-WT处理的小鼠的INR与经过α-β-Gal处理的小鼠相比有所降低并且在第14天达到与αASGR1-RSPO2-RA-IgG相同的效果。因此,肝特异性αASGR1-RSPO2-RA-IgG分子可以改善慢性肝病模型中的肝合成功能。

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[0341] 实例6

[0342] 组织靶向RSPO模拟物对慢性CCL_4诱导的小鼠肝纤维化模型中的肝功能的影响

[0343] 在用CCl_4加烯丙醇生成的第二小鼠肝纤维化模型中检查αASGR1-RSPO2-RA-IgG的活性和功效。在10天内用CCl_4(在第1天、第4天、第7天、第10天时0.5mL/kg)加烯丙醇(在第2天、第5天、第8天时0.0125mL/kg)间歇地处理五十四只8-9周龄C57BL/6雄性小鼠(杰克逊实验室),然后进行8周的CCl_4处理(0.5mL/kg,两次/周)。图12中展示了处理方案。在CCl_4处理后,以不连续的CCl_4处理用蛋白质向小鼠给药2周。处理组如下:10mg/kgαASGR1-RSPO2-RA-IgG2,n=8(每天给药);10mg/kgαGFP-RSPO2-RA-IgG,n=8(每天给药);4.6mg/kg Fc-RSPO2-WT,n=7(两次/周给药);10mg/kgα-β-Gal-IgG,n=8(两次/周给药);非蛋白对照,n=8。另外的对照组包含非CCl_4处理(橄榄油载体(0.5mL/kg)),n=8;原初对照,n=7。在第0天、第3天、第7天(蛋白质给药的第一天表示为第0天)取小鼠血液进行INR(国际标准化比率)测试。在第14天终结所有小鼠。

[0344] 处死后,测量总体重和肝重,对血液、肝和小肠组织进行收集和保存以进行测试。在用RSPO2阳性对照处理的组以及用RSPO模拟物αASGR1-RSPO2-RA-IgG2处理的那些组中,肝重示出了上升趋势。当测量肝/体重比时,仅经过RSPO2处理的小鼠具有统计学上显著的增加。

[0345] 在蛋白质处理的第0天、第7天和第14天,测量小鼠血液中III型前胶原N端肽(P3NP),作为组织修复和纤维化的度量。与经过橄榄油处理的组和原初对照相比,在用CCl_4处理的所有组中均观察到显著增加,这与标记的肝纤维化一致。与用αGFP-RSPO2-RA-IgG(缺乏对肝的组织靶向)处理的动物(其中P3NP回降至原初小鼠中的水平(数据未示出))相比,用RSPO模拟物αASGR1-RSPO2-RA-IgG2处理的动物中P3NP水平保持较高,从而表明组织修复和细胞外基质周转正在进行。

[0346] 在两周的蛋白质处理后,作为血凝结时间的度量的凝血酶原时间(PT)指示未看到时间增加,并且在用RSPO2蛋白处理的动物中,时间实际上显著减少(数据未示出)。

[0347] 在蛋白质处理一周和两周后的时间点,在血清中进行标准肝图测量。在第7天时从尾部放血并且在第14天时从终末放血收集小鼠血清。将血清送到IDEXX实验室(加利福尼亚州佛瑞蒙)以进行肝图血清化学测量。每组含有6-8只小鼠,并且数据在表4和5中作为平均值±SEM呈现。

[0348] 表4.蛋白质处理后一周和两周在动物血液中测量的丙氨酸转氨酶(ALT)、天冬氨酸转氨酶(AST)和碱性磷酸酶(ALP)水平。

[0349]

处理组	ALT U/L +/- SEM		AST U/L +/- SEM		ALP U/L +/- SEM	
	第1周	第2周	第1周	第2周	第1周	第2周
原初	24.0 +/- 1.9	32.0 +/- 2.6	44.6 +/- 2.4	41.5 +/- 4.1	68.6 +/- 4.1	55.5 +/- 3.9
油对照	22.8 +/- 0.9	30.8 +/- 4.2	43.0 +/- 1.7	53.8 +/- 9.7	78.1 +/- 4.7	65.6 +/- 3.1
CCl_4小鼠中无蛋白质	33.2 +/- 1.0	36.4 +/- 2.5	53.6 +/- 3.9	54.8 +/- 4.0	108.6 +/- 3.5	87.8 +/- 4.1

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[0350]

CCl_4小鼠中有α-β-Gal-IgG	28.7 +/- 1.7	33.9 +/- 3.3	48.3 +/- 3.5	68.9 +/- 17.5	113.3 +/- 7.1	102.9 +/- 4.3
CCl_4小鼠中有Fc-RSPO2-WT	51.7 +/- 14.4	42.1 +/- 5.1	83.0 +/- 14.0	74.4 +/- 9.8	83.0 +/- 8.5	28.4 +/- 5.2
CCl_4小鼠中有α-GFP-RSPO2-RA-IgG	27.9 +/- 1.2	36.4 +/- 5.7	52.9 +/- 4.6	69.0 +/- 13.3	117.9 +/- 9.4	70.3 +/- 2.5
CCl_4小鼠中有αASGR1-RSPO2-RA-IgG2	59.4 +/- 27.7	57.9 +/- 18.7	85.6 +/- 33.0	98.1 +/- 20.2	***411.4 +/- 63.9**	****164.9 +/- 24.0**

[0351] *统计学上不同于经过α-β-Gal-IgG和αGFP-RSPO2-RA-IgG处理的组，$p<0.0001$；**统计学上不同于经过α-β-Gal-IgG（$p=0.0012$）和αGFP-RSPO2-RA-IgG（$p<0.0001$）处理的组；单向ANOVA。

[0352] 如表4中所示出的，ALT值和AST值与蛋白质处理和对照中的任何蛋白质处理和对照都没有统计学上的差异。然而，在一周时间点和两周时间点两者时，ALP在统计学上更高，这与如在ASGR1 KO小鼠模型中描述的由于ASGR受体的消除而引起的碱性磷酸酶蛋白水平的上调一致（参见例如《细胞宿主微生物（Cell Host Microbe）》.2018年10月10日；24（4）：500-513）。

[0353] 表5.蛋白质处理后一周和两周在动物的血液中测量的白蛋白和胆红素水平。

[0354]

处理组	白蛋白 g/dL +/- SEM		胆红素 mg/dL +/- SEM	
	第1周	第2周	第1周	第2周
原初	3.1 +/- 0.2	2.9 +/- 0.0	0.2 +/- 0.0	0.1 +/- 0.0
溏对照	3.2 +/- 0.1	2.8 +/- 0.0	0.2 +/- 0.0	0.2 +/- 0.0
CCl_4小鼠中无蛋白质	3.5 +/- 0.1	2.8 +/- 0.0	0.2 +/- 0.0	0.2 +/- 0.0
CCl_4小鼠中有α-β-Gal-IgG	3.2 +/- 0.2	2.8 +/- 0.0	0.2 +/- 0.0	0.2 +/- 0.0
CCl_4小鼠中有Fc-RSPO2-WT	2.6 +/- 0.1	***1.6 +/- 0.1**	0.2 +/- 0.0	0.1 +/- 0.0
CCl_4小鼠中有α-GFP-RSPO2-RA-IgG	3.0 +/- 0.1	2.5 +/- 0.0	0.2 +/- 0.0	0.2 +/- 0.0
CCl_4小鼠中有αASGR1-RSPO2-RA-IgG2	2.5 +/- 0.1	***2.2 +/- 0.1**	0.2 +/- 0.0	0.2 +/- 0.0

[0355] *统计学上不同于经过α-β-Gal-IgG处理的组，Fc-RSPO2-WT为$p<0.0001$，并且αASGR1-RSPO2-RA-IgG2为$p=0.0009$；**统计学上不同于经过α-β-Gal-IgG（$p<0.0001$）和α-GFP-RSPO2_RA-IgG（$p<0.0009$）处理的组；单向ANOVA。

[0356] 虽然在处理后一周对白蛋白、胆红素水平没有显著影响，但在蛋白质处理两周后与α-β-Gal-IgG蛋白对照和α-GFP-RSPO2_RA-IgG蛋白对照相比在RSPO2阳性对照和RSPO模拟物（αASGR1-RSPO2-RA-IgG2）处理组两者中观察到血液中的白蛋白显著减少。此结果表明，由于增加的Wnt信号传导诱导中心周围肝细胞扩张增加，门静脉周围肝细胞的功能出现预期的临时关闭。

[0357] 使用半定量PCR来测量用蛋白质处理的肝和小肠中基因表达的变化（表6）。

[0358] 表6.如通过qPCR测量的肝和小肠中Wnt诱导型基因和增殖标志物基因的表达的变化

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[0359]

处理组	肝				小肠		
	Axin2	*Hal*	*Ki67*	*细胞周期蛋白D1*	*Axin2*	*Ki67*	*细胞周期蛋白D1*
原初	1.0 +/- 0.1	1.0 +/- 0.00	1.0 +/- 0.1	1.0 +/- 0.1	1.0 +/- 0.1	1.0 +/- 0.1	1.0 +/- 0.2
沫对照	0.7 +/- 0.1	0.8 +/- 0.0	0.6 +/- 0.1	1.1 +/- 0.1	0.7 +/- 0.0	0.7 +/- 0.1	0.7 +/- 0.1
CCl_4小鼠中无蛋白质	1.0 +/- 0.1	1.0 +/- 0.1	2.3 +/- 0.4	2.0 +/- 0.3	0.8 +/- 0.1	0.9 +/- 0.1	0.6 +/- 0.1
CCl_4小鼠中有α-βGal-IgG	2.2 +/- 0.2	1.0 +/- 0.1	2.8 +/- 0.4	2.8 +/- 0.4	1.0 +/- 0.1	0.6 +/- 0.1	1.4 +/- 0.3
CCl_4小鼠中有 Fc-RSPO2-WT	3.3 +/- 0.8	**0.4 +/- 0.2**	**13.8 +/- 3.3**	**14.1 +/- 4.4**	1.8 +/- 0.7	0.5 +/- 0.2	0.6 +/- 0.2
CCl_4小鼠中有 αGFP-RSPO2-RA-IgG	1.8 +/- 0.2	1.0 +/- 0.1	7.2 +/- 0.9	3.6 +/- 0.5	0.6 +/- 0.1	0.7 +/- 0.0	0.4 +/- 0.1
CCl_4小鼠中有 αASGR1-RSPO2-RA-IgG2	**4.2 +/- 1.0**	**0.4 +/- 0.1**	**11.4 +/- 3.2**	6.3 +/- 1.8	0.6 +/- 0.1	0.6 +/- 0.0	0.8 +/- 0.2

[0360] *统计学上不同的变化以粗体示出。Axin2:αASGR1-RSPO2-RA-IgG2相对于α-GFP-RSPO2-RA-IgG,p＝0.0092。Hal:Fc-RSPO2-WT相对于α-βGal-IgG,p＝0.0259;αASGR1-RSPO2-RA-IgG2相对于α--Gal-IgG,p＝0.0042;αASGR1-RSPO2-RA-IgG2相对于α-GFP-RSPO2-RA-IgG,p＝0.0018。Ki67:Fc-RSPO2-WT相对于α-βGal-IgG,p＝0.0010;αASGR1-RSPO2-RA-IgG2相对于α-βGal-IgG,p＝0.0135。细胞周期蛋白D1:FcRSPO2-WT相对于α-βGal-IgG,p＝0.0004。通过单向ANOVA计算。

[0361] 用Fc-RSPO2-WT阳性对照蛋白或RPSO模拟蛋白αASGR1-RSPO2-RA-IgG2处理小鼠均引起肝中Wnt诱导型Axin2基因的表达增加并且Wnt阻遏型Hal基因的表达减少。所测量的统计学上显著的变化在表6中以粗体示出。小肠中Axin2表达没有显著变化。这些数据表明,Wnt信号传导是以组织特异性方式诱导的。

[0362] 用Fc-RPSO2-WT和αASGR1-RSPO2-RA-IgG2处理还揭示出Ki67增殖标志物和细胞周期蛋白D1增殖标志物在肝中增加但在小肠中没有增加。达到统计显著性的变化以粗体示出。用任何处理在小肠中均未看到显著的变化(表6)。这些数据表明,增殖是以组织特异性方式诱导的。

[0363] 进行了另外的qPCR分析以测量具体肝细胞类型中的变化,包含肝细胞、胆管细胞、不成熟肝细胞和卵圆细胞(表7)。

[0364] 表7.如通过qPCR测量的用作用蛋白质处理的肝细胞类型的标志物的基因的表达的变化

[0365]

处理组	肝细胞	胆管细胞	不成熟肝细胞	胆管细胞/卵圆细胞
	CK8	*CK19*	*Afp*	*Sox9*
原初	1.0 +/- 0.1	1.0 +/- 0.1	1.0 +/- 0.1	1.0 +/- 0.1

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[0366]

油对照	0.8 +/- 0.0	0.9 +/- 0.1	1.1 +/- 0.1	0.8 +/- 0.1
CCl_4小鼠中无蛋白质	0.9 +/- 0.1	1.4 +/- 0.1	1.3 +/- 0.2	1.2 +/- 0.1
CCl_4小鼠中有 α-βGal-IgG	0.7 +/- 0.1	1.0 +/- 0.1	1.3 +/- 0.1	1.5 +/- 0.1
CCl_4小鼠中有 Fc-RSPO2-WT	***1.4 +/- 0.3**	0.7 +/- 0.1	***3.5 +/- 0.3**	1.3 +/- 0.1
CCl_4小鼠中有 αGFP-RSPO2-RA-IgG	0.6 +/- 0.0	1.0 +/- 0.1	1.6 +/- 0.1	1.2 +/- 0.1
CCl_4小鼠中有 αASGR1-RSPO2-RA-IgG2	***1.8 +/- 0.2**	1.5 +/- 0.2	***3.7 +/- 0.7**	1.0 +/- 0.1

[0367] *统计学上不同的变化以粗体示出。CK8:αASGR1-RSPO2-RA-IgG2相对于α-βGal-IgG,p=0.0001;αASGR1-RSPO2-RA-IgG2相对于α-GFP-RSPO2-RA-IgG,p<0.0001。Afp:Fc-RSPO2-WT相对于α-βGal-IgG,p=0.0002;αASGR1-RSPO2-RA-IgG2相对于α-βGal-IgG,p<0.0001;αASGR1-RSPO2-RA-IgG2相对于α-GFP-RSPO2-RA-IgG,p=0.0001。通过单向ANOVA计算。

[0368] 对肝细胞标志物CK8中有统计学上显著的变化但胆管细胞标志物CK19没有的评估表明,肝中的增殖性反应限于肝细胞。此外,Afp的统计学上显著的增加揭示出不成熟肝细胞的激增(表7)。卵圆细胞没有显著变化。

[0369] 表8.如通过半定量PCR测量的用蛋白质处理的肝细胞和门静脉周围肝细胞的功能相关的基因表达的变化

[0370]

处理组	肝细胞功能	中心周围肝细胞功能	中心周围肝细胞功能	门静脉周围肝细胞功能
	因子X	*Cyp1a2*	*Cyp2e1*	*Cyp2f2*
原初	1.0 +/- 0.1	1.0 +/- 0.1	1.0 +/- 0.1	1.0 +/- 0.2
油对照	0.9 +/- 0.1	0.9 +/- 0.1	0.9 +/- 1.2	0.8 +/- 0.1
CCl_4小鼠中无蛋白质	1.1 +/- 0.1	0.6 +/- 0.0	1.0 +/- 0.1	1.2 +/- 0.1
CCl_4小鼠中有 α-βGal-IgG	1.2 +/- 0.1	0.8 +/- 0.1	1.0 +/- 0.1	0.8 +/- 0.1
CCl_4小鼠中有 Fc-RSPO2-WT	***1.9 +/- 0.3**	0.7 +/- 0.3	1.2 +/- 0.2	***0.1 +/- 0.0**
CCl_4小鼠中有 αGFP-RSPO2-RA-IgG	1.0 +/- 0.2	0.5 +/- 0.1	0.8 +/- 0.1	0.8 +/- 0.0
CCl_4小鼠中有 αASGR1-RSPO2-RA-IgG2	1.2 +/- 0.1	***2.0 +/- 0.4**	***2.7 +/- 0.5**	***0.1 +/- 0.0**

[0371] *统计学上不同的变化以粗体示出。因子X:Fc-RSPO2-WT相对于α-β-Gal-IgG,p=0.0463。Cyp1a2:αASGR1-RSPO2-RA-IgG2相对于α-βGal-IgG,p=0.0044;αASGR1-RSPO2-RA-IgG2相对于αGFP-RSPO2-RA-IgG,p=0.0001。Cyp2e1:αASGR1-RSPO2-RA-IgG2相对于α-β-Gal-IgG,p<0.0001;αASGR1-RSPO2-RA-IgG2相对于αGFP-RSPO2-RA-IgG,p<0.0001。Cyp2f2:Fc RSPO2-WT相对于α-βGal-IgG,p<0.0001;αASGR1-RSPO2-RA-IgG2相对于α-βGal-IgG,p<0.0001;αASGR1-RSPO2-RA-IgG2相对于αGFP-RSPO2-RA-IgG,p<0.0001。通过单向ANOVA计算。

[0372] Wnt信号传导主要控制中心周围肝细胞(参考)中两种CypP450酶Cyp2e1和Cyp1a2的表达。用RSPO模拟物处理小鼠显著地增加了这两种酶的基因的表达(表xx)。另外,显著较低的Cyp2f2表明,由于中心周围区的临时扩张,门静脉周围肝细胞功能临时下降。

[0373] 在蛋白质处理两周后,用天狼星红对小鼠肝进行染色以测量所有小鼠中天狼星红染色的胶原含量的水平(图13和表9)。将小鼠通过异氟醚吸入麻醉、心脏放血并且然后进行

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颈脱位法。新鲜收获肝并且将其立即浸没到10％中性缓冲福尔马林中以温育过夜。第二天，将肝转移到70％乙醇并且准备进行石蜡包埋。将肝组织切成5μm厚、脱蜡并且按酒精梯度水化。将切片用Picro天狼星红溶液(西格玛奥德里奇公司)染色并且用酸化水洗涤。用三种变化的100％乙醇脱水、在二甲苯中澄清、风干并且用盖玻片封固。通过Image J(NIH)对经过天狼星红染色的区域进行定量，并且相对于经过抗βgal对照处理的CCl4小鼠的肝进行标准化(设置为100％)。每组含有7-8只小鼠，并且数据作为平均值±SD呈现。

[0374] 表9.相对于经过抗βGal处理的CCl_4小鼠标准化的肝组织的天狼星红染色的定量

[0375]

处理组	天狼星红百分比（相对于βGal）
CCl_4小鼠中无蛋白质	93.0 +/- 4.8
CCl_4小鼠中有α-β-Gal-IgG	100 +/- 5.4
CCl_4小鼠中有Fc-RSPO2-WT	***60.0 +/- 2.9**
CCl_4小鼠中有αGFP-RSPO2-RA-IgG	87.0 +/- 7.1
CCl_4小鼠中有αASGR1-RSPO2-RA-IgG2	***66.3 +/- 3.2**

[0376] *统计学上不同的变化以粗体示出。Fc-RSPO2-WT相对于α-β-Gal-IgG，$p<0.0001$；Fc-RSPO2-WT相对于αGFP-RSPO2-RA-IgG，$p=0.0059$；α-ASGR1-RSPO2-RA-IgG2相对于α-β-Gal-IgG，$p=0.0003$；α-ASGR1-RSPO2-RA-IgG2相对于αGFP-RSPO2-RA-IgG，$p=0.0410$；通过单向ANOVA计算。

[0377] 处理后，使用天狼星红对本研究中所有小鼠的肝纤维化的量进行定量。对于此方法，将小鼠通过异氟醚吸入麻醉、心脏放血并且然后进行颈脱位法。新鲜收获肝并且将其立即浸没到10％中性缓冲福尔马林中以温育过夜。第二天，将肝转移到70％乙醇并且准备进行石蜡包埋。将肝组织切成5μm厚、脱蜡并且按酒精梯度水化。将切片用Picro天狼星红溶液(西格玛奥德里奇公司)染色并且用酸化水洗涤。用三种变化的100％乙醇脱水、在二甲苯中澄清、风干并且用盖玻片封固。通过Image J(NIH)对经过天狼星红染色的区域进行定量，并且相对于经过α-β-Gal-IgG对照处理的CCl_4小鼠的肝进行标准化(设置为100％)。每组含有7-8只小鼠，并且数据作为平均值±SD呈现。

[0378] 在用Fc-RSPO2-WT或RPSO模拟物αASGR1-RSPO2-RA-IgG2处理两周后，经过CCl_4处理的小鼠的天狼星红染色比在用对照蛋白处理的小鼠中看到的减少约40％，这表明肝纤维化在这些小鼠中比在用对照蛋白处理的小鼠中消退得更快(图13和表9)

[0379] 利用免疫组织化学进行另外的实验，从而在此研究中对来自所有动物的石蜡固定的肝组织上的HNF4α和Ki67进行染色。在经过Fc-RSPO2-WT和αASGR1-RSPO2-RA-IgG2两者处理的小鼠中，在整个肝中看到了HNF4α肝细胞标志物和Ki67增殖标志物的显著共定位(数据未示出)。相比之下，在经过α-β-Gal-IgG处理的对照小鼠中看到的双染色细胞少得多。这些结果证实，Fc-RSPO2-WT和αASGR1-RSPO2-RA-IgG2可以诱导这些小鼠的肝细胞增殖。

[0380] 这些数据一起表明，RSPO模拟物αASGR1-RSPO2-RA-IgG2对此纤维化肝病模型中小鼠可以消退纤维化并再生功能性肝细胞的速率具有显著影响。

[0381] 实例7

[0382] 使用新颖ASGR1结合剂对肝靶向RSPO模拟分子的构建

[0383] 人ASGR1的新颖结合剂作为杂交瘤被开发，所述杂交瘤是针对人ASGR1培育的并且基于与重组人和猕猴ASGR1 ECD结构域的交叉反应性而选择的。对杂交瘤进行进一步排名以通过流式细胞术对Huh-7细胞进行特异性染色(使用HEK293作为对照)。对所选命中进行

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亚克隆并测序以推断其VH序列和VL序列(SEQ ID NO:274-305)。为了制成肝特异性RSPO模拟物,制成了融合蛋白,其中ASGR1结合剂表达为含有无效应子突变N297G的人IgG2或人IgG1,而突变RSPO模块通过接头(SEQ ID NO:190-271)融合到重链的N端和C端。重组蛋白通过瞬时转染表达在Expi293细胞中并且通过蛋白A树脂、然后通过尺寸排阻色谱法纯化。在重组WNT替代物R2M3-26存在的情况下比较Huh-7和HEK293 STF报告基因细胞系中的活性的荧光素酶测定中,对肝细胞特异性Wnt信号增强进行分析(参见例如WO2019/126398)。图12证明了Huh-7细胞中16个新颖ASGR1靶向RSPO模拟分子作为IgG1或IgG2融合物的特异性活性。

[0384] 实例8

[0385] 小鼠肝中的组织靶向RSPO模拟物的药效动力学(PD)分析

[0386] 为了测量肝靶向RSPO模拟物的体内活性,将5-6周龄C57BL/6雄性小鼠JAX(共56只小鼠)人源化以进行人ASGR基因表达。向小鼠注射(IV)表达hASGR1基因和hASGR2基因的AAV8载体(1×10^{11}个基因组拷贝/小鼠)。

[0387] 6天后,通过腹膜内注射以5mg/kg的剂量向小鼠施用多种ASGR1靶向RSPO模拟物以及对照(图15A)。

[0388] 24小时后,使小鼠安乐死;将肝切下并速冻以进行RNA分离。进行mRNA分析以确定Axin2的相对表达。使用半定量PCR来测量来自经过处理的小鼠的肝组织中的相对基因表达。将值相对于组成型肌动蛋白B基因表达的表达标准化(图15B)。

[0389] 与α-β-Gal-IgG相比,αASGR1-IgG(RO-01)未诱导Axin2表达,这表明此结合剂自身对Wnt信号传导没有影响。类似地,αGFP-RSPO2-RA-IgG未诱导Axin2,这证实突变RSPO2模块自身也不具有活性。相比之下,αASGR1-RSPO2-RA-IgG(用结合剂RO-01构建的原型肝靶向RSPO模拟物)证明肝中有强有力的Axin2诱导,这与靶向模块的要求一致。

[0390] 所有另外的ASGR1靶向RSPO模拟分子(用内部消除的结合剂构建)示出Axin2表达的趋势或显著诱导。通过单向ANOVA,基于7B13、8M24、2I13和9M16的RSPO模拟分子与α-β-Gal-IgG对照相比在刺激Axin2表达方面示出了统计学上显著的增加,而3A24、2I22、1P13、1N15、3E20示出刺激Axin2表达的趋势(图15B)。

[0391] 上述各种实施例可以被组合以提供另外的实施例。在本说明书中引用和/或在申请数据表中列出的所有美国专利、美国专利申请公开、美国专利申请、外国专利、外国专利申请和非专利公开以全文引用的方式并入本文。如果有必要,则可以修改实施例的各方面以采用各个专利、申请和公开的概念来提供又另外的实施例。

[0392] 鉴于以上详细描述,可以对实施例作出这些和其它改变。总之,在以下权利要求中,所使用的术语不应当被解释为将权利要求限制于本说明书和权利要求中所公开的具体实施例,而是应当被解释为包含所有可能的实施例连同这种权利要求有权获得的等同物的整个范围。因此,权利要求并不受本公开的限制。

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<120> 组织特异性Wnt信号增强分子和其用途

<130> SRZN-010/03WO 328202-20469

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<212> PRT

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20 25 30
Ser Ala Glu Gly Ser Gln Ala Cys Ala Lys Gly Cys Glu Leu Cys Ser
35 40 45
Glu Val Asn Gly Cys Leu Lys Cys Ser Pro Lys Leu Phe Ile Leu Leu
50 55 60
Glu Arg Asn Asp Ile Arg Gln Val Gly Val Cys Leu Pro Ser Cys Pro
65 70 75 80
Pro Gly Tyr Phe Asp Ala Arg Asn Pro Asp Met Asn Lys Cys Ile Lys
85 90 95
Cys Lys Ile Glu His Cys Glu Ala Cys Phe Ser His Asn Phe Cys Thr
100 105 110
Lys Cys Lys Glu Gly Leu Tyr Leu His Lys Gly Arg Cys Tyr Pro Ala
115 120 125
Cys Pro Glu Gly Ser Ser Ala Ala Asn Gly Thr Met Glu Cys Ser Ser
130 135 140
Pro Ala Gln Cys Glu Met Ser Glu Trp Ser Pro Trp Gly Pro Cys Ser
145 150 155 160
Lys Lys Gln Gln Leu Cys Gly Phe Arg Arg Gly Ser Glu Glu Arg Thr
165 170 175

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Arg Arg Val Leu His Ala Pro Val Gly Asp His Ala Ala Cys Ser Asp
180 185 190
Thr Lys Glu Thr Arg Arg Cys Thr Val Arg Arg Val Pro Cys Pro Glu
195 200 205
Gly Gln Lys Arg Arg Lys Gly Gly Gln Gly Arg Arg Glu Asn Ala Asn
210 215 220
Arg Asn Leu Ala Arg Lys Glu Ser Lys Glu Ala Gly Ala Gly Ser Arg
225 230 235 240
Arg Arg Lys Gly Gln Gln Gln Gln Gln Gln Gly Thr Val Gly Pro
245 250 255
Leu Thr Ser Ala Gly Pro Ala
260

<210> 2
<211> 243
<212> PRT
<213> 智人(Homo sapiens)
<400> 2
Met Gln Phe Arg Leu Phe Ser Phe Ala Leu Ile Ile Leu Asn Cys Met
1 5 10 15
Asp Tyr Ser His Cys Gln Gly Asn Arg Trp Arg Arg Ser Lys Arg Ala
20 25 30
Ser Tyr Val Ser Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys
35 40 45
Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg
50 55 60
Arg Glu Gly Met Arg Gln Tyr Gly Glu Cys Leu His Ser Cys Pro Ser
65 70 75 80
Gly Tyr Tyr Gly His Arg Ala Pro Asp Met Asn Arg Cys Ala Arg Cys
85 90 95
Arg Ile Glu Asn Cys Asp Ser Cys Phe Ser Lys Asp Phe Cys Thr Lys
100 105 110
Cys Lys Val Gly Phe Tyr Leu His Arg Gly Arg Cys Phe Asp Glu Cys
115 120 125
Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr Met Glu Cys Val Glu Gly
130 135 140
Cys Glu Val Gly His Trp Ser Glu Trp Gly Thr Cys Ser Arg Asn Asn
145 150 155 160
Arg Thr Cys Gly Phe Lys Trp Gly Leu Glu Thr Arg Thr Arg Gln Ile
165 170 175

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Val Lys Lys Pro Val Lys Asp Thr Ile Leu Cys Pro Thr Ile Ala Glu
180 185 190
Ser Arg Arg Cys Lys Met Thr Met Arg His Cys Pro Gly Gly Lys Arg
195 200 205
Thr Pro Lys Ala Lys Glu Lys Arg Asn Lys Lys Lys Lys Arg Lys Leu
210 215 220
Ile Glu Arg Ala Gln Glu Gln His Ser Val Phe Leu Ala Thr Asp Arg
225 230 235 240
Ala Asn Gln

<210> 3
<211> 272
<212> PRT
<213> 智人(Homo sapiens)
<400> 3
Met His Leu Arg Leu Ile Ser Trp Leu Phe Ile Ile Leu Asn Phe Met
1 5 10 15
Glu Tyr Ile Gly Ser Gln Asn Ala Ser Arg Gly Arg Arg Gln Arg Arg
20 25 30
Met His Pro Asn Val Ser Gln Gly Cys Gln Gly Gly Cys Ala Thr Cys
35 40 45
Ser Asp Tyr Asn Gly Cys Leu Ser Cys Lys Pro Arg Leu Phe Phe Ala
50 55 60
Leu Glu Arg Ile Gly Met Lys Gln Ile Gly Val Cys Leu Ser Ser Cys
65 70 75 80
Pro Ser Gly Tyr Tyr Gly Thr Arg Tyr Pro Asp Ile Asn Lys Cys Thr
85 90 95
Lys Cys Lys Ala Asp Cys Asp Thr Cys Phe Asn Lys Asn Phe Cys Thr
100 105 110
Lys Cys Lys Ser Gly Phe Tyr Leu His Leu Gly Lys Cys Leu Asp Asn
115 120 125
Cys Pro Glu Gly Leu Glu Ala Asn Asn His Thr Met Glu Cys Val Ser
130 135 140
Ile Val His Cys Glu Val Ser Glu Trp Asn Pro Trp Ser Pro Cys Thr
145 150 155 160
Lys Lys Gly Lys Thr Cys Gly Phe Lys Arg Gly Thr Glu Thr Arg Val
165 170 175
Arg Glu Ile Ile Gln His Pro Ser Ala Lys Gly Asn Leu Cys Pro Pro
180 185 190
Thr Asn Glu Thr Arg Lys Cys Thr Val Gln Arg Lys Lys Cys Gln Lys

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195 200 205

Gly Glu Arg Gly Lys Lys Gly Arg Glu Arg Lys Arg Lys Lys Pro Asn
210 215 220
Lys Gly Glu Ser Lys Glu Ala Ile Pro Asp Ser Lys Ser Leu Glu Ser
225 230 235 240
Ser Lys Glu Ile Pro Glu Gln Arg Glu Asn Lys Gln Gln Gln Lys Lys
245 250 255
Arg Lys Val Gln Asp Lys Gln Lys Ser Val Ser Val Ser Thr Val His
260 265 270

<210> 4
<211> 234
<212> PRT
<213> 智人(Homo sapiens)
<400> 4

Met Arg Ala Pro Leu Cys Leu Leu Leu Leu Val Ala His Ala Val Asp
1 5 10 15
Met Leu Ala Leu Asn Arg Arg Lys Lys Gln Val Gly Thr Gly Leu Gly
20 25 30
Gly Asn Cys Thr Gly Cys Ile Ile Cys Ser Glu Glu Asn Gly Cys Ser
35 40 45
Thr Cys Gln Gln Arg Leu Phe Leu Phe Ile Arg Arg Glu Gly Ile Arg
50 55 60
Gln Tyr Gly Lys Cys Leu His Asp Cys Pro Pro Gly Tyr Phe Gly Ile
65 70 75 80
Arg Gly Gln Glu Val Asn Arg Cys Lys Lys Cys Gly Ala Thr Cys Glu
85 90 95
Ser Cys Phe Ser Gln Asp Phe Cys Ile Arg Cys Lys Arg Gln Phe Tyr
100 105 110
Leu Tyr Lys Gly Lys Cys Leu Pro Thr Cys Pro Pro Gly Thr Leu Ala
115 120 125
His Gln Asn Thr Arg Glu Cys Gln Gly Glu Cys Glu Leu Gly Pro Trp
130 135 140
Gly Gly Trp Ser Pro Cys Thr His Asn Gly Lys Thr Cys Gly Ser Ala
145 150 155 160
Trp Gly Leu Glu Ser Arg Val Arg Glu Ala Gly Arg Ala Gly His Glu
165 170 175
Glu Ala Ala Thr Cys Gln Val Leu Ser Glu Ser Arg Lys Cys Pro Ile
180 185 190
Gln Arg Pro Cys Pro Gly Glu Arg Ser Pro Gly Gln Lys Lys Gly Arg

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195 200 205

Lys Asp Arg Arg Pro Arg Lys Asp Arg Lys Leu Asp Arg Arg Leu Asp

210 215 220

Val Arg Pro Arg Gln Pro Gly Leu Gln Pro

225 230

<210> 5

<211> 1119

<212> DNA

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的抗GFP和RSPO2野生型融合序列

<400> 5

caggtccagt tggtggaatc cggagggggt ttggtccagc ctggtggaag cctgcgcctc 60
tcatgcgccg ctagcggatt caccttctcc cgatacggca tgcattgggt cagacaggca 120
cccggaaaag gactcgaatg ggtgtcgggc atttcctcga tcgggtcaaa cacctattac 180
gccgactccg tgaagggacg gttcaccatt agccgggata acagcaagaa cactctgtac 240
ttgcaaatga actccctgcg ggctgaggac accgccgtgt actactgtgc gcggtggtac 300
aagacctata ttgacgtctg gggacagggt accctcgtga ccgtgtcatc cggtggtgga 360
ggatccggag gcggaggaag cggaggaggg ggttcagaca tcgaactcac ccagcccccg 420
tcagtgtccg tggcccctgg acagactgcg cgcatctcct gctccggcga caacctgggg 480
aagaaatacg tgtactggta ccagcagaag ccaggtcaag ccctgtgct ggtcatctac 540
ggcgacgacg aaaggccgtc aggcatccca gagcgcttct ccggctccaa ctccgggaat 600
actgccaccc ttaccatttc cggaacccag gccgaggatg aagcggatta ctattgcgcg 660
agctacgata gcagccacat cctgatcgtg tttggaggcg gtactaagct gaccgtgctg 720
ggaagcggtg gatcaaaccc aatttgcaag ggatgcctga gctgtagcaa ggacaacgga 780
tgttcacggt gccagcaaaa gctgtttttc ttcctccggc gggaaggaat gcggcagtac 840
ggcgaatgtc tccactcctg cccctcgggg tattacggac accgcgcgcc tgacatgaac 900
cgatgcgcca gatgccggat cgagaactgc gatagctgct tcagcaagga cttctgcact 960
aagtgcaaag tcggcttcta ccttcaccgg ggcagatgtt ttgacgaatg cccggatggc 1020
ttcgccccgc tggaggagac tatggaatgc gtggagggcg gagactacaa ggacgacgat 1080
gacaagggct cccaccatca ccaccatcat caccactag 1119

<210> 6

<211> 372

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的抗GFP和RSPO2野生型融合序列

<400> 6

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

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1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gly Ile Ser Ser Ile Gly Ser Asn Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Trp Tyr Lys Thr Tyr Ile Asp Val Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125
Gly Gly Gly Ser Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val
130 135 140
Ala Pro Gly Gln Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly
145 150 155 160
Lys Lys Tyr Val Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val
165 170 175
Leu Val Ile Tyr Gly Asp Asp Glu Arg Pro Ser Gly Ile Pro Glu Arg
180 185 190
Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly
195 200 205
Thr Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ser Tyr Asp Ser
210 215 220
Ser His Ile Leu Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
225 230 235 240
Gly Ser Gly Gly Ser Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys Ser
245 250 255
Lys Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe Leu
260 265 270
Arg Arg Glu Gly Met Arg Gln Tyr Gly Glu Cys Leu His Ser Cys Pro
275 280 285
Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met Asn Arg Cys Ala Arg
290 295 300
Cys Arg Ile Glu Asn Cys Asp Ser Cys Phe Ser Lys Asp Phe Cys Thr
305 310 315 320

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Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly Arg Cys Phe Asp Glu
325 330 335
Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr Met Glu Cys Val Glu
340 345 350
Gly Gly Asp Tyr Lys Asp Asp Asp Asp Lys Gly Ser His His His His
355 360 365
His His His His
370

<210> 7
<211> 1119
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的抗GFP和RSPO2突变体融合序列
<400> 7
caggtccagt tggtggaatc cggaggggt ttggtccagc ctggtggaag cctgcgcctc 60
tcatgcgccg ctagcggatt caccttctcc cgatacggca tgcattgggt cagacaggca 120
cccggaaaag gactcgaatg ggtgtcgggc atttcctcga tcgggtcaaa cacctattac 180
gccgactccg tgaagggacg gttcaccatt agccgggata acagcaagaa cactctgtac 240
ttgcaaatga actccctgcg ggctgaggac accgccgtgt actactgtgc gcggtggtac 300
aagacctata ttgacgtctg gggacagggt accctcgtga ccgtgtcatc cggtggtgga 360
ggatccggag gcggaggaag cggaggaggg ggttcagaca tcgaactcac ccagcccccg 420
tcagtgtccg tggcccctgg acagactgcg cgcatctcct gctccggcga caacctgggg 480
aagaaatacg tgtactggta ccagcagaag ccaggtcaag ccctgtgct ggtcatctac 540
ggcgacgacg aaaggccgtc aggcatccca gagcgcttct ccggctccaa ctccgggaat 600
actgccaccc ttaccatttc cggaacccag gccgaggatg aagcggatta ctattgcgcg 660
agctacgata gcagccacat cctgatcgtg tttggaggcg gtactaagct gaccgtgctg 720
ggaagcggtg gatcaaaccc aatttgcaag ggatgcctga gctgtagcaa ggacaacgga 780
tgttcacggt gccagcaaaa gctgtttttc ttcctccggc gggaaggaat gcggcagtac 840
ggcgaatgtc tccactcctg cccctcgggg tattacggac accgcgcgcc tgacatgaac 900
cgatgcgcca gatgccggat cgagaactgc gatagctgcc gcagcaagga cgcctgcact 960
aagtgcaaag tcggcttcta ccttcaccgg ggcagatgtt ttgacgaatg cccggatggc 1020
ttcgccccgc tggaggagac tatggaatgc gtggagggcg gagactacaa ggacgacgat 1080
gacaagggct cccaccatca ccaccatcat caccactag 1119

<210> 8
<211> 372
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>

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<223> 在实验室中制备的抗GFP和RSPO2突变体融合序列

<400> 8

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gly Ile Ser Ser Ile Gly Ser Asn Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Trp Tyr Lys Thr Tyr Ile Asp Val Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125
Gly Gly Gly Ser Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val
130 135 140
Ala Pro Gly Gln Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly
145 150 155 160
Lys Lys Tyr Val Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val
165 170 175
Leu Val Ile Tyr Gly Asp Asp Glu Arg Pro Ser Gly Ile Pro Glu Arg
180 185 190
Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly
195 200 205
Thr Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ser Tyr Asp Ser
210 215 220
Ser His Ile Leu Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
225 230 235 240
Gly Ser Gly Gly Ser Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys Ser
245 250 255
Lys Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe Leu
260 265 270
Arg Arg Glu Gly Met Arg Gln Tyr Gly Glu Cys Leu His Ser Cys Pro
275 280 285
Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met Asn Arg Cys Ala Arg

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290 295 300

Cys Arg Ile Glu Asn Cys Asp Ser Cys Arg Ser Lys Asp Ala Cys Thr
305 310 315 320
Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly Arg Cys Phe Asp Glu
325 330 335
Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr Met Glu Cys Val Glu
340 345 350
Gly Gly Asp Tyr Lys Asp Asp Asp Asp Lys Gly Ser His His His His
355 360 365
His His His His
370

<210> 9
<211> 1119
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的抗GFP和RSPO2突变体融合序列
<400> 9
caggtccagt tggtggaatc cggagggggt ttggtccagc ctggtggaag cctgcgcctc 60
tcatgcgccg ctagcggatt caccttctcc cgatacggca tgcattgggt cagacaggca 120
cccggaaaag gactcgaatg ggtgtcgggc atttcctcga tcgggtcaaa cacctattac 180
gccgactccg tgaagggacg gttcaccatt agccgggata acagcaagaa cactctgtac 240
ttgcaaatga actccctgcg ggctgaggac accgccgtgt actactgtgc gcggtggtac 300
aagacctata ttgacgtctg gggacagggt accctcgtga ccgtgtcatc cggtggtgga 360
ggatccggag gcggaggaag cggaggaggg ggttcagaca tcgaactcac ccagcccccg 420
tcagtgtccg tggcccctgg acagactgcg cgcatctcct gctccggcga caacctgggg 480
aagaaatacg tgtactggta ccagcagaag ccaggtcaag cccctgtgct ggtcatctac 540
ggcgacgacg aaaggccgtc aggcatccca gagcgcttct ccggctccaa ctccgggaat 600
actgccaccc ttaccatttc cggaacccag gccgaggatg aagcggatta ctattgcgcg 660
agctacgata gcagccacat cctgatcgtg tttggaggcg gtactaagct gaccgtgctg 720
ggaagcggtg gatcaaaccc aatttgcaag ggatgcctga gctgtagcaa ggacaacgga 780
tgttcacggt gccagcaaaa gctgtttttc ttcctccggg ccgaaggaat ggccgcatac 840
ggcgaatgtc tccactcctg cccctcgggg tattacggac accgcgcgcc tgacatgaac 900
cgatgcgcca gatgccggat cgagaactgc gatagctgcc gcagcaagga cgcctgcact 960
aagtgcaaag tcggcttcta ccttcaccgg ggcagatgtt ttgacgaatg cccggatggc 1020
ttcgccccgc tggaggagac tatggaatgc gtggagggcg gagactacaa ggacgacgat 1080
gacaagggct cccaccatca ccaccatcat caccactag 1119
<210> 10
<211> 372

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<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的抗GFP和RSPO2突变体融合序列
<400> 10

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gly Ile Ser Ser Ile Gly Ser Asn Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Trp Tyr Lys Thr Tyr Ile Asp Val Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125
Gly Gly Gly Ser Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val
130 135 140
Ala Pro Gly Gln Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly
145 150 155 160
Lys Lys Tyr Val Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val
165 170 175
Leu Val Ile Tyr Gly Asp Asp Glu Arg Pro Ser Gly Ile Pro Glu Arg
180 185 190
Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly
195 200 205
Thr Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ser Tyr Asp Ser
210 215 220
Ser His Ile Leu Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
225 230 235 240
Gly Ser Gly Gly Ser Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys Ser
245 250 255
Lys Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe Leu
260 265 270

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Arg Ala Glu Gly Met Ala Ala Tyr Gly Glu Cys Leu His Ser Cys Pro
275 280 285
Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met Asn Arg Cys Ala Arg
290 295 300
Cys Arg Ile Glu Asn Cys Asp Ser Cys Arg Ser Lys Asp Ala Cys Thr
305 310 315 320
Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly Arg Cys Phe Asp Glu
325 330 335
Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr Met Glu Cys Val Glu
340 345 350
Gly Gly Asp Tyr Lys Asp Asp Asp Asp Lys Gly Ser His His His His
355 360 365
His His His His
370

<210> 11
<211> 1125
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的抗ASGR1和RSPO2野生型融合序列
<400> 11

gaagtgcagc tgctggaatc cgggggcgga ctggtgcaac ccgggggatc cctcagactg 60
tcctgtgccg catcgggttt cactttctcc tcctacgcga tgtcatgggt cagacaggcc 120
cctggaaaag gcctcgaatg ggtgtcggct atctccggat cgggggggatc tacttactac 180
gccgactccg tgaagggccg gttcactatc tcgagggaca actccaagaa taccctgtac 240
ttgcaaatga actccctgcg cgccgaggat accgcggtgt attactgcgc caaggacttc 300
agctcacgcc ggtggtacct tgagtactgg ggacagggaa cccttgtcac cgtgtccagc 360
ggtggcggcg gaagcggcgg gggcggatcc ggtggcgggg gctcagagct cacccaggac 420
cccgctgtgt ccgtggcctt gggacagacc gtgcgcatca catgccaggg cgatagcctg 480
cggagctatt acgcctcgtg gtaccagcag aagcctggtc aagcgccggt cctggtcatc 540
tacggaaaga acaaccgccc gtccggaatt ccagacaggt tcagcggatc cagctcgggg 600
aacaccgcct cactgactat caccggagca caggccgaag atgaagccga ctactactgc 660
aactccctgg agcggattgg atacctgagc tacgtgtttg gtggcggcac gaagctcacc 720
gtgctgggaa gcggtggatc aaacccaatt tgcaagggat gcctgagctg tagcaaggac 780
aacggatgtt cacggtgcca gcaaaagctg tttttcttcc tccggcggga aggaatgcgg 840
cagtacggcg aatgtctcca ctcctgcccc tcggggtatt acggacaccg cgcgcctgac 900
atgaaccgat gcgccagatg ccggatcgag aactgcgata gctgcttcag caaggacttc 960
tgcactaagt gcaaagtcgg cttctacctt caccggggca gatgttttga cgaatgcccg 1020
gatggcttcg ccccgctgga ggagactatg gaatgcgtgg agggcggaga ctacaaggac 1080

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gacgatgaca agggctccca ccatcaccac catcatcacc actag 1125

<210> 12

<211> 374

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的抗ASGR1和RSPO2野生型融合序列

<400> 12

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Asp Phe Ser Ser Arg Arg Trp Tyr Leu Glu Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
115 120 125
Gly Ser Gly Gly Gly Gly Ser Glu Leu Thr Gln Asp Pro Ala Val Ser
130 135 140
Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu
145 150 155 160
Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
165 170 175
Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp
180 185 190
Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr
195 200 205
Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Leu Glu
210 215 220
Arg Ile Gly Tyr Leu Ser Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr
225 230 235 240
Val Leu Gly Ser Gly Gly Ser Asn Pro Ile Cys Lys Gly Cys Leu Ser

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245 250 255

Cys Ser Lys Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys Leu Phe Phe
260 265 270

Phe Leu Arg Arg Glu Gly Met Arg Gln Tyr Gly Glu Cys Leu His Ser
275 280 285

Cys Pro Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met Asn Arg Cys
290 295 300

Ala Arg Cys Arg Ile Glu Asn Cys Asp Ser Cys Phe Ser Lys Asp Phe
305 310 315 320

Cys Thr Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly Arg Cys Phe
325 330 335

Asp Glu Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr Met Glu Cys
340 345 350

Val Glu Gly Gly Asp Tyr Lys Asp Asp Asp Asp Lys Gly Ser His His
355 360 365

His His His His His His
370

<210> 13

<211> 1125

<212> DNA

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的抗ASGR1和RSPO2突变体融合序列

<400> 13

gaagtgcagc tgctggaatc cgggggcgga ctggtgcaac ccgggggatc cctcagactg 60
tcctgtgccg catcgggttt cactttctcc tcctacgcga tgtcatgggt cagacaggcc 120
cctggaaaag gcctcgaatg ggtgtcggct atctccggat cgggggggatc tacttactac 180
gccgactccg tgaagggccg gttcactatc tcgagggaca actccaagaa taccctgtac 240
ttgcaaatga actccctgcg cgccgaggat accgcggtgt attactgcgc caaggacttc 300
agctcacgcc ggtggtacct tgagtactgg ggacagggaa cccttgtcac cgtgtccagc 360
ggtggcggcg gaagcggcgg gggcggatcc ggtggcgggg gctcagagct cacccaggac 420
cccgctgtgt ccgtggcctt gggacagacc gtgcgcatca catgccaggg cgatagcctg 480
cggagctatt acgcctcgtg gtaccagcag aagcctggtc aagcgccggt cctggtcatc 540
tacggaaaga acaaccgccc gtccggaatt ccagacaggt tcagcggatc cagctcgggg 600
aacaccgcct cactgactat caccggagca caggccgaag atgaagccga ctactactgc 660
aactccctgg agcggattgg atacctgagc tacgtgtttg gtggcggcac gaagctcacc 720
gtgctgggaa gcggtggatc aaacccaatt tgcaagggat gcctgagctg tagcaaggac 780
aacggatgtt cacggtgcca gcaaaagctg tttttcttcc tccggcggga aggaatgcgg 840
cagtacggcg aatgtctcca ctcctgcccc tcggggtatt acggacaccg cgcgcctgac 900

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atgaaccgat gcgccagatg ccggatcgag aactgcgata gctgccgcag caaggacgcc 960
tgcactaagt gcaaagtcgg cttctacctt caccggggca gatgttttga cgaatgcccg 1020
gatggcttcg ccccgctgga ggagactatg gaatgcgtgg agggcggaga ctacaaggac 1080
gacgatgaca agggctccca ccatcaccac catcatcacc actag 1125

<210> 14
<211> 374
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的抗ASGR1和RSPO2突变体融合序列
<400> 14

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Asp Phe Ser Ser Arg Arg Trp Tyr Leu Glu Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
115 120 125
Gly Ser Gly Gly Gly Gly Ser Glu Leu Thr Gln Asp Pro Ala Val Ser
130 135 140
Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu
145 150 155 160
Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
165 170 175
Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp
180 185 190
Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr
195 200 205
Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Leu Glu
210 215 220

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Arg Ile Gly Tyr Leu Ser Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr
225 230 235 240
Val Leu Gly Ser Gly Gly Ser Asn Pro Ile Cys Lys Gly Cys Leu Ser
245 250 255
Cys Ser Lys Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys Leu Phe Phe
260 265 270
Phe Leu Arg Arg Glu Gly Met Arg Gln Tyr Gly Glu Cys Leu His Ser
275 280 285
Cys Pro Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met Asn Arg Cys
290 295 300
Ala Arg Cys Arg Ile Glu Asn Cys Asp Ser Cys Arg Ser Lys Asp Ala
305 310 315 320
Cys Thr Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly Arg Cys Phe
325 330 335
Asp Glu Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr Met Glu Cys
340 345 350
Val Glu Gly Gly Asp Tyr Lys Asp Asp Asp Asp Lys Gly Ser His His
355 360 365
His His His His His His
370

<210> 15
<211> 1125
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的抗ASGR1和RSPO2突变体融合序列
<400> 15

gaagtgcagc tgctggaatc cgggggcgga ctggtgcaac ccgggggatc cctcagactg 60
tcctgtgccg catcgggttt cactttctcc tcctacgcga tgtcatgggt cagacaggcc 120
cctggaaaag gcctcgaatg ggtgtcggct atctccggat cgggggggatc tacttactac 180
gccgactccg tgaagggccg gttcactatc tcgagggaca actccaagaa taccctgtac 240
ttgcaaatga actccctgcg cgccgaggat accgcggtgt attactgcgc caaggacttc 300
agctcacgcc ggtggtacct tgagtactgg ggacagggaa cccttgtcac cgtgtccagc 360
ggtggcggcg gaagcggcgg gggcggatcc ggtggcgggg gctcagagct cacccaggac 420
cccgctgtgt ccgtggcctt gggacagacc gtgcgcatca catgccaggg cgatagcctg 480
cggagctatt acgcctcgtg gtaccagcag aagcctggtc aagcgccggt cctggtcatc 540
tacggaaaga acaaccgccc gtccggaatt ccagacaggt tcagcggatc cagctcgggg 600
aacaccgcct cactgactat caccggagca caggccgaag atgaagccga ctactactgc 660
aactccctgg agcggattgg atacctgagc tacgtgtttg gtggcggcac gaagctcacc 720

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gtgctgggaa gcggtggatc aaacccaatt tgcaagggat gcctgagctg tagcaaggac 780
aacggatgtt cacggtgcca gcaaaagctg tttttcttcc tccgggccga aggaatggcc 840
gcatacggcg aatgtctcca ctcctgcccc tcggggtatt acggacaccg cgcgcctgac 900
atgaaccgat gcgccagatg ccggatcgag aactgcgata gctgccgcag caaggacgcc 960
tgcactaagt gcaaagtcgg cttctacctt caccggggca gatgttttga cgaatgcccg 1020
gatggcttcg ccccgctgga ggagactatg gaatgcgtgg agggcggaga ctacaaggac 1080
gacgatgaca agggctccca ccatcaccac catcatcacc actag 1125

<210> 16
<211> 374
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的抗ASGR1和RSPO2突变体融合序列
<400> 16

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Asp Phe Ser Ser Arg Arg Trp Tyr Leu Glu Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
115 120 125
Gly Ser Gly Gly Gly Gly Ser Glu Leu Thr Gln Asp Pro Ala Val Ser
130 135 140
Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu
145 150 155 160
Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
165 170 175
Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp
180 185 190
Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr

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195 200 205

Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Leu Glu
210 215 220

Arg Ile Gly Tyr Leu Ser Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr
225 230 235 240

Val Leu Gly Ser Gly Gly Ser Asn Pro Ile Cys Lys Gly Cys Leu Ser
245 250 255

Cys Ser Lys Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys Leu Phe Phe
260 265 270

Phe Leu Arg Ala Glu Gly Met Ala Ala Tyr Gly Glu Cys Leu His Ser
275 280 285

Cys Pro Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met Asn Arg Cys
290 295 300

Ala Arg Cys Arg Ile Glu Asn Cys Asp Ser Cys Arg Ser Lys Asp Ala
305 310 315 320

Cys Thr Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly Arg Cys Phe
325 330 335

Asp Glu Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr Met Glu Cys
340 345 350

Val Glu Gly Gly Asp Tyr Lys Asp Asp Asp Asp Lys Gly Ser His His
355 360 365

His His His His His His
370

<210> 17

<211> 1134

<212> DNA

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的抗TFR1和RSPO2野生型融合序列

<400> 17

caagtgcaac tccaacaaag cggtcccgag ttggtccgac ccggcgtcag tgtgaaaatc 60
tcatgcaagg ggtccgggta taccttcact gactatgcaa tgcactgggt aaagcagagc 120
cacgccaagt ccttggagtg gatcggaggc attagtacct acttcggacg caccaactac 180
aatcaaaaat ttaagggtcg cgcaaccatg actgtagata aatcatcaag taccgcgtac 240
atggaattgg ctagactgac ttctgaagat tccgcgctgt attactgtgc tcgcggtttg 300
tctggcaact atgttatgga ttactggggg caagggacca gcgtcacggt gtcctctggc 360
ggaggcgggt ccgggggggg tggttctggc ggaggcggat ccgatatagt tctgtttcaa 420
tcccctgcga gcctggcggt aagtttggga cagagagcca cgatttcctg ccgagcgagt 480
gaaagcgtag acgactacgg caattctttc atgcactggt atcaacagaa gccaggccaa 540

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ccgccgaagc tgcttatcta tcgcgcgtcc aatttggagt cagggatccc tgcacgattt 600
tcaggttctg gaagtaggac agactttaca cttacgataa accccgtgga agcggatgac 660
gtcgcaacct actattgtca acaaagcaat gaagcaccac ctaccttcgg aggtggcact 720
aaattggaaa ttaggggaag cggtggatca aacccaattt gcaagggatg cctgagctgt 780
agcaaggaca acggatgttc acggtgccag caaaagctgt ttttcttcct ccggcgggaa 840
ggaatgcggc agtacggcga atgtctccac tcctgcccct cggggtatta cggacaccgc 900
gcgcctgaca tgaaccgatg cgccagatgc cggatcgaga actgcgatag ctgcttcagc 960
aaggacttct gcactaagtg caaagtcggc ttctaccttc accggggcag atgttttgac 1020
gaatgcccgg atggcttcgc cccgctggag gagactatgg aatgcgtgga gggcggagac 1080
tacaaggacg acgatgacaa gggctcccac catcaccacc atcatcacca ctag 1134

<210> 18
<211> 377
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的抗TFR1和RSPO2野生型融合序列
<400> 18

Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Arg Pro Gly Val
1 5 10 15
Ser Val Lys Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30
Ala Met His Trp Val Lys Gln Ser His Ala Lys Ser Leu Glu Trp Ile
35 40 45
Gly Gly Ile Ser Thr Tyr Phe Gly Arg Thr Asn Tyr Asn Gln Lys Phe
50 55 60
Lys Gly Arg Ala Thr Met Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ala Arg Leu Thr Ser Glu Asp Ser Ala Leu Tyr Tyr Cys
85 90 95
Ala Arg Gly Leu Ser Gly Asn Tyr Val Met Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
115 120 125
Ser Gly Gly Gly Gly Ser Asp Ile Val Leu Phe Gln Ser Pro Ala Ser
130 135 140
Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser
145 150 155 160
Glu Ser Val Asp Asp Tyr Gly Asn Ser Phe Met His Trp Tyr Gln Gln
165 170 175

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Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Arg Ala Ser Asn Leu
180 185 190
Glu Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp
195 200 205
Phe Thr Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala Thr Tyr
210 215 220
Tyr Cys Gln Gln Ser Asn Glu Ala Pro Pro Thr Phe Gly Gly Gly Thr
225 230 235 240
Lys Leu Glu Ile Arg Gly Ser Gly Gly Ser Asn Pro Ile Cys Lys Gly
245 250 255
Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys
260 265 270
Leu Phe Phe Phe Leu Arg Arg Glu Gly Met Arg Gln Tyr Gly Glu Cys
275 280 285
Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met
290 295 300
Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp Ser Cys Phe Ser
305 310 315 320
Lys Asp Phe Cys Thr Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly
325 330 335
Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr
340 345 350
Met Glu Cys Val Glu Gly Gly Asp Tyr Lys Asp Asp Asp Asp Lys Gly
355 360 365
Ser His His His His His His His His
370 375

<210> 19
<211> 1134
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的抗TFR1和RSPO2突变体融合序列
<400> 19
caagtgcaac tccaacaaag cggtcccgag ttggtccgac ccggcgtcag tgtgaaaatc 60
tcatgcaagg ggtccgggta taccttcact gactatgcaa tgcactgggt aaagcagagc 120
cacgccaagt ccttggagtg gatcggaggc attagtacct acttcggacg caccaactac 180
aatcaaaaat ttaagggtcg cgcaaccatg actgtagata aatcatcaag taccgcgtac 240
atggaattgg ctagactgac ttctgaagat tccgcgctgt attactgtgc tcgcggtttg 300
tctggcaact atgttatgga ttactggggg caagggacca gcgtcacggt gtcctctggc 360

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ggaggcgggt ccgggggggg tggttctggc ggaggcggat ccgatatagt tctgtttcaa 420
tcccctgcga gcctggcggt aagtttggga cagagagcca cgatttcctg ccgagcgagt 480
gaaagcgtag acgactacgg caattctttc atgcactggt atcaacagaa gccaggccaa 540
ccgccgaagc tgcttatcta tcgcgcgtcc aatttggagt cagggatccc tgcacgattt 600
tcaggttctg gaagtaggac agactttaca cttacgataa accccgtgga agcggatgac 660
gtcgcaacct actattgtca acaaagcaat gaagcaccac ctaccttcgg aggtggcact 720
aaattggaaa ttaggggaag cggtggatca aacccaattt gcaagggatg cctgagctgt 780
agcaaggaca acggatgttc acggtgccag caaaagctgt ttttcttcct ccggcgggaa 840
ggaatgcggc agtacggcga atgtctccac tcctgcccct cggggtatta cggacaccgc 900
gcgcctgaca tgaaccgatg cgccagatgc cggatcgaga actgcgatag ctgccgcagc 960
aaggacgcct gcactaagtg caaagtcggc ttctaccttc accggggcag atgttttgac 1020
gaatgcccgg atggcttcgc cccgctggag gagactatgg aatgcgtgga gggcggagac 1080
tacaaggacg acgatgacaa gggctcccac catcaccacc atcatcacca ctag 1134

<210> 20
<211> 377
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的抗TFR1和RSPO2突变体融合序列
<400> 20

Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Arg Pro Gly Val
1 5 10 15
Ser Val Lys Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30
Ala Met His Trp Val Lys Gln Ser His Ala Lys Ser Leu Glu Trp Ile
35 40 45
Gly Gly Ile Ser Thr Tyr Phe Gly Arg Thr Asn Tyr Asn Gln Lys Phe
50 55 60
Lys Gly Arg Ala Thr Met Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ala Arg Leu Thr Ser Glu Asp Ser Ala Leu Tyr Tyr Cys
85 90 95
Ala Arg Gly Leu Ser Gly Asn Tyr Val Met Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
115 120 125
Ser Gly Gly Gly Gly Ser Asp Ile Val Leu Phe Gln Ser Pro Ala Ser
130 135 140
Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser

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145 150 155 160
Glu Ser Val Asp Asp Tyr Gly Asn Ser Phe Met His Trp Tyr Gln Gln
165 170 175
Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Arg Ala Ser Asn Leu
180 185 190
Glu Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp
195 200 205
Phe Thr Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala Thr Tyr
210 215 220
Tyr Cys Gln Gln Ser Asn Glu Ala Pro Pro Thr Phe Gly Gly Gly Thr
225 230 235 240
Lys Leu Glu Ile Arg Gly Ser Gly Gly Ser Asn Pro Ile Cys Lys Gly
245 250 255
Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys
260 265 270
Leu Phe Phe Phe Leu Arg Arg Glu Gly Met Arg Gln Tyr Gly Glu Cys
275 280 285
Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met
290 295 300
Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp Ser Cys Arg Ser
305 310 315 320
Lys Asp Ala Cys Thr Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly
325 330 335
Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr
340 345 350
Met Glu Cys Val Glu Gly Gly Asp Tyr Lys Asp Asp Asp Asp Lys Gly
355 360 365
Ser His His His His His His His His
370 375

<210> 21
<211> 1134
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的抗TFR1和RSPO2突变体融合序列
<400> 21
caagtgcaac tccaacaaag cggtcccgag ttggtccgac ccggcgtcag tgtgaaaatc 60
tcatgcaagg ggtccgggta taccttcact gactatgcaa tgcactgggt aaagcagagc 120
cacgccaagt ccttggagtg gatcggaggc attagtacct acttcggacg caccaactac 180

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aatcaaaaat ttaagggtcg cgcaaccatg actgtagata aatcatcaag taccgcgtac 240
atggaattgg ctagactgac ttctgaagat tccgcgctgt attactgtgc tcgcggtttg 300
tctggcaact atgttatgga ttactggggg caagggacca gcgtcacggt gtcctctggc 360
ggaggcgggt ccgggggggg tggttctggc ggaggcggat ccgatatagt tctgtttcaa 420
tcccctgcga gcctggcggt aagtttggga cagagagcca cgatttcctg ccgagcgagt 480
gaaagcgtag acgactacgg caattctttc atgcactggt atcaacagaa gccaggccaa 540
ccgccgaagc tgcttatcta tcgcgcgtcc aatttggagt cagggatccc tgcacgattt 600
tcaggttctg gaagtaggac agactttaca cttacgataa accccgtgga agcggatgac 660
gtcgcaacct actattgtca acaaagcaat gaagcaccac ctaccttcgg aggtggcact 720
aaattggaaa ttaggggaag cggtggatca aacccaattt gcaagggatg cctgagctgt 780
agcaaggaca acggatgttc acggtgccag caaaagctgt ttttcttcct ccgggccgaa 840
ggaatggccg catacggcga atgtctccac tcctgcccct cggggtatta cggacaccgc 900
gcgcctgaca tgaaccgatg cgccagatgc cggatcgaga actgcgatag ctgccgcagc 960
aaggacgcct gcactaagtg caaagtcggc ttctaccttc accggggcag atgttttgac 1020
gaatgcccgg atggcttcgc cccgctggag gagactatgg aatgcgtgga gggcggagac 1080
tacaaggacg acgatgacaa gggctcccac catcaccacc atcatcacca ctag 1134

<210> 22
<211> 377
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的抗TFR1和RSPO2突变体融合序列
<400> 22

Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Arg Pro Gly Val
1 5 10 15
Ser Val Lys Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30
Ala Met His Trp Val Lys Gln Ser His Ala Lys Ser Leu Glu Trp Ile
35 40 45
Gly Gly Ile Ser Thr Tyr Phe Gly Arg Thr Asn Tyr Asn Gln Lys Phe
50 55 60
Lys Gly Arg Ala Thr Met Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ala Arg Leu Thr Ser Glu Asp Ser Ala Leu Tyr Tyr Cys
85 90 95
Ala Arg Gly Leu Ser Gly Asn Tyr Val Met Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
115 120 125

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Ser Gly Gly Gly Gly Ser Asp Ile Val Leu Phe Gln Ser Pro Ala Ser
130 135 140
Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser
145 150 155 160
Glu Ser Val Asp Asp Tyr Gly Asn Ser Phe Met His Trp Tyr Gln Gln
165 170 175
Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Arg Ala Ser Asn Leu
180 185 190
Glu Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp
195 200 205
Phe Thr Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala Thr Tyr
210 215 220
Tyr Cys Gln Gln Ser Asn Glu Ala Pro Pro Thr Phe Gly Gly Gly Thr
225 230 235 240
Lys Leu Glu Ile Arg Gly Ser Gly Gly Ser Asn Pro Ile Cys Lys Gly
245 250 255
Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys
260 265 270
Leu Phe Phe Phe Leu Arg Ala Glu Gly Met Ala Ala Tyr Gly Glu Cys
275 280 285
Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met
290 295 300
Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp Ser Cys Arg Ser
305 310 315 320
Lys Asp Ala Cys Thr Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly
325 330 335
Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr
340 345 350
Met Glu Cys Val Glu Gly Gly Asp Tyr Lys Asp Asp Asp Asp Lys Gly
355 360 365
Ser His His His His His His His His
370 375

<210> 23
<211> 1053
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的Fc-RSPO2融合序列
<400> 23

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gacaaaactc acacatgccc accgtgccca gcacctgaag ccgcgggggg accgtcagtc 60
ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca 120
tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac 180
ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac 240
cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag 300
tgcaaggtct ccaacaaagc cctcggagcc cccatcgaga aaaccatctc caaagccaaa 360
gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag 420
aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag 480
tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc 540
gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 600
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 660
ctctccctgt ctccgggtaa aggtggtggt ggctcgggag gaggaggctc cggtggcggt 720
ggcagctcaa atcccatttg caagggttgt ttgtcttgtt caaaggacaa tgggtgtagc 780
cgatgtcaac agaagttgtt cttcttcctt cgaagagaag ggatgcgcca gtatggagag 840
tgcctgcatt cctgcccatc cgggtactat ggacaccgag ccccagatat gaacagatgt 900
gcaagatgca gaatagaaaa ctgtgattct tgctttagca aagacttttg taccaagtgc 960
aaagtaggct tttatttgca tagaggccgt tgctttgatg aatgtccaga tggttttgca 1020
ccattagaag aaaccatgga atgtgtggaa tga 1053

<210> 24
<211> 350
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的Fc-RSPO2融合序列
<400> 24

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1 5 10 15
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35 40 45
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50 55 60
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65 70 75 80
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
85 90 95
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile
100 105 110

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Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
115 120 125
Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
130 135 140
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145 150 155 160
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
165 170 175
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
180 185 190
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
195 200 205
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
210 215 220
Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
225 230 235 240
Gly Ser Ser Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp
245 250 255
Asn Gly Cys Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg
260 265 270
Glu Gly Met Arg Gln Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly
275 280 285
Tyr Tyr Gly His Arg Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg
290 295 300
Ile Glu Asn Cys Asp Ser Cys Phe Ser Lys Asp Phe Cys Thr Lys Cys
305 310 315 320
Lys Val Gly Phe Tyr Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro
325 330 335
Asp Gly Phe Ala Pro Leu Glu Glu Thr Met Glu Cys Val Glu
340 345 350

<210> 25
<211> 642
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的抗GFP轻链序列
<400> 25
gacatcgaac tcacccagcc cccgtcagtg tccgtggccc ctggacagac tgcgcgcatc 60
tcctgctccg gcgacaacct ggggaagaaa tacgtgtact ggtaccagca gaagccaggt 120

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caagcccctg tgctggtcat ctacggcgac gacgaaaggc cgtcaggcat cccagagcgc 180
ttctccggct ccaactccgg gaatactgcc acccttacca tttccggaac ccaggccgag 240
gatgaagcgg attactattg cgcgagctac gatagcagcc acatcctgat cgtgtttgga 300
ggcggtacca agcttaccgt cctaggtcag cccaaggctg ccccctcggt cactctgttc 360
ccgccctcct ctgaggagct tcaagccaac aaggccacac tggtgtgtct cataagtgac 420
ttctacccgg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 480
gtggagacca ccacaccctc caaacaaagc aacaacaagt acgcggccag cagctatctg 540
agcctgacgc ctgagcagtg gaagtcccac agaagctaca gctgccaggt cacgcatgaa 600
gggagcaccg tggagaagac agtggccccct acagaatgtt ca 642

<210> 26
<211> 214
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的抗GFP轻链序列
<400> 26

Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15
Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly Lys Lys Tyr Val
20 25 30
Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45
Gly Asp Asp Glu Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Ala Ser Tyr Asp Ser Ser His Ile Leu
85 90 95
Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110
Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser

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180 185 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val

195 200 205

Ala Pro Thr Glu Cys Ser

210

<210> 27

<211> 1695

<212> DNA

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的RSPO2突变体和抗GFP重链IgG2融合多核苷酸

<400> 27

aacccaattt gcaagggatg cctgagctgt agcaaggaca acggatgttc acggtgccag 60
caaaagctgt ttttcttcct ccggcgggaa ggaatgcggc agtacggcga atgtctccac 120
tcctgcccct cggggtatta cggacaccgc gcgcctgaca tgaaccgatg cgccagatgc 180
cggatcgaga actgcgatag ctgccgcagc aaggacgcct gcactaagtg caaagtcggc 240
ttctaccttc accggggcag atgttttgac gaatgcccgg atggcttcgc cccgctggag 300
gagactatgg aatgcgtgga gggtggtggt ggctcgggag gaggaggctc cggtggcggt 360
ggcagccagg tccagttggt ggaatccgga gggggtttgg tccagcctgg tggaagcctg 420
cgcctctcat gcgccgctag cggattcacc ttctcccgat acggcatgca ttgggtcaga 480
caggcacccg gaaaaggact cgaatgggtg tcgggcattt cctcgatcgg gtcaaacacc 540
tattacgccg actccgtgaa gggacggttc accattagcc gggataacag caagaacact 600
ctgtacttgc aaatgaactc cctgcgggct gaggacaccg ccgtgtacta ctgtgcgcgg 660
tggtacaaga cctatattga cgtctgggga cagggtaccc tcgtgaccgt gtcgagtgct 720
agcaccaagg gcccatcggt cttccccctg gcgccctgct ccaggagcac ctccgagagc 780
acagcggccc tgggctgcct ggtcaaggac tacttccccg aaccggtgac ggtgtcgtgg 840
aactcaggcg ctctgaccag cggcgtgcac accttcccag ctgtcctaca gtcctcagga 900
ctctactccc tcagcagcgt ggtgaccgtg ccctccagca acttcggcac ccagacctac 960
acctgcaacg tagatcacaa gcccagcaac accaaggtgg acaagacagt tgagcgcaaa 1020
tgttgtgtcg agtgcccacc gtgcccagca ccacctgtgg caggaccgtc agtcttcctc 1080
ttccccccaa aacccaagga caccctcatg atctcccgga cccctgaggt cacgtgcgtg 1140
gtggtggacg tgagccacga agaccccgag gtccagttca actggtacgt ggacggcgtg 1200
gaggtgcata atgccaagac aaagccacgg gaggagcagt tcaacagcac gttccgtgtg 1260
gtcagcgtcc tcaccgttgt gcaccaggac tggctgaacg gcaaggagta caagtgcaag 1320
gtctccaaca aaggcctccc agcccccatc gagaaaacca tctccaaaac caaagggcag 1380
ccccgagaac cacaggtgta caccctgccc ccatcccggg aggagatgac caagaaccag 1440
gtcagcctga cctgcctggt caaaggcttc taccccagcg acatcgccgt ggagtgggag 1500
agcaatgggc agccggagaa caactacaag accacgcctc ccatgctgga ctccgacggc 1560
tccttcttcc tctacagcaa gctcaccgtg gacaagagca ggtggcagca ggggaacgtc 1620

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ttctcatgct ccgtgatgca tgaggctctg cacaaccact acacgcagaa gagcctctcc 1680
ctgtctccgg gtaaa 1695

<210> 28
<211> 565
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的RSPO2突变体和抗GFP重链IgG2融合多肽
<400> 28

Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys
1 5 10 15
Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met
20 25 30
Arg Gln Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly
35 40 45
His Arg Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn
50 55 60
Cys Asp Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly
65 70 75 80
Phe Tyr Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe
85 90 95
Ala Pro Leu Glu Glu Thr Met Glu Cys Val Glu Gly Gly Gly Gly Ser
100 105 110
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val Glu
115 120 125
Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys
130 135 140
Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr Gly Met His Trp Val Arg
145 150 155 160
Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Gly Ile Ser Ser Ile
165 170 175
Gly Ser Asn Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile
180 185 190
Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu
195 200 205
Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Trp Tyr Lys Thr
210 215 220
Tyr Ile Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
225 230 235 240

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Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser
245 250 255
Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
260 265 270
Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
275 280 285
Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
290 295 300
Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr
305 310 315 320
Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr
325 330 335
Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro
340 345 350
Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
355 360 365
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
370 375 380
Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
385 390 395 400
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
405 410 415
Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu
420 425 430
Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala
435 440 445
Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro
450 455 460
Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
465 470 475 480
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
485 490 495
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
500 505 510
Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
515 520 525
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
530 535 540
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser

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545 550 555 560
Leu Ser Pro Gly Lys
565

<210> 29
<211> 645
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的抗ASGR1轻链多核苷酸
<400> 29
gacatcgagc tcacccagga ccccgctgtg tccgtggcct tgggacagac cgtgcgcatc 60
acatgccagg gcgatagcct gcggagctat tacgcctcgt ggtaccagca gaagcctggt 120
caagcgccgg tcctggtcat ctacggaaag aacaaccgcc cgtccggaat tccagacagg 180
ttcagcggat ccagctcggg gaacaccgcc tcactgacta tcaccggagc acaggccgaa 240
gatgaagccg actactactg caactccctg gagcggattg gatacctgag ctacgtgttt 300
ggtggcggta ccaagcttac cgtcctaggt cagcccaagg ctgccccctc ggtcactctg 360
ttcccgccct cctctgagga gcttcaagcc aacaaggcca cactggtgtg tctcataagt 420
gacttctacc cgggagccgt gacagtggcc tggaaggcag atagcagccc cgtcaaggcg 480
ggagtggaga ccaccacacc ctccaaacaa agcaacaaca agtacgcggc cagcagctat 540
ctgagcctga cgcctgagca gtggaagtcc cacagaagct acagctgcca ggtcacgcat 600
gaagggagca ccgtggagaa gacagtggcc cctacagaat gttca 645

<210> 30
<211> 215
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的抗ASGR1轻链多肽
<400> 30
Asp Ile Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
1 5 10 15
Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala
20 25 30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45
Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
50 55 60
Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Leu Glu Arg Ile Gly Tyr Leu

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85 90 95
Ser Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
100 105 110
Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
115 120 125
Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
130 135 140
Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
145 150 155 160
Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
165 170 175
Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
180 185 190
Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
195 200 205
Val Ala Pro Thr Glu Cys Ser
210 215

<210> 31
<211> 1344
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的RSPO2突变体和抗ASGR1重链IgG2融合多核苷酸
<400> 31
caggtccagt tggtggaatc cggaggggt ttggtccagc ctggtggaag cctgcgcctc 60
tcatgcgccg ctagcggatt caccttctcc cgatacggca tgcattgggt cagacaggca 120
cccggaaaag gactcgaatg ggtgtcgggc atttcctcga tcgggtcaaa cacctattac 180
gccgactccg tgaagggacg gttcaccatt agccgggata acagcaagaa cactctgtac 240
ttgcaaatga actccctgcg ggctgaggac accgccgtgt actactgtgc gcggtggtac 300
aagacctata ttgacgtctg gggacagggt accctcgtga ccgtgtcgag tgctagcacc 360
aagggcccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg 420
gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca 480
ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac 540
tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc 600
aacgtgaatc acaagcccag caacaccaag gtggacaaga aagttgagcc caaatcttgt 660
gacaaaactc acacatgccc accgtgccca gcacctgaac tcctgggggg accgtcagtc 720
ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca 780
tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac 840
ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac 900

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cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag 960
tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa 1020
gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag 1080
aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag 1140
tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc 1200
gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1260
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1320
ctctccctgt ctccgggtaa atga 1344

<210> 32
<211> 568
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的RSPO2突变体和抗ASGR1重链IgG2融合多肽
<400> 32

Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys
1 5 10 15
Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met
20 25 30
Arg Gln Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly
35 40 45
His Arg Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn
50 55 60
Cys Asp Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly
65 70 75 80
Phe Tyr Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe
85 90 95
Ala Pro Leu Glu Glu Thr Met Glu Cys Val Glu Gly Gly Gly Gly Ser
100 105 110
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu
115 120 125
Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys
130 135 140
Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met Ser Trp Val Arg
145 150 155 160
Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala Ile Ser Gly Ser
165 170 175
Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile
180 185 190

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Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu
195 200 205
Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Lys Asp Phe Ser Ser
210 215 220
Arg Arg Trp Tyr Leu Glu Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
225 230 235 240
Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys
245 250 255
Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys
260 265 270
Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu
275 280 285
Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu
290 295 300
Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr
305 310 315 320
Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val
325 330 335
Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro
340 345 350
Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
355 360 365
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
370 375 380
Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
385 390 395 400
Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
405 410 415
Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln
420 425 430
Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
435 440 445
Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro
450 455 460
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
465 470 475 480
Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
485 490 495
Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr

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500 505 510

Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
515 520 525

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
530 535 540

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
545 550 555 560

Ser Leu Ser Leu Ser Pro Gly Lys
565

<210> 33
<211> 1344
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的SZC-09033-pFUSEss-aGFP-VH-CHIg-hG1融合多核苷酸
<400> 33

caggtccagt tggtggaatc cggagggggt ttggtccagc ctggtggaag cctgcgcctc 60
tcatgcgccg ctagcggatt caccttctcc cgatacggca tgcattgggt cagacaggca 120
cccggaaaag gactcgaatg ggtgtcgggc atttcctcga tcgggtcaaa cacctattac 180
gccgactccg tgaagggacg gttcaccatt agccgggata acagcaagaa cactctgtac 240
ttgcaaatga actccctgcg ggctgaggac accgccgtgt actactgtgc gcggtggtac 300
aagacctata ttgacgtctg gggacagggt accctcgtga ccgtgtcgag tgctagcacc 360
aagggcccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg 420
gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca 480
ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac 540
tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc 600
aacgtgaatc acaagcccag caacaccaag gtggacaaga aagttgagcc caaatcttgt 660
gacaaaactc acacatgccc accgtgccca gcacctgaac tcctgggggg accgtcagtc 720
ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca 780
tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac 840
ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac 900
cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag 960
tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa 1020
gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag 1080
aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag 1140
tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc 1200
gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1260
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1320
ctctccctgt ctccgggtaa atga 1344

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<210> 34
<211> 447
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的SZC-09033-pFUSEss-aGFP-VH-CHIg-hG1融合多肽
<400> 34

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gly Ile Ser Ser Ile Gly Ser Asn Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Trp Tyr Lys Thr Tyr Ile Asp Val Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190
Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205
Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220
Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225 230 235 240
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

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Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270
Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285
Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320
Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350
Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 35
<211> 693
<212> DNA
<213> 智人(Homo sapiens)
<400> 35

cagaacagcc agctccagga agaactgagg ggcctccgcg aaaccttctc caacttcacg 60
gcttcgaccg aagctcaagt caaggggttg tccacacaag gcggcaacgt cggacgcaag 120
atgaagtcgc tggagtccca gctggaaaag cagcagaagg atctctccga ggatcacagc 180
tcactgctgt tgcacgtgaa gcagttcgtg tcggacctga ggtccctgag ctgtcagatg 240
gcggcactgc agggaaacgg ttccgaaaga acttgctgcc ctgtgaattg ggtggagcac 300
gagagaagct gctactggtt ctcgcggtcc ggcaaagcct gggcggacgc cgacaactat 360
tgtcggctgg aggatgcgca cctggtggtc gtgacctcct gggaggaaca gaagtttgtg 420
cagcaccata tcggtcccgt gaacacttgg atggggctgc acgaccaaaa cggaccgtgg 480
aaatgggtgg atgggactga ttacgaaacc ggattcaaga actggcgccc agagcagccc 540
gacgattggt acggacatgg actgggggggc ggagaggact gcgcccactt caccgacgac 600

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ggccggtgga acgacgacgt gtgccagcgg ccgtaccgct gggtctgcga aaccgagctg 660
gacaaggcca gccaggagcc acctctcctt tga 693

<210> 36
<211> 230
<212> PRT
<213> 智人(Homo sapiens)
<400> 36

Gln Asn Ser Gln Leu Gln Glu Glu Leu Arg Gly Leu Arg Glu Thr Phe
1 5 10 15
Ser Asn Phe Thr Ala Ser Thr Glu Ala Gln Val Lys Gly Leu Ser Thr
20 25 30
Gln Gly Gly Asn Val Gly Arg Lys Met Lys Ser Leu Glu Ser Gln Leu
35 40 45
Glu Lys Gln Gln Lys Asp Leu Ser Glu Asp His Ser Ser Leu Leu Leu
50 55 60
His Val Lys Gln Phe Val Ser Asp Leu Arg Ser Leu Ser Cys Gln Met
65 70 75 80
Ala Ala Leu Gln Gly Asn Gly Ser Glu Arg Thr Cys Cys Pro Val Asn
85 90 95
Trp Val Glu His Glu Arg Ser Cys Tyr Trp Phe Ser Arg Ser Gly Lys
100 105 110
Ala Trp Ala Asp Ala Asp Asn Tyr Cys Arg Leu Glu Asp Ala His Leu
115 120 125
Val Val Val Thr Ser Trp Glu Glu Gln Lys Phe Val Gln His His Ile
130 135 140
Gly Pro Val Asn Thr Trp Met Gly Leu His Asp Gln Asn Gly Pro Trp
145 150 155 160
Lys Trp Val Asp Gly Thr Asp Tyr Glu Thr Gly Phe Lys Asn Trp Arg
165 170 175
Pro Glu Gln Pro Asp Asp Trp Tyr Gly His Gly Leu Gly Gly Gly Glu
180 185 190
Asp Cys Ala His Phe Thr Asp Asp Gly Arg Trp Asn Asp Asp Val Cys
195 200 205
Gln Arg Pro Tyr Arg Trp Val Cys Glu Thr Glu Leu Asp Lys Ala Ser
210 215 220
Gln Glu Pro Pro Leu Leu
225 230

<210> 37
<211> 684

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<212> DNA
<213> 智人(Homo sapiens)
<400> 37
aggggcgcac agctgcaagc cgagctgcgg tccctgaagg aagctttctc aaacttctcg 60
agctcgaccc tcaccgaagt gcaggccatt agcacccacg ggggttccgt gggggacaag 120
atcacctcgc tgggagcgaa gctggagaag cagcagcaag acctcaaggc cgaccacgac 180
gcgctgctgt tccacttgaa gcacttccca gtggacttgc ggttcgtggc gtgccagatg 240
gagctgctgc actccaatgg gagccagaga acttgttgcc ctgtgaactg ggtggaacac 300
cagggatcct gctactggtt tagccactcc ggaaaggcct gggccgaagc cgagaagtac 360
tgccagcttg agaacgcgca cctggtcgtg atcaactcct gggaagaaca gaagttcatt 420
gtgcaacaca ctaacccgtt caacacctgg atcggcctga ccgactccga cggctcatgg 480
aaatgggtgg acggaaccga ttaccggcat aactataaga actgggccgt gactcagccg 540
gataattggc acggacacga gctgggtgga tccgaggact gcgtcgaagt gcagcccgac 600
ggcagatgga acgatgactt ctgtctgcaa gtgtaccgct gggtctgcga gaagcgccgc 660
aacgccactg gcgaagtggc ttga 684
<210> 38
<211> 227
<212> PRT
<213> 智人(Homo sapiens)
<400> 38
Arg Gly Ala Gln Leu Gln Ala Glu Leu Arg Ser Leu Lys Glu Ala Phe
1 5 10 15
Ser Asn Phe Ser Ser Ser Thr Leu Thr Glu Val Gln Ala Ile Ser Thr
20 25 30
His Gly Gly Ser Val Gly Asp Lys Ile Thr Ser Leu Gly Ala Lys Leu
35 40 45
Glu Lys Gln Gln Gln Asp Leu Lys Ala Asp His Asp Ala Leu Leu Phe
50 55 60
His Leu Lys His Phe Pro Val Asp Leu Arg Phe Val Ala Cys Gln Met
65 70 75 80
Glu Leu Leu His Ser Asn Gly Ser Gln Arg Thr Cys Cys Pro Val Asn
85 90 95
Trp Val Glu His Gln Gly Ser Cys Tyr Trp Phe Ser His Ser Gly Lys
100 105 110
Ala Trp Ala Glu Ala Glu Lys Tyr Cys Gln Leu Glu Asn Ala His Leu
115 120 125
Val Val Ile Asn Ser Trp Glu Glu Gln Lys Phe Ile Val Gln His Thr
130 135 140
Asn Pro Phe Asn Thr Trp Ile Gly Leu Thr Asp Ser Asp Gly Ser Trp

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145 150 155 160
Lys Trp Val Asp Gly Thr Asp Tyr Arg His Asn Tyr Lys Asn Trp Ala
165 170 175
Val Thr Gln Pro Asp Asn Trp His Gly His Glu Leu Gly Gly Ser Glu
180 185 190
Asp Cys Val Glu Val Gln Pro Asp Gly Arg Trp Asn Asp Asp Phe Cys
195 200 205
Leu Gln Val Tyr Arg Trp Val Cys Glu Lys Arg Arg Asn Ala Thr Gly
210 215 220
Glu Val Ala
225

<210> 39
<211> 690
<212> DNA
<213> 智人(Homo sapiens)
<400> 39
caaaacgccc agctgcagcg ggagctgcgg ggcctgagag agacgctcag caacttcaca 60
gcgagcaccg aggcccaggt caagggcttg agcacccagg gaggcaatgt gggaagaaag 120
atgaagtcgc tggagtccca gctggagaaa cagcagaagg acttgagtga agatcactcc 180
agcctgctgc tccacgtgaa gcagttcgtg tctgacctgc ggagcctgag ctgtcagatg 240
gcggcgctcc agggcaatgg ctcggaaagg gcctgctgcc cagtcaactg ggtggagcac 300
gagcgcagct gctactggtt ctctcgctcc gggaaggcct gggccgacgc cgacaactac 360
tgccggctgg aggacgcgca cctggtggtg gtcacgtcct gggaggagca gaaatttgtc 420
cagcaccaca taggtcctgt gaacacctgg atgggcctcc acgaccaaaa cgggcctgg 480
aagtgggtgg acgggacgga ctacgagacg ggcttcaaga actggagacc ggagcagccg 540
gacgactggt acggccacgg gctcgggggga ggggaggact gtgcccactt caccgacgac 600
ggccgctgga acgacgacgt ctgccagagg ccctaccgct gggtctgcga gacagagctg 660
gacaaggcca gtcaggagcc acctctcctt 690

<210> 40
<211> 230
<212> PRT
<213> 智人(Homo sapiens)
<400> 40
Gln Asn Ala Gln Leu Gln Arg Glu Leu Arg Gly Leu Arg Glu Thr Leu
1 5 10 15
Ser Asn Phe Thr Ala Ser Thr Glu Ala Gln Val Lys Gly Leu Ser Thr
20 25 30
Gln Gly Gly Asn Val Gly Arg Lys Met Lys Ser Leu Glu Ser Gln Leu
35 40 45

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Glu Lys Gln Gln Lys Asp Leu Ser Glu Asp His Ser Ser Leu Leu Leu
50 55 60
His Val Lys Gln Phe Val Ser Asp Leu Arg Ser Leu Ser Cys Gln Met
65 70 75 80
Ala Ala Leu Gln Gly Asn Gly Ser Glu Arg Ala Cys Cys Pro Val Asn
85 90 95
Trp Val Glu His Glu Arg Ser Cys Tyr Trp Phe Ser Arg Ser Gly Lys
100 105 110
Ala Trp Ala Asp Ala Asp Asn Tyr Cys Arg Leu Glu Asp Ala His Leu
115 120 125
Val Val Val Thr Ser Trp Glu Glu Gln Lys Phe Val Gln His His Ile
130 135 140
Gly Pro Val Asn Thr Trp Met Gly Leu His Asp Gln Asn Gly Pro Trp
145 150 155 160
Lys Trp Val Asp Gly Thr Asp Tyr Glu Thr Gly Phe Lys Asn Trp Arg
165 170 175
Pro Glu Gln Pro Asp Asp Trp Tyr Gly His Gly Leu Gly Gly Gly Glu
180 185 190
Asp Cys Ala His Phe Thr Asp Asp Gly Arg Trp Asn Asp Asp Val Cys
195 200 205
Gln Arg Pro Tyr Arg Trp Val Cys Glu Thr Glu Leu Asp Lys Ala Ser
210 215 220
Gln Glu Pro Pro Leu Leu
225 230

<210> 41
<211> 684
<212> DNA
<213> 智人(Homo sapiens)
<400> 41

caaagtgcac agctgcaagc agagatgcgg agcctgaagg aagctttcag caacttctcc 60
tcgagcacgc tggtggaggt ccatgctctc ggcacccacg gaggcagcgt gggtgacaag 120
atcacatccc taggagacaa gttggagaaa cagcagcacg acctgaaagc agatcatgac 180
atcctgctcc tccatctgaa gcacttcccc gtggacctgc gcttcgtggc ctgccagatg 240
gagctcctcc acagcaacgg ctcccaaagg acctgctgcc ctgtcaactg ggtggagcac 300
caaggcagct gctactggtt ctctcgctcc gggaaggcct gggccgaggc ggagaagtac 360
tgccagctgg agaactcaca cctggtggtc atcaactcct gggaggagca gaaattcatt 420
gtacaacaca cgaacccctt caatacctgg ataggtctca cggacagtga tggctcctgg 480
aaatgggtgg acggcacaga ctataggcac aactacaaga actgggctgt cactcagcca 540
gatgattggc acgggcatga gctgggcgga agtgaagact gtgttgaagt ccggccggat 600

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ggccgctgga acgatgattt ctgcctgcag gtgcaccgct gggtgtgtga gaagaggcgg 660
aatgccaccg gcgaggcagc ctga 684

<210> 42
<211> 227
<212> PRT
<213> 智人(Homo sapiens)
<400> 42

Gln Ser Ala Gln Leu Gln Ala Glu Met Arg Ser Leu Lys Glu Ala Phe
1 5 10 15
Ser Asn Phe Ser Ser Ser Thr Leu Val Glu Val His Ala Leu Gly Thr
20 25 30
His Gly Gly Ser Val Gly Asp Lys Ile Thr Ser Leu Gly Asp Lys Leu
35 40 45
Glu Lys Gln Gln His Asp Leu Lys Ala Asp His Asp Ile Leu Leu Leu
50 55 60
His Leu Lys His Phe Pro Val Asp Leu Arg Phe Val Ala Cys Gln Met
65 70 75 80
Glu Leu Leu His Ser Asn Gly Ser Gln Arg Thr Cys Cys Pro Val Asn
85 90 95
Trp Val Glu His Gln Gly Ser Cys Tyr Trp Phe Ser Arg Ser Gly Lys
100 105 110
Ala Trp Ala Glu Ala Glu Lys Tyr Cys Gln Leu Glu Asn Ser His Leu
115 120 125
Val Val Ile Asn Ser Trp Glu Glu Gln Lys Phe Ile Val Gln His Thr
130 135 140
Asn Pro Phe Asn Thr Trp Ile Gly Leu Thr Asp Ser Asp Gly Ser Trp
145 150 155 160
Lys Trp Val Asp Gly Thr Asp Tyr Arg His Asn Tyr Lys Asn Trp Ala
165 170 175
Val Thr Gln Pro Asp Asp Trp His Gly His Glu Leu Gly Gly Ser Glu
180 185 190
Asp Cys Val Glu Val Arg Pro Asp Gly Arg Trp Asn Asp Asp Phe Cys
195 200 205
Leu Gln Val His Arg Trp Val Cys Glu Lys Arg Arg Asn Ala Thr Gly
210 215 220
Glu Ala Ala
225

<210> 43
<211> 468

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<212> DNA
<213> 智人(Homo sapiens)
<400> 43
cagaaagcta ttatcagagt gatccccttg aaaatggacc ccacaggaaa actgaatctc 60
actttggaag gtgtgtttgc tggtgttgct gaaataactc cagcagaagg aaaattaatg 120
cagtcccacc cgctgtacct gtgcaatgcc agtgatgacg acaatctgga gcctggattc 180
atcagcatcg tcaagctgga gagtcctcga cgggcccccc gcccctgcct gtcactggct 240
agcaaggctc ggatggcggg tgagcgagga gccagtgctg tcctctttga catcactgag 300
gatcgagctg ctgctgagca gctgcagcag ccgctggggc tgacctggcc agtggtgttg 360
atctggggta atgacgctga gaagctgatg gagtttgtgt acaagaacca aaaggcccat 420
gtgaggattg agctgaagga gcccccggcc tggccagatt atgattga 468
<210> 44
<211> 155
<212> PRT
<213> 智人(Homo sapiens)
<400> 44
Gln Lys Ala Ile Ile Arg Val Ile Pro Leu Lys Met Asp Pro Thr Gly
1 5 10 15
Lys Leu Asn Leu Thr Leu Glu Gly Val Phe Ala Gly Val Ala Glu Ile
20 25 30
Thr Pro Ala Glu Gly Lys Leu Met Gln Ser His Pro Leu Tyr Leu Cys
35 40 45
Asn Ala Ser Asp Asp Asp Asn Leu Glu Pro Gly Phe Ile Ser Ile Val
50 55 60
Lys Leu Glu Ser Pro Arg Arg Ala Pro Arg Pro Cys Leu Ser Leu Ala
65 70 75 80
Ser Lys Ala Arg Met Ala Gly Glu Arg Gly Ala Ser Ala Val Leu Phe
85 90 95
Asp Ile Thr Glu Asp Arg Ala Ala Ala Glu Gln Leu Gln Gln Pro Leu
100 105 110
Gly Leu Thr Trp Pro Val Val Leu Ile Trp Gly Asn Asp Ala Glu Lys
115 120 125
Leu Met Glu Phe Val Tyr Lys Asn Gln Lys Ala His Val Arg Ile Glu
130 135 140
Leu Lys Glu Pro Pro Ala Trp Pro Asp Tyr Asp
145 150 155
<210> 45
<211> 495
<212> DNA

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<213> 智人(Homo sapiens)

<400> 45

aaggagacgg cgttcgtgga ggtggtgctg ttcgagtcga gcccaagcgg cgattacacc 60
acctacacca ccggcctcac gggccgcttc tcgcgggccg gggccacgct cagcgccgag 120
ggcgagatcg tgcagatgca cccactgggc ctatgtaata acaatgacga agaggacttg 180
tatgaatatg gctgggtagg agtggtgaag ctggaacagc cagaattgga cccgaaacca 240
tgcctcactg tcctaggcaa ggccaagcga gcagtacagc ggggagctac tgcagtcatc 300
tttgatgtgt ctgaaaaccc agaagctatt gatcagctga accagggctc tgaagacccg 360
ctcaagaggc cggtggtgta tgtgaagggt gcagatgcca ttaagctgat gaacatcgtc 420
aacaagcaga aagtggctcg agcaaggatc cagcaccgcc ctcctcgaca acccactgaa 480
tactttgaca tgtga 495

<210> 46

<211> 164

<212> PRT

<213> 智人(Homo sapiens)

<400> 46

Lys Glu Thr Ala Phe Val Glu Val Val Leu Phe Glu Ser Ser Pro Ser
1 5 10 15
Gly Asp Tyr Thr Thr Tyr Thr Thr Gly Leu Thr Gly Arg Phe Ser Arg
20 25 30
Ala Gly Ala Thr Leu Ser Ala Glu Gly Glu Ile Val Gln Met His Pro
35 40 45
Leu Gly Leu Cys Asn Asn Asn Asp Glu Glu Asp Leu Tyr Glu Tyr Gly
50 55 60
Trp Val Gly Val Val Lys Leu Glu Gln Pro Glu Leu Asp Pro Lys Pro
65 70 75 80
Cys Leu Thr Val Leu Gly Lys Ala Lys Arg Ala Val Gln Arg Gly Ala
85 90 95
Thr Ala Val Ile Phe Asp Val Ser Glu Asn Pro Glu Ala Ile Asp Gln
100 105 110
Leu Asn Gln Gly Ser Glu Asp Pro Leu Lys Arg Pro Val Val Tyr Val
115 120 125
Lys Gly Ala Asp Ala Ile Lys Leu Met Asn Ile Val Asn Lys Gln Lys
130 135 140
Val Ala Arg Ala Arg Ile Gln His Arg Pro Pro Arg Gln Pro Thr Glu
145 150 155 160
Tyr Phe Asp Met

<210> 47

<211> 103

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<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 47

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Phe Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Gly Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Arg Pro Gly Gln Ala Pro Arg Pro Leu Ile
35 40 45
Tyr Asp Ala Thr Asn Arg Ala Thr Gly Ile Pro Thr Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln His Arg Arg Thr Phe Gly Arg
85 90 95
Gly Thr Lys Leu Glu Ile Lys
100

<210> 48
<211> 122
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 48

Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15
Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
20 25 30
Ser Ala Ala Trp Asn Trp Met Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45
Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
50 55 60
Val Ser Val Lys Ser Arg Met Thr Ile Asn Pro Asp Thr Ser Arg Asn
65 70 75 80
Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Leu Glu Asp Thr Ala Val
85 90 95
Tyr Tyr Cys Ala Arg Trp Asn His Glu Glu His Tyr Phe Asp Tyr Trp

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100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 49
<211> 103
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 49

Asp Val Val Met Thr Gln Ser Pro Ala Thr Leu Ser Phe Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Gly Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Arg Pro Gly Gln Ala Pro Arg Pro Leu Ile
35 40 45
Tyr Asp Ala Thr Asn Arg Ala Thr Gly Ile Pro Thr Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln His Arg Arg Thr Phe Gly Arg
85 90 95
Gly Thr Lys Leu Glu Ile Lys
100

<210> 50
<211> 122
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 50

Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15
Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Ala Ser Val Ser Ser Asn
20 25 30
Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45
Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
50 55 60

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Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65 70 75 80
Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Gly Asp Thr Ala Val
85 90 95
Tyr Tyr Cys Ala Arg Trp Asn His Glu Glu His Tyr Phe Asp Tyr Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 51
<211> 103
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 51

Asp Ile Gln Leu Thr Gln Ser Pro Ala Thr Leu Ser Phe Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Gly Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Arg Pro Gly Gln Ala Pro Arg Pro Leu Ile
35 40 45
Tyr Asp Ala Thr Asn Arg Ala Thr Gly Ile Pro Thr Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln His Arg Arg Thr Phe Gly Arg
85 90 95
Gly Thr Lys Leu Glu Ile Lys
100

<210> 52
<211> 120
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 52

Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15
Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn

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20 25 30

Ser Val Ala Trp Asn Trp Met Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Tyr Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65 70 75 80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95

Tyr Tyr Cys Ala Ser Trp Thr Arg Gly Ala Phe Asp Ile Trp Gly Gln
100 105 110

Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 53
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 53

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Gly Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Leu Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 54
<211> 117
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>

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<223> 在实验室中制备的合成的链
<400> 54

Glu Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Val Ser Asp Gly Tyr Asp Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser
115

<210> 55
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 55

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
His Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Ile Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Val
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

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<210> 56
<211> 117
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 56

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ser Phe Gly Val Gly Ala Pro Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser
115

<210> 57
<211> 112
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 57

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30
Asp Gly His Asn Tyr Leu Gln Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45
Pro Gln Leu Leu Ile Leu Leu Gly Ser Tyr Arg Ala Ser Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile

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65 70 75 80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85 90 95
Thr His Trp Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 58
<211> 114
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 58
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Thr Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu
50 55 60
Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ser Ala Gly Gly Gly Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
100 105 110
Ser Ser

<210> 59
<211> 107
<212> PRT
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<220>
<223> 在实验室中制备的合成的链
<400> 59
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asn Ile Tyr Thr Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile

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35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Asn Tyr Pro Ile
85 90 95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 60
<211> 117
<212> PRT
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<400> 60

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
20 25 30

His Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val
35 40 45

Gly Gly Ile Ile Pro Val Phe Gly Ala Pro Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Gly Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Met
100 105 110

Val Thr Val Ser Ser
115

<210> 61
<211> 107
<212> PRT
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<220>
<223> 在实验室中制备的合成的链
<400> 61

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Tyr Asp Phe Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 62
<211> 120
<212> PRT
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<223> 在实验室中制备的合成的链
<400> 62
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Gly Gly Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Thr Gly Ala Thr Ala Glu Tyr Phe Gln His Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 63
<211> 107

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<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 63

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Thr Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu
85 90 95
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 64
<211> 119
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 64

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Asn
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Gly Ile Ile Pro Met Phe Gly Thr Val Lys Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Asp Arg Gly Tyr Arg Phe Asp Phe Asp Leu Trp Gly Arg Gly

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100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 65
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 65

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ala Thr Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Val
85 90 95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> 66
<211> 123
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 66

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Tyr Ile Ser Ser Tyr Asn Ser His Thr Asn Asp Ala Asp Ser Val
50 55 60

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Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Trp Ala Val Ala Ala Gly Gly Gln Tyr Tyr Tyr Met Asp Val
100 105 110
Trp Gly Lys Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 67
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 67

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Arg Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Leu Arg Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Tyr Thr Ile Pro Ile
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 68
<211> 122
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 68

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Thr Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Asn Tyr

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20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Pro Lys Ser Gly Gly Thr Lys Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Arg Gly Ile Thr Met Val Arg Gly Val Met Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 69
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
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<223> 在实验室中制备的合成的链
<400> 69

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Gln Ala Ser Asn Lys Asp Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Tyr Ser Thr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 70
<211> 122
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>

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<223> 在实验室中制备的合成的链
<400> 70

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Thr Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Thr Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Ile Asn Pro Asn Gly Gly Gly Thr Asn Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Asp Arg Thr Ala Met Ala Pro Glu Gly Ala Phe Asp Ile Trp
100 105 110
Gly Gln Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 71
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 71

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Asn Asn Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

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<210> 72
<211> 117
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 72

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Asp Tyr
20 25 30
Tyr Val His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Arg Asn Gly Arg Thr Ser Tyr Ala Gln Arg Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp His Leu Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr
100 105 110
Val Thr Val Ser Ser
115

<210> 73
<211> 112
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 73

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45
Pro Gln Leu Leu Ile Tyr Ala Ala Ser Asn Leu Gln Ser Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile

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65 70 75 80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85 90 95
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 74
<211> 127
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 74
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Asn
20 25 30
Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Asp Ser Pro Ile Val Arg Arg Gly Glu Arg Gly Arg Tyr Tyr
100 105 110
Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 75
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 75
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Asn Trp
20 25 30

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Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Arg Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Tyr Ala Ile Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 76
<211> 118
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 76
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30
Asn Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Met Asn Pro Asn Thr Gly Asn Thr Ala Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Lys Asn Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr
100 105 110
Thr Val Thr Val Ser Ser
115

<210> 77
<211> 119
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链

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<400> 77

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Asp
1 5 10 15
Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly His Thr Phe Ser Ser Tyr
20 25 30
Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45
Ala Ala Ile Ser Gln Ser Gly Tyr Val Arg Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Lys Pro Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Asn Ala Arg Trp Gly Ala Gly Ser Leu Phe Ala Ser Trp Gly Gln Gly
100 105 110
Thr Gln Val Thr Val Ser Ser
115

<210> 78

<211> 107

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的合成的链

<400> 78

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser Ile Arg Thr Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Ile
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 79

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<211> 117
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 79

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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                  10                  15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
            20                  25                  30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Gly Arg Gln Gly Val Trp Asp Tyr Trp Gly Arg Gly Thr Leu
            100                 105                 110
Val Thr Val Ser Ser
        115
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<210> 80
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 80

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                  10                  15
Asp Arg Val Thr Ile Thr Cys Arg Val Ser Gln Gly Ile Ser Ser Tyr
            20                  25                  30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
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Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Gly Ala Pro Leu
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 81
<211> 128
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 81
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Leu His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Asn Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Gly Asp Phe Trp Ser Gly Tyr Tyr Pro Tyr Tyr Tyr Tyr Tyr
100 105 110
Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 82
<211> 112
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 82
Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser

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35 40 45

Pro Gln Leu Leu Ile Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Thr
85 90 95

Leu His Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 83
<211> 119
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 83

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ala Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Asn Gly Gly Arg Thr Thr Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Phe Gly Val Ala Gly Thr Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 84
<211> 113
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 84

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Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15
Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30
Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45
Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60
Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80
Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95
Tyr Tyr Ser Asp Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile
100 105 110
Lys

<210> 85
<211> 118
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 85

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Asp Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Val Ile Asn Pro Gly Gly Ser Asp Thr Thr Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Gly Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr
100 105 110
Thr Val Thr Val Ser Ser
115

<210> 86

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<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 86

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Asn Ile His Lys Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Tyr Ser Thr Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 87
<211> 121
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 87

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Ile Asn Pro His Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

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Ala Arg Glu Asp Tyr Asn Trp Asn Asp Gly Trp Phe Asp Pro Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 88
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 88

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asn Ile Tyr Asp Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Tyr Ser Thr Pro Phe
85 90 95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> 89
<211> 127
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 89

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Asn Tyr
20 25 30
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe

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50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Asp Ser Gly Tyr Cys Ser Ser Thr Ser Cys Tyr Asp Gly Gly
100 105 110
Tyr Phe Asp Leu Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 90
<211> 112
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 90

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Tyr Arg Ala Ser Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85 90 95
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 91
<211> 120
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 91

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ala Ile Ser Gly Ser Gly Thr Tyr Tyr Ala Asp Ser Val Lys Gly
50 55 60
Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Leu Tyr Leu Gln
65 70 75 80
Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
85 90 95
Asp Gln Gly His Asp Tyr Gly Asp Tyr Glu Ile Asp Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 92
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 92

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Arg Ser Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Asp Tyr Asp Tyr Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 93
<211> 120
<212> PRT
<213> 人工序列(Artificial Sequence)

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<220>
<223> 在实验室中制备的合成的链
<400> 93

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                  10                  15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
            20                  25                  30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Ala Asn Tyr Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Pro Val Arg Gly Ile Ser Ala Phe Asp Tyr Trp Gly Gln
            100                 105                 110
Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 94
<211> 128
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 94

```
Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Val Ile Asn Ser Gly Gly Gly Ser Thr Ser Tyr Ala Glu Ser Val
    50                  55                  60
Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Gly Thr Tyr Tyr Ser Gly Ser Tyr Tyr Tyr Pro Ala Leu Tyr
```


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100 105 110
Tyr Gly Met Asp Tyr Trp Gly Lys Gly Thr Gln Val Thr Val Ser Ser
115 120 125

<210> 95
<211> 108
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 95

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
85 90 95
Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 96
<211> 121
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 96

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Ala Met His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
35 40 45
Gly Trp Ile Asn Ala Gly Asn Gly Asn Thr Lys Tyr Ser Gln Thr Phe
50 55 60

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Gln Gly Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Leu Met Val Arg Gly Gly Pro Pro Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 97
<211> 108
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 97

Glu Thr Thr Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Asn Ser Arg
20 25 30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Leu Thr
50 55 60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Arg
85 90 95
Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 98
<211> 122
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 98

Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15
Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn

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20 25 30
Ser Ala Ala Trp Tyr Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45
Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr His Asp Tyr Ala
50 55 60
Val Ser Val Lys Ser Arg Ile Thr Ile Asn Ala Asp Thr Ser Lys Asn
65 70 75 80
Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95
Tyr Tyr Cys Ala Arg Val Val Arg Ala Val Asp Ala Phe Asp Ile Trp
100 105 110
Gly Gln Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 99
<211> 108
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 99
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30
Asn Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45
Ile Tyr Ala Thr Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln
65 70 75 80
Ser Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
85 90 95
Ile Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 100
<211> 124
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>

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<223> 在实验室中制备的合成的链

<400> 100

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Gly Arg Val Val Arg Gly Val Ile Ile Ser Tyr Gly Met Asp
100 105 110
Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 101

<211> 107

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的合成的链

<400> 101

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asn Ile Arg Ser Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Ser Leu Gln Arg Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Pro
85 90 95
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

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<210> 102
<211> 122
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 102

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1               5                   10                  15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Asp Thr Phe Thr Gly Tyr
            20                  25                  30
Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Gly Ile Ile Pro Ile Phe Asp Ala Ala Thr Tyr Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Thr Arg Ala Arg Gly Gln Arg Ser Gly Tyr Ser Tyr Phe Asp Leu Trp
            100                 105                 110
Gly Arg Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 103
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 103

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15
Asp Arg Val Thr Ile Thr Cys Arg Ala Gly Gln Ser Ile Ser Arg Phe
            20                  25                  30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
```


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65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 104
<211> 119
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 104
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Thr Ser
20 25 30
Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Met Asn Pro Asn Thr Gly Gly Ile Lys Tyr Ser Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Ser Arg Ala Leu Lys Gly Ser Tyr Thr Ser Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 105
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 105
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Arg Trp
20 25 30

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Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Ser Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Tyr Ser Phe Pro Trp
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 106
<211> 120
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 106
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Asn Thr
20 25 30
Asp Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Val Gly Gly Arg Ser Gly Trp Ile Trp Tyr Phe Asp Leu Trp Gly Arg
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 107
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链

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<400> 107

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Asp Ile Ser Arg Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Arg Pro Phe
85 90 95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> 108

<211> 119

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的合成的链

<400> 108

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Asn Tyr
20 25 30
Ser Leu Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Arg Arg Gly Ser Thr Arg Tyr Ala Gln Asn Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Gly Leu Gly Val Asp Ala Phe Asp Ile Trp Gly Gln Gly
100 105 110
Thr Met Val Thr Val Ser Ser
115

<210> 109

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<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 109

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                  10                  15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Asn Ser
            20                  25                  30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Pro Pro His
                85                  90                  95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 110
<211> 118
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 110

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
            20                  25                  30
Ala Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Tyr Ile Ser Arg Ser Ser Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```


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Ala Arg Arg Arg Asp Gly Tyr Asn Trp Gly Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 111
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 111

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Phe Ile Ser Thr Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Ser Leu Pro Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Ser Trp
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 112
<211> 127
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 112

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Arg Ile Lys Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe

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50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Gly Arg Arg Ser Arg Gly Ser Ser Ser Leu Gly Tyr Tyr Tyr
100 105 110
Tyr Met Asp Val Trp Gly Lys Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 113
<211> 112
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 113

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ser
85 90 95
Leu Glu Ala Pro Leu Ala Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 114
<211> 123
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 114

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Arg Tyr
20 25 30
Phe Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Arg Tyr Ala Gln Asn Leu
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Gln Lys Gly Lys Ser Ser Ser Trp Phe Arg Phe Asp Pro
100 105 110
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 115
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 115

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Tyr Arg Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Phe Ala Ala Ser Ser Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Thr Thr Pro Ile
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 116
<211> 119
<212> PRT
<213> 人工序列(Artificial Sequence)

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<220>
<223> 在实验室中制备的合成的链
<400> 116

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30
Lys Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Lys Ile Asn Pro Ser Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Gly Ala Gly Met Trp Tyr Phe Asp Leu Trp Gly Arg Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 117
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 117

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Arg Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys

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100 105

<210> 118
<211> 117
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 118

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Arg Arg Tyr
20 25 30
Pro Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Lys Val Gly Ala Ile Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser
115

<210> 119
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 119

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Thr Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Ser Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 120
<211> 117
<212> PRT
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<220>
<223> 在实验室中制备的合成的链
<400> 120

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Gly Gly Ser Gly Trp Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser
115

<210> 121
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 121

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Arg Trp

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20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Phe Ser Thr Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 122
<211> 119
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 122

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Arg Ile Ser Pro Asn Arg Gly Gly Thr Lys Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Ser Trp Leu Arg Gly Ala Trp Gly Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 123
<211> 113
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>

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<223> 在实验室中制备的合成的链
<400> 123

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15
Glu Arg Ala Thr Ile Asn Cys Thr Ser Ser Gln Ser Val Leu His Ser
20 25 30
Ser Asn Lys Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45
Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Ala Ser Gly Val
50 55 60
Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80
Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95
Tyr His Ser Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
100 105 110
Lys

<210> 124
<211> 117
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 124

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Asn Phe
20 25 30
Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gly Ile Ser Ala Ser Gly Arg Asn Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Arg Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Thr Arg His Gly Ser Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser

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115

<210> 125
<211> 113
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 125

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15
Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30
Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45
Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60
Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80
Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95
Tyr Tyr Ser Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
100 105 110
Lys

<210> 126
<211> 125
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 126

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ile Gly Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Leu
35 40 45
Gly Trp Val Asn Pro Lys Asn Gly His Thr Gly Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr

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65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Asp Leu Glu His Thr Gly Tyr Ser Ser Gly Trp Ala Gly Phe
100 105 110
Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125
<210> 127
<211> 112
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 127
Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45
Pro Gln Leu Leu Ile Tyr Gly Ala Ser Ser Leu Gln Ser Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
85 90 95
Thr His Trp Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Asp Ile Lys
100 105 110
<210> 128
<211> 120
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 128
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Arg Phe Thr Asn Tyr
20 25 30

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Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Ile Ser Pro Asn Ser Gly Ala Thr Asn Tyr Ala Gln Asn Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Gly Gly Arg Thr Thr Val Thr Thr Met Ala Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 129
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 129

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Arg Thr Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 130
<211> 118
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链

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<400> 130

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ala Phe Ser Asn Phe
20 25 30
Ala Met Ile Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Leu Arg Ala Asn Tyr Gly Met Asp Val Trp Gly Gln Gly Thr
100 105 110
Thr Val Thr Val Ser Ser
115

<210> 131

<211> 107

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的合成的链

<400> 131

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ala Ser
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys His Gln Tyr Phe Ser Pro Pro Met
85 90 95
Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 132

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<211> 120
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 132

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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Glu Tyr
            20                  25                  30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Trp Met Asn Pro Asn Ser Gly His Ala Gly Ser Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Gly Arg Arg Ser Gly Leu Ser Pro Pro Ala Tyr Trp Gly Gln
            100                 105                 110
Gly Thr Leu Val Thr Val Ser Ser
        115                 120
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<210> 133
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 133

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Tyr Ile Gly Ser Tyr
            20                  25                  30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
```


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Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Pro Pro Phe
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 134
<211> 117
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 134
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30
Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Ile Ser Ala Asp Asn Gly Asn Thr Asn Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Gly Arg Ser Gly Asn Trp Lys Phe Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser
115

<210> 135
<211> 112
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 135
Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser

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35 40 45

Pro Gln Leu Leu Ile Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
85 90 95

Thr His Trp Pro Tyr Ala Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105 110

<210> 136
<211> 116
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 136

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Leu Met
35 40 45

Gly Trp Ile Asn Pro Asn Ser Gly Asn Thr Lys Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Ser Asn Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val
100 105 110

Thr Val Ser Ser
115

<210> 137
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 137

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Asn Asn Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Thr Phe Pro Ile
85 90 95
Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 138
<211> 116
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 138
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Asn Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ala Ile Ser Gly Ser Gly Arg Thr Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Arg Thr Ser Ser Phe Ser Leu Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser
115

<210> 139
<211> 113

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<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 139

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15
Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30
Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45
Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60
Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80
Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95
Tyr Tyr Ser Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
100 105 110
Lys

<210> 140
<211> 121
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 140

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Ala Gly Thr Phe Ser Asn Tyr
20 25 30
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Gly Ile Ile Pro Ile Phe Asp Ala Thr Asn Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

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Ala Arg Arg Gln Tyr Ser Gly Tyr Asp Thr His Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 141
<211> 108
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 141

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Asp Ser Ser
20 25 30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45
Ile Tyr Ala Ala Ser Ala Arg Ala Ala Gly Ile Pro Ala Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln
65 70 75 80
Ser Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Arg Ser Pro
85 90 95
Pro Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 142
<211> 121
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 142

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Arg Phe Thr Ser Tyr
20 25 30
Tyr Leu His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Met Asn Pro Lys Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe

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50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Gly Gly Arg Ser Tyr Gly Tyr Trp Tyr Phe Asp Leu Trp Gly
100 105 110
Arg Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 143
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 143
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 144
<211> 117
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 144
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg His
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Gly Ser Leu Gly Tyr Phe Asp Leu Trp Gly Arg Gly Thr Leu
100 105 110
Val Thr Val Ser Ser
115

<210> 145
<211> 106
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 145
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Arg Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Thr Val Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Leu Gln Pro Glu
65 70 75 80
Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Arg Ser Pro Tyr Thr
85 90 95
Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 146
<211> 119
<212> PRT
<213> 人工序列(Artificial Sequence)

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<220>
<223> 在实验室中制备的合成的链
<400> 146
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Ile Asn Pro Asn Thr Gly Gly Thr Lys Ser Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Val Leu Arg Gly Ser Leu Gly Phe Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115
<210> 147
<211> 106
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 147
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Asn
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Thr
85 90 95
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

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100 105

<210> 148
<211> 120
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 148

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Gly Val Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Arg Gly Gly Ser Thr Ser Tyr Ala Gln Asn Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Tyr Ser Ser Ser Trp Ser Trp Pro Phe Asp Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 149
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 149

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Ser Ser Phe Pro Leu
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Asp Ile Lys
100 105

<210> 150
<211> 119
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 150
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Gly Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Ile Asn Pro Asn Arg Gly Gly Thr Ser Tyr Ala Gln Asn Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Gly Met Tyr Ser Ser Ser Trp Leu Arg Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 151
<211> 112
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 151
Glu Val Val Met Thr Gln Thr Pro Leu Thr Leu Ser Val Thr Ile Gly
1 5 10 15
Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser

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20 25 30

Asp Gly Lys Thr Tyr Leu Asn Trp Leu Leu Gln Arg Pro Gly Gln Ser
35 40 45

Pro Lys Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp Ser Gly Val Pro
50 55 60

Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Trp Gln Gly
85 90 95

Thr His Phe Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 152
<211> 121
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 152

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Lys Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Asn Thr Tyr
20 25 30

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Arg Ile Arg Ser Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
50 55 60

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Glu Ser Met
65 70 75 80

Leu Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Met Tyr
85 90 95

Tyr Cys Val Arg Pro Arg Tyr Asp Tyr Trp Tyr Phe Asp Val Trp Gly
100 105 110

Thr Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 153
<211> 108
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>

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<223> 在实验室中制备的合成的链
<400> 153

Glu Asn Val Leu Thr Gln Ser Pro Ala Ile Met Ala Ala Ser Leu Gly
1 5 10 15
Gln Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Ser Ser
20 25 30
Phe Leu His Trp Tyr Gln Gln Lys Ser Gly Ala Ser Pro Lys Pro Leu
35 40 45
Ile His Arg Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Val Glu
65 70 75 80
Ala Glu Asp Asp Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Gly Tyr Pro
85 90 95
Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 154
<211> 117
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的链
<400> 154

Asp Val Lys Leu Val Glu Ser Gly Glu Gly Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
35 40 45
Ala Tyr Ile Ser Ser Gly Gly Asp Tyr Ile Tyr Tyr Val Asp Thr Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Thr Arg Glu Gly Thr Gly Gly Met Asp Tyr Trp Gly Gln Gly Thr Ser
100 105 110
Val Thr Val Ser Ser
115

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<210> 155
<211> 648
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的可变轻链多核苷酸序列
<400> 155
cagagcgtgt taacccagcc cgccagcgtg agcggcagcc ccggccagag catcaccatc 60
agctgcgccg gcaccagcag cgacgtgggc ggctacaact acgtgagctg gtaccagcag 120
cacccggca aggcccccaa gctgatgatc tacgaggaca gcaagagacc cagcggcgtg 180
agcaacagat tcagcggcag caagagcggc aacaccgcca gcctgaccat cagcggcctg 240
caggccgagg acgaggccga ctactactgc agcagctaca ccaccagaag caccagagtg 300
ttcggcggcg gcaccaagct ggccgtgctg ggtcagccca aggctgcccc ctcggtcact 360
ctgttcccgc cctcctctga ggagcttcaa gccaacaagg ccacactggt gtgtctcata 420
agtgacttct acccgggagc cgtgacagtg gcctggaagg cagatagcag ccccgtcaag 480
gcgggagtgg agaccaccac accctccaaa caaagcaaca acaagtacgc ggccagcagc 540
tatctgagcc tgacgcctga gcagtggaag tcccacagaa gctacagctg ccaggtcacg 600
catgaaggga gcaccgtgga gaagacagtg gcccctacag aatgttca 648
<210> 156
<211> 216
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的可变轻链多肽序列
<400> 156
Gln Ser Val Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15
Ser Ile Thr Ile Ser Cys Ala Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45
Met Ile Tyr Glu Asp Ser Lys Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Thr Arg
85 90 95
Ser Thr Arg Val Phe Gly Gly Gly Thr Lys Leu Ala Val Leu Gly Gln
100 105 110

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Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
130 135 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145 150 155 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
165 170 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
195 200 205
Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> 157
<211> 1353
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的抗β-Gal重链IgG1-LALAPG构建体
<400> 157

gaggtgcagc tggtggagag cggcggcagc ctggtgaagc ccggcggcag cctgagactg 60
agctgcgccg ccagcggctt caccttcagc aactacagca tgaactgggt gagacaggcc 120
cccggcaagg gcctggagtg gatcagcagc atcagcggca gcagcagata catctactac 180
gccgacttcg tgaagggcag attcaccatc agcagagaca acgccaccaa cagcctgtac 240
ctgcagatga acagcctgag agccgaggac accgccgtgt actactgcgt gagaagcagc 300
atcaccatct tcggcggcgg catggacgtg tggggcagag gcaccctggt gaccgtgagc 360
agcgctagca ccaagggccc atcggtcttc cccctggcac cctcctccaa gagcacctct 420
gggggcacag cggccctggg ctgcctggtc aaggactact tccccgaacc ggtgacggtg 480
tcgtggaact caggcgccct gaccagcggc gtgcacacct tcccggctgt cctacagtcc 540
tcaggactct actccctcag cagcgtggtg accgtgccct ccagcagctt gggcacccag 600
acctacatct gcaacgtgaa tcacaagccc agcaacacca aggtggacaa gaaagttgag 660
cccaaatctt gtgacaaaac tcacacatgc ccaccgtgcc cagcacctga agccgcgggg 720
ggaccgtcag tcttcctctt cccccaaaa cccaaggaca ccctcatgat ctcccggacc 780
cctgaggtca catgcgtggt ggtggacgtg agccacgaag accctgaggt caagttcaac 840
tggtacgtgg acggcgtgga ggtgcataat gccaagacaa agccgcggga ggagcagtac 900
aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg gctgaatggc 960
aaggagtaca agtgcaaggt ctccaacaaa gccctcggag cccccatcga gaaaaccatc 1020
tccaaagcca aagggcagcc ccgagaacca caggtgtaca ccctgccccc atcccgggag 1080

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gagatgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta tcccagcgac 1140
atcgccgtgg agtgggagag caatgggcag ccggagaaca actacaagac cacgcctccc 1200
gtgctggact ccgacggctc cttcttcctc tacagcaagc tcaccgtgga caagagcagg 1260
tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac 1320
acgcagaaga gcctctccct gtctccgggt aaa 1353

<210> 158
<211> 451
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的抗β-Gal重链IgG1-LALAPG构建体构建体
<400> 158

Glu Val Gln Leu Val Glu Ser Gly Gly Ser Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30
Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Ser Ser Ile Ser Gly Ser Ser Arg Tyr Ile Tyr Tyr Ala Asp Phe Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Thr Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Val Arg Ser Ser Ile Thr Ile Phe Gly Gly Gly Met Asp Val Trp Gly
100 105 110
Arg Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
130 135 140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys

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210 215 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
225 230 235 240
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
245 250 255
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
260 265 270
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
275 280 285
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
290 295 300
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305 310 315 320
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile
325 330 335
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
340 345 350
Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
355 360 365
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
405 410 415
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445
Pro Gly Lys
450

<210> 159
<211> 1341
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的抗β-Gal重链IgG2多核苷酸序列
<400> 159
gaggtgcagc tggtggagag cggcggcagc ctggtgaagc ccggcggcag cctgagactg 60

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agctgcgccg ccagcggctt caccttcagc aactacagca tgaactgggt gagacaggcc 120
cccggcaagg gcctggagtg gatcagcagc atcagcggca gcagcagata catctactac 180
gccgacttcg tgaagggcag attcaccatc agcagagaca acgccaccaa cagcctgtac 240
ctgcagatga acagcctgag agccgaggac accgccgtgt actactgcgt gagaagcagc 300
atcaccatct tcggcggcgg catggacgtg tggggcagag gcaccctggt gaccgtgagc 360
agcgctagca ccaagggccc atcggtcttc cccctggcgc cctgctccag gagcacctcc 420
gagagcacag cggccctggg ctgcctggtc aaggactact tccccgaacc ggtgacggtg 480
tcgtggaact caggcgctct gaccagcggc gtgcacacct tcccagctgt cctacagtcc 540
tcaggactct actccctcag cagcgtggtg accgtgccct ccagcaactt cggcacccag 600
acctacacct gcaacgtaga tcacaagccc agcaacacca aggtggacaa gacagttgag 660
cgcaaatgtt gtgtcgagtg cccaccgtgc ccagcaccac ctgtggcagg accgtcagtc 720
ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcacg 780
tgcgtggtgg tggacgtgag ccacgaagac cccgaggtcc agttcaactg gtacgtggac 840
ggcgtggagg tgcataatgc caagacaaag ccacgggagg agcagttcaa cagcacgttc 900
cgtgtggtca gcgtcctcac cgttgtgcac caggactggc tgaacggcaa ggagtacaag 960
tgcaaggtct ccaacaaagg cctcccagcc cccatcgaga aaaccatctc caaaaccaaa 1020
gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag 1080
aaccaggtca gcctgacctg cctggtcaaa ggcttctacc ccagcgacat cgccgtggag 1140
tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccat gctggactcc 1200
gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1260
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1320
ctctccctgt ctccgggtaa a 1341

<210> 160
<211> 447
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的抗β-Gal重链IgG2多肽序列
<400> 160

Glu Val Gln Leu Val Glu Ser Gly Gly Ser Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30
Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Ser Ser Ile Ser Gly Ser Ser Arg Tyr Ile Tyr Tyr Ala Asp Phe Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Thr Asn Ser Leu Tyr
65 70 75 80

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Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Val Arg Ser Ser Ile Thr Ile Phe Gly Gly Gly Met Asp Val Trp Gly
100 105 110
Arg Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125
Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
130 135 140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190
Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His
195 200 205
Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys
210 215 220
Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
225 230 235 240
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270
Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285
Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser
290 295 300
Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320
Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335
Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350
Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser

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385 390 395 400
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 161
<211> 702
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的抗ASGR1 VH-CH1多核苷酸序列
<400> 161
gaagtgcagc tgctggaatc cgggggcgga ctggtgcaac ccgggggatc cctcagactg 60
tcctgtgccg catcgggttt cactttctcc tcctacgcga tgtcatgggt cagacaggcc 120
cctggaaaag gcctcgaatg ggtgtcggct atctccggat cgggggatc tacttactac 180
gccgactccg tgaagggccg gttcactatc tcgagggaca actccaagaa taccctgtac 240
ttgcaaatga actccctgcg cgccgaggat accgcggtgt attactgcgc caaggacttc 300
agctcacgcc ggtggtacct tgagtactgg ggacagggaa cccttgtcac cgtgtccagc 360
gctagcacca agggcccatc ggtcttcccc ctggcaccct cctccaagag cacctctggg 420
ggcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg 480
tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca 540
ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacccagacc 600
tacatctgca acgtgaatca caagcccagc aacaccaagg tggacaagaa agttgagccc 660
aaatcttgtg gatccggctc cggacatcat catcaccatc ac 702

<210> 162
<211> 234
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的抗ASGR1 VH-CH1多肽序列
<400> 162
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

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Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Asp Phe Ser Ser Arg Arg Trp Tyr Leu Glu Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly
210 215 220
Ser Gly Ser Gly His His His His His His
225 230

<210> 163
<211> 765
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 合成的鼠类ASGR1细胞外结构域——多核苷酸
<400> 163
caaaattccc aactccggga agatctgctg gctctaaggc agaatttcag caacctcact 60
gtgagcactg aggaccaggt caaggccctg agcacccagg gaagtagtgt gggaagaaag 120
atgaagttag tggagtcgaa gctggaaaaa cagcagaagg atctgactga agatcactcc 180
agtttgctac tgcacgtgaa gcagttagtg tctgacgtgc gaagcttgag ctgccagatg 240
gctgcatttc ggggcaatgg ctctgaaagg acctgctgcc ccatcaactg ggtggagtat 300
gaaggcagct gctactggtt ctccagctct gtgaggcctt ggactgaagc tgacaagtac 360
tgccagctgg aaaatgccca tctggtggtg gtgacctcca gggatgagca gaacttcctc 420
cagcgccaca tgggcccctt aaacacttgg attggcctaa ctgaccagaa cgggccctgg 480

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aaatgggtgg atggaacaga ctacgagaca ggcttccaga attggagacc agagcagcca 540
gataactggt acggacatgg gcttggagga ggcgaggact gtgcccactt cacgacggat 600
ggccgctgga atgacgacgt ctgcaggagg ccctaccgct gggtctgtga gacaaagttg 660
gataaggcta attccggctc cggaggtctt aatgatattt tcgaggctca gaagattgag 720
tggcatgaag gatccggctc ccaccaccat catcaccacc accac 765

<210> 164
<211> 255
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 合成的鼠类ASGR1细胞外结构域——多肽
<400> 164

Gln Asn Ser Gln Leu Arg Glu Asp Leu Leu Ala Leu Arg Gln Asn Phe
1 5 10 15
Ser Asn Leu Thr Val Ser Thr Glu Asp Gln Val Lys Ala Leu Ser Thr
20 25 30
Gln Gly Ser Ser Val Gly Arg Lys Met Lys Leu Val Glu Ser Lys Leu
35 40 45
Glu Lys Gln Gln Lys Asp Leu Thr Glu Asp His Ser Ser Leu Leu Leu
50 55 60
His Val Lys Gln Leu Val Ser Asp Val Arg Ser Leu Ser Cys Gln Met
65 70 75 80
Ala Ala Phe Arg Gly Asn Gly Ser Glu Arg Thr Cys Cys Pro Ile Asn
85 90 95
Trp Val Glu Tyr Glu Gly Ser Cys Tyr Trp Phe Ser Ser Ser Val Arg
100 105 110
Pro Trp Thr Glu Ala Asp Lys Tyr Cys Gln Leu Glu Asn Ala His Leu
115 120 125
Val Val Val Thr Ser Arg Asp Glu Gln Asn Phe Leu Gln Arg His Met
130 135 140
Gly Pro Leu Asn Thr Trp Ile Gly Leu Thr Asp Gln Asn Gly Pro Trp
145 150 155 160
Lys Trp Val Asp Gly Thr Asp Tyr Glu Thr Gly Phe Gln Asn Trp Arg
165 170 175
Pro Glu Gln Pro Asp Asn Trp Tyr Gly His Gly Leu Gly Gly Gly Glu
180 185 190
Asp Cys Ala His Phe Thr Thr Asp Gly Arg Trp Asn Asp Asp Val Cys
195 200 205
Arg Arg Pro Tyr Arg Trp Val Cys Glu Thr Lys Leu Asp Lys Ala Asn

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210 215 220

Ser Gly Ser Gly Gly Leu Asn Asp Ile Phe Glu Ala Gln Lys Ile Glu
225 230 235 240

Trp His Glu Gly Ser Gly Ser His His His His His His His His
245 250 255

<210> 165
<211> 111
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的可变轻链序列
<400> 165

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Glu Ser Val Asp Ser Tyr
20 25 30

Gly Asn Ser Phe Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Leu Ala Ser Asn Leu Glu Ser Gly Val Pro Asp
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Asn Asn
85 90 95

Glu Asp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 166
<211> 118
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的可变重链序列
<400> 166

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Asn Ile Lys Asp Thr
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

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Gly Arg Ile Asp Pro Ala Asn Gly Lys Ala Asn Tyr Asp Pro Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Phe Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Leu Gly Gly Gly Tyr Tyr Gly Met Asp Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 167
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的可变轻链序列
<400> 167
Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15
Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Ser Val Arg Pro Ala
20 25 30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Ala Leu Ile
35 40 45
Tyr Leu Ala Ser Asn Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser
65 70 75 80
Glu Asp Leu Ala Asp Tyr Phe Cys Leu Gln His Trp Asn Tyr Pro Tyr
85 90 95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 168
<211> 117
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的可变重链序列
<400> 168
Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ala

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1 5 10 15
Ser Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Asp
20 25 30
Tyr Ile His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Glu Trp Ile
35 40 45
Gly Trp Ile Asp Pro Glu Asn Gly Asp Thr Lys Tyr Ala Ser Lys Phe
50 55 60
Pro Gly Lys Ala Thr Met Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
65 70 75 80
Leu Gln Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Thr Ala Ser Arg Thr Thr Ala Leu Asp Tyr Trp Gly Pro Gly Thr Thr
100 105 110
Leu Thr Val Ser Ser
115

<210> 169
<211> 108
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的可变轻链序列
<400> 169
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15
Thr Ala Ser Ile Thr Cys Ser Gly Asp Ser Leu Gly Ser Tyr Tyr Val
20 25 30
His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45
Arg Asn Lys Gln Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Tyr Asp Trp Met Tyr Ser Ser
85 90 95
Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 170
<211> 121
<212> PRT

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<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的可变重链序列
<400> 170

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30
Gly Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Gly Arg Ile Lys Ser Lys Thr Asp Gly Gly Ile Thr Glu Tyr Ala Ala
    50                  55                  60
Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65                  70                  75                  80
Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85                  90                  95
Tyr Cys Ala Arg Ala Ile Tyr Tyr Leu Glu Ala Phe Asp Val Trp Gly
            100                 105                 110
Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 171
<211> 109
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的可变轻链序列
<400> 171

```
Asp Ile Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
1               5                  10                  15
Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala
            20                  25                  30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35                  40                  45
Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
    50                  55                  60
Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65                  70                  75                  80
Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Leu Glu Arg Ile Gly Tyr Leu
                85                  90                  95
```


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Ser Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 172
<211> 109
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的可变轻链序列
<400> 172

Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
1 5 10 15
Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala
20 25 30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45
Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
50 55 60
Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Leu Glu Arg Ile Gly Tyr Leu
85 90 95
Ser Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 173
<211> 120
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的可变重链序列
<400> 173

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

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65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Asp Phe Ser Ser Arg Arg Trp Tyr Leu Glu Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 174
<211> 108
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的可变轻链序列
<400> 174
Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
1 5 10 15
Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala
20 25 30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45
Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
50 55 60
Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Leu Arg Ser Gly Lys Met
85 90 95
Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 175
<211> 120
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的可变重链序列
<400> 175
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

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Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Ser Trp Tyr Leu Pro Gly Arg Gly Phe Asp Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 176
<211> 108
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的可变轻链序列
<400> 176
Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
1 5 10 15
Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala
20 25 30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45
Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
50 55 60
Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Lys Ser Ser Ser Lys Asn
85 90 95
Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 177
<211> 120
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的可变重链序列

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<400> 177

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Ser Ser Phe Thr Phe Gly Arg Tyr Phe Asp Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 178

<211> 107

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的合成的可变轻链序列

<400> 178

Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
1 5 10 15
Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala
20 25 30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45
Gly Arg Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
50 55 60
Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Arg Arg Gly Tyr Ser
85 90 95
Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 179

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<211> 120
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的可变重链序列
<400> 179

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Lys Ser Ser Phe Ser Tyr Leu Arg Ala Phe Asp Tyr Trp Gly Gln
            100                 105                 110
Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 180
<211> 119
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的可变重链序列
<400> 180

```
Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Arg Pro Gly Val
1               5                  10                  15
Ser Val Lys Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30
Ala Met His Trp Val Lys Gln Ser His Ala Lys Ser Leu Glu Trp Ile
        35                  40                  45
Gly Gly Ile Ser Thr Tyr Phe Gly Arg Thr Asn Tyr Asn Gln Lys Phe
    50                  55                  60
Lys Gly Arg Ala Thr Met Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80
```


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Met Glu Leu Ala Arg Leu Thr Ser Glu Asp Ser Ala Leu Tyr Tyr Cys
85 90 95
Ala Arg Gly Leu Ser Gly Asn Tyr Val Met Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Ser Val Thr Val Ser Ser
115

<210> 181
<211> 111
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的可变轻链序列
<400> 181
Asp Ile Val Leu Phe Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1 5 10 15
Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Asp Asp Tyr
20 25 30
Gly Asn Ser Phe Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45
Lys Leu Leu Ile Tyr Arg Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala
50 55 60
Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asn
65 70 75 80
Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln Gln Ser Asn
85 90 95
Glu Ala Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 182
<211> 117
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的可变重链序列
<400> 182
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30
Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

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35 40 45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Thr Ser
115

<210> 183
<211> 111
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的可变轻链序列
<400> 183

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30

Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65 70 75 80

Ala Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Arg
85 90 95

Leu Asn Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 184
<211> 123
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的可变重链序列
<400> 184

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Glu Val Gln Leu Gln Gln Ser Gly Thr Val Leu Ala Arg Pro Gly Ala
1 5 10 15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ala Ser Tyr
20 25 30
Trp Ile His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45
Gly Ser Ile Tyr Pro Gly Asn Ser Asp Thr Thr Tyr Asn Gln Lys Phe
50 55 60
Lys Gly Lys Ala Lys Leu Thr Val Val Thr Ser Ala Ser Ser Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Thr Asn Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95
Thr Glu Pro Thr Tyr Tyr Ser Tyr Asp Asp Tyr Tyr Ala Met Asp Tyr
100 105 110
Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 185
<211> 108
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的可变轻链序列
<400> 185

Glu Ile Val Leu Thr Gln Ser Pro Ala Leu Met Ala Ala Ser Pro Gly
1 5 10 15
Glu Lys Val Thr Ile Thr Cys Ser Val Ser Ser Ser Ile Ser Ser Ser
20 25 30
Asn Leu His Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Pro Trp
35 40 45
Ile Tyr Gly Thr Ser Asn Leu Ala Ser Gly Val Pro Val Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Thr Met Glu
65 70 75 80
Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Tyr Pro
85 90 95
Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 186
<211> 1707

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<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的抗β-Gal重链IgG2、RSPO2(F105R/F109A)
多核苷酸序列
<400> 186
gaggtgcagc tggtggagag cggcggcagc ctggtgaagc ccggcggcag cctgagactg 60
agctgcgccg ccagcggctt caccttcagc aactacagca tgaactgggt gagacaggcc 120
cccggcaagg gcctggagtg gatcagcagc atcagcggca gcagcagata catctactac 180
gccgacttcg tgaagggcag attcaccatc agcagagaca acgccaccaa cagcctgtac 240
ctgcagatga acagcctgag agccgaggac accgccgtgt actactgcgt gagaagcagc 300
atcaccatct tcggcggcgg catggacgtg tggggcagag gcaccctggt gaccgtgagc 360
agcgctagca ccaagggccc atcggtcttc cccctggcgc cctgctccag gagcacctcc 420
gagagcacag cggccctggg ctgcctggtc aaggactact tccccgaacc ggtgacggtg 480
tcgtggaact caggcgctct gaccagcggc gtgcacacct tcccagctgt cctacagtcc 540
tcaggactct actccctcag cagcgtggtg accgtgccct ccagcaactt cggcacccag 600
acctacacct gcaacgtaga tcacaagccc agcaacacca aggtggacaa gacagttgag 660
cgcaaatgtt gtgtcgagtg cccaccgtgc ccagcaccac ctgtggcagg accgtcagtc 720
ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcacg 780
tgcgtggtgg tggacgtgag ccacgaagac cccgaggtcc agttcaactg gtacgtggac 840
ggcgtggagg tgcataatgc caagacaaag ccacgggagg agcagttcaa cagcacgttc 900
cgtgtggtca gcgtcctcac cgttgtgcac caggactggc tgaacggcaa ggagtacaag 960
tgcaaggtct ccaacaaagg cctcccagcc cccatcgaga aaaccatctc caaaaccaaa 1020
gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag 1080
aaccaggtca gcctgacctg cctggtcaaa ggcttctacc ccagcgacat cgccgtggag 1140
tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccat gctggactcc 1200
gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1260
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1320
ctctccctgt ctccgggtaa aggtggtggt ggctcgggat ccggaggctc cggtggcggt 1380
ggcagcaacc caatttgcaa gggatgctta agctgtagca aggacaacgg atgttcacgg 1440
tgccagcaaa agctgttttt cttcctccgg cgggaaggaa tgcggcagta cggcgaatgt 1500
ctccactcct gcccctcggg gtattacgga caccgcgcgc ctgacatgaa ccgatgcgcc 1560
agatgccgga tcgagaactg cgatagctgc cgcagcaagg acgcctgcac taagtgcaaa 1620
gtcggcttct accttcaccg gggcagatgt tttgacgaat gcccggatgg cttcgccccg 1680
ctggaggaga ctatggaatg cgtggag 1707
<210> 187
<211> 569
<212> PRT
<213> 人工序列(Artificial Sequence)

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<220>

<223> 在实验室中制备的合成的抗β-Gal重链IgG2、RSPO2(F105R/F109A)多肽序列

<400> 187

Glu Val Gln Leu Val Glu Ser Gly Gly Ser Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30
Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Ser Ser Ile Ser Gly Ser Ser Arg Tyr Ile Tyr Tyr Ala Asp Phe Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Thr Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Val Arg Ser Ser Ile Thr Ile Phe Gly Gly Gly Met Asp Val Trp Gly
100 105 110
Arg Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125
Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
130 135 140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190
Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His
195 200 205
Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys
210 215 220
Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
225 230 235 240
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270
Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys

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275 280 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser

290 295 300

Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys

305 310 315 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile

325 330 335

Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro

340 345 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu

355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn

370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser

385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg

405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu

420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly

435 440 445

Gly Gly Gly Ser Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Asn Pro

450 455 460

Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys Ser Arg

465 470 475 480

Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met Arg Gln

485 490 495

Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly His Arg

500 505 510

Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp

515 520 525

Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly Phe Tyr

530 535 540

Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro

545 550 555 560

Leu Glu Glu Thr Met Glu Cys Val Glu

565

<210> 188

<211> 1707

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<212> DNA

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的合成的抗GFP重链IgG2、RSPO2(F105R/F109A)

多核苷酸序列

<400> 188

caggtccagt tggtggaatc cggaggggt ttggtccagc ctggtggaag cctgcgcctc 60
tcatgcgccg ctagcggatt caccttctcc cgatacggca tgcattgggt cagacaggca 120
cccggaaaag gactcgaatg ggtgtcgggc atttcctcga tcgggtcaaa cacctattac 180
gccgactccg tgaagggacg gttcaccatt agccgggata acagcaagaa cactctgtac 240
ttgcaaatga actccctgcg ggctgaggac accgccgtgt actactgtgc gcggtggtac 300
aagacctata ttgacgtctg gggacagggt accctcgtga ccgtgtctag cgctagcacc 360
aagggcccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg 420
gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca 480
ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac 540
tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc 600
aacgtgaatc acaagcccag caacaccaag gtggacaaga aagttgagcc caaatcttgt 660
gacaaaactc acacatgccc accgtgccca gcacctgaac tcctgggggg accgtcagtc 720
ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca 780
tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac 840
ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacgg cagcacgtac 900
cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag 960
tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa 1020
gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag 1080
aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag 1140
tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc 1200
gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1260
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1320
ctctccctgt ctccgggtaa aggtggtggt ggctcgggat ccggaggctc cggtggcggt 1380
ggcagcaacc caatttgcaa gggatgctta agctgtagca aggacaacgg atgttcacgg 1440
tgccagcaaa agctgttttt cttcctccgg cgggaaggaa tgcggcagta cggcgaatgt 1500
ctccactcct gcccctcggg gtattacgga caccgcgcgc ctgacatgaa ccgatgcgcc 1560
agatgccgga tcgagaactg cgatagctgc cgcagcaagg acgcctgcac taagtgcaaa 1620
gtcggcttct accttcaccg gggcagatgt tttgacgaat gcccggatgg cttcgccccg 1680
ctggaggaga ctatggaatg cgtggag 1707

<210> 189

<211> 569

<212> PRT

<213> 人工序列(Artificial Sequence)

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<220>

<223> 在实验室中制备的合成的抗GFP重链IgG2、RSPO2(F105R/F109A)多肽序列

<400> 189

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gly Ile Ser Ser Ile Gly Ser Asn Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Trp Tyr Lys Thr Tyr Ile Asp Val Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190
Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205
Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220
Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225 230 235 240
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270
Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys

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275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser

290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys

305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile

325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro

340 345 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu

355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn

370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser

385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg

405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu

420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly

435 440 445

Gly Gly Gly Ser Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Asn Pro

450 455 460

Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys Ser Arg

465 470 475 480

Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met Arg Gln

485 490 495

Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly His Arg

500 505 510

Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp

515 520 525

Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly Phe Tyr

530 535 540

Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro

545 550 555 560

Leu Glu Glu Thr Met Glu Cys Val Glu

565

<210> 190

<211> 657

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<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-1F8轻链多核苷酸序列
<400> 190
gacattgtga tgtcacagtc tccatcctcc ctggctgtgt cagcaggaga gaaggtcact 60
atgagctgca agtccagtca gagtctgttc aacagtagaa cccgaaagaa ctacttggct 120
tggtaccagc agaaaccagg gcagtctcct aaactgctga tctactgggc atccactagg 180
gaatctgggg tccctgatcg cttcacaggc agtggatctg ggacagattt cactctcacc 240
atcagcagtg tgcaggctga agacctggca gtttattact gcaagcaatc ttattatctg 300
ctcacgttcg gtgctgggac caagctggag ctgaaacgta cggtggctgc accatctgtc 360
ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 420
ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 480
tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 540
agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 600
gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgt 657
<210> 191
<211> 219
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-1F8轻链多肽序列
<400> 191
Asp Ile Val Met Ser Gln Ser Pro Ser Ser Leu Ala Val Ser Ala Gly
1 5 10 15
Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Phe Asn Ser
20 25 30
Arg Thr Arg Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45
Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60
Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80
Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Lys Gln
85 90 95
Ser Tyr Tyr Leu Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105 110
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

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Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140
Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160
Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175
Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190
Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205
Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 192
<211> 1707
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-1F8重链IgG2、RSPO2(F105R/F109A)多核苷酸序列
<400> 192

gaagtgaaac tggtggagtc tgggggaggc ttagtgaagc ctggagggtc cctgaaactc 60
tcctgtgcag cctctggatt cactttcagt acctatacca tgtcttgggt tcgccagact 120
ccggcgaaga ggctggagtg ggtcgcaacc attagtagta ttggtgttaa cacctactat 180
ccagacagtg tgaagggccg attcaccatc tccagagaca atgccaggaa caccctgtac 240
ctgcaagtga gcagtctgag gtctgaggac acggccatgt attactgtgc aagacatgtg 300
gattactacg atgggatttc ctttgactac tggggccaag gcaccactct cacagtctcc 360
agcgctagca ccaagggccc atcggtcttc cccctggcgc cctgctccag gagcacctcc 420
gagagcacag cggccctggg ctgcctggtc aaggactact tccccgaacc ggtgacggtg 480
tcgtggaact caggcgctct gaccagcggc gtgcacacct tcccagctgt cctacagtcc 540
tcaggactct actccctcag cagcgtggtg accgtgccct ccagcaactt cggcacccag 600
acctacacct gcaacgtaga tcacaagccc agcaacacca aggtggacaa gacagttgag 660
cgcaaatgtt gtgtcgagtg cccaccgtgc ccagcaccac ctgtggcagg accgtcagtc 720
ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcacg 780
tgcgtggtgg tggacgtgag ccacgaagac cccgaggtcc agttcaactg gtacgtggac 840
ggcgtggagg tgcataatgc caagacaaag ccacgggagg agcagttcaa cagcacgttc 900
cgtgtggtca gcgtcctcac cgttgtgcac caggactggc tgaacggcaa ggagtacaag 960
tgcaaggtct ccaacaaagg cctcccagcc cccatcgaga aaaccatctc caaaaccaaa 1020
gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag 1080
aaccaggtca gcctgacctg cctggtcaaa ggcttctacc ccagcgacat cgccgtggag 1140

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tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccat gctggactcc 1200
gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1260
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1320
ctctccctgt ctccgggtaa aggtggtggt ggctcgggat ccggaggctc cggtggcggt 1380
ggcagcaacc caatttgcaa gggatgctta agctgtagca aggacaacgg atgttcacgg 1440
tgccagcaaa agctgttttt cttcctccgg cgggaaggaa tgcggcagta cggcgaatgt 1500
ctccactcct gcccctcggg gtattacgga caccgcgcgc ctgacatgaa ccgatgcgcc 1560
agatgccgga tcgagaactg cgatagctgc cgcagcaagg acgcctgcac taagtgcaaa 1620
gtcggcttct accttcaccg gggcagatgt tttgacgaat gcccggatgg cttcgccccg 1680
ctggaggaga ctatggaatg cgtggag 1707

<210> 193
<211> 569
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-1F8重链IgG2、RSPO2(F105R/F109A)多肽序列
<400> 193

Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30
Thr Met Ser Trp Val Arg Gln Thr Pro Ala Lys Arg Leu Glu Trp Val
35 40 45
Ala Thr Ile Ser Ser Ile Gly Val Asn Thr Tyr Tyr Pro Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Leu Tyr
65 70 75 80
Leu Gln Val Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg His Val Asp Tyr Tyr Asp Gly Ile Ser Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125
Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
130 135 140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala

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165 170 175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190
Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His
195 200 205
Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys
210 215 220
Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
225 230 235 240
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270
Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285
Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser
290 295 300
Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320
Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335
Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350
Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser
385 390 395 400
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly
435 440 445
Gly Gly Gly Ser Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Asn Pro
450 455 460
Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys Ser Arg
465 470 475 480

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Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met Arg Gln
485 490 495
Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly His Arg
500 505 510
Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp
515 520 525
Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly Phe Tyr
530 535 540
Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro
545 550 555 560
Leu Glu Glu Thr Met Glu Cys Val Glu
565

<210> 194
<211> 642
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-1N15轻链多核苷酸序列
<400> 194
gacatcaaga tgacccagtc tccatcttcc atgtatgcat ctctaggaga gagagttact 60
atcacttgca aggcgagtca ggacattaat agccatttaa gctggttcca gcagaaacca 120
gggaaatctc ctaagaccct gatcattcgt gcaaacagat tggtagatgg ggtcccatca 180
aggttcagtg gcagtggatc tgggcaagat tattctctca ccatcagcag cccggagtat 240
gaagaaatgg gaatttatta ctgtctacag tatgatgagt ttccgttcac gttcggaggg 300
gggaccaagc tggaaataaa acgtacggtg gctgcaccat ctgtcttcat cttcccgcca 360
tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat 420
cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 480
gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 540
ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 600
ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt 642
<210> 195
<211> 214
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-1N15轻链多肽序列
<400> 195
Asp Ile Lys Met Thr Gln Ser Pro Ser Ser Met Tyr Ala Ser Leu Gly
1 5 10 15

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Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile Asn Ser His
20 25 30
Leu Ser Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
35 40 45
Ile Arg Ala Asn Arg Leu Val Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Pro Glu Tyr
65 70 75 80
Glu Glu Met Gly Ile Tyr Tyr Cys Leu Gln Tyr Asp Glu Phe Pro Phe
85 90 95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
100 105 110
Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125
Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140
Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205
Phe Asn Arg Gly Glu Cys
210

<210> 196
<211> 1683
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-1N15重链IgG2、RSPO2(F105R/F109A)多核苷酸序列
<400> 196
gaggtccagc tgcaacagtc tggacctgag ctggtgaagc ctggggcttc agtgaagatg 60
tcctgtaagg cttctggata cacattcact gactactaca tgaactgggt gaagcagagt 120
catggagaga gccttgagtg gattggacgt gttattccta gcaatggtgg tactaactac 180
aaccagaagt tcaagggcaa ggccacattg acagtagaca aatccctcac cacagcctac 240
atgcagctca acagcctgac atctgaagac tctgcggtct atttctgtgc aagagggatg 300

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gactactggg gtccaggaac ctcagtcacc gtctccagcg ctagcaccaa gggcccatcg 360
gtcttccccc tggcgccctg ctccaggagc acctccgaga gcacagcggc cctgggctgc 420
ctggtcaagg actacttccc cgaaccggtg acggtgtcgt ggaactcagg cgctctgacc 480
agcggcgtgc acaccttccc agctgtccta cagtcctcag gactctactc cctcagcagc 540
gtggtgaccg tgccctccag caacttcggc acccagacct acacctgcaa cgtagatcac 600
aagcccagca acaccaaggt ggacaagaca gttgagcgca aatgttgtgt cgagtgccca 660
ccgtgcccag caccacctgt ggcaggaccg tcagtcttcc tcttcccccc aaaacccaag 720
gacaccctca tgatctcccg gacccctgag gtcacgtgcg tggtggtgga cgtgagccac 780
gaagaccccg aggtccagtt caactggtac gtggacggcg tggaggtgca taatgccaag 840
acaaagccac gggaggagca gttcaacagc acgttccgtg tggtcagcgt cctcaccgtt 900
gtgcaccagg actggctgaa cggcaaggag tacaagtgca aggtctccaa caaaggcctc 960
ccagccccca tcgagaaaac catctccaaa accaaagggc agccccgaga accacaggtg 1020
tacaccctgc ccccatcccg ggaggagatg accaagaacc aggtcagcct gacctgcctg 1080
gtcaaaggct tctaccccag cgacatcgcc gtggagtggg agagcaatgg gcagccggag 1140
aacaactaca agaccacgcc tcccatgctg gactccgacg gctccttctt cctctacagc 1200
aagctcaccg tggacaagag caggtggcag caggggaacg tcttctcatg ctccgtgatg 1260
catgaggctc tgcacaacca ctacacgcag aagagcctct ccctgtctcc gggtaaaggt 1320
ggtggtggct cgggatccgg aggctccggt ggcggtggca gcaacccaat ttgcaaggga 1380
tgcttaagct gtagcaagga caacggatgt tcacggtgcc agcaaaagct gtttttcttc 1440
ctccggcggg aaggaatgcg gcagtacggc gaatgtctcc actcctgccc ctcggggtat 1500
tacggacacc gcgcgcctga catgaaccga tgcgccagat gccggatcga gaactgcgat 1560
agctgccgca gcaaggacgc ctgcactaag tgcaaagtcg gcttctacct tcaccggggc 1620
agatgttttg acgaatgccc ggatggcttc gccccgctgg aggagactat ggaatgcgtg 1680
gag 1683

<210> 197
<211> 561
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-1N15重链IgG2、RSPO2(F105R/F109A)多肽序列
<400> 197

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30
Tyr Met Asn Trp Val Lys Gln Ser His Gly Glu Ser Leu Glu Trp Ile
35 40 45
Gly Arg Val Ile Pro Ser Asn Gly Gly Thr Asn Tyr Asn Gln Lys Phe

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50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Leu Thr Thr Ala Tyr
65 70 75 80

Met Gln Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
85 90 95

Ala Arg Gly Met Asp Tyr Trp Gly Pro Gly Thr Ser Val Thr Val Ser
100 105 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
115 120 125

Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130 135 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145 150 155 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165 170 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln
180 185 190

Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205

Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala
210 215 220

Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
225 230 235 240

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
245 250 255

Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
260 265 270

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
275 280 285

Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp
290 295 300

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
305 310 315 320

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg
325 330 335

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
340 345 350

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
355 360 365

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Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
370 375 380
Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
385 390 395 400
Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
405 410 415
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
420 425 430
Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Ser Gly Gly
435 440 445
Ser Gly Gly Gly Gly Ser Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys
450 455 460
Ser Lys Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe
465 470 475 480
Leu Arg Arg Glu Gly Met Arg Gln Tyr Gly Glu Cys Leu His Ser Cys
485 490 495
Pro Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met Asn Arg Cys Ala
500 505 510
Arg Cys Arg Ile Glu Asn Cys Asp Ser Cys Arg Ser Lys Asp Ala Cys
515 520 525
Thr Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly Arg Cys Phe Asp
530 535 540
Glu Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr Met Glu Cys Val
545 550 555 560
Glu

<210> 198
<211> 642
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-1P13轻链多核苷酸序列
<400> 198
gacatccaga tgactcagtc tccagcctcc ctatctgcat ctgtgggaca aactgttatc 60
atcacatgtc gaacaagtga gaatatttac agtaatttag catggtatca gcagaaacag 120
ggaaaatctc ctcagctcct ggtctatgct gcaacaaact tagcagatgg tgtgccatca 180
aggttcagtg gcagtggttc aggcacacag tattacctca agatcaacag cctgcagtct 240
gaagattttg ggagttatta ctgtcaacat ttttggggta gtacgtggac gttcggtgga 300
ggcaccaagc tggacatcaa acgtacggtg gctgcaccat ctgtcttcat cttcccgcca 360
tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat 420

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cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 480
gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 540
ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 600
ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt 642

<210> 199
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-1P13轻链多肽序列
<400> 199

Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Gln Thr Val Ile Ile Thr Cys Arg Thr Ser Glu Asn Ile Tyr Ser Asn
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro Gln Leu Leu Val
35 40 45
Tyr Ala Ala Thr Asn Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Gln Tyr Tyr Leu Lys Ile Asn Ser Leu Gln Ser
65 70 75 80
Glu Asp Phe Gly Ser Tyr Tyr Cys Gln His Phe Trp Gly Ser Thr Trp
85 90 95
Thr Phe Gly Gly Gly Thr Lys Leu Asp Ile Lys
100 105

<210> 200
<211> 1707
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-1P13重链IgG2、RSPO2多核苷酸序列
<400> 200

gaggttcaac tgcagcagtc tggacctgaa ctggtgaagc ctggggcttc agtgaagata 60
tcctgcaagg cttctggtta ctcatttact gactacttta tgaactgggt gaagcagagc 120
catggaaaga gccttgagtg gattggacgt tttaatcctt tcaatggtca aactttctac 180
aatcaggagt tcaagggcaa ggccacatta actgtagaca aatcctctag caccgcccac 240
atggagctcc ggagcctgac atctgaggac tctgcagtct attattgtgc aagaagagga 300
aggtacgacg tttactatgt tctggactac tggggtcaag gaacctcagt caccgtctcc 360
agcgctagca ccaagggccc atcggtcttc cccctggcgc cctgctccag gagcacctcc 420

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gagagcacag cggccctggg ctgcctggtc aaggactact tccccgaacc ggtgacggtg 480
tcgtggaact caggcgctct gaccagcggc gtgcacacct tcccagctgt cctacagtcc 540
tcaggactct actccctcag cagcgtggtg accgtgccct ccagcaactt cggcacccag 600
acctacacct gcaacgtaga tcacaagccc agcaacacca aggtggacaa gacagttgag 660
cgcaaatgtt gtgtcgagtg cccaccgtgc ccagcaccac ctgtggcagg accgtcagtc 720
ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcacg 780
tgcgtggtgg tggacgtgag ccacgaagac cccgaggtcc agttcaactg gtacgtggac 840
ggcgtggagg tgcataatgc caagacaaag ccacgggagg agcagttcaa cagcacgttc 900
cgtgtggtca gcgtcctcac cgttgtgcac caggactggc tgaacggcaa ggagtacaag 960
tgcaaggtct ccaacaaagg cctcccagcc cccatcgaga aaaccatctc caaaaccaaa 1020
gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag 1080
aaccaggtca gcctgacctg cctggtcaaa ggcttctacc ccagcgacat cgccgtggag 1140
tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccat gctggactcc 1200
gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1260
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1320
ctctccctgt ctccgggtaa aggtggtggt ggctcgggat ccggaggctc cggtggcggt 1380
ggcagcaacc caatttgcaa gggatgctta agctgtagca aggacaacgg atgttcacgg 1440
tgccagcaaa agctgttttt cttcctccgg cgggaaggaa tgcggcagta cggcgaatgt 1500
ctccactcct gcccctcggg gtattacgga caccgcgcgc ctgacatgaa ccgatgcgcc 1560
agatgccgga tcgagaactg cgatagctgc cgcagcaagg acgcctgcac taagtgcaaa 1620
gtcggcttct accttcaccg gggcagatgt tttgacgaat gcccggatgg cttcgccccg 1680
ctggaggaga ctatggaatg cgtggag 1707

<210> 201
<211> 569
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-1P13重链IgG2、RSPO2多肽序列
<400> 201

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Asp Tyr
20 25 30
Phe Met Asn Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45
Gly Arg Phe Asn Pro Phe Asn Gly Gln Thr Phe Tyr Asn Gln Glu Phe
50 55 60
Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala His
65 70 75 80

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Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Arg Gly Arg Tyr Asp Val Tyr Tyr Val Leu Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125
Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
130 135 140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190
Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His
195 200 205
Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys
210 215 220
Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
225 230 235 240
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270
Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285
Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser
290 295 300
Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320
Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335
Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350
Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser

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385 390 395 400
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly
435 440 445
Gly Gly Gly Ser Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Asn Pro
450 455 460
Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys Ser Arg
465 470 475 480
Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met Arg Gln
485 490 495
Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly His Arg
500 505 510
Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp
515 520 525
Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly Phe Tyr
530 535 540
Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro
545 550 555 560
Leu Glu Glu Thr Met Glu Cys Val Glu
565

<210> 202
<211> 642
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-1P5轻链多核苷酸序列
<400> 202
gacattgtga tgacccagtc tcaaaaattc atgtccacat cagtaggaga cagggtcagc 60
gtcacctgca aggccagtca gaatgtgggt actaatgtag cctggtatca acagaaacca 120
ggacaatctc ctaaagcact gatttactcg gcatcttatc ggtacagtgg agtccctgat 180
cgcttcacag gcagtggatc tgggacagat ttcactctca ccatcagcaa tgtgcagtct 240
gaagacttgg cagagtattt ctgtcaacaa tataacagct atccgctcac gttcggtgct 300
gggaccaagc tggagctgaa acgtacggtg gctgcaccat ctgtcttcat cttcccgcca 360
tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat 420
cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 480
gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 540

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ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 600
ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt 642
<210> 203
<211> 214
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-1P5轻链多肽序列
<400> 203

Asp	Ile	Val	Met	Thr	Gln	Ser	Gln	Lys	Phe	Met	Ser	Thr	Ser	Val	Gly
1				5				10					15		
Asp	Arg	Val	Ser	Val	Thr	Cys	Lys	Ala	Ser	Gln	Asn	Val	Gly	Thr	Asn
			20					25				30			
Val	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ser	Pro	Lys	Ala	Leu	Ile
		35					40					45			
Tyr	Ser	Ala	Ser	Tyr	Arg	Tyr	Ser	Gly	Val	Pro	Asp	Arg	Phe	Thr	Gly
	50					55					60				
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Asn	Val	Gln	Ser
65					70					75					80
Glu	Asp	Leu	Ala	Glu	Tyr	Phe	Cys	Gln	Gln	Tyr	Asn	Ser	Tyr	Pro	Leu
				85					90					95	
Thr	Phe	Gly	Ala	Gly	Thr	Lys	Leu	Glu	Leu	Lys	Arg	Thr	Val	Ala	Ala
			100					105					110		
Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly
		115					120					125			
Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala
	130					135					140				
Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln
145					150					155					160
Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser
				165					170					175	
Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr
			180					185					190		
Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys	Ser
		195					200					205			
Phe	Asn	Arg	Gly	Glu	Cys										
	210														

<210> 204
<211> 1704

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<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-1P5重链IgG2、RSPO2(F105R/F109A)
多核苷酸序列
<400> 204
caggtccagc tgcagcaatc tggacctgag ctggtgaggc ctgggacttc agtgaagata 60
tcctgcaagg cttctggcta taccttcctc acctactgga tgaactgggt gaagcagagg 120
cctggacagg gccttgagtg gattggacag attttccctg caactggtat tacttactac 180
agtgagatgt tcaaggacaa ggccacattg actgaagaca catcctccac cacagcctac 240
atgcaactca gcagcctgac atctgaggcc actgctgtct atttctgtgc aagaagaagg 300
gcctaccata gtaacttttt tgactactgg ggccaaggca ccactctcac agtctccagc 360
gctagcacca agggcccatc ggtcttcccc ctggcgccct gctccaggag cacctccgag 420
agcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg 480
tggaactcag gcgctctgac cagcggcgtg cacaccttcc cagctgtcct acagtcctca 540
ggactctact ccctcagcag cgtggtgacc gtgccctcca gcaacttcgg cacccagacc 600
tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagac agttgagcgc 660
aaatgttgtg tcgagtgccc accgtgccca gcaccacctg tggcaggacc gtcagtcttc 720
ctcttccccc caaaacccaa ggacaccctc atgatctccc ggacccctga ggtcacgtgc 780
gtggtggtgg acgtgagcca cgaagacccc gaggtccagt tcaactggta cgtggacggc 840
gtggaggtgc ataatgccaa gacaaagcca cgggaggagc agttcaacag cacgttccgt 900
gtggtcagcg tcctcaccgt tgtgcaccag gactggctga acggcaagga gtacaagtgc 960
aaggtctcca acaaaggcct cccagccccc atcgagaaaa ccatctccaa aaccaaaggg 1020
cagccccgag aaccacaggt gtacaccctg cccccatccc gggaggagat gaccaagaac 1080
caggtcagcc tgacctgcct ggtcaaaggc ttctacccca gcgacatcgc cgtggagtgg 1140
gagagcaatg ggcagccgga gaacaactac aagaccacgc ctcccatgct ggactccgac 1200
ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac 1260
gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 1320
tccctgtctc cgggtaaagg tggtggtggc tcgggatccg gaggctccgg tggcggtggc 1380
agcaacccaa tttgcaaggg atgcttaagc tgtagcaagg acaacggatg ttcacggtgc 1440
cagcaaaagc tgtttttctt cctccggcgg gaaggaatgc ggcagtacgg cgaatgtctc 1500
cactcctgcc cctcggggta ttacggacac cgcgcgcctg acatgaaccg atgcgccaga 1560
tgccggatcg agaactgcga tagctgccgc agcaaggacg cctgcactaa gtgcaaagtc 1620
ggcttctacc ttcaccgggg cagatgtttt gacgaatgcc cggatggctt cgccccgctg 1680
gaggagacta tggaatgcgt ggag 1704
<210> 205
<211> 568
<212> PRT
<213> 人工序列(Artificial Sequence)

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<220>

<223> 在实验室中制备的合成的LP1-1P5重链IgG2、RSPO2(F105R/F109A)多肽序列

<400> 205

Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Arg Pro Gly Thr
1 5 10 15
Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Leu Thr Tyr
20 25 30
Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45
Gly Gln Ile Phe Pro Ala Thr Gly Ile Thr Tyr Tyr Ser Glu Met Phe
50 55 60
Lys Asp Lys Ala Thr Leu Thr Glu Asp Thr Ser Ser Thr Thr Ala Tyr
65 70 75 80
Met Gln Leu Ser Ser Leu Thr Ser Glu Ala Thr Ala Val Tyr Phe Cys
85 90 95
Ala Arg Arg Arg Ala Tyr His Ser Asn Phe Phe Asp Tyr Trp Gly Gln
100 105 110
Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125
Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
130 135 140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190
Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys
195 200 205
Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val
210 215 220
Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe
225 230 235 240
Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255
Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270
Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr

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275 280 285

Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val

290 295 300

Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys

305 310 315 320

Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser

325 330 335

Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro

340 345 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val

355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly

370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp

385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp

405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His

420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly

435 440 445

Gly Gly Ser Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Asn Pro Ile

450 455 460

Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys Ser Arg Cys

465 470 475 480

Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met Arg Gln Tyr

485 490 495

Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly His Arg Ala

500 505 510

Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp Ser

515 520 525

Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly Phe Tyr Leu

530 535 540

His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro Leu

545 550 555 560

Glu Glu Thr Met Glu Cys Val Glu

565

<210> 206

<211> 657

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<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-2E12轻链多核苷酸序列
<400> 206
gatgttgtgg tgactcaaac tccactctcc ctgcctgtca gctttggaga tcgagtttct 60
atctcttgca ggtctagtca gagtcttgca aacagttatg ggaacaccta tttgtcttgg 120
tacctgcaca agcctggcca gtctccacag ctcctcatct atgggatttc caacagattt 180
tctggggtgc cagacaggtt cagtggcagt ggttcaggga cagatttcac actcaagatc 240
agcacaataa agcctgagga cttgggaatg tattactgct tacaaggtac acatcagcct 300
ctcacgttcg gtgctgggac caagctggag ctgaaacgta cggtggctgc accatctgtc 360
ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 420
ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 480
tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 540
agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 600
gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgt 657
<210> 207
<211> 219
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-2E12轻链多肽序列
<400> 207
Asp Val Val Val Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Phe Gly
1 5 10 15
Asp Arg Val Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Ala Asn Ser
20 25 30
Tyr Gly Asn Thr Tyr Leu Ser Trp Tyr Leu His Lys Pro Gly Gln Ser
35 40 45
Pro Gln Leu Leu Ile Tyr Gly Ile Ser Asn Arg Phe Ser Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80
Ser Thr Ile Lys Pro Glu Asp Leu Gly Met Tyr Tyr Cys Leu Gln Gly
85 90 95
Thr His Gln Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105 110
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

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Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140
Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160
Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175
Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190
Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205
Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 208
<211> 1689
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-2E12重链IgG2、RSPO2(F105R/F109A)多核苷酸序列
<400> 208

gatgtacaac ttcaggagtc aggacctggc ctcgtgaaac cttctcagtc tctgtctctc 60
acctgctctg tcactggcta ctccatcacc agtggttatt actggaactg gatccggcag 120
tttccaggaa acaaactgga atggatgggc tccataggct acgatgatac caatcactac 180
aacccatctc tcaaaaatcg aatctccatc actcgtgaca catctaagaa ccagtttttc 240
ctgaagttga attctgtgac aactgaggac acagccacat attactgtgc aggtgactac 300
ccctttgctt tctggggcca agggactctg gtcactgtct ctgcagctag caccaagggc 360
ccatcggtct tccccctggc gccctgctcc aggagcacct ccgagagcac agcggccctg 420
ggctgcctgg tcaaggacta cttccccgaa ccggtgacgg tgtcgtggaa ctcaggcgct 480
ctgaccagcg gcgtgcacac cttcccagct gtcctacagt cctcaggact ctactccctc 540
agcagcgtgg tgaccgtgcc ctccagcaac ttcggcaccc agacctacac ctgcaacgta 600
gatcacaagc ccagcaacac caaggtggac aagacagttg agcgcaaatg ttgtgtcgag 660
tgcccaccgt gcccagcacc acctgtggca ggaccgtcag tcttcctctt ccccccaaaa 720
cccaaggaca ccctcatgat ctcccggacc cctgaggtca cgtgcgtggt ggtggacgtg 780
agccacgaag accccgaggt ccagttcaac tggtacgtgg acggcgtgga ggtgcataat 840
gccaagacaa agccacggga ggagcagttc aacagcacgt tccgtgtggt cagcgtcctc 900
accgttgtgc accaggactg gctgaacggc aaggagtaca agtgcaaggt ctccaacaaa 960
ggcctcccag cccccatcga gaaaaccatc tccaaaacca aagggcagcc ccgagaacca 1020
caggtgtaca ccctgccccc atcccgggag gagatgacca agaaccaggt cagcctgacc 1080
tgcctggtca aaggcttcta ccccagcgac atcgccgtgg agtgggagag caatgggcag 1140

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ccggagaaca actacaagac cacgcctccc atgctggact ccgacggctc cttcttcctc 1200
tacagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc 1260
gtgatgcatg aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt 1320
aaaggtggtg gtggctcggg atccggaggc tccggtggcg gtggcagcaa cccaatttgc 1380
aagggatgct taagctgtag caaggacaac ggatgttcac ggtgccagca aaagctgttt 1440
ttcttcctcc ggcgggaagg aatgcggcag tacggcgaat gtctccactc ctgcccctcg 1500
gggtattacg gacaccgcgc gcctgacatg aaccgatgcg ccagatgccg gatcgagaac 1560
tgcgatagct gccgcagcaa ggacgcctgc actaagtgca aagtcggctt ctaccttcac 1620
cggggcagat gttttgacga atgcccggat ggcttcgccc cgctggagga gactatggaa 1680
tgcgtggag 1689

<210> 209
<211> 563
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-2E12重链IgG2、RSPO2(F105R/F109A)多肽序列
<400> 209

Asp Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15
Ser Leu Ser Leu Thr Cys Ser Val Thr Gly Tyr Ser Ile Thr Ser Gly
20 25 30
Tyr Tyr Trp Asn Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu Trp
35 40 45
Met Gly Ser Ile Gly Tyr Asp Asp Thr Asn His Tyr Asn Pro Ser Leu
50 55 60
Lys Asn Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe Phe
65 70 75 80
Leu Lys Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys
85 90 95
Ala Gly Asp Tyr Pro Phe Ala Phe Trp Gly Gln Gly Thr Leu Val Thr
100 105 110
Val Ser Ala Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
115 120 125
Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val
130 135 140
Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
145 150 155 160
Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly

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165 170 175
Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly
180 185 190
Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys
195 200 205
Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
210 215 220
Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
225 230 235 240
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
245 250 255
Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
260 265 270
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
275 280 285
Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His
290 295 300
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
305 310 315 320
Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln
325 330 335
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
340 345 350
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
355 360 365
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
370 375 380
Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
385 390 395 400
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
405 410 415
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
420 425 430
Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Ser
435 440 445
Gly Gly Ser Gly Gly Gly Gly Ser Asn Pro Ile Cys Lys Gly Cys Leu
450 455 460
Ser Cys Ser Lys Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys Leu Phe
465 470 475 480

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Phe Phe Leu Arg Arg Glu Gly Met Arg Gln Tyr Gly Glu Cys Leu His
485 490 495
Ser Cys Pro Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met Asn Arg
500 505 510
Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp Ser Cys Arg Ser Lys Asp
515 520 525
Ala Cys Thr Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly Arg Cys
530 535 540
Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr Met Glu
545 550 555 560
Cys Val Glu

<210> 210
<211> 639
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-2I13轻链多核苷酸序列
<400> 210
gacatccaga tgactcagtc tccagcctcc ctatctgcat ctgtgggaga aactgtcacc 60
atcacatgtc gagcaagtga gaatatttac agttatttag tatggtatca gcagaaacag 120
ggaaaatctc ctcagctcct ggtctataat gcaaaaacct tagcagaagg tgtgccatca 180
aggttcagtg gcagtggatc aggcacacag ttttctctga agatcaacag cctgcagcct 240
gaagattttg ggagttatta ctgtcaacat cattatggta cttggacgtt cggtggaggc 300
ataaagctgg aaatcaaacg tacggtggct gcaccatctg tcttcatctt cccgccatct 360
gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc tgctgaataa cttctatccc 420
agagaggcca aagtacagtg gaaggtggat aacgccctcc aatcgggtaa ctcccaggag 480
agtgtcacag agcaggacag caaggacagc acctacagcc tcagcagcac cctgacgctg 540
agcaaagcag actacgagaa acacaaagtc tacgcctgcg aagtcaccca tcagggcctg 600
agctcgcccg tcacaaagag cttcaacagg ggagagtgt 639

<210> 211
<211> 213
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-2I13轻链多肽序列
<400> 211
Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Glu Thr Val Thr Ile Thr Cys Arg Ala Ser Glu Asn Ile Tyr Ser Tyr

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20 25 30

Leu Val Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro Gln Leu Leu Val
35 40 45

Tyr Asn Ala Lys Thr Leu Ala Glu Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Gln Phe Ser Leu Lys Ile Asn Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Gly Ser Tyr Tyr Cys Gln His His Tyr Gly Thr Trp Thr
85 90 95

Phe Gly Gly Gly Ile Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro
100 105 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
115 120 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
130 135 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145 150 155 160

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
165 170 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
180 185 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
195 200 205

Asn Arg Gly Glu Cys
210

<210> 212

<211> 1716

<212> DNA

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的合成的LP1-2I13重链IgG2、RSPO2(F105R/F109A)多核苷酸序列

<400> 212

gaggtgcagc tggtggagtc tgggggaggc ttagtgaagc ctggagggtc ccggaaactc 60
tcctgtgcag cctctggatt cactttcagt gactatggaa tgcactgggt ccgtcaggct 120
ccagagaagg ggctggagtg ggttgcctac attagtagtg gcagtagtac catctactat 180
gcagacacag tgaagggccg attcaccatc tccagagaca atgccaagaa caccctgttc 240
ctacaaatga ccagtctaag gtctgaggac acagccatgt attactgttc aaggaaggga 300
gggtttggtg actacgagaa aagctatgct atggactact ggggtcaagg aacctcagtc 360

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accgtctcca gcgctagcac caagggccca tcggtcttcc ccctggcgcc ctgctccagg 420
agcacctccg agagcacagc ggccctgggc tgcctggtca aggactactt ccccgaaccg 480
gtgacggtgt cgtggaactc aggcgctctg accagcggcg tgcacacctt cccagctgtc 540
ctacagtcct caggactcta ctccctcagc agcgtggtga ccgtgccctc cagcaacttc 600
ggcacccaga cctacacctg caacgtagat cacaagccca gcaacaccaa ggtggacaag 660
acagttgagc gcaaatgttg tgtcgagtgc ccaccgtgcc cagcaccacc tgtggcagga 720
ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct 780
gaggtcacgt gcgtggtggt ggacgtgagc cacgaagacc ccgaggtcca gttcaactgg 840
tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cacgggagga gcagttcaac 900
agcacgttcc gtgtggtcag cgtcctcacc gttgtgcacc aggactggct gaacggcaag 960
gagtacaagt gcaaggtctc caacaaaggc ctcccagccc ccatcgagaa aaccatctcc 1020
aaaaccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggaggag 1080
atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctaccc cagcgacatc 1140
gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctcccatg 1200
ctggactccg acggctcctt cttcctctac agcaagctca ccgtggacaa gagcaggtgg 1260
cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg 1320
cagaagagcc tctccctgtc tccgggtaaa ggtggtggtg gctcgggatc cggaggctcc 1380
ggtggcggtg gcagcaaccc aatttgcaag ggatgcttaa gctgtagcaa ggacaacgga 1440
tgttcacggt gccagcaaaa gctgtttttc ttcctccggc gggaaggaat gcggcagtac 1500
ggcgaatgtc tccactcctg cccctcgggg tattacggac accgcgcgcc tgacatgaac 1560
cgatgcgcca gatgccggat cgagaactgc gatagctgcc gcagcaagga cgcctgcact 1620
aagtgcaaag tcggcttcta ccttcaccgg ggcagatgtt ttgacgaatg cccggatggc 1680
ttcgccccgc tggaggagac tatggaatgc gtggag 1716

<210> 213
<211> 572
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-2I13重链IgG2、RSP02(F105R/F109A)多肽序列
<400> 213

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Arg Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
35 40 45
Ala Tyr Ile Ser Ser Gly Ser Ser Thr Ile Tyr Tyr Ala Asp Thr Val
50 55 60

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Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Phe
65 70 75 80
Leu Gln Met Thr Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ser Arg Lys Gly Gly Phe Gly Asp Tyr Glu Lys Ser Tyr Ala Met Asp
100 105 110
Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Ser Thr Lys
115 120 125
Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu
130 135 140
Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
145 150 155 160
Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
165 170 175
Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
180 185 190
Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn
195 200 205
Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg
210 215 220
Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly
225 230 235 240
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270
Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
290 295 300
Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320
Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu
325 330 335
Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp

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370 375 380
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met
385 390 395 400
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445
Gly Lys Gly Gly Gly Gly Ser Gly Ser Gly Gly Ser Gly Gly Gly Gly
450 455 460
Ser Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly
465 470 475 480
Cys Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly
485 490 495
Met Arg Gln Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr
500 505 510
Gly His Arg Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu
515 520 525
Asn Cys Asp Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val
530 535 540
Gly Phe Tyr Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly
545 550 555 560
Phe Ala Pro Leu Glu Glu Thr Met Glu Cys Val Glu
565 570

<210> 214
<211> 642
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-2I22轻链多核苷酸序列
<400> 214
gacatccaga tgactcagtc tccagcctcc ctatctgcat ctgtgggaga aactgttatc 60
atcacatgtc gagcaagtga gaatatttac agtaatttag catggtatca gcagaaacag 120
ggaaaatctc ctcagctcct ggtctatggt gcaacaaact tagcagatgg tgtgacatca 180
aggttcagtg gcagtggttc aggcacacag ttttccctca agatcgacag cctgcagtct 240
gaagattttg ggagttatta ctgtcaacat ttttggggta ctacgtggac gttcggtgga 300
ggcaccaagc tggaaatcaa acgtacggtg gctgcaccat ctgtcttcat cttcccgcca 360
tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat 420

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cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 480
gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 540
ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 600
ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt 642

<210> 215
<211> 214
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-2I22轻链多肽序列
<400> 215

Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Glu Thr Val Ile Ile Thr Cys Arg Ala Ser Glu Asn Ile Tyr Ser Asn
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro Gln Leu Leu Val
35 40 45
Tyr Gly Ala Thr Asn Leu Ala Asp Gly Val Thr Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Gln Phe Ser Leu Lys Ile Asp Ser Leu Gln Ser
65 70 75 80
Glu Asp Phe Gly Ser Tyr Tyr Cys Gln His Phe Trp Gly Thr Thr Trp
85 90 95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
100 105 110
Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125
Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140
Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205
Phe Asn Arg Gly Glu Cys
210

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<210> 216
<211> 1707
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-2I22重链IgG2、RSP02(F105R/F109A)
多核苷酸序列
<400> 216
gaggttcaac tgcagcagtc tggacctgaa ctggtgaagc ctggggcttc agtgaagata 60
tcctgcaagg cttctggtta ctcatttact ggctacttta tgaactgggt gaagcagagc 120
catggaaaga gccttgagtg gattggacgt tttaatcctt tcaatggtca aactttctac 180
aatcaggagt tcaagggcaa ggccacatta actgttgaca aatcctctga caccgcccac 240
atggaactcc ggagcctgac atctgaggac tctgcagtct attattgtgc aagaagagga 300
aggtacgacg tttactatgc tctggactac tggggtcaag gaacctcagt caccgtctcc 360
agcgctagca ccaagggccc atcggtcttc cccctggcgc cctgctccag gagcacctcc 420
gagagcacag cggccctggg ctgcctggtc aaggactact tccccgaacc ggtgacggtg 480
tcgtggaact caggcgctct gaccagcggc gtgcacacct tcccagctgt cctacagtcc 540
tcaggactct actccctcag cagcgtggtg accgtgccct ccagcaactt cggcacccag 600
acctacacct gcaacgtaga tcacaagccc agcaacacca aggtggacaa gacagttgag 660
cgcaaatgtt gtgtcgagtg cccaccgtgc ccagcaccac ctgtggcagg accgtcagtc 720
ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcacg 780
tgcgtggtgg tggacgtgag ccacgaagac cccgaggtcc agttcaactg gtacgtggac 840
ggcgtggagg tgcataatgc caagacaaag ccacgggagg agcagttcaa cagcacgttc 900
cgtgtggtca gcgtcctcac cgttgtgcac caggactggc tgaacggcaa ggagtacaag 960
tgcaaggtct ccaacaaagg cctcccagcc cccatcgaga aaaccatctc caaaaccaaa 1020
gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag 1080
aaccaggtca gcctgacctg cctggtcaaa ggcttctacc ccagcgacat cgccgtggag 1140
tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccat gctggactcc 1200
gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1260
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1320
ctctccctgt ctccgggtaa aggtggtggt ggctcgggat ccggaggctc cggtggcggt 1380
ggcagcaacc caatttgcaa gggatgctta agctgtagca aggacaacgg atgttcacgg 1440
tgccagcaaa agctgttttt cttcctccgg cgggaaggaa tgcggcagta cggcgaatgt 1500
ctccactcct gcccctcggg gtattacgga caccgcgcgc ctgacatgaa ccgatgcgcc 1560
agatgccgga tcgagaactg cgatagctgc cgcagcaagg acgcctgcac taagtgcaaa 1620
gtcggcttct accttcaccg gggcagatgt tttgacgaat gcccggatgg cttcgccccg 1680
ctggaggaga ctatggaatg cgtggag 1707
<210> 217
<211> 569

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<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-2I22重链IgG2、RSPO2(F105R/F109A)多肽序列
<400> 217

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
20 25 30
Phe Met Asn Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45
Gly Arg Phe Asn Pro Phe Asn Gly Gln Thr Phe Tyr Asn Gln Glu Phe
50 55 60
Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Asp Thr Ala His
65 70 75 80
Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Arg Gly Arg Tyr Asp Val Tyr Tyr Ala Leu Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125
Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
130 135 140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190
Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His
195 200 205
Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys
210 215 220
Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
225 230 235 240
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu

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260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser
290 295 300

Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly
435 440 445

Gly Gly Gly Ser Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Asn Pro
450 455 460

Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys Ser Arg
465 470 475 480

Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met Arg Gln
485 490 495

Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly His Arg
500 505 510

Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp
515 520 525

Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly Phe Tyr
530 535 540

Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro
545 550 555 560

Leu Glu Glu Thr Met Glu Cys Val Glu
565

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<210> 218
<211> 642
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-3A24轻链多核苷酸序列
<400> 218
gacattgtga tgacccagtc tcaaaaattc atgtccacat cagtaggaga cagggtcagc 60
gtcacctgca aggccagtca gaatgtgggt agtaatgtag cctggtttca acagaaacca 120
gggcaatctc ctaaagcact gatttactcg tcatcctacc ggtacagtgg agtccctgat 180
cgcttcacgg gcagtggatc tgggacagat ttcactctca ccatcaccaa tgtgcagtct 240
gaagacttgg cagagtattt ctgtcagcaa tataacagct ttcctctcac gttcggtgct 300
gggaccaagc tggaactgaa acgtacggtg gctgcaccat ctgtcttcat cttcccgcca 360
tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat 420
cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 480
gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 540
ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 600
ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt 642
<210> 219
<211> 214
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-3A24轻链多肽序列
<400> 219
Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15
Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn Val Gly Ser Asn
20 25 30
Val Ala Trp Phe Gln Gln Lys Pro Gly Gln Ser Pro Lys Ala Leu Ile
35 40 45
Tyr Ser Ser Ser Tyr Arg Tyr Ser Gly Val Pro Asp Arg Phe Thr Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr Asn Val Gln Ser
65 70 75 80
Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln Tyr Asn Ser Phe Pro Leu
85 90 95
Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr Val Ala Ala
100 105 110

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Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125
Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140
Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205
Phe Asn Arg Gly Glu Cys
210

<210> 220
<211> 1683
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-3A24重链IgG2、RSP02(F105R/F109A)多核苷酸序列
<400> 220

gaggtccagc tgcaacagtc tggacctgag ctggtgaagc ctggggcttc agtgaagatg 60
tcctgtaagg cttctggata cacattcact gactactaca taaactgggt gaggcagagt 120
catggaaaga gccttgagtg gattggacgt gttattccta gcaatggtgg tagtaactac 180
aaccagaagt tcaagggcaa ggccacattg acagtagaca aatccctcag tacagcctac 240
atgcacctca acagcctgac atctgaggac tctgcggtct attactgtgc aacccagctg 300
ggacggtggg gccaagggac tctggtcact gtctctgcag ctagcaccaa gggcccatcg 360
gtcttccccc tggcgccctg ctccaggagc acctccgaga gcacagcggc cctgggctgc 420
ctggtcaagg actacttccc cgaaccggtg acggtgtcgt ggaactcagg cgctctgacc 480
agcggcgtgc acaccttccc agctgtccta cagtcctcag gactctactc cctcagcagc 540
gtggtgaccg tgccctccag caacttcggc acccagacct acacctgcaa cgtagatcac 600
aagcccagca acaccaaggt ggacaagaca gttgagcgca aatgttgtgt cgagtgccca 660
ccgtgcccag caccacctgt ggcaggaccg tcagtcttcc tcttcccccc aaaacccaag 720
gacaccctca tgatctcccg gacccctgag gtcacgtgcg tggtggtgga cgtgagccac 780
gaagaccccg aggtccagtt caactggtac gtggacggcg tggaggtgca taatgccaag 840
acaaagccac gggaggagca gttcaacagc acgttccgtg tggtcagcgt cctcaccgtt 900
gtgcaccagg actggctgaa cggcaaggag tacaagtgca aggtctccaa caaaggcctc 960
ccagccccca tcgagaaaac catctccaaa accaaagggc agccccgaga accacaggtg 1020

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tacaccctgc ccccatcccg ggaggagatg accaagaacc aggtcagcct gacctgcctg 1080
gtcaaaggct tctaccccag cgacatcgcc gtggagtggg agagcaatgg gcagccggag 1140
aacaactaca agaccacgcc tcccatgctg gactccgacg gctccttctt cctctacagc 1200
aagctcaccg tggacaagag caggtggcag caggggaacg tcttctcatg ctccgtgatg 1260
catgaggctc tgcacaacca ctacacgcag aagagcctct ccctgtctcc gggtaaaggt 1320
ggtggtggct cgggatccgg aggctccggt ggcggtggca gcaacccaat ttgcaaggga 1380
tgcttaagct gtagcaagga caacggatgt tcacggtgcc agcaaaagct gtttttcttc 1440
ctccggcggg aaggaatgcg gcagtacggc gaatgtctcc actcctgccc ctcggggtat 1500
tacggacacc gcgcgcctga catgaaccga tgcgccagat gccggatcga gaactgcgat 1560
agctgccgca gcaaggacgc ctgcactaag tgcaaagtcg gcttctacct tcaccggggc 1620
agatgttttg acgaatgccc ggatggcttc gccccgctgg aggagactat ggaatgcgtg 1680
gag 1683

<210> 221
<211> 561
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-3A24重链IgG2、RSPO2(F105R/F109A)多肽序列
<400> 221

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30
Tyr Ile Asn Trp Val Arg Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45
Gly Arg Val Ile Pro Ser Asn Gly Gly Ser Asn Tyr Asn Gln Lys Phe
50 55 60
Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Leu Ser Thr Ala Tyr
65 70 75 80
Met His Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95
Ala Thr Gln Leu Gly Arg Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100 105 110
Ala Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
115 120 125
Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130 135 140
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr

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145 150 155 160
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165 170 175
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln
180 185 190
Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205
Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala
210 215 220
Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
225 230 235 240
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
245 250 255
Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
260 265 270
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
275 280 285
Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp
290 295 300
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
305 310 315 320
Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg
325 330 335
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
340 345 350
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
355 360 365
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
370 375 380
Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
385 390 395 400
Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
405 410 415
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
420 425 430
Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Ser Gly Gly
435 440 445
Ser Gly Gly Gly Gly Ser Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys
450 455 460

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Ser Lys Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe
465 470 475 480
Leu Arg Arg Glu Gly Met Arg Gln Tyr Gly Glu Cys Leu His Ser Cys
485 490 495
Pro Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met Asn Arg Cys Ala
500 505 510
Arg Cys Arg Ile Glu Asn Cys Asp Ser Cys Arg Ser Lys Asp Ala Cys
515 520 525
Thr Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly Arg Cys Phe Asp
530 535 540
Glu Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr Met Glu Cys Val
545 550 555 560
Glu

<210> 222
<211> 639
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-3E20轻链多核苷酸序列
<400> 222
gacatcaaga tgacccagtc tccatcttcc atgtatgcat ctctaggaga gagagtcact 60
atcacttgca aggcgagtca ggacattaat agctatttaa gctggttcca gcagaaacca 120
gggaaatctc ctaagaccct gatctatcgt gcaaacagat tggtagatgg ggtcccatca 180
aggttcagtg gcagtggatc tgggcaagat tattctctca ccatcagcag cctagagtat 240
gaagatatgg gaatttatta ttgtctacag tatgatgact tgtggacgtt cggtggaggc 300
accaagctgg aaatcaaacg tacggtggct gcaccatctg tcttcatctt cccgccatct 360
gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc tgctgaataa cttctatccc 420
agagaggcca aagtacagtg gaaggtggat aacgccctcc aatcgggtaa ctcccaggag 480
agtgtcacag agcaggacag caaggacagc acctacagcc tcagcagcac cctgacgctg 540
agcaaagcag actacgagaa acacaaagtc tacgcctgcg aagtcaccca tcagggcctg 600
agctcgcccg tcacaaagag cttcaacagg ggagagtgt 639
<210> 223
<211> 213
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-3E20轻链多肽序列
<400> 223
Asp Ile Lys Met Thr Gln Ser Pro Ser Ser Met Tyr Ala Ser Leu Gly

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1 5 10 15
Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile Asn Ser Tyr
20 25 30
Leu Ser Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
35 40 45
Tyr Arg Ala Asn Arg Leu Val Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Tyr
65 70 75 80
Glu Asp Met Gly Ile Tyr Tyr Cys Leu Gln Tyr Asp Asp Leu Trp Thr
85 90 95
Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro
100 105 110
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
115 120 125
Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
130 135 140
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145 150 155 160
Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
165 170 175
Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
180 185 190
Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
195 200 205
Asn Arg Gly Glu Cys
210

<210> 224
<211> 1707
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-3E20重链IgG2、RSPO2(F105R/F109A)多核苷酸序列
<400> 224
caggtccaac tgcagcagtc tggggctgaa ctggcaaaac ctggggcctc agtgaagatg 60
tcctgcaagg cttctggcta cacctttact agctactgga tacactgggt aaaacagagg 120
cctggacagg gtctggaatg gattggatac attaatccta gcagtggtta tgctgagtac 180
aatcagaagt tcaaggtcag ggccacattg actgcagaca aatcctccag cacagcctac 240

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atgcaactaa gcagcctgac atctgaggac tctgcagtct attactgtgc aagagaaagt 300
tactatagtt tcgactatac tatggactac tggggtcaag gaacctcagt caccgtctcc 360
agcgctagca ccaagggccc atcggtcttc cccctggcgc cctgctccag gagcacctcc 420
gagagcacag cggccctggg ctgcctggtc aaggactact tccccgaacc ggtgacggtg 480
tcgtggaact caggcgctct gaccagcggc gtgcacacct tcccagctgt cctacagtcc 540
tcaggactct actccctcag cagcgtggtg accgtgccct ccagcaactt cggcacccag 600
acctacacct gcaacgtaga tcacaagccc agcaacacca aggtggacaa gacagttgag 660
cgcaaatgtt gtgtcgagtg cccaccgtgc ccagcaccac ctgtggcagg accgtcagtc 720
ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcacg 780
tgcgtggtgg tggacgtgag ccacgaagac cccgaggtcc agttcaactg gtacgtggac 840
ggcgtggagg tgcataatgc caagacaaag ccacgggagg agcagttcaa cagcacgttc 900
cgtgtggtca gcgtcctcac cgttgtgcac caggactggc tgaacggcaa ggagtacaag 960
tgcaaggtct ccaacaaagg cctcccagcc cccatcgaga aaaccatctc caaaaccaaa 1020
gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag 1080
aaccaggtca gcctgacctg cctggtcaaa ggcttctacc ccagcgacat cgccgtggag 1140
tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccat gctggactcc 1200
gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1260
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1320
ctctccctgt ctccgggtaa aggtggtggt ggctcgggat ccggaggctc cggtggcggt 1380
ggcagcaacc caatttgcaa gggatgctta agctgtagca aggacaacgg atgttcacgg 1440
tgccagcaaa agctgttttt cttcctccgg cgggaaggaa tgcggcagta cggcgaatgt 1500
ctccactcct gcccctcggg gtattacgga caccgcgcgc ctgacatgaa ccgatgcgcc 1560
agatgccgga tcgagaactg cgatagctgc cgcagcaagg acgcctgcac taagtgcaaa 1620
gtcggcttct accttcaccg gggcagatgt tttgacgaat gcccggatgg cttcgccccg 1680
ctggaggaga ctatggaatg cgtggag 1707

<210> 225
<211> 569
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-3E20重链IgG2、RSPO2(F105R/F109A)多肽序列
<400> 225

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Trp Ile His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

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Gly Tyr Ile Asn Pro Ser Ser Gly Tyr Ala Glu Tyr Asn Gln Lys Phe
50 55 60
Lys Val Arg Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80
Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Ser Tyr Tyr Ser Phe Asp Tyr Thr Met Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125
Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
130 135 140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190
Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His
195 200 205
Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys
210 215 220
Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
225 230 235 240
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270
Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285
Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser
290 295 300
Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320
Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335
Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350
Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu

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355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly
435 440 445

Gly Gly Gly Ser Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Asn Pro
450 455 460

Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys Ser Arg
465 470 475 480

Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met Arg Gln
485 490 495

Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly His Arg
500 505 510

Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp
515 520 525

Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly Phe Tyr
530 535 540

Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro
545 550 555 560

Leu Glu Glu Thr Met Glu Cys Val Glu
565

<210> 226

<211> 657

<212> DNA

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的合成的LP1-6H3轻链多核苷酸序列

<400> 226

gatgttgtga tgacccagac tccactcact ttgtcggtta ccattggaca accagcctcc 60

atctcttgca agtcaagtca gagcctctta gatagtgatg gaaagacata tttgaattgg 120

ttgttacaga ggccaggcca gtctccaaag cgcctaatct atctggtgtc taaactggac 180

tctggagtcc ctgacaggtt cactggcagt ggatcaggga cagatttcac actgaaaatc 240

agcagagtgg aggctgagga tttgggagtt tattattgct ggcaaggtac acattttcct 300

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cacacgttcg gctcggggac aaagttggaa ataaaacgta cggtggctgc accatctgtc 360
ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 420
ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 480
tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 540
agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 600
gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgt 657

<210> 227
<211> 219
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-6H3轻链多肽序列
<400> 227

Asp Val Val Met Thr Gln Thr Pro Leu Thr Leu Ser Val Thr Ile Gly
1 5 10 15
Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30
Asp Gly Lys Thr Tyr Leu Asn Trp Leu Leu Gln Arg Pro Gly Gln Ser
35 40 45
Pro Lys Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp Ser Gly Val Pro
50 55 60
Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80
Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Trp Gln Gly
85 90 95
Thr His Phe Pro His Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
100 105 110
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125
Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140
Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160
Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175
Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190
Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

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Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 228
<211> 1689
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-6H3重链IgG2、RSPO2(F105R/F109A)
多核苷酸序列
<400> 228

caggcttatc tacagcagtc tggggctgag ctggtgaggc ctggggcctc agtgaagatg 60
tcctgtaagg cttctggcta cacattttcc cgtttcgata tgcactgggt aaagcagaca 120
cctagacagg gcctggaatg gattggagtt atttatccag gaaatggtga tacttcctac 180
aatcagaagt tcagggacaa ggcctcactg actgtagaca aatcctccag cacagcctac 240
atgcagctca gcagcctgac atctgaagac tctgcggtct atttctgtgc aagctcctac 300
tatggtaacc cctggggcca aggcaccact ctcacagtct ccagcgctag caccaagggc 360
ccatcggtct tccccctggc gccctgctcc aggagcacct ccgagagcac agcggccctg 420
ggctgcctgg tcaaggacta cttccccgaa ccggtgacgg tgtcgtggaa ctcaggcgct 480
ctgaccagcg gcgtgcacac cttcccagct gtcctacagt cctcaggact ctactccctc 540
agcagcgtgg tgaccgtgcc ctccagcaac ttcggcaccc agacctacac ctgcaacgta 600
gatcacaagc ccagcaacac caaggtggac aagacagttg agcgcaaatg ttgtgtcgag 660
tgcccaccgt gcccagcacc acctgtggca ggaccgtcag tcttcctctt cccccaaaa 720
cccaaggaca ccctcatgat ctcccggacc cctgaggtca cgtgcgtggt ggtggacgtg 780
agccacgaag accccgaggt ccagttcaac tggtacgtgg acggcgtgga ggtgcataat 840
gccaagacaa agccacggga ggagcagttc aacagcacgt tccgtgtggt cagcgtcctc 900
accgttgtgc accaggactg gctgaacggc aaggagtaca agtgcaaggt ctccaacaaa 960
ggcctcccag cccccatcga gaaaaccatc tccaaaacca aagggcagcc ccgagaacca 1020
caggtgtaca ccctgccccc atcccgggag gagatgacca agaaccaggt cagcctgacc 1080
tgcctggtca aaggcttcta ccccagcgac atcgccgtgg agtgggagag caatgggcag 1140
ccggagaaca actacaagac cacgcctccc atgctggact ccgacggctc cttcttcctc 1200
tacagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc 1260
gtgatgcatg aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt 1320
aaaggtggtg gtggctcggg atccggaggc tccggtggcg gtggcagcaa cccaatttgc 1380
aagggatgct taagctgtag caaggacaac ggatgttcac ggtgccagca aaagctgttt 1440
ttcttcctcc ggcgggaagg aatgcggcag tacggcgaat gtctccactc ctgcccctcg 1500
gggtattacg gacaccgcgc gcctgacatg aaccgatgcg ccagatgccg gatcgagaac 1560
tgcgatagct gccgcagcaa ggacgcctgc actaagtgca aagtcggctt ctaccttcac 1620
cggggcagat gttttgacga atgcccggat ggcttcgccc cgctggagga gactatggaa 1680
tgcgtggag 1689

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<210> 229
<211> 563
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-6H3重链IgG2、RSPO2(F105R/F109A)多肽序列
<400> 229

Gln Ala Tyr Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ala
1 5 10 15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Arg Phe
20 25 30
Asp Met His Trp Val Lys Gln Thr Pro Arg Gln Gly Leu Glu Trp Ile
35 40 45
Gly Val Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe
50 55 60
Arg Asp Lys Ala Ser Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80
Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
85 90 95
Ala Ser Ser Tyr Tyr Gly Asn Pro Trp Gly Gln Gly Thr Thr Leu Thr
100 105 110
Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
115 120 125
Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val
130 135 140
Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
145 150 155 160
Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
165 170 175
Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly
180 185 190
Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys
195 200 205
Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
210 215 220
Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
225 230 235 240
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val

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245 250 255

Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
260 265 270

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
275 280 285

Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His
290 295 300

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
305 310 315 320

Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln
325 330 335

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
340 345 350

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
355 360 365

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
370 375 380

Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
385 390 395 400

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
405 410 415

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
420 425 430

Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Ser
435 440 445

Gly Gly Ser Gly Gly Gly Gly Ser Asn Pro Ile Cys Lys Gly Cys Leu
450 455 460

Ser Cys Ser Lys Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys Leu Phe
465 470 475 480

Phe Phe Leu Arg Arg Glu Gly Met Arg Gln Tyr Gly Glu Cys Leu His
485 490 495

Ser Cys Pro Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met Asn Arg
500 505 510

Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp Ser Cys Arg Ser Lys Asp
515 520 525

Ala Cys Thr Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly Arg Cys
530 535 540

Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr Met Glu
545 550 555 560

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Cys Val Glu

<210> 230

<211> 642

<212> DNA

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的合成的LP1-7B13轻链多核苷酸序列

<400> 230

gatattgtgc taactcagtc tccagccacc ctgtctgtga ctccaggaga tagagtcagt 60
ctttcctgca gggccagtca aagtattagc aactacctac actggtatca acaaaaatca 120
catgagtctc caaggcttct catcaagttt gcttcccagt ccatctctgg gatcccctcc 180
aggttcagtg gcagtggatc agggacggat ttcactctca ctatcaacag tgtggagact 240
gaagattttg gaatgtattt ctgtcaacag agtaacagct ggccgctcac gttcggtgct 300
gggaccaagc tggagctgaa acgtacggtg gctgcaccat ctgtcttcat cttcccgcca 360
tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat 420
cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 480
gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 540
ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 600
ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt 642

<210> 231

<211> 214

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的合成的LP1-7B13轻链多肽序列

<400> 231

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Val Thr Pro Gly
1 5 10 15
Asp Arg Val Ser Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Asn Tyr
20 25 30
Leu His Trp Tyr Gln Gln Lys Ser His Glu Ser Pro Arg Leu Leu Ile
35 40 45
Lys Phe Ala Ser Gln Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Val Glu Thr
65 70 75 80
Glu Asp Phe Gly Met Tyr Phe Cys Gln Gln Ser Asn Ser Trp Pro Leu
85 90 95
Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr Val Ala Ala

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100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 232

<211> 1689

<212> DNA

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的合成的LP1-7B13重链IgG2、RSPO2(F105R/F109A)多核苷酸序列

<400> 232

gaggtccagc tgcaacaatc tggacctgag gtggtgaagc ctggggcttc agtgaagatg 60
tcctgtaaga cttctggatt cacattcact gactactaca tgaactgggt gaagcagggt 120
catggaaaga gccttgagtg gattggacgt gttaatccta gcaatgatga tactaggtac 180
aatcagaagt tcaagggaaa ggccacattg acagtagaca agtccctcag cacagcctac 240
atgcagctca acagcctgac atctgaggac tctgcggtct attactgtac aaggtggttc 300
tactttgact actggggcca aggcactact ctcacagtct ccagcgctag caccaagggc 360
ccatcggtct tccccctggc gccctgctcc aggagcacct ccgagagcac agcggccctg 420
ggctgcctgg tcaaggacta cttccccgaa ccggtgacgg tgtcgtggaa ctcaggcgct 480
ctgaccagcg gcgtgcacac cttcccagct gtcctacagt cctcaggact ctactccctc 540
agcagcgtgg tgaccgtgcc ctccagcaac ttcggcaccc agacctacac ctgcaacgta 600
gatcacaagc ccagcaacac caaggtggac aagacagttg agcgcaaatg ttgtgtcgag 660
tgcccaccgt gcccagcacc acctgtggca ggaccgtcag tcttcctctt ccccccaaaa 720
cccaaggaca ccctcatgat ctcccggacc cctgaggtca cgtgcgtggt ggtggacgtg 780
agccacgaag accccgaggt ccagttcaac tggtacgtgg acggcgtgga ggtgcataat 840
gccaagacaa agccacggga ggagcagttc aacagcacgt tccgtgtggt cagcgtcctc 900
accgttgtgc accaggactg gctgaacggc aaggagtaca agtgcaaggt ctccaacaaa 960

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ggcctcccag cccccatcga gaaaaccatc tccaaaacca aagggcagcc ccgagaacca 1020
caggtgtaca ccctgccccc atcccgggag gagatgacca agaaccaggt cagcctgacc 1080
tgcctggtca aaggcttcta ccccagcgac atcgccgtgg agtgggagag caatgggcag 1140
ccggagaaca actacaagac cacgcctccc atgctggact ccgacggctc cttcttcctc 1200
tacagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc 1260
gtgatgcatg aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt 1320
aaaggtggtg gtggctcggg atccggaggc tccggtggcg gtggcagcaa cccaatttgc 1380
aagggatgct taagctgtag caaggacaac ggatgttcac ggtgccagca aaagctgttt 1440
ttcttcctcc ggcgggaagg aatgcggcag tacggcgaat gtctccactc ctgcccctcg 1500
gggtattacg gacaccgcgc gcctgacatg aaccgatgcg ccagatgccg gatcgagaac 1560
tgcgatagct gccgcagcaa ggacgcctgc actaagtgca aagtcggctt ctaccttcac 1620
cggggcagat gttttgacga atgcccggat ggcttcgccc cgctggagga gactatggaa 1680
tgcgtggag 1689

<210> 233
<211> 563
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-7B13重链IgG2、RSPO2(F105R/F109A)多肽序列
<400> 233

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Val Val Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Met Ser Cys Lys Thr Ser Gly Phe Thr Phe Thr Asp Tyr
20 25 30
Tyr Met Asn Trp Val Lys Gln Gly His Gly Lys Ser Leu Glu Trp Ile
35 40 45
Gly Arg Val Asn Pro Ser Asn Asp Asp Thr Arg Tyr Asn Gln Lys Phe
50 55 60
Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Leu Ser Thr Ala Tyr
65 70 75 80
Met Gln Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95
Thr Arg Trp Phe Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr
100 105 110
Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
115 120 125
Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val
130 135 140

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Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
145 150 155 160
Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
165 170 175
Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly
180 185 190
Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys
195 200 205
Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
210 215 220
Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
225 230 235 240
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
245 250 255
Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
260 265 270
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
275 280 285
Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His
290 295 300
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
305 310 315 320
Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln
325 330 335
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
340 345 350
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
355 360 365
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
370 375 380
Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
385 390 395 400
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
405 410 415
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
420 425 430
Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Ser
435 440 445
Gly Gly Ser Gly Gly Gly Gly Ser Asn Pro Ile Cys Lys Gly Cys Leu

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450 455 460

Ser Cys Ser Lys Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys Leu Phe
465 470 475 480
Phe Phe Leu Arg Arg Glu Gly Met Arg Gln Tyr Gly Glu Cys Leu His
485 490 495
Ser Cys Pro Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met Asn Arg
500 505 510
Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp Ser Cys Arg Ser Lys Asp
515 520 525
Ala Cys Thr Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly Arg Cys
530 535 540
Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr Met Glu
545 550 555 560
Cys Val Glu

<210> 234
<211> 642
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-7I20轻链多核苷酸序列
<400> 234
gacatccaga tgactcagtc tccagcctcc ctatctgcat ctgtgggaga aactgtcacc 60
atcacatgtc gaacaagtga gaatatttac agttatttag catggtatca gcagaaacag 120
ggaaaatctc ctcagctcct ggtctataat gcaaaaacct tagcaaaagg tgtgccatca 180
aggttcagtg gcagtggatc aggcacacag ttttctctga agatcaacgg cctgcagcct 240
gaagattttg ggaattatta ctgtcaacat cattatggta ctccgtacac gttcggaggg 300
gggaccaagg tggaaataaa acgtacggtg gctgcaccat ctgtcttcat cttcccgcca 360
tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat 420
cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 480
gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 540
ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 600
ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt 642

<210> 235
<211> 214
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-7I20轻链多肽序列
<400> 235

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Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Glu Thr Val Thr Ile Thr Cys Arg Thr Ser Glu Asn Ile Tyr Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro Gln Leu Leu Val
35 40 45
Tyr Asn Ala Lys Thr Leu Ala Lys Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Gln Phe Ser Leu Lys Ile Asn Gly Leu Gln Pro
65 70 75 80
Glu Asp Phe Gly Asn Tyr Tyr Cys Gln His His Tyr Gly Thr Pro Tyr
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110
Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125
Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140
Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205
Phe Asn Arg Gly Glu Cys
210

<210> 236
<211> 1692
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-7I20重链IgG2、RSPO2(F105R/F109A)多核苷酸序列
<400> 236
gaggtgaagc tggtggagtc tggaggaggc ttggtacagc ctgggggttc tctgagtctc 60
tcctgtgcag cttctggatt caccttcact gattactaca tgagctgggt ccgccagccc 120
ccagggaagg cacttgagtg gttggctttg attagaaaca aagctaatgg ttacacaaca 180

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gagtacagtg catctgtgaa gggtcggttc accatctcca gggataattc ccaaagcatc 240
ctctatcttc aaatgaatgc cctgagagct gaggacagtg ccacttatta ctgtgcagtt 300
acctacgggg cttactgggg ccaagggact ctggtcactg tctctgcagc tagcaccaag 360
ggcccatcgg tcttcccccc ggcgccctgc tccaggagca cctccgagag cacagcggcc 420
ctgggctgcc tggtcaagga ctacttcccc gaaccggtga cggtgtcgtg gaactcaggc 480
gctctgacca gcggcgtgca caccttccca gctgtcctac agtcctcagg actctactcc 540
ctcagcagcg tggtgaccgt gccctccagc aacttcggca cccagaccta cacctgcaac 600
gtagatcaca agcccagcaa caccaaggtg gacaagacag ttgagcgcaa atgttgtgtc 660
gagtgcccac cgtgcccagc accacctgtg gcaggaccgt cagtcttcct cttcccccca 720
aaacccaagg acaccctcat gatctcccgg acccctgagg tcacgtgcgt ggtggtggac 780
gtgagccacg aagaccccga ggtccagttc aactggtacg tggacggcgt ggaggtgcat 840
aatgccaaga caaagccacg ggaggagcag ttcaacagca cgttccgtgt ggtcagcgtc 900
ctcaccgttg tgcaccagga ctggctgaac ggcaaggagt acaagtgcaa ggtctccaac 960
aaaggcctcc cagccccccat cgagaaaacc atctccaaaa ccaaagggca gccccgagaa 1020
ccacaggtgt acaccctgcc cccatcccgg gaggagatga ccaagaacca ggtcagcctg 1080
acctgcctgg tcaaaggctt ctaccccagc gacatcgccg tggagtggga gagcaatggg 1140
cagccggaga acaactacaa gaccacgcct cccatgctgg actccgacgg ctccttcttc 1200
ctctacagca agctcaccgt ggacaagagc aggtggcagc aggggaacgt cttctcatgc 1260
tccgtgatgc atgaggctct gcacaaccac tacacgcaga agagcctctc cctgtctccg 1320
ggtaaaggtg gtggtggctc gggatccgga ggctccggtg gcggtggcag caacccaatt 1380
tgcaagggat gcttaagctg tagcaaggac aacggatgtt cacggtgcca gcaaaagctg 1440
tttttcttcc tccggcggga aggaatgcgg cagtacggcg aatgtctcca ctcctgcccc 1500
tcggggtatt acggacaccg cgcgcctgac atgaaccgat gcgccagatg ccggatcgag 1560
aactgcgata gctgccgcag caaggacgcc tgcactaagt gcaaagtcgg cttctacctt 1620
caccggggca gatgttttga cgaatgcccg gatggcttcg ccccgctgga ggagactatg 1680
gaatgcgtgg ag 1692

<210> 237
<211> 564
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-7I20重链IgG2、RSPO2(F105R/F109A)多肽序列
<400> 237

Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Ser Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Asp Tyr
20 25 30
Tyr Met Ser Trp Val Arg Gln Pro Pro Gly Lys Ala Leu Glu Trp Leu

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35 40 45

Ala Leu Ile Arg Asn Lys Ala Asn Gly Tyr Thr Thr Glu Tyr Ser Ala
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Gln Ser Ile
65 70 75 80

Leu Tyr Leu Gln Met Asn Ala Leu Arg Ala Glu Asp Ser Ala Thr Tyr
85 90 95

Tyr Cys Ala Val Thr Tyr Gly Ala Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ala Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe
180 185 190

Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro
210 215 220

Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro
225 230 235 240

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
245 250 255

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp
260 265 270

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
275 280 285

Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val
290 295 300

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
305 310 315 320

Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly
325 330 335

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
340 345 350

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Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
355 360 365
Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
370 375 380
Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe
385 390 395 400
Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
405 410 415
Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
420 425 430
Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly
435 440 445
Ser Gly Gly Ser Gly Gly Gly Gly Ser Asn Pro Ile Cys Lys Gly Cys
450 455 460
Leu Ser Cys Ser Lys Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys Leu
465 470 475 480
Phe Phe Phe Leu Arg Arg Glu Gly Met Arg Gln Tyr Gly Glu Cys Leu
485 490 495
His Ser Cys Pro Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met Asn
500 505 510
Arg Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp Ser Cys Arg Ser Lys
515 520 525
Asp Ala Cys Thr Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly Arg
530 535 540
Cys Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr Met
545 550 555 560
Glu Cys Val Glu

<210> 238
<211> 693
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-8M24轻链多核苷酸序列
<400> 238
gaggttcagc tgcagcagtc tggggctgag cttgtgaggc caggggcctc agtcaagttg 60
tcctgcacag cttctggctt taccattaaa gacgactata ttcactgggt gaagcagggg 120
cctgaacagg gcctggagtg gattggaaga attgatcctg cggatgatga tactaaatat 180
gccccgaagt tccaggacaa ggccactata actgcagaca catcctccaa cacagcctac 240
ctgcagctca gcagcctgac atctgaggac actgccgtct attactgtgc tagaagttcc 300

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atggcctggt ttgcttactg ggcccaaggg actctggtca ctgtctctac agctagcacc 360
aagggcccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg 420
gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca 480
ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac 540
tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc 600
aacgtgaatc acaagcccag caacaccaag gtggacaaga aagttgagcc caaatcttgt 660
ggatccggct ccggacatca tcatcaccat cac 693

<210> 239
<211> 231
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-8M24轻链多肽序列
<400> 239

Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ala
1 5 10 15
Ser Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Thr Ile Lys Asp Asp
20 25 30
Tyr Ile His Trp Val Lys Gln Gly Pro Glu Gln Gly Leu Glu Trp Ile
35 40 45
Gly Arg Ile Asp Pro Ala Asp Asp Asp Thr Lys Tyr Ala Pro Lys Phe
50 55 60
Gln Asp Lys Ala Thr Ile Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
65 70 75 80
Leu Gln Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Ser Met Ala Trp Phe Ala Tyr Trp Ala Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Thr Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190
Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn

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195 200 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly Ser Gly Ser

210 215 220

Gly His His His His His His

225 230

<210> 240

<211> 642

<212> DNA

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的合成的LP1-8M24重链IgG2、RSPO2(F105R/F109A)多核苷酸序列

<400> 240

gacatccaga tgacacagag ccctagcagc ctgtctgcca gcgtgggaga cagagtgacc 60
atcacctgtc ggatcagcga gaacatctac agcaacctgg cctggtatca gcagaagcct 120
ggcaaggccc ctaagctgct gatctacgcc gccatcaatc tggccgatgg cgtgccaagc 180
agattttctg gcagcggctc tggcaccgac ttcaccctga ccatatctag cctgcagcct 240
gaggacttcg ccacctacta ctgccagcac ttttggggca ccccttcac ctttggccag 300
ggcaccaagc tggaaatcaa gcgtacggtg gctgcaccat ctgtcttcat cttcccgcca 360
tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat 420
cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 480
gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 540
ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 600
ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt 642

<210> 241

<211> 214

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的合成的LP1-8M24重链IgG2、RSPO2(F105R/F109A)多肽序列

<400> 241

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly

1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ile Ser Glu Asn Ile Tyr Ser Asn

20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile

35 40 45

Tyr Ala Ala Ile Asn Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly

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50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln His Phe Trp Gly Thr Pro Phe
85 90 95
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
100 105 110
Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125
Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140
Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205
Phe Asn Arg Gly Glu Cys
210

<210> 242
<211> 657
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-9C3轻链多核苷酸序列
<400> 242
gatgttgtgg tgactcaaac tccactctcc ctgcctgtca gctttggaga tcaagtttct 60
atctcttgca ggtctagtca gagtcttgca aacagttatg ggaacaccta tttgtcttgg 120
tacctgcaca agcctggcca gtctccacag ctcctcatct atgggatttc caacagattt 180
tctggggtgc cagacaggtt cagtggcagt ggttcaggga cagatttcac actcaagatc 240
agcacaataa agcctgagga cttgggaatc tattactgct tacaagctac acatcagccg 300
tggacgttcg gtggaggcac caagctggaa atcaaacgta cggtggctgc accatctgtc 360
ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 420
ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 480
tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 540
agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 600
gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgt 657

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<210> 243
<211> 219
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-9C3轻链多肽序列
<400> 243

Asp Val Val Val Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Phe Gly
1 5 10 15
Asp Gln Val Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Ala Asn Ser
20 25 30
Tyr Gly Asn Thr Tyr Leu Ser Trp Tyr Leu His Lys Pro Gly Gln Ser
35 40 45
Pro Gln Leu Leu Ile Tyr Gly Ile Ser Asn Arg Phe Ser Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80
Ser Thr Ile Lys Pro Glu Asp Leu Gly Ile Tyr Tyr Cys Leu Gln Ala
85 90 95
Thr His Gln Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125
Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140
Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160
Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175
Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190
Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205
Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 244
<211> 1695
<212> DNA
<213> 人工序列(Artificial Sequence)

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<220>
<223> 在实验室中制备的合成的LP1-9C3重链IgG2、RSPO2(F105R/F109A)
多核苷酸序列
<400> 244
caggttactc tgaaagagtc tggccctggg atattgcagc cctcccagac cctcagtctg 60
acttgttctt tctctgggtt ttcactgagc acttcttata tgggtgtgag ctggattcgt 120
aagccttcag gaaagggtct ggagtggctg gcacacattt tctgggatga tgacaagcgc 180
tataacccat ccctgaagag ccggctcaca atctccaagg atacctccag caaccaggta 240
ttcctcatga tcaccagtgt ggaaactgca gatactgcca catactactg tgggggtccc 300
tactatccgt ttacttactg gggccaaggg actctggtca ctgtctctgc agctagcacc 360
aagggcccat cggtcttccc cctggcgccc tgctccagga gcacctccga gagcacagcg 420
gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca 480
ggcgctctga ccagcggcgt gcacaccttc ccagctgtcc tacagtcctc aggactctac 540
tccctcagca gcgtggtgac cgtgccctcc agcaacttcg gcacccagac ctacacctgc 600
aacgtagatc acaagcccag caacaccaag gtggacaaga cagttgagcg caaatgttgt 660
gtcgagtgcc caccgtgccc agcaccacct gtggcaggac cgtcagtctt cctcttcccc 720
ccaaaaccca aggacaccct catgatctcc cggacccctg aggtcacgtg cgtggtggtg 780
gacgtgagcc acgaagaccc cgaggtccag ttcaactggt acgtggacgg cgtggaggtg 840
cataatgcca agacaaagcc acgggaggag cagttcaaca gcacgttccg tgtggtcagc 900
gtcctcaccg ttgtgcacca ggactggctg aacggcaagg agtacaagtg caaggtctcc 960
aacaaaggcc tcccagcccc catcgagaaa accatctcca aaaccaaagg gcagccccga 1020
gaaccacagg tgtacaccct gcccccatcc cgggaggaga tgaccaagaa ccaggtcagc 1080
ctgacctgcc tggtcaaagg cttctacccc agcgacatcg ccgtggagtg ggagagcaat 1140
gggcagccgg agaacaacta caagaccacg cctcccatgc tggactccga cggctccttc 1200
ttcctctaca gcaagctcac cgtggacaag agcaggtggc agcaggggaa cgtcttctca 1260
tgctccgtga tgcatgaggc tctgcacaac cactacacgc agaagagcct ctccctgtct 1320
ccgggtaaag gtggtggtgg ctcgggatcc ggaggctccg gtggcggtgg cagcaaccca 1380
atttgcaagg gatgcttaag ctgtagcaag gacaacggat gttcacggtg ccagcaaaag 1440
ctgtttttct tcctccggcg ggaaggaatg cggcagtacg gcgaatgtct ccactcctgc 1500
ccctcggggt attacggaca ccgcgcgcct gacatgaacc gatgcgccag atgccggatc 1560
gagaactgcg atagctgccg cagcaaggac gcctgcacta agtgcaaagt cggcttctac 1620
cttcaccggg gcagatgttt tgacgaatgc ccggatggct tcgccccgct ggaggagact 1680
atggaatgcg tggag 1695
<210> 245
<211> 565
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-9C3重链IgG2、RSPO2(F105R/F109A)

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多肽序列

〈400〉 245

Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln Pro Ser Gln
1 5 10 15
Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30
Tyr Met Gly Val Ser Trp Ile Arg Lys Pro Ser Gly Lys Gly Leu Glu
35 40 45
Trp Leu Ala His Ile Phe Trp Asp Asp Asp Lys Arg Tyr Asn Pro Ser
50 55 60
Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Ser Asn Gln Val
65 70 75 80
Phe Leu Met Ile Thr Ser Val Glu Thr Ala Asp Thr Ala Thr Tyr Tyr
85 90 95
Cys Gly Gly Pro Tyr Tyr Pro Phe Thr Tyr Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ala Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125
Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys
130 135 140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn
180 185 190
Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn
195 200 205
Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro
210 215 220
Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro
225 230 235 240
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
245 250 255
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn
260 265 270
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
275 280 285
Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val

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290 295 300

Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
305 310 315 320
Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys
325 330 335
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
340 345 350
Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
355 360 365
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
370 375 380
Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe
385 390 395 400
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
405 410 415
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
420 425 430
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser
435 440 445
Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Asn Pro Ile Cys Lys Gly
450 455 460
Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys
465 470 475 480
Leu Phe Phe Phe Leu Arg Arg Glu Gly Met Arg Gln Tyr Gly Glu Cys
485 490 495
Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met
500 505 510
Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp Ser Cys Arg Ser
515 520 525
Lys Asp Ala Cys Thr Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly
530 535 540
Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr
545 550 555 560
Met Glu Cys Val Glu
565

<210> 246
<211> 642
<212> DNA
<213> 人工序列(Artificial Sequence)

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<220>
<223> 在实验室中制备的合成的LP1-9M16轻链多核苷酸序列
<400> 246
gacatcaaga tgacccagtc tccatcttcc atgtatgcat ctctaggaga gagagtcact 60
atcacttgca aggcgagtca ggacattaat agctatttaa gctggttcca gcagaaacca 120
gggaaatctc ctaagaccct gatctatcgt gcaaacagat tggcagatgg ggtcccatca 180
aggttcagtg gcagtggatc tgggcaagat tattctctca ccatcagcaa cctggagtat 240
gaagatatgg gaatttatta ttgtctacag tatgatgagt ttccgctcac gttcggtgct 300
gggaccaagc tggagctgaa acgtacggtg gctgcaccat ctgtcttcat cttcccgcca 360
tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat 420
cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 480
gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 540
ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 600
ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt 642
<210> 247
<211> 214
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-9M16轻链多肽序列
<400> 247
Asp Ile Lys Met Thr Gln Ser Pro Ser Ser Met Tyr Ala Ser Leu Gly
1 5 10 15
Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile Asn Ser Tyr
20 25 30
Leu Ser Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
35 40 45
Tyr Arg Ala Asn Arg Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Tyr
65 70 75 80
Glu Asp Met Gly Ile Tyr Tyr Cys Leu Gln Tyr Asp Glu Phe Pro Leu
85 90 95
Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr Val Ala Ala
100 105 110
Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125
Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

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Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205
Phe Asn Arg Gly Glu Cys
210

<210> 248
<211> 1686
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-9M16重链IgG2、RSPO2(F105R/F109A)多核苷酸序列
<400> 248

gaggtccagc tgcaacagtc tggacctgag ctggtgaagc ctggggcttc agtgaagatg 60
tcctgtaagg cttctggata cacattcact gactactaca tgaactgggt gaagcagagt 120
catggaaaga gccttgagtg gattggacgt gttaatccta acaatggtgg ttctaactac 180
aaccagaaat tcaagggcaa ggccacattg acagtagaca aatccctcag cacagcctac 240
atgcagctca acagcctgac atctgaggac tctgcggtct attactgtgc aagtcgaaac 300
ttcgatgtct ggggcgcagg gaccacggtc accgtctcca gcgctagcac caagggccca 360
tcggtcttcc ccctggcgcc ctgctccagg agcacctccg agagcacagc ggccctgggc 420
tgcctggtca aggactactt ccccgaaccg gtgacggtgt cgtggaactc aggcgctctg 480
accagcggcg tgcacacctt cccagctgtc ctacagtcct caggactcta ctccctcagc 540
agcgtggtga ccgtgccctc cagcaacttc ggcacccaga cctacacctg caacgtagat 600
cacaagccca gcaacaccaa ggtggacaag acagttgagc gcaaatgttg tgtcgagtgc 660
ccaccgtgcc cagcaccacc tgtggcagga ccgtcagtct tcctcttccc cccaaaaccc 720
aaggacaccc tcatgatctc ccggacccct gaggtcacgt gcgtggtggt ggacgtgagc 780
cacgaagacc ccgaggtcca gttcaactgg tacgtggacg gcgtggaggt gcataatgcc 840
aagacaaagc cacgggagga gcagttcaac agcacgttcc gtgtggtcag cgtcctcacc 900
gttgtgcacc aggactggct gaacggcaag gagtacaagt gcaaggtctc caacaaaggc 960
ctcccagccc ccatcgagaa aaccatctcc aaaaccaaag ggcagccccg agaaccacag 1020
gtgtacaccc tgcccccatc ccgggaggag atgaccaaga accaggtcag cctgacctgc 1080
ctggtcaaag gcttctaccc cagcgacatc gccgtggagt gggagagcaa tgggcagccg 1140
gagaacaact acaagaccac gcctcccatg ctggactccg acggctcctt cttcctctac 1200
agcaagctca ccgtggacaa gagcaggtgg cagcagggga acgtcttctc atgctccgtg 1260

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atgcatgagg ctctgcacaa ccactacacg cagaagagcc tctccctgtc tccgggtaaa 1320
ggtggtggtg gctcgggatc cggaggctcc ggtggcggtg gcagcaaccc aatttgcaag 1380
ggatgcttaa gctgtagcaa ggacaacgga tgttcacggt gccagcaaaa gctgtttttc 1440
ttcctccggc gggaaggaat gcggcagtac ggcgaatgtc tccactcctg cccctcgggg 1500
tattacggac accgcgcgcc tgacatgaac cgatgcgcca gatgccggat cgagaactgc 1560
gatagctgcc gcagcaagga cgcctgcact aagtgcaaag tcggcttcta ccttcaccgg 1620
ggcagatgtt ttgacgaatg cccggatggc ttcgccccgc tggaggagac tatggaatgc 1680
gtggag 1686

<210> 249

<211> 562

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的合成的LP1-9M16重链IgG2、RSPO2(F105R/F109A)多肽序列

<400> 249

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30
Tyr Met Asn Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45
Gly Arg Val Asn Pro Asn Asn Gly Gly Ser Asn Tyr Asn Gln Lys Phe
50 55 60
Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Leu Ser Thr Ala Tyr
65 70 75 80
Met Gln Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95
Ala Ser Arg Asn Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val
100 105 110
Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys
115 120 125
Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys
130 135 140
Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu
145 150 155 160
Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu
165 170 175
Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr

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180 185 190

Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val

195 200 205

Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro

210 215 220

Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro

225 230 235 240

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val

245 250 255

Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val

260 265 270

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln

275 280 285

Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln

290 295 300

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly

305 310 315 320

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro

325 330 335

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr

340 345 350

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser

355 360 365

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr

370 375 380

Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr

385 390 395 400

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe

405 410 415

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys

420 425 430

Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Ser Gly

435 440 445

Gly Ser Gly Gly Gly Gly Ser Asn Pro Ile Cys Lys Gly Cys Leu Ser

450 455 460

Cys Ser Lys Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys Leu Phe Phe

465 470 475 480

Phe Leu Arg Arg Glu Gly Met Arg Gln Tyr Gly Glu Cys Leu His Ser

485 490 495

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Cys Pro Ser Gly Tyr Tyr Gly His Arg Ala Pro Asp Met Asn Arg Cys
500 505 510
Ala Arg Cys Arg Ile Glu Asn Cys Asp Ser Cys Arg Ser Lys Asp Ala
515 520 525
Cys Thr Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly Arg Cys Phe
530 535 540
Asp Glu Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr Met Glu Cys
545 550 555 560
Val Glu

<210> 250
<211> 657
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-10C22轻链多核苷酸序列
<400> 250
gatgttttga tgacccaaac tccactctcc ctgcctgtca gtcttggaga tcaagcctcc 60
atctcttgca gatctagtca gggcattgta catagtaatg gaaacatcta tttagaatgg 120
tacctgcaga aaccaggcca gtctccaaag ctcctgatct acaaagtttc caaccgattt 180
tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc 240
agcagagtgg aggctgagga tctgggagtt tattactgct ttcaaggttc acatgttcct 300
cccacgttcg gaggggggac caagctggaa ataaaacgta cggtggctgc accatctgtc 360
ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 420
ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 480
tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 540
agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 600
gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgt 657

<210> 251
<211> 219
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-10C22轻链多肽序列
<400> 251
Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1 5 10 15
Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Gly Ile Val His Ser
20 25 30
Asn Gly Asn Ile Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser

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35 40 45
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80
Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly
85 90 95
Ser His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125
Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140
Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160
Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175
Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190
Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205
Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 252
<211> 1704
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-10C22重链IgG2、RSP02(F105R/F109A)多核苷酸序列
<400> 252
gaggtgcagc tggtggagtc tgggggagac ttagtgaagc ctggagggtc cctgaaactc 60
tcctgtgcag cctctggatt cactttcagt agttatggca tgtcttgggt tcgccagact 120
ccagacaaga ggctggagtg ggtcgcaagt attagtagtg gtggtagtta tacctactat 180
ccagacagtg tgaaggggcg attcaccatc tccagagaca atgcccagaa caccctgtac 240
ctgcaaatga gcagtctgaa gtctgaggac acagccatgt attactgtgt aagacatgag 300
gagtatggta aatccggatt tgcttactgg ggccaaggga ccctgattac tgtctctgca 360
gctagcacca agggcccatc ggtcttcccc ctggcgccct gctccaggag cacctccgag 420
agcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg 480

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tggaactcag gcgctctgac cagcggcgtg cacaccttcc cagctgtcct acagtcctca 540
ggactctact ccctcagcag cgtggtgacc gtgccctcca gcaacttcgg cacccagacc 600
tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagac agttgagcgc 660
aaatgttgtg tcgagtgccc accgtgccca gcaccacctg tggcaggacc gtcagtcttc 720
ctcttccccc caaaacccaa ggacaccctc atgatctccc ggacccctga ggtcacgtgc 780
gtggtggtgg acgtgagcca cgaagacccc gaggtccagt tcaactggta cgtggacggc 840
gtggaggtgc ataatgccaa gacaaagcca cgggaggagc agttcaacag cacgttccgt 900
gtggtcagcg tcctcaccgt tgtgcaccag gactggctga acggcaagga gtacaagtgc 960
aaggtctcca acaaaggcct cccagccccc atcgagaaaa ccatctccaa aaccaaaggg 1020
cagccccgag aaccacaggt gtacaccctg cccccatccc gggaggagat gaccaagaac 1080
caggtcagcc tgacctgcct ggtcaaaggc ttctacccca gcgacatcgc cgtggagtgg 1140
gagagcaatg ggcagccgga gaacaactac aagaccacgc ctcccatgct ggactccgac 1200
ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac 1260
gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 1320
tccctgtctc cgggtaaagg tggtggtggc tcgggatccg gaggctccgg tggcggtggc 1380
agcaacccaa tttgcaaggg atgcttaagc tgtagcaagg acaacggatg ttcacggtgc 1440
cagcaaaagc tgtttttctt cctccggcgg gaaggaatgc ggcagtacgg cgaatgtctc 1500
cactcctgcc cctcggggta ttacggacac cgcgcgcctg acatgaaccg atgcgccaga 1560
tgccggatcg agaactgcga tagctgccgc agcaaggacg cctgcactaa gtgcaaagtc 1620
ggcttctacc ttcaccgggg cagatgtttt gacgaatgcc cggatggctt cgccccgctg 1680
gaggagacta tggaatgcgt ggag 1704

<210> 253
<211> 568
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-10C22重链IgG2、RSPO2(F105R/F109A)多肽序列
<400> 253

Glu Val Gln Leu Val Glu Ser Gly Gly Asp Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met Ser Trp Val Arg Gln Thr Pro Asp Lys Arg Leu Glu Trp Val
35 40 45
Ala Ser Ile Ser Ser Gly Gly Ser Tyr Thr Tyr Tyr Pro Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Gln Asn Thr Leu Tyr
65 70 75 80

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Leu Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Val Arg His Glu Glu Tyr Gly Lys Ser Gly Phe Ala Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Ile Thr Val Ser Ala Ala Ser Thr Lys Gly Pro Ser Val
115 120 125
Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
130 135 140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190
Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys
195 200 205
Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val
210 215 220
Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe
225 230 235 240
Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255
Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270
Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285
Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val
290 295 300
Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320
Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335
Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350
Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365
Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380
Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp

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385 390 395 400
Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415
Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430
Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly
435 440 445
Gly Gly Ser Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Asn Pro Ile
450 455 460
Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys Ser Arg Cys
465 470 475 480
Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met Arg Gln Tyr
485 490 495
Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly His Arg Ala
500 505 510
Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp Ser
515 520 525
Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly Phe Tyr Leu
530 535 540
His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro Leu
545 550 555 560
Glu Glu Thr Met Glu Cys Val Glu
565

<210> 254
<211> 1695
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的RSPO2(F105R/F109A)、LP1-1N15重链IgG1 N297G多核苷酸序列
<400> 254
aacccaattt gcaagggatg cttaagctgt agcaaggaca acggatgttc acggtgccag 60
caaaagctgt ttttcttcct ccggcgggaa ggaatgcggc agtacggcga atgtctccac 120
tcctgcccct cggggtatta cggacaccgc gcgcctgaca tgaaccgatg cgccagatgc 180
cggatcgaga actgcgatag ctgccgcagc aaggacgcct gcactaagtg caaagtcggc 240
ttctaccttc accggggcag atgttttgac gaatgcccgg atggcttcgc cccgctggag 300
gagactatgg aatgcgtgga gggtggtggt ggctcgggat ccggaggctc cggtggcggt 360
ggcagcgagg tccagctgca acagtctgga cctgagctgg tgaagcctgg ggcttcagtg 420
aagatgtcct gtaaggcttc tggatacaca ttcactgact actacatgaa ctgggtgaag 480

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cagagtcatg gagagagcct tgagtggatt ggacgtgtta ttcctagcaa tggtggtact 540
aactacaacc agaagttcaa gggcaaggcc acattgacag tagacaaatc cctcaccaca 600
gcctacatgc agctcaacag cctgacatct gaagactctg cggtctattt ctgtgcaaga 660
gggatggact actggggtcc aggaacctca gtcaccgtct ccagcgctag caccaagggc 720
ccatcggtct tccccctggc accctcctcc aagagcacct ctgggggcac agcggccctg 780
ggctgcctgg tcaaggacta cttccccgaa ccggtgacgg tgtcgtggaa ctcaggcgcc 840
ctgaccagcg gcgtgcacac cttcccggct gtcctacagt cctcaggact ctactccctc 900
agcagcgtgg tgaccgtgcc ctccagcagc ttgggcaccc agacctacat ctgcaacgtg 960
aatcacaagc ccagcaacac caaggtggac aagaaagttg agcccaaatc ttgtgacaaa 1020
actcacacat gcccaccgtg cccagcacct gaactcctgg ggggaccgtc agtcttcctc 1080
ttccccccaa aacccaagga caccctcatg atctcccgga cccctgaggt cacatgcgtg 1140
gtggtggacg tgagccacga agaccctgag gtcaagttca actggtacgt ggacggcgtg 1200
gaggtgcata atgccaagac aaagccgcgg gaggagcagt acggcagcac gtaccgtgtg 1260
gtcagcgtcc tcaccgtcct gcaccaggac tggctgaatg gcaaggagta caagtgcaag 1320
gtctccaaca aagccctccc agcccccatc gagaaaacca tctccaaagc caaagggcag 1380
ccccgagaac cacaggtgta caccctgccc ccatcccggg aggagatgac caagaaccag 1440
gtcagcctga cctgcctggt caaaggcttc tatcccagcg acatcgccgt ggagtgggag 1500
agcaatgggc agccggagaa caactacaag accacgcctc ccgtgctgga ctccgacggc 1560
tccttcttcc tctacagcaa gctcaccgtg gacaagagca ggtggcagca ggggaacgtc 1620
ttctcatgct ccgtgatgca tgaggctctg cacaaccact acacgcagaa gagcctctcc 1680
ctgtctccgg gtaaa 1695

<210> 255
<211> 565
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的RSPO2(F105R/F109A)、LP1-1N15重链IgG1 N297G多肽序列
<400> 255

Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys
1 5 10 15
Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met
20 25 30
Arg Gln Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly
35 40 45
His Arg Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn
50 55 60
Cys Asp Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly
65 70 75 80

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Phe Tyr Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe
85 90 95
Ala Pro Leu Glu Glu Thr Met Glu Cys Val Glu Gly Gly Gly Gly Ser
100 105 110
Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Gln Gln
115 120 125
Ser Gly Pro Glu Leu Val Lys Pro Gly Ala Ser Val Lys Met Ser Cys
130 135 140
Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr Tyr Met Asn Trp Val Lys
145 150 155 160
Gln Ser His Gly Glu Ser Leu Glu Trp Ile Gly Arg Val Ile Pro Ser
165 170 175
Asn Gly Gly Thr Asn Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu
180 185 190
Thr Val Asp Lys Ser Leu Thr Thr Ala Tyr Met Gln Leu Asn Ser Leu
195 200 205
Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Gly Met Asp Tyr
210 215 220
Trp Gly Pro Gly Thr Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly
225 230 235 240
Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
245 250 255
Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
260 265 270
Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
275 280 285
Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
290 295 300
Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
305 310 315 320
Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
325 330 335
Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
340 345 350
Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
355 360 365
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
370 375 380
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val

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385 390 395 400
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser
405 410 415
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
420 425 430
Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
435 440 445
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
450 455 460
Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
465 470 475 480
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
485 490 495
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
500 505 510
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
515 520 525
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
530 535 540
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
545 550 555 560
Leu Ser Pro Gly Lys
565

<210> 256
<211> 1719
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的RSPO2(F105R/F109A)、LP1-1P13重链
IgG1 N297G多核苷酸序列
<400> 256
aacccaattt gcaagggatg cttaagctgt agcaaggaca acggatgttc acggtgccag 60
caaaagctgt ttttcttcct ccggcgggaa ggaatgcggc agtacggcga atgtctccac 120
tcctgcccct cggggtatta cggacaccgc gcgcctgaca tgaaccgatg cgccagatgc 180
cggatcgaga actgcgatag ctgccgcagc aaggacgcct gcactaagtg caaagtcggc 240
ttctaccttc accggggcag atgttttgac gaatgcccgg atggcttcgc cccgctggag 300
gagactatgg aatgcgtgga gggtggtggt ggctcgggat ccggaggctc cggtggcggt 360
ggcagcgagg ttcaactgca gcagtctgga cctgaactgg tgaagcctgg ggcttcagtg 420
aagatatcct gcaaggcttc tggttactca tttactgact actttatgaa ctgggtgaag 480

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cagagccatg gaaagagcct tgagtggatt ggacgtttta atcctttcaa tggtcaaact 540
ttctacaatc aggagttcaa gggcaaggcc acattaactg tagacaaatc ctctagcacc 600
gcccacatgg agctccggag cctgacatct gaggactctg cagtctatta ttgtgcaaga 660
agaggaaggt acgacgttta ctatgttctg gactactggg gtcaaggaac ctcagtcacc 720
gtctccagcg ctagcaccaa gggcccatcg gtcttccccc tggcaccctc ctccaagagc 780
acctctgggg gcacagcggc cctgggctgc ctggtcaagg actacttccc cgaaccggtg 840
acggtgtcgt ggaactcagg cgccctgacc agcggcgtgc acaccttccc ggctgtccta 900
cagtcctcag gactctactc cctcagcagc gtggtgaccg tgccctccag cagcttgggc 960
acccagacct acatctgcaa cgtgaatcac aagcccagca acaccaaggt ggacaagaaa 1020
gttgagccca aatcttgtga caaaactcac acatgcccac cgtgcccagc acctgaactc 1080
ctgggggggac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 1140
cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 1200
ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag 1260
cagtacggca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 1320
aatggcaagg agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa 1380
accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatcc 1440
cgggaggaga tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatccc 1500
agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg 1560
cctcccgtgc tggactccga cggctccttc ttcctctaca gcaagctcac cgtggacaag 1620
agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 1680
cactacacgc agaagagcct ctccctgtct ccgggtaaa 1719

<210> 257
<211> 573
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的RSPO2(F105R/F109A)、LP1-1P13重链 IgG1 N297G多肽序列
<400> 257

Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys
1 5 10 15
Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met
20 25 30
Arg Gln Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly
35 40 45
His Arg Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn
50 55 60
Cys Asp Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly
65 70 75 80

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Phe Tyr Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe
85 90 95
Ala Pro Leu Glu Glu Thr Met Glu Cys Val Glu Gly Gly Gly Gly Ser
100 105 110
Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Gln Gln
115 120 125
Ser Gly Pro Glu Leu Val Lys Pro Gly Ala Ser Val Lys Ile Ser Cys
130 135 140
Lys Ala Ser Gly Tyr Ser Phe Thr Asp Tyr Phe Met Asn Trp Val Lys
145 150 155 160
Gln Ser His Gly Lys Ser Leu Glu Trp Ile Gly Arg Phe Asn Pro Phe
165 170 175
Asn Gly Gln Thr Phe Tyr Asn Gln Glu Phe Lys Gly Lys Ala Thr Leu
180 185 190
Thr Val Asp Lys Ser Ser Ser Thr Ala His Met Glu Leu Arg Ser Leu
195 200 205
Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Arg Gly Arg Tyr
210 215 220
Asp Val Tyr Tyr Val Leu Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr
225 230 235 240
Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
245 250 255
Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
260 265 270
Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
275 280 285
Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
290 295 300
Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
305 310 315 320
Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
325 330 335
Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
340 345 350
Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
355 360 365
Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
370 375 380
Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys

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385 390 395 400
Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
405 410 415
Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu
420 425 430
Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
435 440 445
Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
450 455 460
Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
465 470 475 480
Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
485 490 495
Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
500 505 510
Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
515 520 525
Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
530 535 540
Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
545 550 555 560
His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
565 570

<210> 258
<211> 1728
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的RSPO2(F105R/F109A)、LP1-2I22重链IgG1 N297G多核苷酸序列
<400> 258
aacccaattt gcaagggatg cttaagctgt agcaaggaca acggatgttc acggtgccag 60
caaaagctgt ttttcttcct ccggcgggaa ggaatgcggc agtacggcga atgtctccac 120
tcctgcccct cggggtatta cggacaccgc gcgcctgaca tgaaccgatg cgccagatgc 180
cggatcgaga actgcgatag ctgccgcagc aaggacgcct gcactaagtg caaagtcggc 240
ttctaccttc accggggcag atgttttgac gaatgcccgg atggcttcgc cccgctggag 300
gagactatgg aatgcgtgga gggtggtggt ggctcgggat ccggaggctc cggtggcggt 360
ggcagcgagg tccaactcgt agaatcaggt ggtggtttgg tcaaaccagg tggctctcgg 420
aagttgtcct gtgctgcctc tggatttaca ttcagtgact acggtatgca ctgggtccgt 480

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caggctccag agaaggggct ggagtgggtt gcctacatta gtagtggcag tagtaccatc 540
tactatgcag acacagtgaa gggccgattc accatctcca gagacaatgc caagaacacc 600
ctgttcctac aaatgaccag tctaaggtct gaggacacag ccatgtatta ctgttcaagg 660
aagggagggt ttggtgacta cgagaaaagc tatgctatgg actactgggg tcaaggaacc 720
tcagtcaccg tctccagcgc tagcaccaag ggcccatcgg tcttcccccc ggcaccctcc 780
tccaagagca cctctggggg cacagcggcc ctgggctgcc tggtcaagga ctacttcccc 840
gaaccggtga cggtgtcgtg gaactcaggc gccctgacca gcggcgtgca caccttcccg 900
gctgtcctac agtcctcagg actctactcc ctcagcagcg tggtgaccgt gccctccagc 960
agcttgggca cccagaccta catctgcaac gtgaatcaca agcccagcaa caccaaggtg 1020
gacaagaaag ttgagcccaa atcttgtgac aaaactcaca catgcccacc gtgcccagca 1080
cctgaactcc tgggggggacc gtcagtcttc ctcttccccc caaaacccaa ggacaccctc 1140
atgatctccc ggacccctga ggtcacatgc gtggtggtgg acgtgagcca cgaagaccct 1200
gaggtcaagt tcaactggta cgtggacggc gtggaggtgc ataatgccaa gacaaagccg 1260
cgggaggagc agtacggcag cacgtaccgt gtggtcagcg tcctcaccgt cctgcaccag 1320
gactggctga atggcaagga gtacaagtgc aaggtctcca acaaagccct cccagccccc 1380
atcgagaaaa ccatctccaa agccaaaggg cagccccgag aaccacaggt gtacaccctg 1440
cccccatccc gggaggagat gaccaagaac caggtcagcc tgacctgcct ggtcaaaggc 1500
ttctatccca gcgacatcgc cgtggagtgg gagagcaatg ggcagccgga gaacaactac 1560
aagaccacgc ctcccgtgct ggactccgac ggctccttct tcctctacag caagctcacc 1620
gtggacaaga gcaggtggca gcaggggaac gtcttctcat gctccgtgat gcatgaggct 1680
ctgcacaacc actacacgca gaagagcctc tccctgtctc cgggtaaa 1728

<210> 259
<211> 576
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的RSPO2(F105R/F109A)、LP1-2I22重链IgG1 N297G多肽序列
<400> 259

Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys
1 5 10 15
Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met
20 25 30
Arg Gln Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly
35 40 45
His Arg Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn
50 55 60
Cys Asp Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly
65 70 75 80

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Phe Tyr Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe
85 90 95
Ala Pro Leu Glu Glu Thr Met Glu Cys Val Glu Gly Gly Gly Gly Ser
100 105 110
Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu
115 120 125
Ser Gly Gly Gly Leu Val Lys Pro Gly Gly Ser Arg Lys Leu Ser Cys
130 135 140
Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr Gly Met His Trp Val Arg
145 150 155 160
Gln Ala Pro Glu Lys Gly Leu Glu Trp Val Ala Tyr Ile Ser Ser Gly
165 170 175
Ser Ser Thr Ile Tyr Tyr Ala Asp Thr Val Lys Gly Arg Phe Thr Ile
180 185 190
Ser Arg Asp Asn Ala Lys Asn Thr Leu Phe Leu Gln Met Thr Ser Leu
195 200 205
Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys Ser Arg Lys Gly Gly Phe
210 215 220
Gly Asp Tyr Glu Lys Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr
225 230 235 240
Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
245 250 255
Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
260 265 270
Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
275 280 285
Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
290 295 300
Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
305 310 315 320
Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
325 330 335
Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
340 345 350
His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
355 360 365
Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
370 375 380
Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro

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385 390 395 400
Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
405 410 415
Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Val Val
420 425 430
Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
435 440 445
Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
450 455 460
Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
465 470 475 480
Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
485 490 495
Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
500 505 510
Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
515 520 525
Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
530 535 540
Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
545 550 555 560
Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
565 570 575

<210> 260
<211> 1719
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的RSPO2(F105R/F109A)、LP1-2I22重链IgG1 N297G多核苷酸序列
<400> 260
aacccaattt gcaagggatg cttaagctgt agcaaggaca acggatgttc acggtgccag 60
caaaagctgt ttttcttcct ccggcgggaa ggaatgcggc agtacggcga atgtctccac 120
tcctgcccct cggggtatta cggacaccgc gcgcctgaca tgaaccgatg cgccagatgc 180
cggatcgaga actgcgatag ctgccgcagc aaggacgcct gcactaagtg caaagtcggc 240
ttctaccttc accggggcag atgttttgac gaatgcccgg atggcttcgc cccgctggag 300
gagactatgg aatgcgtgga gggtggtggt ggctcgggat ccggaggctc cggtggcggt 360
ggcagcgagg ttcaactgca gcagtctgga cctgaactgg tgaagcctgg ggcttcagtg 420
aagatatcct gcaaggcttc tggttactca tttactggct actttatgaa ctgggtgaag 480

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cagagccatg gaaagagcct tgagtggatt ggacgtttta atcctttcaa tggtcaaact 540
ttctacaatc aggagttcaa gggcaaggcc acattaactg ttgacaaatc ctctgacacc 600
gcccacatgg aactccggag cctgacatct gaggactctg cagtctatta ttgtgcaaga 660
agaggaaggt acgacgttta ctatgctctg gactactggg gtcaaggaac ctcagtcacc 720
gtctccagcg ctagcaccaa gggcccatcg gtcttccccc tggcaccctc ctccaagagc 780
acctctgggg gcacagcggc cctgggctgc ctggtcaagg actacttccc cgaaccggtg 840
acggtgtcgt ggaactcagg cgccctgacc agcggcgtgc acaccttccc ggctgtccta 900
cagtcctcag gactctactc cctcagcagc gtggtgaccg tgccctccag cagcttgggc 960
acccagacct acatctgcaa cgtgaatcac aagcccagca acaccaaggt ggacaagaaa 1020
gttgagccca aatcttgtga caaaactcac acatgcccac cgtgcccagc acctgaactc 1080
ctgggggggac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 1140
cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 1200
ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag 1260
cagtacggca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 1320
aatggcaagg agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa 1380
accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatcc 1440
cgggaggaga tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatccc 1500
agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg 1560
cctcccgtgc tggactccga cggctccttc ttcctctaca gcaagctcac cgtggacaag 1620
agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 1680
cactacacgc agaagagcct ctccctgtct ccgggtaaa 1719

<210> 261
<211> 573
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的RSPO2(F105R/F109A)、LP1-2I22重链IgG1 N297G多肽序列
<400> 261

Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys
1 5 10 15
Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met
20 25 30
Arg Gln Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly
35 40 45
His Arg Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn
50 55 60
Cys Asp Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly
65 70 75 80

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Phe Tyr Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe
85 90 95
Ala Pro Leu Glu Glu Thr Met Glu Cys Val Glu Gly Gly Gly Gly Ser
100 105 110
Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Gln Gln
115 120 125
Ser Gly Pro Glu Leu Val Lys Pro Gly Ala Ser Val Lys Ile Ser Cys
130 135 140
Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr Phe Met Asn Trp Val Lys
145 150 155 160
Gln Ser His Gly Lys Ser Leu Glu Trp Ile Gly Arg Phe Asn Pro Phe
165 170 175
Asn Gly Gln Thr Phe Tyr Asn Gln Glu Phe Lys Gly Lys Ala Thr Leu
180 185 190
Thr Val Asp Lys Ser Ser Asp Thr Ala His Met Glu Leu Arg Ser Leu
195 200 205
Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Arg Gly Arg Tyr
210 215 220
Asp Val Tyr Tyr Ala Leu Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr
225 230 235 240
Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
245 250 255
Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
260 265 270
Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
275 280 285
Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
290 295 300
Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
305 310 315 320
Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
325 330 335
Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
340 345 350
Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
355 360 365
Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
370 375 380
Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys

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385 390 395 400
Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
405 410 415
Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu
420 425 430
Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
435 440 445
Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
450 455 460
Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
465 470 475 480
Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
485 490 495
Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
500 505 510
Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
515 520 525
Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
530 535 540
Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
545 550 555 560
His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
565 570

<210> 262
<211> 1695
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的RSPO2(F105R/F109A)、LP1-3A24重链IgG1 N297G多核苷酸序列
<400> 262
aacccaattt gcaagggatg cttaagctgt agcaaggaca acggatgttc acggtgccag 60
caaaagctgt ttttcttcct ccggcgggaa ggaatgcggc agtacggcga atgtctccac 120
tcctgcccct cggggtatta cggacaccgc gcgcctgaca tgaaccgatg cgccagatgc 180
cggatcgaga actgcgatag ctgccgcagc aaggacgcct gcactaagtg caaagtcggc 240
ttctaccttc accggggcag atgttttgac gaatgcccgg atggcttcgc cccgctggag 300
gagactatgg aatgcgtgga gggtggtggt ggctcgggat ccggaggctc cggtggcggt 360
ggcagcgagg tccagctgca acagtctgga cctgagctgg tgaagcctgg ggcttcagtg 420
aagatgtcct gtaaggcttc tggatacaca ttcactgact actacataaa ctgggtgagg 480

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cagagtcatg gaaagagcct tgagtggatt ggacgtgtta ttcctagcaa tggtggtagt 540
aactacaacc agaagttcaa gggcaaggcc acattgacag tagacaaatc cctcagtaca 600
gcctacatgc acctcaacag cctgacatct gaggactctg cggtctatta ctgtgcaacc 660
cagctgggac ggtggggcca agggactctg gtcactgtct ctgcagctag caccaagggc 720
ccatcggtct tccccctggc accctcctcc aagagcacct ctgggggcac agcggccctg 780
ggctgcctgg tcaaggacta cttccccgaa ccggtgacgg tgtcgtggaa ctcaggcgcc 840
ctgaccagcg gcgtgcacac cttcccggct gtcctacagt cctcaggact ctactccctc 900
agcagcgtgg tgaccgtgcc ctccagcagc ttgggcaccc agacctacat ctgcaacgtg 960
aatcacaagc ccagcaacac caaggtggac aagaaagttg agcccaaatc ttgtgacaaa 1020
actcacacat gcccaccgtg cccagcacct gaactcctgg ggggaccgtc agtcttcctc 1080
ttccccccaa aacccaagga caccctcatg atctcccgga cccctgaggt cacatgcgtg 1140
gtggtggacg tgagccacga agaccctgag gtcaagttca actggtacgt ggacggcgtg 1200
gaggtgcata atgccaagac aaagccgcgg gaggagcagt acggcagcac gtaccgtgtg 1260
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gtctccaaca aagccctccc agcccccatc gagaaaacca tctccaaagc caaagggcag 1380
ccccgagaac cacaggtgta caccctgccc ccatcccggg aggagatgac caagaaccag 1440
gtcagcctga cctgcctggt caaaggcttc tatcccagcg acatcgccgt ggagtgggag 1500
agcaatgggc agccggagaa caactacaag accacgcctc ccgtgctgga ctccgacggc 1560
tccttcttcc tctacagcaa gctcaccgtg gacaagagca ggtggcagca ggggaacgtc 1620
ttctcatgct ccgtgatgca tgaggctctg cacaaccact acacgcagaa gagcctctcc 1680
ctgtctccgg gtaaa 1695

<210> 263
<211> 565
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的RSPO2(F105R/F109A)、LP1-3A24重链 IgG1 N297G多肽序列
<400> 263

Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys
1 5 10 15
Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met
20 25 30
Arg Gln Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly
35 40 45
His Arg Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn
50 55 60
Cys Asp Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly
65 70 75 80

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Phe Tyr Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe
85 90 95
Ala Pro Leu Glu Glu Thr Met Glu Cys Val Glu Gly Gly Gly Gly Ser
100 105 110
Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Gln Gln
115 120 125
Ser Gly Pro Glu Leu Val Lys Pro Gly Ala Ser Val Lys Met Ser Cys
130 135 140
Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr Tyr Ile Asn Trp Val Arg
145 150 155 160
Gln Ser His Gly Lys Ser Leu Glu Trp Ile Gly Arg Val Ile Pro Ser
165 170 175
Asn Gly Gly Ser Asn Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu
180 185 190
Thr Val Asp Lys Ser Leu Ser Thr Ala Tyr Met His Leu Asn Ser Leu
195 200 205
Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Thr Gln Leu Gly Arg
210 215 220
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Ala Ser Thr Lys Gly
225 230 235 240
Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
245 250 255
Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
260 265 270
Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
275 280 285
Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
290 295 300
Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
305 310 315 320
Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
325 330 335
Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
340 345 350
Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
355 360 365
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
370 375 380
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val

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385 390 395 400
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser
405 410 415
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
420 425 430
Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
435 440 445
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
450 455 460
Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
465 470 475 480
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
485 490 495
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
500 505 510
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
515 520 525
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
530 535 540
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
545 550 555 560
Leu Ser Pro Gly Lys
565

<210> 264
<211> 1719
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的RSPO2(F105R/F109A)、LP1-3E20重链IgG1 N297G多核苷酸序列
<400> 264
aacccaattt gcaagggatg cttaagctgt agcaaggaca acggatgttc acggtgccag 60
caaaagctgt ttttcttcct ccggcgggaa ggaatgcggc agtacggcga atgtctccac 120
tcctgcccct cggggtatta cggacaccgc gcgcctgaca tgaaccgatg cgccagatgc 180
cggatcgaga actgcgatag ctgccgcagc aaggacgcct gcactaagtg caaagtcggc 240
ttctaccttc accggggcag atgttttgac gaatgcccgg atggcttcgc cccgctggag 300
gagactatgg aatgcgtgga gggtggtggt ggctcgggat ccggaggctc cggtggcggt 360
ggcagccagg tccaactgca gcagtctggg gctgaactgg caaaacctgg ggcctcagtg 420
aagatgtcct gcaaggcttc tggctacacc tttactagct actggataca ctgggtaaaa 480

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cagaggcctg gacagggtct ggaatggatt ggatacatta atcctagcag tggttatgct 540
gagtacaatc agaagttcaa ggtcagggcc acattgactg cagacaaatc ctccagcaca 600
gcctacatgc aactaagcag cctgacatct gaggactctg cagtctatta ctgtgcaaga 660
gaaagttact atagtttcga ctatactatg gactactggg gtcaaggaac ctcagtcacc 720
gtctccagcg ctagcaccaa gggcccatcg gtcttccccc tggcaccctc ctccaagagc 780
acctctgggg gcacagcggc cctgggctgc ctggtcaagg actacttccc cgaaccggtg 840
acggtgtcgt ggaactcagg cgccctgacc agcggcgtgc acaccttccc ggctgtccta 900
cagtcctcag gactctactc cctcagcagc gtggtgaccg tgccctccag cagcttgggc 960
acccagacct acatctgcaa cgtgaatcac aagcccagca acaccaaggt ggacaagaaa 1020
gttgagccca aatcttgtga caaaactcac acatgcccac cgtgcccagc acctgaactc 1080
ctgggggggac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 1140
cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 1200
ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag 1260
cagtacggca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 1320
aatggcaagg agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa 1380
accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatcc 1440
cgggaggaga tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatccc 1500
agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg 1560
cctcccgtgc tggactccga cggctccttc ttcctctaca gcaagctcac cgtggacaag 1620
agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 1680
cactacacgc agaagagcct ctccctgtct ccgggtaaa 1719

<210> 265
<211> 573
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的RSPO2(F105R/F109A)、LP1-3E20重链IgG1 N297G多肽序列
<400> 265

Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys
1 5 10 15
Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met
20 25 30
Arg Gln Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly
35 40 45
His Arg Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn
50 55 60
Cys Asp Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly
65 70 75 80

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Phe Tyr Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe
85 90 95
Ala Pro Leu Glu Glu Thr Met Glu Cys Val Glu Gly Gly Gly Gly Ser
100 105 110
Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Gln
115 120 125
Ser Gly Ala Glu Leu Ala Lys Pro Gly Ala Ser Val Lys Met Ser Cys
130 135 140
Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Trp Ile His Trp Val Lys
145 150 155 160
Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser
165 170 175
Ser Gly Tyr Ala Glu Tyr Asn Gln Lys Phe Lys Val Arg Ala Thr Leu
180 185 190
Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu
195 200 205
Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Glu Ser Tyr Tyr
210 215 220
Ser Phe Asp Tyr Thr Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr
225 230 235 240
Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
245 250 255
Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
260 265 270
Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
275 280 285
Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
290 295 300
Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
305 310 315 320
Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
325 330 335
Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
340 345 350
Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
355 360 365
Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
370 375 380
Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys

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385 390 395 400
Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
405 410 415
Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu
420 425 430
Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
435 440 445
Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
450 455 460
Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
465 470 475 480
Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
485 490 495
Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
500 505 510
Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
515 520 525
Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
530 535 540
Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
545 550 555 560
His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
565 570

<210> 266
<211> 1701
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的RSPO2(F105R/F109A)、LP1-7B13重链IgG1 N297G多核苷酸序列
<400> 266
aacccaattt gcaagggatg cttaagctgt agcaaggaca acggatgttc acggtgccag 60
caaaagctgt ttttcttcct ccggcgggaa ggaatgcggc agtacggcga atgtctccac 120
tcctgcccct cggggtatta cggacaccgc gcgcctgaca tgaaccgatg cgccagatgc 180
cggatcgaga actgcgatag ctgccgcagc aaggacgcct gcactaagtg caaagtcggc 240
ttctaccttc accggggcag atgttttgac gaatgcccgg atggcttcgc cccgctggag 300
gagactatgg aatgcgtgga gggtggtggt ggctcgggat ccggaggctc cggtggcggt 360
ggcagcgagg tccagctgca acaatctgga cctgaggtgg tgaagcctgg ggcttcagtg 420
aagatgtcct gtaagacttc tggattcaca ttcactgact actacatgaa ctgggtgaag 480

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cagggtcatg gaaagagcct tgagtggatt ggacgtgtta atcctagcaa tgatgatact 540
aggtacaatc agaagttcaa gggaaaggcc acattgacag tagacaagtc cctcagcaca 600
gcctacatgc agctcaacag cctgacatct gaggactctg cggtctatta ctgtacaagg 660
tggttctact ttgactactg gggccaaggc actactctca cagtctccag cgctagcacc 720
aagggcccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg 780
gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca 840
ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac 900
tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc 960
aacgtgaatc acaagcccag caacaccaag gtggacaaga aagttgagcc caaatcttgt 1020
gacaaaactc acacatgccc accgtgccca gcacctgaac tcctgggggg accgtcagtc 1080
ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca 1140
tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac 1200
ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacgg cagcacgtac 1260
cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag 1320
tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa 1380
gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag 1440
aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag 1500
tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc 1560
gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1620
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1680
ctctccctgt ctccgggtaa a 1701

<210> 267
<211> 567
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的RSPO2(F105R/F109A)、LP1-7B13重链IgG1 N297G多肽序列
<400> 267

Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys
1 5 10 15
Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met
20 25 30
Arg Gln Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly
35 40 45
His Arg Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn
50 55 60
Cys Asp Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly
65 70 75 80

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Phe Tyr Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe
85 90 95
Ala Pro Leu Glu Glu Thr Met Glu Cys Val Glu Gly Gly Gly Gly Ser
100 105 110
Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Gln Gln
115 120 125
Ser Gly Pro Glu Val Val Lys Pro Gly Ala Ser Val Lys Met Ser Cys
130 135 140
Lys Thr Ser Gly Phe Thr Phe Thr Asp Tyr Tyr Met Asn Trp Val Lys
145 150 155 160
Gln Gly His Gly Lys Ser Leu Glu Trp Ile Gly Arg Val Asn Pro Ser
165 170 175
Asn Asp Asp Thr Arg Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu
180 185 190
Thr Val Asp Lys Ser Leu Ser Thr Ala Tyr Met Gln Leu Asn Ser Leu
195 200 205
Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Thr Arg Trp Phe Tyr Phe
210 215 220
Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr
225 230 235 240
Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
245 250 255
Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
260 265 270
Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
275 280 285
Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
290 295 300
Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
305 310 315 320
Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
325 330 335
Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
340 345 350
Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
355 360 365
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
370 375 380
Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp

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385 390 395 400
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
405 410 415
Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
420 425 430
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
435 440 445
Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
450 455 460
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
465 470 475 480
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
485 490 495
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
500 505 510
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
515 520 525
Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
530 535 540
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
545 550 555 560
Leu Ser Leu Ser Pro Gly Lys
565

<210> 268
<211> 708
<212> DNA
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的RSPO2(F105R/F109A)、LP1-8M24重链IgG1 N297G多核苷酸序列
<400> 268
caggttcagc tgcagcagtc tggagctgag ctggcgaggc ctggggcttc agtgaagctg 60
tcctgcaagg cttctggcta caccttcaca aattatggta taaactgggt gaagcagaga 120
actggacagg gccttgagtg gattggagag atttttccta gaagtgataa tactttctac 180
aatgagaagt tcaagggcaa ggccacactg actgcagaca aatcctccac cacagcgtac 240
atggagctcc gcagcctgac atctgaggac tctgcggtct atttctgtgc aagaaaaggc 300
agggactacg gtactagcca ctactttgac tactggggtc aaggcaccac tctcacagtc 360
tccagcgcta gcaccaaggg cccatcggtc ttcccccctgg caccctcctc caagagcacc 420
tctgggggca cagcggccct gggctgcctg gtcaaggact acttccccga accggtgacg 480

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gtgtcgtgga actcaggcgc cctgaccagc ggcgtgcaca ccttcccggc tgtcctacag 540
tcctcaggac tctactccct cagcagcgtg gtgaccgtgc cctccagcag cttgggcacc 600
cagacctaca tctgcaacgt gaatcacaag cccagcaaca ccaaggtgga caagaaagtt 660
gagcccaaat cttgtggatc cggctccgga catcatcatc accatcac 708

<210> 269
<211> 236
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的RSPO2(F105R/F109A)、LP1-8M24重链IgG1 N297G多肽序列
<400> 269

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala
1 5 10 15
Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30
Gly Ile Asn Trp Val Lys Gln Arg Thr Gly Gln Gly Leu Glu Trp Ile
35 40 45
Gly Glu Ile Phe Pro Arg Ser Asp Asn Thr Phe Tyr Asn Glu Lys Phe
50 55 60
Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Thr Thr Ala Tyr
65 70 75 80
Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
85 90 95
Ala Arg Lys Gly Arg Asp Tyr Gly Thr Ser His Tyr Phe Asp Tyr Trp
100 105 110
Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125
Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
130 135 140
Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145 150 155 160
Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
165 170 175
Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190
Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
195 200 205
His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser

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210 215 220

Cys Gly Ser Gly Ser Gly His His His His His His

225 230 235

<210> 270

<211> 1698

<212> DNA

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的合成的RSPO2(F105R/F109A)、LP1-9M16重链IgG1 N297G多核苷酸序列

<400> 270

aacccaattt gcaagggatg cttaagctgt agcaaggaca acggatgttc acggtgccag 60
caaaagctgt ttttcttcct ccggcgggaa ggaatgcggc agtacggcga atgtctccac 120
tcctgcccct cggggtatta cggacaccgc gcgcctgaca tgaaccgatg cgccagatgc 180
cggatcgaga actgcgatag ctgccgcagc aaggacgcct gcactaagtg caaagtcggc 240
ttctaccttc accggggcag atgttttgac gaatgcccgg atggcttcgc cccgctggag 300
gagactatgg aatgcgtgga gggtggtggt ggctcgggat ccggaggctc cggtggcggt 360
ggcagcgagg tccagctgca acagtctgga cctgagctgg tgaagcctgg ggcttcagtg 420
aagatgtcct gtaaggcttc tggatacaca ttcactgact actacatgaa ctgggtgaag 480
cagagtcatg gaaagagcct tgagtggatt ggacgtgtta atcctaacaa tggtggttct 540
aactacaacc agaaattcaa gggcaaggcc acattgacag tagacaaatc cctcagcaca 600
gcctacatgc agctcaacag cctgacatct gaggactctg cggtctatta ctgtgcaagt 660
cgaaacttcg atgtctgggg cgcagggacc acggtcaccg tctccagcgc tagcaccaag 720
ggcccatcgg tcttcccccc ggcaccctcc tccaagagca cctctggggg cacagcggcc 780
ctgggctgcc tggtcaagga ctacttcccc gaaccggtga cggtgtcgtg gaactcaggc 840
gccctgacca gcggcgtgca caccttcccg gctgtcctac agtcctcagg actctactcc 900
ctcagcagcg tggtgaccgt gccctccagc agcttgggca cccagaccta catctgcaac 960
gtgaatcaca agcccagcaa caccaaggtg gacaagaaag ttgagcccaa atcttgtgac 1020
aaaactcaca catgcccacc gtgcccagca cctgaactcc tgggggggacc gtcagtcttc 1080
ctcttccccc caaaacccaa ggacaccctc atgatctccc ggacccctga ggtcacatgc 1140
gtggtggtgg acgtgagcca cgaagaccct gaggtcaagt tcaactggta cgtggacggc 1200
gtggaggtgc ataatgccaa gacaaagccg cgggaggagc agtacggcag cacgtaccgt 1260
gtggtcagcg tcctcaccgt cctgcaccag gactggctga atggcaagga gtacaagtgc 1320
aaggtctcca acaaagccct cccagccccc atcgagaaaa ccatctccaa agccaaaggg 1380
cagccccgag aaccacaggt gtacaccctg cccccatccc gggaggagat gaccaagaac 1440
caggtcagcc tgacctgcct ggtcaaaggc ttctatccca gcgacatcgc cgtggagtgg 1500
gagagcaatg ggcagccgga gaacaactac aagaccacgc ctcccgtgct ggactccgac 1560
ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac 1620
gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 1680

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tccctgtctc cgggtaaa 1698

<210> 271

<211> 566

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的合成的RSPO2(F105R/F109A)、LP1-9M16重链IgG1 N297G多肽序列

<400> 271

```
Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys Asp Asn Gly Cys
1               5                  10                  15
Ser Arg Cys Gln Gln Lys Leu Phe Phe Phe Leu Arg Arg Glu Gly Met
            20                  25                  30
Arg Gln Tyr Gly Glu Cys Leu His Ser Cys Pro Ser Gly Tyr Tyr Gly
        35                  40                  45
His Arg Ala Pro Asp Met Asn Arg Cys Ala Arg Cys Arg Ile Glu Asn
    50                  55                  60
Cys Asp Ser Cys Arg Ser Lys Asp Ala Cys Thr Lys Cys Lys Val Gly
65                  70                  75                  80
Phe Tyr Leu His Arg Gly Arg Cys Phe Asp Glu Cys Pro Asp Gly Phe
                85                  90                  95
Ala Pro Leu Glu Glu Thr Met Glu Cys Val Glu Gly Gly Gly Gly Ser
            100                 105                 110
Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Gln Gln
        115                 120                 125
Ser Gly Pro Glu Leu Val Lys Pro Gly Ala Ser Val Lys Met Ser Cys
    130                 135                 140
Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr Tyr Met Asn Trp Val Lys
145                 150                 155                 160
Gln Ser His Gly Lys Ser Leu Glu Trp Ile Gly Arg Val Asn Pro Asn
                165                 170                 175
Asn Gly Gly Ser Asn Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu
            180                 185                 190
Thr Val Asp Lys Ser Leu Ser Thr Ala Tyr Met Gln Leu Asn Ser Leu
        195                 200                 205
Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Ser Arg Asn Phe Asp
    210                 215                 220
Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys
225                 230                 235                 240
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Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
245 250 255
Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
260 265 270
Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
275 280 285
Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
290 295 300
Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn
305 310 315 320
Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro
325 330 335
Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
340 345 350
Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
355 360 365
Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
370 375 380
Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
385 390 395 400
Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly
405 410 415
Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
420 425 430
Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
435 440 445
Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
450 455 460
Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
465 470 475 480
Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
485 490 495
Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
500 505 510
Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
515 520 525
Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
530 535 540
Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu

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545 550 555 560

Ser Leu Ser Pro Gly Lys

565

<210> 272

<211> 1338

<212> DNA

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的合成的抗ASGR1重链多核苷酸序列

<400> 272

gaagtgcagc tgctggaatc cgggggcgga ctggtgcaac ccgggggatc cctcagactg 60
tcctgtgccg catcgggttt cactttctcc tcctacgcga tgtcatgggt cagacaggcc 120
cctggaaaag gcctcgaatg ggtgtcggct atctccggat cgggggggatc tacttactac 180
gccgactccg tgaagggccg gttcactatc tcgagggaca actccaagaa taccctgtac 240
ttgcaaatga actccctgcg cgccgaggat accgcggtgt attactgcgc caaggacttc 300
agctcacgcc ggtggtacct tgagtactgg ggacagggaa cccttgtcac cgtgtcgagt 360
gctagcacca agggcccatc ggtcttcccc ctggcgccct gctccaggag cacctccgag 420
agcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg 480
tggaactcag gcgctctgac cagcggcgtg cacaccttcc cagctgtcct acagtcctca 540
ggactctact ccctcagcag cgtggtgacc gtgccctcca gcaacttcgg cacccagacc 600
tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagac agttgagcgc 660
aaatgttgtg tcgagtgccc accgtgccca gcaccacctg tggcaggacc gtcagtcttc 720
ctcttccccc caaaacccaa ggacaccctc atgatctccc ggacccctga ggtcacgtgc 780
gtggtggtgg acgtgagcca cgaagacccc gaggtccagt tcaactggta cgtggacggc 840
gtggaggtgc ataatgccaa gacaaagcca cgggaggagc agttcaacag cacgttccgt 900
gtggtcagcg tcctcaccgt tgtgcaccag gactggctga acggcaagga gtacaagtgc 960
aaggtctcca acaaaggcct cccagccccc atcgagaaaa ccatctccaa aaccaaaggg 1020
cagccccgag aaccacaggt gtacaccctg cccccatccc gggaggagat gaccaagaac 1080
caggtcagcc tgacctgcct ggtcaaaggc ttctacccca gcgacatcgc cgtggagtgg 1140
gagagcaatg ggcagccgga gaacaactac aagaccacgc ctcccatgct ggactccgac 1200
ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac 1260
gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 1320
tccctgtctc cgggtaaa 1338

<210> 273

<211> 446

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的合成的抗ASGR1重链多肽序列

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<400> 273

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Asp Phe Ser Ser Arg Arg Trp Tyr Leu Glu Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125
Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
130 135 140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190
Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys
195 200 205
Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val
210 215 220
Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe
225 230 235 240
Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255
Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270
Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285
Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val
290 295 300

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Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320
Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335
Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350
Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365
Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380
Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp
385 390 395 400
Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415
Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430
Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 274
<211> 112
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-1F8 VL多肽序列
<400> 274

Asp Ile Val Met Ser Gln Ser Pro Ser Ser Leu Ala Val Ser Ala Gly
1 5 10 15
Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Phe Asn Ser
20 25 30
Arg Thr Arg Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45
Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60
Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80
Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Lys Gln
85 90 95
Ser Tyr Tyr Leu Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105 110

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<210> 275
<211> 121
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-1F8 VH多肽序列
<400> 275

Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30
Thr Met Ser Trp Val Arg Gln Thr Pro Ala Lys Arg Leu Glu Trp Val
35 40 45
Ala Thr Ile Ser Ser Ile Gly Val Asn Thr Tyr Tyr Pro Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Leu Tyr
65 70 75 80
Leu Gln Val Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg His Val Asp Tyr Tyr Asp Gly Ile Ser Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Thr Leu Thr Val Ser Ser
115 120

<210> 276
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-1N15 VL多肽序列
<400> 276

Asp Ile Lys Met Thr Gln Ser Pro Ser Ser Met Tyr Ala Ser Leu Gly
1 5 10 15
Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile Asn Ser His
20 25 30
Leu Ser Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
35 40 45
Ile Arg Ala Asn Arg Leu Val Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Pro Glu Tyr

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65 70 75 80
Glu Glu Met Gly Ile Tyr Tyr Cys Leu Gln Tyr Asp Glu Phe Pro Phe
85 90 95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 277
<211> 113
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-1N15 VH多肽序列
<400> 277
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30
Tyr Met Asn Trp Val Lys Gln Ser His Gly Glu Ser Leu Glu Trp Ile
35 40 45
Gly Arg Val Ile Pro Ser Asn Gly Gly Thr Asn Tyr Asn Gln Lys Phe
50 55 60
Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Leu Thr Thr Ala Tyr
65 70 75 80
Met Gln Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
85 90 95
Ala Arg Gly Met Asp Tyr Trp Gly Pro Gly Thr Ser Val Thr Val Ser
100 105 110
Ser

<210> 278
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-1P13 VL多肽序列
<400> 278
Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Gln Thr Val Ile Ile Thr Cys Arg Thr Ser Glu Asn Ile Tyr Ser Asn
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro Gln Leu Leu Val

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35 40 45
Tyr Ala Ala Thr Asn Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Gln Tyr Tyr Leu Lys Ile Asn Ser Leu Gln Ser
65 70 75 80
Glu Asp Phe Gly Ser Tyr Tyr Cys Gln His Phe Trp Gly Ser Thr Trp
85 90 95
Thr Phe Gly Gly Gly Thr Lys Leu Asp Ile Lys
100 105

<210> 279
<211> 121
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-1P13 VH多肽序列
<400> 279
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Asp Tyr
20 25 30
Phe Met Asn Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45
Gly Arg Phe Asn Pro Phe Asn Gly Gln Thr Phe Tyr Asn Gln Glu Phe
50 55 60
Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala His
65 70 75 80
Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Arg Gly Arg Tyr Asp Val Tyr Tyr Val Leu Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 280
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-1P5 VL多肽序列
<400> 280

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Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15
Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn Val Gly Thr Asn
20 25 30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Ala Leu Ile
35 40 45
Tyr Ser Ala Ser Tyr Arg Tyr Ser Gly Val Pro Asp Arg Phe Thr Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser
65 70 75 80
Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
85 90 95
Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 281
<211> 120
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-1P5 VH多肽序列
<400> 281
Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Arg Pro Gly Thr
1 5 10 15
Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Leu Thr Tyr
20 25 30
Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45
Gly Gln Ile Phe Pro Ala Thr Gly Ile Thr Tyr Tyr Ser Glu Met Phe
50 55 60
Lys Asp Lys Ala Thr Leu Thr Glu Asp Thr Ser Ser Thr Thr Ala Tyr
65 70 75 80
Met Gln Leu Ser Ser Leu Thr Ser Glu Ala Thr Ala Val Tyr Phe Cys
85 90 95
Ala Arg Arg Arg Ala Tyr His Ser Asn Phe Phe Asp Tyr Trp Gly Gln
100 105 110
Gly Thr Thr Leu Thr Val Ser Ser
115 120

<210> 282
<211> 112

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<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-2E12 VL多肽序列
<400> 282

Asp Val Val Val Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Phe Gly
1 5 10 15
Asp Arg Val Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Ala Asn Ser
20 25 30
Tyr Gly Asn Thr Tyr Leu Ser Trp Tyr Leu His Lys Pro Gly Gln Ser
35 40 45
Pro Gln Leu Leu Ile Tyr Gly Ile Ser Asn Arg Phe Ser Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80
Ser Thr Ile Lys Pro Glu Asp Leu Gly Met Tyr Tyr Cys Leu Gln Gly
85 90 95
Thr His Gln Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105 110

<210> 283
<211> 115
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-2E12 VH多肽序列
<400> 283

Asp Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15
Ser Leu Ser Leu Thr Cys Ser Val Thr Gly Tyr Ser Ile Thr Ser Gly
20 25 30
Tyr Tyr Trp Asn Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu Trp
35 40 45
Met Gly Ser Ile Gly Tyr Asp Asp Thr Asn His Tyr Asn Pro Ser Leu
50 55 60
Lys Asn Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe Phe
65 70 75 80
Leu Lys Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys
85 90 95
Ala Gly Asp Tyr Pro Phe Ala Phe Trp Gly Gln Gly Thr Leu Val Thr

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100 105 110

Val Ser Ala
115

<210> 284
<211> 106
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-2I13 VL多肽序列
<400> 284

Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Glu Thr Val Thr Ile Thr Cys Arg Ala Ser Glu Asn Ile Tyr Ser Tyr
20 25 30
Leu Val Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro Gln Leu Leu Val
35 40 45
Tyr Asn Ala Lys Thr Leu Ala Glu Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Gln Phe Ser Leu Lys Ile Asn Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Gly Ser Tyr Tyr Cys Gln His His Tyr Gly Thr Trp Thr
85 90 95
Phe Gly Gly Gly Ile Lys Leu Glu Ile Lys
100 105

<210> 285
<211> 124
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-2I13 VH多肽序列
<400> 285

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Arg Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
35 40 45
Ala Tyr Ile Ser Ser Gly Ser Ser Thr Ile Tyr Tyr Ala Asp Thr Val
50 55 60

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Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Phe
65 70 75 80
Leu Gln Met Thr Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ser Arg Lys Gly Gly Phe Gly Asp Tyr Glu Lys Ser Tyr Ala Met Asp
100 105 110
Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 286
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-2I22 VL多肽序列
<400> 286

Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Glu Thr Val Ile Ile Thr Cys Arg Ala Ser Glu Asn Ile Tyr Ser Asn
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro Gln Leu Leu Val
35 40 45
Tyr Gly Ala Thr Asn Leu Ala Asp Gly Val Thr Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Gln Phe Ser Leu Lys Ile Asp Ser Leu Gln Ser
65 70 75 80
Glu Asp Phe Gly Ser Tyr Tyr Cys Gln His Phe Trp Gly Thr Thr Trp
85 90 95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 287
<211> 121
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-2I22 VH多肽序列
<400> 287

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr

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20 25 30

Phe Met Asn Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Arg Phe Asn Pro Phe Asn Gly Gln Thr Phe Tyr Asn Gln Glu Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Asp Thr Ala His
65 70 75 80

Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Gly Arg Tyr Asp Val Tyr Tyr Ala Leu Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 288
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-3A24 VL多肽序列
<400> 288

Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn Val Gly Ser Asn
20 25 30

Val Ala Trp Phe Gln Gln Lys Pro Gly Gln Ser Pro Lys Ala Leu Ile
35 40 45

Tyr Ser Ser Ser Tyr Arg Tyr Ser Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr Asn Val Gln Ser
65 70 75 80

Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln Tyr Asn Ser Phe Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 289
<211> 113
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>

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<223> 在实验室中制备的合成的LP1-3A24 VH多肽序列
<400> 289
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30
Tyr Ile Asn Trp Val Arg Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45
Gly Arg Val Ile Pro Ser Asn Gly Gly Ser Asn Tyr Asn Gln Lys Phe
50 55 60
Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Leu Ser Thr Ala Tyr
65 70 75 80
Met His Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95
Ala Thr Gln Leu Gly Arg Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100 105 110
Ala
<210> 290
<211> 106
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-3E20 VL多肽序列
<400> 290
Asp Ile Lys Met Thr Gln Ser Pro Ser Ser Met Tyr Ala Ser Leu Gly
1 5 10 15
Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile Asn Ser Tyr
20 25 30
Leu Ser Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
35 40 45
Tyr Arg Ala Asn Arg Leu Val Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Tyr
65 70 75 80
Glu Asp Met Gly Ile Tyr Tyr Cys Leu Gln Tyr Asp Asp Leu Trp Thr
85 90 95
Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105
<210> 291

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<211> 121
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-3E20 VH多肽序列
<400> 291

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Trp Ile His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45
Gly Tyr Ile Asn Pro Ser Ser Gly Tyr Ala Glu Tyr Asn Gln Lys Phe
50 55 60
Lys Val Arg Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80
Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Ser Tyr Tyr Ser Phe Asp Tyr Thr Met Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 292
<211> 112
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-6H3 VL多肽序列
<400> 292

Asp Val Val Met Thr Gln Thr Pro Leu Thr Leu Ser Val Thr Ile Gly
1 5 10 15
Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30
Asp Gly Lys Thr Tyr Leu Asn Trp Leu Leu Gln Arg Pro Gly Gln Ser
35 40 45
Pro Lys Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp Ser Gly Val Pro
50 55 60
Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

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Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Trp Gln Gly
85 90 95
Thr His Phe Pro His Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 293
<211> 115
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-6H3 VH多肽序列
<400> 293

Gln Ala Tyr Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ala
1 5 10 15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Arg Phe
20 25 30
Asp Met His Trp Val Lys Gln Thr Pro Arg Gln Gly Leu Glu Trp Ile
35 40 45
Gly Val Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe
50 55 60
Arg Asp Lys Ala Ser Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80
Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
85 90 95
Ala Ser Ser Tyr Tyr Gly Asn Pro Trp Gly Gln Gly Thr Thr Leu Thr
100 105 110
Val Ser Ser
115

<210> 294
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-7B13 VL多肽序列
<400> 294

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Val Thr Pro Gly
1 5 10 15
Asp Arg Val Ser Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Asn Tyr
20 25 30
Leu His Trp Tyr Gln Gln Lys Ser His Glu Ser Pro Arg Leu Leu Ile

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35 40 45

Lys Phe Ala Ser Gln Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Val Glu Thr
65 70 75 80

Glu Asp Phe Gly Met Tyr Phe Cys Gln Gln Ser Asn Ser Trp Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 295
<211> 115
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-7B13 VH多肽序列
<400> 295

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Val Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Thr Ser Gly Phe Thr Phe Thr Asp Tyr
20 25 30

Tyr Met Asn Trp Val Lys Gln Gly His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Arg Val Asn Pro Ser Asn Asp Asp Thr Arg Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Leu Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Trp Phe Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr
100 105 110

Val Ser Ser
115

<210> 296
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-7I20 VL多肽序列
<400> 296

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Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Glu Thr Val Thr Ile Thr Cys Arg Thr Ser Glu Asn Ile Tyr Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro Gln Leu Leu Val
35 40 45
Tyr Asn Ala Lys Thr Leu Ala Lys Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Gln Phe Ser Leu Lys Ile Asn Gly Leu Gln Pro
65 70 75 80
Glu Asp Phe Gly Asn Tyr Tyr Cys Gln His His Tyr Gly Thr Pro Tyr
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 297
<211> 116
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-7I20 VH多肽序列
<400> 297
Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Ser Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Asp Tyr
20 25 30
Tyr Met Ser Trp Val Arg Gln Pro Pro Gly Lys Ala Leu Glu Trp Leu
35 40 45
Ala Leu Ile Arg Asn Lys Ala Asn Gly Tyr Thr Thr Glu Tyr Ser Ala
50 55 60
Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Gln Ser Ile
65 70 75 80
Leu Tyr Leu Gln Met Asn Ala Leu Arg Ala Glu Asp Ser Ala Thr Tyr
85 90 95
Tyr Cys Ala Val Thr Tyr Gly Ala Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ala
115

<210> 298
<211> 107

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<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-8M24 VL多肽序列
<400> 298

```
Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Val Ser Val Gly
1               5                  10                  15
Glu Thr Val Thr Ile Thr Cys Arg Ile Ser Glu Asn Ile Tyr Ser Asn
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro His Leu Leu Val
        35                  40                  45
Tyr Ala Ala Ile Asn Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Gln Phe Ser Leu Lys Ile Asn Ser Leu Gln Ser
65                  70                  75                  80
Glu Asp Phe Gly Ser Tyr Tyr Cys Gln His Phe Trp Gly Thr Pro Phe
                85                  90                  95
Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
            100                 105
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<210> 299
<211> 122
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-7I20 VH多肽序列
<400> 299

```
Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala
1               5                  10                  15
Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
            20                  25                  30
Gly Ile Asn Trp Val Lys Gln Arg Thr Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45
Gly Glu Ile Phe Pro Arg Ser Asp Asn Thr Phe Tyr Asn Glu Lys Phe
    50                  55                  60
Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Thr Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
                85                  90                  95
Ala Arg Lys Gly Arg Asp Tyr Gly Thr Ser His Tyr Phe Asp Tyr Trp
```


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100 105 110

Gly Gln Gly Thr Thr Leu Thr Val Ser Ser
115 120

<210> 300
<211> 112
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-9C3 VL多肽序列
<400> 300

Asp Val Val Val Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Phe Gly
1 5 10 15
Asp Gln Val Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Ala Asn Ser
20 25 30
Tyr Gly Asn Thr Tyr Leu Ser Trp Tyr Leu His Lys Pro Gly Gln Ser
35 40 45
Pro Gln Leu Leu Ile Tyr Gly Ile Ser Asn Arg Phe Ser Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80
Ser Thr Ile Lys Pro Glu Asp Leu Gly Ile Tyr Tyr Cys Leu Gln Ala
85 90 95
Thr His Gln Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 301
<211> 117
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-9C3 VH多肽序列
<400> 301

Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln Pro Ser Gln
1 5 10 15
Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30
Tyr Met Gly Val Ser Trp Ile Arg Lys Pro Ser Gly Lys Gly Leu Glu
35 40 45
Trp Leu Ala His Ile Phe Trp Asp Asp Asp Lys Arg Tyr Asn Pro Ser
50 55 60

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Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Ser Asn Gln Val
65 70 75 80
Phe Leu Met Ile Thr Ser Val Glu Thr Ala Asp Thr Ala Thr Tyr Tyr
85 90 95
Cys Gly Gly Pro Tyr Tyr Pro Phe Thr Tyr Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ala
115

<210> 302
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-9M16 VL多肽序列
<400> 302
Asp Ile Lys Met Thr Gln Ser Pro Ser Ser Met Tyr Ala Ser Leu Gly
1 5 10 15
Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile Asn Ser Tyr
20 25 30
Leu Ser Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
35 40 45
Tyr Arg Ala Asn Arg Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Tyr
65 70 75 80
Glu Asp Met Gly Ile Tyr Tyr Cys Leu Gln Tyr Asp Glu Phe Pro Leu
85 90 95
Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 303
<211> 114
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-9M16 VH多肽序列
<400> 303
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr

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20 25 30
Tyr Met Asn Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45
Gly Arg Val Asn Pro Asn Asn Gly Gly Ser Asn Tyr Asn Gln Lys Phe
50 55 60
Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Leu Ser Thr Ala Tyr
65 70 75 80
Met Gln Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95
Ala Ser Arg Asn Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val
100 105 110
Ser Ser

<210> 304
<211> 112
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-10C22 VL多肽序列
<400> 304
Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1 5 10 15
Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Gly Ile Val His Ser
20 25 30
Asn Gly Asn Ile Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80
Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly
85 90 95
Ser His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 305
<211> 120
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的LP1-10C22多肽序列

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<400> 305
Glu Val Gln Leu Val Glu Ser Gly Gly Asp Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met Ser Trp Val Arg Gln Thr Pro Asp Lys Arg Leu Glu Trp Val
35 40 45
Ala Ser Ile Ser Ser Gly Gly Ser Tyr Thr Tyr Tyr Pro Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Gln Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Val Arg His Glu Glu Tyr Gly Lys Ser Gly Phe Ala Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Ile Thr Val Ser Ala
115 120
<210> 306
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH1序列
<400> 306
Asp Ser Val Ser Ser Asn Ser Ala Ala Trp Tyr
1 5 10
<210> 307
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH1序列
<400> 307
Asp Thr Phe Thr Gly Tyr Tyr Ile His
1 5
<210> 308
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)

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<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH1序列
<400> 308
Phe Ala Phe Ser Asn Phe Ala Met Ile
1 5
<210> 309
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
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<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH1序列
<400> 309
Phe Ser Phe Ser Asn Tyr Ala Met Ser
1 5
<210> 310
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
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<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH1序列
<400> 310
Phe Thr Phe Asn Asn Phe Gly Met Ser
1 5
<210> 311
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH1序列
<400> 311
Phe Thr Phe Ser Asn Tyr Ala Met Gly
1 5
<210> 312
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH1序列
<400> 312

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Phe Thr Phe Ser Ser Tyr Ala Met His
1 5
<210> 313
<211> 7
<212> PRT
<213> 人工序列(Artificial Sequence)
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<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH1序列
<400> 313
Gly Phe Asn Ile Lys Asp Asp
1 5
<210> 314
<211> 7
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH1序列
<400> 314
Gly Phe Asn Ile Lys Asp Thr
1 5
<210> 315
<211> 7
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH1序列
<400> 315
Gly Phe Thr Phe Ser Asp Tyr
1 5
<210> 316
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH1序列
<400> 316
Gly Thr Phe Ser Gly Tyr Tyr Met His
1 5
<210> 317

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<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH1序列
<400> 317
Gly Thr Phe Ser Asn Thr Asp Ile Asn
1 5
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<211> 9
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<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH1序列
<400> 318
Gly Thr Phe Ser Asn Tyr Ala Ile Ser
1 5
<210> 319
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH1序列
<400> 319
Gly Thr Phe Ser Asn Tyr Ser Leu Ser
1 5
<210> 320
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH1序列
<400> 320
Gly Thr Phe Ser Ser Tyr Ala Ile Ser
1 5
<210> 321
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)

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<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH1序列
<400> 321
Gly Thr Phe Ser Thr Ser Gly Ile Thr
1 5
<210> 322
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH1序列
<400> 322
Tyr Arg Phe Thr Asn Tyr Tyr Met His
1 5
<210> 323
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH1序列
<400> 323
Tyr Arg Phe Thr Ser Tyr Tyr Leu His
1 5
<210> 324
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH1序列
<400> 324
Tyr Thr Phe Ile Gly Tyr Tyr Met His
1 5
<210> 325
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH1序列
<400> 325

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Tyr Thr Phe Arg Arg Tyr Pro Met His
1 5
<210> 326
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH1序列
<400> 326
Tyr Thr Phe Ser Arg Tyr Phe Met His
1 5
<210> 327
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH1序列
<400> 327
Tyr Thr Phe Thr Ala Tyr Tyr Met His
1 5
<210> 328
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH1序列
<400> 328
Tyr Thr Phe Thr Glu Tyr Tyr Met His
1 5
<210> 329
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH1序列
<400> 329
Tyr Thr Phe Thr Gly Tyr Tyr Met His
1 5
<210> 330

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<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH1序列
<400> 330
Tyr Thr Phe Thr Asn Tyr Gly Ile Ser
1 5
<210> 331
<211> 9
<212> PRT
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<400> 331
Tyr Thr Phe Thr Asn Tyr Lys Met His
1 5
<210> 332
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH1序列
<400> 332
Tyr Thr Phe Thr Asn Tyr Tyr Met His
1 5
<210> 333
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
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<400> 333
Tyr Thr Phe Thr Arg His Tyr Met His
1 5
<210> 334
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)

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<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH1序列
<400> 334
Tyr Thr Phe Thr Arg Tyr Tyr Met His
1 5
<210> 335
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH1序列
<400> 335
Tyr Thr Phe Thr Ser Tyr Ala Met His
1 5
<210> 336
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH1序列
<400> 336
Tyr Thr Phe Thr Ser Tyr Asp Ile Asn
1 5
<210> 337
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH1序列
<400> 337
Tyr Thr Phe Thr Ser Tyr Gly Val Ser
1 5
<210> 338
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH1序列
<400> 338

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Tyr Thr Phe Thr Ser Tyr Tyr Leu His
1 5
<210> 339
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH1序列
<400> 339
Tyr Thr Phe Thr Ser Tyr Tyr Met His
1 5
<210> 340
<211> 6
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 340
Asp Pro Ala Asn Gly Lys
1 5
<210> 341
<211> 6
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 341
Asp Pro Glu Asn Gly Asp
1 5
<210> 342
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 342
Gly Gly Ile Ile Pro Ile Phe Asp Ala Ala Thr Tyr Ala
1 5 10
<210> 343

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<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 343
Gly Gly Ile Ile Pro Ile Phe Asp Ala Thr Asn Tyr Ala
1 5 10
<210> 344
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 344
Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala
1 5 10
<210> 345
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 345
Gly Ile Ile Asn Pro Asn Gly Gly Arg Thr Thr Tyr Ala
1 5 10
<210> 346
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 346
Gly Ile Ile Asn Pro Arg Gly Gly Ser Thr Ser Tyr Ala
1 5 10
<210> 347
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)

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<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 347
Gly Ile Ile Asn Pro Arg Arg Gly Ser Thr Arg Tyr Ala
1 5 10
<210> 348
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 348
Gly Ile Ile Asn Pro Ser Gly Gly Ser Ala Asn Tyr Ala
1 5 10
<210> 349
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 349
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala
1 5 10
<210> 350
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 350
Gly Lys Ile Asn Pro Ser Ser Gly Ser Thr Ser Tyr Ala
1 5 10
<210> 351
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 351

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Gly Arg Ile Lys Pro Asn Ser Gly Asn Thr Gly Tyr Ala
1 5 10

<210> 352
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 352
Gly Arg Ile Ser Pro Asn Arg Gly Gly Thr Lys Tyr Ala
1 5 10

<210> 353
<211> 14
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 353
Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr His Asp Tyr Ala
1 5 10

<210> 354
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 354
Gly Val Ile Asn Pro Gly Gly Ser Asp Thr Thr Tyr Ala
1 5 10

<210> 355
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 355
Gly Trp Ile Asn Ala Gly Asn Gly Asn Thr Lys Tyr Ser
1 5 10

<210> 356

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<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 356
Gly Trp Ile Asn Pro His Ser Gly Gly Thr Asn Tyr Ala
1 5 10
<210> 357
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 357
Gly Trp Ile Asn Pro Asn Arg Gly Gly Thr Ser Tyr Ala
1 5 10
<210> 358
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 358
Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala
1 5 10
<210> 359
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 359
Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Arg Tyr Ala
1 5 10
<210> 360
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)

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<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 360
Gly Trp Ile Asn Pro Asn Ser Gly Asn Thr Lys Tyr Ala
1 5 10
<210> 361
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 361
Gly Trp Ile Asn Pro Asn Thr Gly Gly Thr Lys Ser Ala
1 5 10
<210> 362
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 362
Gly Trp Ile Ser Ala Asp Asn Gly Asn Thr Asn Tyr Ala
1 5 10
<210> 363
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 363
Gly Trp Ile Ser Pro Asn Ser Gly Ala Thr Asn Tyr Ala
1 5 10
<210> 364
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 364

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Gly Trp Met Asn Pro Lys Ser Gly Gly Thr Asn Tyr Ala
1 5 10

<210> 365
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 365
Gly Trp Met Asn Pro Asn Ser Gly His Ala Gly Ser Ala
1 5 10

<210> 366
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 366
Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala
1 5 10

<210> 367
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 367
Gly Trp Met Asn Pro Asn Thr Gly Gly Ile Lys Tyr Ser
1 5 10

<210> 368
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 368
Gly Trp Val Asn Pro Lys Asn Gly His Thr Gly Tyr Ala
1 5 10

<210> 369

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<211> 8
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 369
Lys Ser Lys Thr Asp Gly Gly Ile
1 5
<210> 370
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 370
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala
1 5 10
<210> 371
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 371
Ser Ala Ile Ser Gly Ser Gly Arg Thr Thr Tyr Tyr Ala
1 5 10
<210> 372
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 372
Ser Ala Ile Ser Gly Ser Gly Thr Tyr Tyr Ala
1 5 10
<210> 373
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)

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<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
<400> 373
Ser Gly Ile Ser Ala Ser Gly Arg Asn Thr Tyr Tyr Ala
1 5 10
<210> 374
<211> 10
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列
<400> 374
Ala Ile Tyr Tyr Leu Glu Ala Phe Asp Val
1 5 10
<210> 375
<211> 20
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列
<400> 375
Cys Ala Lys Asp Leu Glu His Thr Gly Tyr Ser Ser Gly Trp Ala Gly
1 5 10 15
Phe Asp Tyr Trp
20
<210> 376
<211> 22
<212> PRT
<213> 人工序列(Artificial Sequence)
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<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列
<400> 376
Cys Ala Lys Asp Ser Gly Tyr Cys Ser Ser Thr Ser Cys Tyr Asp Gly
1 5 10 15
Gly Tyr Phe Asp Leu Trp
20
<210> 377
<211> 14
<212> PRT

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<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列
<400> 377
Cys Ala Lys Ser Arg Ala Leu Lys Gly Ser Tyr Thr Ser Trp
1 5 10
<210> 378
<211> 14
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列
<400> 378
Cys Ala Arg Asp Gly Leu Gly Val Asp Ala Phe Asp Ile Trp
1 5 10
<210> 379
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列
<400> 379
Cys Ala Arg Asp Gly Tyr Tyr Tyr Gly Met Asp Val Trp
1 5 10
<210> 380
<211> 12
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列
<400> 380
Cys Ala Arg Asp Lys Val Gly Ala Ile Asp Tyr Trp
1 5 10
<210> 381
<211> 16
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列

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<400> 381
Cys Ala Arg Asp Leu Met Val Arg Gly Gly Pro Pro Phe Asp Tyr Trp
1 5 10 15
<210> 382
<211> 15
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列
<400> 382
Cys Ala Arg Asp Pro Val Arg Gly Ile Ser Ala Phe Asp Tyr Trp
1 5 10 15
<210> 383
<211> 17
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列
<400> 383
Cys Ala Arg Asp Gln Gly His Asp Tyr Gly Asp Tyr Glu Ile Asp Tyr
1 5 10 15
Trp
<210> 384
<211> 18
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列
<400> 384
Cys Ala Arg Asp Gln Lys Gly Lys Ser Ser Ser Trp Phe Arg Phe Asp
1 5 10 15
Pro Trp
<210> 385
<211> 14
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列
<400> 385

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Cys Ala Arg Asp Ser Trp Leu Arg Gly Ala Trp Gly Tyr Trp
1 5 10

<210> 386
<211> 16
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列
<400> 386
Cys Ala Arg Glu Asp Tyr Asn Trp Asn Asp Gly Trp Phe Asp Pro Trp
1 5 10 15

<210> 387
<211> 12
<212> PRT
<213> 人工序列(Artificial Sequence)
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<400> 387
Cys Ala Arg Glu Thr Arg His Gly Ser Asp Tyr Trp
1 5 10

<210> 388
<211> 23
<212> PRT
<213> 人工序列(Artificial Sequence)
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<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列
<400> 388
Cys Ala Arg Gly Asp Phe Trp Ser Gly Tyr Tyr Pro Tyr Tyr Tyr Tyr
1 5 10 15
Tyr Tyr Gly Met Asp Val Trp
20

<210> 389
<211> 16
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列
<400> 389
Cys Ala Arg Gly Gly Arg Ser Tyr Gly Tyr Trp Tyr Phe Asp Leu Trp

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1 5 10 15

<210> 390

<211> 15

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列

<400> 390

Cys Ala Arg Gly Gly Arg Thr Thr Val Thr Thr Met Ala Tyr Trp

1 5 10 15

<210> 391

<211> 12

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列

<400> 391

Cys Ala Arg Gly Gly Ser Gly Trp Leu Asp Tyr Trp

1 5 10

<210> 392

<211> 14

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列

<400> 392

Cys Ala Arg Gly Met Tyr Ser Ser Ser Trp Leu Arg Tyr Trp

1 5 10

<210> 393

<211> 12

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列

<400> 393

Cys Ala Arg Gly Arg Gln Gly Val Trp Asp Tyr Trp

1 5 10

<210> 394

<211> 15

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<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列
<400> 394
Cys Ala Arg Gly Arg Arg Ser Gly Leu Ser Pro Pro Ala Tyr Trp
1 5 10 15
<210> 395
<211> 22
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列
<400> 395
Cys Ala Arg Gly Arg Arg Ser Arg Gly Ser Ser Ser Leu Gly Tyr Tyr
1 5 10 15
Tyr Tyr Met Asp Val Trp
20
<210> 396
<211> 12
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列
<400> 396
Cys Ala Arg Gly Arg Ser Gly Asn Trp Lys Phe Trp
1 5 10
<210> 397
<211> 19
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列
<400> 397
Cys Ala Arg Gly Arg Val Val Arg Gly Val Ile Ile Ser Tyr Gly Met
1 5 10 15
Asp Val Trp
<210> 398
<211> 12

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<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列
<400> 398
Cys Ala Arg Gly Ser Leu Gly Tyr Phe Asp Leu Trp
1 5 10
<210> 399
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列
<400> 399
Cys Ala Arg Gly Ser Asn Gly Met Asp Val Trp
1 5 10
<210> 400
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列
<400> 400
Cys Ala Arg Leu Arg Ala Asn Tyr Gly Met Asp Val Trp
1 5 10
<210> 401
<211> 16
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列
<400> 401
Cys Ala Arg Arg Gln Tyr Ser Gly Tyr Asp Thr His Phe Asp Tyr Trp
1 5 10 15
<210> 402
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>

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<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列
<400> 402
Cys Ala Arg Arg Arg Asp Gly Tyr Asn Trp Gly Tyr Trp
1 5 10
<210> 403
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列
<400> 403
Cys Ala Arg Arg Thr Ser Ser Phe Ser Leu Trp
1 5 10
<210> 404
<211> 14
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列
<400> 404
Cys Ala Arg Ser Phe Gly Val Ala Gly Thr Leu Asp Tyr Trp
1 5 10
<210> 405
<211> 14
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列
<400> 405
Cys Ala Arg Ser Gly Ala Gly Met Trp Tyr Phe Asp Leu Trp
1 5 10
<210> 406
<211> 14
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列
<400> 406
Cys Ala Arg Val Leu Arg Gly Ser Leu Gly Phe Asp Tyr Trp

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1 5 10

<210> 407

<211> 14

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列

<400> 407

Cys Ala Arg Val Val Arg Ala Val Asp Ala Phe Asp Ile Trp

1 5 10

<210> 408

<211> 15

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列

<400> 408

Cys Ala Arg Tyr Ser Ser Ser Trp Ser Trp Pro Phe Asp Tyr Trp

1 5 10 15

<210> 409

<211> 17

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列

<400> 409

Cys Thr Arg Ala Arg Gly Gln Arg Ser Gly Tyr Ser Tyr Phe Asp Leu

1 5 10 15

Trp

<210> 410

<211> 15

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列

<400> 410

Cys Val Gly Gly Arg Ser Gly Trp Ile Trp Tyr Phe Asp Leu Trp

1 5 10 15

<210> 411

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<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列
<400> 411
Gly Gly Gly Tyr Tyr Gly Met Asp Tyr
1 5
<210> 412
<211> 8
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH3序列
<400> 412
Ser Arg Thr Thr Ala Leu Asp Tyr
1 5
<210> 413
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL1序列
<400> 413
Lys Ala Ser Gln Ser Val Arg Pro Ala Val Ala
1 5 10
<210> 414
<211> 17
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL1序列
<400> 414
Lys Ser Ser Gln Ser Val Leu Tyr Ser Ser Asn Asn Lys Asn Tyr Leu
1 5 10 15
Ala
<210> 415
<211> 11
<212> PRT

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<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL1序列
<400> 415
Gln Ala Ser Gln Asp Ile Ser Arg Tyr Leu Asn
1 5 10
<210> 416
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL1序列
<400> 416
Arg Ala Gly Gln Ser Ile Ser Arg Phe Leu Asn
1 5 10
<210> 417
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL1序列
<400> 417
Arg Ala Ser Glu Asn Ile His Lys Tyr Leu Asn
1 5 10
<210> 418
<211> 15
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL1序列
<400> 418
Arg Ala Ser Glu Ser Val Asp Ser Tyr Gly Asn Ser Phe Met His
1 5 10 15
<210> 419
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL1序列

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<400> 419
Arg Ala Ser Gln Asp Ile Ser Asn Ser Leu Asn
1 5 10
<210> 420
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL1序列
<400> 420
Arg Ala Ser Gln Asp Ile Ser Arg Tyr Leu Ala
1 5 10
<210> 421
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL1序列
<400> 421
Arg Ala Ser Gln Asp Ile Tyr Arg Tyr Leu Asn
1 5 10
<210> 422
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL1序列
<400> 422
Arg Ala Ser Gln Phe Ile Ser Thr Tyr Leu Asn
1 5 10
<210> 423
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL1序列
<400> 423
Arg Ala Ser Gln Gly Ile Ser Asn Asn Leu Asn
1 5 10

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<210> 424
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL1序列
<400> 424
Arg Ala Ser Gln Gly Ile Ser Asn Tyr Leu Ala
1 5 10
<210> 425
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL1序列
<400> 425
Arg Ala Ser Gln Asn Ile Arg Ser Trp Leu Ala
1 5 10
<210> 426
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL1序列
<400> 426
Arg Ala Ser Gln Asn Ile Tyr Asp Trp Leu Ala
1 5 10
<210> 427
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL1序列
<400> 427
Arg Ala Ser Gln Ser Ile Asn Asn Trp Leu Ala
1 5 10
<210> 428
<211> 11
<212> PRT

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<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL1序列
<400> 428
Arg Ala Ser Gln Ser Ile Arg Ser Tyr Leu Asn
1 5 10
<210> 429
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL1序列
<400> 429
Arg Ala Ser Gln Ser Ile Ser Arg Trp Leu Ala
1 5 10
<210> 430
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL1序列
<400> 430
Arg Ala Ser Gln Ser Ile Ser Ser Trp Leu Ala
1 5 10
<210> 431
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL1序列
<400> 431
Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn
1 5 10
<210> 432
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL1序列

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<400> 432
Arg Ala Ser Gln Ser Ile Ser Thr Trp Leu Ala
1 5 10
<210> 433
<211> 12
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL1序列
<400> 433
Arg Ala Ser Gln Ser Val Asp Ser Ser Tyr Leu Ala
1 5 10
<210> 434
<211> 12
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL1序列
<400> 434
Arg Ala Ser Gln Ser Val Asn Ser Arg Tyr Leu Ala
1 5 10
<210> 435
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL1序列
<400> 435
Arg Ala Ser Gln Ser Val Ser Ala Ser Leu Ala
1 5 10
<210> 436
<211> 12
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL1序列
<400> 436
Arg Ala Ser Gln Ser Val Ser Ser Ser Asn Leu Ala
1 5 10

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<210> 437
<211> 12
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL1序列
<400> 437
Arg Ala Ser Gln Ser Val Ser Ser Ser Tyr Leu Ala
1 5 10
<210> 438
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL1序列
<400> 438
Arg Ala Ser Gln Tyr Ile Gly Ser Tyr Leu Asn
1 5 10
<210> 439
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL1序列
<400> 439
Arg Ser Ser Gln Ser Ile Arg Thr Tyr Leu Asn
1 5 10
<210> 440
<211> 16
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL1序列
<400> 440
Arg Ser Ser Gln Ser Leu Leu His Ser Asn Gly Tyr Asn Tyr Leu Asp
1 5 10 15
<210> 441
<211> 11
<212> PRT

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<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL1序列
<400> 441
Arg Val Ser Gln Gly Ile Ser Ser Tyr Leu Asn
1 5 10
<210> 442
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL1序列
<400> 442
Ser Gly Asp Ser Leu Gly Ser Tyr Tyr Val His
1 5 10
<210> 443
<211> 17
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL1序列
<400> 443
Thr Ser Ser Gln Ser Val Leu His Ser Ser Asn Lys Lys Asn Tyr Leu
1 5 10 15
Ala
<210> 444
<211> 7
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL2序列
<400> 444
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1 5
<210> 445
<211> 7
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>

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<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL2序列
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Ala Ala Ser Ser Leu His Ser
1 5
<210> 446
<211> 7
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<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL2序列
<400> 446
Ala Ala Ser Ser Leu Gln Arg
1 5
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<400> 447
Ala Ala Ser Ser Leu Gln Ser
1 5
<210> 448
<211> 7
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<213> 人工序列(Artificial Sequence)
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1 5
<210> 449
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<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL2序列
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Ala Ala Ser Thr Val Glu Ser

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1 5

<210> 450

<211> 7

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL2序列

<400> 450

Ala Thr Ser Thr Arg Ala Thr

1 5

<210> 451

<211> 7

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL2序列

<400> 451

Asp Ala Ser Asn Leu Glu Thr

1 5

<210> 452

<211> 7

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL2序列

<400> 452

Asp Ala Ser Ser Leu Glu Thr

1 5

<210> 453

<211> 7

<212> PRT

<213> 人工序列(Artificial Sequence)

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<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL2序列

<400> 453

Asp Ala Ser Ser Leu Pro Ser

1 5

<210> 454

<211> 7

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<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
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Asp Ala Ser Ser Leu Gln Arg
1 5
<210> 455
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<400> 455
Gly Ala Ser Ser Leu Gln Ser
1 5
<210> 456
<211> 7
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<213> 人工序列(Artificial Sequence)
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<400> 456
Gly Ala Ser Ser Arg Ala Thr
1 5
<210> 457
<211> 7
<212> PRT
<213> 人工序列(Artificial Sequence)
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<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL2序列
<400> 457
Gly Ala Ser Thr Arg Ala Thr
1 5
<210> 458
<211> 7
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>

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<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL2序列
<400> 458
Lys Ala Ser Ser Leu Glu Ser
1 5
<210> 459
<211> 7
<212> PRT
<213> 人工序列(Artificial Sequence)
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<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL2序列
<400> 459
Leu Ala Ser Asn Leu Glu Ser
1 5
<210> 460
<211> 7
<212> PRT
<213> 人工序列(Artificial Sequence)
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<400> 460
Leu Ala Ser Asn Arg His Thr
1 5
<210> 461
<211> 7
<212> PRT
<213> 人工序列(Artificial Sequence)
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<400> 461
Leu Gly Ser Asn Arg Ala Ser
1 5
<210> 462
<211> 7
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
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<400> 462
Leu Gly Ser Tyr Arg Ala Ser

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1 5

<210> 463

<211> 7

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL2序列

<400> 463

Arg Asn Lys Gln Arg Pro Ser

1 5

<210> 464

<211> 7

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL2序列

<400> 464

Trp Ala Ser Thr Arg Ala Ser

1 5

<210> 465

<211> 7

<212> PRT

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<220>

<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL2序列

<400> 465

Trp Ala Ser Thr Arg Glu Ser

1 5

<210> 466

<211> 11

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL3序列

<400> 466

Cys His Gln Tyr Phe Ser Pro Pro Met Thr Phe

1 5 10

<210> 467

<211> 11

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<212> PRT
<213> 人工序列(Artificial Sequence)
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<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL3序列
<400> 467
Cys Leu Gln Asp Tyr Asp Tyr Pro Leu Thr Phe
1 5 10
<210> 468
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL3序列
<400> 468
Cys Met Gln Ala Leu Gln Thr Pro Leu Thr Phe
1 5 10
<210> 469
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL3序列
<400> 469
Cys Met Gln Gly Thr His Trp Pro Arg Thr Phe
1 5 10
<210> 470
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL3序列
<400> 470
Cys Met Gln Gly Thr His Trp Pro Tyr Ala Phe
1 5 10
<210> 471
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>

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<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL3序列
<400> 471
Cys Met Gln Ser Leu Glu Ala Pro Leu Ala Phe
1 5 10
<210> 472
<211> 11
<212> PRT
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<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL3序列
<400> 472
Cys Met Gln Thr Leu His Thr Pro Tyr Thr Phe
1 5 10
<210> 473
<211> 11
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<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL3序列
<400> 473
Cys Gln Gln Ala Asn Ser Phe Pro Ile Thr Phe
1 5 10
<210> 474
<211> 11
<212> PRT
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<400> 474
Cys Gln Gln Ala Asn Thr Phe Pro Ile Thr Phe
1 5 10
<210> 475
<211> 11
<212> PRT
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<400> 475
Cys Gln Gln Ala Tyr Ser Phe Pro Trp Thr Phe

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1 5 10

<210> 476

<211> 11

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL3序列

<400> 476

Cys Gln Gln Gly Ser Ser Phe Pro Leu Thr Phe

1 5 10

<210> 477

<211> 11

<212> PRT

<213> 人工序列(Artificial Sequence)

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<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL3序列

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Cys Gln Gln Gly Tyr Ser Thr Pro Tyr Thr Phe

1 5 10

<210> 478

<211> 11

<212> PRT

<213> 人工序列(Artificial Sequence)

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<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL3序列

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Cys Gln Gln Ser Phe Ser Thr Pro Tyr Thr Phe

1 5 10

<210> 479

<211> 11

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL3序列

<400> 479

Cys Gln Gln Ser Tyr Gly Ala Pro Leu Thr Phe

1 5 10

<210> 480

<211> 11

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<212> PRT
<213> 人工序列(Artificial Sequence)
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<400> 480
Cys Gln Gln Ser Tyr Arg Ser Pro Tyr Thr Phe
1 5 10
<210> 481
<211> 11
<212> PRT
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Cys Gln Gln Ser Tyr Arg Thr Pro Tyr Thr Phe
1 5 10
<210> 482
<211> 11
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Cys Gln Gln Ser Tyr Ser Pro Pro Phe Thr Phe
1 5 10
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<211> 11
<212> PRT
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Cys Gln Gln Ser Tyr Ser Pro Pro His Thr Phe
1 5 10
<210> 484
<211> 11
<212> PRT
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<220>

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<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL3序列
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Cys Gln Gln Ser Tyr Ser Arg Pro Phe Thr Phe
1 5 10
<210> 485
<211> 11
<212> PRT
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Cys Gln Gln Ser Tyr Ser Ser Pro Leu Thr Phe
1 5 10
<210> 486
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<400> 486
Cys Gln Gln Ser Tyr Ser Thr Pro Leu Thr Phe
1 5 10
<210> 487
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL3序列
<400> 487
Cys Gln Gln Ser Tyr Ser Thr Pro Pro Thr Phe
1 5 10
<210> 488
<211> 10
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<213> 人工序列(Artificial Sequence)
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<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL3序列
<400> 488
Cys Gln Gln Ser Tyr Ser Thr Pro Thr Phe

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1 5 10

<210> 489

<211> 11

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL3序列

<400> 489

Cys Gln Gln Ser Tyr Ser Thr Pro Tyr Thr Phe

1 5 10

<210> 490

<211> 11

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL3序列

<400> 490

Cys Gln Gln Ser Tyr Ser Thr Ser Trp Thr Phe

1 5 10

<210> 491

<211> 11

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL3序列

<400> 491

Cys Gln Gln Ser Tyr Thr Thr Pro Ile Thr Phe

1 5 10

<210> 492

<211> 11

<212> PRT

<213> 人工序列(Artificial Sequence)

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<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL3序列

<400> 492

Cys Gln Gln Thr Tyr Ser Thr Pro Phe Thr Phe

1 5 10

<210> 493

<211> 11

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<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL3序列
<400> 493
Cys Gln Gln Tyr Gly Ser Ser Pro Ile Thr Phe
1 5 10
<210> 494
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
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<400> 494
Cys Gln Gln Tyr Gly Ser Ser Pro Arg Thr Phe
1 5 10
<210> 495
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL3序列
<400> 495
Cys Gln Gln Tyr Gly Ser Ser Arg Leu Thr Phe
1 5 10
<210> 496
<211> 11
<212> PRT
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<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL3序列
<400> 496
Cys Gln Gln Tyr His Ser Thr Pro Tyr Thr Phe
1 5 10
<210> 497
<211> 11
<212> PRT
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<220>

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<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL3序列
<400> 497
Cys Gln Gln Tyr Tyr Arg Ser Pro Pro Thr Phe
1 5 10
<210> 498
<211> 11
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<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL3序列
<400> 498
Cys Gln Gln Tyr Tyr Ser Asp Pro Ile Thr Phe
1 5 10
<210> 499
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
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<400> 499
Cys Gln Gln Tyr Tyr Ser Thr Pro Leu Thr Phe
1 5 10
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<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL3序列
<400> 500
Cys Gln Gln Tyr Tyr Ser Thr Pro Pro Thr Phe
1 5 10
<210> 501
<211> 9
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<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL3序列
<400> 501
Leu Gln His Trp Asn Tyr Pro Tyr Thr

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1 5

<210> 502

<211> 9

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL3序列

<400> 502

Gln Gln Asn Asn Glu Asp Pro Leu Thr

1 5

<210> 503

<211> 11

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRL3序列

<400> 503

Gln Thr Tyr Asp Trp Met Tyr Ser Ser Arg Val

1 5 10

<210> 504

<211> 11

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH1序列

<400> 504

Ala Ser Val Ser Ser Asn Ser Ala Ala Trp Asn

1 5 10

<210> 505

<211> 11

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH1序列

<400> 505

Asp Ser Val Ser Ser Asn Ser Ala Ala Trp Asn

1 5 10

<210> 506

<211> 11

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<212> PRT
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<400> 506
Phe Ser Leu Ser Thr Ser Tyr Met Gly Val Ser
1 5 10
<210> 507
<211> 9
<212> PRT
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<400> 507
Phe Thr Phe Ser Asp Tyr Gly Met His
1 5
<210> 508
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH1序列
<400> 508
Phe Thr Phe Ser Ser Tyr Ala Met Ser
1 5
<210> 509
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH1序列
<400> 509
Phe Thr Phe Ser Ser Tyr Ala Met Ser
1 5
<210> 510
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>

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<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH1序列
<400> 510
Phe Thr Phe Ser Ser Tyr Gly Met Ser
1 5
<210> 511
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH1序列
<400> 511
Phe Thr Phe Ser Thr Tyr Thr Met Ser
1 5
<210> 512
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH1序列
<400> 512
Phe Thr Phe Thr Asp Tyr Tyr Met Asn
1 5
<210> 513
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
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<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH1序列
<400> 513
Phe Thr Phe Thr Asp Tyr Tyr Met Ser
1 5
<210> 514
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH1序列
<400> 514
Phe Thr Val Ser Ser Asn Tyr Met Ser

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1 5

<210> 515

<211> 7

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH1序列

<400> 515

Gly Phe Ser Phe Asn Thr Tyr

1 5

<210> 516

<211> 7

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH1序列

<400> 516

Gly Phe Thr Phe Ser Ser Tyr

1 5

<210> 517

<211> 9

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH1序列

<400> 517

Gly Thr Phe Ser Ser Tyr Ala Ile Ser

1 5

<210> 518

<211> 9

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH1序列

<400> 518

His Thr Phe Ser Ser Tyr Ala Met Gly

1 5

<210> 519

<211> 9

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<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH1序列
<400> 519
Tyr Ser Phe Thr Asp Tyr Phe Met Asn
1 5
<210> 520
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH1序列
<400> 520
Tyr Ser Phe Thr Gly Asn Tyr Met His
1 5
<210> 521
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH1序列
<400> 521
Tyr Ser Phe Thr Gly Tyr Phe Met Asn
1 5
<210> 522
<211> 10
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH1序列
<400> 522
Tyr Ser Ile Thr Ser Gly Tyr Tyr Trp Asn
1 5 10
<210> 523
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>

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<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH1序列
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Tyr Thr Phe Leu Thr Tyr Trp Met Asn
1 5
<210> 524
<211> 9
<212> PRT
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<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH1序列
<400> 524
Tyr Thr Phe Ser Asp Tyr Tyr Val His
1 5
<210> 525
<211> 9
<212> PRT
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<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH1序列
<400> 525
Tyr Thr Phe Ser Asn Tyr Tyr Met His
1 5
<210> 526
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH1序列
<400> 526
Tyr Thr Phe Ser Arg Phe Asp Met His
1 5
<210> 527
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH1序列
<400> 527
Tyr Thr Phe Thr Asp Tyr Asn Met His

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1 5

<210> 528

<211> 9

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH1序列

<400> 528

Tyr Thr Phe Thr Asp Tyr Tyr Ile Asn

1 5

<210> 529

<211> 9

<212> PRT

<213> 人工序列(Artificial Sequence)

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<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH1序列

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Tyr Thr Phe Thr Asp Tyr Tyr Met Asn

1 5

<210> 530

<211> 9

<212> PRT

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<220>

<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH1序列

<400> 530

Tyr Thr Phe Thr Gly Tyr His Met His

1 5

<210> 531

<211> 9

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH1序列

<400> 531

Tyr Thr Phe Thr Gly Tyr Tyr Met His

1 5

<210> 532

<211> 9

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<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
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<400> 532
Tyr Thr Phe Thr Asn Tyr Gly Ile Asn
1 5
<210> 533
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH1序列
<400> 533
Tyr Thr Phe Thr Ser Tyr Gly Ile Ser
1 5
<210> 534
<211> 9
<212> PRT
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<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH1序列
<400> 534
Tyr Thr Phe Thr Ser Tyr Trp Ile His
1 5
<210> 535
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
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<400> 535
Tyr Thr Phe Thr Thr Tyr Tyr Met His
1 5
<210> 536
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>

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<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列
<400> 536
Ala Ala Ile Ser Gln Ser Gly Tyr Val Arg Tyr Tyr Ala
1 5 10
<210> 537
<211> 12
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列
<400> 537
Ala His Ile Phe Trp Asp Asp Asp Lys Arg Tyr Asn
1 5 10
<210> 538
<211> 12
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列
<400> 538
Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala
1 5 10
<210> 539
<211> 15
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列
<400> 539
Ala Leu Ile Arg Asn Lys Ala Asn Gly Tyr Thr Thr Glu Tyr Ser
1 5 10 15
<210> 540
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列
<400> 540
Ala Ser Ile Ser Ser Gly Gly Ser Tyr Thr Tyr Tyr Pro

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1 5 10

<210> 541

<211> 13

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列

<400> 541

Ala Thr Ile Ser Ser Ile Gly Val Asn Thr Tyr Tyr Pro

1 5 10

<210> 542

<211> 13

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列

<400> 542

Ala Tyr Ile Ser Ser Gly Ser Ser Thr Ile Tyr Tyr Ala

1 5 10

<210> 543

<211> 13

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列

<400> 543

Gly Glu Ile Phe Pro Arg Ser Asp Asn Thr Phe Tyr Asn

1 5 10

<210> 544

<211> 13

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列

<400> 544

Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala

1 5 10

<210> 545

<211> 13

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<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列
<400> 545
Gly Gly Ile Ile Pro Met Phe Gly Thr Val Lys Tyr Ala
1 5 10
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<211> 13
<212> PRT
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<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列
<400> 546
Gly Gly Ile Ile Pro Val Phe Gly Ala Pro Asn Tyr Ala
1 5 10
<210> 547
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列
<400> 547
Gly Ile Ile Asn Pro Arg Asn Gly Arg Thr Ser Tyr Ala
1 5 10
<210> 548
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列
<400> 548
Gly Ile Ile Asn Pro Ser Gly Gly Gly Thr Ser Tyr Ala
1 5 10
<210> 549
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>

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<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列
<400> 549
Gly Gln Ile Phe Pro Ala Thr Gly Ile Thr Tyr Tyr Ser
1 5 10
<210> 550
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列
<400> 550
Gly Arg Phe Asn Pro Phe Asn Gly Gln Thr Phe Tyr Asn
1 5 10
<210> 551
<211> 14
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列
<400> 551
Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
1 5 10
<210> 552
<211> 14
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列
<400> 552
Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Tyr Asp Tyr Ala
1 5 10
<210> 553
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列
<400> 553
Gly Arg Val Ile Pro Ser Asn Gly Gly Ser Asn Tyr Asn

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1 5 10

<210> 554

<211> 13

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列

<400> 554

Gly Arg Val Ile Pro Ser Asn Gly Gly Thr Asn Tyr Asn

1 5 10

<210> 555

<211> 13

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列

<400> 555

Gly Arg Val Asn Pro Asn Asn Gly Gly Ser Asn Tyr Asn

1 5 10

<210> 556

<211> 13

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列

<400> 556

Gly Arg Val Asn Pro Ser Asn Asp Asp Thr Arg Tyr Asn

1 5 10

<210> 557

<211> 12

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列

<400> 557

Gly Ser Ile Gly Tyr Asp Asp Thr Asn His Tyr Asn

1 5 10

<210> 558

<211> 13

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<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列
<400> 558
Gly Val Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn
1 5 10
<210> 559
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列
<400> 559
Gly Trp Ile Asn Pro Lys Ser Gly Gly Thr Lys Tyr Ala
1 5 10
<210> 560
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列
<400> 560
Gly Trp Ile Asn Pro Asn Gly Gly Gly Thr Asn Tyr Ala
1 5 10
<210> 561
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列
<400> 561
Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala
1 5 10
<210> 562
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>

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<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列
<400> 562
Gly Trp Met Asn Pro Asn Thr Gly Asn Thr Ala Tyr Ala
1 5 10
<210> 563
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列
<400> 563
Gly Tyr Ile Asn Pro Ser Ser Gly Tyr Ala Glu Tyr Asn
1 5 10
<210> 564
<211> 8
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列
<400> 564
Arg Ser Lys Ser Asn Asn Tyr Ala
1 5
<210> 565
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列
<400> 565
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala
1 5 10
<210> 566
<211> 6
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列
<400> 566
Ser Gly Ser Gly Gly Ser

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1 5

<210> 567

<211> 6

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列

<400> 567

Ser Ser Gly Gly Asp Tyr

1 5

<210> 568

<211> 13

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH2序列

<400> 568

Ser Tyr Ile Ser Ser Tyr Asn Ser His Thr Asn Asp Ala

1 5 10

<210> 569

<211> 10

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH3序列

<400> 569

Cys Ala Gly Asp Tyr Pro Phe Ala Phe Trp

1 5 10

<210> 570

<211> 14

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH3序列

<400> 570

Cys Ala Lys Asp Arg Gly Tyr Arg Phe Asp Phe Asp Leu Trp

1 5 10

<210> 571

<211> 17

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<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH3序列
<400> 571
Cys Ala Lys Asp Arg Thr Ala Met Ala Pro Glu Gly Ala Phe Asp Ile
1 5 10 15
Trp
<210> 572
<211> 22
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH3序列
<400> 572
Cys Ala Lys Asp Ser Pro Ile Val Arg Arg Gly Glu Arg Gly Arg Tyr
1 5 10 15
Tyr Gly Met Asp Val Trp
20
<210> 573
<211> 15
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH3序列
<400> 573
Cys Ala Lys Ser Ser Phe Ser Tyr Leu Arg Ala Phe Asp Tyr Trp
1 5 10 15
<210> 574
<211> 15
<212> PRT
<213> 人工序列(Artificial Sequence)
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<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH3序列
<400> 574
Cys Ala Lys Ser Ser Phe Thr Phe Gly Arg Tyr Phe Asp Tyr Trp
1 5 10 15
<210> 575
<211> 15

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<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH3序列
<400> 575
Cys Ala Lys Ser Trp Tyr Leu Pro Gly Arg Gly Phe Asp Tyr Trp
1 5 10 15
<210> 576
<211> 12
<212> PRT
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<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH3序列
<400> 576
Cys Ala Arg Asp Gly Gly Tyr Gly Met Asp Val Trp
1 5 10
<210> 577
<211> 12
<212> PRT
<213> 人工序列(Artificial Sequence)
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<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH3序列
<400> 577
Cys Ala Arg Asp His Leu Tyr Gly Met Asp Val Trp
1 5 10
<210> 578
<211> 13
<212> PRT
<213> 人工序列(Artificial Sequence)
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<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH3序列
<400> 578
Cys Ala Arg Asp Lys Asn Tyr Tyr Gly Met Asp Val Trp
1 5 10
<210> 579
<211> 17
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>

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<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH3序列
<400> 579
Cys Ala Arg Asp Arg Gly Ile Thr Met Val Arg Gly Val Met Asp Tyr
1 5 10 15
Trp
<210> 580
<211> 15
<212> PRT
<213> 人工序列(Artificial Sequence)
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<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH3序列
<400> 580
Cys Ala Arg Asp Thr Gly Ala Thr Ala Glu Tyr Phe Gln His Trp
1 5 10 15
<210> 581
<211> 16
<212> PRT
<213> 人工序列(Artificial Sequence)
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<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH3序列
<400> 581
Cys Ala Arg Glu Ser Tyr Tyr Ser Phe Asp Tyr Thr Met Asp Tyr Trp
1 5 10 15
<210> 582
<211> 8
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH3序列
<400> 582
Cys Ala Arg Gly Met Asp Tyr Trp
1 5
<210> 583
<211> 16
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH3序列
<400> 583

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Cys Ala Arg His Val Asp Tyr Tyr Asp Gly Ile Ser Phe Asp Tyr Trp
1 5 10 15

<210> 584
<211> 17
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH3序列
<400> 584
Cys Ala Arg Lys Gly Arg Asp Tyr Gly Thr Ser His Tyr Phe Asp Tyr
1 5 10 15
Trp

<210> 585
<211> 16
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH3序列
<400> 585
Cys Ala Arg Arg Gly Arg Tyr Asp Val Tyr Tyr Ala Leu Asp Tyr Trp
1 5 10 15

<210> 586
<211> 16
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH3序列
<400> 586
Cys Ala Arg Arg Gly Arg Tyr Asp Val Tyr Tyr Val Leu Asp Tyr Trp
1 5 10 15

<210> 587
<211> 15
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH3序列
<400> 587
Cys Ala Arg Arg Arg Ala Tyr His Ser Asn Phe Phe Asp Tyr Trp
1 5 10 15

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<210> 588
<211> 18
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH3序列
<400> 588
Cys Ala Arg Trp Ala Val Ala Ala Gly Gly Gln Tyr Tyr Tyr Met Asp
1 5 10 15
Val Trp
<210> 589
<211> 14
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH3序列
<400> 589
Cys Ala Arg Trp Asn His Glu Glu His Tyr Phe Asp Tyr Trp
1 5 10
<210> 590
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)
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1 5
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<400> 591
Cys Ala Ser Phe Gly Val Gly Ala Pro Asp Tyr Trp
1 5 10
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<212> PRT
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Cys Ala Ser Ser Tyr Tyr Gly Asn Pro Trp
1 5 10
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1 5 10
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<211> 8
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Cys Ala Thr Gln Leu Gly Arg Trp
1 5
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<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH3序列
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Cys Ala Val Ser Asp Gly Tyr Asp Leu Asp Tyr Trp
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Cys Ala Val Thr Tyr Gly Ala Tyr Trp
1 5
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1 5 10
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<211> 14
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Cys Asn Ala Arg Trp Gly Ala Gly Ser Leu Phe Ala Ser Trp
1 5 10
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Cys Ser Arg Lys Gly Gly Phe Gly Asp Tyr Glu Lys Ser Tyr Ala Met

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1 5 10 15

Asp Tyr Trp

<210> 601

<211> 10

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH3序列

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Cys Thr Arg Trp Phe Tyr Phe Asp Tyr Trp

1 5 10

<210> 602

<211> 15

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<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH3序列

<400> 602

Cys Val Arg His Glu Glu Tyr Gly Lys Ser Gly Phe Ala Tyr Trp

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<210> 603

<211> 11

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<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRH3序列

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1 5 10

<210> 604

<211> 8

<212> PRT

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1 5

<210> 605

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<211> 10
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Pro Arg Tyr Asp Tyr Trp Tyr Phe Asp Val
1 5 10
<210> 606
<211> 11
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Lys Ala Ser Gln Asp Ile Asn Ser His Leu Ser
1 5 10
<210> 607
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Lys Ala Ser Gln Asp Ile Asn Ser Tyr Leu Ser
1 5 10
<210> 608
<211> 11
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Lys Ala Ser Gln Asn Val Gly Ser Asn Val Ala
1 5 10
<210> 609
<211> 11
<212> PRT
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<220>
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Lys Ala Ser Gln Asn Val Gly Thr Asn Val Ala
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<211> 17
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Lys Ser Ser Gln Ser Leu Phe Asn Ser Arg Thr Arg Lys Asn Tyr Leu
1 5 10 15
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<210> 611
<211> 16
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Lys Ser Ser Gln Ser Leu Leu Asp Ser Asp Gly Lys Thr Tyr Leu Asn
1 5 10 15
<210> 612
<211> 16
<212> PRT
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Lys Ser Ser Gln Ser Leu Leu Asp Ser Asp Gly Lys Thr Tyr Leu Asn
1 5 10 15
<210> 613
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
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<400> 613
Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala Ser
1 5 10
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<211> 11
<212> PRT
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Arg Ala Ser Glu Asn Ile Tyr Ser Asn Leu Ala
1 5 10
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1 5 10
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Arg Ala Ser Gln Gly Ile Ala Thr Trp Leu Ala
1 5 10
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Arg Ala Ser Gln Gly Ile Ser Ser Trp Leu Ala
1 5 10

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<210> 618
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1 5 10
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Arg Ala Ser Gln Ser Ile Ser Asn Trp Leu Ala
1 5 10
<210> 621
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Arg Ala Ser Gln Ser Ile Ser Asn Tyr Leu His
1 5 10
<210> 622
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<213> 人工序列(Artificial Sequence)
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1 5 10
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1 5 10
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<400> 626
Arg Ala Ser Gln Ser Val Ser Ser Tyr Leu Ala
1 5 10
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<211> 11
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1 5 10
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Arg Ser Ser Gln Ser Leu Ala Asn Ser Tyr Gly Asn Thr Tyr Leu Ser
1 5 10 15
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Arg Ser Ser Gln Ser Leu Leu His Ser Asp Gly His Asn Tyr Leu Gln
1 5 10 15

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<210> 631
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Arg Thr Ser Glu Asn Ile Tyr Ser Asn Leu Ala
1 5 10
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Arg Thr Ser Glu Asn Ile Tyr Ser Tyr Leu Ala
1 5 10
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Ser Ala Ser Ser Ser Val Ser Ser Ser Phe Leu His
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<210> 635
<211> 7
<212> PRT

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<213> 人工序列(Artificial Sequence)
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Ala Ala Ile Asn Leu Ala Asp
1 5
<210> 636
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<212> PRT
<213> 人工序列(Artificial Sequence)
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Ala Ala Ser Arg Leu Gln Ser
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<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRL2序列

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<400> 639
Ala Ala Thr Asn Leu Ala Asp
1 5
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<212> PRT
<213> 人工序列(Artificial Sequence)
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Ala Ala Thr Thr Leu Gln Ser
1 5
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Asp Ala Ser Asn Leu Gln Ser
1 5
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Asp Ala Ser Asn Leu Arg Ser
1 5
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Asp Ala Ser Asn Arg Ala Thr
1 5

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<210> 644
<211> 7
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
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1 5
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Phe Ala Ser Gln Ser Ile Ser
1 5
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1 5
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<400> 647
Gly Ile Ser Asn Arg Phe Ser
1 5
<210> 648
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<212> PRT

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<213> 人工序列(Artificial Sequence)
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Gly Lys Asn Asn Arg Pro Ser
1 5
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<220>
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Gly Arg Asn Asn Arg Pro Ser
1 5
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<211> 7
<212> PRT
<213> 人工序列(Artificial Sequence)
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Lys Val Ser Asn Arg Phe Ser
1 5
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<400> 651
Leu Gly Ser Tyr Arg Ala Ser
1 5
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<211> 7
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<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRL2序列

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<400> 652
Leu Val Ser Lys Leu Asp Ser
1 5
<210> 653
<211> 7
<212> PRT
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<220>
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Asn Ala Lys Thr Leu Ala Glu
1 5
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Asn Ala Lys Thr Leu Ala Lys
1 5
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Gln Ala Ser Asn Lys Asp Thr
1 5
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<211> 7
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Arg Ala Asn Arg Leu Ala Asp
1 5

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<210> 657
<211> 7
<212> PRT
<213> 人工序列(Artificial Sequence)
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<400> 657
Arg Ala Asn Arg Leu Val Asp
1 5
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<213> 人工序列(Artificial Sequence)
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<400> 658
Arg Thr Ser Asn Leu Ala Ser
1 5
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Ser Ala Ser Tyr Arg Tyr Ser
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<211> 7
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<400> 660
Ser Ser Ser Tyr Arg Tyr Ser
1 5
<210> 661
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<212> PRT

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<213> 人工序列(Artificial Sequence)
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<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRL2序列
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Trp Ala Ser Thr Arg Glu Ser
1 5
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Cys Phe Gln Gly Ser His Val Pro Pro Thr Phe
1 5 10
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<400> 663
Cys Lys Gln Ser Tyr Tyr Leu Leu Thr Phe
1 5 10
<210> 664
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<213> 人工序列(Artificial Sequence)
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<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRL3序列
<400> 664
Cys Leu Gln Ala Thr His Gln Pro Trp Thr Phe
1 5 10
<210> 665
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
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<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRL3序列

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<400> 665
Cys Leu Gln Gly Thr His Gln Pro Leu Thr Phe
1 5 10
<210> 666
<211> 10
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Cys Leu Gln Tyr Asp Asp Leu Trp Thr Phe
1 5 10
<210> 667
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Cys Leu Gln Tyr Asp Glu Phe Pro Phe Thr Phe
1 5 10
<210> 668
<211> 11
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<213> 人工序列(Artificial Sequence)
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Cys Leu Gln Tyr Asp Glu Phe Pro Leu Thr Phe
1 5 10
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<211> 11
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Cys Met Gln Ala Leu Gln Thr Pro Leu Thr Phe
1 5 10

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<210> 670
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
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Cys Met Gln Ala Thr His Trp Pro Pro Thr Phe
1 5 10
<210> 671
<211> 12
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Cys Asn Ser Arg Asp Arg Arg Gly Tyr Ser Val Phe
1 5 10
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Cys Asn Ser Arg Lys Ser Ser Ser Lys Asn Val Val Phe
1 5 10
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1 5 10
<210> 674
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<212> PRT

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<213> 人工序列(Artificial Sequence)
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<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRL3序列
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Cys Gln His Phe Trp Gly Ser Thr Trp Thr Phe
1 5 10
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1 5 10
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Cys Gln His His Tyr Gly Thr Pro Tyr Thr Phe
1 5 10
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<400> 678
Cys Gln His His Tyr Gly Thr Trp Thr Phe
1 5 10
<210> 679
<211> 7
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Cys Gln His Arg Arg Thr Phe
1 5
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1 5 10
<210> 681
<211> 11
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Cys Gln Gln Ala Asn Ser Phe Pro Val Thr Phe
1 5 10
<210> 682
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<400> 682
Cys Gln Gln Ala Tyr Asp Phe Pro Leu Thr Phe
1 5 10

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<210> 683
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
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<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRL3序列
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Cys Gln Gln Gly Tyr Ser Thr Pro Leu Thr Phe
1 5 10
<210> 684
<211> 11
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Cys Gln Gln Gly Tyr Thr Ile Pro Ile Thr Phe
1 5 10
<210> 685
<211> 11
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Cys Gln Gln Arg Ser Asn Trp Pro Leu Thr Phe
1 5 10
<210> 686
<211> 11
<212> PRT
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<400> 686
Cys Gln Gln Arg Ser Asn Trp Pro Val Thr Phe
1 5 10
<210> 687
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<212> PRT

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<213> 人工序列(Artificial Sequence)
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<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRL3序列
<400> 687
Cys Gln Gln Ser Asn Ser Trp Pro Leu Thr Phe
1 5 10
<210> 688
<211> 11
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<213> 人工序列(Artificial Sequence)
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<400> 688
Cys Gln Gln Ser Tyr Ser Thr Pro Leu Thr Phe
1 5 10
<210> 689
<211> 11
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<213> 人工序列(Artificial Sequence)
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Cys Gln Gln Thr Tyr Ala Ile Pro Leu Thr Phe
1 5 10
<210> 690
<211> 11
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<213> 人工序列(Artificial Sequence)
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<400> 690
Cys Gln Gln Tyr Asn Ser Phe Pro Leu Thr Phe
1 5 10
<210> 691
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
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<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRL3序列

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<400> 691
Cys Gln Gln Tyr Asn Ser Tyr Pro Leu Thr Phe
1 5 10
<210> 692
<211> 11
<212> PRT
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Cys Gln Gln Tyr Tyr Asn Tyr Pro Ile Thr Phe
1 5 10
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<211> 11
<212> PRT
<213> 人工序列(Artificial Sequence)
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<223> 在实验室中制备的针对hASGR1/2的结合剂的合成的CDRL3序列
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Cys Trp Gln Gly Thr His Phe Pro His Thr Phe
1 5 10
<210> 694
<211> 12
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Asn Ser Leu Glu Arg Ile Gly Tyr Leu Ser Tyr Val
1 5 10
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Gln Gln Trp Ser Gly Tyr Pro Tyr Thr
1 5

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<210> 696
<211> 9
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Trp Gln Gly Thr His Phe Pro Tyr Thr
1 5
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<223> 在实验室中制备的针对hRNF43/ZNRF3的结合剂的合成的CDRH2序列
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Ser Tyr Ile Ser Arg Ser Ser Ser Thr Ile Tyr Tyr Ala
1 5 10
<210> 698
<211> 4
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<213> 人工序列(Artificial Sequence)
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<223> 在实验室中制备的合成的肽接头
<400> 698
Gly Gly Gly Gly
1
<210> 699
<211> 5
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<213> 人工序列(Artificial Sequence)
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<223> 在实验室中制备的合成的肽接头
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Gly Gly Gly Gly Gly
1 5
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<212> PRT

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<213> 人工序列(Artificial Sequence)
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<223> 在实验室中制备的合成的肽接头
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Gly Gly Gly Gly Gly Gly Gly
1 5
<210> 701
<211> 5
<212> PRT
<213> 人工序列(Artificial Sequence)
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<223> 在实验室中制备的合成的肽接头
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Gly Gly Gly Gly Ser
1 5
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<211> 6
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<213> 人工序列(Artificial Sequence)
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<223> 在实验室中制备的合成的肽接头
<400> 702
Gly Gly Gly Gly Gly Lys
1 5
<210> 703
<211> 7
<212> PRT
<213> 人工序列(Artificial Sequence)
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<223> 在实验室中制备的合成的肽接头
<400> 703
Gly Gly Gly Gly Gly Lys Arg
1 5
<210> 704
<211> 8
<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的合成的肽接头

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<400> 704
Gly Gly Gly Lys Gly Gly Gly Gly
1 5
<210> 705
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequene)
<220>
<223> 在实验室中制备的CDRH1
<400> 705
Gly Phe Thr Phe Ser His Tyr Thr Leu
1 5
<210> 706
<211> 17
<212> PRT
<213> 人工序列(Artificial Sequene)
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<223> 在实验室中制备的CDRH2
<400> 706
Val Ile Ser Gly Asp Gly Ser Tyr Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15
Gly
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<213> 人工序列(Artificial Sequence)
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Asn Phe Ile Lys Tyr Val Phe Ala Asn
1 5
<210> 708
<211> 11
<212> PRT
<213> 人工序列(Artificial Sequene)
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<223> 在实验室中制备的CDRL1
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Ser Gly Asp Lys Leu Gly Lys Lys Tyr Ala Ser

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1 5 10

<210> 709

<211> 11

<212> PRT

<213> 人工序列(Artificial Sequene)

<220>

<223> 在实验室中制备的CDRL1

<400> 709

Ser Gly Asp Asn Ile Gly Ser Phe Tyr Val His

1 5 10

<210> 710

<211> 8

<212> PRT

<213> 人工序列(Artificial Sequence)

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<223> 在实验室中制备的CDRL2

<400> 710

Glu Lys Asp Asn Arg Pro Ser Gly

1 5

<210> 711

<211> 8

<212> PRT

<213> 人工序列(Artificial Sequence)

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<223> 在实验室中制备的CDRL2

<400> 711

Asp Lys Ser Asn Arg Pro Ser Gly

1 5

<210> 712

<211> 8

<212> PRT

<213> 人工序列(Artificial Sequence)

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<223> 在实验室中制备的CDRL3

<400> 712

Ser Ser Phe Ala Gly Asn Ser Leu

1 5

<210> 713

<211> 8

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<212> PRT
<213> 人工序列(Artificial Sequence)
<220>
<223> 在实验室中制备的CDRL3
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Gln Ser Tyr Ala Asn Thr Leu Ser
1 5
<210> 714
<211> 90
<212> PRT
<213> 智人(Homo sapiens)
<400> 714
Lys Met Tyr His Thr Lys Gly Gln Glu Gly Ser Val Cys Leu Arg Ser
1 5 10 15
Ser Asp Cys Ala Ser Gly Leu Cys Cys Ala Arg His Phe Trp Ser Lys
20 25 30
Ile Cys Lys Pro Val Leu Lys Glu Gly Gln Val Cys Thr Lys His Arg
35 40 45
Arg Lys Gly Ser His Gly Leu Glu Ile Phe Gln Arg Cys Tyr Cys Gly
50 55 60
Glu Gly Leu Ser Cys Arg Ile Gln Lys Asp His His Gln Ala Ser Asn
65 70 75 80
Ser Ser Arg Leu His Thr Cys Gln Arg His
85 90
<210> 715
<211> 88
<212> PRT
<213> 智人(Homo sapiens)
<400> 715
Lys Met Ser His Ile Lys Gly His Glu Gly Asp Pro Cys Leu Arg Ser
1 5 10 15
Ser Asp Cys Ile Glu Gly Phe Cys Cys Ala Arg His Phe Trp Thr Lys
20 25 30
Ile Cys Lys Pro Val Leu His Gln Gly Glu Val Cys Thr Lys Gln Arg
35 40 45
Lys Lys Gly Ser His Gly Leu Glu Ile Phe Gln Arg Cys Asp Cys Ala
50 55 60
Lys Gly Leu Ser Cys Lys Val Trp Lys Asp Ala Thr Tyr Ser Ser Lys
65 70 75 80

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Ala Arg Leu His Val Cys Gln Lys
85

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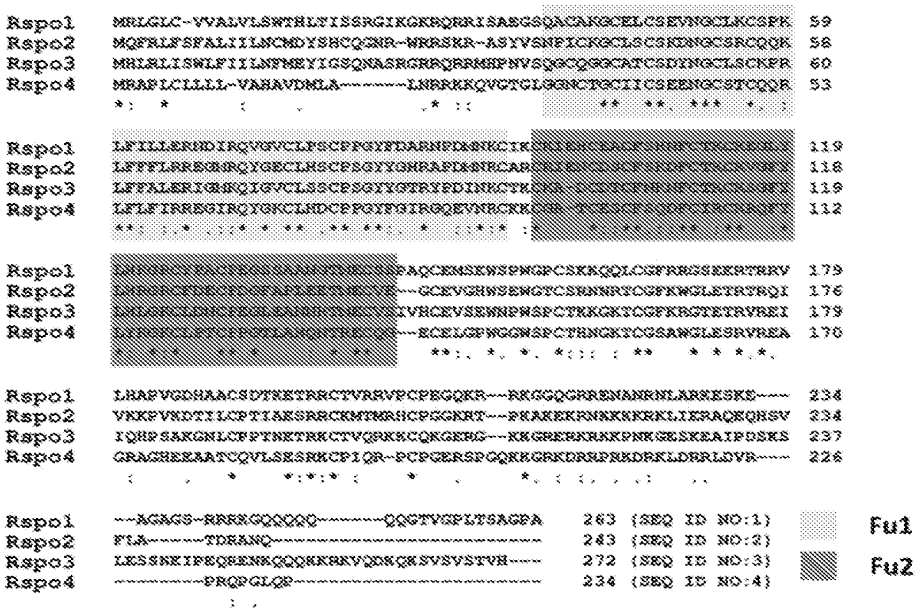


图1A

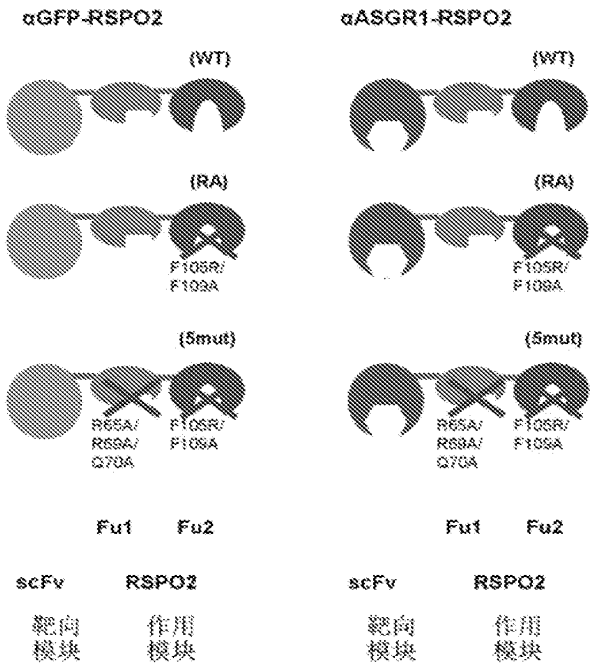


图1B

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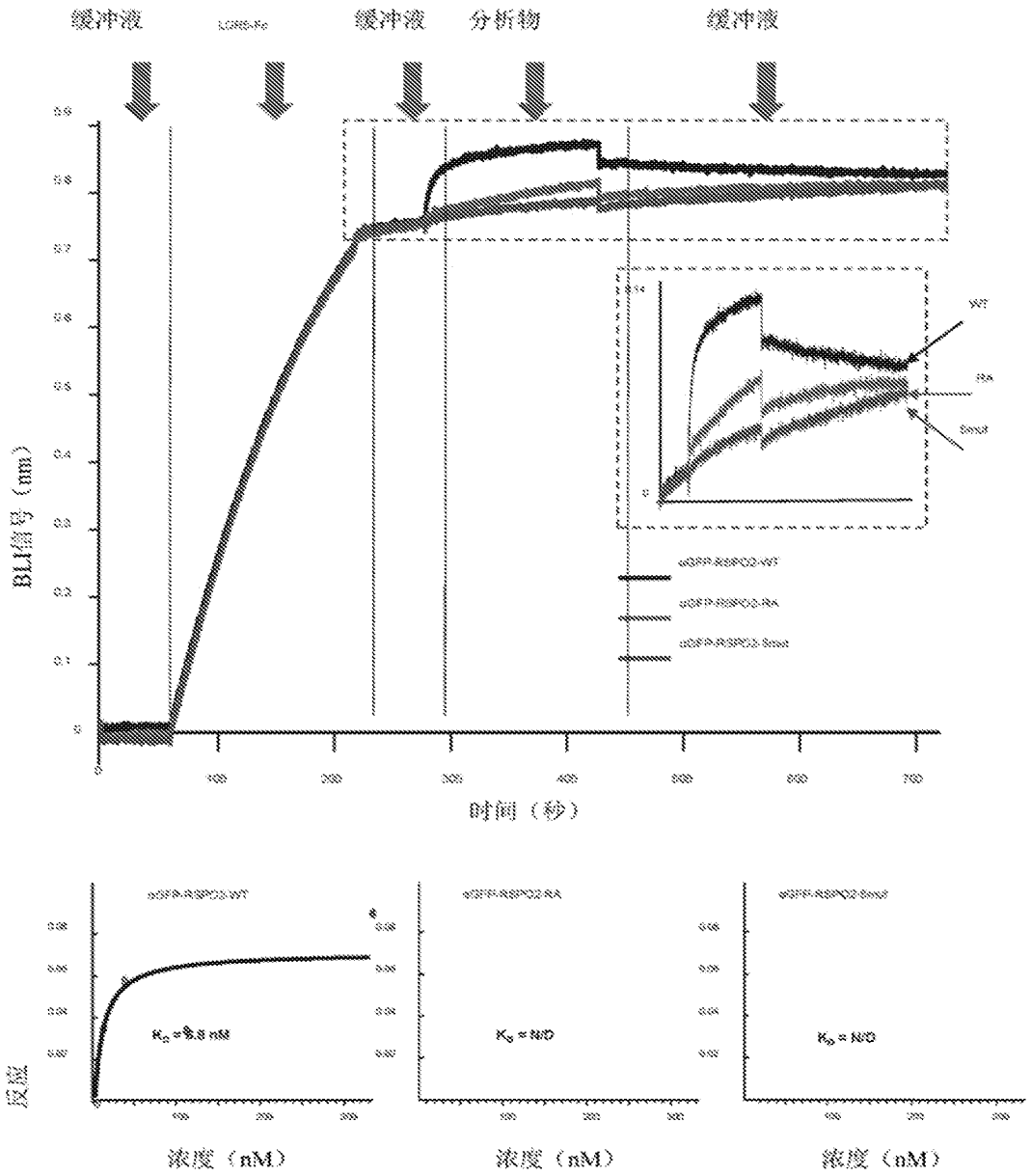


图1C

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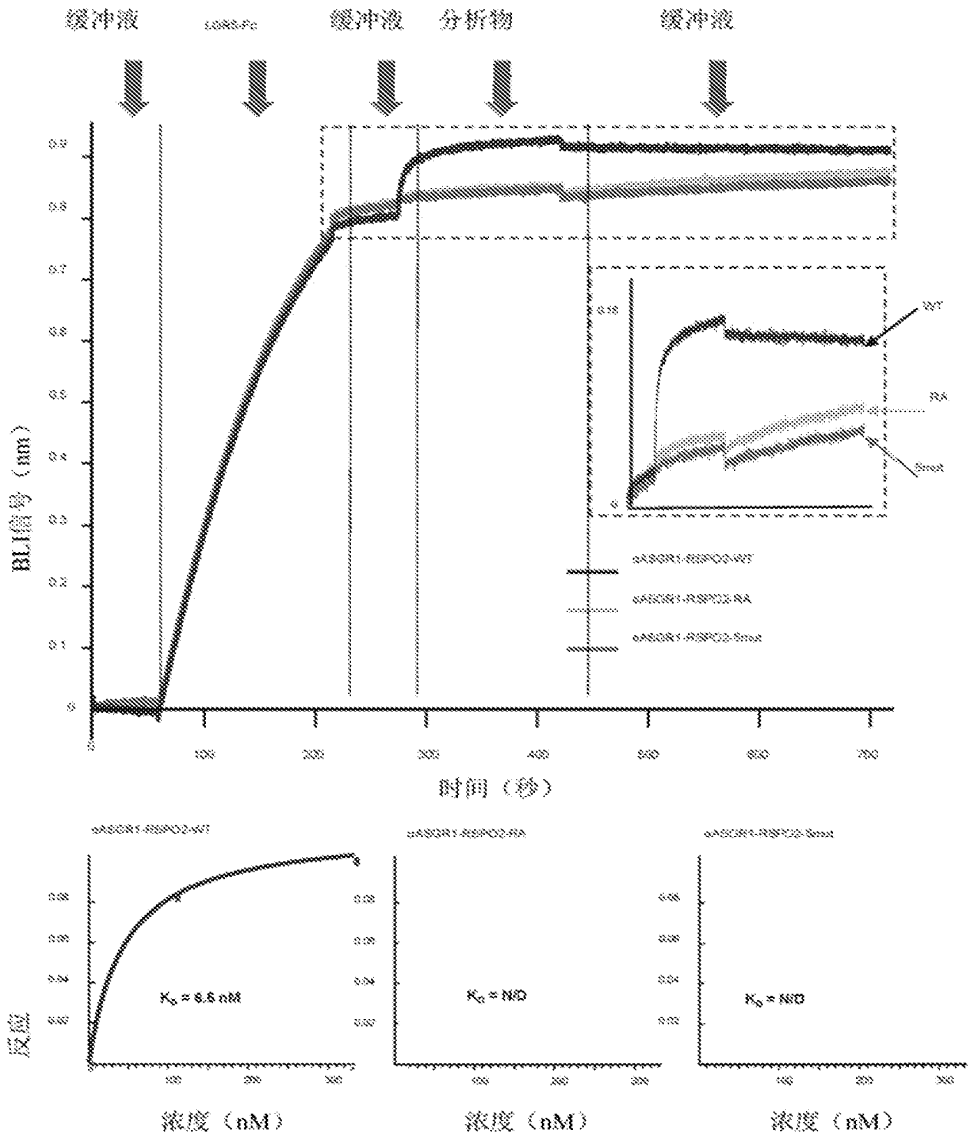


图1C(续)

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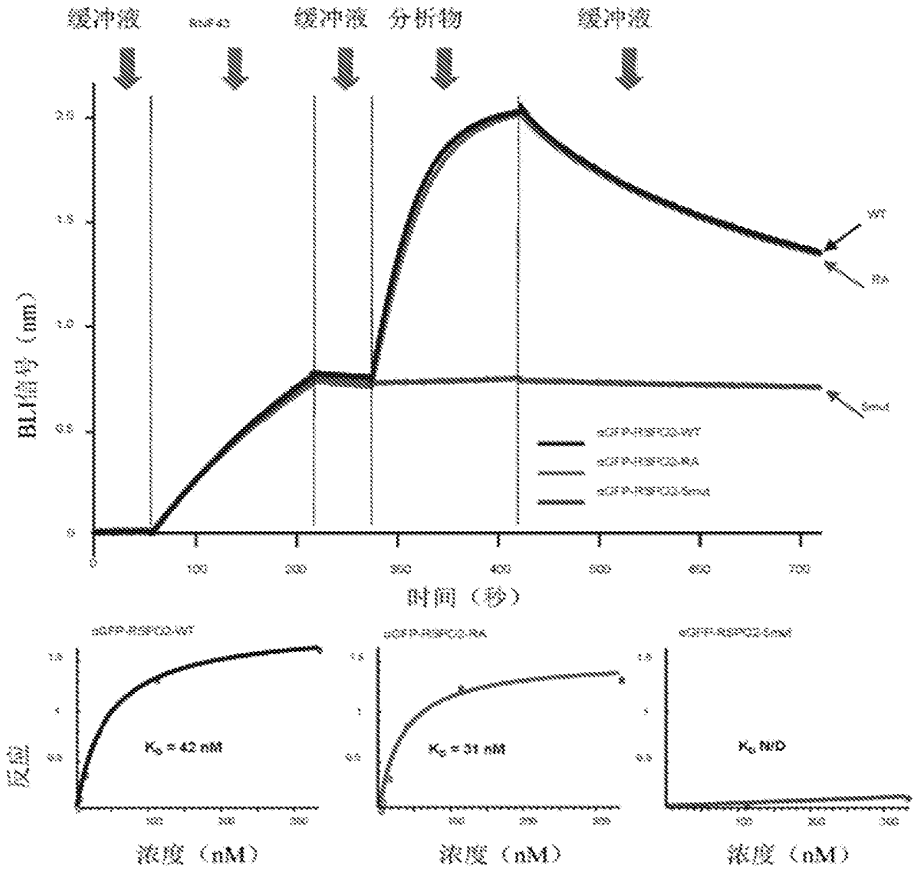


图1D

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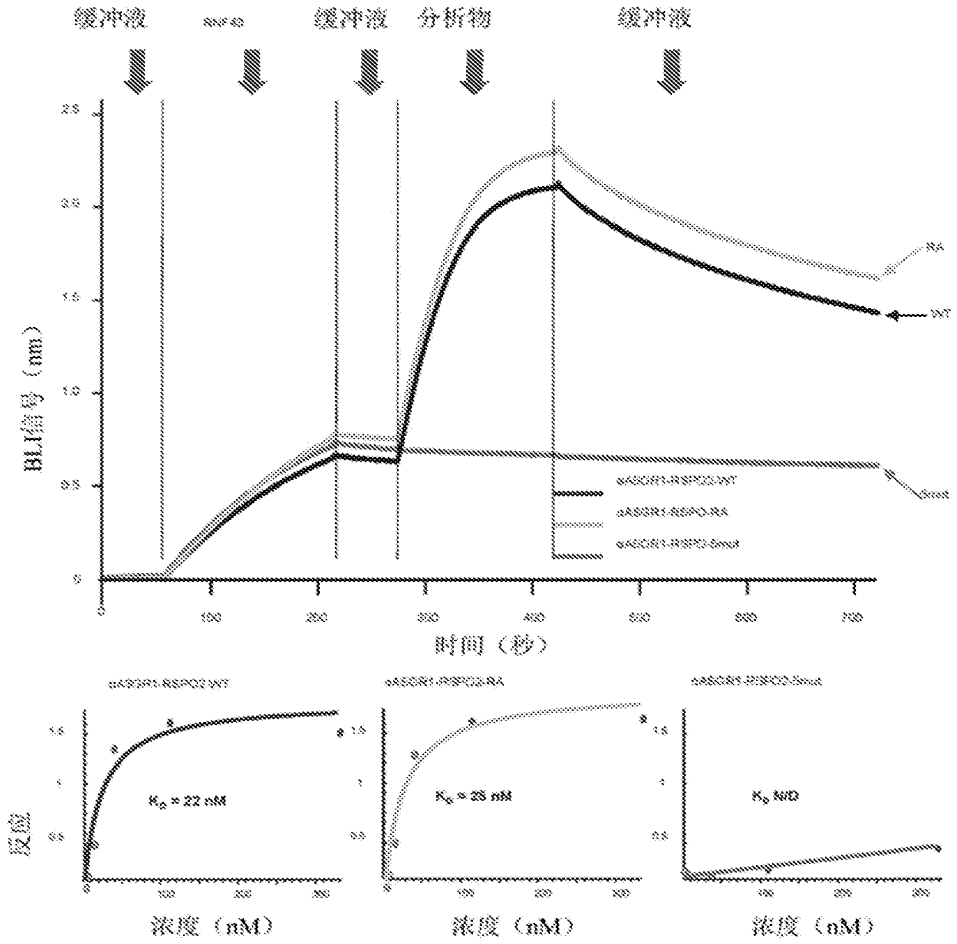


图1D(续)

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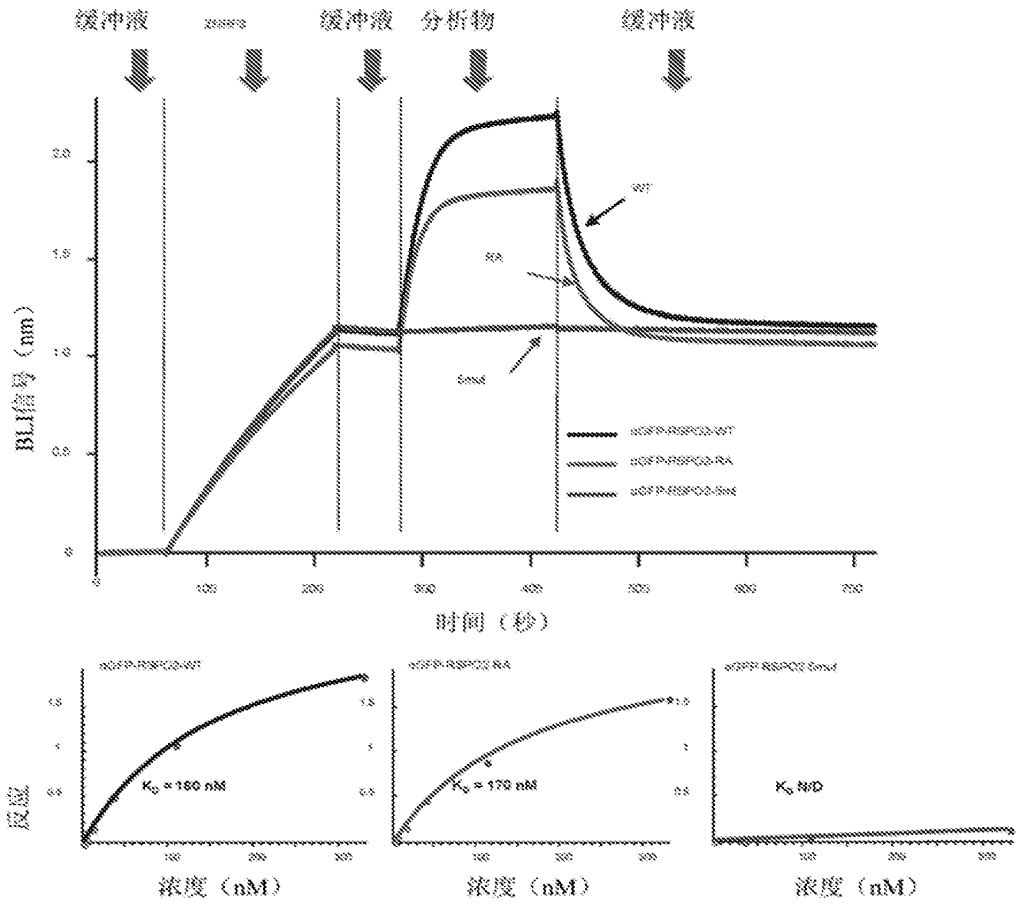


图1D(续)

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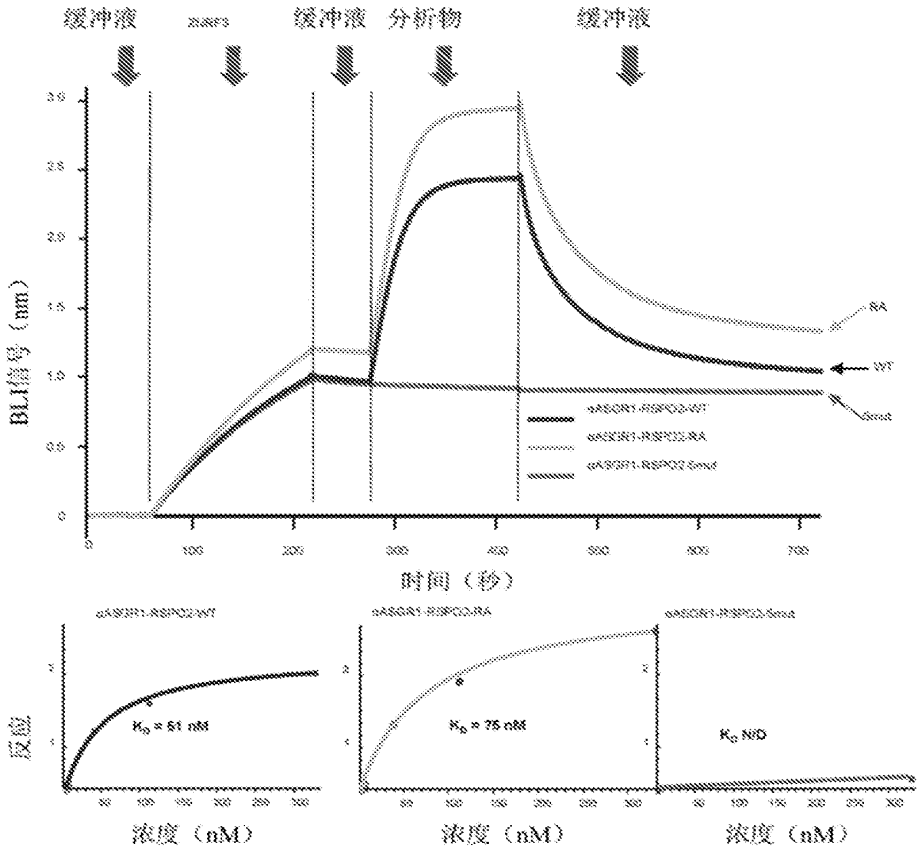


图1D(续)

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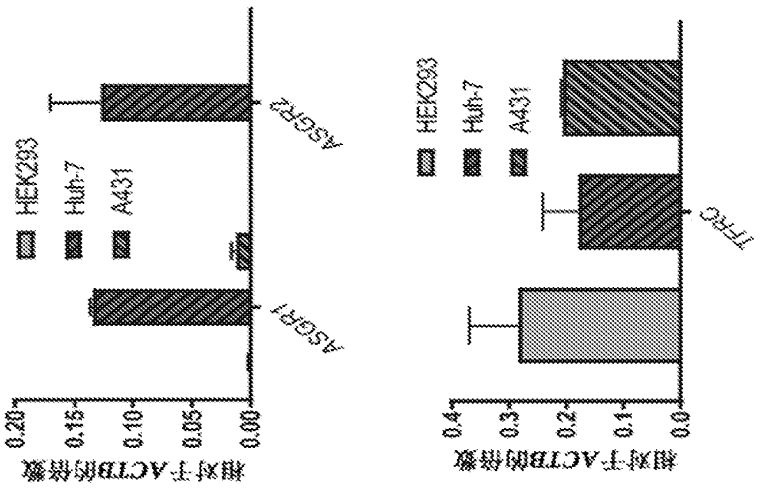


图2A

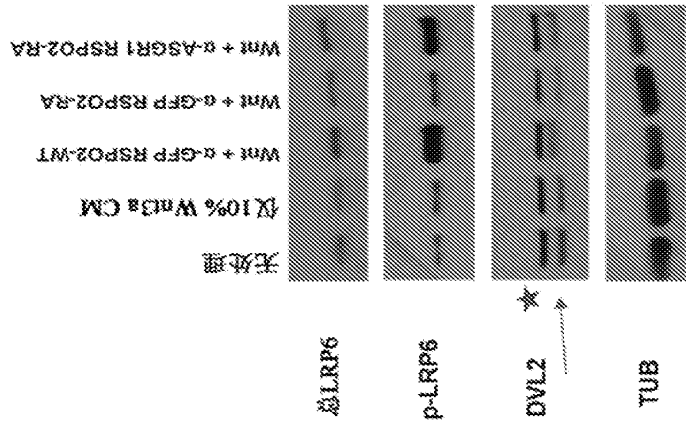


图2C

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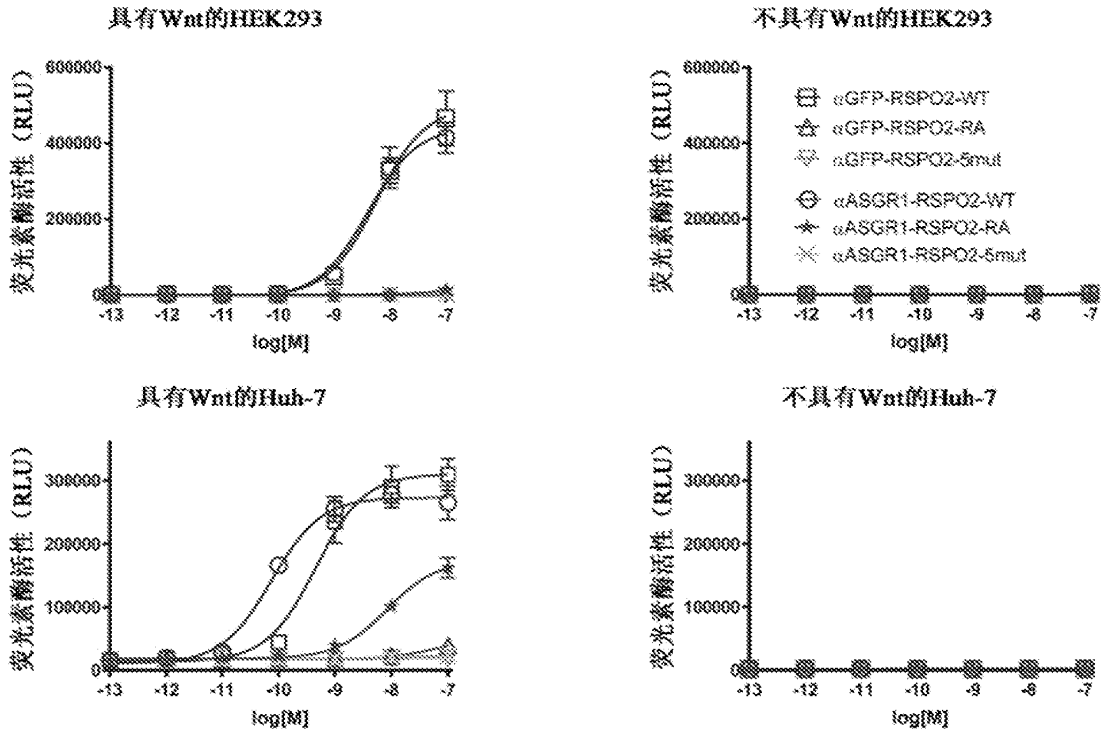


图2B

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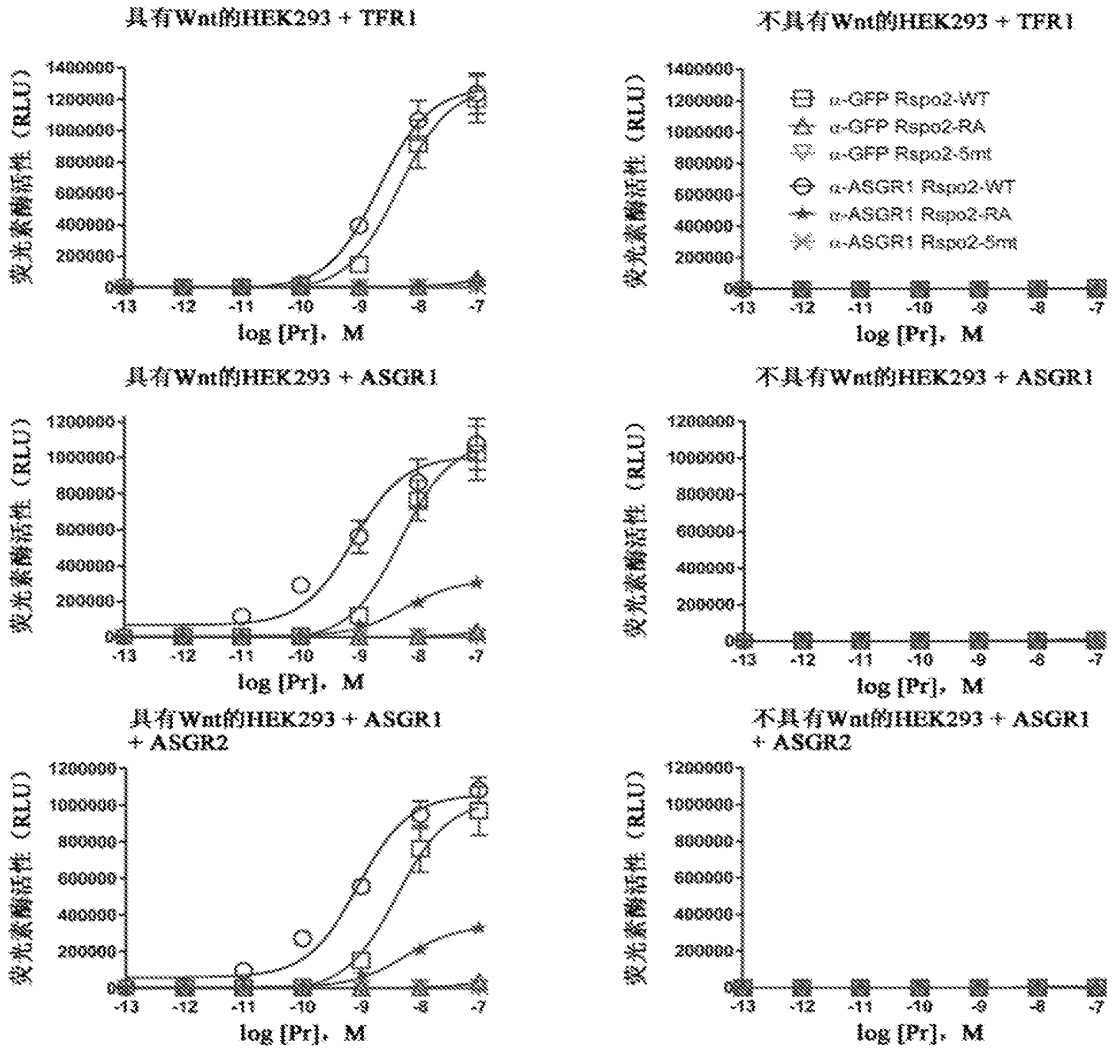


图3A

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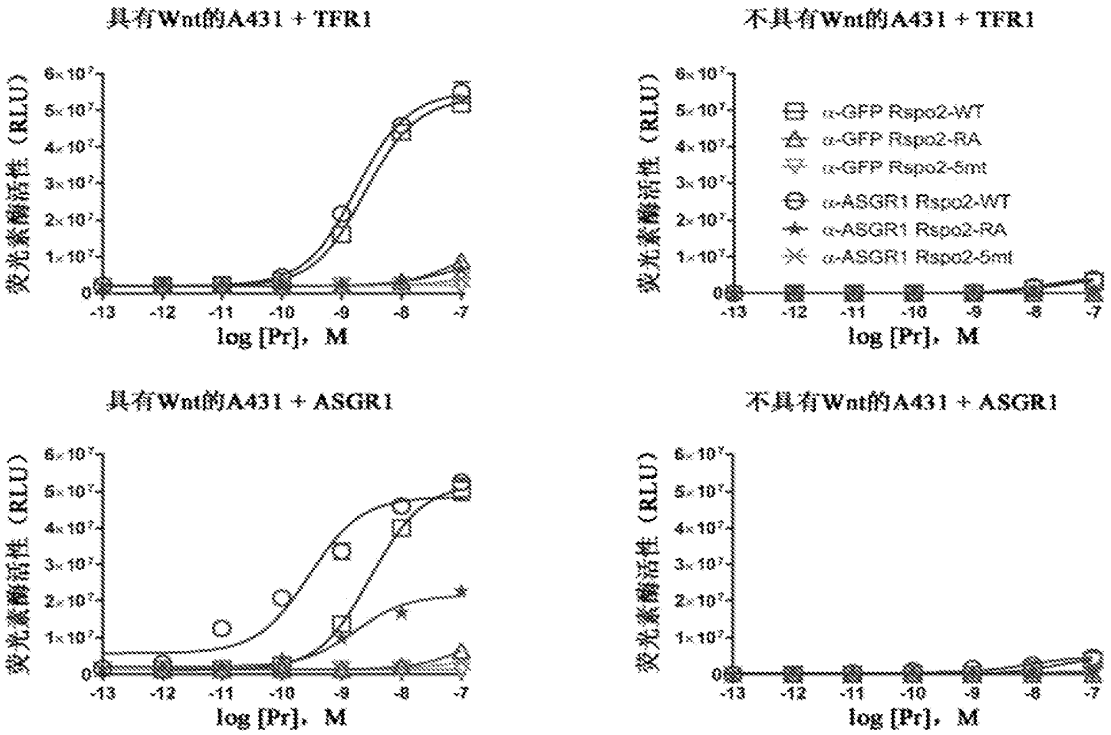


图3B

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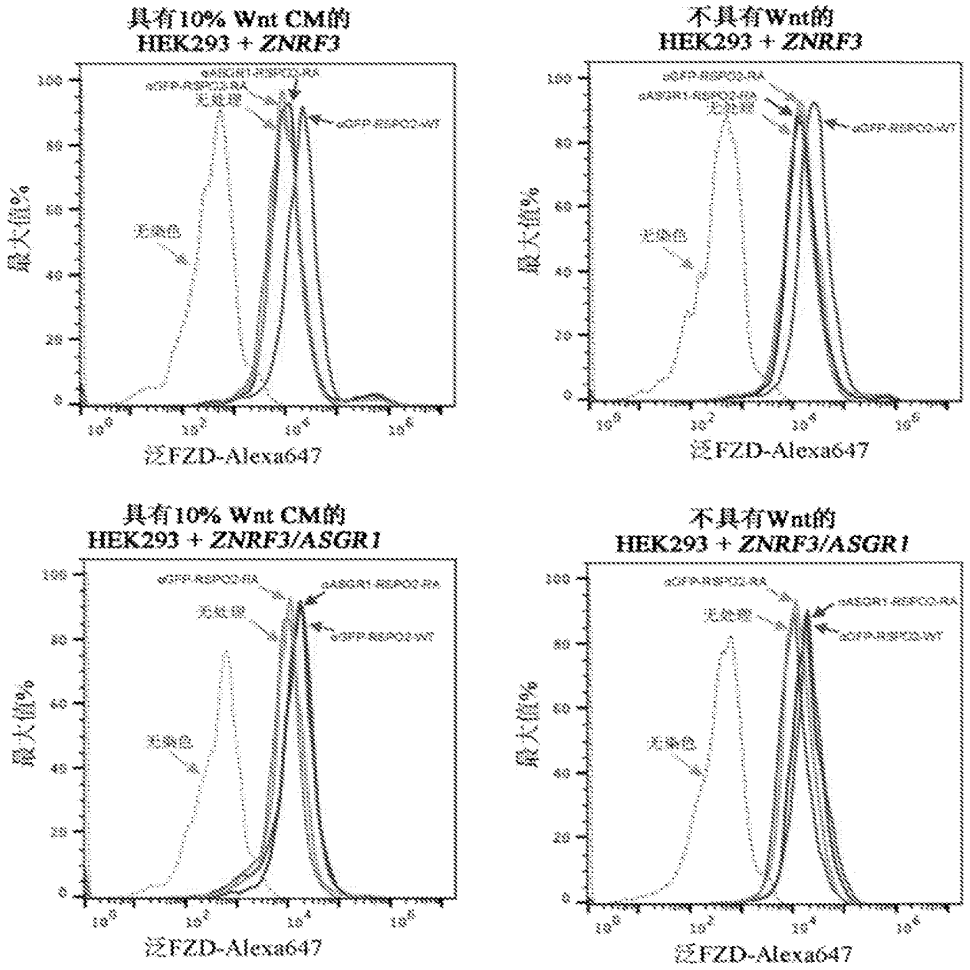


图3C

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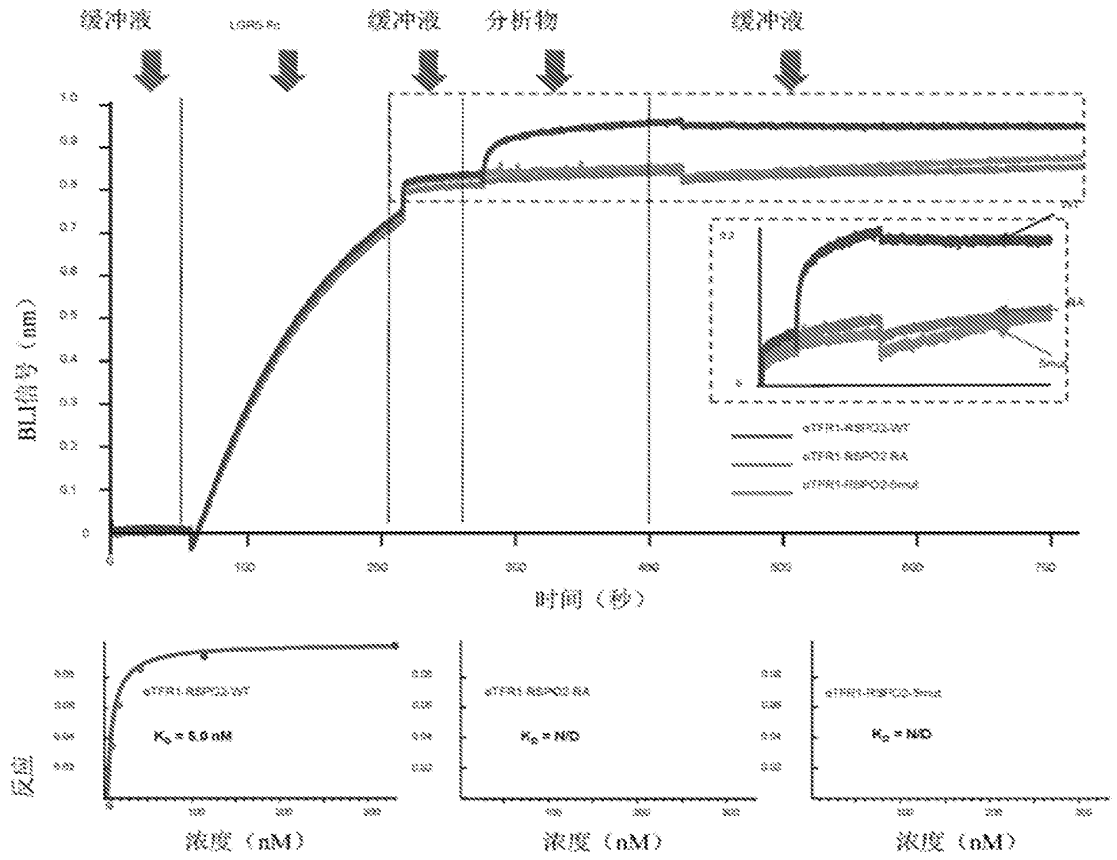


图4A

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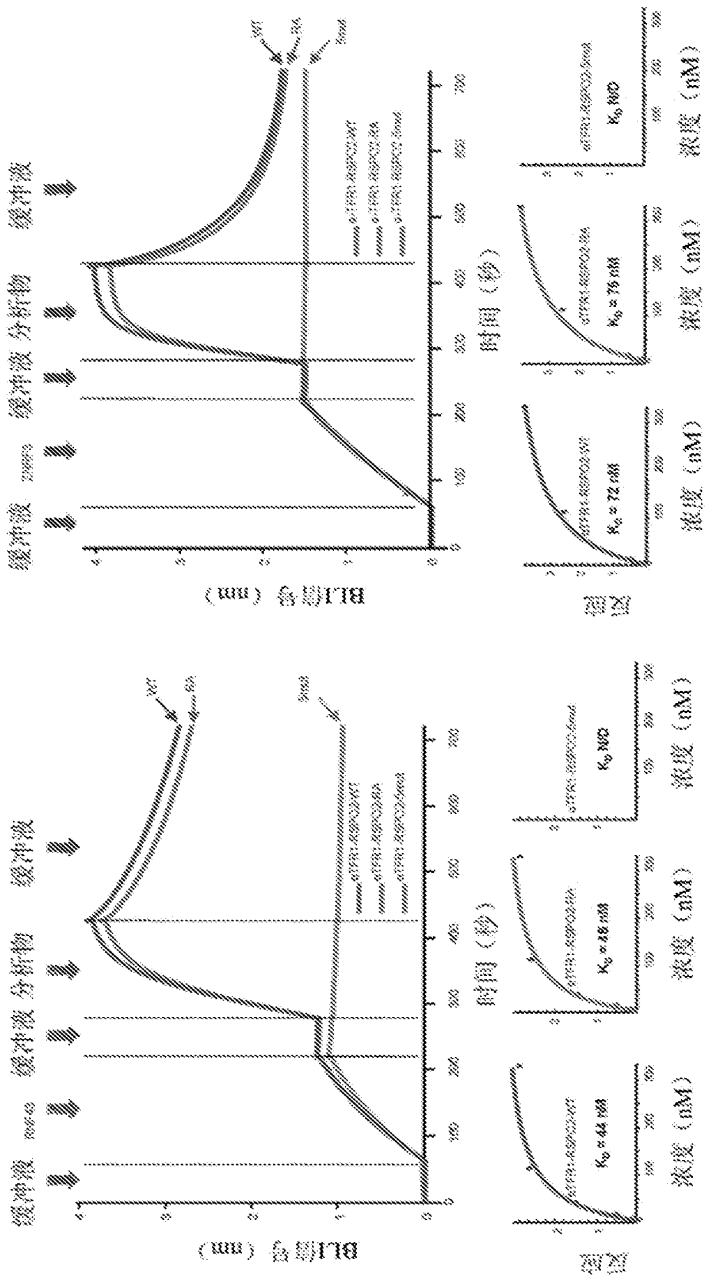


图4B

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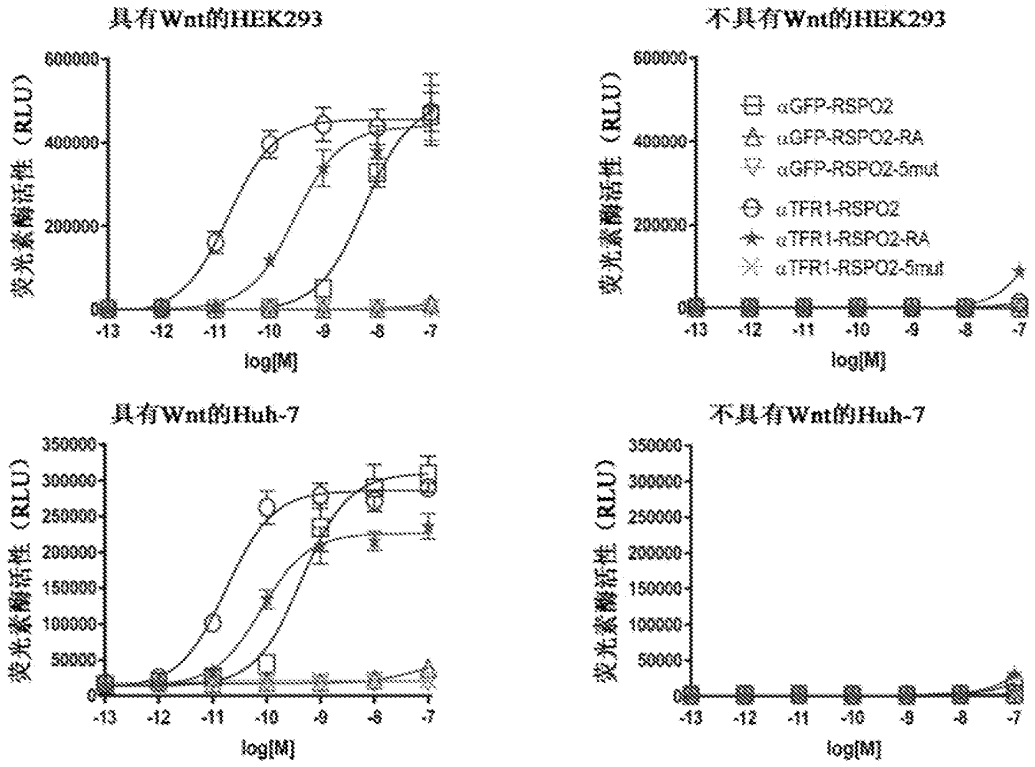


图4C

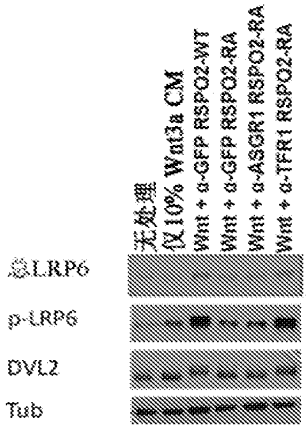


图4D

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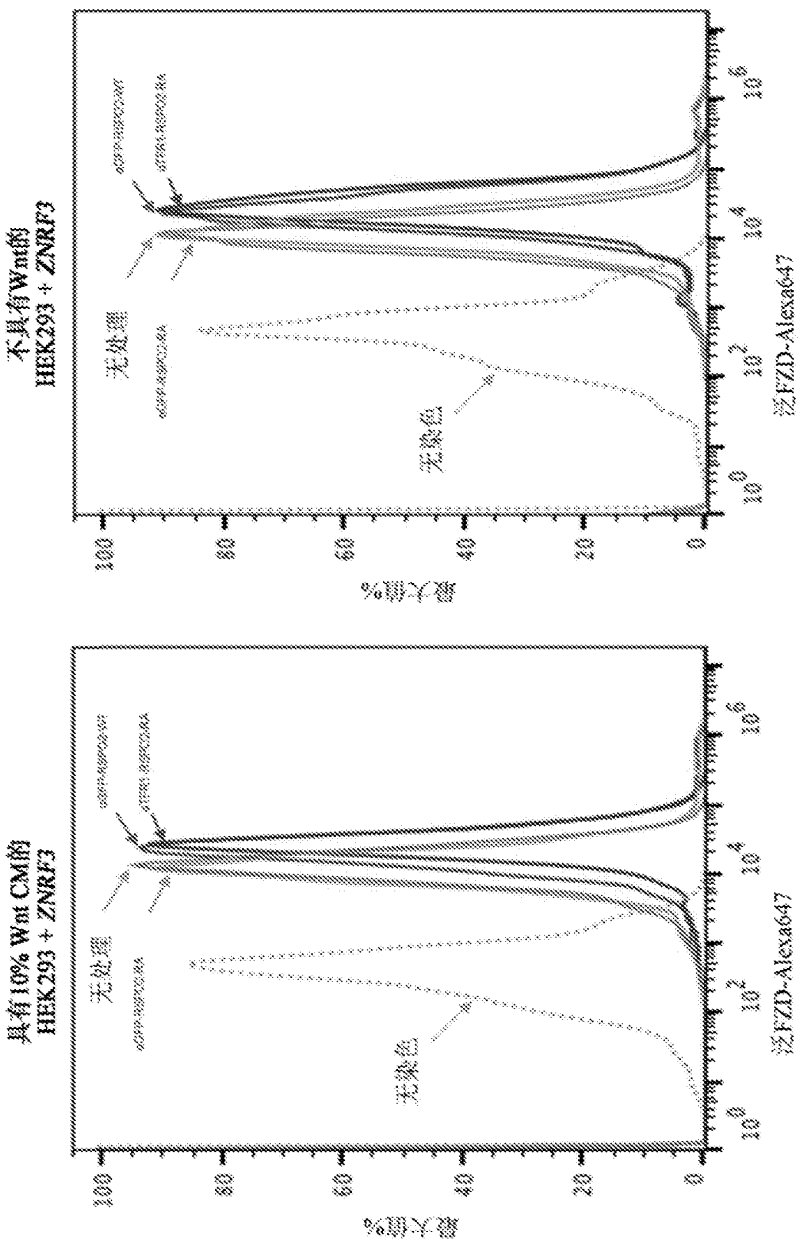


图4E

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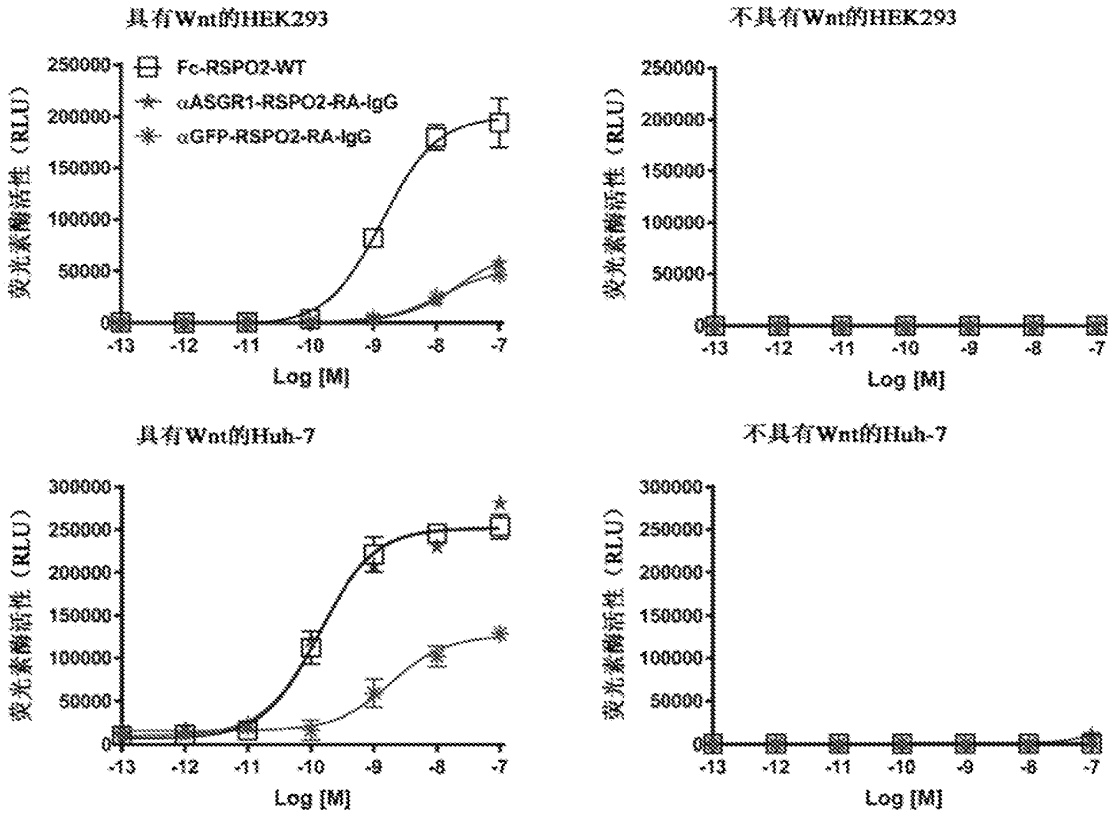


图5A

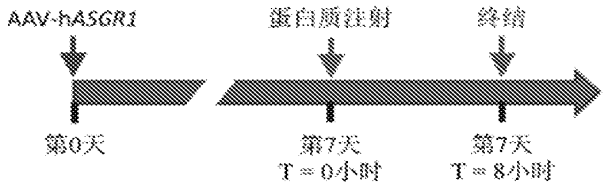


图5B

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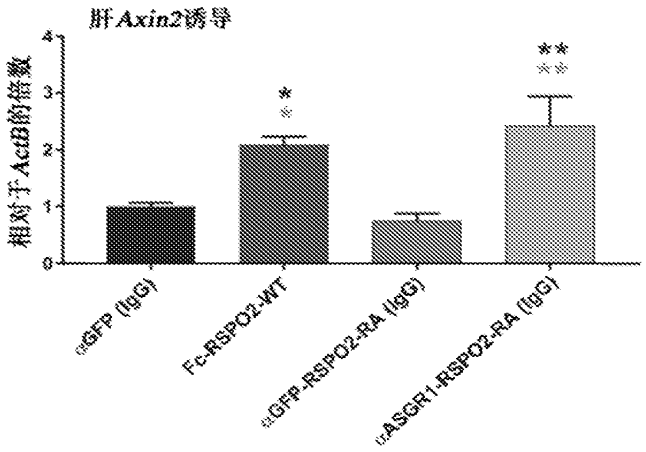


图5C

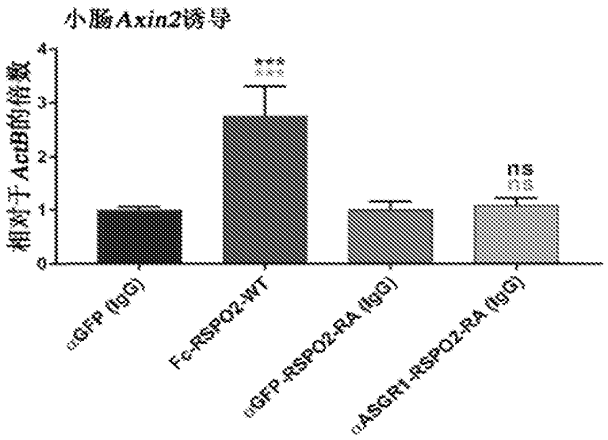


图5D

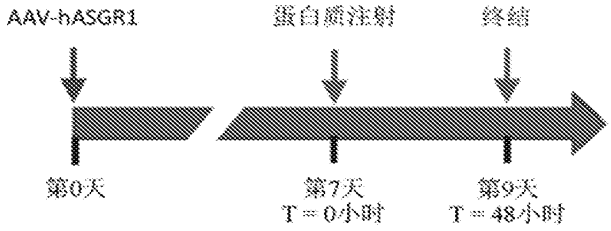


图6A

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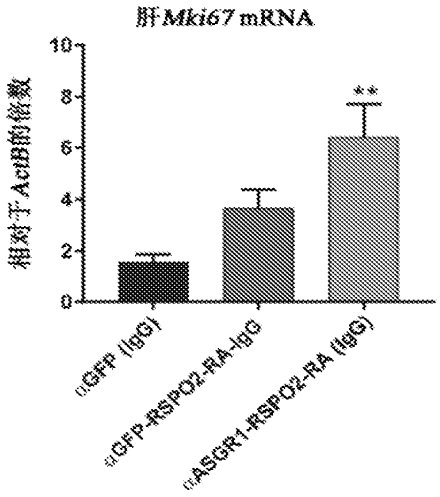


图6B

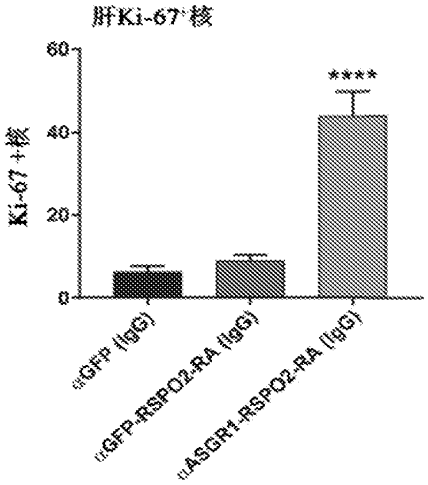


图6C

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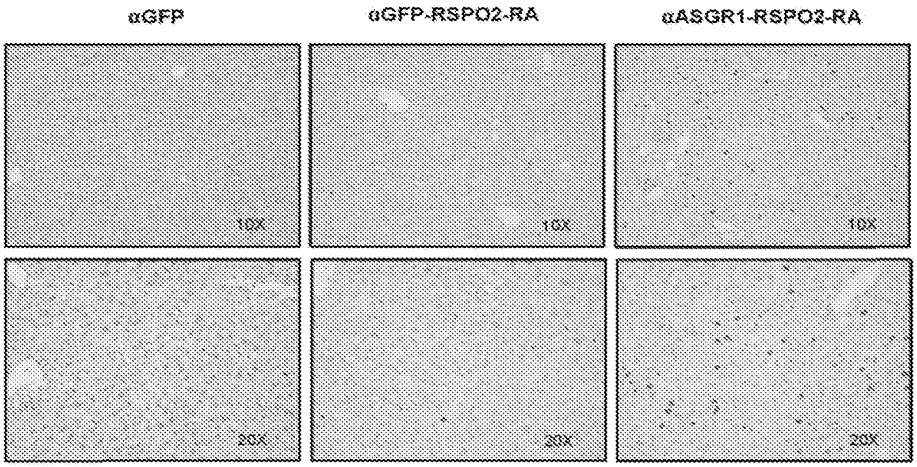


图6D

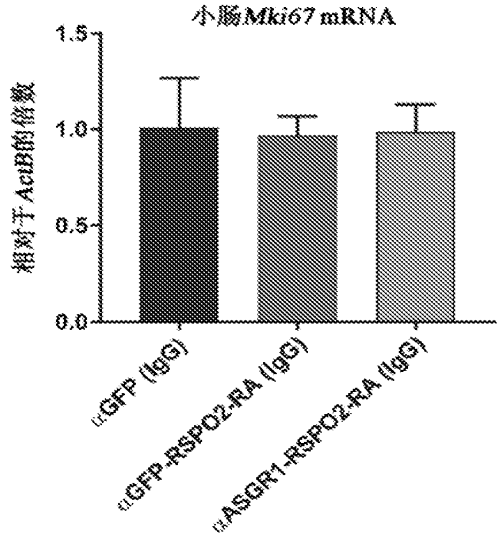


图6E

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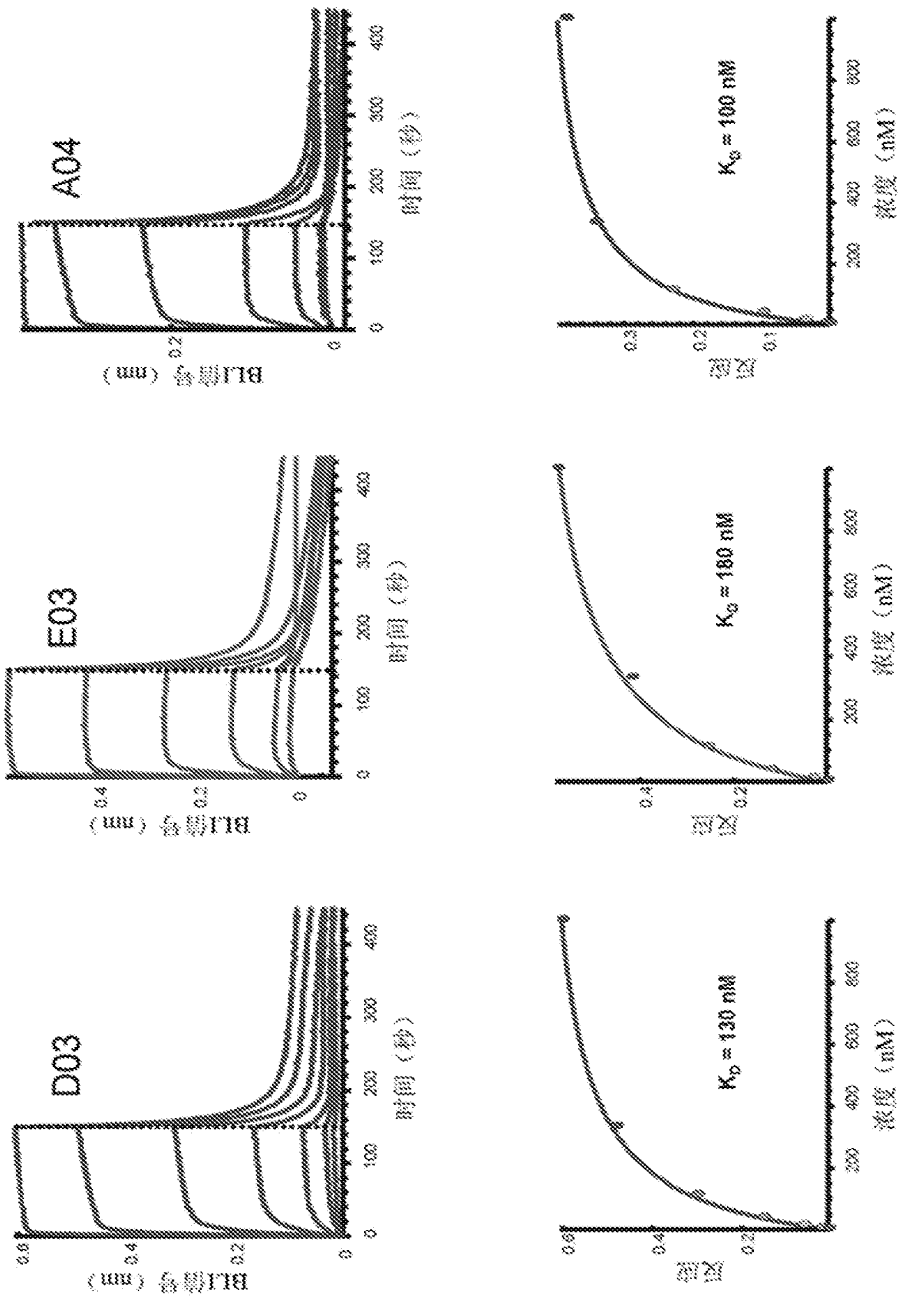


图7A

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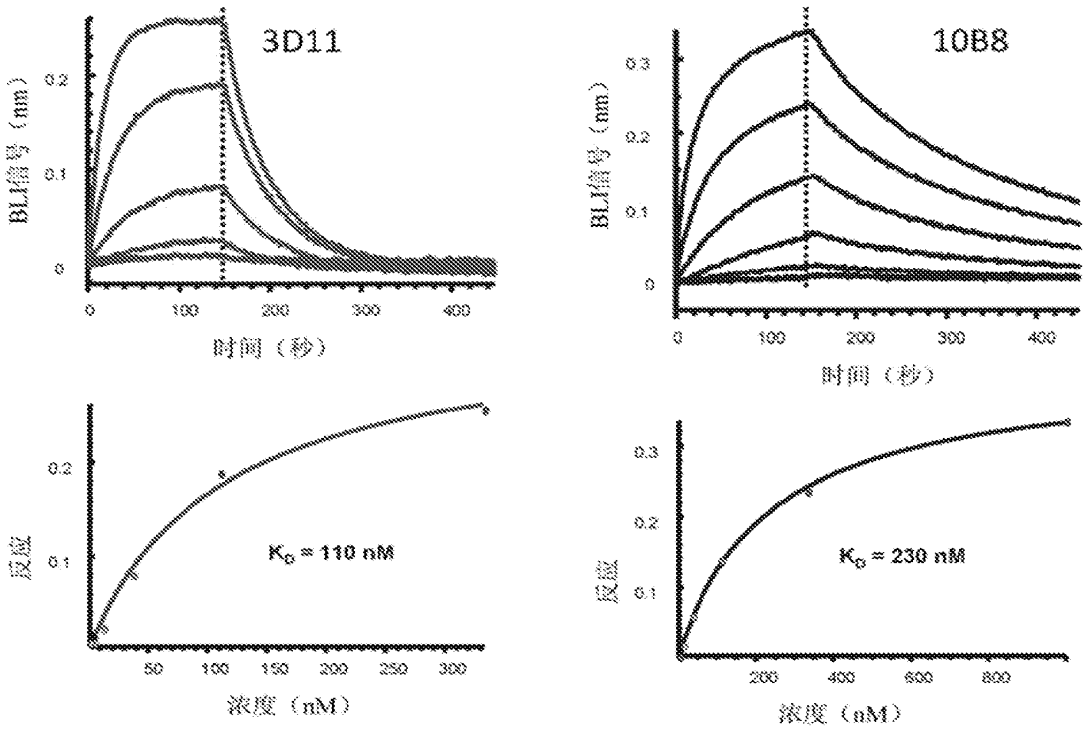


图7B

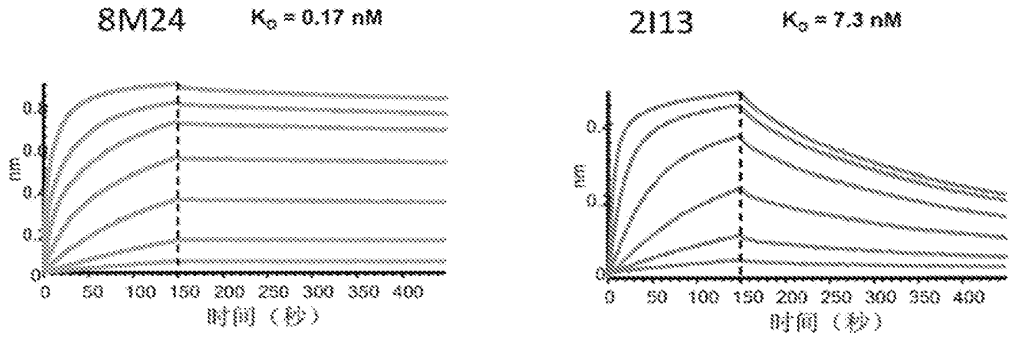


图7C

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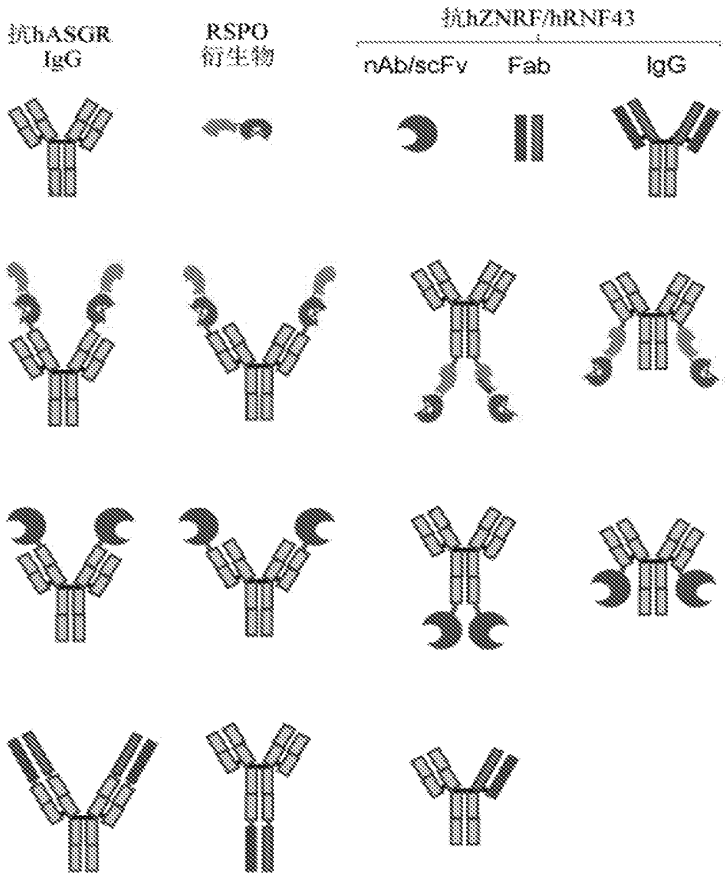


图8

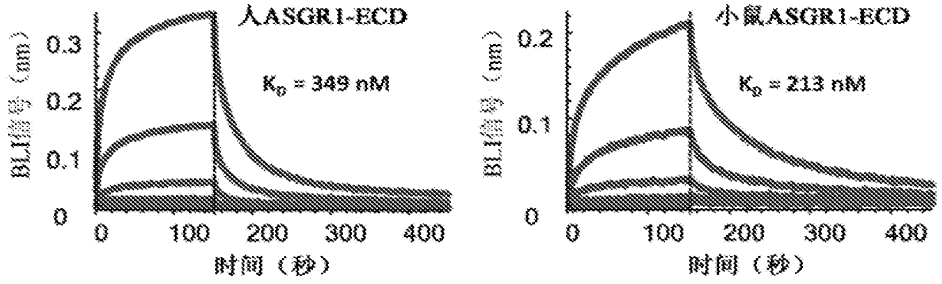


图9A

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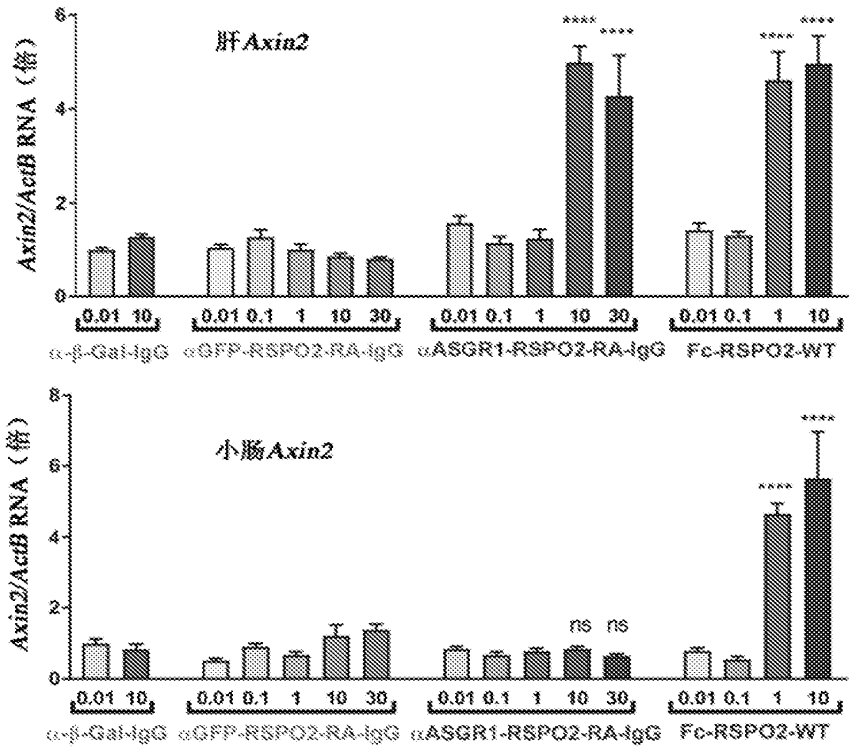


图9B

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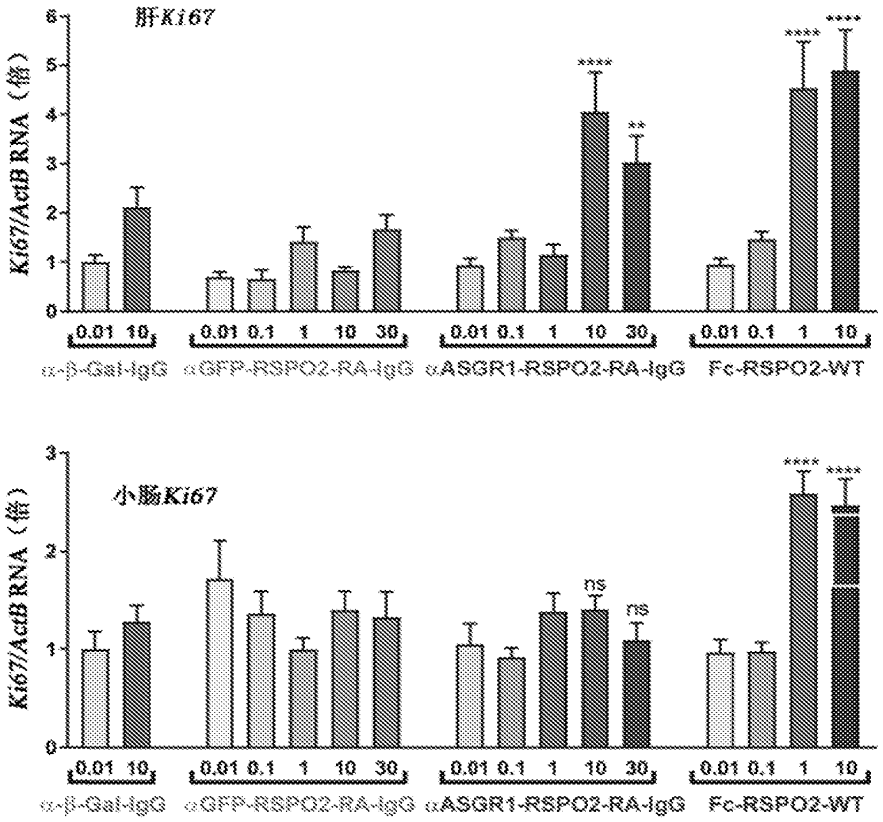


图9C

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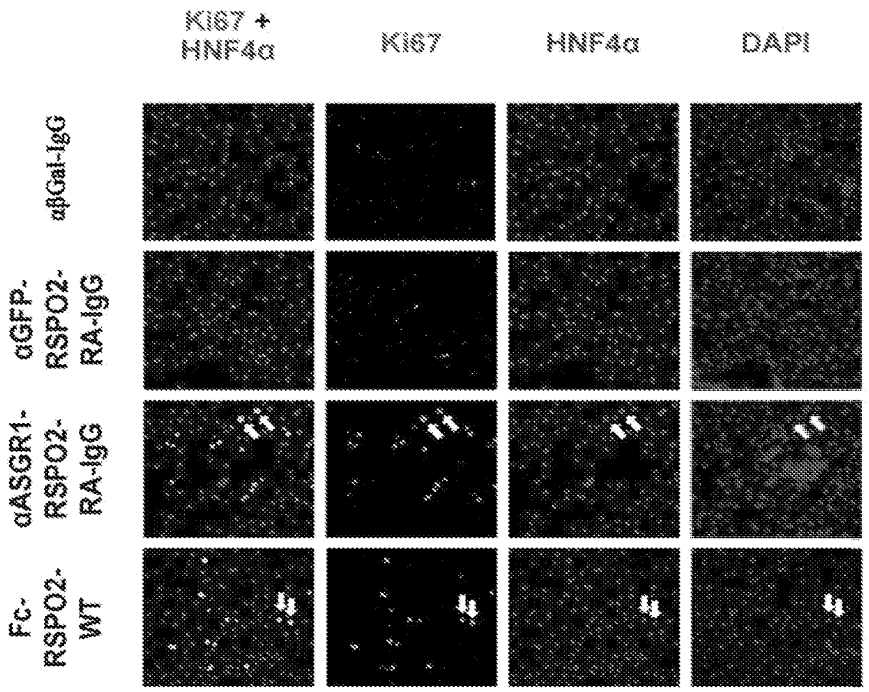


图9D

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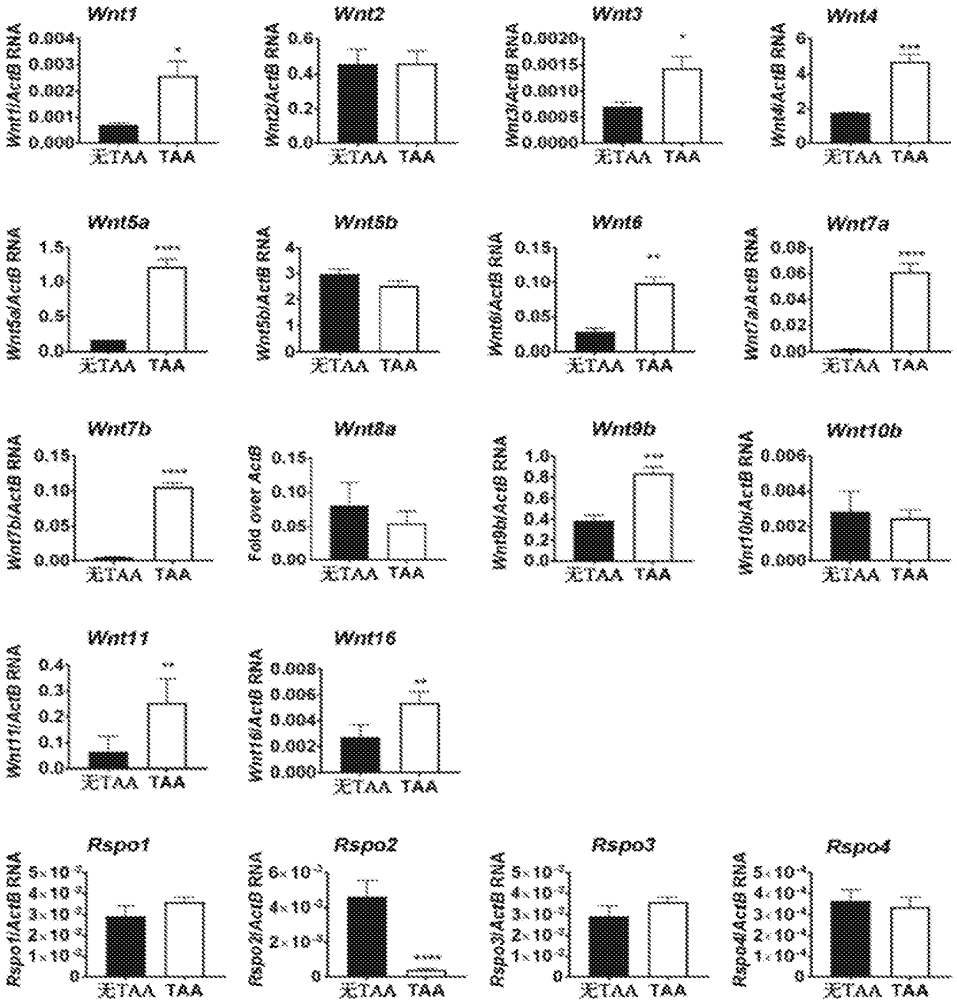


图10A

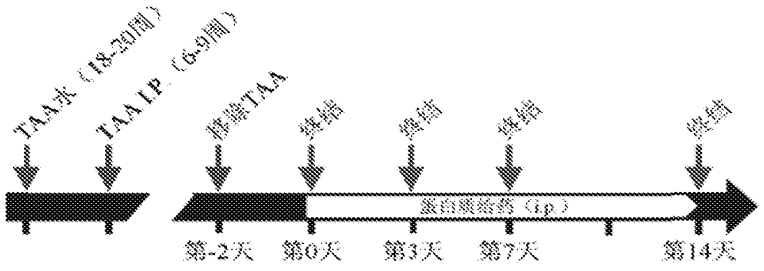


图10B

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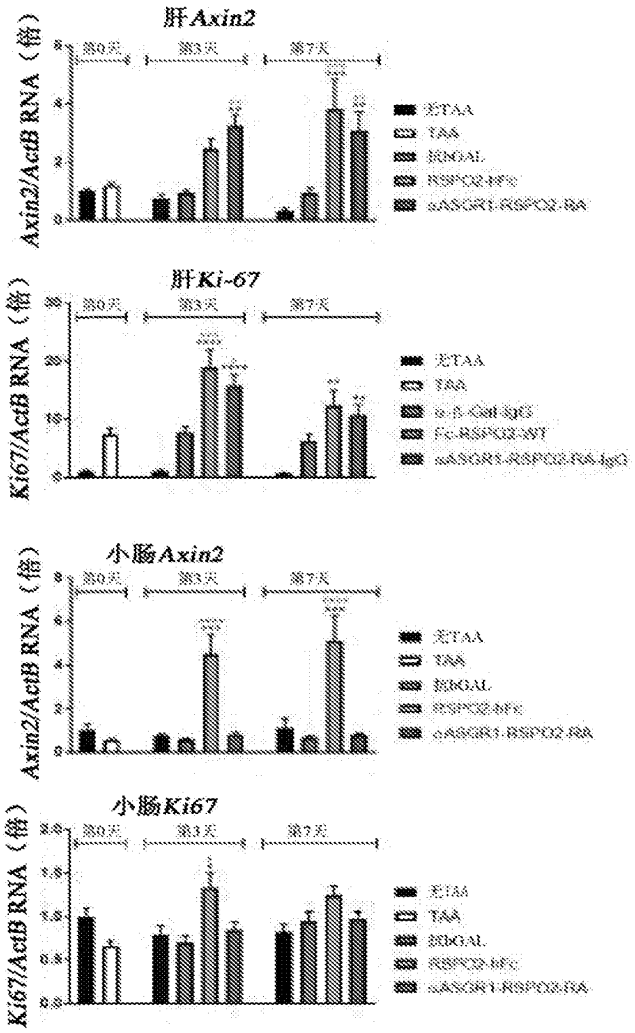


图10C

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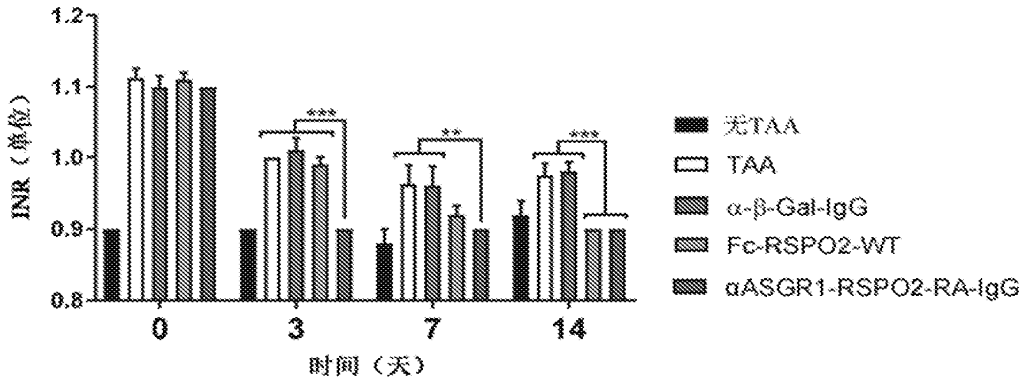


图10D

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Wnt信号增强子序列

抗GFP RSPO2野生型——多核苷酸（SEQ ID NO: 5）

CAGGTCCAGTTGGTGGAATCCGGAGGGGGTTTGGTCCAGCCTGGTGGAAGCCTG
CGCCTCTCATGCGCCGCTAGCGGATTCACCTTCTCCCGATACGGCATGCATTGGG
TCAGACAGGCACCCGGAAAAGGACTCGAATGGGTGTCGGGCATTTCCTCGATCG
GGTCAAACACCTATTACGCCGACTCCGTGAAGGGACGGTTCACCATTAGCCGGG
ATAACAGCAAGAACACTCTGTACTTGCAAATGAACTCCCTGCGGGCTGAGGACA
CCGCCGTGTACTACTGTGCGCGGTGGTACAAGACCTATATTGACGTCTGGGGACA
GGGTACCCTCGTGACCGTGTCATCCGGTGGTGGAGGATCCGGAGGCGGAGGAAG
CGGAGGAGGGGGTTCAGACATCGAACTCACCCAGCCCCCGTCAGTGTCCGTGGC
CCCTGGACAGACTGCGCGCATCTCCTGCTCCGGCGACAACCTGGGGAAGAAATA
CGTGTACTGGTACCAGCAGAAGCCAGGTCAAGCCCCTGTGCTGGTCATCTACGGC
GACGACGAAAGGCCGTCAGGCATCCCAGAGCGCTTCTCCGGCTCCAACTCCGGG
AATACTGCCACCCTTACCATTTCCGGAACCCAGGCCGAGGATGAAGCGGATTACT
ATTGCGCGAGCTACGATAGCAGCCACATCCTGATCGTGTTTGGAGGCGGTACTAA
GCTGACCGTGCTGGGAAGCGGTGGATCAAACCCAATTTGCAAGGGATGCCTGAG
CTGTAGCAAGGACAACGGATGTTCACGGTGCCAGCAAAAGCTGTTTTTCTTCCTC
CGGCGGGAAGGAATGCGGCAGTACGGCGAATGTCTCCACTCCTGCCCCTCGGGG
TATTACGGACACCGCGCGCCTGACATGAACCGATGCGCCAGATGCCGGATCGAG
AACTGCGATAGCTGCTTCAGCAAGGACTTCTGCACTAAGTGCAAAGTCGGCTTCT
ACCTTCACCGGGGCAGATGTTTTGACGAATGCCCGGATGGCTTCGCCCCGCTGGA
GGAGACTATGGAATGCGTGGAGGGCGGAGACTACAAGGACGACGATGACAAGG
GCTCCCACCATCACCACCATCATCACCACTAG

抗GFP RSPO2野生型——多肽（SEQ ID NO: 6）

QVQLVESGGGLVQPGGSLRLSCAASGFTFSRYGMHWVRQAPGKGLEWVSGISSIGS
NTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARWYKTYIDVWGQGT
LVTVSSGGGGSGGGGSGGGGSDIELTQPPSVSVAPGQTARISCSGDNLGKKYVYWY
QQKPGQAPVLVIYGDDERPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCASYDSS
HILIVFGGGTKLTVLGSGGSNPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGEC
LHSCPSGYYGHRAPDMNRCARCRIENCDSCFSKDFCTKCKVGFYLHRGRCFDECPD
GFAPLEETMECVEGGDYKDDDDKGSHHHHHHHHH

图11A

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抗GFP RSPO2（F105R/F109A）——多核苷酸（SEQ ID NO: 7）

CAGGTCCAGTTGGTGGAATCCGGAGGGGGTTTGGTCCAGCCTGGTGGAAGCCTG
CGCCTCTCATGCGCCGCTAGCGGATTCACCTTCTCCCGATACGGCATGCATTGGG
TCAGACAGGCACCCGGAAAAGGACTCGAATGGGTGTCGGGCATTTCCTCGATCG
GGTCAAACACCTATTACGCCGACTCCGTGAAGGGACGGTTCACCATTAGCCGGG
ATAACAGCAAGAACACTCTGTACTTGCAAATGAACTCCCTGCGGGCTGAGGACA
CCGCCGTGTACTACTGTGCGCGGTGGTACAAGACCTATATTGACGTCTGGGGACA
GGGTACCCTCGTGACCGTGTCATCCGGTGGTGGAGGATCCGGAGGCGGAGGAAG
CGGAGGAGGGGGTTCAGACATCGAACTCACCCAGCCCCCGTCAGTGTCCGTGGC
CCCTGGACAGACTGCGCGCATCTCCTGCTCCGGCGACAACCTGGGGAAGAAATA
CGTGTACTGGTACCAGCAGAAGCCAGGTCAAGCCCCTGTGCTGGTCATCTACGGC
GACGACGAAAGGCCGTCAGGCATCCCAGAGCGCTTCTCCGGCTCCAACTCCGGG
AATACTGCCACCCTTACCATTTCCGGAACCCAGGCCGAGGATGAAGCGGATTACT
ATTGCGCGAGCTACGATAGCAGCCACATCCTGATCGTGTTTGGAGGCGGTACTAA
GCTGACCGTGCTGGGAAGCGGTGGATCAAACCCAATTTGCAAGGGATGCCTGAG
CTGTAGCAAGGACAACGGATGTTCACGGTGCCAGCAAAAGCTGTTTTTCTTCCTC
CGGCGGGAAGGAATGCGGCAGTACGGCGAATGTCTCCACTCCTGCCCCTCGGGG
TATTACGGACACCGCGCGCCTGACATGAACCGATGCGCCAGATGCCGGATCGAG
AACTGCGATAGCTGCCGCAGCAAGGACGCCTGCACTAAGTGCAAAGTCGGCTTC
TACCTTCACCGGGGCAGATGTTTTGACGAATGCCCGGATGGCTTCGCCCCGCTGG
AGGAGACTATGGAATGCGTGGAGGGCGGAGACTACAAGGACGACGATGACAAG
GGCTCCCACCATCACCACCATCATCACCACTAG

抗GFP RSPO2（F105R/F109A）——多肽（SEQ ID NO: 8）

QVQLVESGGGLVQPGGSLRLSCAASGFTFSRYGMHWVRQAPGKGLEWVSGISSIGS
NTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARWYKTYIDVWGQGT
LVTVSSGGGGSGGGGSGGGGSDIELTQPPSVSVAPGQTARISCSGDNLGKKYVYWY
QQKPGQAPVLVIYGDDERPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCASYDSS
HILIVFGGGTKLTVLGSGGSNPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGEC
LHSCPSGYYGHRAPDMNRCARCRIENCDSCRSKDACTKCKVGFYLHRGRCFDECPD
GFAPLEETMECVEGGDYKDDDDKGSHHHHHHHH

图11B

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抗GFP RSPO2（R65A/R69A/Q70A/F105R/F109A）——多核苷酸（SEQ ID NO: 9）

CAGGTCCAGTTGGTGGAATCCGGAGGGGGTTTGGTCCAGCCTGGTGGAAGCCTG
CGCCTCTCATGCGCCGCTAGCGGATTCACCTTCTCCCGATACGGCATGCATTGGG
TCAGACAGGCACCCGGAAAAGGACTCGAATGGGTGTCGGGCATTTCCTCGATCG
GGTCAAACACCTATTACGCCGACTCCGTGAAGGGACGGTTCACCATTAGCCGGG
ATAACAGCAAGAACACTCTGTACTTGCAAATGAACTCCCTGCGGGCTGAGGACA
CCGCCGTGTACTACTGTGCGCGGTGGTACAAGACCTATATTGACGTCTGGGGACA
GGGTACCCTCGTGACCGTGTCATCCGGTGGTGGAGGATCCGGAGGCGGAGGAAG
CGGAGGAGGGGGTTCAGACATCGAACTCACCCAGCCCCCGTCAGTGTCCGTGGC
CCCTGGACAGACTGCGCGCATCTCCTGCTCCGGCGACAACCTGGGGAAGAAATA
CGTGTACTGGTACCAGCAGAAGCCAGGTCAAGCCCCTGTGCTGGTCATCTACGGC
GACGACGAAAGGCCGTCAGGCATCCCAGAGCGCTTCTCCGGCTCCAACTCCGGG
AATACTGCCACCCTTACCATTTCCGGAACCCAGGCCGAGGATGAAGCGGATTACT
ATTGCGCGAGCTACGATAGCAGCCACATCCTGATCGTGTTTGGAGGCGGTACTAA
GCTGACCGTGCTGGGAAGCGGTGGATCAAACCCAATTTGCAAGGGATGCCTGAG
CTGTAGCAAGGACAACGGATGTTCACGGTGCCAGCAAAAGCTGTTTTTCTTCCTC
CGGGCCGAAGGAATGGCCGCATACGGCGAATGTCTCCACTCCTGCCCCTCGGGG
TATTACGGACACCGCGCGCCTGACATGAACCGATGCGCCAGATGCCGGATCGAG
AACTGCGATAGCTGCCGCAGCAAGGACGCCTGCACTAAGTGCAAAGTCGGCTTC
TACCTTCACCGGGGCAGATGTTTTGACGAATGCCCGGATGGCTTCGCCCCGCTGG
AGGAGACTATGGAATGCGTGGAGGGCGGAGACTACAAGGACGACGATGACAAG
GGCTCCCACCATCACCACCATCATCACCACTAG

抗GFP RSPO2（R65A/R69A/Q70A/F105R/F109A）——多肽（SEQ ID NO: 10）

QVQLVESGGGLVQPGGSLRLSCAASGFTFSRYGMHWVRQAPGKGLEWVSGISSIGS
NTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARWYKTYIDVWGQGT
LVTVSSGGGGSGGGGSGGGGSDIELTQPPSVSVAPGQTARISCSGDNLGKKYVYWY
QQKPGQAPVLVIYGDDERPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCASYDSS
HILIVFGGGTKLTVLGSGGSNPICKGCLSCSKDNGCSRCQQKLFFFLRAEGMAAYGE
CLHSCPSGYYGHRAPDMNRCARCRIENCDSCRSKDACTKCKVGFYLHRGRCFDECP
DGFAPLEETMECVEGGDYKDDDDKGSHHHHHHHH

图11C

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抗ASGR1 RSPO2野生型——多核苷酸（SEQ ID NO: 11）

GAAGTGCAGCTGCTGGAATCCGGGGGCGGACTGGTGCAACCCGGGGGATCCCTC
AGACTGTCCTGTGCCGCATCGGGTTTCACTTTCTCCTCCTACGCGATGTCATGGGT
CAGACAGGCCCCTGGAAAAGGCCTCGAATGGGTGTCGGCTATCTCCGGATCGGG
GGGATCTACTTACTACGCCGACTCCGTGAAGGGCCGGTTCACTATCTCGAGGGAC
AACTCCAAGAATACCCTGTACTTGCAAATGAACTCCCTGCGCGCCGAGGATACC
GCGGTGTATTACTGCGCCAAGGACTTCAGCTCACGCCGGTGGTACCTTGAGTACT
GGGGACAGGGAACCCTTGTCACCGTGTCCAGCGGTGGCGGCGGAAGCGGCGGGG
GCGGATCCGGTGGCGGGGGCTCAGAGCTCACCCAGGACCCCGCTGTGTCCGTGG
CCTTGGGACAGACCGTGCGCATCACATGCCAGGGCGATAGCCTGCGGAGCTATT
ACGCCTCGTGGTACCAGCAGAAGCCTGGTCAAGCGCCGGTCCTGGTCATCTACG
GAAAGAACAACCGCCCGTCCGGAATTCCAGACAGGTTCAGCGGATCCAGCTCGG
GGAACACCGCCTCACTGACTATCACCGGAGCACAGGCCGAAGATGAAGCCGACT
ACTACTGCAACTCCCTGGAGCCGGATTGGATACCTGAGCTACGTGTTTGGTGGCGG
CACGAAGCTCACCGTGCTGGGAAGCGGTGGATCAAACCCAATTTGCAAGGGATG
CCTGAGCTGTAGCAAGGACAACGGATGTTCACGGTGCCAGCAAAAGCTGTTTTTC
TTCCTCCGGCGGGAAGGAATGCGGCAGTACGGCGAATGTCTCCACTCCTGCCCCT
CGGGGTATTACGGACACCGCGCGCCTGACATGAACCGATGCGCCAGATGCCGGA
TCGAGAACTGCGATAGCTGCTTCAGCAAGGACTTCTGCACTAAGTGCAAAGTCG
GCTTCTACCTTCACCGGGGCAGATGTTTTGACGAATGCCCGGATGGCTTCGCCCC
GCTGGAGGAGACTATGGAATGCGTGGAGGGCGGAGACTACAAGGACGACGATG
ACAAGGGCTCCCACCATCACCACCATCATCACCACTAG

抗ASGR1 RSPO2野生型——多肽（SEQ ID NO: 12）

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGG
STYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDFSSRRWYLEYWG
QGTLVTVSSGGGGSGGGGSGGGGSELTQDPAVSVALGQTVRITCQGDSLRSYYASW
YQQKPGQAPVLVIYGKNNRPSGIPDRFSGSSSGNTASLTITGAQAEDEADYYCNSLER
IGYLSYVFGGGTKLTVLGSGGSNPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQY
GECLHSCPSGYYGHRAPDMNRCARCRIENCDSCFSKDFCTKCKVGFYLHRGRCFDE
CPDGFAPLEETMECVEGGDYKDDDDKGSHHHHHHHH

图11D

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抗ASGR1 RSPO2（F105R/F109A）——多核苷酸（SEQ ID NO: 13）

GAAGTGCAGCTGCTGGAATCCGGGGGCGGACTGGTGCAACCCGGGGGATCCCTC
AGACTGTCCTGTGCCGCATCGGGTTTCACTTTCTCCTCCTACGCGATGTCATGGGT
CAGACAGGCCCCTGGAAAAGGCCTCGAATGGGTGTCGGCTATCTCCGGATCGGG
GGGATCTACTTACTACGCCGACTCCGTGAAGGGCCGGTTCACTATCTCGAGGGAC
AACTCCAAGAATACCCTGTACTTGCAAATGAACTCCCTGCGCGCCGAGGATACC
GCGGTGTATTACTGCGCCAAGGACTTCAGCTCACGCCGGTGGTACCTTGAGTACT
GGGGACAGGGAACCCTTGTCACCGTGTCCAGCGGTGGCGGCGGAAGCGGCGGGG
GCGGATCCGGTGGCGGGGGCTCAGAGCTCACCCAGGACCCCGCTGTGTCCGTGG
CCTTGGGACAGACCGTGCGCATCACATGCCAGGGCGATAGCCTGCGGAGCTATT
ACGCCTCGTGGTACCAGCAGAAGCCTGGTCAAGCGCCGGTCCTGGTCATCTACG
GAAAGAACAACCGCCCGTCCGGAATTCCAGACAGGTTCAGCGGATCCAGCTCGG
GGAACACCGCCTCACTGACTATCACCGGAGCACAGGCCGAAGATGAAGCCGACT
ACTACTGCAACTCCCTGGAGCGGATTGGATACCTGAGCTACGTGTTTGGTGGCGG
CACGAAGCTCACCGTGCTGGGAAGCGGTGGATCAAACCCAATTTGCAAGGGATG
CCTGAGCTGTAGCAAGGACAACGGATGTTCACGGTGCCAGCAAAAGCTGTTTTTC
TTCCTCCGGCGGGAAGGAATGCGGCAGTACGGCGAATGTCTCCACTCCTGCCCCT
CGGGGTATTACGGACACCGCGCGCCTGACATGAACCGATGCGCCAGATGCCGGA
TCGAGAACTGCGATAGCTGCCGCAGCAAGGACGCCTGCACTAAGTGCAAAGTCG
GCTTCTACCTTCACCGGGGCAGATGTTTTGACGAATGCCCGGATGGCTTCGCCCC
GCTGGAGGAGACTATGGAATGCGTGGAGGGCGGAGACTACAAGGACGACGATG
ACAAGGGCTCCCACCATCACCACCATCATCACCACTAG

抗ASGR1 RSPO2（F105R/F109A）——多肽（SEQ ID NO: 14）

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGG
STYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDFSSRRWYLEYWG
QGTLVTVSSGGGGSGGGGSGGGGSELTQDPAVSVALGQTVRITCQGDSLRSYYASW
YQQKPGQAPVLVIYGKNNRPSGIPDRFSGSSSGNTASLTITGAQAEDEADYYCNSLER
IGYLSYVFGGGTKLTVLGSGGSNPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQY
GECLHSCPSGYYGHRAPDMNRCARCRIENCDSCRSKDACTKCKVGFYLHRGRCFDE
CPDGFAPLEETMECVEGGDYKDDDDKGSHHHHHHHHH

图11E

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抗ASGR1 RSPO2（R65A/R69A/Q70A/F105R/F109A）——多核苷酸（SEQ ID NO: 15）

GAAGTGCAGCTGCTGGAATCCGGGGGCGGACTGGTGCAACCCGGGGGATCCCTC
AGACTGTCCTGTGCCGCATCGGGTTTCACTTTCTCCTCCTACGCGATGTCATGGGT
CAGACAGGCCCCTGGAAAAGGCCTCGAATGGGTGTCGGCTATCTCCGGATCGGG
GGGATCTACTTACTACGCCGACTCCGTGAAGGGCCGGTTCACTATCTCGAGGGAC
AACTCCAAGAATACCCTGTACTTGCAAATGAACTCCCTGCGCGCCGAGGATACC
GCGGTGTATTACTGCGCCAAGGACTTCAGCTCACGCCGGTGGTACCTTGAGTACT
GGGGACAGGGAACCCTTGTCACCGTGTCCAGCGGTGGCGGCGGAAGCGGCGGGG
GCGGATCCGGTGGCGGGGGCTCAGAGCTCACCCAGGACCCCGCTGTGTCCGTGG
CCTTGGGACAGACCGTGCGCATCACATGCCAGGGCGATAGCCTGCGGAGCTATT
ACGCCTCGTGGTACCAGCAGAAGCCTGGTCAAGCGCCGGTCCTGGTCATCTACG
GAAAGAACAACCGCCCGTCCGGAATTCCAGACAGGTTCAGCGGATCCAGCTCGG
GGAACACCGCCTCACTGACTATCACCGGAGCACAGGCCGAAGATGAAGCCGACT
ACTACTGCAACTCCCTGGAGCGGATTGGATACCTGAGCTACGTGTTTGGTGGCGG
CACGAAGCTCACCGTGCTGGGAAGCGGTGGATCAAACCCAATTTGCAAGGGATG
CCTGAGCTGTAGCAAGGACAACGGATGTTCACGGTGCCAGCAAAAGCTGTTTTTC
TTCCTCCGGGCCGAAGGAATGGCCGCATACGGCGAATGTCTCCACTCCTGCCCCT
CGGGGTATTACGGACACCGCGCCGCCTGACATGAACCGATGCGCCAGATGCCGGA
TCGAGAACTGCGATAGCTGCCGCAGCAAGGACGCCTGCACTAAGTGCAAAGTCG
GCTTCTACCTTCACCGGGGCAGATGTTTTGACGAATGCCCCGGATGGCTTCGCCCC
GCTGGAGGAGACTATGGAATGCGTGGAGGGCGGAGACTACAAGGACGACGATG
ACAAGGGCTCCCACCATCACCACCATCATCACCACTAG

抗ASGR1 RSPO2（R65A/R69A/Q70A/F105R/F109A）——多肽（SEQ ID NO: 16）

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGG
STYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDFSSRRWYLEYWG
QGTLVTVSSGGGGSGGGGSGGGGSELTQDPAVSVALGQTVRITCQGDSLRSYYASW
YQQKPGQAPVLVIYGKNNRPSGIPDRFSGSSSGNTASLTITGAQAEDEADYYCNSLER
IGYLSYVFGGGTKLTVLGSGGSNPICKGCLSCSKDNGCSRCQQKLFFFLRAEGMAAY
GECLHSCPSGYYGHRAPDMNRCARCRIENCDSCRSKDACTKCKVGFYLHRGRCFDE
CPDGFAPLEETMECVEGGDYKDDDDKGSHHHHHHHH

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抗TFR1 RSPO2野生型——多核苷酸（SEQ ID NO: 17）

CAAGTGCAACTCCAACAAAGCGGTCCCGAGTTGGTCCGACCCGGCGTCAGTGTG
AAAATCTCATGCAAGGGGTCCGGGTATACCTTCACTGACTATGCAATGCACTGGG
TAAAGCAGAGCCACGCCAAGTCCTTGGAGTGGATCGGAGGCATTAGTACCTACT
TCGGACGCACCAACTACAATCAAAAATTTAAGGGTCGCGCAACCATGACTGTAG
ATAAATCATCAAGTACCGCGTACATGGAATTGGCTAGACTGACTTCTGAAGATTC
CGCGCTGTATTACTGTGCTCGCGGTTTGTCTGGCAACTATGTTATGGATTACTGGG
GGCAAGGGACCAGCGTCACGGTGTCCTCTGGCGGAGGCGGGTCCGGGGGGGGTG
GTTCTGGCGGAGGCGGATCCGATATAGTTCTGTTTCAATCCCCTGCGAGCCTGGC
GGTAAGTTTGGGACAGAGAGCCACGATTTCCTGCCGAGCGAGTGAAAGCGTAGA
CGACTACGGCAATTCTTTCATGCACTGGTATCAACAGAAGCCAGGCCAACCGCC
GAAGCTGCTTATCTATCGCGCGTCCAATTTGGAGTCAGGGATCCCTGCACGATTT
TCAGGTTCTGGAAGTAGGACAGACTTTACACTTACGATAAACCCCGTGGAAGCG
GATGACGTCGCAACCTACTATTGTCAACAAAGCAATGAAGCACCACCTACCTTCG
GAGGTGGCACTAAATTGGAAATTAGGGGAAGCGGTGGATCAAACCCAATTTGCA
AGGGATGCCTGAGCTGTAGCAAGGACAACGGATGTTCACGGTGCCAGCAAAAGC
TGTTTTTCTTCCTCCGGCGGGAAGGAATGCGGCAGTACGGCGAATGTCTCCACTC
CTGCCCCTCGGGGTATTACGGACACCGCGCGCCTGACATGAACCGATGCGCCAG
ATGCCGGATCGAGAACTGCGATAGCTGCTTCAGCAAGGACTTCTGCACTAAGTG
CAAAGTCGGCTTCTACCTTCACCGGGGCAGATGTTTTGACGAATGCCCGGATGGC
TTCGCCCCGCTGGAGGAGACTATGGAATGCGTGGAGGGCGGAGACTACAAGGAC
GACGATGACAAGGGCTCCCACCATCACCACCATCATCACCACTAG

抗TFR1 RSPO2野生型——多肽（SEQ ID NO: 18）

QVQLQQSGPELVRPGVSVKISCKGSGYTFTDYAMHWVKQSHAKSLEWIGGISTYFG
RTNYNQKFKGRATMTVDKSSSTAYMELARLTSEDSALYYCARGLSGNYVMDYWG
QGTSVTVSSGGGGSGGGGSGGGGSDIVLFQSPASLAVSLGQRATISCRASESVDDYG
NSFMHWYQQKPGQPPKLLIYRASNLESGIPARFSGSGSRTDFTLTINPVEADDVATYY
CQQSNEAPPTFGGGTKLEIRGSGGSNPICKGCLSCSKDNGCSRCQQKLFFFLRREGMR
QYGECLHSCPSGYYGHRAPDMNRCARCRIENCDSCFSKDFCTKCKVGFYLHRGRCF
DECPDGFAPLEETMECVEGGDYKDDDDKGSHHHHHHHH

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抗TFR1 RSPO2（F105R/F109A）——多核苷酸（SEQ ID NO: 19）

CAAGTGCAACTCCAACAAAGCGGTCCCGAGTTGGTCCGACCCGGCGTCAGTGTG
AAAATCTCATGCAAGGGGTCCGGGTATACCTTCACTGACTATGCAATGCACTGGG
TAAAGCAGAGCCACGCCAAGTCCTTGGAGTGGATCGGAGGCATTAGTACCTACT
TCGGACGCACCAACTACAATCAAAAATTTAAGGGTCGCGCAACCATGACTGTAG
ATAAATCATCAAGTACCGCGTACATGGAATTGGCTAGACTGACTTCTGAAGATTC
CGCGCTGTATTACTGTGCTCGCGGTTTGTCTGGCAACTATGTTATGGATTACTGGG
GGCAAGGGACCAGCGTCACGGTGTCCTCTGGCGGAGGCGGGTCCGGGGGGGGTG
GTTCTGGCGGAGGCGGATCCGATATAGTTCTGTTTCAATCCCCTGCGAGCCTGGC
GGTAAGTTTGGGACAGAGAGCCACGATTTCCTGCCGAGCGAGTGAAAGCGTAGA
CGACTACGGCAATTCTTTCATGCACTGGTATCAACAGAAGCCAGGCCAACCGCC
GAAGCTGCTTATCTATCGCGCGTCCAATTTGGAGTCAGGGATCCCTGCACGATTT
TCAGGTTCTGGAAGTAGGACAGACTTTACACTTACGATAAACCCCGTGGAAGCG
GATGACGTCGCAACCTACTATTGTCAACAAAGCAATGAAGCACCACCTACCTTCG
GAGGTGGCACTAAATTGGAAATTAGGGGAAGCGGTGGATCAAACCCAATTTGCA
AGGGATGCCTGAGCTGTAGCAAGGACAACGGATGTTCACGGTGCCAGCAAAAGC
TGTTTTTCTTCCTCCGGCGGGAAGGAATGCGGCAGTACGGCGAATGTCTCCACTC
CTGCCCCTCGGGGTATTACGGACACCGCGCGCCTGACATGAACCGATGCGCCAG
ATGCCGGATCGAGAACTGCGATAGCTGCCGCAGCAAGGACGCCTGCACTAAGTG
CAAAGTCGGCTTCTACCTTCACCGGGGCAGATGTTTTGACGAATGCCCGGATGGC
TTCGCCCCGCTGGAGGAGACTATGGAATGCGTGGAGGGCGGAGACTACAAGGAC
GACGATGACAAGGGCTCCCACCATCACCACCATCATCACCACTAG

抗TFR1 RSPO2（F105R/F109A）——多肽（SEQ ID NO: 20）

QVQLQQSGPELVRPGVSVKISCKGSGYTFTDYAMHWVKQSHAKSLEWIGGISTYFG
RTNYNQKFKGRATMTVDKSSSTAYMELARLTSEDSALYYCARGLSGNYVMDYWG
QGTSVTVSSGGGGSGGGGSGGGGSDIVLFQSPASLAVSLGQRATISCRASESVDDYG
NSFMHWYQQKPGQPPKLLIYRASNLESGIPARFSGSGSRTDFTLTINPVEADDVATYY
CQQSNEAPPTFGGGTKLEIRGSGGSNPICKGCLSCSKDNGCSRCQQKLFFFLRREGMR
QYGECLHSCPSGYYGHRAPDMNRCARCRIENCDSCRSKDACTKCKVGFYLHRGRCF
DECPDGFAPLEETMECVEGGDYKDDDDKGSHHHHHHHH

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抗TFR1 RSPO2（R65A/R69A/Q70A/F105R/F109A）-----多核苷酸（SEQ ID NO: 21）

CAAGTGCAACTCCAACAAAGCGGTCCCGAGTTGGTCCGACCCGGCGTCAGTGTG
AAAATCTCATGCAAGGGGTCCGGGTATACCTTCACTGACTATGCAATGCACTGGG
TAAAGCAGAGCCACGCCAAGTCCTTGGAGTGGATCGGAGGCATTAGTACCTACT
TCGGACGCACCAACTACAATCAAAAATTTAAGGGTCGCGCAACCATGACTGTAG
ATAAATCATCAAGTACCGCGTACATGGAATTGGCTAGACTGACTTCTGAAGATTC
CGCGCTGTATTACTGTGCTCGCGGTTTGTCTGGCAACTATGTTATGGATTACTGGG
GGCAAGGGACCAGCGTCACGGTGTCCTCTGGCGGAGGCGGGTCCGGGGGGGGTG
GTTCTGGCGGAGGCGGATCCGATATAGTTCTGTTTCAATCCCCTGCGAGCCTGGC
GGTAAGTTTGGGACAGAGAGCCACGATTTCCTGCCGAGCGAGTGAAAGCGTAGA
CGACTACGGCAATTCTTTCATGCACTGGTATCAACAGAAGCCAGGCCAACCGCC
GAAGCTGCTTATCTATCGCGCGTCCAATTTGGAGTCAGGGATCCCTGCACGATTT
TCAGGTTCTGGAAGTAGGACAGACTTTACACTTACGATAAACCCCGTGGAAGCG
GATGACGTCGCAACCTACTATTGTCAACAAAGCAATGAAGCACCACCTACCTTCG
GAGGTGGCACTAAATTGGAAATTAGGGGAAGCGGTGGATCAAACCCAATTTGCA
AGGGATGCCTGAGCTGTAGCAAGGACAACGGATGTTCACGGTGCCAGCAAAAGC
TGTTTTTCTTCCTCCGGGCCGAAGGAATGGCCGCATACGGCGAATGTCTCCACTC
CTGCCCCTCGGGGTATTACGGACACCGCGCGCCTGACATGAACCGATGCGCCAG
ATGCCGGATCGAGAACTGCGATAGCTGCCGCAGCAAGGACGCCTGCACTAAGTG
CAAAGTCGGCTTCTACCTTCACCGGGGCAGATGTTTTGACGAATGCCCGGATGGC
TTCGCCCCGCTGGAGGAGACTATGGAATGCGTGGAGGGCGGAGACTACAAGGAC
GACGATGACAAGGGCTCCCACCATCACCACCATCATCACCACTAG

抗TFR1 RSPO2（R65A/R69A/Q70A/F105R/F109A）-----多肽（SEQ ID NO: 22）

QVQLQQSGPELVRPGVSVKISCKGSGYTFTDYAMHWVKQSHAKSLEWIGGISTYFG
RTNYNQKFKGRATMTVDKSSSTAYMELARLTSEDSALYYCARGLSGNYVMDYWG
QGTSVTVSSGGGGSGGGGSGGGGSDIVLFQSPASLAVSLGQRATISCRASESVDDYG
NSFMHWYQQKPGQPPKLLIYRASNLESGIPARFSGSGSRTDFTLTINPVEADDVATYY
CQQSNEAPPTFGGGTKLEIRGSGGSNPICKGCLSCSKDNGCSRCQQKLFFFLRAEGM
AAYGECLHSCPSGYYGHRAPDMNRCARCRIENCDSCRSKDACTKCKVGFYLHRGR
CFDECPDGFAPLEETMECVEGGDYKDDDDKGSHHHHHHHH

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Fc-RSPO2——多核苷酸（SEQ ID NO: 23）

GACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAGCCGCGGGGGGACCG
TCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCC
CTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGT
TCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGG
AGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACC
AGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCG
GAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCAC
AGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCC
TGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGA
GCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCG
ACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGC
AGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACAC
GCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAGGTGGTGGTGGCTCGGGAGGAGG
AGGCTCCGGTGGCGGTGGCAGCtcaAATCCCATTTGCAAGGGTTGTTTGTCTTGTTC
AAAGGACAATGGGTGTAGCCGATGTCAACAGAAGTTGTTCTTCTTCCTTCGAAGA
GAAGGGATGCGCCAGTATGGAGAGTGCCTGCATTCCTGCCCATCCGGGTACTAT
GGACACCGAGCCCCAGATATGAACAGATGTGCAAGATGCAGAATAGAAAACTGT
GATTCTTGCTTTAGCAAAGACTTTTGTACCAAGTGCAAAGTAGGCTTTTATTTGCA
TAGAGGCCGTTGCTTTGATGAATGTCCAGATGGTTTTGCACCATTAGAAGAAACC
ATGGAATGTGTGGAATGA

Fc-RSPO2——多肽（SEQ ID NO: 24）

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW
YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPI
EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP
GKGGGGSGGGGSGGGGSSNPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGEC
LHSCPSGYYGHRAPDMNRCARCRIENCDSCFSKDFCTKCKVGFYLHRGRCFDECPD
GFAPLEETMECVE

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抗GFP轻链——多核苷酸（SEQ ID NO: 25）

GACATCGAACTCACCCAGCCCCCGTCAGTGTCCGTGGCCCCTGGACAGACTGCGC
GCATCTCCTGCTCCGGCGACAACCTGGGGAAGAAATACGTGTACTGGTACCAGC
AGAAGCCAGGTCAAGCCCCTGTGCTGGTCATCTACGGCGACGACGAAAGGCCGT
CAGGCATCCCAGAGCGCTTCTCCGGCTCCAACTCCGGGAATACTGCCACCCTTAC
CATTTCCGGAACCCAGGCCGAGGATGAAGCGGATTACTATTGCGCGAGCTACGA
TAGCAGCCACATCCTGATCGTGTTTGGAGGCGGTACCAAGCTTACCGTCCTAGGT
CAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTC
AAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCG
TGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACC
ACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGC
CTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACGCAT
GAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCA

抗GFP轻链——多肽（SEQ ID NO: 26）

DIELTQPPSVSVAPGQTARISCSGDNLGKKYVYWYQQKPGQAPVLVIYGDDERPSGI
PERFSGSNSGNTATLTISGTQAEDEADYYCASYDSSHILIVFGGGTKLTVLGQPKAAP
SVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNN
KYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

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RSPO2（F105R/F109A）、抗GFP重链IgG2——多核苷酸（SEQ ID NO: 27）

AACCCAATTTGCAAGGGATGCCTGAGCTGTAGCAAGGACAACGGATGTTCACGG
TGCCAGCAAAAGCTGTTTTTCTTCCTCCGGCGGGAAGGAATGCGGCAGTACGGC
GAATGTCTCCACTCCTGCCCCTCGGGGTATTACGGACACCGCGCGCCTGACATGA
ACCGATGCGCCAGATGCCGGATCGAGAACTGCGATAGCTGCCGCAGCAAGGACG
CCTGCACTAAGTGCAAAGTCGGCTTCTACCTTCACCGGGGCAGATGTTTTGACGA
ATGCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCGTGGAGGGTGG
TGGTGGCTCGGGAGGAGGAGGCTCCGGTGGCGGTGGCAGCCAGGTCCAGTTGGT
GGAATCCGGAGGGGGTTTGGTCCAGCCTGGTGGAAGCCTGCGCCTCTCATGCGC
CGCTAGCGGATTCACCTTCTCCCGATACGGCATGCATTGGGTCAGACAGGCACCC
GGAAAAGGACTCGAATGGGTGTCGGGCATTTCCTCGATCGGGTCAAACACCTAT
TACGCCGACTCCGTGAAGGGACGGTTCACCATTAGCCGGGATAACAGCAAGAAC
ACTCTGTACTTGCAAATGAACTCCCTGCGGGCTGAGGACACCGCCGTGTACTACT
GTGCGCGGTGGTACAAGACCTATATTGACGTCTGGGGACAGGGTACCCTCGTGA
CCGTGTCGAGTGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTC
CAGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTT
CCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCTCTGACCAGCGGCGTGCA
CACCTTCCCAGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTG
ACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGTAGATCACA
AGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTGTGTCGAGT
GCCCACCGTGCCCAGCACCACCTGTGGCAGGACCGTCAGTCTTCCTCTTCCCCCC
AAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGT
GGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGACGG
CGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAGCAGTTCAACAGCA
CGTTCCGTGTGGTCAGCGTCCTCACCGTTGTGCACCAGGACTGGCTGAACGGCAA
GGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCAGCCCCCATCGAGAAAAC
CATCTCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCC
ATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGG
CTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAA
CAACTACAAGACCACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTAC
AGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGC
TCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGT
CTCCGGGTAAA

RSPO2（F105R/F109A）、抗GFP重链IgG2——多肽（SEQ ID NO: 28）

NPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYGHRAPDMNR
CARCRIENCDSCRSKDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECVEGGGGS
GGGGSGGGGSQVQLVESGGGLVQPGGSLRLSCAASGFTFSRYGMHWVRQAPGKGL
EWVSGISSIGSNTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARWYK
TYIDVWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW
NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTV
ERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNW
YVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIE
KTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
K

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抗ASGR1轻链——多核苷酸（SEQ ID NO: 29）

GACATCGAGCTCACCCAGGACCCCGCTGTGTCCGTGGCCTTGGGACAGACCGTG
CGCATCACATGCCAGGGCGATAGCCTGCGGAGCTATTACGCCTCGTGGTACCAG
CAGAAGCCTGGTCAAGCGCCGGTCCTGGTCATCTACGGAAAGAACAACCGCCCG
TCCGGAATTCCAGACAGGTTCAGCGGATCCAGCTCGGGGAACACCGCCTCACTG
ACTATCACCGGAGCACAGGCCGAAGATGAAGCCGACTACTACTGCAACTCCCTG
GAGCGGATTGGATACCTGAGCTACGTGTTTGGTGGCGGTACCAAGCTTACCGTCC
TAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGA
GCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGA
GCCGTGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGA
GACCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGCCAGCAGCTATCT
GAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCAC
GCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCA

抗ASGR1轻链——多肽（SEQ ID NO: 30）

DIELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPSGI
PDRFSGSSSGNTASLTITGAQAEDEADYYCNSLERIGYLSYVFGGGTKLTVLGQPKA
APSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN
NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

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RSPO2（F105R/F109A）、抗ASGR1重链IgG2——多核苷酸（SEQ ID NO: 31）

AACCCAATTTGCAAGGGATGCCTGAGCTGTAGCAAGGACAACGGATGTTCACGG
TGCCAGCAAAAGCTGTTTTTCTTCCTCCGGCGGGAAGGAATGCGGCAGTACGGC
GAATGTCTCCACTCCTGCCCCTCGGGGTATTACGGACACCGCGCGCCTGACATGA
ACCGATGCGCCAGATGCCGGATCGAGAACTGCGATAGCTGCCGCAGCAAGGACG
CCTGCACTAAGTGCAAAGTCGGCTTCTACCTTCACCGGGGCAGATGTTTTGACGA
ATGCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCGTGGAGGGTGG
TGGTGGCTCGGGAGGAGGAGGCTCCGGTGGCGGTGGCAGCGAAGTGCAGCTGCT
GGAATCCGGGGGCGGACTGGTGCAACCCGGGGGATCCCTCAGACTGTCCTGTGC
CGCATCGGGTTTCACTTTCTCCTCCTACGCGATGTCATGGGTCAGACAGGCCCCT
GGAAAAGGCCTCGAATGGGTGTCGGCTATCTCCGGATCGGGGGGGATCTACTTAC
TACGCCGACTCCGTGAAGGGCCGGTTCACTATCTCGAGGGACAACTCCAAGAAT
ACCCTGTACTTGCAAATGAACTCCCTGCGCGCCGAGGATACCGCGGTGTATTACT
GCGCCAAGGACTTCAGCTCACGCCGGTGGTACCTTGAGTACTGGGGACAGGGAA
CCCTTGTCACCGTGTCGAGTGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGC
GCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAA
GGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCTCTGACCAG
CGGCGTGCACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGC
AGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAAC
GTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGT
TGTGTCGAGTGCCCACCGTGCCCAGCACCACCTGTGGCAGGACCGTCAGTCTTCC
TCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCAC
GTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTA
CGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAGCAGT
TCAACAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTGTGCACCAGGACTGGCT
GAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCAGCCCCCAT
CGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACAC
CCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCT
GGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCA
GCCGGAGAACAACTACAAGACCACGCCTCCCATGCTGGACTCCGACGGCTCCTT
CTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGT
CTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGC
CTCTCCCTGTCTCCGGGTAAA

RSPO2（F105R/F109A）、抗ASGR1重链IgG2——多肽（SEQ ID NO: 32）

NPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYGHRAPDMNR
CARCRIENCDSCRSKDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECVEGGGGS
GGGGSGGGGSEVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLE
WVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDFSS
RRWYLEYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTV
SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDK
TVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQF
NWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLP
APIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP
ENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL
SPGK*

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抗GFP重链IgG1——多核苷酸（SEQ ID NO: 33）

CAGGTCCAGTTGGTGGAATCCGGAGGGGGTTTGGTCCAGCCTGGTGGAAGCCTG
CGCCTCTCATGCGCCGCTAGCGGATTCACCTTCTCCCGATACGGCATGCATTGGG
TCAGACAGGCACCCGGAAAAGGACTCGAATGGGTGTCGGGCATTTCCTCGATCG
GGTCAAACACCTATTACGCCGACTCCGTGAAGGGACGGTTCACCATTAGCCGGG
ATAACAGCAAGAACACTCTGTACTTGCAAATGAACTCCCTGCGGGCTGAGGACA
CCGCCGTGTACTACTGTGCGCGGTGGTACAAGACCTATATTGACGTCTGGGGACA
GGGTACCCTCGTGACCGTGTCGAGTGCTAGCACCAAGGGCCCATCGGTCTTCCCC
CTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTG
GTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTG
ACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCC
TCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTG
CAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCA
AATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGG
GGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCC
CGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAG
GTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAG
CCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTC
CTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAA
GCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGA
GAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAG
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGT
GGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGG
ACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTG
GCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCAC
TACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA

抗GFP重链IgG1——多肽（SEQ ID NO: 34）

QVQLVESGGGLVQPGGSLRLSCAASGFTFSRYGMHWVRQAPGKGLEWVSGISSIGS
NTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARWYKTYIDVWGQGT
LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH
TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTC
PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE
VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP
VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*

图110

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人ASGR1细胞外结构域——多核苷酸（SEQ ID NO: 35）

CAGAACAGCCAGCTCCAGGAAGAACTGAGGGGCCTCCGCGAAACCTTCTCCAAC
TTCACGGCTTCGACCGAAGCTCAAGTCAAGGGGTTGTCCACACAAGGCGGCAAC
GTCGGACGCAAGATGAAGTCGCTGGAGTCCCAGCTGGAAAAGCAGCAGAAGGA
TCTCTCCGAGGATCACAGCTCACTGCTGTTGCACGTGAAGCAGTTCGTGTCGGAC
CTGAGGTCCCTGAGCTGTCAGATGGCGGCACTGCAGGGAAACGGTTCCGAAAGA
ACTTGCTGCCCTGTGAATTGGGTGGAGCACGAGAGAAGCTGCTACTGGTTCTCGC
GGTCCGGCAAAGCCTGGGCGGACGCCGACAACTATTGTCGGCTGGAGGATGCGC
ACCTGGTGGTCGTGACCTCCTGGGAGGAACAGAAGTTTGTGCAGCACCATATCG
GTCCCGTGAACACTTGGATGGGGCTGCACGACCAAAACGGACCGTGGAAATGGG
TGGATGGGACTGATTACGAAACCGGATTCAAGAACTGGCGCCCAGAGCAGCCCG
ACGATTGGTACGGACATGGACTGGGGGGCGGAGAGGACTGCGCCCACTTCACCG
ACGACGGCCGGTGGAACGACGACGTGTGCCAGCGGCCGTACCGCTGGGTCTGCG
AAACCGAGCTGGACAAGGCCAGCCAGGAGCCACCTCTCCTTTGA

人ASGR1细胞外结构域——多肽（SEQ ID NO: 36）

QNSQLQEELRGLRETFSNFTASTEAQVKGLSTQGGNVGRKMKSLESQLEKQQKDLS
EDHSSLLLHVKQFVSDLRSLSCQMAALQGNGSERTCCPVNWVEHERSCYWFSRSGK
AWADADNYCRLEDAHLVVVTSWEEQKFVQHHIGPVNTWMGLHDQNGPWKWVDG
TDYETGFKNWRPEQPDDWYGHGLGGGEDCAHFTDDGRWNDDVCQRPYRWVCETE
LDKASQEPPLL

图11P

人ASGR2细胞外结构域——多核苷酸（SEQ ID NO: 37）

AGGGGCGCACAGCTGCAAGCCGAGCTGCGGTCCCTGAAGGAAGCTTTCTCAAAC
TTCTCGAGCTCGACCCTCACCGAAGTGCAGGCCATTAGCACCCACGGGGGTTCCG
TGGGGGACAAGATCACCTCGCTGGGAGCGAAGCTGGAGAAGCAGCAGCAAGAC
CTCAAGGCCGACCACGACGCGCTGCTGTTCCACTTGAAGCACTTCCCAGTGGACT
TGCGGTTCGTGGCGTGCCAGATGGAGCTGCTGCACTCCAATGGGAGCCAGAGAA
CTTGTTGCCCTGTGAACTGGGTGGAACACCAGGGATCCTGCTACTGGTTTAGCCA
CTCCGGAAAGGCCTGGGCCGAAGCCGAGAAGTACTGCCAGCTTGAGAACGCGCA
CCTGGTCGTGATCAACTCCTGGGAAGAACAGAAGTTCATTGTGCAACACACTAA
CCCGTTCAACACCTGGATCGGCCTGACCGACTCCGACGGCTCATGGAAATGGGT
GGACGGAACCGATTACCGGCATAACTATAAGAACTGGGCCGTGACTCAGCCGGA
TAATTGGCACGGACACGAGCTGGGTGGATCCGAGGACTGCGTCGAAGTGCAGCC
CGACGGCAGATGGAACGATGACTTCTGTCTGCAAGTGTACCGCTGGGTCTGCGA
GAAGCGCCGCAACGCCACTGGCGAAGTGGCTTGA

人ASGR2细胞外结构域——多肽（SEQ ID NO: 38）

RGAQLQAELRSLKEAFSNFSSSTLTEVQAISTHGGSVGDKITSLGAKLEKQQQDLKA
DHDALLFHLKHFPVDLRFVACQMELLHSNGSQRTCCPVNWVEHQGSCYWFSHSGK
AWAEAEKYCQLENAHLVVINSWEEQKFIVQHTNPFNTWIGLTDSDGSWKWVDGTD
YRHNYKNWAVTQPDNWHGHELGGSEDCVEVQPDGRWNDDFCLQVYRWVCEKRR
NATGEVA

图11Q

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猕猴ASGR1细胞外结构域——多核苷酸（SEQ ID NO: 39）

CAAAACGCCCAGCTGCAGCGGGAGCTGCGGGGCCTGAGAGAGACGCTCAGCAA
CTTCACAGCGAGCACCGAGGCCCAGGTCAAGGGCTTGAGCACCCAGGGAGGCAA
TGTGGGAAGAAAGATGAAGTCGCTGGAGTCCCAGCTGGAGAAACAGCAGAAGG
ACTTGAGTGAAGATCACTCCAGCCTGCTGCTCCACGTGAAGCAGTTCGTGTCTGA
CCTGCGGAGCCTGAGCTGTCAGATGGCGGCGCTCCAGGGCAATGGCTCGGAAAG
GGCCTGCTGCCCAGTCAACTGGGTGGAGCACGAGCGCAGCTGCTACTGGTTCTCT
CGCTCCGGGAAGGCCTGGGCCGACGCCGACAACTACTGCCGGCTGGAGGACGCG
CACCTGGTGGTGGTCACGTCCTGGGAGGAGCAGAAATTTGTCCAGCACCACATA
GGTCCTGTGAACACCTGGATGGGCCTCCACGACCAAAACGGGCCCTGGAAGTGG
GTGGACGGGACGGACTACGAGACGGGCTTCAAGAACTGGAGACCGGAGCAGCC
GGACGACTGGTACGGCCACGGGCTCGGGGGAGGGGAGGACTGTGCCCACTTCAC
CGACGACGGCCCGCTGGAACGACGACGTCTGCCAGAGGCCCTACCGCTGGGTCTG
CGAGACAGAGCTGGACAAGGCCAGTCAGGAGCCACCTCTCCTT

猕猴ASGR1细胞外结构域——多肽（SEQ ID NO: 40）

QNAQLQRELRGLRETLSNFTASTEAQVKGLSTQGGNVGRKMKSLESQLEKQQKDLS
EDHSSLLLHVKQFVSDLRSLSCQMAALQGNGSERACCPVNWVEHERSCYWFSRSGK
AWADADNYCRLEDAHLVVVTSWEEQKFVQHHIGPVNTWMGLHDQNGPWKWVDG
TDYETGFKNWRPEQPDDWYGHGLGGGEDCAHFTDDGRWNDDVCQRPYRWVCETE
LDKASQEPPLL

图11R

猕猴ASGR2细胞外结构域——多核苷酸（SEQ ID NO: 41）

CAAAGTGCACAGCTGCAAGCAGAGaTGcGGAGCCTGAAGGAAGCTTTCAGCAAC
TTCTCCTCGAGCACGCTGgTGGAGGTCCATGCTCTCGGCACCCACGGAGGCAGCG
TGGGTGACAAGATCACATCCCTAGGAGACAAGTTGGAGAAACAGCAGCAcGACC
TGAAAGCAGATCATGACATCCTGCTCCTCCATCTGAAGCACTTCCCCGTGGACCT
GCGCTTCGTGGCCTGCCAGATGGAGCTCCTCCACAGCAACGGCTCCCAAAGGAC
CTGCTGCCCTGTCAACTGGGTGGAGCACCAAGGCAGCTGCTACTGGTTCTCTCGC
TCCGGGAAGGCCTGGGCCGAGGCGGAGAAGTACTGCCAGCTGGAGAACTCACAC
CTGGTGGTCATCAACTCCTGGGAGGAGCAGAAATTCATTGTACAACACACGAAC
CCCTTCAATACCTGGATAGGTCTCACGGACAGTGATGGCTCCTGGAAATGGGTGG
ACGGCACAGACTATAGGCACAACTACAAGAACTGGGCTGTCACTCAGCCAGATG
ATTGGCACGGGCATGAGCTGGGCGGAAGTGAAGACTGTGTTGAAGTCCGGCCGG
ATGGCCGCTGGAACGATGATTTCTGCCTGCAGGTGCACCGCTGGGTGTGTGAGA
AGAGGCGGAATGCCACCGGCGAGGCAGCCTGA

猕猴ASGR2细胞外结构域——多肽（SEQ ID NO: 42）

QSAQLQAEMRSLKEAFSNFSSSTLVEVHALGTHGGSVGDKITSLGDKLEKQQHDLK
ADHDILLLHLKHFPVDLRFVACQMELLHSNGSQRTCCPVNWVEHQGSCYWFSRSGK
AWAEAEKYCQLENSHLVVINSWEEQKFIVQHTNPFNTWIGLTDSDGSWKWVDGTD
YRHNYKNWAVTQPDDWHGHELGGSEDCVEVRPDGRWNDDFCLQVHRWVCEKRR
NATGEAA

图11S

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人RNF43细胞外结构域——多核苷酸（SEQ ID NO: 43）

CAGAAAGCTATTATCAGAGTGATCCCCTTGAAAATGGACCCCACAGGAAAACTG
AATCTCACTTTGGAAGGTGTGTTTGCTGGTGTTGCTGAAATAACTCCAGCAGAAG
GAAAATTAATGCAGTCCCACCCGCTGTACCTGTGCAATGCCAGTGATGACGACA
ATCTGGAGCCTGGATTCATCAGCATCGTCAAGCTGGAGAGTCCTCGACGGGCCCC
CCGCCCCTGCCTGTCACTGGCTAGCAAGGCTCGGATGGCGGGTGAGCGAGGAGC
CAGTGCTGTCCTCTTTGACATCACTGAGGATCGAGCTGCTGCTGAGCAGCTGCAG
CAGCCGCTGGGGCTGACCTGGCCAGTGGTGTTGATCTGGGGTAATGACGCTGAG
AAGCTGATGGAGTTTGTGTACAAGAACCAAAAGGCCCATGTGAGGATTGAGCTG
AAGGAGCCCCCGGCCTGGCCAGATTATGATTGA

人RNF43细胞外结构域——多肽（SEQ ID NO: 44）

QKAIIRVIPLKMDPTGKLNLTLEGVFAGVAEITPAEGKLMQSHPLYLCNASDDDNLEP
GFISIVKLESPRRAPRPCLSLASKARMAGERGASAVLFDITEDRAAAEQLQQPLGLTW
PVVLIWGNDAEKLMEFVYKNQKAHVRIELKEPPAWPDYD

图11T

人ZNRF3细胞外结构域——多核苷酸（SEQ ID NO: 45）

AAGGAGACGGCGTTCGTGGAGGTGGTGCTGTTCGAGTCGAGCCCAAGCGGCGAT
TACACCACCTACACCACCGGCCTCACGGGCCGCTTCTCGCGGGCCGGGGCCACG
CTCAGCGCCGAGGGCGAGATCGTGCAGATGCACCCACTGGGCCTATGTAATAAC
AATGACGAAGAGGACTTGTATGAATATGGCTGGGTAGGAGTGGTGAAGCTGGAA
CAGCCAGAATTGGACCCGAAACCATGCCTCACTGTCCTAGGCAAGGCCAAGCGA
GCAGTACAGCGGGGAGCTACTGCAGTCATCTTTGATGTGTCTGAAAACCCAGAA
GCTATTGATCAGCTGAACCAGGGCTCTGAAGACCCGCTCAAGAGGCCGGTGGTG
TATGTGAAGGGTGCAGATGCCATTAAGCTGATGAACATCGTCAACAAGCAGAAA
GTGGCTCGAGCAAGGATCCAGCACCGCCCTCCTCGACAACCCACTGAATACTTTG
ACATGTGA

人ZNRF3细胞外结构域——多肽（SEQ ID NO: 46）

KETAFVEVVLFESSPSGDYTTYTTGLTGRFSRAGATLSAEGEIVQMHPLGLCNNNDE
EDLYEYGWVGVVKLEQPELDPKPCLTVLGKAKRAVQRGATAVIFDVSENPEAIDQL
NQGSEDPLKRPVVYVKGADAIKLMNIVNKQKVARARIQHRPPRQPTEYFDM

图11U

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抗β-Gal轻链——多核苷酸（SEQ ID NO: 155）

CAGAGCGTGTTAACCCAGCCCGCCAGCGTGAGCGGCAGCCCCGGCCAGAGCATC
ACCATCAGCTGCGCCGGCACCAGCAGCGACGTGGGCGGCTACAACTACGTGAGC
TGGTACCAGCAGCACCCCGGCAAGGCCCCCAAGCTGATGATCTACGAGGACAGC
AAGAGACCCAGCGGCGTGAGCAACAGATTCAGCGGCAGCAAGAGCGGCAACAC
CGCCAGCCTGACCATCAGCGGCCTGCAGGCCGAGGACGAGGCCGACTACTACTG
CAGCAGCTACACCACCAGAAGCACCAGAGTGTTCGGCGGCGGCACCAAGCTGGC
CGTGCTGGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCT
GAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACC
CGGGAGCCGTGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGA
GTGGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGCCAGCAGC
TATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAG
GTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCA

抗β-Gal轻链——多肽（SEQ ID NO: 156）

QSVLTQPASVSGSPGQSITISCAGTSSDVGGYNYVSWYQQHPGKAPKLMIYEDSKRP
SGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTTRSTRVFGGGTKLAVLGQPK
AAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQS
NNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

图11V

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抗β-Gal 重链IgG1-LALAPG——多核苷酸（SEQ ID NO: 157）

GAGGTGCAGCTGGTGGAGAGCGGCGGCAGCCTGGTGAAGCCCGGCGGCAGCCTG
AGACTGAGCTGCGCCGCCAGCGGCTTCACCTTCAGCAACTACAGCATGAACTGG
GTGAGACAGGCCCCCGGCAAGGGCCTGGAGTGGATCAGCAGCATCAGCGGCAGC
AGCAGATACATCTACTACGCCGACTTCGTGAAGGGCAGATTCACCATCAGCAGA
GACAACGCCACCAACAGCCTGTACCTGCAGATGAACAGCCTGAGAGCCGAGGAC
ACCGCCGTGTACTACTGCGTGAGAAGCAGCATCACCATCTTCGGCGGCGGCATG
GACGTGTGGGGCAGAGGCACCCTGGTGACCGTGAGCAGCGCTAGCACCAAGGGC
CCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGG
CCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAA
CTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCA
GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCC
AGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGA
AAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCAC
CTGAAGCCGCGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACA
CCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCA
CGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAA
TGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAG
CGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAA
GGTCTCCAACAAAGCCCTCGGAGCCCCCATCGAGAAAACCATCTCCAAAGCCAA
AGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGAT
GACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGA
CATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCA
CGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGT
GGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGA
GGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

抗β-Gal重链IgG1-LALAPG——多肽（SEQ ID NO: 158）

EVQLVESGGSLVKPGGSLRLSCAASGFTFSNYSMNWVRQAPGKGLEWISSISGSSRYI
YYADFVKGRFTISRDNATNSLYLQMNSLRAEDTAVYYCVRSSITIFGGGMDVWGRG
TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV
HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT
CPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV
EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISK
AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP
PVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

图11W

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抗β-Gal重链IgG2——多核苷酸（SEQ ID NO: 159）

GAGGTGCAGCTGGTGGAGAGCGGCGGCAGCCTGGTGAAGCCCGGCGGCAGCCTG
AGACTGAGCTGCGCCGCCAGCGGCTTCACCTTCAGCAACTACAGCATGAACTGG
GTGAGACAGGCCCCCGGCAAGGGCCTGGAGTGGATCAGCAGCATCAGCGGCAGC
AGCAGATACATCTACTACGCCGACTTCGTGAAGGGCAGATTCACCATCAGCAGA
GACAACGCCACCAACAGCCTGTACCTGCAGATGAACAGCCTGAGAGCCGAGGAC
ACCGCCGTGTACTACTGCGTGAGAAGCAGCATCACCATCTTCGGCGGCGGCATG
GACGTGTGGGGCAGAGGCACCCTGGTGACCGTGAGCAGCGCTAGCACCAAGGGC
CCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGG
CCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAA
CTCAGGCGCTCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCCTACAGTCCTCA
GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCC
AGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGA
CAGTTGAGCGCAAATGTTGTGTCGAGTGCCCACCGTGCCCAGCACCACCTGTGGC
AGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCC
CGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAG
GTCCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAG
CCACGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTG
TGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAG
GCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAG
AACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGG
TCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTG
GGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCATGCTGGA
CTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGG
CAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACT
ACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

抗β-Gal重链IgG2——多肽（SEQ ID NO: 160）

EVQLVESGGSLVKPGGSLRLSCAASGFTFSNYSMNWVRQAPGKGLEWISSISGSSRYI
YYADFVKGRFTISRDNATNSLYLQMNSLRAEDTAVYYCVRSSITIFGGGMDVWGRG
TLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH
TFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPP
CPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHN
AKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQP
REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDS
DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*

图11X

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抗ASGR1 VH-CH1——多核苷酸（SEQ ID NO: 161）

GAAGTGCAGCTGCTGGAATCCGGGGGCGGACTGGTGCAACCCGGGGGATCCCTC
AGACTGTCCTGTGCCGCATCGGGTTTCACTTTCTCCTCCTACGCGATGTCATGGGT
CAGACAGGCCCCTGGAAAAGGCCTCGAATGGGTGTCGGCTATCTCCGGATCGGG
GGGATCTACTTACTACGCCGACTCCGTGAAGGGCCGGTTCACTATCTCGAGGGAC
AACTCCAAGAATACCCTGTACTTGCAAATGAACTCCCTGCGCGCCGAGGATACC
GCGGTGTATTACTGCGCCAAGGACTTCAGCTCACGCCGGTGGTACCTTGAGTACT
GGGGACAGGGAACCCTTGTCACCGTGTCCAGCGCTAGCACCAAGGGCCCATCGG
TCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGG
CTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGC
GCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCT
ACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTA
CATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGA
GCCCAAATCTTGTGGATCCGGCTCCGGACATCATCATCACCATCAC

抗ASGR1 VH-CH1——多肽（SEQ ID NO: 162）

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGG
STYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDFSSRRWYLEYWG
QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS
GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCGS
GSGHHHHHH

图11Y

鼠类ASGR1细胞外结构域——多核苷酸（SEQ ID NO: 163）

CAAAATTCCCAACTCCGGGAAGATCTGCTGGCTCTAAGGCAGAATTTCAGCAAC
CTCACTGTGAGCACTGAGGACCAGGTCAAGGCCCTGAGCACCCAGGGAAGTAGT
GTGGGAAGAAAGATGAAGTTAGTGGAGTCGAAGCTGGAAAAACAGCAGAAGGA
TCTGACTGAAGATCACTCCAGTTTGCTACTGCACGTGAAGCAGTTAGTGTCTGAC
GTGCGAAGCTTGAGCTGCCAGATGGCTGCATTTCGGGGCAATGGCTCTGAAAGG
ACCTGCTGCCCCATCAACTGGGTGGAGTATGAAGGCAGCTGCTACTGGTTCTCCA
GCTCTGTGAGGCCTTGGACTGAAGCTGACAAGTACTGCCAGCTGGAAAATGCCC
ATCTGGTGGTGGTGACCTCCAGGGATGAGCAGAACTTCCTCCAGCGCCACATGG
GCCCCTTAAACACTTGGATTGGCCTAACTGACCAGAACGGGCCCTGGAAATGGG
TGGATGGAACAGACTACGAGACAGGCTTCCAGAATTGGAGACCAGAGCAGCCAG
ATAACTGGTACGGACATGGGCTTGGAGGAGGCGAGGACTGTGCCCACTTCACGA
CGGATGGCCGCTGGAATGACGACGTCTGCAGGAGGCCCTACCGCTGGGTCTGTG
AGACAAAGTTGGATAAGGCTAATTCCGGCTCCGGAGGTCTTAATGATATTTTCGA
GGCTCAGAAGATTGAGTGGCATGAAGGATCCGGCTCCCACCACCATCATCACCA
CCACCAC

鼠类ASGR1细胞外结构域——多肽（SEQ ID NO: 164）

QNSQLREDLLALRQNFSNLTVSTEDQVKALSTQGSSVGRKMKLVESKLEKQQKDLT
EDHSSLLLHVKQLVSDVRSLSCQMAAFRGNGSERTCCPINWVEYEGSCYWFSSSVRP
WTEADKYCQLENAHLVVVTSRDEQNFLQRHMGPLNTWIGLTDQNGPWKWVDGTD
YETGFQNWRPEQPDNWYGHGLGGGEDCAHFTTDGRWNDDVCRRPYRWVCETKLD
KANSGSGGLNDIFEAQKIEWHEGSGSHHHHHHHH

图11Z

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抗β-Gal重链IgG2、RSPO2（F105R/F109A）多核苷酸（SID NO: 186）

GAGGTGCAGCTGGTGGAGAGCGGCGGCAGCCTGGTGAAGCCCGGCGGCAGCCTG
AGACTGAGCTGCGCCGCCAGCGGCTTCACCTTCAGCAACTACAGCATGAACTGG
GTGAGACAGGCCCCCGGCAAGGGCCTGGAGTGGATCAGCAGCATCAGCGGCAGC
AGCAGATACATCTACTACGCCGACTTCGTGAAGGGCAGATTCACCATCAGCAGA
GACAACGCCACCAACAGCCTGTACCTGCAGATGAACAGCCTGAGAGCCGAGGAC
ACCGCCGTGTACTACTGCGTGAGAAGCAGCATCACCATCTTCGGCGGCGGCATG
GACGTGTGGGGCAGAGGCACCCTGGTGACCGTGAGCAGCGCTAGCACCAAGGGC
CCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGG
CCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAA
CTCAGGCGCTCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCCTACAGTCCTCA
GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCC
AGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGA
CAGTTGAGCGCAAATGTTGTGTCGAGTGCCCACCGTGCCCAGCACCACCTGTGGC
AGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCC
CGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAG
GTCCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAG
CCACGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTG
TGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAG
GCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAG
AACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGG
TCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTG
GGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCATGCTGGA
CTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGG
CAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACT
ACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAGGTGGTGGTGGCTCGGGAT
CCGGAGGCTCCGGTGGCGGTGGCAGCAACCCAATTTGCAAGGGATGCTTAAGCT
GTAGCAAGGACAACGGATGTTCACGGTGCCAGCAAAAGCTGTTTTTCTTCCTCCG
GCGGGAAGGAATGCGGCAGTACGGCGAATGTCTCCACTCCTGCCCCTCGGGGTA
TTACGGACACCGCGCGCCTGACATGAACCGATGCGCCAGATGCCGGATCGAGAA
CTGCGATAGCTGCCGCAGCAAGGACGCCTGCACTAAGTGCAAAGTCGGCTTCTA
CCTTCACCGGGGCAGATGTTTTGACGAATGCCCGGATGGCTTCGCCCCGCTGGAG
GAGACTATGGAATGCGTGGAG

抗β-Gal重链IgG2、RSPO2（F105R/F109A）多肽（SID NO: 187）

EVQLVESGGSLVKPGGSLRLSCAASGFTFSNYSMNWVRQAPGKGLEWISSISGSSRYI
YYADFVKGRFTISRDNATNSLYLQMNSLRAEDTAVYYCVRSSITIFGGGMDVWGRG
TLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH
TFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPP
CPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHN
AKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQP
REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDS
DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGSGG
SGGGGSNPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYGHR
APDMNRCARCRIENCDSCRSKDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECV
E

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抗GFP重链IgG2、RSPO2（F105R/F109A）多核苷酸（SEQ ID NO: 188）

CAGGTCCAGTTGGTGGAATCCGGAGGGGGTTTGGTCCAGCCTGGTGGAAGCCTG
CGCCTCTCATGCGCCGCTAGCGGATTCACCTTCTCCCGATACGGCATGCATTGGG
TCAGACAGGCACCCGGAAAAGGACTCGAATGGGTGTCGGGCATTTCCTCGATCG
GGTCAAACACCTATTACGCCGACTCCGTGAAGGGACGGTTCACCATTAGCCGGG
ATAACAGCAAGAACACTCTGTACTTGCAAATGAACTCCCTGCGGGCTGAGGACA
CCGCCGTGTACTACTGTGCGCGGTGGTACAAGACCTATATTGACGTCTGGGGACA
GGGTACCCTCGTGACCGTGTCTAGCGCTAGCACCAAGGGCCCATCGGTCTTCCCC
CTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTG
GTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTG
ACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCC
TCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTG
CAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCA
AATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGG
GGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCC
CGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAG
GTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAG
CCGCGGGAGGAGCAGTACGGCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTC
CTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAA
GCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGA
GAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAG
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGT
GGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGG
ACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTG
GCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCAC
TACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAGGTGGTGGTGGCTCGGGA
TCCGGAGGCTCCGGTGGCGGTGGCAGCAACCCAATTTGCAAGGGATGCTTAAGC
TGTAGCAAGGACAACGGATGTTCACGGTGCCAGCAAAAGCTGTTTTTCTTCCTCC
GGCGGGAAGGAATGCGGCAGTACGGCGAATGTCTCCACTCCTGCCCCTCGGGGT
ATTACGGACACCGCGCGCCTGACATGAACCGATGCGCCAGATGCCGGATCGAGA
ACTGCGATAGCTGCCGCAGCAAGGACGCCTGCACTAAGTGCAAAGTCGGCTTCT
ACCTTCACCGGGGCAGATGTTTTGACGAATGCCCGGATGGCTTCGCCCCGCTGGA
GGAGACTATGGAATGCGTGGAG

抗GFP重链IgG2、RSPO2（F105R/F109A）多肽（SEQ ID NO: 189）

QVQLVESGGGLVQPGGSLRLSCAASGFTFSRYGMHWVRQAPGKGLEWVSGISSIGS
NTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARWYKTYIDVWGQGT
LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH
TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTC
PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE
VHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP
VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGS
GSGGSGGGGSNPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYY
GHRAPDMNRCARCRIENCDSCRSKDACTKCKVGFYLHRGRCFDECPDGFAPLEETM
ECVE

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LP1-1F8轻链多核苷酸（SEQ ID NO: 190）

GACATTGTGATGTCACAGTCTCCATCCTCCCTGGCTGTGTCAGCAGGAGAGAAGG
TCACTATGAGCTGCAAGTCCAGTCAGAGTCTGTTCAACAGTAGAACCCGAAAGA
ACTACTTGGCTTGGTACCAGCAGAAACCAGGGCAGTCTCCTAAACTGCTGATCTA
CTGGGCATCCACTAGGGAATCTGGGGTCCCTGATCGCTTCACAGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTGTGCAGGCTGAAGACCTGGCAGTTT
ATTACTGCAAGCAATCTTATTATCTGCTCACGTTCGGTGCTGGGACCAAGCTGGA
GCTGAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAG
CAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCA
GAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCC
AGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGC
ACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAA
GTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAG
TGT

LP1-1F8轻链多肽（SEQ ID NO: 191）

DIVMSQSPSSLAVSAGEKVTMSCKSSQSLFNSRTRKNYLAWYQQKPGQSPKLLIYW
ASTRESGVPDRFTGSGSGTDFTLTISSVQAEDLAVYYCKQSYYLLTFGAGTKLELKRT
VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ
DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

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LP1-1F8重链IgG2、RSPO2（F105R/F109A）多核苷酸（SEQ ID NO: 192）

GAAGTGAAACTGGTGGAGTCTGGGGGAGGCTTAGTGAAGCCTGGAGGGTCCCTG
AAACTCTCCTGTGCAGCCTCTGGATTCACTTTCAGTACCTATACCATGTCTTGGGT
TCGCCAGACTCCGGCGAAGAGGCTGGAGTGGGTCGCAACCATTAGTAGTATTGG
TGTTAACACCTACTATCCAGACAGTGTGAAGGGCCGATTCACCATCTCCAGAGAC
AATGCCAGGAACACCCTGTACCTGCAAGTGAGCAGTCTGAGGTCTGAGGACACG
GCCATGTATTACTGTGCAAGACATGTGGATTACTACGATGGGATTTCCTTTGACT
ACTGGGGCCAAGGCACCACTCTCACAGTCTCCAGCGCTAGCACCAAGGGCCCAT
CGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCT
GGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTC
AGGCGCTCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCCTACAGTCCTCAGGA
CTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGA
CCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGACAG
TTGAGCGCAAATGTTGTGTCGAGTGCCCACCGTGCCCAGCACCACCTGTGGCAGG
ACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGG
ACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTC
CAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCA
CGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTGTGC
ACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCC
TCCCAGCCCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAAC
CACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCA
GCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGG
AGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCATGCTGGACT
CCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCA
GCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTAC
ACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAGGTGGTGGTGGCTCGGGATCC
GGAGGCTCCGGTGGCGGTGGCAGCAACCCAATTTGCAAGGGATGCTTAAGCTGT
AGCAAGGACAACGGATGTTCACGGTGCCAGCAAAAGCTGTTTTTCTTCCTCCGGC
GGGAAGGAATGCGGCAGTACGGCGAATGTCTCCACTCCTGCCCCTCGGGGTATT
ACGGACACCGCGCGCCTGACATGAACCGATGCGCCAGATGCCGGATCGAGAACT
GCGATAGCTGCCGCAGCAAGGACGCCTGCACTAAGTGCAAAGTCGGCTTCTACC
TTCACCGGGGCAGATGTTTTGACGAATGCCCGGATGGCTTCGCCCCGCTGGAGGA
GACTATGGAATGCGTGGAG

LP1-1F8重链IgG2、RSPO2（F105R/F109A）多肽（SEQ ID NO: 193）

EVKLVESGGGLVKPGGSLKLSCAASGFTFSTYTMSWVRQTPAKRLEWVATISSIGVN
TYYPDSVKGRFTISRDNARNTLYLQVSSLRSEDTAMYYCARHVDYYDGISFDYWGQ
GTTLTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV
HTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECP
PCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVH
NAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKG
QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPML
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGS
GGSGGGGSNPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYG
HRAPDMNRCARCRIENCDSCRSKDACTKCKVGFYLHRGRCFDECPDGFAPLEETME
CVE

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LP1-1N15轻链多核苷酸（SEQ ID NO: 194）

GACATCAAGATGACCCAGTCTCCATCTTCCATGTATGCATCTCTAGGAGAGAGAG
TTACTATCACTTGCAAGGCGAGTCAGGACATTAATAGCCATTTAAGCTGGTTCCA
GCAGAAACCAGGGAAATCTCCTAAGACCCTGATCATTCGTGCAAACAGATTGGT
AGATGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCTGGGCAAGATTATTCTCTC
ACCATCAGCAGCCCGGAGTATGAAGAAATGGGAATTTATTACTGTCTACAGTAT
GATGAGTTTCCGTTCACGTTCGGAGGGGGGACCAAGCTGGAAATAAAACGTACG
GTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTG
GAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGT
ACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCAC
AGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAG
CAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGG
CCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

LP1-1N15轻链多肽（SEQ ID NO: 195）

DIKMTQSPSSMYASLGERVTITCKASQDINSHLSWFQQKPGKSPKTLIIRANRLVDGV
PSRFSGSGSGQDYSLTISSPEYEEMGIYYCLQYDEFPFTFGGGTKLEIKRTVAAPSVFIF
PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

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LP1-1N15重链IgG2、RSPO2（F105R/F109A）多核苷酸（SEQ ID NO: 196）

GAGGTCCAGCTGCAACAGTCTGGACCTGAGCTGGTGAAGCCTGGGGCTTCAGTG
AAGATGTCCTGTAAGGCTTCTGGATACACATTCACTGACTACTACATGAACTGGG
TGAAGCAGAGTCATGGAGAGAGCCTTGAGTGGATTGGACGTGTTATTCCTAGCA
ATGGTGGTACTAACTACAACCAGAAGTTCAAGGGCAAGGCCACATTGACAGTAG
ACAAATCCCTCACCACAGCCTACATGCAGCTCAACAGCCTGACATCTGAAGACTC
TGCGGTCTATTTCTGTGCAAGAGGGATGGACTACTGGGGTCCAGGAACCTCAGTC
ACCGTCTCCAGCGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCT
CCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACT
TCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCTCTGACCAGCGGCGTGC
ACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGT
GACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGTAGATCAC
AAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTGTGTCGAG
TGCCCACCGTGCCCAGCACCACCTGTGGCAGGACCGTCAGTCTTCCTCTTCCCCC
CAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGG
TGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGACG
GCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAGCAGTTCAACAGC
ACGTTCCGTGTGGTCAGCGTCCTCACCGTTGTGCACCAGGACTGGCTGAACGGCA
AGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCAGCCCCCATCGAGAAAA
CCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCC
CATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAG
GCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGA
ACAACTACAAGACCACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTA
CAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATG
CTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTG
TCTCCGGGTAAAGGTGGTGGTGGCTCGGGATCCGGAGGCTCCGGTGGCGGTGGC
AGCAACCCAATTTGCAAGGGATGCTTAAGCTGTAGCAAGGACAACGGATGTTCA
CGGTGCCAGCAAAAGCTGTTTTTCTTCCTCCGGCGGGAAGGAATGCGGCAGTAC
GGCGAATGTCTCCACTCCTGCCCCTCGGGGTATTACGGACACCGCGCGCCTGACA
TGAACCGATGCGCCAGATGCCGGATCGAGAACTGCGATAGCTGCCGCAGCAAGG
ACGCCTGCACTAAGTGCAAAGTCGGCTTCTACCTTCACCGGGGCAGATGTTTTGA
CGAATGCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCGTGGAG

LP1-1N15重链IgG2、RSPO2（F105R/F109A）多肽（SEQ ID NO: 197）

EVQLQQSGPELVKPGASVKMSCKASGYTFTDYYMNWVKQSHGESLEWIGRVIPSNG
GTNYNQKFKGKATLTVDKSLTTAYMQLNSLTSEDSAVYFCARGMDYWGPGTSVTV
SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPP
VAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTK
PREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQ
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSF
FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGSGGSGG
GGSNPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYGHRAPD
MNRCARCRIENCDSCRSKDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECVE

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LP1-1P13轻链多核苷酸（SEQ ID NO: 198）

GACATCCAGATGACTCAGTCTCCAGCCTCCCTATCTGCATCTGTGGGACAAACTG
TTATCATCACATGTCGAACAAGTGAGAATATTTACAGTAATTTAGCATGGTATCA
GCAGAAACAGGGAAAATCTCCTCAGCTCCTGGTCTATGCTGCAACAAACTTAGC
AGATGGTGTGCCATCAAGGTTCAGTGGCAGTGGTTCAGGCACACAGTATTACCTC
AAGATCAACAGCCTGCAGTCTGAAGATTTTGGGAGTTATTACTGTCAACATTTTT
GGGGTAGTACGTGGACGTTCGGTGGAGGCACCAAGCTGGACATCAAACGTACGG
TGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGG
AACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTA
CAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACA
GAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGC
AAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

LP1-1P13轻链多肽（SEQ ID NO: 199）

DIQMTQSPASLSASVGQTVIITCRTSENIYSNLAWYQQKQGKSPQLLVYAATNLADG
VPSRFSGSGSGTQYYLKINSLQSEDFGSYYCQHFWGSTWTFGGGTKLDIK

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LP1-1P13重链IgG2、RSPO2多核苷酸（SEQ ID NO: 200）

GAGGTTCAACTGCAGCAGTCTGGACCTGAACTGGTGAAGCCTGGGGCTTCAGTG
AAGATATCCTGCAAGGCTTCTGGTTACTCATTTACTGACTACTTTATGAACTGGGT
GAAGCAGAGCCATGGAAAGAGCCTTGAGTGGATTGGACGTTTTAATCCTTTCAAT
GGTCAAACTTTCTACAATCAGGAGTTCAAGGGCAAGGCCACATTAACTGTAGAC
AAATCCTCTAGCACCGCCCACATGGAGCTCCGGAGCCTGACATCTGAGGACTCTG
CAGTCTATTATTGTGCAAGAAGAGGAAGGTACGACGTTTACTATGTTCTGGACTA
CTGGGGTCAAGGAACCTCAGTCACCGTCTCCAGCGCTAGCACCAAGGGCCCATC
GGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTG
GGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCA
GGCGCTCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCCTACAGTCCTCAGGAC
TCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGAC
CTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGACAGT
TGAGCGCAAATGTTGTGTCGAGTGCCCACCGTGCCCAGCACCACCTGTGGCAGG
ACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGG
ACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTC
CAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCA
CGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTGTGC
ACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCC
TCCCAGCCCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAAC
CACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCA
GCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGG
AGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCATGCTGGACT
CCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCA
GCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTAC
ACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAGGTGGTGGTGGCTCGGGATCC
GGAGGCTCCGGTGGCGGTGGCAGCAACCCAATTTGCAAGGGATGCTTAAGCTGT
AGCAAGGACAACGGATGTTCACGGTGCCAGCAAAAGCTGTTTTTCTTCCTCCGGC
GGGAAGGAATGCGGCAGTACGGCGAATGTCTCCACTCCTGCCCCTCGGGGTATT
ACGGACACCGCGCGCCTGACATGAACCGATGCGCCAGATGCCGGATCGAGAACT
GCGATAGCTGCCGCAGCAAGGACGCCTGCACTAAGTGCAAAGTCGGCTTCTACC
TTCACCGGGGCAGATGTTTTGACGAATGCCCGGATGGCTTCGCCCCGCTGGAGGA
GACTATGGAATGCGTGGAG

LP1-1P13重链IgG2、RSPO2多肽（SEQ ID NO: 201）

EVQLQQSGPELVKPGASVKISCKASGYSFTDYFMNWVKQSHGKSLEWIGRFNPFNG
QTFYNQEFKGKATLTVDKSSSTAHMELRSLTSEDSAVYYCARRGRYDVYYVLDYW
GQGTSVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS
GVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVE
CPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVE
VHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKT
KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP
MLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGS
GSGGSGGGGSNPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYY
GHRAPDMNRCARCRIENCDSCRSKDACTKCKVGFYLHRGRCFDECPDGFAPLEETM
ECVE

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LP1-1P5轻链多核苷酸（SEQ ID NO: 202）

GACATTGTGATGACCCAGTCTCAAAAATTCATGTCCACATCAGTAGGAGACAGG
GTCAGCGTCACCTGCAAGGCCAGTCAGAATGTGGGTACTAATGTAGCCTGGTATC
AACAGAAACCAGGACAATCTCCTAAAGCACTGATTTACTCGGCATCTTATCGGTA
CAGTGGAGTCCCTGATCGCTTCACAGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCAGCAATGTGCAGTCTGAAGACTTGGCAGAGTATTTCTGTCAACAATATA
ACAGCTATCCGCTCACGTTCGGTGCTGGGACCAAGCTGGAGCTGAAACGTACGG
TGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGG
AACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTA
CAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACA
GAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGC
AAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

LP1-1P5轻链多肽（SEQ ID NO: 203）

DIVMTQSQKFMSTSVGDRVSVTCKASQNVGTNVAWYQQKPGQSPKALIYSASYRYS
GVPDRFTGSGSGTDFTLTISNVQSEDLAEYFCQQYNSYPLTFGAGTKLELKRTVAAPS
VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS
TYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

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LP1-1P5重链IgG2、RSPO2（F105R/F109A）多核苷酸（SEQ ID NO: 204）

CAGGTCCAGCTGCAGCAATCTGGACCTGAGCTGGTGAGGCCTGGGACTTCAGTG
AAGATATCCTGCAAGGCTTCTGGCTATACCTTCCTCACCTACTGGATGAACTGGG
TGAAGCAGAGGCCTGGACAGGGCCTTGAGTGGATTGGACAGATTTTCCCTGCAA
CTGGTATTACTTACTACAGTGAGATGTTCAAGGACAAGGCCACATTGACTGAAG
ACACATCCTCCACCACAGCCTACATGCAACTCAGCAGCCTGACATCTGAGGCCAC
TGCTGTCTATTTCTGTGCAAGAAGAAGGGCCTACCATAGTAACTTTTTTGACTACT
GGGGCCAAGGCACCACTCTCACAGTCTCCAGCGCTAGCACCAAGGGCCCATCGG
TCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGG
CTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGC
GCTCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTCT
ACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTA
CACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGA
GCGCAAATGTTGTGTCGAGTGCCCACCGTGCCCAGCACCACCTGTGGCAGGACC
GTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACC
CCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAG
TTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGG
GAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTGTGCACC
AGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCC
CAGCCCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCAC
AGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCC
TGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGA
GCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCATGCTGGACTCCG
ACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGC
AGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACAC
GCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAGGTGGTGGTGGCTCGGGATCCGG
AGGCTCCGGTGGCGGTGGCAGCAACCCAATTTGCAAGGGATGCTTAAGCTGTAG
CAAGGACAACGGATGTTCACGGTGCCAGCAAAAGCTGTTTTTCTTCCTCCGGCGG
GAAGGAATGCGGCAGTACGGCGAATGTCTCCACTCCTGCCCCTCGGGGTATTAC
GGACACCGCCGCCTGACATGAACCGATGCGCCAGATGCCGGATCGAGAACTGC
GATAGCTGCCGCAGCAAGGACGCCTGCACTAAGTGCAAAGTCGGCTTCTACCTTC
ACCGGGGCAGATGTTTTGACGAATGCCCGGATGGCTTCGCCCCGCTGGAGGAGA
CTATGGAATGCGTGGAG

LP1-1P5重链IgG2、RSPO2（F105R/F109A）多肽（SEQ ID NO: 205）

QVQLQQSGPELVRPGTSVKISCKASGYTFLTYWMNWVKQRPGQGLEWIGQIFPATGI
TYYSEMFKDKATLTEDTSSTTAYMQLSSLTSEATAVYFCARRRAYHSNFFDYWGQG
TTLTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH
TFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPP
CPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHN
AKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQP
REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDS
DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGSGG
SGGGGSNPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYGHR
APDMNRCARCRIENCDSCRSKDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECV
E

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LP1-2E12轻链多核苷酸（SEQ ID NO: 206）

GATGTTGTGGTGACTCAAACTCCACTCTCCCTGCCTGTCAGCTTTGGAGATCGAG
TTTCTATCTCTTGCAGGTCTAGTCAGAGTCTTGCAAACAGTTATGGGAACACCTA
TTTGTCTTGGTACCTGCACAAGCCTGGCCAGTCTCCACAGCTCCTCATCTATGGG
ATTTCCAACAGATTTTCTGGGGTGCCAGACAGGTTCAGTGGCAGTGGTTCAGGGA
CAGATTTCACACTCAAGATCAGCACAATAAAGCCTGAGGACTTGGGAATGTATT
ACTGCTTACAAGGTACACATCAGCCTCTCACGTTCGGTGCTGGGACCAAGCTGGA
GCTGAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAG
CAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCA
GAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCC
AGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGC
ACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAA
GTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAG
TGT

LP1-2E12轻链多肽（SEQ ID NO: 207）

DVVVTQTPLSLPVSFGDRVSISCRSSQSLANSYGNTYLSWYLHKPGQSPQLLIYGISN
RFSGVPDRFSGSGSGTDFTLKISTIKPEDLGMYYCLQGTHQPLTFGAGTKLELKRTVA
APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS
KDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

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LP1-2E12重链IgG2、RSPO2（F105R/F109A）多核苷酸（SEQ ID NO: 208）

GATGTACAACTTCAGGAGTCAGGACCTGGCCTCGTGAAACCTTCTCAGTCTCTGT
CTCTCACCTGCTCTGTCACTGGCTACTCCATCACCAGTGGTTATTACTGGAACTGG
ATCCGGCAGTTTCCAGGAAACAAACTGGAATGGATGGGCTCCATAGGCTACGAT
GATACCAATCACTACAACCCATCTCTCAAAAATCGAATCTCCATCACTCGTGACA
CATCTAAGAACCAGTTTTTCCTGAAGTTGAATTCTGTGACAACTGAGGACACAGC
CACATATTACTGTGCAGGTGACTACCCCTTTGCTTTCTGGGGCCAAGGGACTCTG
GTCACTGTCTCTGCAGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCT
GCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACT
ACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCTCTGACCAGCGGCG
TGCACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGT
GGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGTAGAT
CACAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTGTGTC
GAGTGCCCACCGTGCCCAGCACCACCTGTGGCAGGACCGTCAGTCTTCCTCTTCC
CCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGT
GGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGA
CGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAGCAGTTCAACA
GCACGTTCCGTGTGGTCAGCGTCCTCACCGTTGTGCACCAGGACTGGCTGAACGG
CAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCAGCCCCCATCGAGAA
AACCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCC
CCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAA
AGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGA
GAACAACTACAAGACCACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTC
TACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCA
TGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCC
TGTCTCCGGGTAAAGGTGGTGGTGGCTCGGGATCCGGAGGCTCCGGTGGCGGTG
GCAGCAACCCAATTTGCAAGGGATGCTTAAGCTGTAGCAAGGACAACGGATGTT
CACGGTGCCAGCAAAAGCTGTTTTTCTTCCTCCGGCGGGAAGGAATGCGGCAGT
ACGGCGAATGTCTCCACTCCTGCCCCTCGGGGTATTACGGACACCGCGCGCCTGA
CATGAACCGATGCGCCAGATGCCGGATCGAGAACTGCGATAGCTGCCGCAGCAA
GGACGCCTGCACTAAGTGCAAAGTCGGCTTCTACCTTCACCGGGGCAGATGTTTT
GACGAATGCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCGTGGAG

LP1-2E12重链IgG2、RSPO2（F105R/F109A）多肽（SEQ ID NO: 209）

DVQLQESGPGLVKPSQSLSLTCSVTGYSITSGYYWNWIRQFPGNKLEWMGSIGYDDT
NHYNPSLKNRISITRDTSKNQFFLKLNSVTTEDTATYYCAGDYPFAFWGQGTLVTVS
AASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPV
AGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKP
REEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFF
LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGSGGSGGG
GSNPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYGHRAPDM
NRCARCRIENCDSCRSKDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECVE

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LP1-2I13轻链多核苷酸（SEQ ID NO: 210）

GACATCCAGATGACTCAGTCTCCAGCCTCCCTATCTGCATCTGTGGGAGAAACTG
TCACCATCACATGTCGAGCAAGTGAGAATATTTACAGTTATTTAGTATGGTATCA
GCAGAAACAGGGAAAATCTCCTCAGCTCCTGGTCTATAATGCAAAAACCTTAGC
AGAAGGTGTGCCATCAAGGTTCAGTGGCAGTGGATCAGGCACACAGTTTTCTCTG
AAGATCAACAGCCTGCAGCCTGAAGATTTTGGGAGTTATTACTGTCAACATCATT
ATGGTACTTGGACGTTCGGTGGAGGCATAAAGCTGGAAATCAAACGTACGGTGG
CTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAAC
TGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAG
TGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAG
CAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAA
GCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTG
AGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

LP1-2I13轻链多肽（SEQ ID NO: 211）

DIQMTQSPASLSASVGETVTITCRASENIYSYLVWYQQKQGKSPQLLVYNAKTLAEG
VPSRFSGSGSGTQFSLKINSLQPEDFGSYYCQHHYGTWTFGGGTKLEIKRTVAAPSVFI
FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY
SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

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LP1-2I13重链IgG2、RSPO2（F105R/F109A）多核苷酸（SEQ ID NO: 212）

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTAGTGAAGCCTGGAGGGTCCCGG
AAACTCTCCTGTGCAGCCTCTGGATTCACTTTCAGTGACTATGGAATGCACTGGG
TCCGTCAGGCTCCAGAGAAGGGGCTGGAGTGGGTTGCCTACATTAGTAGTGGCA
GTAGTACCATCTACTATGCAGACACAGTGAAGGGCCGATTCACCATCTCCAGAG
ACAATGCCAAGAACACCCTGTTCCTACAAATGACCAGTCTAAGGTCTGAGGACA
CAGCCATGTATTACTGTTCAAGGAAGGGAGGGTTTGGTGACTACGAGAAAAGCT
ATGCTATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCAGCGCTAGCAC
CAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGC
ACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTG
TCGTGGAACTCAGGCGCTCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCCTAC
AGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTT
CGGCACCCAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGT
GGACAAGACAGTTGAGCGCAAATGTTGTGTCGAGTGCCCACCGTGCCCAGCACC
ACCTGTGGCAGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTC
ATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCACGAA
GACCCCGAGGTCCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCC
AAGACAAAGCCACGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTC
CTCACCGTTGTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTC
TCCAACAAAGGCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAACCAAAGGG
CAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACC
AAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATC
GCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCC
TCCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGAC
AAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCT
CTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAGGTGGT
GGTGGCTCGGGATCCGGAGGCTCCGGTGGCGGTGGCAGCAACCCAATTTGCAAG
GGATGCTTAAGCTGTAGCAAGGACAACGGATGTTCACGGTGCCAGCAAAAGCTG
TTTTTCTTCCTCCGGCGGGAAGGAATGCGGCAGTACGGCGAATGTCTCCACTCCT
GCCCCTCGGGGTATTACCGACACCGCGCGCCTGACATGAACCGATGCGCCAGAT
GCCGGATCGAGAACTGCGATAGCTGCCGCAGCAAGGACGCCTGCACTAAGTGCA
AAGTCGGCTTCTACCTTCACCGGGGCAGATGTTTTGACGAATGCCCGGATGGCTT
CGCCCCGCTGGAGGAGACTATGGAATGCGTGGAG

LP1-2I13重链IgG2、RSPO2（F105R/F109A）多肽（SEQ ID NO: 213）

EVQLVESGGGLVKPGGSRKLSCAASGFTFSDYGMHWVRQAPEKGLEWVAYISSGSS
TIYYADTVKGRFTISRDNAKNTLFLQMTSLRSEDTAMYYCSRKGGFGDYEKSYAMD
YWGQGTSVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGA
LTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKC
CVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVD
GVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTI
SKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGG
GGSGSGGSGGGGSNPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPS
GYYGHRAPDMNRCARCRIENCDSCRSKDACTKCKVGFYLHRGRCFDECPDGFAPLE
ETMECVE

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LP1-2I22轻链多核苷酸（SEQ ID NO: 214）

GACATCCAGATGACTCAGTCTCCAGCCTCCCTATCTGCATCTGTGGGAGAAACTG
TTATCATCACATGTCGAGCAAGTGAGAATATTTACAGTAATTTAGCATGGTATCA
GCAGAAACAGGGAAAATCTCCTCAGCTCCTGGTCTATGGTGCAACAAACTTAGC
AGATGGTGTGACATCAAGGTTCAGTGGCAGTGGTTCAGGCACACAGTTTTCCCTC
AAGATCGACAGCCTGCAGTCTGAAGATTTTGGGAGTTATTACTGTCAACATTTTT
GGGGTACTACGTGGACGTTCGGTGGAGGCACCAAGCTGGAAATCAAACGTACGG
TGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGG
AACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTA
CAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACA
GAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGC
AAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

LP1-2I22轻链多肽（SEQ ID NO: 215）

DIQMTQSPASLSASVGETVIITCRASENIYSNLAWYQQKQGKSPQLLVYGATNLADG
VTSRFSGSGSGTQFSLKIDSLQSEDFGSYYCQHFWGTTWTFGGGTKLEIKRTVAAPSV
FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDST
YSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

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LP1-2I22重链IgG2、RSPO2（F105R/F109A）多核苷酸（SEQ ID NO: 216）

GAGGTTCAACTGCAGCAGTCTGGACCTGAACTGGTGAAGCCTGGGGCTTCAGTG
AAGATATCCTGCAAGGCTTCTGGTTACTCATTTACTGGCTACTTTATGAACTGGGT
GAAGCAGAGCCATGGAAAGAGCCTTGAGTGGATTGGACGTTTTAATCCTTTCAAT
GGTCAAACTTTCTACAATCAGGAGTTCAAGGGCAAGGCCACATTAACTGTTGAC
AAATCCTCTGACACCGCCCACATGGAACTCCGGAGCCTGACATCTGAGGACTCTG
CAGTCTATTATTGTGCAAGAAGAGGAAGGTACGACGTTTACTATGCTCTGGACTA
CTGGGGTCAAGGAACCTCAGTCACCGTCTCCAGCGCTAGCACCAAGGGCCCATC
GGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTG
GGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCA
GGCGCTCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCCTACAGTCCTCAGGAC
TCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGAC
CTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGACAGT
TGAGCGCAAATGTTGTGTCGAGTGCCCACCGTGCCCAGCACCACCTGTGGCAGG
ACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGG
ACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTC
CAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCA
CGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTGTGC
ACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCC
TCCCAGCCCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAAC
CACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCA
GCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGG
AGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCATGCTGGACT
CCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCA
GCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTAC
ACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAGGTGGTGGTGGCTCGGGATCC
GGAGGCTCCGGTGGCGGTGGCAGCAACCCAATTTGCAAGGGATGCTTAAGCTGT
AGCAAGGACAACGGATGTTCACGGTGCCAGCAAAAGCTGTTTTTCTTCCTCCGGC
GGGAAGGAATGCGGCAGTACGGCGAATGTCTCCACTCCTGCCCCTCGGGGTATT
ACGGACACCGCCGCCTGACATGAACCGATGCGCCAGATGCCGGATCGAGAACT
GCGATAGCTGCCGCAGCAAGGACGCCTGCACTAAGTGCAAAGTCGGCTTCTACC
TTCACCGGGGCAGATGTTTTGACGAATGCCCGGATGGCTTCGCCCCGCTGGAGGA
GACTATGGAATGCGTGGAG

LP1-2I22重链IgG2、RSPO2（F105R/F109A）多肽（SEQ ID NO: 217）

EVQLQQSGPELVKPGASVKISCKASGYSFTGYFMNWVKQSHGKSLEWIGRFNPFNG
QTFYNQEFKGKATLTVDKSSDTAHMELRSLTSEDSAVYYCARRGRYDVYYALDYW
GQGTSVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS
GVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVE
CPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVE
VHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKT
KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP
MLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGS
GSGGSGGGGSNPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYY
GHRAPDMNRCARCRIENCDSCRSKDACTKCKVGFYLHRGRCFDECPDGFAPLEETM
ECVE

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LP1-3A24轻链多核苷酸（SEQ ID NO: 218）

GACATTGTGATGACCCAGTCTCAAAAATTCATGTCCACATCAGTAGGAGACAGG
GTCAGCGTCACCTGCAAGGCCAGTCAGAATGTGGGTAGTAATGTAGCCTGGTTTC
AACAGAAACCAGGGCAATCTCCTAAAGCACTGATTTACTCGTCATCCTACCGGTA
CAGTGGAGTCCCTGATCGCTTCACGGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCACCAATGTGCAGTCTGAAGACTTGGCAGAGTATTTCTGTCAGCAATATA
ACAGCTTTCCTCTCACGTTCGGTGCTGGGACCAAGCTGGAACTGAAACGTACGGT
GGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTAC
AGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAG
AGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCA
AAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCC
TGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

LP1-3A24轻链多肽（SEQ ID NO: 219）

DIVMTQSQKFMSTSVGDRVSVTCKASQNVGSNVAWFQQKPGQSPKALIYSSSYRYS
GVPDRFTGSGSGTDFTLTITNVQSEDLAEYFCQQYNSFPLTFGAGTKLELKRTVAAPS
VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS
TYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

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LP1-3A24重链IgG2、RSPO2（F105R/F109A）多核苷酸（SEQ ID NO: 220）

GAGGTCCAGCTGCAACAGTCTGGACCTGAGCTGGTGAAGCCTGGGGCTTCAGTG
AAGATGTCCTGTAAGGCTTCTGGATACACATTCACTGACTACTACATAAACTGGG
TGAGGCAGAGTCATGGAAAGAGCCTTGAGTGGATTGGACGTGTTATTCCTAGCA
ATGGTGGTAGTAACTACAACCAGAAGTTCAAGGGCAAGGCCACATTGACAGTAG
ACAAATCCCTCAGTACAGCCTACATGCACCTCAACAGCCTGACATCTGAGGACTC
TGCGGTCTATTACTGTGCAACCCAGCTGGGACGGTGGGGCCAAGGGACTCTGGT
CACTGTCTCTGCAGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGC
TCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTAC
TTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCTCTGACCAGCGGCGTG
CACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGG
TGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGTAGATCA
CAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTGTGTCGA
GTGCCCACCGTGCCCAGCACCACCTGTGGCAGGACCGTCAGTCTTCCTCTTCCCC
CCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTG
GTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGAC
GGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAGCAGTTCAACAG
CACGTTCCGTGTGGTCAGCGTCCTCACCGTTGTGCACCAGGACTGGCTGAACGGC
AAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCAGCCCCCATCGAGAAA
ACCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCC
CCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAA
GGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAG
AACAACTACAAGACCACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTCT
ACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCAT
GCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCT
GTCTCCGGGTAAAGGTGGTGGTGGCTCGGGATCCGGAGGCTCCGGTGGCGGTGG
CAGCAACCCAATTTGCAAGGGATGCTTAAGCTGTAGCAAGGACAACGGATGTTC
ACGGTGCCAGCAAAAGCTGTTTTTCTTCCTCCGGCGGGAAGGAATGCGGCAGTA
CGGCGAATGTCTCCACTCCTGCCCCTCGGGGTATTACGGACACCGCGCGCCTGAC
ATGAACCGATGCGCCAGATGCCGGATCGAGAACTGCGATAGCTGCCGCAGCAAG
GACGCCTGCACTAAGTGCAAAGTCGGCTTCTACCTTCACCGGGGCAGATGTTTTG
ACGAATGCCCGGATGGCTTCGCCCCCGCTGGAGGAGACTATGGAATGCGTGGAG

LP1-3A24重链IgG2、RSPO2（F105R/F109A）多肽（SEQ ID NO: 221）

EVQLQQSGPELVKPGASVKMSCKASGYTFTDYYINWVRQSHGKSLEWIGRVIPSNG
GSNYNQKFKGKATLTVDKSLSTAYMHLNSLTSEDSAVYYCATQLGRWGQGTLVTV
SAASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPP
VAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTK
PREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQ
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSF
FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGSGGSGG
GGSNPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYGHRAPD
MNRCARCRIENCDSCRSKDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECVE

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LP1-3E20轻链多核苷酸（SEQ ID NO: 222）

GACATCAAGATGACCCAGTCTCCATCTTCCATGTATGCATCTCTAGGAGAGAGAG
TCACTATCACTTGCAAGGCGAGTCAGGACATTAATAGCTATTTAAGCTGGTTCCA
GCAGAAACCAGGGAAATCTCCTAAGACCCTGATCTATCGTGCAAACAGATTGGT
AGATGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCTGGGCAAGATTATTCTCTC
ACCATCAGCAGCCTAGAGTATGAAGATATGGGAATTTATTATTGTCTACAGTATG
ATGACTTGTGGACGTTCGGTGGAGGCACCAAGCTGGAAATCAAACGTACGGTGG
CTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAAC
TGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAG
TGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAG
CAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAA
GCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTG
AGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

LP1-3E20轻链多肽（SEQ ID NO: 223）

DIKMTQSPSSMYASLGERVTITCKASQDINSYLSWFQQKPGKSPKTLIYRANRLVDG
VPSRFSGSGSGQDYSLTISSLEYEDMGIYYCLQYDDLWTFGGGTKLEIKRTVAAPSVF
IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY
SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

图11AS

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LP1-3E20重链IgG2、RSPO2（F105R/F109A）多核苷酸（SEQ ID NO: 224）

CAGGTCCAACTGCAGCAGTCTGGGGCTGAACTGGCAAAACCTGGGGCCTCAGTG
AAGATGTCCTGCAAGGCTTCTGGCTACACCTTTACTAGCTACTGGATACACTGGG
TAAAACAGAGGCCTGGACAGGGTCTGGAATGGATTGGATACATTAATCCTAGCA
GTGGTTATGCTGAGTACAATCAGAAGTTCAAGGTCAGGGCCACATTGACTGCAG
ACAAATCCTCCAGCACAGCCTACATGCAACTAAGCAGCCTGACATCTGAGGACT
CTGCAGTCTATTACTGTGCAAGAGAAAGTTACTATAGTTTCGACTATACTATGGA
CTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCAGCGCTAGCACCAAGGGCCC
ATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCC
CTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACT
CAGGCGCTCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCCTACAGTCCTCAGG
ACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAG
ACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGACA
GTTGAGCGCAAATGTTGTGTCGAGTGCCCACCGTGCCCAGCACCACCTGTGGCAG
GACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCG
GACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGT
CCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCC
ACGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTGTG
CACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGC
CTCCCAGCCCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAA
CCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTC
AGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGG
GAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCATGCTGGAC
TCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGC
AGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTA
CACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAGGTGGTGGTGGCTCGGGATC
CGGAGGCTCCGGTGGCGGTGGCAGCAACCCAATTTGCAAGGGATGCTTAAGCTG
TAGCAAGGACAACGGATGTTCACGGTGCCAGCAAAAGCTGTTTTTCTTCCTCCGG
CGGGAAGGAATGCGGCAGTACGGCGAATGTCTCCACTCCTGCCCCTCGGGGTAT
TACGGACACCGCGCGCCTGACATGAACCGATGCGCCAGATGCCGGATCGAGAAC
TGCGATAGCTGCCGCAGCAAGGACGCCTGCACTAAGTGCAAAGTCGGCTTCTAC
CTTCACCGGGGCAGATGTTTTGACGAATGCCCGGATGGCTTCGCCCCGCTGGAGG
AGACTATGGAATGCGTGGAG

LP1-3E20重链IgG2、RSPO2（F105R/F109A）多肽（SEQ ID NO: 225）

QVQLQQSGAELAKPGASVKMSCKASGYTFTSYWIHWVKQRPGQGLEWIGYINPSSG
YAEYNQKFKVRATLTADKSSSTAYMQLSSLTSEDSAVYYCARESYYSFDYTMDYW
GQGTSVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS
GVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVE
CPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVE
VHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKT
KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP
MLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGS
GSGGSGGGGSNPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYY
GHRAPDMNRCARCRIENCDSCRSKDACTKCKVGFYLHRGRCFDECPDGFAPLEETM
ECVE

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LP1-6H3轻链多核苷酸（SEQ ID NO: 226）

GATGTTGTGATGACCCAGACTCCACTCACTTTGTCGGTTACCATTGGACAACCAG
CCTCCATCTCTTGCAAGTCAAGTCAGAGCCTCTTAGATAGTGATGGAAAGACATA
TTTGAATTGGTTGTTACAGAGGCCAGGCCAGTCTCCAAAGCGCCTAATCTATCTG
GTGTCTAAACTGGACTCTGGAGTCCCTGACAGGTTCACTGGCAGTGGATCAGGG
ACAGATTTCACACTGAAAATCAGCAGAGTGGAGGCTGAGGATTTGGGAGTTTAT
TATTGCTGGCAAGGTACACATTTTCCTCACACGTTCGGCTCGGGGACAAAGTTGG
AAATAAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGA
GCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCC
AGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCC
CAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAG
CACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGA
AGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGA
GTGT

LP1-6H3轻链（PN和PP）多肽（SEQ ID NO: 227）

DVVMTQTPLTLSVTIGQPASISCKSSQSLLDSDGKTYLNWLLQRPGQSPKRLIYLVSK
LDSGVPDRFTGSGSGTDFTLKISRVEAEDLGVYYCWQGTHFPHTFGSGTKLEIKRTV
AAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD
SKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

图11AU

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LP1-6H3重链IgG2、RSPO2（F105R/F109A）多核苷酸（SEQ ID NO: 228）

CAGGCTTATCTACAGCAGTCTGGGGCTGAGCTGGTGAGGCCTGGGGCCTCAGTG
AAGATGTCCTGTAAGGCTTCTGGCTACACATTTTCCCGTTTCGATATGCACTGGG
TAAAGCAGACACCTAGACAGGGCCTGGAATGGATTGGAGTTATTTATCCAGGAA
ATGGTGATACTTCCTACAATCAGAAGTTCAGGGACAAGGCCTCACTGACTGTAG
ACAAATCCTCCAGCACAGCCTACATGCAGCTCAGCAGCCTGACATCTGAAGACT
CTGCGGTCTATTTCTGTGCAAGCTCCTACTATGGTAACCCCTGGGGCCAAGGCAC
CACTCTCACAGTCTCCAGCGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCG
CCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAG
GACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCTCTGACCAGC
GGCGTGCACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCA
GCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGT
AGATCACAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTG
TGTCGAGTGCCCACCGTGCCCAGCACCACCTGTGGCAGGACCGTCAGTCTTCCTC
TTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGT
GCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTACG
TGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAGCAGTTC
AACAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTGTGCACCAGGACTGGCTGA
ACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCAGCCCCCATCG
AGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCC
TGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG
TCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGC
CGGAGAACAACTACAAGACCACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTT
CCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTT
CTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTC
TCCCTGTCTCCGGGTAAAGGTGGTGGTGGCTCGGGATCCGGAGGCTCCGGTGGC
GGTGGCAGCAACCCAATTTGCAAGGGATGCTTAAGCTGTAGCAAGGACAACGGA
TGTTCACGGTGCCAGCAAAAGCTGTTTTTCTTCCTCCGGCGGGAAGGAATGCGGC
AGTACGGCGAATGTCTCCACTCCTGCCCCTCGGGGTATTACGGACACCGCGCGCC
TGACATGAACCGATGCGCCAGATGCCGGATCGAGAACTGCGATAGCTGCCGCAG
CAAGGACGCCTGCACTAAGTGCAAAGTCGGCTTCTACCTTCACCGGGGCAGATG
TTTTGACGAATGCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCGTG
GAG

LP1-6H3重链IgG2、RSPO2（F105R/F109A）多肽（SEQ ID NO: 229）

QAYLQQSGAELVRPGASVKMSCKASGYTFSRFDMHWVKQTPRQGLEWIGVIYPGN
GDTSYNQKFRDKASLTVDKSSSTAYMQLSSLTSEDSAVYFCASSYYGNPWGQGTTL
TVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP
AVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPA
PPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAK
TKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPRE
PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDG
SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGSGGSG
GGGSNPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYGHRAP
DMNRCARCRIENCDSCRSKDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECVE

图11AV

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LP1-7B13轻链多核苷酸（SEQ ID NO: 230）

GATATTGTGCTAACTCAGTCTCCAGCCACCCTGTCTGTGACTCCAGGAGATAGAG
TCAGTCTTTCCTGCAGGGCCAGTCAAAGTATTAGCAACTACCTACACTGGTATCA
ACAAAAAATCACATGAGTCTCCAAGGCTTCTCATCAAGTTTGCTTCCCAGTCCATC
TCTGGGATCCCCTCCAGGTTCAGTGGCAGTGGATCAGGGACGGATTTCACTCTCA
CTATCAACAGTGTGGAGACTGAAGATTTTGGAATGTATTTCTGTCAACAGAGTAA
CAGCTGGCCGCTCACGTTCGGTGCTGGGACCAAGCTGGAGCTGAAACGTACGGT
GGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTAC
AGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAG
AGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCA
AAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCC
TGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

LP1-7B13轻链多肽（SEQ ID NO: 231）

DIVLTQSPATLSVTPGDRVSLSCRASQSISNYLHWYQQKSHESPRLLIKFASQSISGIPS
RFSGSGSGTDFTLTINSVETEDFGMYFCQQSNSWPLTFGAGTKLELKRTVAAPSVFIF
PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

图11AW

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LP1-7B13重链IgG2、RSPO2（F105R/F109A）多核苷酸（SEQ ID NO: 232）

GAGGTCCAGCTGCAACAATCTGGACCTGAGGTGGTGAAGCCTGGGGCTTCAGTG
AAGATGTCCTGTAAGACTTCTGGATTCACATTCACTGACTACTACATGAACTGGG
TGAAGCAGGGTCATGGAAAGAGCCTTGAGTGGATTGGACGTGTTAATCCTAGCA
ATGATGATACTAGGTACAATCAGAAGTTCAAGGGAAAGGCCACATTGACAGTAG
ACAAGTCCCTCAGCACAGCCTACATGCAGCTCAACAGCCTGACATCTGAGGACT
CTGCGGTCTATTACTGTACAAGGTGGTTCTACTTTGACTACTGGGGCCAAGGCAC
TACTCTCACAGTCTCCAGCGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCG
CCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAG
GACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCTCTGACCAGC
GGCGTGCACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCA
GCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGT
AGATCACAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTG
TGTCGAGTGCCCACCGTGCCCAGCACCACCTGTGGCAGGACCGTCAGTCTTCCTC
TTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGT
GCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTACG
TGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAGCAGTTC
AACAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTGTGCACCAGGACTGGCTGA
ACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCAGCCCCCATCG
AGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCC
TGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG
TCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGC
CGGAGAACAACTACAAGACCACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTT
CCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTT
CTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTC
TCCCTGTCTCCGGGTAAAGGTGGTGGTGGCTCGGGATCCGGAGGCTCCGGTGGC
GGTGGCAGCAACCCAATTTGCAAGGGATGCTTAAGCTGTAGCAAGGACAACGGA
TGTTCACGGTGCCAGCAAAAGCTGTTTTTCTTCCTCCGGCGGGAAGGAATGCGGC
AGTACGGCGAATGTCTCCACTCCTGCCCCTCGGGGTATTACGGACACCGCGCGCC
TGACATGAACCGATGCGCCAGATGCCGGATCGAGAACTGCGATAGCTGCCGCAG
CAAGGACGCCTGCACTAAGTGCAAAGTCGGCTTCTACCTTCACCGGGGCAGATG
TTTTGACGAATGCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCGTG
GAG

LP1-7B13重链IgG2、RSPO2（F105R/F109A）多肽（SEQ ID NO: 233）

EVQLQQSGPEVVKPGASVKMSCKTSGFTFTDYYMNWVKQGHGKSLEWIGRVNPSN
DDTRYNQKFKGKATLTVDKSLSTAYMQLNSLTSEDSAVYYCTRWFYFDYWGQGTT
LTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF
PAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCP
APPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNA
KTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPR
EPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSD
GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGSGGS
GGGGSNPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYGHRA
PDMNRCARCRIENCDSCRSKDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECVE

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LP1-7I20轻链多核苷酸（SEQ ID NO: 234）

GACATCCAGATGACTCAGTCTCCAGCCTCCCTATCTGCATCTGTGGGAGAAACTG
TCACCATCACATGTCGAACAAGTGAGAATATTTACAGTTATTTAGCATGGTATCA
GCAGAAACAGGGAAAATCTCCTCAGCTCCTGGTCTATAATGCAAAAACCTTAGC
AAAAGGTGTGCCATCAAGGTTCAGTGGCAGTGGATCAGGCACACAGTTTTCTCTG
AAGATCAACGGCCTGCAGCCTGAAGATTTTGGGAATTATTACTGTCAACATCATT
ATGGTACTCCGTACACGTTCGGAGGGGGGACCAAGGTGGAAATAAAACGTACGG
TGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGG
AACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTA
CAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACA
GAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGC
AAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

LP1-7I20轻链多肽（SEQ ID NO: 235）

DIQMTQSPASLSASVGETVTITCRTSENIYSYLAWYQQKQGKSPQLLVYNAKTLAKG
VPSRFSGSGSGTQFSLKINGLQPEDFGNYYCQHHYGTPYTFGGGTKVEIKRTVAAPS
VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS
TYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

图11AY

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LP1-7I20重链IgG2、RSPO2（F105R/F109A）多核苷酸（SEQ ID NO: 236）

GAGGTGAAGCTGGTGGAGTCTGGAGGAGGCTTGGTACAGCCTGGGGGTTCTCTG
AGTCTCTCCTGTGCAGCTTCTGGATTCACCTTCACTGATTACTACATGAGCTGGGT
CCGCCAGCCCCCAGGGAAGGCACTTGAGTGGTTGGCTTTGATTAGAAACAAAGC
TAATGGTTACACAACAGAGTACAGTGCATCTGTGAAGGGTCGGTTCACCATCTCC
AGGGATAATTCCCAAAGCATCCTCTATCTTCAAATGAATGCCCTGAGAGCTGAGG
ACAGTGCCACTTATTACTGTGCAGTTACCTACGGGGCTTACTGGGGCCAAGGGAC
TCTGGTCACTGTCTCTGCAGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCG
CCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAG
GACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCTCTGACCAGC
GGCGTGCACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCA
GCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGT
AGATCACAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTG
TGTCGAGTGCCCACCGTGCCCAGCACCACCTGTGGCAGGACCGTCAGTCTTCCTC
TTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGT
GCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTACG
TGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAGCAGTTC
AACAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTGTGCACCAGGACTGGCTGA
ACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCAGCCCCCATCG
AGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCC
TGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG
TCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGC
CGGAGAACAACTACAAGACCACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTT
CCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTT
CTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTC
TCCCTGTCTCCGGGTAAAGGTGGTGGTGGCTCGGGATCCGGAGGCTCCGGTGGC
GGTGGCAGCAACCCAATTTGCAAGGGATGCTTAAGCTGTAGCAAGGACAACGGA
TGTTCACGGTGCCAGCAAAAGCTGTTTTTCTTCCTCCGGCGGGAAGGAATGCGGC
AGTACGGCGAATGTCTCCACTCCTGCCCCTCGGGGTATTACGGACACCGCGCGCC
TGACATGAACCGATGCGCCAGATGCCGGATCGAGAACTGCGATAGCTGCCGCAG
CAAGGACGCCTGCACTAAGTGCAAAGTCGGCTTCTACCTTCACCGGGGCAGATG
TTTTGACGAATGCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCGTG
GAG

LP1-7I20重链IgG2、RSPO2（F105R/F109A）多肽（SEQ ID NO: 237）

EVKLVESGGGLVQPGGSLSLSCAASGFTFTDYYMSWVRQPPGKALEWLALIRNKAN
GYTTEYSASVKGRFTISRDNSQSILYLQMNALRAEDSATYYCAVTYGAYWGQGTLV
TVSAASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP
AVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPA
PPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAK
TKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPRE
PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDG
SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGSGGSG
GGGSNPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYGHRAP
DMNRCARCRIENCDSCRSKDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECVE

图11AZ

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LP1-8M24轻链多核苷酸（SEQ ID NO: 238）

GAGGTTCAGCTGCAGCAGTCTGGGGCTGAGCTTGTGAGGCCAGGGGCCTCAGTC
AAGTTGTCCTGCACAGCTTCTGGCTTTACCATTAAAGACGACTATATTCACTGGG
TGAAGCAGGGGCCTGAACAGGGCCTGGAGTGGATTGGAAGAATTGATCCTGCGG
ATGATGATACTAAATATGCCCCGAAGTTCCAGGACAAGGCCACTATAACTGCAG
ACACATCCTCCAACACAGCCTACCTGCAGCTCAGCAGCCTGACATCTGAGGACA
CTGCCGTCTATTACTGTGCTAGAAGTTCCATGGCCTGGTTTGCTTACTGGGCCCA
AGGGACTCTGGTCACTGTCTCTACAGCTAGCACCAAGGGCCCATCGGTCTTCCCC
CTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTG
GTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTG
ACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCC
TCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTG
CAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCA
AATCTTGTGGATCCGGCTCCGGAcatcatcatcaccatcac

LP1-8M24轻链多肽（SEQ ID NO: 239）

EVQLQQSGAELVRPGASVKLSCTASGFTIKDDYIHWVKQGPEQGLEWIGRIDPADDD
TKYAPKFQDKATITADTSSNTAYLQLSSLTSEDTAVYYCARSSMAWFAYWAQGTLV
TVSTASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP
AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCGSGSGHHH
HHH

图11BA

LP1-8M24重链IgG2、RSPO2（F105R/F109A）多核苷酸（SEQ ID NO: 240）

GACATCCAGATGACACAGAGCCCTAGCAGCCTGTCTGCCAGCGTGGGAGACAGA
GTGACCATCACCTGTCGGATCAGCGAGAACATCTACAGCAACCTGGCCTGGTATC
AGCAGAAGCCTGGCAAGGCCCCTAAGCTGCTGATCTACGCCGCCATCAATCTGG
CCGATGGCGTGCCAAGCAGATTTTCTGGCAGCGGCTCTGGCACCGACTTCACCCT
GACCATATCTAGCCTGCAGCCTGAGGACTTCGCCACCTACTACTGCCAGCACTTT
TGGGGCACCCCTTTCACCTTTGGCCAGGGCACCAAGCTGGAAATCAAGCGTACG
GTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTG
GAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGT
ACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCAC
AGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAG
CAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGG
CCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

LP1-8M24重链IgG2、RSPO2（F105R/F109A）多肽（SEQ ID NO: 241）

DIQMTQSPSSLSASVGDRVTITCRISENIYSNLAWYQQKPGKAPKLLIYAAINLADGV
PSRFSGSGSGTDFTLTISSLQPEDFATYYCQHFWGTPFTFGQGTKLEIKRTVAAPSVFI
FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY
SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

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LP1-9C3轻链多核苷酸（SEQ ID NO: 242）

GATGTTGTGGTGACTCAAACTCCACTCTCCCTGCCTGTCAGCTTTGGAGATCAAG
TTTCTATCTCTTGCAGGTCTAGTCAGAGTCTTGCAAACAGTTATGGGAACACCTA
TTTGTCTTGGTACCTGCACAAGCCTGGCCAGTCTCCACAGCTCCTCATCTATGGG
ATTTCCAACAGATTTTCTGGGGTGCCAGACAGGTTCAGTGGCAGTGGTTCAGGGA
CAGATTTCACACTCAAGATCAGCACAATAAAGCCTGAGGACTTGGGAATCTATT
ACTGCTTACAAGCTACACATCAGCCGTGGACGTTCGGTGGAGGCACCAAGCTGG
AAATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGA
GCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCC
AGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCC
CAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAG
CACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGA
AGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGA
GTGT

LP1-9C3轻链多肽（SEQ ID NO: 243）

DVVVTQTPLSLPVSFGDQVSISCRSSQSLANSYGNTYLSWYLHKPGQSPQLLIYGISN
RFSGVPDRFSGSGSGTDFTLKISTIKPEDLGIYYCLQATHQPWTFGGGTKLEIKRTVA
APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS
KDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

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LP1-9C3重链IgG2、RSPO2（F105R/F109A）多核苷酸（SEQ ID NO: 244）

CAGGTTACTCTGAAAGAGTCTGGCCCTGGGATATTGCAGCCCTCCCAGACCCTCA
GTCTGACTTGTTCTTTCTCTGGGTTTTCACTGAGCACTTCTTATATGGGTGTGAGC
TGGATTCGTAAGCCTTCAGGAAAGGGTCTGGAGTGGCTGGCACACATTTTCTGGG
ATGATGACAAGCGCTATAACCCATCCCTGAAGAGCCGGCTCACAATCTCCAAGG
ATACCTCCAGCAACCAGGTATTCCTCATGATCACCAGTGTGGAAACTGCAGATAC
TGCCACATACTACTGTGGGGGTCCCTACTATCCGTTTACTTACTGGGGCCAAGGG
ACTCTGGTCACTGTCTCTGCAGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGG
CGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCA
AGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCTCTGACCA
GCGGCGTGCACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAG
CAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAAC
GTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGT
TGTGTCGAGTGCCCACCGTGCCCAGCACCACCTGTGGCAGGACCGTCAGTCTTCC
TCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCAC
GTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTA
CGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAGCAGT
TCAACAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTGTGCACCAGGACTGGCT
GAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCAGCCCCCAT
CGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACAC
CCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCT
GGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCA
GCCGGAGAACAACTACAAGACCACGCCTCCCATGCTGGACTCCGACGGCTCCTT
CTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGT
CTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGC
CTCTCCCTGTCTCCGGGTAAAGGTGGTGGTGGCTCGGGATCCGGAGGCTCCGGTG
GCGGTGGCAGCAACCCAATTTGCAAGGGATGCTTAAGCTGTAGCAAGGACAACG
GATGTTCACGGTGCCAGCAAAAGCTGTTTTTCTTCCTCCGGCGGGAAGGAATGCG
GCAGTACGGCGAATGTCTCCACTCCTGCCCCTCGGGGTATTACGGACACCGCGCG
CCTGACATGAACCGATGCGCCAGATGCCGGATCGAGAACTGCGATAGCTGCCGC
AGCAAGGACGCCTGCACTAAGTGCAAAGTCGGCTTCTACCTTCACCGGGGCAGA
TGTTTTGACGAATGCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCG
TGGAG

LP1-9C3重链IgG2、RSPO2（F105R/F109A）多肽（SEQ ID NO: 245）

QVTLKESGPGILQPSQTLSLTCSFSGFSLSTSYMGVSWIRKPSGKGLEWLAHIFWDDD
KRYNPSLKSRLTISKDTSSNQVFLMITSVETADTATYYCGGPYYPFTYWGQGTLVTV
SAASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPP
VAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTK
PREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQ
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSF
FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGSGGSGG
GGSNPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYGHRAPD
MNRCARCRIENCDSCRSKDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECVE

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LP1-9M16轻链多核苷酸（SEQ ID NO: 246）

GACATCAAGATGACCCAGTCTCCATCTTCCATGTATGCATCTCTAGGAGAGAGAG
TCACTATCACTTGCAAGGCGAGTCAGGACATTAATAGCTATTTAAGCTGGTTCCA
GCAGAAACCAGGGAAATCTCCTAAGACCCTGATCTATCGTGCAAACAGATTGGC
AGATGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCTGGGCAAGATTATTCTCTC
ACCATCAGCAACCTGGAGTATGAAGATATGGGAATTTATTATTGTCTACAGTATG
ATGAGTTTCCGCTCACGTTCGGTGCTGGGACCAAGCTGGAGCTGAAACGTACGGT
GGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTAC
AGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAG
AGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCA
AAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCC
TGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

LP1-9M16轻链多肽（SEQ ID NO: 247）

DIKMTQSPSSMYASLGERVTITCKASQDINSYLSWFQQKPGKSPKTLIYRANRLADG
VPSRFSGSGSGQDYSLTISNLEYEDMGIYYCLQYDEFPLTFGAGTKLELKRTVAAPSV
FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDST
YSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

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LP1-9M16重链IgG2、RSPO2（F105R/F109A）多核苷酸（SID NO: 248）

GAGGTCCAGCTGCAACAGTCTGGACCTGAGCTGGTGAAGCCTGGGGCTTCAGTG
AAGATGTCCTGTAAGGCTTCTGGATACACATTCACTGACTACTACATGAACTGGG
TGAAGCAGAGTCATGGAAAGAGCCTTGAGTGGATTGGACGTGTTAATCCTAACA
ATGGTGGTTCTAACTACAACCAGAAATTCAAGGGCAAGGCCACATTGACAGTAG
ACAAATCCCTCAGCACAGCCTACATGCAGCTCAACAGCCTGACATCTGAGGACT
CTGCGGTCTATTACTGTGCAAGTCGAAACTTCGATGTCTGGGGCGCAGGGACCAC
GGTCACCGTCTCCAGCGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCC
TGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGAC
TACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCTCTGACCAGCGGC
GTGCACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCG
TGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGTAGA
TCACAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTGTGT
CGAGTGCCCACCGTGCCCAGCACCACCTGTGGCAGGACCGTCAGTCTTCCTCTTC
CCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGTGC
GTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTACGTG
GACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAGCAGTTCAA
CAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTGTGCACCAGGACTGGCTGAAC
GGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCAGCCCCCATCGAG
AAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTG
CCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTC
AAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCG
GAGAACAACTACAAGACCACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCC
TCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCT
CATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTC
CCTGTCTCCGGGTAAAGGTGGTGGTGGCTCGGGATCCGGAGGCTCCGGTGGCGG
TGGCAGCAACCCAATTTGCAAGGGATGCTTAAGCTGTAGCAAGGACAACGGATG
TTCACGGTGCCAGCAAAAGCTGTTTTTCTTCCTCCGGCGGGAAGGAATGCGGCAG
TACGGCGAATGTCTCCACTCCTGCCCCTCGGGGTATTACGGACACCGCGCGCCTG
ACATGAACCGATGCGCCAGATGCCGGATCGAGAACTGCGATAGCTGCCGCAGCA
AGGACGCCTGCACTAAGTGCAAAGTCGGCTTCTACCTTCACCGGGGCAGATGTTT
TGACGAATGCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCGTGGA
G

LP1-9M16重链IgG2、RSPO2（F105R/F109A）多肽（SEQ ID NO: 249）

EVQLQQSGPELVKPGASVKMSCKASGYTFTDYYMNWVKQSHGKSLEWIGRVNPNN
GGSNYNQKFKGKATLTVDKSLSTAYMQLNSLTSEDSAVYYCASRNFDVWGAGTTV
TVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP
AVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPA
PPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAK
TKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPRE
PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDG
SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGSGGSG
GGGSNPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYGHRAP
DMNRCARCRIENCDSCRSKDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECVE

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LP1-10C22轻链多核苷酸（SEQ ID NO: 250）

GATGTTTTGATGACCCAAACTCCACTCTCCCTGCCTGTCAGTCTTGGAGATCAAG
CCTCCATCTCTTGCAGATCTAGTCAGGGCATTGTACATAGTAATGGAAACATCTA
TTTAGAATGGTACCTGCAGAAACCAGGCCAGTCTCCAAAGCTCCTGATCTACAAA
GTTTCCAACCGATTTTCTGGGGTCCCAGACAGGTTCAGTGGCAGTGGATCAGGGA
CAGATTTCACACTCAAGATCAGCAGAGTGGAGGCTGAGGATCTGGGAGTTTATT
ACTGCTTTCAAGGTTCACATGTTCCTCCCACGTTCGGAGGGGGGACCAAGCTGGA
AATAAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAG
CAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCA
GAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCC
AGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGC
ACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAA
GTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAG
TGT

LP1-10C22轻链多肽（SEQ ID NO: 251）

DVLMTQTPLSLPVSLGDQASISCRSSQGIVHSNGNIYLEWYLQKPGQSPKLLIYKVSN
RFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYYCFQGSHVPPTFGGGTKLEIKRTVA
APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS
KDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

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LP1-10C22重链IgG2、RSPO2（F105R/F109A）多核苷酸（SID NO: 252）

GAGGTGCAGCTGGTGGAGTCTGGGGGAGACTTAGTGAAGCCTGGAGGGTCCCTG
AAACTCTCCTGTGCAGCCTCTGGATTCACTTTCAGTAGTTATGGCATGTCTTGGGT
TCGCCAGACTCCAGACAAGAGGCTGGAGTGGGTCGCAAGTATTAGTAGTGGTGG
TAGTTATACCTACTATCCAGACAGTGTGAAGGGGCGATTCACCATCTCCAGAGAC
AATGCCCAGAACACCCTGTACCTGCAAATGAGCAGTCTGAAGTCTGAGGACACA
GCCATGTATTACTGTGTAAGACATGAGGAGTATGGTAAATCCGGATTTGCTTACT
GGGGCCAAGGGACCCTGATTACTGTCTCTGCAGCTAGCACCAAGGGCCCATCGG
TCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGG
CTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGC
GCTCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTCT
ACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTA
CACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGA
GCGCAAATGTTGTGTCGAGTGCCCACCGTGCCCAGCACCACCTGTGGCAGGACC
GTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACC
CCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAG
TTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGG
GAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTGTGCACC
AGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCC
CAGCCCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCAC
AGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCC
TGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGA
GCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCATGCTGGACTCCG
ACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGC
AGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACAC
GCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAGGTGGTGGTGGCTCGGGATCCGG
AGGCTCCGGTGGCGGTGGCAGCAACCCAATTTGCAAGGGATGCTTAAGCTGTAG
CAAGGACAACGGATGTTCACGGTGCCAGCAAAAGCTGTTTTTCTTCCTCCGGCGG
GAAGGAATGCGGCAGTACGGCGAATGTCTCCACTCCTGCCCCTCGGGGTATTAC
GGACACCGCGCGCCTGACATGAACCGATGCGCCAGATGCCGGATCGAGAACTGC
GATAGCTGCCGCAGCAAGGACGCCTGCACTAAGTGCAAAGTCGGCTTCTACCTTC
ACCGGGGCAGATGTTTTGACGAATGCCCGGATGGCTTCGCCCCGCTGGAGGAGA
CTATGGAATGCGTGGAG

LP1-10C22重链IgG2、RSPO2（F105R/F109A）多肽（SEQ ID NO: 253）

EVQLVESGGDLVKPGGSLKLSCAASGFTFSSYGMSWVRQTPDKRLEWVASISSGGS
YTYYPDSVKGRFTISRDNAQNTLYLQMSSLKSEDTAMYYCVRHEEYGKSGFAYWG
QGTLITVSAASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSG
VHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVEC
PPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEV
HNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTK
GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPM
LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSG
SGGSGGGGSNPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYG
HRAPDMNRCARCRIENCDSCRSKDACTKCKVGFYLHRGRCFDECPDGFAPLEETME
CVE

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RSPO2（F105R/F109A）、LP1-1N15重链IgG1 N297G多核苷酸（SID NO: 254）

AACCCAATTTGCAAGGGATGCTTAAGCTGTAGCAAGGACAACGGATGTTCACGG
TGCCAGCAAAAGCTGTTTTTCTTCCTCCGGCGGGAAGGAATGCGGCAGTACGGC
GAATGTCTCCACTCCTGCCCCTCGGGGTATTACGGACACCGCGCGCCTGACATGA
ACCGATGCGCCAGATGCCGGATCGAGAACTGCGATAGCTGCCGCAGCAAGGACG
CCTGCACTAAGTGCAAAGTCGGCTTCTACCTTCACCGGGGCAGATGTTTTGACGA
ATGCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCGTGGAGGGTGG
TGGTGGCTCGGGATCCGGAGGCTCCGGTGGCGGTGGCAGCGAGGTCCAGCTGCA
ACAGTCTGGACCTGAGCTGGTGAAGCCTGGGGCTTCAGTGAAGATGTCCTGTAA
GGCTTCTGGATACACATTCACTGACTACTACATGAACTGGGTGAAGCAGAGTCAT
GGAGAGAGCCTTGAGTGGATTGGACGTGTTATTCCTAGCAATGGTGGTACTAACT
ACAACCAGAAGTTCAAGGGCAAGGCCACATTGACAGTAGACAAATCCCTCACCA
CAGCCTACATGCAGCTCAACAGCCTGACATCTGAAGACTCTGCGGTCTATTTCTG
TGCAAGAGGGATGGACTACTGGGGTCCAGGAACCTCAGTCACCGTCTCCAGCGC
TAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCT
GGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTG
ACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCT
GTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCA
GCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACA
CCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCC
CACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCC
AAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGT
GGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGG
CGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGGCAGCA
CGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAA
GGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAAC
CATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCC
ATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGG
CTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAA
CAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTAC
AGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGC
TCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGT
CTCCGGGTAAA

RSPO2（F105R/F109A）、LP1-1N15重链IgG1 N297G多肽（SID NO: 255）

NPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYGHRAPDMNR
CARCRIENCDSCRSKDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECVEGGGGS
GSGGSGGGGSEVQLQQSGPELVKPGASVKMSCKASGYTFTDYYMNWVKQSHGESL
EWIGRVIPSNGGTNYNQKFKGKATLTVDKSLTTAYMQLNSLTSEDSAVYFCARGMD
YWGPGTSVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA
LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC
DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY
VDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
K

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RSPO2（F105R/F109A）、LP1-1P13重链IgG1 N297G多核苷酸（SEQ ID NO: 256）

AACCCAATTTGCAAGGGATGCTTAAGCTGTAGCAAGGACAACGGATGTTCACGG
TGCCAGCAAAAGCTGTTTTTCTTCCTCCGGCGGGAAGGAATGCGGCAGTACGGC
GAATGTCTCCACTCCTGCCCCTCGGGGTATTACGGACACCGCGCGCCTGACATGA
ACCGATGCGCCAGATGCCGGATCGAGAACTGCGATAGCTGCCGCAGCAAGGACG
CCTGCACTAAGTGCAAAGTCGGCTTCTACCTTCACCGGGGCAGATGTTTTGACGA
ATGCCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCGTGGAGGGTGG
TGGTGGCTCGGGATCCGGAGGCTCCGGTGGCGGTGGCAGCGAGGTTCAACTGCA
GCAGTCTGGACCTGAACTGGTGAAGCCTGGGGCTTCAGTGAAGATATCCTGCAA
GGCTTCTGGTTACTCATTTACTGACTACTTTATGAACTGGGTGAAGCAGAGCCAT
GGAAAGAGCCTTGAGTGGATTGGACGTTTTAATCCTTTCAATGGTCAAACTTTCT
ACAATCAGGAGTTCAAGGGCAAGGCCACATTAACTGTAGACAAATCCTCTAGCA
CCGCCCACATGGAGCTCCGGAGCCTGACATCTGAGGACTCTGCAGTCTATTATTG
TGCAAGAAGAGGAAGGTACGACGTTTACTATGTTCTGGACTACTGGGGTCAAGG
AACCTCAGTCACCGTCTCCAGCGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTG
GCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTC
AAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACC
AGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCA
GCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCA
ACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAAT
CTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGG
GACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCG
GACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGT
CAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCC
GCGGGAGGAGCAGTACGGCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCT
GCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGC
CCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGA
ACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGT
CAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGG
GAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGAC
TCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGC
AGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTA
CACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

RSPO2（F105R/F109A）、LP1-1P13重链IgG1 N297G多肽（SEQ ID NO: 257）

NPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYGHRAPDMNR
CARCRIENCDSCRSKDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECVEGGGGS
GSGGSGGGGSEVQLQQSGPELVKPGASVKISCKASGYSFTDYFMNWVKQSHGKSLE
WIGRFNPFNGQTFYNQEFKGKATLTVDKSSSTAHMELRSLTSEDSAVYYCARRGRY
DVYYVLDYWGQGTSVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT
VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD
KKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED
PEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGK

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RSPO2（F105R/F109A）、LP1-2I22重链IgG1 N297G多核苷酸（SEQ ID NO: 258）

AACCCAATTTGCAAGGGATGCTTAAGCTGTAGCAAGGACAACGGATGTTCACGG
TGCCAGCAAAAGCTGTTTTTCTTCCTCCGGCGGGAAGGAATGCGGCAGTACGGC
GAATGTCTCCACTCCTGCCCCTCGGGGTATTACGGACACCGCGCGCCTGACATGA
ACCGATGCGCCAGATGCCGGATCGAGAACTGCGATAGCTGCCGCAGCAAGGACG
CCTGCACTAAGTGCAAAGTCGGCTTCTACCTTCACCGGGGCAGATGTTTTGACGA
ATGCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCGTGGAGGGTGG
TGGTGGCTCGGGATCCGGAGGCTCCGGTGGCGGTGGCAGCGAGGTCCAACTCGT
AGAATCAGGTGGTGGTTTGGTCAAACCAGGTGGCTCTCGGAAGTTGTCCTGTGCT
GCCTCTGGATTTACATTCAGTGACTACGGTATGCACTGGGTCCGTCAGGCTCCAG
AGAAGGGGCTGGAGTGGGTTGCCTACATTAGTAGTGGCAGTAGTACCATCTACT
ATGCAGACACAGTGAAGGGCCGATTCACCATCTCCAGAGACAATGCCAAGAACA
CCCTGTTCCTACAAATGACCAGTCTAAGGTCTGAGGACACAGCCATGTATTACTG
TTCAAGGAAGGGAGGGTTTGGTGACTACGAGAAAAGCTATGCTATGGACTACTG
GGGTCAAGGAACCTCAGTCACCGTCTCCAGCGCTAGCACCAAGGGCCCATCGGT
CTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGC
TGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGC
GCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCT
ACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTA
CATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGA
GCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTC
CTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGA
TCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACC
CTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGA
CAAAGCCGCGGGAGGAGCAGTACGGCAGCACGTACCGTGTGGTCAGCGTCCTCA
CCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCA
ACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGC
CCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGA
ACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGT
GGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCG
TGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAG
CAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCAC
AACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

RSPO2（F105R/F109A）、LP1-2I22重链IgG1 N297G多肽（SID NO: 259）

NPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYGHRAPDMNR
CARCRIENCDSCRSKDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECVEGGGGS
GSGGSGGGGSEVQLVESGGGLVKPGGSRKLSCAASGFTFSDYGMHWVRQAPEKGL
EWVAYISSGSSTIYYADTVKGRFTISRDNAKNTLFLQMTSLRSEDTAMYYCSRKGGF
GDYEKSYAMDYWGQGTSVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP
EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT
KVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
HEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKC
KVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH
YTQKSLSLSPGK

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RSPO2（F105R/F109A）、LP1-2I22重链IgG1 N297G多核苷酸（SEQ ID NO: 260）

AACCCAATTTGCAAGGGATGCTTAAGCTGTAGCAAGGACAACGGATGTTCACGG
TGCCAGCAAAAGCTGTTTTTCTTCCTCCGGCGGGAAGGAATGCGGCAGTACGGC
GAATGTCTCCACTCCTGCCCCTCGGGGTATTACGGACACCGCGCGCCTGACATGA
ACCGATGCGCCAGATGCCGGATCGAGAACTGCGATAGCTGCCGCAGCAAGGACG
CCTGCACTAAGTGCAAAGTCGGCTTCTACCTTCACCGGGGCAGATGTTTTGACGA
ATGCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCGTGGAGGGTGG
TGGTGGCTCGGGATCCGGAGGCTCCGGTGGCGGTGGCAGCGAGGTTCAACTGCA
GCAGTCTGGACCTGAACTGGTGAAGCCTGGGGCTTCAGTGAAGATATCCTGCAA
GGCTTCTGGTTACTCATTTACTGGCTACTTTATGAACTGGGTGAAGCAGAGCCAT
GGAAAGAGCCTTGAGTGGATTGGACGTTTTAATCCTTTCAATGGTCAAACTTTCT
ACAATCAGGAGTTCAAGGGCAAGGCCACATTAACTGTTGACAAATCCTCTGACA
CCGCCCACATGGAACTCCGGAGCCTGACATCTGAGGACTCTGCAGTCTATTATTG
TGCAAGAAGAGGAAGGTACGACGTTTACTATGCTCTGGACTACTGGGGTCAAGG
AACCTCAGTCACCGTCTCCAGCGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTG
GCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTC
AAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACC
AGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCA
GCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCA
ACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAAT
CTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGG
GACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCG
GACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGT
CAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCC
GCGGGAGGAGCAGTACGGCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCT
GCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGC
CCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGA
ACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGT
CAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGG
GAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGAC
TCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGC
AGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTA
CACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

RSPO2（F105R/F109A）、LP1-2I22重链IgG1 N297G多肽（SID NO: 261）

NPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYGHRAPDMNR
CARCRIENCDSCRSKDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECVEGGGGS
GSGGSGGGGSEVQLQQSGPELVKPGASVKISCKASGYSFTGYFMNWVKQSHGKSLE
WIGRFNPFNGQTFYNQEFKGKATLTVDKSSDTAHMELRSLTSEDSAVYYCARRGRY
DVYYALDYWGQGTSVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT
VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD
KKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED
PEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGK

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RSPO2（F105R/F109A）、LP1-3A24重链IgG1 N297G多核苷酸（SEQ ID NO: 262）

AACCCAATTTGCAAGGGATGCTTAAGCTGTAGCAAGGACAACGGATGTTCACGG
TGCCAGCAAAAGCTGTTTTTCTTCCTCCGGCGGGAAGGAATGCGGCAGTACGGC
GAATGTCTCCACTCCTGCCCCTCGGGGTATTACGGACACCGCGCGCCTGACATGA
ACCGATGCGCCAGATGCCGGATCGAGAACTGCGATAGCTGCCGCAGCAAGGACG
CCTGCACTAAGTGCAAAGTCGGCTTCTACCTTCACCGGGGCAGATGTTTTGACGA
ATGCCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCGTGGAGGGTGG
TGGTGGCTCGGGATCCGGAGGCTCCGGTGGCGGTGGCAGCGAGGTCCAGCTGCA
ACAGTCTGGACCTGAGCTGGTGAAGCCTGGGGCTTCAGTGAAGATGTCCTGTAA
GGCTTCTGGATACACATTCACTGACTACTACATAAACTGGGTGAGGCAGAGTCAT
GGAAAGAGCCTTGAGTGGATTGGACGTGTTATTCCTAGCAATGGTGGTAGTAACT
ACAACCAGAAGTTCAAGGGCAAGGCCACATTGACAGTAGACAAATCCCTCAGTA
CAGCCTACATGCACCTCAACAGCCTGACATCTGAGGACTCTGCGGTCTATTACTG
TGCAACCCAGCTGGGACGGTGGGGCCAAGGGACTCTGGTCACTGTCTCTGCAGC
TAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCT
GGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTG
ACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCT
GTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCA
GCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACA
CCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCC
CACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCC
AAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGT
GGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGG
CGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGGCAGCA
CGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAA
GGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAAC
CATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCC
ATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGG
CTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAA
CAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTAC
AGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGC
TCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGT
CTCCGGGTAAA

RSPO2（F105R/F109A）、LP1-3A24重链IgG1 N297G多肽（SEQ ID NO: 263）

NPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYGHRAPDMNR
CARCRIENCDSCRSKDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECVEGGGGS
GSGGSGGGGSEVQLQQSGPELVKPGASVKMSCKASGYTFTDYYINWVRQSHGKSLE
WIGRVIPSNGGSNYNQKFKGKATLTVDKSLSTAYMHLNSLTSEDSAVYYCATQLGR
WGQGTLVTVSAASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL
TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCD
KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV
DGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK
TISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY
KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

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RSPO2（F105R/F109A）、LP1-3E20重链IgG1 N297G多核苷酸（SEQ ID NO: 264）

AACCCAATTTGCAAGGGATGCTTAAGCTGTAGCAAGGACAACGGATGTTCACGG
TGCCAGCAAAAGCTGTTTTTCTTCCTCCGGCGGGAAGGAATGCGGCAGTACGGC
GAATGTCTCCACTCCTGCCCCTCGGGGTATTACGGACACCGCGCGCCTGACATGA
ACCGATGCCGCCAGATGCCGGATCGAGAACTGCGATAGCTGCCGCAGCAAGGACG
CCTGCACTAAGTGCAAAGTCGGCTTCTACCTTCACCGGGGCAGATGTTTTGACGA
ATGCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCGTGGAGGGTGG
TGGTGGCTCGGGATCCGGAGGCTCCGGTGGCGGTGGCAGCCAGGTCCAACTGCA
GCAGTCTGGGGCTGAACTGGCAAAACCTGGGGCCTCAGTGAAGATGTCCTGCAA
GGCTTCTGGCTACACCTTTACTAGCTACTGGATACACTGGGTAAAACAGAGGCCT
GGACAGGGTCTGGAATGGATTGGATACATTAATCCTAGCAGTGGTTATGCTGAGT
ACAATCAGAAGTTCAAGGTCAGGGCCACATTGACTGCAGACAAATCCTCCAGCA
CAGCCTACATGCAACTAAGCAGCCTGACATCTGAGGACTCTGCAGTCTATTACTG
TGCAAGAGAAAGTTACTATAGTTTCGACTATACTATGGACTACTGGGGTCAAGGA
ACCTCAGTCACCGTCTCCAGCGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGG
CACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCA
AGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCA
GCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAG
CAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAAC
GTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCT
TGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGGA
CCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGA
CCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCA
AGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGC
GGGAGGAGCAGTACGGCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGC
ACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCC
TCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAAC
CACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCA
GCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGA
GAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTC
CGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCA
GCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTAC
ACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

RSPO2（F105R/F109A）、LP1-3E20重链IgG1 N297G多肽（SID NO: 265）

NPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYGHRAPDMNR
CARCRIENCDSCRSKDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECVEGGGGS
GSGGSGGGGSQVQLQQSGAELAKPGASVKMSCKASGYTFTSYWIHWVKQRPGQGL
EWIGYINPSSGYAEYNQKFKVRATLTADKSSSTAYMQLSSLTSEDSAVYYCARESYY
SFDYTMDYWGQGTSVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT
VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD
KKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED
PEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGK

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RSPO2（F105R/F109A）、LP1-7B13重链IgG1 N297G多核苷酸（SEQ ID NO: 266）

AACCCAATTTGCAAGGGATGCTTAAGCTGTAGCAAGGACAACGGATGTTCACGG
TGCCAGCAAAAGCTGTTTTTCTTCCTCCGGCGGGAAGGAATGCGGCAGTACGGC
GAATGTCTCCACTCCTGCCCCTCGGGGTATTACGGACACCGCGCGCCTGACATGA
ACCGATGCGCCAGATGCCGGATCGAGAACTGCGATAGCTGCCGCAGCAAGGACG
CCTGCACTAAGTGCAAAGTCGGCTTCTACCTTCACCGGGGCAGATGTTTTGACGA
ATGCCCCGGATGGCTTCGCCCCCGCTGGAGGAGACTATGGAATGCGTGGAGGGTGG
TGGTGGCTCGGGATCCGGAGGCTCCGGTGGCGGTGGCAGCGAGGTCCAGCTGCA
ACAATCTGGACCTGAGGTGGTGAAGCCTGGGGCTTCAGTGAAGATGTCCTGTAA
GACTTCTGGATTCACATTCACTGACTACTACATGAACTGGGTGAAGCAGGGTCAT
GGAAAGAGCCTTGAGTGGATTGGACGTGTTAATCCTAGCAATGATGATACTAGG
TACAATCAGAAGTTCAAGGGAAAGGCCACATTGACAGTAGACAAGTCCCTCAGC
ACAGCCTACATGCAGCTCAACAGCCTGACATCTGAGGACTCTGCGGTCTATTACT
GTACAAGGTGGTTCTACTTTGACTACTGGGGCCAAGGCACTACTCTCACAGTCTC
CAGCGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGC
ACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAA
CCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTC
CCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGC
CCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCA
GCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACTCACA
CATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTT
CCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGC
GTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTG
GACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGG
CAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAAT
GGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAG
AAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTG
CCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTC
AAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCG
GAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCC
TCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCT
CATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTC
CCTGTCTCCGGGTAAA

RSPO2（F105R/F109A）、LP1-7B13重链IgG1 N297G多肽（SEQ ID NO: 267）

NPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYGHRAPDMNR
CARCRIENCDSCRSKDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECVEGGGGS
GSGGSGGGGSEVQLQQSGPEVVKPGASVKMSCKTSGFTFTDYYMNWVKQGHGKSL
EWIGRVNPSNDDTRYNQKFKGKATLTVDKSLSTAYMQLNSLTSEDSAVYYCTRWF
YFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP
KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF
NWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP
APIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP
ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL
SPGK

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RSPO2（F105R/F109A）、LP1-8M24重链IgG1 N297G多核苷酸（SEQ ID NO: 268）

CAGGTTCAGCTGCAGCAGTCTGGAGCTGAGCTGGCGAGGCCTGGGGCTTCAGTG
AAGCTGTCCTGCAAGGCTTCTGGCTACACCTTCACAAATTATGGTATAAACTGGG
TGAAGCAGAGAACTGGACAGGGCCTTGAGTGGATTGGAGAGATTTTTCCTAGAA
GTGATAATACTTTCTACAATGAGAAGTTCAAGGGCAAGGCCACACTGACTGCAG
ACAAATCCTCCACCACAGCGTACATGGAGCTCCGCAGCCTGACATCTGAGGACT
CTGCGGTCTATTTCTGTGCAAGAAAAGGCAGGGACTACGGTACTAGCCACTACTT
TGACTACTGGGGTCAAGGCACCACTCTCACAGTCTCCAGCGCTAGCACCAAGGG
CCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCG
GCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGA
ACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTC
AGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACC
CAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAG
AAAGTTGAGCCCAAATCTTGTGGATCCGGCTCCGGACATCATCATCACCATCAC

RSPO2（F105R/F109A）、LP1-8M24重链IgG1 N297G多肽（SEQ ID NO: 269）

QVQLQQSGAELARPGASVKLSCKASGYTFTNYGINWVKQRTGQGLEWIGEIFPRSD
NTFYNEKFKGKATLTADKSSTTAYMELRSLTSEDSAVYFCARKGRDYGTSHYFDYW
GQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS
GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCGS
GSGHHHHHH

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RSPO2（F105R/F109A）、LP1-9M16重链IgG1 N297G多核苷酸（SEQ ID NO: 270）

AACCCAATTTGCAAGGGATGCTTAAGCTGTAGCAAGGACAACGGATGTTCACGG
TGCCAGCAAAAGCTGTTTTTCTTCCTCCGGCGGGAAGGAATGCGGCAGTACGGC
GAATGTCTCCACTCCTGCCCCTCGGGGTATTACGGACACCGCGCGCCTGACATGA
ACCGATGCGCCAGATGCCGGATCGAGAACTGCGATAGCTGCCGCAGCAAGGACG
CCTGCACTAAGTGCAAAGTCGGCTTCTACCTTCACCGGGGCAGATGTTTTGACGA
ATGCCCGGATGGCTTCGCCCCGCTGGAGGAGACTATGGAATGCGTGGAGGGTGG
TGGTGGCTCGGGATCCGGAGGCTCCGGTGGCGGTGGCAGCGAGGTCCAGCTGCA
ACAGTCTGGACCTGAGCTGGTGAAGCCTGGGGCTTCAGTGAAGATGTCCTGTAA
GGCTTCTGGATACACATTCACTGACTACTACATGAACTGGGTGAAGCAGAGTCAT
GGAAAGAGCCTTGAGTGGATTGGACGTGTTAATCCTAACAATGGTGGTTCTAACT
ACAACCAGAAATTCAAGGGCAAGGCCACATTGACAGTAGACAAATCCCTCAGCA
CAGCCTACATGCAGCTCAACAGCCTGACATCTGAGGACTCTGCGGTCTATTACTG
TGCAAGTCGAAACTTCGATGTCTGGGGCGCAGGGACCACGGTCACCGTCTCCAG
CGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACC
TCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCG
GTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCG
GCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCT
CCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCA
ACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACTCACACAT
GCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCC
CCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGT
GGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGA
CGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGGCA
GCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGG
CAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAA
AACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCC
CCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAA
AGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGA
GAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTC
TACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCA
TGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCC
TGTCTCCGGGTAAA

RSPO2（F105R/F109A）、LP1-9M16重链IgG1 N297G多肽（SID NO: 271）

NPICKGCLSCSKDNGCSRCQQKLFFFLRREGMRQYGECLHSCPSGYYGHRAPDMNR
CARCRIENCDSCRSKDACTKCKVGFYLHRGRCFDECPDGFAPLEETMECVEGGGGS
GSGGSGGGGSEVQLQQSGPELVKPGASVKMSCKASGYTFTDYYMNWVKQSHGKSL
EWIGRVNPNNGGSNYNQKFKGKATLTVDKSLSTAYMQLNSLTSEDSAVYYCASRNF
DVWGAGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG
ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS
CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW
YVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI
EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP
GK

图11BQ

MS&D Exhibit 1008, Page 2908 of 4223

抗ASGR1重链多核苷酸（SEQ ID NO: 272）

GAAGTGCAGCTGCTGGAATCCGGGGGCGGACTGGTGCAACCCGGGGGATCCCTC
AGACTGTCCTGTGCCGCATCGGGTTTCACTTTCTCCTCCTACGCGATGTCATGGGT
CAGACAGGCCCCTGGAAAAGGCCTCGAATGGGTGTCGGCTATCTCCGGATCGGG
GGGATCTACTTACTACGCCGACTCCGTGAAGGGCCGGTTCACTATCTCGAGGGAC
AACTCCAAGAATACCCTGTACTTGCAAATGAACTCCCTGCGCGCCGAGGATACC
GCGGTGTATTACTGCGCCAAGGACTTCAGCTCACGCCGGTGGTACCTTGAGTACT
GGGGACAGGGAACCCTTGTCACCGTGTCGAGTGCTAGCACCAAGGGCCCATCGG
TCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGG
CTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGC
GCTCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTCT
ACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTA
CACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGA
GCGCAAATGTTGTGTCGAGTGCCCACCGTGCCCAGCACCACCTGTGGCAGGACC
GTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACC
CCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAG
TTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGG
GAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTGTGCACC
AGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCC
CAGCCCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCAC
AGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCC
TGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGA
GCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCATGCTGGACTCCG
ACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGC
AGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACAC
GCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

抗ASGR1重链多肽（SEQ ID NO: 273）

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGG
STYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDFSSRRWYLEYWG
QGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSG
VHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVEC
PPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEV
HNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTK
GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPM
LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

图11BR

MS&D Exhibit 1008, Page 2909 of 4223

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
18/361,782	07/28/2023		3660	SRZN-006/04US 328202-2203	8	1

CONFIRMATION NO. 9001

UPDATED FILING RECEIPT

157070
Cooley LLP / Surrozen Operating, Inc.
Attn: IP Docketing Department
1299 Pennsylvania Avenue, NW, Suite 700
Washington, DC 20004

Date Mailed: 01/25/2024

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

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Inventor(s)

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Applicant(s)

Surrozen Operating, Inc., South San Francisco, CA;

Power of Attorney: The patent practitioners associated with Customer Number 157070

Domestic Priority data as claimed by applicant

This application is a CON of 16/954,484 06/16/2020 PAT 11,773,171
which is a 371 of PCT/US2018/066616 12/19/2018
which claims benefit of 62/607,875 12/19/2017
and claims benefit of 62/641,217 03/09/2018
and claims benefit of 62/680,522 06/04/2018

Foreign Applications for which priority is claimed (You may be eligible to benefit from the Patent Prosecution Highway program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 09/12/2023
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 18/361,782**
Projected Publication Date: 05/02/2024
Non-Publication Request: No
Early Publication Request: No
Title

WNT SURROGATE MOLECULES AND USES THEREOF

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET Substitute for Form PTO-1360 (For use with Form PTO/SB/06)	Application Number 18/361,782	Filing Date
	Applicant(s) Yang LI	

* May be used for additional claims or amendments

CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT	
	Indep	Depend	Indep	Depend	Indep	Depend
1	1		1			
2		1	---	---		
3		1	---	---		
4		1	---	---		
5		2	---	---		
6		(1)	---	---		
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49		(1)	---	---		
50		(1)	---	---		
Total Indep	1		1			
Total Depend	70	↵	7	↵		↵
Total Claims	71		8		0	

CLAIMS	*		*		*	
	Indep	Depend	Indep	Depend	Indep	Depend
51		(1)	---	---		
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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 18/361,782

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	320
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	700
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	800
TOTAL CLAIMS (37 CFR 1.16(i))	8 minus 20 =	* 0			OR	x =	0
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*				x =	0
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						1680
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	3500

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)	OR	RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
18/361,782	07/28/2023	Yang LI	SRZN-006/04US 328202-2203

CONFIRMATION NO. 9001

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Attn: IP Docketing Department
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PUBLICATION NOTICE

OC000000072067177

Date Mailed: 05/02/2024

Title:WNT SURROGATE MOLECULES AND USES THEREOF

Publication No.US-2024-0141049-A1
Publication Date:05/02/2024

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The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

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Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
18/361,782	07/28/2023	Yang LI	SRZN-006/04US 328202-2203

CONFIRMATION NO. 9001

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Cooley LLP / Surrozen Operating, Inc.
Attn: IP Docketing Department
1299 Pennsylvania Avenue, NW, Suite 700
Washington, DC 20004

PUBLICATION NOTICE

OC000000072070362

Date Mailed: 05/02/2024

Title:WNT SURROGATE MOLECULES AND USES THEREOF

Publication No.US-2024-0141049-A1
Publication Date:05/02/2024

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Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

Notice of References Cited	Application/Control No. 18/361,782	Applicant(s)/Patent Under Reexamination LI et al.	
	Examiner CHEOM-GIL CHEONG	Art Unit 1645	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date YYYY-MM-DD	Name	CPC Classification	US Classification
*	A	US-20230295347-A1	2023-09-21	CHEN; Hui	C12N15/63	424/136.1
*	B	US-20210292422-A1	2021-09-23	LI; Yang	C07K16/28	1/1
*	C	US-20240150473-A1	2024-05-09	FLETCHER; Russell	C07K16/244	1/1
	D					
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FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date YYYY-MM-DD	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Wu et al, Nature Biotechnology, vol 25, 1290-1297 (2007) (Year: 2007)
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in YYYY-MM-DD format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/361,782	LI et al.
	Examiner	Art Unit
	CHEOM-GIL CHEONG	1645

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
Reviewed prosecution history of parent case 16/954,484	06/05/2024	cc
Inventor name search	06/05/2024	cc
Reviewed pending claims of 18/311,082; 18/148,448; 16/954,482; 17/257,817; 18/652,070; 17/623,006; 17/801,624; 17/414,265; 17/429,584; 18/281,253; 17/438,303; 17/438,806;	06/05/2024	cc
Reviewed issued claims of US11746150, US11773171	06/05/2024	cc
Sequence search - see SCV	06/05/2024	cc
PE2E search – see attached	06/05/2024	cc
Google Scholar search – see attached	06/06/2024	cc

/CHEOM-GIL CHEONG/ Examiner, Art Unit 1645	/Meera Natarajan/ Primary Examiner, Art Unit 1643

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/361,782	LI et al.
	Examiner	Art Unit
	CHEOM-GIL CHEONG	1645

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
	Sequence search - see SCV	06/05/2024	cc

/CHEOM-GIL CHEONG/ Examiner, Art Unit 1645	/Meera Natarajan/ Primary Examiner, Art Unit 1643

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	95005	(C07K16/2863 OR C07K16/468 OR A61K2039/505 OR C07K2317/30 OR C07K2317/55 OR C07K2317/569 OR C07K2317/622 OR C07K2317/92).cpc.	(US-PGPUB; USPAT; USOCR; FIT (WO))	ADJ	ON	ON	2024/06/05 02:49 PM
L2	4	(C07K16/2863 AND C07K16/468 AND A61K2039/505 AND C07K2317/30 AND C07K2317/55 AND C07K2317/569 AND C07K2317/622 AND C07K2317/92).cpc.	(US-PGPUB; USPAT; USOCR; FIT (WO))	ADJ	ON	ON	2024/06/05 02:50 PM
L3	27	(Artificial Intelligence) More like doc: WO-2019126398-A1 Text: (AU-2018393073-A1 OR EP-3732201-A1 OR CA-3085782-A1 OR US-20200308287-A1 OR US-20210292422-A1 OR US-20240141049-A1 OR JP-2023113950-A OR AU-2019297522-A1 OR EP-3820906-A1 OR WO-2020010308-A1 OR US-11773171-B2 OR JP-2024057106-A OR JP-2024001292-A OR JP-7330977-B2 OR CN-111727203-A OR CA-3170340-A1 OR AU-2021227662-A1 OR EP-4110821-A1 OR EP-3994174-A1 OR WO-2021003416-A1).did.	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	ADJ	ON	ON	2024/06/05 02:50 PM
L4	12	((("SURROZEN") near3 ("OPERATING") near3 ("INC"))).AS,AANM.	(US-PGPUB; USPAT)	ADJ	ON	ON	2024/06/05 02:57 PM
L5	4305	((("LI") near3 ("Yang")) OR (("YUAN") near3 ("Tom")) OR (("SATO") near3 ("Aaron")) OR (("YEH") near3 ("Wen-Chen")) OR (("JANDA")	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2024/06/05 03:15 PM

		near3 ("Claudia")) OR (("FOWLER") near3 ("Tristan")) OR (("BARIBAULT") near3 ("Helene")) OR (("LAI") near3 ("Kuo-Pao")) OR (("XIE") near3 ("Liqin")) OR (("BREZSKI") near3 ("Randall")) OR (("LU") near3 ("Chenggang"))).INV.					
L6	56	((("LI") near3 ("Yang")) OR (("YUAN") near3 ("Tom")) OR (("SATO") near3 ("Aaron")) OR (("YEH") near3 ("Wen-Chen")) OR (("JANDA") near3 ("Claudia")) OR (("FOWLER") near3 ("Tristan")) OR (("BARIBAULT") near3 ("Helene")) OR (("LAI") near3 ("Kuo-Pao")) OR (("XIE") near3 ("Liqin")) OR (("BREZSKI") near3 ("Randall")) OR (("LU") near3 ("Chenggang"))).INV. AND (Fzd OR Frizzled) AND (LRP5 OR LRP6)	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2024/06/05 03:16 PM
L7	25	((("LI") near3 ("Yang")) OR (("YUAN") near3 ("Tom")) OR (("SATO") near3 ("Aaron")) OR (("YEH") near3 ("Wen-Chen")) OR (("JANDA") near3 ("Claudia")) OR (("FOWLER") near3 ("Tristan")) OR (("BARIBAULT") near3 ("Helene")) OR (("LAI") near3 ("Kuo-Pao")) OR (("XIE") near3 ("Liqin")) OR (("BREZSKI") near3 ("Randall")) OR (("LU") near3 ("Chenggang"))).INV. AND (Fzd OR Frizzled).clm. AND (LRP5 OR LRP6).clm.	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2024/06/05 03:17 PM
L8	29	L7 NOT L4	(US-PGPUB; USPAT; USOCR; FIT (WO))	ADJ	ON	ON	2024/06/05 03:17 PM
L9	19	(Artificial Intelligence) Similar to: 18/361,782 with 0 CPC Selections and 0 Text	(US-PGPUB; USPAT; USOCR; FIT (WO))	ADJ	ON	ON	2024/06/05 03:29 PM

		Selections Text: (WO-2019126398-A1 OR AU-2018393073-A1 OR US-20200308287-A1 OR CA-3085782-A1 OR JP-2021506297-A OR CN-111727203-A OR US-20240141049-A1 OR CN-111727203-B OR US-11773171-B2 OR CN-112566940-A OR US-20210292422-A1 OR WO-2020010308-A1 OR JP-7418332-B2 OR JP-2024500839-A OR CA-3104526-A1 OR CN-111655729-B OR JP-2021529796-A OR WO-2022130341-A1 OR JP-2024001287-A OR JP-2023554500-A OR JP-2021508247-A OR CN-116964102-A OR KR-20230122077-A OR WO-2022130342-A1 OR CA-3140580-A1 OR CN-111655729-A OR CN-114423784-A OR US-20230118983-A1 OR CN-116917332-A OR JP-2022539212-A OR WO-2020250156-A1 OR US-20210087280-A1 OR US-20220315659-A1 OR JP-7377288-B2 OR AU-2020291208-A1 OR CA-3144499-A1 OR AU-2018393074-A1 OR CA-3085596-A1 OR WO-2019126399-A1 OR KR-20220024460-A OR CN-117946267-A OR US-20220275095-A1 OR WO-2023250402-A2 OR JP-2023515505-A OR AU-2020300618-A1 OR WO-2021003416-A1 OR US-11746150-B2 OR US-20230138045-A1 OR US-20160235844-A1 OR EP-2911691-B1).did.					
L10	356	Frizzled near11	(US-PGPUB; USPAT;	ADJ	ON	ON	2024/06/06

		receptor near55 LRP5 near55 LRP6	USOCR; FIT (WO))				08:42 PM
L11	231	Frizzled near11 receptor near55 LRP5 near55 LRP6 AND @ad<"20171219"	(US-PGPUB; USPAT; USOCR; FIT (WO))	ADJ	ON	ON	2024/06/06 08:42 PM
L12	11	Frizzled near11 receptor near55 LRP5 near55 LRP6 AND tetravalent AND @ad<"20171219"	(US-PGPUB; USPAT; USOCR; FIT (WO))	ADJ	ON	ON	2024/06/06 08:44 PM
L13	10	Frizzled near11 receptor near55 LRP5/6 AND tetravalent AND @ad<"20171219"	(US-PGPUB; USPAT; USOCR; FIT (WO))	ADJ	ON	ON	2024/06/06 08:44 PM
L14	8	Frizzled near11 receptor near55 LRP5/6 AND VHH AND tetravalent AND @ad<"20171219"	(US-PGPUB; USPAT; USOCR; FIT (WO))	ADJ	ON	ON	2024/06/06 08:45 PM
L15	0	Frizzled near11 receptor near55 LRP5/6 near55 bispecific AND VHH AND tetravalent AND @ad<"20171219"	(US-PGPUB; USPAT; USOCR; FIT (WO))	ADJ	ON	ON	2024/06/06 08:46 PM
L16	8	Frizzled near11 receptor near55 LRP5/6 AND bispecific AND VHH AND tetravalent AND @ad<"20171219"	(US-PGPUB; USPAT; USOCR; FIT (WO))	ADJ	ON	ON	2024/06/06 08:46 PM

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 1 of 41

Complete if Known	
Application Number	18/361,782
Filing Date	07-28-2023
First Named Inventor	LI; Yang
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	SRZN-006/04US 328202-2203

U. S. PATENT DOCUMENTS

Examiner Initials*		Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		001	US-4946778	08-07-1990	LADNER et al.	
		002	US-5091513	02-25-1992	HUSTON; James S. et al.	
		003	US-5132405	07-21-1992	HUSTON; James S. et al.	
		004	US-6005079	12-21-1999	CASTERMAN et al.	
		005	US-6528624	03-04-2003	IDUSOGIE; Esohe Ekinaduese et al.	
		006	US-6538124	03-25-2003	IDUSOGIE; Esohe Ekinaduese et al.	
		007	US-6765087	07-20-2004	CASTERMAN et al.	
		008	US-6838254	01-04-2005	HAMERS et al.	
		009	US-7297775	11-20-2007	IDUSOGIE; Esohe Ekinaduese et al.	
		010	US-7317091	01-08-2008	LAZAR; Gregory Alan et al.	
		011	US-7364731	04-29-2008	IDUSOGIE; Esohe Ekinaduese et al.	
		012	US-7657380	02-02-2010	LAZAR; Gregory Alan et al.	
		013	US-7662925	02-16-2010	LAZAR; Gregory Alan et al.	
		014	US-7982013	07-19-2011	GURNEY et al.	
		015	US-8202966	06-19-2012	McCARTHY; Sean A.	
		016	US-8221751	07-17-2012	NAKAMURA et al.	
		017	US-8343922	01-01-2013	WU et al.	
		018	US-8461155	06-11-2013	WU et al.	
		019	US-8507442	08-13-2013	GURNEY et al.	
		020	US-8637506	01-28-2014	WU et al.	
		021	US-8715941	05-06-2014	ABO et al.	
		022	US-8846041	09-30-2014	BOURHIS et al.	

Examiner Signature		Date Considered	

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Sheet 2 of 41

Complete if Known	
Application Number	18/361,782
Filing Date	07-28-2023
First Named Inventor	LI; Yang
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	SRZN-006/04US 328202-2203

U. S. PATENT DOCUMENTS

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		023	US-8859736	10-14-2014	MA et al.	
		024	US-8883735	11-11-2014	JENKINS et al.	
		025	US-8975044	03-10-2015	GURNEY et al.	
		026	US-9359444	06-07-2016	DUPONT et al.	
		027	US-9573998	02-21-2017	GURNEY et al.	
		028	US-11142577	10-12-2021	GARCIA et al.	
		029	US-20030044409	03-06-2003	CARSON; Dennis A. et al.	
		030	US-20030099647	05-29-2003	DESHPANDE; Rajendra V. et al.	
		031	US-20030157109	08-21-2003	CORVALAN; Jose R. F. et al.	
		032	US-20030165500	09-04-2003	RHEE; Chae-Seo et al.	
		033	US-20050261181	11-24-2005	WU; Dianqing et al.	
		034	US-20060127393	06-15-2006	LI; Ji et al.	
		035	US-20060263791	11-23-2006	MOON; Randall Todd et al.	
		036	US-20070196872	08-23-2007	BEX; Frederick et al.	
		037	US-20070207522	09-06-2007	LAURIE; Gordon et al.	
		038	US-20080038272	02-14-2008	BUEHRING; Hans-Joerg et al.	
		039	US-20080131435	06-05-2008	STAVENHAGEN; Jeffrey et al.	
		040	US-20080138344	06-12-2008	STAVENHAGEN; Jeffrey et al.	
		041	US-20080267955	10-30-2008	SCHLUESENER; Hermann et al.	
		042	US-20080286261	11-20-2008	MORGAN; Bruce A. et al.	
		043	US-20090028869	01-29-2009	DODEL; Richard et al.	
		044	US-20090092599	04-09-2009	LAZAR; Gregory Alan et al.	

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Sheet 3 of 41

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Application Number	18/361,782
Filing Date	07-28-2023
First Named Inventor	LI; Yang
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	SRZN-006/04US 328202-2203

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		045	US-20090291088	11-26-2009	HARIHARAN; Kandasamy et al.	
		046	US-20090311243	12-17-2009	BROCKBANK; Sarah et al.	
		047	US-20100104574	04-29-2010	GURNEY; Austin L. et al.	
		048	US-20100129375	05-27-2010	JUNGE; Harald J. et al.	
		049	US-20100254979	10-07-2010	STAUNTON; Donald E. et al.	
		050	US-20100254980	10-07-2010	CONG; Feng et al.	
		051	US-20110105606	05-05-2011	RABBANI; Elazar et al.	
		052	US-20110177073	07-21-2011	VAN BERKEL; Patrick H. C. et al.	
		053	US-20110223140	09-15-2011	PARK; Sung Sup et al.	
		054	US-20110243963	10-06-2011	ABO; Arie et al.	
		055	US-20120237523	09-20-2012	MASCOLA; John R. et al.	
		056	US-20120322717	12-20-2012	LIU; Dakai et al.	
		057	US-20130058934	03-07-2013	CONG; Feng et al.	
		058	US-20130064823	03-14-2013	CONG; Feng et al.	
		059	US-20130095097	04-18-2013	BLANKENSHIP; John W. et al.	
		060	US-20130095104	04-18-2013	CUMMINGS; W. Jason et al.	
		061	US-20130183320	07-18-2013	WU; Yan et al.	
		062	US-20130230521	09-05-2013	NAKAMURA; Yusuke et al.	
		063	US-20130253172	09-26-2013	GURNEY; Austin L. et al.	
		064	US-20130274215	10-17-2013	THIES; R. Scott et al.	
		065	US-20130295105	11-07-2013	GURNEY; Austin L. et al.	

Examiner Signature		Date Considered	

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Filing Date	07-28-2023
First Named Inventor	LI; Yang
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	SRZN-006/04US 328202-2203

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		066	US-20140044713	02-13-2014	DE LAU; Willibrordus Barend Maria et al.	
		067	US-20140050725	02-20-2014	JENKINS; David et al.	
		068	US-20140105917	04-17-2014	GURNEY; Austin L.	
		069	US-20140154252	06-05-2014	THOMPSON; Peter Armstrong et al.	
		070	US-20140200179	07-17-2014	GARCIA; Kenan Christopher et al.	
		071	US-20140242078	08-28-2014	DUPONT; Jakob et al.	
		072	US-20140363439	12-11-2014	BOURHIS; Eric et al.	
		073	US-20150010560	01-08-2015	XU; Cen et al.	
		074	US-20150119555	04-30-2015	JUNG; Gundram et al.	
		075	US-20150196663	07-16-2015	SHUSTA; Eric V. et al.	
		076	US-20150209407	07-30-2015	PIGNOLO; Robert J.	
		077	US-20150232554	08-20-2015	GURNEY; Austin L. et al.	
		078	US-20150266947	09-24-2015	SIERKS; Michael et al.	
		079	US-20150376252	12-31-2015	XU; Huaqiang Eric et al.	
		080	US-20160002312	01-07-2016	ILAN; Yaron	
		081	US-20160024196	01-28-2016	MAJETI; Jiangwen et al.	
		082	US-20160152947	06-02-2016	PIOSZAK; Augen A.	
		083	US-20160194394	07-07-2016	SIDHU; Sachdev et al.	
		084	US-20160264960	09-15-2016	ISHII; Shinya	
		085	US-20160312207	10-27-2016	KUO; Calvin J. et al.	
		086	US-20170071937	03-16-2017	KARP; Jeffrey M. et al.	

Examiner Signature		Date Considered	

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Sheet 5 of 41

Complete if Known	
Application Number	18/361,782
Filing Date	07-28-2023
First Named Inventor	LI; Yang
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	SRZN-006/04US 328202-2203

U. S. PATENT DOCUMENTS

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		087	US-20170218077	08-03-2017	RAUM; Tobias et al.	
		088	US-20170218078	08-03-2017	RAUM; Tobias et al.	
		089	US-20170240631	08-24-2017	MONROE; Kate et al.	
		090	US-20170253670	09-07-2017	KLEIN; Christian et al.	
		091	US-20170306029	10-26-2017	GARCIA; Kenan Christopher et al.	
		092	US-20170349659	12-07-2017	GARCIA; Kenan Christopher et al.	
		093	US-20170355756	12-14-2017	JULIEN; Jean-Pierre et al.	
		094	US-20180066067	03-08-2018	CONG; Feng et al.	
		095	US-20190093072	03-28-2019	KOEHLER; Karl R. et al.	
		096	US-20190093079	03-28-2019	LOOSE; Christopher et al.	
		097	US-20200024338	01-23-2020	LUCA; Vincent Christopher et al.	
		098	US-20200048324	02-13-2020	ZHANG; Zhengjian et al.	
		099	US-20200199237	06-25-2020	GARCIA; Kenan Christopher et al.	
		100	US-20200199238	06-25-2020	GARCIA; Kenan Christopher et al.	
		101	US-20200308287	10-01-2020	LI; Yang et al.	
		102	US-20210079089	03-18-2021	LI; Yang et al.	
		103	US-20210087280	03-25-2021	LI; Yang et al.	
		104	US-20210292422	09-23-2021	LI; Yang	
		105	US-20210380678	12-09-2021	ZHANG; Zhengjian et al.	
		106	US-20210403578	12-30-2021	GARCIA; Kenan Christopher et al.	
		107	US-20220064337	03-03-2022	LI; Yang et al.	
		108	US-20220112278	04-14-2022	LI; Yang et al.	

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 6 of 41

Complete if Known	
Application Number	18/361,782
Filing Date	07-28-2023
First Named Inventor	LI; Yang
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	SRZN-006/04US 328202-2203

U. S. PATENT DOCUMENTS

Examiner Initials*		Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		109	US-20220175884	06-09-2022	LEE; Sungjin et al.	
		110	US-20220195053	06-23-2022	LI; Yang et al.	
		111	US-20220275095	09-01-2022	LI; Yang et al.	
		112	US-20230138045	05-04-2023	LI; Yang	
		113	US-20230183359	06-15-2023	GARCIA; Kenan Christopher et al.	

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Examiner Initials*		Cite No.[1]	Foreign Patent Document Country Code[3]Number[4]Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
		114	CN-101951954-A	01-19-2011	NOVARTIS AG.		☒
		115	CN-103002911-A	03-27-2013	ONCOMED PHARM INC.		☒
		116	CN-103998462-A	08-20-2014	FATE THERAPEUTICS INC.		☒
		117	EP-1716181-B1	12-16-2009	GENENTECH INC.		☒
		118	EP-2910550-A2	08-26-2015	ENZO THERAPEUTICS INC.		☐
		119	EP-3191526-A4	03-28-2018	UNIV LELAND STANFORD JUNIOR., et al.		☐

Examiner Signature		Date Considered	

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Sheet 7 of 41

Complete if Known	
Application Number	18/361,782
Filing Date	07-28-2023
First Named Inventor	LI; Yang
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	SRZN-006/04US 328202-2203

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		120	JP-2011503025-A	01-27-2011	NOVARTIS AG.		☒
		121	JP-2012503990-A	02-16-2012	ONCOMED PHARMACEUTICALS INC.		☒
		122	JP-2012506568-A	03-15-2012	CAMBRIDGE DISPLAY TECH LTD.		☒
		123	JP-2012516685-A	07-26-2012	KONINK NL AKADEMIE VAN WETENSC.		☒
		124	JP-2013527761-A	07-04-2013	NOVARTIS AG.		☒
		125	JP-2017530099-A	10-12-2017	THE BOARD OF TRUSTEES OF THE LELAND STANFORD JR. UNIVERSITY.		☒
		126	WO-02092635-A2	11-21-2002	UNIV CALIFORNIA.		☐
		127	WO-2004063351-A2	07-29-2004	MACROGENICS INC., et al.		☐
		128	WO-2005032574-A1	04-14-2005	UNIV LELAND STANFORD JUNIOR., et al.		☐
		129	WO-2006040163-A1	04-20-2006	LINIKUM EBERHARD KARLS UNI TUE., et al.		☒
		130	WO-2006079372-A1	08-03-2006	ABLYNX NV., et al.		☐

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Sheet 8 of 41

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Filing Date	07-28-2023
First Named Inventor	LI; Yang
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	SRZN-006/04US 328202-2203

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		131	WO-2006088494-A2	08-24-2006	MACROGENICS INC., et al.		☐
		132	WO-2006105338-A2	10-05-2006	XENCOR INC., et al.		☐
		133	WO-2007012449-A1	02-01-2007	PHASYS GMBH M., et al.		☒
		134	WO-2007024249-A2	03-01-2007	MACROGENICS INC., et al.		☐
		135	WO-2007146968-A2	12-21-2007	TRUBION PHARMACEUTICALS., et al.		☐
		136	WO-2007148417-A1	12-27-2007	ONCOTHERAPY SCIENCE INC., et al.		☐
		137	WO-2008068048-A2	06-12-2008	IST SUPERIORE SANITA., et al.		☐
		138	WO-2008084402-A2	07-17-2008	UNIV MARBURG PHILIPPS., et al.		☐
		139	WO-2008134632-A1	11-06-2008	HARVARD COLLEGE., et al.		☐
		140	WO-2009056634-A2	05-07-2009	NOVARTIS AG., et al.		☐
		141	WO-2009064944-A2	05-22-2009	NUVELO INC., et al.		☐

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Sheet 9 of 41

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Application Number	18/361,782
Filing Date	07-28-2023
First Named Inventor	LI; Yang
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	SRZN-006/04US 328202-2203

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		142	WO-2009080251-A1	07-02-2009	HOFFMANN LA ROCHE., et al.		☐
		143	WO-2010016766-A2	02-11-2010	KONINK NL AKADEMIE VAN WETENSC., et al.		☐
		144	WO-2010021697-A2	02-25-2010	PFIZER., et al.		☐
		145	WO-2010037041-A2	04-01-2010	ONCOMED PHARM INC., et al.		☐
		146	WO-2010054010-A1	05-14-2010	FABRUS LLC., et al.		☐
		147	WO-2010090513-A2	08-12-2010	KONINK NL AKADEMIE VAN WETENSC., et al.		☐
		148	WO-2011088226-A2	07-21-2011	CARIS LIFE SCIENCES LUXEMBOURG HOLDINGS., et al.		☐
		149	WO-2011090762-A1	07-28-2011	EMERGENT PRODUCT DEV SEATTLE., et al.		☐
		150	WO-2011119661-A1	09-29-2011	GENENTECH INC., et al.		☐
		151	WO-2011123785-A2	10-06-2011	ONCOMED PHARM INC., et al.		☐
		152	WO-2011138392-A1	11-10-2011	NOVARTIS AG., et al.		☐

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Sheet 10 of 41

Complete if Known	
Application Number	18/361,782
Filing Date	07-28-2023
First Named Inventor	LI; Yang
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	SRZN-006/04US 328202-2203

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		153	WO-2012014076-A2	02-02-2012	KONINKLIJKE NEDERLANDSE AKADEMIE VAN WETENSCHAPPEN., et al.		☐
		154	WO-2012058768-A1	05-10-2012	ZYMEWORKS INC., et al.		☐
		155	WO-2012103360-A2	08-02-2012	UNIV LELAND STANFORD JUNIOR., et al.		☐
		156	WO-2012140274-A2	10-18-2012	KONINKLIJKE NEDERLANDSE AKADEMIE VAN WETENSCHAPPEN., et al.		☐
		157	WO-2012140274-A9	03-07-2013	KONINKLIJKE NEDERLANDSE AKADEMIE VAN WETENSCHAPPEN., et al.		☐
		158	WO-2013092001-A1	06-27-2013	SYNIMMUNE GMBH.		☐
		159	WO-2013109819-A1	07-25-2013	GENENTECH INC., et al.		☐
		160	WO-2014029752-A1	02-27-2014	GLAXO GROUP LTD.		☐
		161	WO-2014124326-A1	08-14-2014	STEM CENTRX INC.		☐

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Sheet 11 of 41

Complete if Known	
Application Number	18/361,782
Filing Date	07-28-2023
First Named Inventor	LI; Yang
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	SRZN-006/04US 328202-2203

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		162	WO-2014143022-A1	09-18-2014	TRESE MICHAEL T., et al.		☐
		163	WO-2014159580-A1	10-02-2014	ONCOMED PHARM INC.		☐
		164	WO-2015036582-A2	03-19-2015	KIPRIJANOV SERGEJ MICHAILOVIC.		☐
		165	WO-2015063187-A1	05-07-2015	KIPRIJANOV SERGEJ MICHAILOVIC.		☐
		166	WO-2015109212-A1	07-23-2015	PFIZER., et al.		☐
		167	WO-2016023019-A2	02-11-2016	ALECTOR LLC.		☐
		168	WO-2016040895-A1	03-17-2016	THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY, et al.		☐
		169	WO-2016168607-A1	10-20-2016	UNIV TENNESSEE RES FOUND.		☐
		170	WO-2016205551-A2	12-22-2016	UNIV CALIFORNIA.		☐
		171	WO-2016205566-A1	12-22-2016	UNIV CALIFORNIA., et al.		☐

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Sheet 12 of 41

Complete if Known	
Application Number	18/361,782
Filing Date	07-28-2023
First Named Inventor	LI; Yang
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	SRZN-006/04US 328202-2203

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		172	WO-2017127933-A1	08-03-2017	GOVERNING COUNCIL UNIV TORONTO.		☐
		173	WO-2017136820-A2	08-10-2017	EPIMAB BIOTHERAPEUTICS INC., et al.		☐
		174	WO-2017152102-A2	09-08-2017	ALECTOR LLC.		☐
		175	WO-2018132572-A1	07-19-2018	THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY.		☐
		176	WO-2018140821-A1	08-02-2018	SURROZEN INC.		☐
		177	WO-2018220080-A1	12-06-2018	BOEHRINGER INGELHEIM INT.		☐
		178	WO-2019126398-A1	06-27-2019	SURROZEN INC.		☐
		179	WO-2019126399-A1	06-27-2019	SURROZEN INC.		☐
		180	WO-2019126401-A1	06-27-2019	SURROZEN INC.		☐
		181	WO-2019159084-A1	08-22-2019	ANGERS STEPHANE., et al.		☐
		182	WO-2020010308-A1	01-09-2020	SURROZEN INC.		☐

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Sheet 13 of 41

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Application Number	18/361,782
Filing Date	07-28-2023
First Named Inventor	LI; Yang
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	SRZN-006/04US 328202-2203

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		183	WO-2020014271-A1	01-16-2020	SURROZEN INC.		☐
		184	WO-2020132356-A1	06-25-2020	SURROZEN INC.		☐
		185	WO-2020167848-A1	08-20-2020	SURROZEN INC.		☐
		186	WO-2020185960-A1	09-17-2020	SURROZEN INC., et al.		☐
		187	WO-2020206005-A1	10-08-2020	SURROZEN INC.		☐
		188	WO-2021003054-A1	01-07-2021	RAMPART COMMUNICATIONS INC.		☐
		189	WO-2021003416-A1	01-07-2021	SURROZEN INC.		☐
		190	WO-2021173726-A1	09-02-2021	SURROZEN INC.		☐
		191	WO-2022104280-A1	05-19-2022	SURROZEN OPERATING INC.		☐
		192	WO-2022192445-A1	09-15-2022	SURROZEN OPERATING INC.		☐
		193	WO-2023044348-A1	03-23-2023	SURROZEN OPERATING INC.		☐

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Sheet 14 of 41

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Filing Date	07-28-2023
First Named Inventor	LI; Yang
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	SRZN-006/04US 328202-2203

FOREIGN PATENT DOCUMENTS

Examiner Initials*		Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
		194	WO-2023115048-A1	06-22-2023	SURROZEN OPERATING INC.		☐
		195	WO-2023130055-A2	07-06-2023	SURROZEN OPERATING INC.		☐
		196	WO-9627011-A1	09-06-1996	GENENTECH INC.		☐
		197	WO-9850431-A2	11-12-1998	GENENTECH INC.		☐

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 15 of 41

Complete if Known	
Application Number	18/361,782
Filing Date	07-28-2023
First Named Inventor	LI; Yang
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	SRZN-006/04US 328202-2203

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		198	ADAMS, T.S. et al. (2020 Jul) Single-cell RNA-seq reveals ectopic and aberrant lung-resident cell populations in idiopathic pulmonary fibrosis. Sci Adv, 6:eaba1983, 16 pages.	☐
		199	AHN, V. E., et al. (2011) "Structural basis of Wnt signaling inhibition by Dickkopf binding to LRP5/6" Developmental cell, 21(5):862-873.	☐
		200	AIHARA, E. et al. (2017) "Trefoil factor peptides and gastrointestinal function" Annual Review of Physiology, 79:357-380.	☐
		201	AKHMETSHINA, A. et al. (2012 Mar) Activation of canonical Wnt signalling is required for TGF-ß-mediated fibrosis. Nature Communications, 3:735; DOI:10.1038/ncomms1734, 12 pages.	☐
		202	ALSAFADI, H. et al. (2017 Mar) An ex vivo model to induce early fibrosis-like changes in human precision-cut lung slices. Am J Physiol Lung Cell Mol Physiol, 312:L896-L902.	☐
		203	ANTONI, L. et al. (2014) "Intestinal barrier in inflammatory bowel disease" World Journal of Gastroenterology: WJG, 20(5):1165-1179.	☐
		204	ARAN et al. (2019) "Reference-based analysis of lung single-cell sequencing reveals a transitional profibrotic macrophage". Nature Immunology, 20(2): 163-172.	☐
		205	ARIKE, L. et al. (2017) "Intestinal Muc2 mucin O-glycosylation is affected by microbiota and regulated by differential expression of glycosyltranferases" Glycobiology, 27(4):318-328.	☐
		206	ATKINSON, P.J., et al. (2014) "Hair cell regeneration after ATOH1 gene therapy in the cochlea of profoundly deaf adult guinea pigs." PLoS ONE 9(7):e102077, 1-11.	☐

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		207	BAARSMA, H. et al. (2017) Noncanonical WNT-5A signaling impairs endogenous lung repair in COPD. J Exp Med, 214:143-163.	☐
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		209	BAFICO, A. et al. (2001 Jul) "Novel mechanism of Wnt signalling inhibition mediated by Dickkopf-1 interaction with LRP6/Arrow" Nature Cell Biology, 3(7):683-686.	☐
		210	BARBAS et al., "Human antibody recognition of DNA." Proceedings of the National Academy of Sciences (1995); 92(7): 2529-2533.	☐
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		212	BARKAUSKAS, C.E. et al. (2013 Jul) Type 2 alveolar cells are stem cells in adult lung. Journal of Clinical Investigation 123(7):3025-3036.	☐
		213	BARKAUSKAS et al. (2017) "Lung organoids: current uses and future promise". Development, 144(6): 986-997.	☐
		214	BARKER, N. et al. (2007) "Identification of stem cells in small intestine and colon by marker gene Lgr5" Nature, 449(7165):1003-1007.	☐
		215	BARKER et al. (2009) Crypt stem cells as the cells-of-origin of intestinal cancer. Nature, 457(7229):608-611, Methods, 1 page.	☐
		216	BARKER, N. et al. (2010 Jan) "Lgr5+ ve stem cells drive self-renewal in the stomach and build long-lived gastric units in vitro" Cell stem cell, 6(1):25-36.	☐
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		218	BASIL et al., (2022) "Human distal airways contain a multipotent secretory cell that can regenerate alveoli". Nature, 604(7904): 120-126.	☐
		219	BERGSTRÖM, J.H. et al. (2016 Nov) "Gram-positive bacteria are held at a distance in the colon mucus by the lectin-like protein ZG16" Proceedings of the National Academy of Sciences, 113(48):13833-13838.	☐
		220	BERGSTRÖM, J.H. et al. (2014) "AGR2, an endoplasmic reticulum protein, is secreted into the gastrointestinal mucus" PLoS One, 9(8):e104186, 1-8.	☐
		221	BEUMER, J. et al. (2016) "Regulation and plasticity of intestinal stem cells during homeostasis and regeneration" Development, 143(20):3639-3649.	☐
		222	BHALLA, P. et al. (2015 Apr) Disseminated, persistent, and fatal infection due to the vaccine strain of varicella-zoster virus in an adult following stem cell transplantation. Clin Infect Dis, 60(7):1068-1074.	☐
		223	BIRD, R. E., et al., "Single-chain antigen-binding proteins", Science (1988); 242 (4877): 423-426.	☐
		224	BLAGODATSKI et al. (2014) "Targeting the Wnt pathways for therapies". Molecular Cell Therapy 2(28): 15 pages.	☐
		225	BOHNE, B.A. et al. (1976) Irreversible Inner Ear Damage From Rock Music. Trans Sect Otolaryngol Am Acad Ophthalmol Otolaryngol. 82(1):50-59.	☐
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		227	BRADLEY, P. et al. (2005 Sep) "Toward high-resolution de novo structure prediction for small proteins." Science 309(5742):1868-1871.	☐

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		228	BRAMHALL et al. (2014). "Lgr5-Positive Supporting Cells Generate New Hair Cells in the Postnatal Cochlea." Stem Cell Reports. 2(3): 311-322.	☐
		229	BRAMHALL, N.F. et al. (2017) Auditory Brainstem Response Altered in Humans With Noise Exposure Despite Normal Outer Hair Cell Function. Ear Hear, 38(1):e1-e12. U.S. Department of Veterans Affairs Public Access Author Manuscript, 27 pages.	☐
		230	BRINKMANN, U. et al (2017) The making of bispecific antibodies. MAbs, 9(2):182-212.	☐
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		232	CAO, H. et al. (2018) Inhibition of Wnt/ß-catenin signaling suppresses myofibroblast differentiation of lung resident mesenchymal stem cells and pulmonary fibrosis. Scientific Reports, 8:13644, 14 pages.	☐
		233	CARLIER, F.M. et al. (2020). Canonical WNT pathway is activated in the airway epithelium in chronic obstructive pulmonary disease. EBioMedicine, 61:103034, 17 pages.	☐
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		237	CHEN et al. (2009). "Aminoglycoside-induced histone deacetylation and hair cell death in the mouse cochlea," J. Neurochem., 108(5): 1226-1236.	☐
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		246	CHILOSI et al. (2003) "Aberrant Wnt/β-catenin pathway activation in idiopathic pulmonary fibrosis". The American Journal of Pathology, 162(5): 1495-1502.	☐
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		266	FOWLER, T. W et al. (2021) "Development of selective bispecific Wnt mimetics for bone loss and repair." Nature Communications, 12(1):3247, pp. 1-13.	☐
		267	FRANK et al. (2016) "Emergence of a wave of Wnt signaling that regulates lung alveologenesis by controlling epithelial self-renewal and differentiation". Cell Reports, 17(9): 2312-2325.	☐
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		270	FUJIOKA et al. (2015). "Manipulating cell fate in the cochlea: a feasible therapy for hearing loss." Trends Neurosci. 38, 139-44.	☐
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		273	GenBank Accession No. AF177395.1 "Homo sapiens dickkopf-2 (DKK-2) mRNA, complete cds" October 16, 1999, 2 pages.	☐
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Sheet 23 of 41

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Application Number	18/361,782
Filing Date	07-28-2023
First Named Inventor	LI; Yang
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	SRZN-006/04US 328202-2203

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		276	GenBank Accession No. NM_014421.3 "Homo sapiens dickkopf WNT signaling pathway inhibitor 2 (DKK2), mRNA" February 13, 2021, 4 pages.	☐
		277	GenBank Accession No. NM_015881.6 "Homo sapiens dickkopf WNT signaling pathway inhibitor 3 (DKK3), transcript variant 1, mRNA" February 23, 2021, 5 pages.	☐
		278	GenBank Accession No. NP_004054.3 "cadherin-17 precursor [Homo sapiens]" May 25, 2022, 4 pages.	☐
		279	GenBank Accession No. NP_005805.1 "cell surface A33 antigen precursor [Homo sapiens]" June 3, 2022, 4 pages.	☐
		280	GenBank Accession No. NP_036374.1 "dickkopf-related protein 1 precursor [Homo sapiens]" March 3, 2021, 3 pages.	☐
		281	GenBank Accession No. NP_055236.1 "dickkopf-related protein 2 precursor [Homo sapiens]" February 13, 2021, 3 pages.	☐
		282	GenBank Accession No. NP_149038.3 "mucin-13 precursor [Homo sapiens]" October 17, 2021, 4 pages.	☐
		283	"GenVec Provides Investor Update: Highlights ongoing Initiatives Involving the AdenoVerse Gene Delivery Platform" GenVec Press Release, Jan 20, 2016, 1 page.	☐
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		287	GIBBS, S. et al. (1993) Molecular Characterization and Evolution of the SPRR Family of Keratinocyte Differentiation Markers Encoding Small Proline-Rich Proteins. Genomics, 16:630-637.	☐
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		293	GOUGELET, A., et al. (2014) "T-cell factor 4 and ß-catenin chromatin occupancies pattern zonal liver metabolism in mice." Hepatology, 59(6):2344-2357.	☐
		294	GUBBELS et al. (2008) "Functional auditory hair cells produced in the mammalian cochlea by in utero gene transfer." Nature, 455(7212):537-541.	☐
		295	GULATI, S. et al. (2018 May 18) "Targeting G protein-coupled receptor signaling at the G protein level with a selective nanobody inhibitor." Nature Communications, 9(1):1996; 15 pages.	☐
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		297	GURNEY, A., et al., (2012 Jul) "Wnt pathway inhibition via the targeting of frizzled receptors results in decreased growth and tumorigenicity of human tumors" Proc Natl Acad Sci USA, 109(29):11717-11722.	☐
		298	HAAS, M. et al. (2019) DeltaN-Tp63 Mediates Wnt/ß-Catenin-Induced Inhibition of Differentiation in Basal Stem Cells of Mucociliary Epithelia. Cell Reports, 28:3338-3352.	☐
		299	HABERMANN, A.C. et al. (2020 Jul) Single-cell RNA sequencing reveals profibrotic roles of distinct epithelial and mesenchymal lineages in pulmonary fibrosis. Sci Adv, 6:eaba1972, 15 pages.	☐
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		301	HAO, H-X. et al. (2012 May 10) "ZNRF3 promotes Wnt receptor turnover in an R-spondin-sensitive manner" Nature, 485(7397):195-200.	☐
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		306	HIRATA et al. (2013) "Dose-dependent roles for canonical Wnt signalling in de novo crypt formation and cell cycle properties of the colonic epithelium" Development and Stem Cells, 140:66-75.	☐
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		308	HOLLNAGEL, et al. (1999) "Id genes are direct targets of bone morphogenetic protein induction in embryonic stem cells." Journal of Biological Chemistry 274(28):19838-19845.	☐
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		312	International Preliminary Report on Patentability for International Patent Application No. PCT/US2018/066616, dated June 23, 2020, 8 pages.	☐
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		316	JACQUES, B.E. et al. (2013) A dual function for canonical Wnt/β-catenin signaling in the developing mammalian cochlea. Development, 139:4395-4404. Erratum, Development 140:247.	☐
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First Named Inventor	LI; Yang
Art Unit	Not Yet Assigned
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		325	KAWAMOTO et al. (2003). "Math1 gene transfer generates new cochlear hair cells in mature guinea pigs in vivo." Journal of Neuroscience. 23(11): 4395-400.	☐
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		356	LIU et al. (2012) "Age-dependent in vivo conversion of mouse cochlear pillar and Deiters' cells to immature hair cells by Atoh1 ectopic expression." Journal of Neuroscience. 32(19):6600-6610.	☐
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Sheet 32 of 41

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Application Number	18/361,782
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First Named Inventor	LI; Yang
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		366	METEOGLU, I. et al. (2008) Id-I: Regulator of EGFR and VEGF and potential target for colorectal cancer therapy. J Exp Clin Cancer Res, 27:69, 7 pages.	☐
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		435	WU et al. (2013). "In vivo delivery of Atoh1 gene to rat cochlea using a dendrimer-based nanocarrier." Journal of biomedical nanotechnology. 9(10): 1736-45.	☐
		436	XIAO, SA , et al., "Establishment of long-term serum-free culture for lacrimal gland stem cells aiming at lacrimal gland repair," Stem Cell Research & Therapy, (2020 Jan 8), 11:20, 13 pages.	☐
		437	XIE, Y. et al. (2013 Oct) "Interaction with both ZNRF3 and LGR4 is required for the signalling activity of R-spondin" EMBO Reports, 14(12):1120-1126.	☐
		438	XU et al. (2016) "Single-cell RNA sequencing identifies diverse roles of epithelial cells in idiopathic pulmonary fibrosis". JCI Insight, 1(20): 1-19.	☐
		439	YAN, K.S. et al. (2017 May). Non-equivalence of Wnt and R-spondin ligands during Lgr5+ intestinal stem-cell self-renewal. Nature, 545(7653):238-242. doi:10.1038/nature22313; HHS Public Access Author Manuscript, 36 pages.	☐
		440	ZACHARIAS et al. (2018) "Regeneration of the lung alveolus by an evolutionarily conserved epithelial progenitor". Nature, 555(7695): 251-255.	☐
		441	ZAPATA et al., Engineering linear F(ab')2 fragments for efficient production in Escherichia coli and enhanced antiproliferative activity, Protein Engineering, Design and Selection, October 1995, pp. 1057-1062.	☐

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

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Form used in lieu of PTO/SB/08a/b (07-09)
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 40 of 41

Complete if Known	
Application Number	18/361,782
Filing Date	07-28-2023
First Named Inventor	LI; Yang
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	SRZN-006/04US 328202-2203

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*		Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
		442	ZATORSKI, H. et al. (2019) Role of glucagon-like peptides in inflammatory bowel diseases-current knowledge and future perspectives. Nauryn-Schmiedeberg's Archives of Pharmacology, 392:1321-1330.	☐
		443	ZEPP et al. (2017) "Distinct mesenchymal lineages and niches promote epithelial self-renewal and myofibrogenesis in the lung". Cell, 170(6): 1134-1148.	☐
		444	ZHANG et al. (2015) "3D structural fluctuation of IgG1 antibody revealed by individual particle electron tomography" Scientific Reports 5:09803 1-13.	☐
		445	ZHANG, M. et al. (2020 Mar) Targeting the Wnt signaling pathway through R-spondin 3 identifies an anti-fibrosis treatment strategy for multiple organs. PLoS ONE, 15(3):e0229445, 1-21.	☐
		446	ZHANG, S. et al. (2019 Jul) Frizzled-9+ Supporting Cells Are Progenitors for the Generation of Hair Cells in the Postnatal Mouse Cochlea. Front Mol Neurosci, 12:184, doi:10.3389/fnmol.2019.00184, 11 pages.	☐
		447	ZHANG, T. et al. (2018) Overexpression of FOXQ1 enhances anti-senescence and migration effects of human umbilical cord mesenchymal stem cells in vitro and in vivo. Cell and Tissue Research, 373:379-393.	☐
		448	ZHAO, J. et al. (2007) R-spondin1, A Novel Intestinotrophic Mitogen, Ameliorates Experimental Colitis in Mice. Gastroenterology, 132(4):1331-1343. https://doi.org/10.1053/j.gastro.2007.02.001.	☐
		449	ZHENG, W. et al. (2006) Evaluation of AGR2 and AGR3 as candidate genes for inflammatory bowel disease. Genes and Immunity, 7:11-18.	☐
		450	ZHOU, B. et al. (2020 Nov) The angiocrine Rspondin3 instructs interstitial macrophage transition via metabolic–epigenetic reprogramming and resolves inflammatory injury; with Methods. Nat Immunol, 21:1430–1443, 28 pages.	☐

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 41 of 41

Complete if Known	
Application Number	18/361,782
Filing Date	07-28-2023
First Named Inventor	LI; Yang
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	SRZN-006/04US 328202-2203

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*		Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
		451	ZOUKHRI "Mechanisms Involved in Injury and Repair of the Murine Lacrimal Gland: Role of Programmed Cell Death and Mesenchymal Stem Cells", Ocul Surf., (2010); 8(2):60-69.	☐

Examiner Signature	/CHEOM-GIL CHEONG/	Date Considered	06/02/2024

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Form used in lieu of PTO/SB/08a/b (07-09)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	18/361,782
Filing Date	07-28-2023
First Named Inventor	Yang LI
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	SRZN-006/04US 328202-2203

U. S. PATENT DOCUMENTS

Examiner Initials*		Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		001	US-11746150	09-05-2023	LI; Yang et al.	
		002	US-11773171	10-03-2023	LI; Yang et al.	
		003	US-20230374090	11-23-2023	LI; Yang et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*		Cite No.[1]	Foreign Patent Document Country Code[3]Number[4]Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
		004	CN-112654363-A	04-13-2021	SURROZEN INC.		☒
		005	JP-2020506701-A	03-05-2020	SURROZEN OPERATING, INC.		☒
		006	WO-2021173712-A1	09-02-2021	UNIV TEXAS.		☐
		007	WO-2023250291-A2	12-28-2023	SURROZEN OPERATING INC., et al.		☐

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*		Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
		008	CLEVERS et al., "Stem cell signaling. An integral program for tissue renewal and regeneration: Wnt signaling and stem cell control," Science (October 2014); 346(6205):1248012, 7 pages.	☐

Examiner Signature	/CHEOM-GIL CHEONG/	Date Considered	06/02/2024

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.C./

Bibliographic Data

Application No: 18/361,782

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☑ No ☐ Met After Allowance

Verified and Acknowledged: /CHEOM-GIL CHEONG/ Examiner's Signature | Initials

Title: WNT SURROGATE MOLECULES AND USES THEREOF

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
07/28/2023	424	1645	SRZN-006/04US 328202-2203
RULE			

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CONTINUING DATA

This application is a CON of 16954484 06/16/2020 PAT 11773171

16954484 is a 371 of PCT/US2018/066616 12/19/2018

PCT/US2018/066616 has PRO of 62680522 06/04/2018

PCT/US2018/066616 has PRO of 62641217 03/09/2018

PCT/US2018/066616 has PRO of 62607875 12/19/2017

FOREIGN APPLICATIONS

IF REQUIRED, FOREIGN LICENSE GRANTED**

09/12/2023

STATE OR COUNTRY

UNITED STATES

ADDRESS

Cooley LLP / Surrozen Operating, Inc.
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1299 Pennsylvania Avenue, NW, Suite 700
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UNITED STATES

FILING FEE RECEIVED

$5,140

Web Search History

date, time	web site	search string
5/31/2024 8:57:33 PM	Google Scholar	bispecific antibody that binds to Frizzled receptor and LRP5 or LRP6
5/31/2024 8:58:10 PM	Google Scholar	bispecific antibody that binds to Frizzled receptor and LRP5 or LRP6 [before:2017]
6/2/2024 6:59:30 PM	Google Scholar	dual variable domain immunoglobulin
6/2/2024 6:59:40 PM	Google Scholar	dual variable domain immunoglobulin benefit over diabody
6/2/2024 7:02:04 PM	Google Scholar	dual variable domain immunoglobulin benefit over diabody [before:2015]
6/6/2024 9:00:24 PM	Google Scholar	bispecific antibody LRP5
6/6/2024 9:00:29 PM	Google Scholar	bispecific antibody LRP6
6/6/2024 9:00:35 PM	Google Scholar	bispecific antibody LRP5/6
6/6/2024 9:00:59 PM	Google Scholar	bispecific antibody Frizzled receptor

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/361,782	07/28/2023	Yang LI	SRZN-006/04US 328202-2203	9001

157070 7590 06/13/2024

Cooley LLP / Surrozen Operating, Inc.
Attn: IP Docketing Department
1299 Pennsylvania Avenue, NW, Suite 700
Washington, DC 20004

EXAMINER	
CHEONG, CHEOM-GIL	

ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
06/13/2024	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

zIPPatentDocketingMailboxUS@cooley.com

Office Action Summary	**Application No.** 18/361,782	**Applicant(s)** LI et al.	
	Examiner CHEOM-GIL CHEONG	**Art Unit** 1645	**AIA (FITF) Status** Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 1/18/2024.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1,14-15,17,55 and 71-73 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1,14-15,17,55 and 71-73 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 1/18/2024 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Claim Status

Claim(s) 2-13, 16, 18-54, and 56-70 were/was canceled.

Claims 1, 14-15, 17, 55 and 71-73 are pending and under consideration.

Claim Objections

Claim(s) 14 is/are objected to because of the following informalities: preamble "The Wnt surrogate of claim 1" should read "The Wnt surrogate **molecule** of claim 1". Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 17 and 55 is/are rejected under 35 U.S.C. 103 as being unpatentable over Garcia et al (US2017/0306029; 8/7/2023 IDS) in view of Wu et al (Nature Biotechnology, vol 25, 1290-1297 (2007); PTO-892).

Regarding claim 1, Garcia teaches that the molecules of the invention are water soluble; bind with high affinity to both (i) frizzled (Fzd) proteins and (ii) Lrp5/6; and directly activate canonical wnt pathway signaling (paragraph 011).

Regarding claim 55, Garcia teaches a pharmaceutical composition as claimed (claim 34).

However, Garcia does not teach dual variable domain (DVD) format of bispecific antibody.

Regarding claim 1 and 17, Wu teaches “Here, we describe a generally applicable model of a dual-specific, tetravalent immunoglobulin G (IgG)-like molecule—termed **dual-variable-domain immunoglobulin (DVD-Ig)**—that can be engineered from any two monoclonal antibodies while preserving activities of the parental antibodies. This molecule can be efficiently produced from mammalian cells and exhibits **good**

physicochemical and pharmacokinetic properties. Preclinical studies of a DVD-Ig protein in an animal disease model demonstrate its potential for therapeutic application in human diseases" (abstract). Wu further teaches "The DVD-Ig protein is an IgG-like molecule that can be efficiently produced by conventional mammalian expression systems as a single species **for easy manufacturing and purification**, while maintaining the affinities and potencies of the two parental mAbs. In addition, it is **highly stable and exhibits excellent, IgG-like physicochemical and pharmacokinetic properties**" (page 1290, right column, first paragraph).

It would have been obvious to one of ordinary skill in the art before the filing date of the claimed invention to have prepared bispecific antibody of Garcia in the format of DVD-Ig taught by Wu because Wu teaches that DVD-Ig format bispecific antibody is highly stable and exhibits excellent, IgG-like physicochemical and pharmacokinetic properties. One of ordinary skill in the art would be motivated to use DVD-Ig format to prepare bispecific antibody because DVD-Ig format provides advantageous properties for therapeutics for human disease. Therefore, the invention as a whole would have been obvious to one of ordinary skill in the art.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success because Wu teaches that DVD-Ig format bispecific antibody is highly stable and exhibits excellent, IgG-like physicochemical and pharmacokinetic properties and because making bispecific antibody in a different format is well known in the art and routine experimentation. Therefore, the invention as a whole would have been *prima facie* obvious to one of

ordinary skill in the art before the effective filing date of the claimed invention, as evidenced by the references, especially in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file

provisions of the AIA as explained in MPEP § 2159. See MPEP § 2146 *et seq.* for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The filing of a terminal disclaimer by itself is not a complete reply to a nonstatutory double patenting (NSDP) rejection. A complete reply requires that the terminal disclaimer be accompanied by a reply requesting reconsideration of the prior Office action. Even where the NSDP rejection is provisional the reply must be complete. See MPEP § 804, subsection I.B.1. For a reply to a non-final Office action, see 37 CFR 1.111(a). For a reply to final Office action, see 37 CFR 1.113(c). A request for reconsideration while not provided for in 37 CFR 1.113(c) may be filed after final for consideration. See MPEP §§ 706.07(e) and 714.13.

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The actual filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/apply/applying-online/eterminal-disclaimer.

Claim 1, 17 and 55 are rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1-10 of U.S. Patent No. 11773171 (hereinafter patent'171; 1/18/2024 IDS). Although the claims at issue are not

identical, they are not patentably distinct from each other because of the following reasons.

Regarding claim 1 and 17, patent'171 claims as follows.

1. A soluble, multivalent, multispecific Wnt surrogate molecule, wherein the Wnt surrogate molecule comprises:

(i) one or more Fzd binding regions that specifically binds to one or more Frizzled (Fzd) receptors, wherein the one or more Fzd binding regions comprise one or more antibody or antigen-binding fragment of the antibody, wherein the one or more antibody or the antigen-binding fragment comprises: a CDRH1 of SEQ ID NO: 307, a CDRH2 of SEQ ID NO: 501, a CDRH3 of SEQ ID NO: 964, a CDRL1 of SEQ ID NO: 1098, a CDRL2 of SEQ ID NO: 1175, and a CDRL3 of SEQ ID NO: 1372; and

(ii) one or more LRP5/6 binding regions that specifically binds to a Low-density lipoprotein (LDL) receptor-related protein 5 (LRP5) and/or a Low-density lipoprotein (LDL) receptor-related protein 6 (LRP6), wherein the one or more LRP5/6 binding regions comprise one or more antibody or antigen-binding fragment of the antibody, wherein the one or more antibody or the antigen-binding fragment comprises: a CDRH1 of SEQ ID NO: 1618, a CDRH2 of SEQ ID NO: 1715, and a CDRH3 of SEQ ID NO: 2012.

2. The Wnt surrogate molecule of claim 1, wherein the Wnt surrogate molecule comprises one or more polypeptides having at least 90% identity to the sequence set forth in SEQ ID NO: 137 and one or more polypeptide having at least 90% identity to the sequence set forth in SEQ ID NO: 153.

3. The Wnt surrogate molecule of claim 1, wherein the Fzd binding region comprises a full immunoglobulin G (IgG), comprising two light chains and two heavy chains, and the LRP5/6 binding region comprises a VHH.

4. The Wnt surrogate molecule of claim 3, wherein each of the one or more LRP5/6 binding regions is fused to the N-terminus of one of the light chains.

5. A pharmaceutical composition comprising a physiologically acceptable excipient, diluent, or carrier, and the Wnt surrogate molecule according to claim 1.

6. The Wnt Surrogate molecule of claim 4, wherein each of the one or more LRP5/6 binding regions is fused to one of the light chains via a linker moiety.

7. The Wnt surrogate molecule of claim 6, wherein the Wnt surrogate molecule comprises:

(i) two Fzd binding regions, wherein each of the Fzd binding regions comprise one or more antibody or antigen-binding fragment thereof, wherein the one or more antibody or the antigen-binding fragment thereof comprises: a CDRH1 of SEQ ID NO: 307, a CDRH2 of SEQ ID NO: 501, a CDRH3 of SEQ ID NO: 964, a CDRL1 of SEQ ID NO: 1098, a CDRL2 of SEQ ID NO: 1175, and a CDRL3 of SEQ ID NO: 1372; and

(ii) two LRP5/6 binding regions, wherein each of the LRP5/6 binding regions comprise one or more antibody or antigen-binding fragment thereof, wherein the one or more antibody or the antigen-binding fragment thereof comprises: a CDRH1 of SEQ ID NO: 1618, a CDRH2 of SEQ ID NO: 1715, and a CDRH3 of SEQ ID NO: 2012.

Regarding claim 55, patent'171 claims as follows.

9. A pharmaceutical composition comprising the physiologically acceptable excipient, diluent, or carrier, and the Wnt surrogate molecule of claim 7.

Claim 1 and 55 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1 and 15-16 of copending Application No. 18/148,448 (hereinafter application'448; US2023/0295347; PTO-

892). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons.

Regarding claim 1, claim 1, 15 and 16(III)(e) of application'448 claims as follows.

1. (Original) A multispecific antibody or antibody fragment comprising at least:

(A) a first antigen-binding region which specifically binds to frizzled class receptor 4 (Fzd4) and comprises a first heavy chain variable domain (VH1) and a first light chain variable domain (VL1),

(B) a second antigen-binding region which specifically binds to low density lipoprotein receptor-related protein 5 and/or 6 (LRP5 and/or LRP6) and comprises at least a second heavy chain variable domain (VH2).

15. (Currently Amended) The multispecific antibody or antibody fragment of ~~any one of claims 1-13~~claim 1, which comprises:

(A) two or more Fzd4-binding regions, wherein at least one of said Fzd4-binding regions is, comprises, or is comprised in said first antigen-binding region; and/or

(B) two or more LRP5 and/or LRP6-binding regions, wherein at least one of said LRP5 and/or LRP6-binding regions is, comprises, or is comprised in said second antigen-binding region.

16. (Original) The multispecific antibody or antibody fragment of claim 15, wherein:

(III) the multispecific antibody or antibody fragment comprises:

(e) two identical Fzd4-binding regions, each of which is, comprises, or is comprised in said first antigen-binding region; and two identical LRP5 and/or LRP6-binding region, each of which is, comprises, or is comprised in said second antigen-binding region;

Regarding claim 55, claim 23 of application'448 claims pharmaceutical composition as claimed.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Claim 1, 17 and 55 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1, 10-12 and 26 of copending Application No. 18/652,070 (hereinafter application'070). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons.

Regarding claim 1 and 17, claim 1 and 10-12 of application'070 claims

1. An isolated antibody, or an antigen-binding fragment thereof, that binds to one or more Frizzled receptor, comprising a sequence comprising:

(i) CDRH1, CDRH2 and CDRH3 sequences set forth for any of the antibodies of Table 1A;

(ii) CDRL1, CDRL2 and CDRL3 sequences set forth for any of the antibodies of Table 1A; and/or

(iii) the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences set forth in Table 2,

10. The isolated antibody, or antigen-binding fragment thereof, of any of claims 1-9, wherein the antibody, or antigen-binding fragment thereof, is a fusion protein.

11. The isolated antibody, or antigen-binding fragment thereof, of claim 10, wherein the antibody, or antigen-binding fragment thereof, is fused to a polypeptide sequence that binds LRP5 or LRP6.

12. The isolated antibody, or antigen-binding fragment thereof, of claim 11, wherein the polypeptide sequence that binds LRP5 or LRP6 is an antibody, or an antigen-binding fragment thereof, that binds to LRP5 or LRP6.

Regarding claim 55, claim 26 of application'070 claims

26. A pharmaceutical composition comprising a physiologically acceptable excipient, diluent, or carrier, and a therapeutically effective amount of the isolated antibody, or antigen-binding fragment thereof, according to any of claims 1-22 or 36.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Claim 1, 14-15, 17, 55 and 71-73 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1, 27, 34, 39 and 46 of copending Application No. 17/257,817 (hereinafter application'817;

US2021/0292422; PTO-892). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons.

Regarding claim 1, claim 1 and 27 of application'817 claims

1. (Original) A multispecific Wnt surrogate molecule, wherein the Wnt surrogate molecule comprises:

(i) a plurality of regions that each specifically bind to a set of one or more Frizzled (Fzd) receptor epitopes (Fzd binding regions), wherein at least two Fzd binding regions bind to different sets of one or more Fzd receptor epitopes, and

(ii) one or more regions that specifically bind to a Low-density lipoprotein (LDL) receptor-related protein 5 (LRP5) and/or a LDL receptor-related protein 6 (LRP6) (LRP5/6 binding regions).

27. (Previously Presented) The Wnt surrogate molecule of claim 1, wherein the Fzd binding regions and the LRP5/6 binding regions are in a ratio of:

c) Fzd binding regions to LRP5/6 binding regions (Fzd:LRP5/6) comprising:

i) 2 Fzd binding regions and 2 LRP5/6 binding regions;

Regarding claim 17, claim 34 of application'817 claims

34. (Original) The Wnt surrogate molecule of claim 33, comprising a first LRP5/6 binding region fused to an N-terminus of the first light chain, a C-terminus of the first light chain, an N-terminus of the first heavy chain, or a C-terminus of the first heavy chain.

Regarding claim 55 and 73, claim 46 of application'817 claims

46. (Previously Presented) A pharmaceutical composition comprising a pharmaceutically acceptable excipient, diluent, or carrier, and the Wnt surrogate molecule according to claim 1.

Regarding claim 14, claim 39 of application'817 claims

39. (Previously Presented) The Wnt surrogate molecule of claim 33, wherein: (i) the first heavy chain and/or the second heavy chain comprise an amino acid sequence having at least 90% identity to any of the sequences set forth in SEQ ID NOs: 110, 112, 114, 116, 118, 120, and 122, and (ii) the first light chain and/or the second light chain comprise an amino acid sequence having at least 90% identity to any of the sequences set forth in SEQ ID NOs: 109, 111, 113, 115, 117, 119, and 121.

SEQ ID NO: 115 of application'817 comprises instant SEQ ID NO: 1617, 1716, and 2065 of anti-LRP5/6 VHH recited by instant claim 14 (result 12 of 1617fus1716fus2065.rapbm).

result 12 of 1617fus1716fus2065.rapbm

```
Qy          1 NINSIETLG-------------ANMRGGGYMKYA-------------------------- 21
              |||||||||              ||||||||||||
Db         49 NINSIETLGWYRQAPGKQRELIANMRGGGYMKYAGSLKGRFTMSTESAKNTMYLQMNSLK 108

Qy         22 --------CYVKLRDDDYVYR 34
                    |||||||||||||
Db        109 PEDTAVYYCYVKLRDDDYVYR 129
```

SEQ ID NO: 115 of application'817 comprises instant SEQ ID NO: 1098, 1175 and 1372 of anti-Fzd VL recited by instant claim 14 (result 290 of 1098fus1175fus1372.rapbm).

result 290 of 1098fus1175fus1372.rapbm

```
Qy          1 RASQSISSYLN---------------AASSLQS--------------------------- 18
              ||||||||||||               |||||||
Db        168 RASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDF 227

Qy         19 ----CQQSYSTPLTF 29
                  ||||||||||||
Db        228 ATYYCQQSYSTPLTF 242
```

SEQ ID NO: 120 of application'817 comprises instant SEQ ID NO: 248, 600 and 757 of anti-Fzd VH recited by instant claim 14 (result 8 of 248fus600fus757.rapbm).

result 8 of 248fus600fus757.rapbm

```
Qy          1 FTFTNYAMS-------------SAISGSGGSTYYA------------------------ 22
              |||||||||             ||||||||||||
Db         49 FTFTNYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDDSKNTLYLQMNSL 108

Qy         23 ---------CARATGFGTVVFDYW 37
                      ||||||||||||||
Db        109 KTEDTAVYYCARATGFGTVVFDYW 132
```

Regarding claims 15 and 71-72, claim 39 of application'817 claims SEQ ID NO: 115 which is 98.9% identical to instant SEQ ID NO: 144 (result 5 of 144.rapbm). Claim 39 of application'817 claims SEQ ID NO: 120 and 122 which is 99.3% and 95.2% identical to instant SEQ ID NO: 155, respectively (result 2 and result 7 of 155.rapbm, respectively).

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Claim 1, 17 and 55 are rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1-10 of U.S. Patent No. 11746150 (hereinafter patent'150; IDS). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons.

Regarding claim 1 and 17, claim 1 and 5-6 of patent'150 claims

1. An isolated antibody, or an antigen-binding fragment thereof, that binds to one or more LRP5 or LRP6 receptor, comprising a sequence comprising:

a CDRH1 sequence of SEQ ID NO:107, a CDRH2 sequence of SEQ ID NO:203 and a CDRH3 sequence of SEQ ID NO:452 or any one of SEQ ID NOs: 609-618.

5. The isolated antibody, or antigen-binding fragment thereof, of claim 1, wherein the antibody, or antigen-binding fragment thereof, comprises a fusion protein.

6. The isolated antibody, or antigen-binding fragment thereof, of claim 5, wherein the antibody, or antigen-binding fragment thereof, is fused to a polypeptide sequence that binds one or more Frizzled (Fzd) receptors.

Although patent'150 does not expressly claim two binding domains each for Fzd and LRP5/6 binding domains, it is well known in the art that monoclonal antibody or full length antibody comprises two binding domains for same antigen.

Regarding claim 55, claim 10 of patent'150 claims

10. A pharmaceutical composition comprising a physiologically acceptable excipient, diluent, or carrier, and a therapeutically effective amount of the isolated antibody, or antigen-binding fragment thereof, according to claim 1.

Claim 1, 17 and 55 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1, 6-7 and 23 of copending Application No. 17/623,006 (hereinafter application'006; US2022/0275095; 8/7/2023 IDS). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons.

Regarding claim 1 and 17, claim 1 and 6-7 of application'006 claims

1. (Original) An isolated antibody, or an antigen-binding fragment thereof, that binds to one or more Frizzled receptor, comprising a sequence comprising:

(i) CDRH1, CDRH2 and CDRH3 sequences set forth for any of the antibodies of Table 2; and

(ii) CDRL1, CDRL2 and CDRL3 sequences set forth for any of the antibodies of Table 2, or a variant of said antibody, or antigen-binding fragment thereof, comprising one or more amino acid modifications, wherein said variant comprises less than 8 amino acid substitutions in said CDR sequences.

6. (Currently Amended) The isolated antibody, or antigen-binding fragment thereof, of claims 1-5, wherein the antibody, or antigen-binding fragment thereof, is a fusion protein.

7. (Original) The isolated antibody, or antigen-binding fragment thereof, of claim 6, wherein the antibody, or antigen-binding fragment thereof, is fused to a polypeptide sequence that binds LRP5 or LRP6.

Although application'006 does not expressly claim two binding domains each for Fzd and LRP5/6 binding domains, it is well known in the art that monoclonal antibody or full length antibody comprises two binding domains for same antigen.

Regarding claim 55, claim 23 of application'006 claims

23. (Currently Amended) A pharmaceutical composition comprising a physiologically acceptable excipient, diluent, or carrier, and a therapeutically effective amount of the isolated antibody, or antigen-binding fragment thereof, according to ~~any of~~ claims ~~1-19 or 29~~.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Claim 1, 17 and 55 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1, 3-4, 9-10, 20 and 43 of copending Application No. 17/801,624 (hereinafter application'624; US2023/0138045; 8/7/2023 IDS). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons.

Regarding claim 1 and 17, claim 1, 3, 4, 9-10 and 43 of application'624 claims

1. (Currently Amended) A WNT super agonist molecule, comprising:

a) a Frizzled (FZD) binding domain that binds one or more FZD receptor;

b) an LRP5/6 binding domain that binds one or more of LRP5 and/or LRP6; and

c) an E3 ligase binding domain that binds Zinc and Ring Finger 3 (ZNRF3) and/or Ring Finger Protein 43 (RNF43),

wherein the super agonist molecule activates the canonical WNT signaling pathway in a cell.

3. (Currently Amended) The super agonist molecule of claim 1 ~~or claim 2~~, comprising one or more polypeptides, wherein at least one polypeptide comprises a FZD binding domain fused to an LRP5/6 binding domain, and wherein at least one polypeptide comprises an E3 ligase binding domain fused to a FZD binding domain or an LRP5/6 binding domain.

4. (Original) The super agonist molecule of claim 3, wherein the fused binding domains are fused directly together and/or fused via a peptide linker.

43. (Currently Amended) A WNT surrogate comprising:

a) a Frizzled (FZD) binding domain; and

b) an LRP5/6 binding domain,

wherein the WNT surrogate~~super agonist~~ molecule activates the canonical WNT signaling pathway in a cell.

Regarding structure of instant claim 1, claim 9-10 of application'624 claims

9. (Currently Amended) The super agonist of ~~any one of~~ claim[[s]] 1[[-8]], wherein at least one of the binding domains is fused to an Fc fragment, ~~optionally~~ wherein the Fc fragment is from an IgG, IgM, IgA, IgD or IgE antibody isotype or an α, δ, ε, γ, or μ antibody heavy chain.

10. (Original) The super agonist molecule of claim 9, having a structure depicted in Table 3 or Table 4.

Table 3 of application'624 disclosed Fv-IgG and Fab-IgG structure (page 76-77). IgG antibody comprises **two** binding domains against same antigen in Y-shaped structure. Therefore, super agonist claimed by claim 10 of application'624 has two Fzd binding domains and two LRP5/6 binding domains as claimed by instant claim 1.

Regarding claim 55, claim 20 of application'624 claims

20. (Currently Amended) A pharmaceutical composition comprising the WNT super agonist molecule according to ~~any of~~ claim[[s]] 1[[-19]] and a pharmaceutically acceptable diluent, excipient, or carrier.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Claim 1, 17 and 55 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1-3 and 6 of copending Application No. 18/281,253 (hereinafter application'253; US2024/0150473; PTO-892). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons.

Regarding claim 1 and 17, claim 1-3 of application'253 claims

1. (Currently Amended) An engineered WNT agonist comprising:
(a) one or more binding domains that bind to one or more FZD, and
(b) one or more binding domains that bind to LRP5, LRP6, or both LRP5 and LRP6,
wherein the engineered WNT agonist comprises a polypeptide comprising a sequence having at least 90%, at least 95%, at least 98%, or at least 99% sequence identity to ~~any of~~ SEQ ID NOs:~~1-259~~ and a polypeptide comprising a sequence having at least 90%, at least 95%, at least 98%, or at least 99% sequence identity to SEQ ID NO:10, ~~or a polypeptide sequence~~

2. (Currently Amended) The engineered WNT agonist of claim 1, comprising:

(a) ~~a~~ two polypeptides comprising a sequence having at least 90%, at least 95%, at least 98%, or at least 99% sequence identity to ~~any one of~~ SEQ ID NOs: ~~9-25 or a sequence disclosed in Table 3~~; or

(b) ~~a~~ two polypeptides comprising a sequence having at least 90%, at least 95%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 10~~comprising two or three of the CDR~~

As evidenced by page 92 of specification of application'253, SEQ ID NO: 9 and 10 claimed by claims 1-3 of application'253 have same structure recited by instant claim 1 and 17.

Regarding claim 55, claim 6 of application'253 claims

6. (Currently Amended) A pharmaceutical composition comprising the engineered WNT agonist of ~~any one of~~ claims ~~1-5~~ and a pharmaceutically acceptable carrier, diluent, or excipient.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHEOM-GIL CHEONG whose telephone number is (571)272-6251. The examiner can normally be reached Monday - Friday 9:00 am - 5:00 pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/CHEOM-GIL CHEONG/
Examiner, Art Unit 1645

/Meera Natarajan/
Primary Examiner, Art Unit 1643

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 18/361,782	Filing Date 07/28/2023	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $480 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	10/11/2024	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 8	Minus	** 20	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $480 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/YOLANDA CHADWICK/
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The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

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APPLICATION #	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET #
18361782	07/28/2023	Yang LI	SRZN-006/04US 328202-2203

Title of Invention

WNT SURROGATE MOLECULES AND USES THEREOF

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✓	This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

Owner	Percent interest
Surrozen Operating, Inc.	100%
Total	**100%**

The owner(s) of percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number(s)

Application #	Filing Date
18652070	05/01/2024

17801624	08/23/2022
17257817	01/04/2021
17623006	12/27/2021

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Patent #
11773171
11746150

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I hereby declare that all statements made herein of my own knowledge are true and that all statemnts made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I certify, in accordance with 37 CFR 1.4(d)(4) that I am: An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application

Signature	Name	Registration #
/Carol D. Laherty/	Carol Laherty	51909

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* Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner). Form PTO/SB/96 may be used for making this certification. See MPEP 324.

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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/361,782	**10/11/2024 05:52:38 PM Z ET**	**SRZN-006/04US 328202-2203**

Title of Invention

WNT SURROGATE MOLECULES AND USES THEREOF

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	9001	FILED BY	Susan Clingerman
PATENT CENTER #	67534990	AUTHORIZED BY	Carol Laherty
CUSTOMER #	157070	FILING DATE	07/28/2023
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Yang LI

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 501283	**E20240AH55556805**	**Carol Laherty**

PRE-AUTHORIZED ACCOUNT	PRE-AUTHORIZED CATEGORY
501283	**37 CFR 1.16 (National application filing, search, and examination fees); 37 CFR 1.17 (Patent application and reexamination processing fees); 37 CFR 1.19 (Document supply fees); 37 CFR 1.20 (Post Issuance fees); 37 CFR 1.21 (Miscellaneous fees and charges)**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
1814	STATUTORY DISCLAIMER, INCLUDING TERMINAL DISCLAIMER	170.00	1	170.00
			TOTAL AMOUNT:	**$170.00**

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPROVAL LETTER

APPLICATION #	FILING DATE	APPLICANT/PATENT UNDER REEXAMINATION
18/361,782	07/28/2023	Yang LI

Title of Invention

WNT SURROGATE MOLECULES AND USES THEREOF

Electronic terminal disclaimer filed on 10/11/2024

☑ Approved

This patent is subject to a Terminal Disclaimer

Approved / Disapproved by: Electronic Terminal Disclaimer automatically approved

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/361,782	**10/11/2024 05:52:38 PM Z ET**	**SRZN-006/04US 328202-2203**

Title of Invention

WNT SURROGATE MOLECULES AND USES THEREOF

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	9001	FILED BY	Susan Clingerman
PATENT CENTER #	67534990	FILING DATE	07/28/2023
CUSTOMER #	157070	FIRST NAMED INVENTOR	Yang LI
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Carol Laherty

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
petition-request.pdf	3	Terminal Disclaimer-Filed (Electronic)	47 KB
grantLetter.pdf	1	Terminal Disclaimer-Electronic-Approved	18 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
petition-request.pdf	72706E0BD6FE94A5B4B99ABE1AF7855E0CFC874872ED21D8 3A34C8AE857EC5D9F9D87F53B382FD3C1BA2862DB1CBF340 0E6D42E81EAF666DD49AC94C8B6F2F56
grantLetter.pdf	5D499111221A2A0B602F3EB4848678A194B5D7A9AD75786E14

875AFCE3D167181194F30E8214CB44C00301EDE944E7D6BFD
2705762632B07F5E1AFEAF3056DE6

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ELECTRONIC PAYMENT RECEIPT

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Title of Invention

WNT SURROGATE MOLECULES AND USES THEREOF

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	9001	FILED BY	MaxVal Group
PATENT CENTER #	67499875	AUTHORIZED BY	Ashley Sherrid
CUSTOMER #	157070	FILING DATE	07/28/2023
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Yang LI

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1806	SUBMISSION OF AN INFORMATION DISCLOSURE STATEMENT	260.00	1	260.00
			TOTAL AMOUNT:	**$260.00**

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New Applications Under 35 U.S.C. 111

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Docket No.: SRZN-006/04US 328202-2203
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor:	Yang LI	Confirmation No.:	9001
Application No.:	18/361,782	Group Art Unit:	1645
Filed:	July 28, 2023	Examiner:	CHEOM-GIL CHEONG

For: WNT SURROGATE MOLECULES AND USES THEREOF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

In accordance with the duty of disclosure set forth in 37 CFR § 1.56, Applicant hereby submits the following information in compliance with 37 CFR §§ 1.97 and 1.98. It is respectfully requested that the information be expressly considered during the prosecution of this Application, and the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

In accordance with **37 CFR § 1.97(c)**, this Information Disclosure Statement is filed after the period specified in 37 CFR § 1.97(b), but before the mailing of any of the following: a final action under 37 CFR § 1.113; a notice of allowance under 37 CFR § 1.311; or action that otherwise closes prosecution in this Application.

This Information Disclosure Statement is accompanied by the fee set forth under 37 CFR § 1.17(p) in the amount of $260.00, in accordance with 37 CFR § 1.97(c).

In agreement with 37 CFR § 1.97(g), this Information Disclosure Statement shall not be construed as a representation that a search has been made.

In agreement with 37 CFR § 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that the information cited in the statement is, or is

considered to be, relevant, analogous, or material to patentability as defined by 37 CFR § 1.56(b).

As required by **37 CFR § 1.98(a)(2)**, Applicant submits a copy of any Foreign Patent and Non-Patent Literature information cited on the attached Form used in lieu of PTO/SB/08.

As authorized by 37 CFR § 1.98(a)(2)(ii), Applicant does not submit a copy of any U.S. Publication or Patent information cited on the attached Form used in lieu of PTO/SB/08.

As authorized by the Waiver of the Copy Requirement set forth in 37 CFR § 1.98(a) for Cited Pending U.S. Patent Applications, issued October 19, 2004, Applicant does not submit a copy of any pending unpublished U.S. Patent Application cited on the attached Form used in lieu of PTO/SB/08, because a copy is stored in the USPTO's Image File Wrapper system and can be readily viewed by Examiners and the Applicant.

REMARKS

It is respectfully requested that the Examiner consider the above-noted information and return an initialed copy of the attached Form used in lieu of PTO/SB/08 to the undersigned.

The Examiner is encouraged to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present Application.

The Director is hereby authorized to charge any appropriate fees set forth in 37 CFR § 1.17(p) that may be required by this Information Disclosure Statement, and to credit any overpayment, to Deposit Account No. 50-1283, referencing Docket No. SRZN-006/04US 328202-2203.

Dated: October 9, 2024

Respectfully submitted,
COOLEY LLP

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(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *with international search report (Art. 21(3))*

— *with sequence listing part of description (Rule 5.2(a))*

WO 2017/093478 A1

(54) **Title**: BIPARATOPIC POLYPEPTIDES ANTAGONIZING WNT SIGNALING IN TUMOR CELLS

(57) **Abstract**: The invention provides novel biparatopic LRP5/LRP6 cross-reactive binding polypeptides, and more specifically novel biparatopic LRP5/LRP6 cross-reactive immunoglobulin single variable domain constructs which can inhibit Wnt signaling pathways. The invention also relates to specific sequences of such polypeptides, methods of their production, and methods of using them, including methods of treatment of diseases such as cancer.

BIPARATOPIC POLYPEPTIDES ANTAGONIZING WNT SIGNALING IN TUMOR CELLS

FIELD OF THE INVENTION

The present invention relates to novel low-density lipoprotein receptor-like protein 5 (LRP5) and low-density lipoprotein receptor-like protein 6 (LRP6) binding polypeptides. The invention also relates to nucleic acids encoding such polypeptides; to methods for preparing such polypeptides; to host cells expressing or capable of expressing such polypeptides; to compositions comprising such polypeptides; and to uses of such polypeptides or such compositions, in particular for therapeutic purposes in the field of cancer diseases.

BACKGROUND OF THE INVENTION

Activation of the Wnt signaling pathway requires binding of extracellular Wnt ligands to the Frizzled receptor and to the co-receptor LRP5 (Accession number: UniProtKB -O75197 / LRP5_HUMAN) or its closely related homologue LRP6 (Accession number: UniProtKB - O75581 / LRP6_HUMAN). There are 19 Wnt proteins and 10 Frizzled receptors in mammalian cells. In the absence of Wnt ligand, cytoplasmic beta-catenin is phosphorylated by a protein complex consisting of the scaffolding proteins Axin and APC and the kinases GSK3beta and CK1a. Subsequent recognition by the ubiquitin ligase beta-TrcP leads to ubiquitin-mediated degradation of beta-catenin. In the presence of Wnt ligand, binding of Wnt to Frizzled and LRP5 or LRP6 leads to recruitment of the cytoplasmic effector protein Dvl and phosphorylation of the LRP5 or LRP6 cytoplasmic tail, which provides the docking site for Axin. Axin sequestration by LRP5 or LRP6 leads to the inactivation of the Axin-APC-GSK3beta complex and, therefore, intracellular beta-catenin stabilization and accumulation. Hence,

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cytoplasmic levels of beta-catenin rise, and beta-catenin migrates to the nucleus and complexes with members of the T-cell factor (TCF)/Lymphoid enhancer-binding factor (LEF) family of transcription factors. Basal transcription machinery and transcriptional co-activators are then recruited, including cAMP response element-binding protein (CREB)–binding protein (CBP) or its homolog p300, leading to expression of various target genes, including Axin2, cyclin D1 and c-Myc.

An additional level of ligand-dependent Wnt pathway regulation is mediated by the E3 ligase RNF43, and its closely related homologue ZNRF3, and by the secreted R-Spondin proteins (de Lau *et al*. "The R-spondin/Lgr5/Rnf43 module: regulator of Wnt signal strength". *Genes Dev*. 2014; 28(4):305-16). RNF43 mediates the ubiquitination of the Frizzled/LRP5 or LRP6 receptor complex at the cell surface, leading to its degradation and, thereby, inhibiting ligand-dependent Wnt pathway activity. The activity of RNF43 is counteracted by the R spondin family members (R-spondin 1 to 4 ligands). When R-Spondin ligand is present, it removes RNF43 from the cell surface, allowing Frizzled/LRP5 or LRP6 complex accumulation and enhancement of Wnt signaling in the presence of Wnt ligands.

LRP5 and LRP6 function as gatekeepers of ligand dependent Wnt signaling activation and, therefore, may be considered as targets to achieve complete blockade of the pathway mediated by all 19 Wnt ligands and 10 Frizzled receptors and enhanced by R-spondin ligands. In particular, Wnt ligands can be divided into a Wnt1 class and a Wnt3a class, each binding to different epitopes/regions of LRP5 and LRP6 for signaling. The ectodomain of LRP5 and LRP6 comprises four repeating units of a beta-propeller connected to an EGF-like domain, followed by three LDLR-type A repeats. Combined structural and functional analyses of LRP5 and LRP6 suggest that Wnt1 (Wnt1-class ligand) binds to a fragment containing beta-propeller 1 and 2 and Wnt3a binds to a fragment containing beta-propeller 3 and 4 of LRP6. So far, only a low-resolution picture of LRP6 ectodomain containing beta-propeller from 1 to 4 regions is

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reported (Ahn *et al.*" Structural basis of Wnt signaling inhibition by Dickkopf binding to LRP5/6". *Dev Cell*. 2011; 21(5):862-73). However, the uncertainties of these low-resolution reconstructions (40 A°) and the absence of structural data of the LRP6 ectodomain in complex with the Wnt ligands do not allow defining the exact epitopes involved in Wnt1 or Wnt3a ligand binding.

Hyperactivation of Wnt signaling is involved in the pathogenesis of various types of cancer. In some cancer types frequent mutations in downstream signaling molecules contribute to constitutively activated Wnt pathway (e.g. APC mutations in colorectal cancer; beta-catenin activating mutation in hepatocellular carcinoma). In contrast, in Triple Negative Breast Cancer (TNBC), Non Small Cell Lung Cancer (NSCLC), pancreatic adenocarcinoma and in a subset of Colo-Rectal Cancer (CRC) and endometrial cancers, Wnt signaling activation is driven by a ligand dependent mechanism (i.e. by an autocrine/paracrine Wnt activation), as detected by beta-catenin intracellular accumulation. In NSCLC, TNBC and pancreatic adenocarcinoma, ligand dependent Wnt activation is mediated by multiple mechanisms, including increased expression of the Wnt ligands and/or of LRP5 and LRP6 receptors, or silencing of LRP5 and LRP6 negative regulator DKK1 (TNBC: Liu *et al*." LRP6 overexpression defines a class of breast cancer subtype and is a target for therapy". *Proc Natl Acad Sci U S A* 2010; 107 (11):5136-41; Khramtsov *et al*. "Wnt/beta-catenin pathway activation is enriched in basal-like breast cancers and predicts poor outcome". *Am J Pathol*. 2010; 176(6): 2911-20; NSCLC: Nakashima *et al.* "Wnt1 overexpression associated with tumor proliferation and a poor prognosis in non-small cell lung cancer patients". *Oncol Rep*. 2008; 19(1):203-9; Pancreatic cancer: Zhang *et al*. "Canonical wnt signaling is required for pancreatic carcinogenesis". *Cancer Res*. 2013; 73(15):4909-22). In particular, published data have shown that in healthy tissues (e.g. mammary and lung epithelium), beta-catenin is localized solely at the plasma membrane. In contrast, the majority of TNBC, NSCLC and pancreatic adenocarcinoma primary clinical samples showed beta-catenin intracellular accumulation (i.e. in the cytoplasm/ nucleus; biomarker of Wnt signaling

activation), due to aberrant Wnt signaling. Recent publications have shown that ligand dependent Wnt signaling activation is mediated by mutated/inactivated RNF43 (Giannakis *et al.* "RNF43 is frequently mutated in colorectal and endometrial cancers". *Nat Genet*. 2014; 46(12):1264-6) or by activating R-Spondin fusion transcripts (encoding R-spondin2 or R-spondin3 proteins driven by constitutively active strong promoters; Seshagiri *et al*. "Recurrent R-spondin fusions in colon cancer". *Nature* 2012; 488(7413):660-4) in a subset of CRC and endometrial cancers. Inactivating RNF43 mutations and R-Spondin fusion transcripts have both been shown to augment ligand dependent Wnt signaling *in vitro* by increasing the abundance of Frizzled on the cell surface. Ligand dependent Wnt activation in tumors was shown to drive tumor growth and resistance to chemotherapy or immunotherapy, and is linked to recurrence in pre-clinical models.

Some LRP5 or LRP6 binding molecules, able to modulate the Wnt signaling pathway, are known in the art:

Dickkopf-1 (DKK1) is a LRP5 and LRP6 inhibitor. DKK1 associates with both the Wnt co-receptors, LRP5 and 6, and the transmembrane protein, Kremen, inhibits Wnt signaling and leads to rapid LRP5 and LRP6 internalization. It is shown that DKK1 inhibits both Wnt1 and Wnt3a mediated signaling. Structural modeling studies show that a single DKK1 molecule cooperatively binds to an extended region of the LRP6 ectodomain (from beta-propeller 1 to 3). The structural analyses suggest a DKK1 cooperative binding-interaction with LRP6 with an initial binding to the beta-propeller 3 region that facilitates the interaction/binding to the beta-propeller 1 and 2 region via a conformation change of the LRP6 ectodomain. However, elucidation of the defined epitopes within the beta-propeller 1, 2 and 3 domains involved in the DKK1 binding to LRP6 is lacking due to the low resolution of the structural reconstructions of the full LRP6 ectodomain bound to DKK1, as mentioned.

It was shown that DKK1 treatment *in vivo* causes severe toxicity in the gastrointestinal tract. In particular, it was shown that adenovirus mediated expression of DKK1 in adult mice markedly inhibited proliferation in small intestine and colon, accompanied by progressive architectural degeneration,severe body weight loss and mortality from colitis and systemic infection. In particular, LRP5 and LRP6 are expressed in the intestine in the proliferative epithelial cells and are required for proliferation of the intestinal epithelium, suggesting that LRP5 and LRP6 inhibition may be toxic for this and other normal tissues (Zhong *et al*. "Lrp5 and Lrp6 play compensatory roles in mouse intestinal development". *J Cell Biochem*. 2012; 113(1):31-8). This makes it doubtful whether agents which inhibit LRP5 and LRP6, or which inhibit the Wnt (Wnt1 and Wnt3a) signaling pathway in general, can be used for therapeutic purposes, e.g. can be developed as anti-cancer drugs.

WO2009/056634 refers to LRP6 binding molecules that may either interact with the Wnt1 signaling pathway or with the Wnt3/3a signaling pathway, which may be antagonistic or agonistic, and which may be used for diagnostic purposes or to treat "Wnt signaling-related disorders", such as osteoarthritis, polycystic kidney disease, or cancer. No specific examples for such binding molecules, defined by their amino acid sequence, are provided in this document.

WO2011/138391 and WO2011/138392 are disclosing multivalent LRP6 binding antibodies. WO2011/138391 is claiming antibodies which are blocking one Wnt signaling pathway (Wnt1 or Wnt3) without potentiating the other pathway (Wnt3 or Wnt1, respectively). WO2011/138392 i.a. provides antibodies or antibody fragments which potentiate Wnt signaling by LRP6 receptor clustering.

WO2011/138391 explains that for achieving the desired effect, LRP6 binding molecules need to be formatted into full length IgG antibodies. Examples of LRP6 biparatopic molecules are provided which include an IgG molecule, having a first binding specificity, coupled to a single chain Fv portion, having the second

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binding specificity. Some formats are described as having significantly reduced thermal stability (Tm of 50 to 52°C). An Fc portion may impart effector functions on an IgG molecule, such as complement-dependent cytotoxicity (CDC) or antibody-dependent cellular toxicity (ADCC).

WO2013/067355 discloses half-life extended biparatopic LRP6 binding scFv immunoglobulin constructs, derived from IgG molecules disclosed in WO2011/138391.

WO2011/119661 discloses antibodies that bind to LRP6 and inhibit the signaling induced by a first Wnt isoform, esp. by Wnt3 or Wnt3a, but potentiate signaling induced by a second Wnt isoform, which may be a Wnt1, 2, 2b, 4, 6, 7a, 7b, 8a, 9a, 9b, 10a or 10b isoform. Bispecific molecules are disclosed which bind to the E1-E2 region of LRP6 as well as to the E3-E4 region of LRP6. The knob-in-hole technique was used to generate bispecific antibodies.

Identification of the binding epitopes (defined amino acid residues within the LRP6 ectodomain / beta-propeller regions) involved in the binding of the LRP6 antibodies is not provided in WO2009/056634, nor in WO2011/138391 or WO2013/067355, and only partially in WO2011/119661. In particular, LRP6 binding antibodies can inhibit Wnt signaling via alternative mechanisms according to binding to different regions of LRP6, including competing with Wnts directly or inhibiting formation of ternary receptor complexes (Wnt-LRP6-Frizzled), whereas others enhance signaling, possibly by receptor clustering (Ahn *et al*." Structural basis of Wnt signaling inhibition by Dickkopf binding to LRP5/6". *Dev Cell*. 2011; 21(5):862-73).

However, none of the binding molecules described in the art has so far been authorized by health authorities for the use as a medicament to treat any disease. Specifically, such use requires very specific binding properties, the right specificity, so that such molecules does or does not bind, activate or inhibit other

targets (e.g. resulting in undesired activation or inhibition of other signaling pathways, or lack of activation or inhibition with respect to target isoforms), in the case of bi- or multispecific agents the right balance between the two or more binding specificities, suitable pharmacokinetic and –dynamic properties, an acceptable toxicological profile, and of course *in vivo* efficacy.

In view of the above, there is a need for novel therapeutic agents that allow an efficient treatment of several types of cancer diseases and tumors. It is thus an object of the invention to provide such pharmacologically active agents that can be used in the treatment of several cancer diseases, including NSCLC and TNBC.

In particular, it is an object of the invention to provide such pharmacologically active agents, compositions and/or methods of treatment that provide certain advantages compared to the agents, compositions and/or methods currently used and/or known in the art. These advantages include *in vivo* efficacy, improved therapeutic and pharmacological properties, less side effects, and other advantageous properties such as improved ease of preparation or reduced costs of goods, especially as compared to candidate drugs already known in the art.

BRIEF SUMMARY OF THE INVENTION

According to a first aspect of the invention, the present invention provides polypeptides which specifically bind to LRP5 or LRP6, wherein such polypeptide of the invention comprises a first immunoglobulin single variable domain (a) selected from the group of immunoglobulin single variable domains (i) to (iii) defined by having the following CDR sequences:

(i):

CDR1: TYTVG (= SEQ ID NO:1)

CDR2: AIRRRGSSTYYADSVKG (= SEQ ID NO:2)

CDR3: DTRTVALLQYRYDY (= SEQ ID NO:3)

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(ii):
CDR1: SYAMG (= SEQ ID NO:4)
CDR2: AIRRSGRRTYYADSVKG (= SEQ ID NO:5)
CDR3: ARRVRSSTRYNTGTWWWEY (= SEQ ID NO:6)
(iii):
CDR1: RYTMG (= SEQ ID NO:7)
CDR2: AIVRSGGSTYYADSVKG (= SEQ ID NO:8)
CDR3: DRRGRGENYILLYSSGRYEY (= SEQ ID NO:9),

and a second immunoglobulin single variable domain (b) selected from the group of immunoglobulin single variable domains (iv) and (v) defined by having the following CDR sequences:

(iv):
CDR1: SYAMG (= SEQ ID NO:10)
CDR2: AISWSGGSTYYADSVKG (= SEQ ID NO:11)
CDR3: SPIPYGSLLRRRNNYDY (= SEQ ID NO:12)
(v):
CDR1: SYAMG (= SEQ ID NO:13)
CDR2: AISWRSGSTYYADSVKG (= SEQ ID NO:14)
CDR3: DPRGYGVAYVSAYYEY (= SEQ ID NO:15).

The terms “first” and “second” with respect to such immunoglobulin single variable domains is solely intended to indicate that these domains are two different domains (as they will at least include different CDR sequences). Thus, these terms shall not be understood to refer to the exact order or sequence of the domains within such polypeptide chain.

The polypeptides of the invention optionally comprise a third immunoglobulin single variable domain, such as especially an albumin binding immunoglobulin single variable domain, such as the Alb11 domain, comprising the following CDRs:

CDR1(Alb11): SFGMS (= SEQ ID NO:16)
CDR2(Alb11): SISGSGSDTLYADSVKG (= SEQ ID NO:17)

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CDR3(Alb11): GGSLSR (= SEQ ID NO:18).

According to a more specific embodiment, the polypeptides of the invention include immunoglobulin single variable domains which are VHH domains, and preferably humanized VHH domains.

According to an even more specific embodiment, the polypeptides of the invention include a first immunoglobulin single variable domain (a) selected from the group of immunoglobulin single variable domains (i) to (iii) having the following sequences:

(i):

AVQLVESGGGLVQPGGSLRLSCAASGRTFSTYTVGWFRQAPGKEREF
VAAIRRRGSSTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVYY
CAADTRTVALLQYRYDYWGQGTLVTVSS
(= SEQ ID NO:19)

(ii):

AVQLVESGGGLVQPGGSLRLSCAASGGTFSSYAMGWFRQAPGKERE
FVAAIRRSGRRTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVYY
CAAARRVRSSTRYNTGTWWWEYWGQGTLVTVSS
(= SEQ ID NO:20)

(iii):

AVQLVESGGGLVQPGGSLRLSCAASGLTFSRYTMGWFRQAPGKEREF
VAAIVRSGGSTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVYY
CAADRRGRGENYILLYSSGRYEYWGQGTLVTVSS
(= SEQ ID NO:21),

and a second immunoglobulin single variable domain (b) selected from the group consisting of immunoglobulin single variable domains (iv) and (v) having the following sequences:

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(iv):

EVQLVESGGGLVQPGGSLRLSCAASGRTFSSYAMGWFRQAPGKERE
FVAAISWSGGSTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVY
YCAASPIPYGSLLRRRNNYDYWGQGTLVTVSS
(= SEQ ID NO:22), and

(v):

EVQLVESGGGLVQPGGSLRLSCAASGGTFSSYAMGWFRQAPGKERE
FVAAISWRSGSTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVY
YCAADPRGYGVAYVSAYYEYWGQGTLVTVSS
(= SEQ ID NO:23).

According to a specifically preferred embodiment, the polypeptides of the invention additionally include a half-life extending moiety, wherein said half-life extending moiety is covalently linked to said polypeptide and is optionally selected from the group consisting of an albumin binding moiety, such as an albumin binding peptide or an albumin binding immunoglobulin domain, preferably an albumin binding immunoglobulin single variable domain, more preferably the Alb11 domain, a transferrin binding moiety, such as an anti-transferrin immunoglobulin domain, a polyethylene glycol molecule, human serum albumin, and a fragment of human serum albumin.

Specifically preferred are polypeptides which include, in addition to the two immunoglobulin single variable domains (a) and (b) as outlined above, an Alb11 domain having the following sequence:

EVQLVESGGGLVQPGNSLRLSCAASGFTFSSFGMSWVRQAPGKGLEW
VSSISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLRPEDTAVYYCTI
GGSLSRSSQGTLVTVSS
(= SEQ ID NO:24)

According to a further embodiment, the invention specifically includes polypeptides comprising or consisting of any of the following three polypeptide chains:
F13500575, having the sequence SEQ ID NO:25,
F13500571, having the sequence SEQ ID NO:26, and
F13500720, having the sequence SEQ ID NO:27.

According to further aspects, the invention relates to nucleic acid molecules, expression vectors, host cells, and methods of manufacturing used in the production of a polypeptide of the invention. Nucleic acid molecules encoding the polypeptides of the invention can be used, in an isolated form, for constructing respective expression vectors, which then may be transfected into host cells used for biopharmaceutical production of the polypeptides of the invention. Such method of manufacturing typically comprises the steps of culturing the host cell under conditions that allow expression of the polypeptide, recovering the polypeptide and purifying it according to methods known in the art.

Further aspects, embodiments, uses and methods involving the polypeptides of the invention will become clear from the following detailed description of the invention and from the appended claims.

The invention provides for novel molecules that allow a more efficient treatment of several cancer types, such as TNBC, CRC, and NSCLC, with less side effects. The polypeptides of the invention provide for a surprising therapeutic effect (i.e. efficacy) in the treatment of cancer patients, in that they may induce tumor regression resulting in pathological complete response (pCR). This, in turn, is expected to result in significant improvement of progression free survival and overall survival, especially in high unmet medical need indications such as e.g. in breast cancer. Thus, the polypeptides of the invention provide for novel therapeutic options in the treatment of several cancer types, esp. those showing a deregulated Wnt signaling pathway and beta-catenin accumulation.

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Furthermore, the polypeptides of the invention are easy to manufacture, have a high stability and low antigenicity, and offer a variety of options regarding administration routes, in addition to injection and infusion.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a schematic representation of biparatopic polypeptides antagonizing Wnt1 and Wnt3a signaling. They consist of three domains, with two domains binding to distinct epitopes of LRP5 and LRP6 (Wnt1 and Wnt3a blocker) and one domain for half-life extension (human serum albumin binder).

Figure 2 shows the lack of correlation between binding FACS and ELISA assays for a representative number of LRP6 binding VHHs derived from the llama immunization. The number "1" panel of VHHs is characterized by high affinity to cells expressing LRP6 on the plasma membrane, as detected by FACS binding assays (on the y axis MCF values are reported). The number "2" panel of VHHs is characterized by high affinity to recombinant human LRP6 ectodomain (rhLRP6-Fc), as detected by ELISA binding assays (on the x axis OD405 values are reported).

Figure 3 shows the binding of three half-life extended biparatopic LRP5/LRP6 cross-reactive VHH constructs to human LRP5 (Figure 3A) and human LRP6 (Figure 3B) overexpressing HEK293 cell lines when compared to the negative control consisting of a non-targeting binder (VHH construct that binds to a bacterial protein which is not expressed in HEK293 cells).

Figure 4 shows complete DKK1 competition of three half-life extended biparatopic LRP5/LRP6 cross-reactive VHH constructs for binding to both human LRP5 (Figure 4A) and human LRP6 (Figure 4B) overexpressing HEK293 cell lines, as detected by a FACS-based DKK1 competition assay.

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Figure 5 shows complete inhibition of Wnt1 and Wnt3a pathway of three half-life extended biparatopic LRP5/LRP6 cross-reactive VHH constructs (Figure 5A) and comparison to other LRP6 binding molecules (Figure 5B: Knob HC YW210.09 and MOR08168IgG1LALA 6475 scfv; Figure 5C: 802T) in combined Wnt1 and Wnt3a reporter assay.

Figure 6 shows inhibition of Wnt signaling in cancer cells, as detected by inhibition of relative Axin2 mRNA expression (Figure 6A), and cell proliferation (Figure 6B) as detected by decreased percentage (%) of viable cells, after treatment with three half-life extended biparatopic LRP5/LRP6 cross-reactive VHH constructs (final concentration of 1mM) and by treatment with 802T, compared to F013500571 and untreated (control) cells (left-hand side / right-hand side diagram of Figure 6B); dose-response curves are shown for treatment with one half-life extended biparatopic LRP5/LRP6 construct (Figure 6C) and 802T (Figure 6D).

Figure 7 shows *in vivo* efficacy of the half-life extended biparatopic LRP5/LRP6 cross-reactive VHH constructs (F013500571 in Figure 7A and F013500720 in Figure 7B) and of the of Knob HC YW210.09 (Figure 7C) in a Wnt driven tumor models (MMTV-Wnt1 xenograft model).

Figure 8 shows Wnt pathway inhibition in tumors treated with the half-life extended biparatopic LRP5/LRP6 cross-reactive VHH constructs F013500571 and F013500720, as detected by reduction of Axin2 mRNA expression relative to the control group.

Figure 9 shows the effect of Wnt3a driven signaling inhibition on pro-inflammatory cytokine TNFalpha release by dendritic cells (Figure 9A) and the effect on T-cell activation, as determined by interferon-gamma release (Figure 9B) upon treatment with a half-life extended biparatopic LRP5/LRP6

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cross-reactive VHH construct. Each symbol represents a unique dendritic cell (DC) donor. Data shown are normalized to TNFalpha levels of the untreated control (Figure 9A) and each symbol represents a unique donor pair for DC and T cells (Panel B).

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The above and other aspects and embodiments of the invention will become clear from the further description herein, in which:

a) Unless indicated or defined otherwise, all terms used have their usual meaning in the art, which will be clear to the skilled person. Reference is for example made to the standard handbooks, such as Sambrook et al, "Molecular Cloning: A Laboratory Manual" (2nd Ed.), Vols. 1-3, Cold Spring Harbor Laboratory Press (1989); Lewin, "Genes IV", Oxford University Press, New York, (1990), and Roitt *et al.*, "Immunology" (2nd Ed.), Gower Medical Publishing, London, New York (1989), as well as to the general background art cited herein. Furthermore, unless indicated otherwise, all methods, steps, techniques and manipulations that are not specifically described in detail can be performed and have been performed in a manner known *per se*, as will be clear to the skilled person. Reference is for example again made to the standard handbooks, to the general background art referred to above and to the further references cited therein.

b) Unless indicated otherwise, the terms "*immunoglobulin*" and "*immunoglobulin sequence*" - whether used herein to refer to a *heavy chain antibody* or to a *conventional 4-chain antibody* - are used as general terms to include both the full-size antibody, the individual chains thereof, as well as all parts, domains or fragments thereof (including but not limited to antigen-binding domains or fragments such as VHH domains or VH/VL domains, respectively). In addition,

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the term "sequence" as used herein (for example in terms like "immunoglobulin sequence", "antibody sequence", "(single) variable domain sequence", "VHH sequence" or "protein sequence"), should generally be understood to include both the relevant amino acid sequence as well as nucleic acid sequences or nucleotide sequences encoding the same, unless the context requires a more limited interpretation;

c) The term "*domain*" (of a polypeptide or protein) as used herein refers to a folded protein structure which has the ability to retain its tertiary structure independently of the rest of the protein. Generally, domains are responsible for discrete functional properties of proteins, and in many cases may be added, removed or transferred to other proteins without loss of function of the remainder of the protein and/or of the domain.

d) The term "*immunoglobulin domain*" as used herein refers to a globular region of an antibody chain (such as e.g. a chain of a conventional 4-chain antibody or of a heavy chain antibody), or to a polypeptide that essentially consists of such a globular region. Immunoglobulin domains are characterized in that they retain the immunoglobulin fold characteristic of antibody molecules, which consists of a 2-layer sandwich of about 7 antiparallel beta-strands arranged in two beta-sheets, optionally stabilized by a conserved disulphide bond.

e) The term "*immunoglobulin variable domain*" as used herein means an immunoglobulin domain essentially consisting of four "framework regions" which are referred to in the art and hereinbelow as "framework region 1" or "FR1"; as "framework region 2" or"FR2"; as "framework region 3" or "FR3"; and as "framework region 4" or "FR4", respectively; which framework regions are interrupted by three "complementarity determining regions" or "CDRs", which are referred to in the art and hereinbelow as "complementarity determining region 1"or "CDR1"; as "complementarity determining region 2" or "CDR2"; and as "complementarity determining region 3" or "CDR3", respectively. Thus, the general structure or sequence of an immunoglobulin variable domain can be

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indicated as follows: FR1 - CDR1 - FR2 - CDR2 - FR3 - CDR3 - FR4. It is the immunoglobulin variable domain(s) that confer specificity to an antibody for the antigen by carrying the antigen-binding site.

f) The term "*immunoglobulin single variable domain*" as used herein means an immunoglobulin variable domain which is capable of specifically binding to an epitope of the antigen without pairing with an additional variable immunoglobulin domain. One example of immunoglobulin single variable domains in the meaning of the present invention are "*domain antibodies*", such as the immunoglobulin single variable domains VH and VL (VH domains and VL domains). Another important example of immunoglobulin single variable domains are "*VHH domains*" (or simply "VHHs") from camelids, as defined hereinafter.

In view of the above definition, the antigen-binding domain of a conventional 4-chain antibody (such as an IgG, IgM, IgA, IgD or IgE molecule; known in the art) or of a Fab fragment, a F(ab')2 fragment, an Fv fragment such as a disulphide linked Fv or a scFv fragment, or a diabody (all known in the art) derived from such conventional 4-chain antibody, would normally not be regarded as an immunoglobulin single variable domain, as, in these cases, binding to the respective epitope of an antigen would normally not occur by one (single) immunoglobulin domain but by a pair of (associating) immunoglobulin domains such as light and heavy chain variable domains, i.e. by a VH-VL pair of immunoglobulin domains, which jointly bind to an epitope of the respective antigen.

f1) "*VHH domains*" , also known as VHHs, V_HH domains, VHH antibody fragments, and VHH antibodies, have originally been described as the antigen binding immunoglobulin (variable) domain of "heavy chain antibodies" (i.e. of "antibodies devoid of light chains"; Hamers-Casterman C, Atarhouch T, Muyldermans S, Robinson G, Hamers C, Songa EB, Bendahman N, Hamers R.: "Naturally occurring antibodies devoid of light chains"; Nature 363, 446-448

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(1993)). The term "VHH domain" has been chosen in order to distinguish these variable domains from the heavy chain variable domains that are present in conventional 4-chain antibodies (which are referred to herein as "V_H domains" or "VH domains") and from the light chain variable domains that are present in conventional 4-chain antibodies (which are referred to herein as "V_L domains" or "VL domains"). VHH domains can specifically bind to an epitope without an additional antigen binding domain (as opposed to VH or VL domains in a conventional 4-chain antibody, in which case the epitope is recognized by a VL domain together with a VH domain). VHH domains are small, robust and efficient antigen recognition units formed by a single immunoglobulin domain.

In the context of the present invention, the terms VHH domain, VHH, V_HH domain, VHH antibody fragment, VHH antibody, as well as "Nanobody®" and "Nanobody® domain" ("Nanobody" being a trademark of the company Ablynx N.V.; Ghent; Belgium) are used interchangeably and are representatives of immunoglobulin single variable domains (having the structure: FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4 and specifically binding to an epitope without requiring the presence of a second immunoglobulin variable domain), and which may also be distinguished from VH domains by the so-called "hallmark residues", as defined in e.g. WO2009/109635, Fig. 1.

The amino acid residues of a VHH domain are numbered according to the general numbering for V_H domains given by Kabat *et al.* ("Sequence of proteins of immunological interest", US Public Health Services, NIH Bethesda, MD, Publication No. 91), as applied to VHH domains from Camelids, as shown e.g. in Figure 2 of Riechmann and Muyldermans, J. Immunol. Methods 231, 25-38 (1999). According to this numbering,

- FR1 comprises the amino acid residues at positions 1-30,
- CDR1 comprises the amino acid residues at positions 31-35,
- FR2 comprises the amino acids at positions 36-49,
- CDR2 comprises the amino acid residues at positions 50-65,

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- FR3 comprises the amino acid residues at positions 66-94,
- CDR3 comprises the amino acid residues at positions 95-102, and
- FR4 comprises the amino acid residues at positions 103-113.

However, it should be noted that - as is well known in the art for V_H domains and for VHH domains - the total number of amino acid residues in each of the CDRs may vary and may not correspond to the total number of amino acid residues indicated by the Kabat numbering (that is, one or more positions according to the Kabat numbering may not be occupied in the actual sequence, or the actual sequence may contain more amino acid residues than the number allowed for by the Kabat numbering). This means that, generally, the numbering according to Kabat may or may not correspond to the actual numbering of the amino acid residues in the actual sequence.

Alternative methods for numbering the amino acid residues of V_H domains, which methods can also be applied in an analogous manner to VHH domains, are known in the art. However, in the present description, claims and figures, the numbering according to Kabat and applied to VHH domains as described above will be followed, unless indicated otherwise.

The total number of amino acid residues in a VHH domain will usually be in the range of from 110 to 120, often between 112 and 115. It should however be noted that smaller and longer sequences may also be suitable for the purposes described herein.

Further structural characteristics and functional properties of VHH domains and polypeptides containing the same can be summarized as follows:

VHH domains (which have been "designed" by nature to functionally bind to an antigen without the presence of, and without any interaction with, a light chain variable domain) can function as a single, relatively small, functional antigen-binding structural unit, domain or polypeptide. This distinguishes the VHH

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domains from the VH and VL domains of conventional 4-chain antibodies, which by themselves are generally not suited for practical application as single antigen-binding proteins or immunoglobulin single variable domains, but need to be combined in some form or another to provide a functional antigen-binding unit (as in for example conventional antibody fragments such as Fab fragments; in scFv's, which consist of a VH domain covalently linked to a VL domain).

Because of these unique properties, the use of VHH domains - either alone or as part of a larger polypeptide - offers a number of significant advantages over the use of conventional VH and VL domains, scFv's or conventional antibody fragments (such as Fab- or F(ab')2-fragments):

- only a single domain is required to bind an antigen with high affinity and with high selectivity, so that there is no need to have two separate domains present, nor to assure that these two domains are present in the right spacial conformation and configuration (i.e. through the use of especially designed linkers, as with scFv's);
- VHH domains can be expressed from a single gene and require no post-translational folding or modifications;
- VHH domains can easily be engineered into multivalent and multispecific formats (as further discussed herein);
- VHH domains are highly soluble and do not have a tendency to aggregate (as with the mouse-derived antigen-binding domains described by Ward *et al.*, Nature 341: 544-546 (1989));
- VHH domains are highly stable to heat, pH, proteases and other denaturing agents or conditions and, thus, may be prepared, stored or transported without the use of refrigeration equipments, conveying a cost, time and environmental savings;
- VHH domains are easy and relatively cheap to prepare, even on a scale required for production. For example, VHH domains and polypeptides containing the same can be produced using microbial fermentation (e.g. as further described

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below) and do not require the use of mammalian expression systems, as with for example conventional antibody fragments;
- VHH domains are relatively small (approximately 15 kDa, or 10 times smaller than a conventional IgG) compared to conventional 4-chain antibodies and antigen-binding fragments thereof, and therefore
-- show high(er) penetration into tissues and
-- can be administered in higher doses
than such conventional 4-chain antibodies and antigen-binding fragments thereof;
- VHH domains can show so-called cavity-binding properties (inter alia due to their extended CDR3 loop, compared to conventional VH domains) and can therefore also access targets and epitopes not accessible to conventional 4-chain antibodies and antigen-binding fragments thereof.

Methods of obtaining VHH domains binding to a specific antigen or epitope have been described earlier, e.g. in WO2006/040153 and WO2006/122786. As also described therein in detail, VHH domains derived from camelids can be "humanized" by replacing one or more amino acid residues in the amino acid sequence of the original VHH sequence by one or more of the amino acid residues that occur at the corresponding position(s) in a VH domain from a conventional 4-chain antibody from a human being. A humanized VHH domain can contain one or more fully human framework region sequences, and, in an even more specific embodiment, can contain human framework region sequences derived from DP-29, DP-47, DP-51, or parts thereof, optionally combined with JH sequences, such as JH5.

f2) "*Domain antibodies*", also known as "Dab"s, "Domain Antibodies", and "dAbs" (the terms "Domain Antibodies" and "dAbs" being used as trademarks by the GlaxoSmithKline group of companies) have been described in e.g. Ward, E.S., *et al.*: "Binding activities of a repertoire of single immunoglobulin variable domains secreted from Escherichia coli"; Nature 341: 544-546 (1989); Holt, L.J.

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et al.: "Domain antibodies: proteins for therapy"; TRENDS in Biotechnology 21(11): 484-490 (2003); and WO2003/002609.

Domain antibodies essentially correspond to the VH or VL domains of non-camelid mammalians, in particular human 4-chain antibodies. In order to bind an epitope as a single antigen binding domain, i.e. without being paired with a VL or VH domain, respectively, specific selection for such antigen binding properties is required, e.g. by using libraries of human single VH or VL domain sequences. Domain antibodies have, like VHHs, a molecular weight of approximately 13 to approximately 16 kDa and, if derived from fully human sequences, do not require humanization for e.g. therapeutical use in humans. As in the case of VHH domains, they are well expressed also in prokaryotic expression systems, providing a significant reduction in overall manufacturing cost.

Domain antibodies, as well as VHH domains, can be subjected to affinity maturation by introducing one or more alterations in the amino acid sequence of one or more CDRs, which alterations result in an improved affinity of the resulting immunoglobulin single variable domain for its respective antigen, as compared to the respective parent molecule. Affinity-matured immunoglobulin single variable domain molecules of the invention may be prepared by methods known in the art, for example, as described by Marks *et al.*, 1992, Biotechnology 10:779-783, or Barbas, *et al.*, 1994, Proc. Nat. Acad. Sci, USA 91: 3809-3813.; Shier *et al.*, 1995, Gene 169:147-155; Yelton *et al.*, 1995, Immunol. 155: 1994-2004; Jackson *et al.*, 1995, J. Immunol. 154(7):3310-9; and Hawkins *et al.*, 1992, J. Mol. Biol. 226(3): 889 896; KS Johnson and RE Hawkins, "Affinity maturation of antibodies using phage display", Oxford University Press 1996.

f3) Furthermore, it will also be clear to the skilled person that it is possible to "graft" one or more of the CDRs mentioned above onto other "scaffolds", including but not limited to human scaffolds or non-immunoglobulin scaffolds. Suitable scaffolds and techniques for such CDR grafting are known in the art.

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g) The terms "*epitope*" and "*antigenic determinant*", which can be used interchangeably, refer to the part of a macromolecule, such as a polypeptide, that is recognized by antigen-binding molecules, such as conventional antibodies or the polypeptides of the invention, and more particularly by the antigen-binding site of said molecules. Epitopes define the minimum binding site for an immunoglobulin, and thus represent the target of specificity of an immunoglobulin.

The part of an antigen-binding molecule (such as a conventional antibody or a polypeptide of the invention) that recognizes the epitope is called a *paratope*.

h) The term "*biparatopic*" (antigen-)binding molecule or "biparatopic" polypeptide as used herein shall mean a polypeptide comprising a first immunoglobulin single variable domain and a second immunoglobulin single variable domain as herein defined, wherein these two variable domains are capable of binding to two different epitopes of one antigen, which epitopes are not normally bound at the same time by one monospecific immunoglobulin, such as e.g. a conventional antibody or one immunoglobulin single variable domain. The biparatopic polypeptides according to the invention are composed of variable domains which have different epitope specificities, and do not contain mutually complementary variable domain pairs which bind to the same epitope. They do therefore not compete with each other for binding to LRP5 or LRP6.

i) A polypeptide (such as an immunoglobulin, an antibody, an immunoglobulin single variable domain, a polypeptide of the invention, or generally an antigen binding molecule or a fragment thereof) that can "*bind*", "*bind to*", "*specifically bind*", or "*specifically bind to*", that "*has affinity for*" and/or that "*has specificity for*" a certain epitope, antigen or protein (or for at least one part, fragment or epitope thereof) is said to be "*against*" or "*directed against*" said epitope, antigen or protein or is a "*binding*" molecule with respect to such epitope, antigen or protein.

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k) Generally, the term "*specificity*" refers to the number of different types of antigens or epitopes to which a particular antigen-binding molecule or antigen-binding protein (such as an immunoglobulin, an antibody, an immunoglobulin single variable domain, or a polypeptide of the invention) can bind. The specificity of an antigen-binding protein can be determined based on its affinity and/or avidity. The affinity, represented by the equilibrium constant for the dissociation of an antigen with an antigen-binding protein (K_D), is a measure for the binding strength between an epitope and an antigen-binding site on the antigen-binding protein: the lesser the value of the K_D, the stronger the binding strength between an epitope and the antigen-binding molecule (alternatively, the affinity can also be expressed as the affinity constant (K_A), which is $1/K_D$). As will be clear to the skilled person (for example on the basis of the further disclosure herein), affinity can be determined in a manner known *per se*, depending on the specific antigen of interest. Avidity is the measure of the strength of binding between an antigen-binding molecule (such as an immunoglobulin, an antibody, an immunoglobulin single variable domain, or a polypeptide of the invention) and the pertinent antigen. Avidity is related to both the affinity between an epitope and its antigen binding site on the antigen-binding molecule and the number of pertinent binding sites present on the antigen-binding molecule.

Typically, antigen-binding proteins (such as the polypeptides of the invention) will bind with a dissociation constant (K_D) of 10E-5 to 10E-14 moles/liter (M) or less, and preferably 10E-7 to 10E-14 moles/liter (M) or less, more preferably 10E-8 to 10E-14 moles/liter, and even more preferably 10E-11 to 10E-13 (as measured e.g. in a Kinexa assay; known in the art), and/or with an association constant (K_A) of at least 10E7 ME-1 , preferably at least 10E8 ME-1, more preferably at least 10E9 ME-1, such as at least 10E11 ME-1. Any K_D value greater than 10E-4 M is generally considered to indicate non-specific binding. Preferably, a polypeptide of the invention will bind to the desired antigen with a K_D less than 500 nM, preferably less than 200 nM, more preferably less than 10 nM, such as less than 500 pM. Specific binding of an antigen-binding protein to an antigen or epitope

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can be determined in any suitable manner known *per se*, including, for example, the assays described herein, Scatchard analysis and/or competitive binding assays, such as radioimmunoassays (RIA), enzyme immunoassays (EIA) and sandwich competition assays, and the different variants thereof known *per se* in the art.

l) The term "*cross-reactive*" in connection with binding molecules which are able to bind to LRP5 as well as to LRP6 ("*LRP5/LRP6 cross-reactive*") is intended to mean that such binding molecules can specifically bind to an epitope comprised in the LRP5 molecule, and can, alternatively, also specifically bind to an epitope comprised in the LRP6 molecule. Usually, such cross-reactivity may arise in case that the epitopes of the different proteins bound by such binding molecule have a similar structure and/or sequence, e.g. represent conserved epitopes, e.g. are shared by proteins belonging to the same protein family (e.g. LRP5 and LRP6, belonging to the LRP protein family).

m) Amino acid residues will be indicated according to the standard three-letter or one-letter amino acid code, as generally known and agreed upon in the art. When comparing two amino acid sequences, the term "*amino acid difference*" refers to insertions, deletions or substitutions of the indicated number of amino acid residues at a position of the reference sequence, compared to a second sequence. In case of substitution(s), such substitution(s) will preferably be conservative amino acid substitution(s), which means that an amino acid residue is replaced with another amino acid residue of similar chemical structure and which has little or essentially no influence on the function, activity or other biological properties of the polypeptide. Such conservative amino acid substitutions are well known in the art, for example from WO 98/49185, wherein conservative amino acid substitutions preferably are substitutions in which one amino acid within the following groups (i) - (v) is substituted by another amino acid residue within the same group: (i) small aliphatic, nonpolar or slightly polar residues: Ala, Ser, Thr, Pro and Gly; (ii) polar, negatively charged residues and

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their (uncharged) amides: Asp, Asn, Glu and Gln; (iii) polar, positively charged residues: His, Arg and Lys; (iv) large aliphatic, nonpolar residues: Met, Leu, Ile, Val and Cys; and (v) aromatic residues: Phe, Tyr and Trp. Particularly preferred conservative amino acid substitutions are as follows:

Ala into Gly or into Ser;
Arg into Lys;
Asn into Gln or into His;
Asp into Glu;
Cys into Ser;
Gln into Asn;
Glu into Asp;
Gly into Ala or into Pro;
His into Asn or into Gln;
Ile into Leu or into Val;
Leu into Ile or into Val;
Lys into Arg, into Gln or into Glu;
Met into Leu, into Tyr or into Ile;
Phe into Met, into Leu or into Tyr;
Ser into Thr;
Thr into Ser;
Trp into Tyr;
Tyr into Trp or into Phe;
Val into Ile or into Leu.

n) A nucleic acid or polypeptide molecule is considered to be "*(in) essentially isolated (form)*" - for example, when compared to its native biological source and/or the reaction medium or cultivation medium from which it has been obtained - when it has been separated from at least one other component with which it is usually associated in said source or medium, such as another nucleic acid, another protein/polypeptide, another biological component or macromolecule or at least one contaminant, impurity or minor component. In

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particular, a nucleic acid or polypeptide molecule is considered "essentially isolated" when it has been purified at least 2-fold, in particular at least 10- fold, more in particular at least 100-fold, and up to 1000-fold or more. A nucleic acid or polypeptide molecule that is "in essentially isolated form" is preferably essentially homogeneous, as determined using a suitable technique, such as a suitable chromatographical technique, such as polyacrylamide-gelelectrophoresis;

o) "*Sequence identity*" between e.g. two immunoglobulin single variable domain sequences indicates the percentage of amino acids that are identical between these two sequences. It may be calculated or determined as described in paragraph f) on pages 49 and 50 of WO2008/020079. "*Sequence similarity*" indicates the percentage of amino acids that either are identical or that represent conservative amino acid substitutions.

Target specificity

The polypeptides of the invention have specificity for LRP5 as well as LRP6, in that they comprise immunoglobulin single variable domains specifically binding to epitopes included in both of these molecules (LRP5/LRP6 cross-reactive binding molecules).
The molecules of the invention shall bind to the human forms of LRP5 and LRP6, and preferably also to counterparts in other species relevant for drug development, i.e. cynomolgus and mouse LRP5 and LRP6.

Polypeptides of the invention

In its broadest sense, the invention provides novel pharmacologically active agents for the treatment of cancer diseases. The agents according to the invention belong to a novel class of binding molecules, namely LRP5/LRP6 cross-reactive biparatopic polypeptides, comprising two or more immunoglobulin single variable domains binding to LRP5 and/or LRP6 at different epitopes. The

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terms “cross-reactive” and “biparatopic” are explained above, so that LRP5/LRP6 cross-reactive biparatopic molecules can be defined as molecules being able to bind to LRP5 at two different epitopes comprised in the LRP5 protein, and also being able to bind to LRP6 at the corresponding two epitopes comprised in the LRP6 protein.

More specifically, the polypeptides of the invention include:

- a first immunoglobulin single variable domain which is able to specifically bind to LRP5 as well as to LRP6 (LRP5/LRP6 cross-reactive) via an epitope / in a manner that results in inhibition of the Wnt1 signaling pathway, so that Wnt1-driven target gene transcription is inhibited, and
- a second immunoglobulin single variable domain which is able to specifically bind to LRP5 as well as to LRP6 (LRP5/LRP6 cross-reactive) via an epitope / in a manner that results in inhibition of the Wnt3a signaling pathway, so that Wnt3a-driven target gene transcription is inhibited.

Due to the two immunoglobulin single variable domains present in such polypeptide, wherein the two domains are binding to different epitopes (Wnt1 / Wnt3a signaling related), these molecules are biparatopic binding molecules. This biparatopic binding mode is schematically shown in Figure 1.

In this context, it should be noted that it is assumed that the polypeptides of the invention can bind to one single LRP5 or LRP6 molecule via both of its LRP5/LRP6 binding domains, as shown in Fig. 1 (intramolecular binding mode). However, other binding modes may occur as well.

Finally, it is assumed that the polypeptides of the invention are able to compete with DKK1 – a natural ligand of LRP5 and LRP6, and interfering with Wnt1 and Wnt3a signaling – for binding to LRP5 and LRP6, thereby inhibiting the Wnt1 as well as the Wnt3a signaling pathway. However, also this theory should not be understood as limiting the scope of the invention.

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More specifically, the polypeptides according to the invention specifically bind to LRP5 or LRP6, wherein such polypeptides comprise a first immunoglobulin single variable domain (a) selected from the group of immunoglobulin single variable domains (i) to (iii) defined by having the following CDR sequences:

(i):

CDR1: TYTVG (= SEQ ID NO:1)

CDR2: AIRRRGSSTYYADSVKG (= SEQ ID NO:2)

CDR3: DTRTVALLQYRYDY (= SEQ ID NO:3)

[= CDRs of the Wnt1-333E06mod domain]

(ii):

CDR1: SYAMG (= SEQ ID NO:4)

CDR2: AIRRSGRRTYYADSVKG (= SEQ ID NO:5)

CDR3: ARRVRSSTRYNTGTWWWEY (= SEQ ID NO:6)

[= CDRs of the Wnt1-333G06 domain]

(iii):

CDR1: RYTMG (= SEQ ID NO:7)

CDR2: AIVRSGGSTYYADSVKG (= SEQ ID NO:8)

CDR3: DRRGRGENYILLYSSGRYEY (= SEQ ID NO:9)

[= CDRs of the Wnt1-332D03mod domain],

and a second immunoglobulin single variable domain (b) selected from the group of immunoglobulin single variable domains (iv) and (v) defined by having the following CDR sequences:

(iv):

CDR1: SYAMG (= SEQ ID NO:10)

CDR2: AISWSGGSTYYADSVKG (= SEQ ID NO:11)

CDR3: SPIPYGSLLRRRNNYDY (= SEQ ID NO:12)

[= CDRs of the Wnt3a-093A01 domain]

(v):

CDR1: SYAMG (= SEQ ID NO:13)

CDR2: AISWRSGSTYYADSVKG (= SEQ ID NO:14)

CDR3: DPRGYGVAYVSAYYEY (= SEQ ID NO:15)

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[= CDRs of the Wnt3a-367B10 domain].

The use of the terms “first” and “second” with respect to such immunoglobulin single variable domains is solely intended to indicate that these domains are different domains, as they will include different CDR sequences and will bind to different epitopes. These terms shall, however, not be understood to refer to the exact order or sequence of the domains within such polypeptide chain. In other words, the above immunoglobulin single variable domains (a) and (b) may either be arranged in the order (a) – (b) or in the order (b) – (a) within such polypeptide of the invention.

The term “specifically bind to LRP5 or LRP6” is intended to mean that the immunoglobulin single variable domains (a) and (b) are cross-reactive with respect to LRP5 and LRP6. Of course, the binding properties of such molecules are determined by their (CDR) sequences, so that the feature “specifically binding to LRP5 or LRP6” set out above and in the claims is only intended to illustrate the utility of the invention, and not to limit the scope of this invention.

Immunoglobulin single variable domains typically essentially consist of four framework regions (FR1 to FR4, respectively) and three complementarity determining regions (CDR1 to CDR3, respectively). To be located within one polypeptide, or polypeptide chain, said first and said second immunoglobulin single variable domains need to be covalently linked, either directly or by a linker peptide.

Thus, the general structure of the molecules of the invention can also be depicted as follows:
FR(a)1 - CDR(a)1 - FR(a)2 - CDR(a)2 - FR(a)3 - CDR(a)3 - FR(a)4 – [linker peptide] - FR(b)1 - CDR(b)1 - FR(b)2 - CDR(b)2 - FR(b)3 - CDR(b)3 - FR(b)4
wherein

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FR(a) denotes a framework region of the first immunoglobulin single variable domain,
FR(b) denotes a framework region of the second immunoglobulin single variable domain,
CDR(a) denotes a CDR of the first immunoglobulin single variable domain,
CDR(b) denotes a CDR of the second immunoglobulin single variable domain,
[linker peptide] denotes a linker peptide that may optionally be present,
wherein the CDRs are having the sequences as set out above.

Again, it shall be understood that (a) and (b) can be exchanged, i.e. that molecules having the general structure
FR(b)1 - CDR(b)1 - FR(b)2 - CDR(b)2 - FR(b)3 - CDR(b)3 - FR(b)4 – [linker peptide] - FR(a)1 - CDR(a)1 - FR(a)2 - CDR(a)2 - FR(a)3 - CDR(a)3 - FR(a)4
shall also be encompassed by the present invention.

The linker peptide optionally comprises or consists of a third domain, such as e.g. an albumin binding immunoglobulin single variable domain, such as the Alb11 domain, comprising the following CDRs:

CDR(Alb11)1: SFGMS (= SEQ ID NO:16)
CDR(Alb11)2: SISGSGSDTLYADSVKG (= SEQ ID NO:17)
CDR(Alb11)3: GGSLSR (= SEQ ID NO:18)

This results in a group of polypeptides of the invention having the following general structure:
FR(a)1 - CDR(a)1 - FR(a)2 - CDR(a)2 - FR(a)3 - CDR(a)3 - FR(a)4 – [linker peptide] - FR(Alb11)1 - CDR(Alb11)1 - FR(Alb11)2 - CDR(Alb11)2 - FR(Alb11)3 - CDR(Alb11)3 - FR(Alb11)4 - [linker peptide] - FR(b)1 - CDR(b)1 - FR(b)2 - CDR(b)2 - FR(b)3 - CDR(b)3 - FR(b)4.

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Again, the order of the three immunoglobulin single variable domains (a), (b), and Alb11 is not fixed but polypeptides in which the above domains are arranged in the order:

(b) – Alb11 – (a)

shall be encompassed as well.

Furthermore, polypeptides having the Alb11 domain at the N- or C-terminal end of the polypeptide (e.g. Alb11 – (a) – (b), Alb11 – (b) – (a), (a) – (b) – Alb11, or (b) – (a) – Alb11) shall also be encompassed by the invention.

In three preferred embodiments, the polypeptides of the invention include immunoglobulin single variable domains defined as follows:

First preferred embodiment: Polypeptides comprising a first immunoglobulin single variable domain having the following CDR sequences:

CDR1: TYTVG (= SEQ ID NO:1)

CDR2: AIRRRGSSTYYADSVKG (= SEQ ID NO:2)

CDR3: DTRTVALLQYRYDY (= SEQ ID NO:3)

and a second immunoglobulin single variable domain having the following CDR sequences:

CDR1: SYAMG (= SEQ ID NO:10)

CDR2: AISWSGGSTYYADSVKG (= SEQ ID NO:11)

CDR3: SPIPYGSLLRRRNNYDY (= SEQ ID NO:12).

Second preferred embodiment: Polypeptides comprising a first immunoglobulin single variable domain having the following CDR sequences:

CDR1: SYAMG (= SEQ ID NO:4)

CDR2: AIRRSGRRTYYADSVKG (= SEQ ID NO:5)

CDR3: ARRVRSSTRYNTGTWWWEY (= SEQ ID NO:6)

and a second immunoglobulin single variable domain having the following CDR sequences:

CDR1: SYAMG (= SEQ ID NO:13)

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CDR2: AISWRSGSTYYADSVKG (= SEQ ID NO:14)
CDR3: DPRGYGVAYVSAYYEY (= SEQ ID NO:15).

Third preferred embodiment: Polypeptides comprising a first immunoglobulin single variable domain having the following CDR sequences:

CDR1: RYTMG (= SEQ ID NO:7)
CDR2: AIVRSGGSTYYADSVKG (= SEQ ID NO:8)
CDR3: DRRGRGENYILLYSSGRYEY (= SEQ ID NO:9)

and a second immunoglobulin single variable domain having the following CDR sequences:

CDR1: SYAMG (= SEQ ID NO:13)
CDR2: AISWRSGSTYYADSVKG (= SEQ ID NO:14)
CDR3: DPRGYGVAYVSAYYEY (= SEQ ID NO:15).

Of course, the variants as set out above – i.e. optionally including linker peptides and/or further domains, esp. including an Alb11 domain, different orders of the immunoglobulin single variable domains – shall apply to these three preferred embodiments as well.

In a specifically preferred embodiment, the albumin binding immunoglobulin single variable domain is located between the two LRP5/LRP6 binding immunoglobulin single variable domains. Thus, three specifically preferred embodiments can be envisaged as follows:

First specifically preferred embodiment: Polypeptides comprising a first (LRP5/LRP6 binding) immunoglobulin single variable domain having the following CDR sequences:

CDR1: TYTVG (= SEQ ID NO:1)
CDR2: AIRRRGSSTYYADSVKG (= SEQ ID NO:2)
CDR3: DTRTVALLQYRYDY (= SEQ ID NO:3)

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an albumin binding immunoglobulin single variable domain having the following CDR sequences:

CDR1: SFGMS (= SEQ ID NO:16)

CDR2: SISGSGSDTLYADSVKG (= SEQ ID NO:17)

CDR3: GGSLSR (= SEQ ID NO:18);

and a second (LRP5/LRP6 binding) immunoglobulin single variable domain having the following CDR sequences:

CDR1: SYAMG (= SEQ ID NO:10)

CDR2: AISWSGGSTYYADSVKG (= SEQ ID NO:11)

CDR3: SPIPYGSLLRRRNNYDY (= SEQ ID NO:12);

either in this order, or the order of the above domains being changed.

Second specifically preferred embodiment: Polypeptides comprising a first (LRP5/LRP6 binding) immunoglobulin single variable domain having the following CDR sequences:

CDR1: SYAMG (= SEQ ID NO:4)

CDR2: AIRRSGRRTYYADSVKG (= SEQ ID NO:5)

CDR3: ARRVRSSTRYNTGTWWWEY (= SEQ ID NO:6);

an albumin binding immunoglobulin single variable domain having the following CDR sequences:

CDR1: SFGMS (= SEQ ID NO:16)

CDR2: SISGSGSDTLYADSVKG (= SEQ ID NO:17)

CDR3: GGSLSR (= SEQ ID NO:18);

and a second (LRP5/LRP6 binding) immunoglobulin single variable domain having the following CDR sequences:

CDR1: SYAMG (= SEQ ID NO:13)

CDR2: AISWRSGSTYYADSVKG (= SEQ ID NO:14)

CDR3: DPRGYGVAYVSAYYEY (= SEQ ID NO:15);

either in this order, or the order of the above domains being changed.

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Third specifically preferred embodiment: Polypeptides comprising first (LRP5/LRP6 binding) immunoglobulin single variable domain having the following CDR sequences:

CDR1: RYTMG (= SEQ ID NO:7)

CDR2: AIVRSGGSTYYADSVKG (= SEQ ID NO:8)

CDR3: DRRGRGENYILLYSSGRYEY (= SEQ ID NO:9);

an albumin binding immunoglobulin single variable domain having the following CDR sequences:

CDR1: SFGMS (= SEQ ID NO:16)

CDR2: SISGSGSDTLYADSVKG (= SEQ ID NO:17)

CDR3: GGSLSR (= SEQ ID NO:18);

and a second (LRP5/LRP6 binding) immunoglobulin single variable domain having the following CDR sequences:

CDR1: SYAMG (= SEQ ID NO:13)

CDR2: AISWRSGSTYYADSVKG (= SEQ ID NO:14)

CDR3: DPRGYGVAYVSAYYEY (= SEQ ID NO:15);

either in this order, or the order of the above domains being changed.

The CDR sequences mentioned above are summarized in Tables IA, IB, and IC:

TABLE IA: CDR sequences of immunoglobulin single variable domains interfering with Wnt1 signaling:

	Wnt1-333E06mod	Wnt1-333G06	Wnt1-332D03mod
CDR1	TYTVG (SEQ ID NO:1)	SYAMG (SEQ ID NO:4)	RYTMG (SEQ ID NO:7)
CDR2	AIRRRGSSTYYADSVKG (SEQ ID NO:2)	AIRRSGRRTYYADSVKG (SEQ ID NO:5)	AIVRSGGSTYYADSVKG (SEQ ID NO:8)
CDR3	DTRTVALLQYRYDY (SEQ ID NO:3)	ARRVRSSTRYNTGTWWWEY (SEQ ID NO:6)	DRRGRGENYILLYSSGRYEY (SEQ ID NO:9)

TABLE IB: CDR sequences of immunoglobulin single variable domains interfering with Wnt3a signaling:

	Wnt3a-093A01	Wnt3a-367B10
CDR1	SYAMG (SEQ ID NO:10)	SYAMG (SEQ ID NO:13)
CDR2	AISWSGGSTYYADSVKG (SEQ ID NO:11)	AISWRSGSTYYADSVKG (SEQ ID NO:14)
CDR3	SPIPYGSLLRRRNNYDY (SEQ ID NO:12)	DPRGYGVAYVSAYYEY (SEQ ID NO:15)

TABLE IC: CDR sequences of immunoglobulin single variable domain binding to serum albumin (Alb11 domain):

	Alb11 domain
CDR1	SFGMS (SEQ ID NO:16)
CDR2	SISGSGSDTLYADSVKG (SEQ ID NO:17)
CDR3	GGSLSR (SEQ ID NO:18)

In addition to the CDR sequences as set out above, the immunoglobulin single variable domains comprised in the polypeptides of the invention include immunoglobulin framework region (FR) sequences. These sequences are preferably not immunogenic in humans, and are therefore preferably human or humanized FR sequences. Suitable human or humanized FR sequences are known in the art. Specifically preferred FR sequences can be taken from the embodiments shown below, disclosing the complete immunoglobulin single variable domains and thereby CDR sequences as well as FR sequences.

According to a more specific embodiment, the polypeptides of the invention include immunoglobulin single variable domains which are VHH domains, and preferably humanized VHH domains.

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According to an even more specific embodiment, the polypeptides of the invention include a first immunoglobulin single variable domain (a) selected from the group consisting of immunoglobulin single variable domains (i) to (iii) having the following sequences:

(i)
AVQLVESGGGLVQPGGSLRLSCAASGRTFSTYTVGWFRQAPGKEREFVA
AIRRRGSSTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVYYCAA
DTRTVALLQYRYDYWGQGTLVTVSS
[= Wnt1-333E06mod domain; = SEQ ID NO:19]

(ii)
AVQLVESGGGLVQPGGSLRLSCAASGGTFSSYAMGWFRQAPGKEREFVA
AIRRSGRRTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVYYCAA
ARRVRSSTRYNTGTWWWEYWGQGTLVTVSS
[= Wnt1-333G06 domain; = SEQ ID NO:20], and

(iii)
AVQLVESGGGLVQPGGSLRLSCAASGLTFSRYTMGWFRQAPGKEREFVA
AIVRSGGSTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVYYCAA
DRRGRGENYILLYSSGRYEYWGQGTLVTVSS
[= Wnt1-332D03mod domain; = SEQ ID NO:21],

and a second immunoglobulin single variable domain (b) selected from the group consisting of immunoglobulin single variable domains (iv) and (v) having the following sequences:

(iv)
EVQLVESGGGLVQPGGSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVA
AISWSGGSTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVYYCAA
SPIPYGSLLRRRNNYDYWGQGTLVTVSS
[= Wnt3a-093A01 domain; = SEQ ID NO:22], and

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(v)
EVQLVESGGGLVQPGGSLRLSCAASGGTFSSYAMGWFRQAPGKEREFVA
AISWRSGSTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVYYCAA
DPRGYGVAYVSAYYEYWGQGTLVTVSS
[= Wnt3a-367B10 domain; = SEQ ID NO:23].

Preferred embodiments are polypeptides comprising
- a first immunoglobulin single variable domain having the amino acid sequence as shown in SEQ ID NO:19 and a second immunoglobulin single variable domain having the amino acid sequence as shown in SEQ ID NO:22; or
- a first immunoglobulin single variable domain having the amino acid sequence as shown in SEQ ID NO:20 and a second immunoglobulin single variable domain having the amino acid sequence as shown in SEQ ID NO:23; or
- a first immunoglobulin single variable domain having the amino acid sequence as shown in SEQ ID NO:21 and a second immunoglobulin single variable domain having the amino acid sequence as shown in SEQ ID NO:23.

Thus, the above embodiments can schematically be presented as
isvd(a) – [linker peptide] – isvd(b),
wherein “isvd” denotes the respective immunoglobulin single variable domain, and wherein otherwise the same definitions and variants shall apply as set out above, esp. with respect to the presence of optional linker peptides and/or further domains, esp. an Alb11 domain, and with respect to different orders of the immunoglobulin single variable domains.

According to specific embodiments of the invention, the above polypeptides may additionally include a half-life extending moiety, wherein said half-life extending moiety is covalently linked to said polypeptide and is optionally selected from the group consisting of an albumin binding moiety, such as an albumin binding peptide or an albumin binding immunoglobulin domain, preferably an albumin binding immunoglobulin single variable domain, more preferably the Alb11

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domain, a transferrin binding moiety, such as an anti-transferrin immunoglobulin domain, a polyethylene glycol molecule, serum albumin, preferably human serum albumin, and a fragment of (human) serum albumin.

The sequence of the above-mentioned Alb11 immunoglobulin single variable domain is as follows:

EVQLVESGGGLVQPGNSLRLSCAASGFTFSSFGMSWVRQAPGKGLEW
VSSISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLRPEDTAVYYCTI
GGSLSRSSQGTLVTVSS

(= Alb11 domain; = SEQ ID NO:24)

Further examples of immunoglobulin single variable domains binding to human serum albumin are known in the art, and are described in further detail in e.g. international patent publications WO2006/122787 and WO2008/028977. Other peptides binding to human serum albumin are described e.g. in WO2008/068280, WO2009/127691, and WO2011/095545.

Thus, three preferred specific embodiments of the invention are as follows:

First preferred specific embodiment: Polypeptides comprising
- a first (LRP5/LRP6 binding) immunoglobulin single variable domain having the amino acid sequence as shown in SEQ ID NO:19;
- an albumin binding immunoglobulin single variable domain having the amino acid sequence as shown in SEQ ID NO:24;
- a second (LRP5/LRP6 binding) immunoglobulin single variable domain having the amino acid sequence as shown in SEQ ID NO:22;

either in this order, or the order of the above three domains being changed.

Second preferred specific embodiment: Polypeptides comprising
- a first (LRP5/LRP6 binding) immunoglobulin single variable domain having the amino acid sequence as shown in SEQ ID NO:20;

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- an albumin binding immunoglobulin single variable domain having the amino acid sequence as shown in SEQ ID NO:24;
- a second (LRP5/LRP6 binding) immunoglobulin single variable domain having the amino acid sequence as shown in SEQ ID NO:23;

either in this order, or the order of the above three domains being changed.

Third preferred specific embodiment: Polypeptides comprising
- a first (LRP5/LRP6 binding) immunoglobulin single variable domain having the amino acid sequence as shown in SEQ ID NO:21;
- an albumin binding immunoglobulin single variable domain having the amino acid sequence as shown in SEQ ID NO:24;
- a second (LRP5/LRP6 binding) immunoglobulin single variable domain having the amino acid sequence as shown in SEQ ID NO:23;

either in this order, or the order of the above three domains being changed.

In even more specifically preferred embodiments, the albumin binding immunoglobulin single variable domain is located between the two LRP5/LRP6 binding immunoglobulin single variable domains.

The sequences of the immunoglobulin single variable domains mentioned above are summarized in Tables IIA, IIB, and IIC:

TABLE IIA: Sequences of immunoglobulin single variable domains interfering with Wnt1 signaling:

VHH ID SEQ ID NO:	**FR1**	**CDR1**	**FR2**	**CDR2**	**FR3**	**CDR3**	**FR4**
Wnt1-333E06 mod SEQ ID NO:19	AVQLVESG GGLVQPG GSLRLSCAA SGRTFS	TYTVG	WFRQAPG KEREFVA	AIRRRGS STYYADS VKG	RFTISRDNSKNTVYL QMNSLRPEDTAVYY CAA	DTRTVA LLQYRY DY	WGQGTL VTVSS

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Wnt1-333G06 SEQ ID NO:20	AVQLVESGGGLVQPGGSLRLSCAASGGTFS	SYAMG	WFRQAPGKEREFVA	AIRRSGRRTYYADSVKG	RFTISRDNSKNTVYLQMNSLRPEDTAVYYCAA	ARRVRSSTRYNTGTWWWEY	WGQGTLVTVSS
Wnt1-332D03 mod SEQ ID NO:21	AVQLVESGGGLVQPGGSLRLSCAASGLTFS	RYTMG	WFRQAPGKEREFVA	AIVRSGGSTYYADSVKG	RFTISRDNSKNTVYLQMNSLRPEDTAVYYCAA	DRRGRGENYILLYSSGRYEY	WGQGTLVTVSS

TABLE IIB: Sequences of immunoglobulin single variable domains interfering with Wnt3a signaling:

VHH ID SEQ ID NO:	**FR1**	**CDR1**	**FR2**	**CDR2**	**FR3**	**CDR3**	**FR4**
Wnt3a-093A01 SEQ ID NO:22	EVQLVESGGGLVQPGGSLRLSCAASGRTFS	SYAMG	WFRQAPGKEREFVA	AISWSGGSTYYADSVKG	RFTISRDNSKNTVYLQMNSLRPEDTAVYYCAA	SPIPYGSLLRRRNNYDY	WGQGTLVTVSS
Wnt3a-367B10 SEQ ID NO:23	EVQLVESGGGLVQPGGSLRLSCAASGGTFS	SYAMG	WFRQAPGKEREFVA	AISWRSGSTYYADSVKG	RFTISRDNSKNTVYLQMNSLRPEDTAVYYCAA	DPRGYGVAYVSAYYEY	WGQGTLVTVSS

TABLE IIC: Sequence of immunoglobulin single variable domain binding to serum albumin (Alb11 domain):

VHH ID SEQ ID NO:	**FR1**	**CDR1**	**FR2**	**CDR2**	**FR3**	**CDR3**	**FR4**
Alb11 SEQ ID NO:24	EVQLVESGGGLVQPGNSLRLSCAASGFTFS	SFGMS	WVRQAPGKGLEWVS	SISGSGSDTLYADSVKG	RFTISRDNAKTTLYLQMNSLRPEDTAVYYCTI	GGSLSR	SSQGTLVTVSS

As set out above, the (at least two) immunoglobulin single variable domains present in a polypeptide of the invention can be linked to each other either directly, without use of a linker, or via a linker. The linker is preferably a linker peptide and will, according to the invention, be selected so as to allow binding of the at least two different immunoglobulin single variable domains to each of their target epitopes.

Suitable linkers will *inter alia* depend on the epitopes and, specifically, the distance between the epitopes on the target molecules to which the immunoglobulin single variable domains shall bind. This will be clear to the skilled person based on the disclosure herein, optionally after some limited degree of routine experimentation.

Thus, suitable linkers may comprise an amino acid sequence, e.g. having a length of 9 or more amino acids, preferably at least 17 amino acids, such as about 20 to 40 amino acids. The linker sequence may be a naturally occurring sequence or a non-naturally occurring sequence. If used for therapeutic purposes, the linker is preferably non-immunogenic in the subject to which the polypeptide of the invention is administered.

One useful group of linker sequences are linkers derived from the hinge region of heavy chain antibodies as described in WO1996/34103 and WO1994/04678. Other examples are poly-alanine linker sequences such as Ala-Ala-Ala.

Further preferred examples of linker sequences are Gly/Ser linkers of different length such as $(gly_xser_y)_z$ linkers, including e.g. $(gly_4ser)_3$, $(gly_4ser)_5$, $(gly_4ser)_7$, $(gly_3ser)_3$, $(gly_3ser)_5$, $(gly_3ser)_7$, $(gly_3ser_2)_3$, $(gly_3ser_2)_5$, and $(gly_3ser_2)_7$.

Alternatively, or in addition, to a polypeptide linker, the at least two immunoglobulin single variable domains present in a polypeptide of the invention may be linked to each other via another moiety, such as another polypeptide

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which, in a preferred but non-limiting embodiment, may be a further immunoglobulin single variable domain as already described above. Such moiety may either be essentially inactive or may have a biological effect such as improving the desired properties of the polypeptide or may confer one or more additional desired properties to the polypeptide. As already set out above, a preferred additional polypeptide domain will increase the half-life of the polypeptide, such as a (human) serum albumin binding domain, such as the Alb11 domain.

Thus, according to a further embodiment, the invention specifically includes polypeptides comprising any of the following sequences, wherein the exact amino acid sequences can be taken from Table III below:

SEQ ID NO:25 (= sequence of polypeptide F013500575),
SEQ ID NO:26 (= sequence of polypeptide F013500571),
and
SEQ ID NO:27 (= sequence of polypeptide F013500720.

According to an even more specific embodiment, the polypeptides of the invention are selected from the following group of molecules:
Polypeptide F013500575, having the sequence SEQ ID NO:25,
Polypeptide F013500571, having the sequence SEQ ID NO:26, and
Polypeptide F013500720, having the sequence SEQ ID NO:27.

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Table III: Sequences of three specific embodiments of polypeptides of the invention

ID SEQ ID NO:	**Amino Acid Sequence** (CDR sequences underlined)
F013500575 SEQ ID NO:25	AVQLVESGGGLVQPGGSLRLSCAASGRTFSTYTVGWFRQAPGKEREFVAAIRRRGSSTYYA DSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVYYCAADTRTVALLQYRYDYWGQGTLVTV SSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGNSLRL SCAASGFTFSSFGMSWVRQAPGKGLEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYL QMNSLRPEDTAVYYCTIGGSLSRSSQGTLVTVSSGGGGSGGGGSGGGGSGGGGSGGGGS GGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVA AISWSGGSTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVYYCAASPIPYGSLLRRRN NYDYWGQGTLVTVSSA
F013500571 SEQ ID NO:26	AVQLVESGGGLVQPGGSLRLSCAASGGTFSSYAMGWFRQAPGKEREFVAAIRRSGRRTYY ADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVYYCAAARRVRSSTRYNTGTWWWEYW GQGTLVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLV QPGNSLRLSCAASGFTFSSFGMSWVRQAPGKGLEWVSSISGSGSDTLYADSVKGRFTISRD NAKTTLYLQMNSLRPEDTAVYYCTIGGSLSRSSQGTLVTVSSGGGGSGGGGSGGGGSGGG GSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGGTFSSYAMGWFRQAP GKEREFVAAISWRSGSTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVYYCAADPRG YGVAYVSAYYEYWGQGTLVTVSSA
F013500720 SEQ ID NO:27	AVQLVESGGGLVQPGGSLRLSCAASGLTFSRYTMGWFRQAPGKEREFVAAIVRSGGSTYY ADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVYYCAADRRGRGENYILLYSSGRYEYWGQ GTLVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQP GNSLRLSCAASGFTFSSFGMSWVRQAPGKGLEWVSSISGSGSDTLYADSVKGRFTISRDNA KTTLYLQMNSLRPEDTAVYYCTIGGSLSRSSQGTLVTVSSGGGGSGGGGSGGGGSGGGGS GGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGGTFSSYAMGWFRQAPGK EREFVAAISWRSGSTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVYYCAADPRGYG VAYVSAYYEYWGQGTLVTVSSA

As explained before, unless indicated otherwise, the polypeptides of the invention may include further moieties and/or additional polypeptide domains, as long as their binding to LRP5/LRP6 will not be prevented by such additional moiety or domain.

The polypeptides of the invention can additionally contain modifications such as glycosyl residues or modified amino acid side chains, and they may be PEGylated in order to increase half-life and other properties of such molecule. Techniques and reagents useful for PEGylating biparatopic immunoglobulin single variable domain constructs may be taken e.g. from WO2011/107507.

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The polypeptides of the invention may have a modified N-terminal sequence, e.g. a deletion of one or more of the N-terminal amino acids, or an exchange of e.g. the first, N-terminal amino acid (e.g. glutamate to alanine), to optimize the molecule for being expressed by using certain expression systems (such as specific vectors or host cells), or for being expressed as inclusion bodies or in soluble form, or for being secreted into the medium or the periplasmic space or for being contained within the cell, or for yielding a more homogenous product. The polypeptides of the invention may have a modified C-terminal sequence, such as an additional alanine (as shown for the three embodiments shown in Table III above), and/or further amino acid exchanges in the C-terminal part or at other defined positions within any of the framework regions, as explained e.g. in WO2012/175741, WO2011/075861, or WO2013/024059, in order to e.g. further enhance stability or reduce immunogenicity of such polypeptides.

Furthermore, half-life of the polypeptides of the invention may be enhanced by adding an albumin domain, i.e. by converting them into albumin fusion proteins. Examples of useful albumin moieties, and how to add them to binding molecules, are e.g. provided in WO2001/079271 and WO2003/059934.

Preferably, the polypeptides of the invention are having binding (EC_{50}) values, measured in a FACS binding assay as described in Example 7.1 below, in the range of 10^{-6} moles/liter or less, more preferably 10^{-9} moles/liter or less, and even more preferably in the range of from 10^{-10} to 10^{-13} moles/liter, or are having an IC_{50} value as measured in a combined Wnt1 and Wnt3a reporter assay as set out in Example 7.3 below, of 10^{-9} moles/liter or below, and preferably in the range of from 5×10^{-10} moles/liter to 10^{-12} moles/liter.

The polypeptides of the invention allow a more efficient treatment of several cancer types, such as TNBC, CRC, and NSCLC. They are having improved *in vitro* characteristics (i.e. higher efficacy of Wnt pathway inhibition), cf. e.g. Examples 7 and 8 below, and significant *in vivo* tumor growth inhibition

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properties, leading to higher *in vivo* efficacy as compared to other LRP6 binding molecules described in the art, as shown in e.g. Examples 9 and 10 below.

In particular, as shown *in vivo* in a Wnt driven tumor model, the LRP5/LRP6 cross-reactive half-life extended biparatopic humanized VHH constructs could inhibit Wnt signaling and tumor growth *in vivo*, and even provided for substantial tumor shrinkage (i.e. tumor growth inhibition higher than 100%), which could not be achieved, under the same experimental settings, with a LRP6 binder known in the art. Tumor shrinkage (i.e. tumor regression) is of course the desired therapeutic effect (i.e. efficacy) for treatment of cancer patients. Furthermore, tumor regression, resulting in pathological complete response (pCR), is an acknowledged clinical endpoint, indicating significant improvement of progression free survival and overall survival.

In the same *in vivo* experiments, no significant body weight changes were observed (< 10%), and results from gastrointestinal histopathological analyses did not indicate any toxic effects of the above polypeptides of the invention. This is specifically surprising in view of the *in vivo* DKK1 expression studies discussed above (i.e. resulting in intestinal mucosa ulceration and body weight loss).

Thus, the polypeptides of the invention are in fact providing for novel therapeutic options for the treatment of cancer diseases, and especially even for use in high unmet medical need indications such as (triple negative) breast cancer.

Surprisingly, the inventors arrived at this solution not by going the conventional route, i.e. trying to develop inhibitors or binding molecules having a high specificity / selectivity for one given target, such as LRP6 (mentioned as a target for the treatment of “Wnt signaling mediated diseases” e.g. in WO2009/056634). In contrast thereto, the inventors developed molecules targeting two related proteins at the same time – LRP6 and LRP5 – and thereby achieved the above significantly improved *in vitro* and *in vivo* effects which could

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not be expected from the prior art.

The underlying molecular mechanism for this superiority is not fully clear, but it may be speculated – without wishing to be bound to a specific theory – that such cross-reactive molecules may have additional, and thereby stronger, effects on the highly complicated signaling cascade of the Wnt signaling pathway.

The above advantageous effects will further be illustrated in the Examples below and by way of the comparative data included therein.

Moreover, the polypeptides of the invention are easy to manufacture and are more soluble, which means that they may be stored and/or administered in higher concentrations compared to conventional antibodies. They are stable at room temperature and have prolonged stability even at extremes of pH, so that they may be prepared, stored and/or transported without the use of refrigeration equipment, conveying cost, time and environmental savings. Due to the above and due to their low immunogenicity, they furthermore offer a variety of options regarding administration routes other than injection and infusion, as well as regarding administration regimens and uses of specific devices.

Nucleic acids, vectors, host cells

According to further aspects, the invention relates to nucleic acid molecules and expression vectors encoding the polypeptides of the invention, as well as to host cells expressing the same. These nucleic acids, vectors, and host cells are useful for manufacturing the polypeptides of the invention, and further aspects and embodiments thereof will be described further below in connection with an outline of methods of manufacturing the polypeptides of the invention.

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Therapeutic use

Due to their biological properties, the polypeptides of the invention are suitable for treating diseases characterised by excessive or abnormal cell proliferation, such as cancer and idiopathic pulmonary fibrosis (IPF).

For example, the following cancers, tumors, and other proliferative diseases may be treated with polypeptides according to the invention, without being restricted thereto:

Cancers of the head and neck; Cancers of the lung, such as e.g. non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC); Neoplasms of the mediastinum, such as e.g. neurogenic tumors and mesenchymal tumors; Cancers of the gastrointestinal (GI) tract, such as e.g. cancers of the esophagus, stomach (gastric cancer), pancreas, liver and biliary tree (including e.g. hepatocellular carcinoma (HCC)), and the small and large intestine (including e.g. colorectal cancer); Cancers of the prostate; Cancers of the testis; Gynecologic cancers, such as e.g. cancers of the ovary; Cancers of the breast, such as e.g. mammary carcinoma, hormone receptor positive breast cancer, Her2 positive breast cancer, and triple negative breast cancer; Cancers of the endocrine system; Sarcomas of the soft tissues, such as e.g. fibrosarcoma, rhabdomyosarcoma, angiosarcoma, Kaposi´s sarcoma; Sarcomas of the bone, such as e.g. myeloma, osteosarcoma, Ewing´s tumor, fibrosarcoma, osteochondroma, osteoblastoma, and chondroblastoma; Mesotheliomas; Cancers of the skin, such as e.g. basal cell carcinoma, squamous cell carcinoma, Merkel´s cell carcinoma, and melanoma; Neoplasms of the central nervous system and brain, such as e.g. astrocytoma, glioblastoma, gliomas neuroblastomas, and retinoblastomas; Lymphomas and leukemias such as e.g. B-cell non-Hodgkin lymphomas (NHL), T-cell non-Hodgkin lymphomas, chronic B-cell lymphocytic leukemia (B-CLL), chronic T-cell lymphocytic leukemia (T-CLL), Hodgkin´s disease (HD), large granular lymphocyte leukemia (LGL),

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chronic myelogenous leukemia (CML), acute myelogenous/myeloid leukemia (AML), acute lymphatic/lymphoblastic leukemia (ALL), multiple myeloma (MM), plasmacytoma, and myelodysplastic syndromes (MDS); and cancers of unknown primary site.

All cancers, tumors, neoplasms, etc., mentioned above which are characterized by their specific location/origin in the body are meant to include both the primary tumors and the metastatic tumors derived therefrom.

More specifically, the polypeptides of the invention are useful for the treatment of diseases, and esp. cancer diseases in which abnormal cell proliferation is caused by, or involves, abnormal (activated) Wnt signaling.

Thus, the polypeptides of the invention are specifically useful for the treatment of solid tumors, and more specifically for the treatment of lung, liver, colon, brain, thyroid, pancreas, breast, ovary and prostate cancers, and even more specifically for the treatment of non-small cell lung cancer (NSCLC), triple-negative breast cancer (TNBC), and colo-rectal cancer (CRC). In particular, the polypeptides of the invention may be used to treat patients with locally advanced or metastatic TNBC, patients with metastatic NSCLC or locally advanced or metastatic CRC, as single agent or in combination, to prolong progression free survival (PFS) and overall survival (OS). Furthermore, the polypeptides of the invention may be used as neoadjuvant treatment for breast cancer patients to achieve pathological complete response (pCR; defined as the absence of residual invasive and *in situ* cancer by histo-pathological evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy).

The polypeptides of the invention may be used in therapeutic regimens in the context of first line, second line, or any further line treatments.

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The polypeptides of the invention may be used for the prevention, short-term or long-term treatment of the above-mentioned diseases, optionally also in combination with radiotherapy and/or surgery.

Likewise, the polypeptides of the invention are specifically useful for the treatment of other diseases caused by abnormal cell proliferation involving the Wnt signaling pathway, such as idiopathic pulmonary fibrosis (IPF) (Königshoff *et al.* "Functional Wnt signaling is increased in idiopathic pulmonary fibrosis". *PLoS One* 2008;3(5):e2142; Lam *et al*. "Wnt coreceptor Lrp5 is a driver of idiopathic pulmonary fibrosis". *Am J Respir Crit Care Med*. 2014;190(2):185-95).

Furthermore, the polypeptides of the invention are specifically useful for the treatment of retinopathies, and esp. for the treatment of diabetic retinopathy, due to abnormal Wnt activation in the inner retina cells, causing the increase in abnormal new retinal vessel formation leading to development and progression of diabetic retinopathy (Chen, Y., *et al*. "Activation of the Wnt pathway plays a pathogenic role in diabetic retinopathy in humans and animal models" *The Am J Pathol.* 2009; 175(6):2676-85., Gao *et al*. "Elevated LRP6 levels correlate with vascular endothelial growth factor in the vitreous of proliferative diabetic retinopathy" *Mol Vis*. 2015;21:665-72).

Finally, as it could be shown that inhibition of Wnt1/Wnt3a signaling pathways can also have an effect on dendritic cells (DCs) and dendritic cell function, the polypeptides of the invention may also be useful in the treatment of immunologic and infectious diseases, as well as for influencing the tumor microenvironment in the various cancer diseases already set out above. Tumors actively suppress antitumor immunity, and DCs play an important role in the cancer immunoescape mechanism. In particular, studies have shown that Wnt ligands in the tumor microenvironment can also initiate paracrine signaling within the immune cells and regulate host antitumor immunity (Hong *et al.* "beta-catenin promotes

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regulatory T-cell responses in tumors by inducing vitamin A metabolism in dendritic cells". *Cancer Res*. 2015;75(4):656-65).

Of course, the above also includes the use of the polypeptides of the invention in various methods of treating the above diseases by administering a therapeutically effective dose to a patient in need thereof, as well as the use of these polypeptides for the manufacture of medicaments for the treatment of such diseases, as well as pharmaceutical compositions including such polypeptides of the inventions, as well as the preparation and/or manufacture of medicaments including such polypeptides of the invention, and the like.

Combinations with other active substances

The polypeptides of the invention may be used on their own or in combination with other pharmacologically active substances, such as state-of-the-art or standard-of-care compounds, such as e.g. cytostatic or cytotoxic substances, cell proliferation inhibitors, anti-angiogenic substances, steroids, immune modulators / checkpoint inhibitors, and the like.

Cytostatic and/or cytotoxic active substances which may be administered in combination with the compounds according to the invention include, without being restricted thereto, hormones, hormone analogues and antihormones, aromatase inhibitors, LHRH agonists and antagonists, inhibitors of growth factors (growth factors such as for example platelet derived growth factor (PDGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), insuline-like growth factors (IGF), human epidermal growth factor (HER, e.g. HER2, HER3, HER4) and hepatocyte growth factor (HGF)), inhibitors are for example (anti-)growth factor antibodies, (anti-)growth factor receptor antibodies and tyrosine kinase inhibitors, such as for example cetuximab, gefitinib, afatinib, nintedanib, imatinib, lapatinib, bosutinib and trastuzumab; antimetabolites (e.g. antifolates such as methotrexate, raltitrexed, pyrimidine

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analogues such as 5-fluorouracil (5-FU), capecitabine and gemcitabine, purine and adenosine analogues such as mercaptopurine, thioguanine, cladribine and pentostatin, cytarabine (ara C), fludarabine); antitumor antibiotics (e.g. anthracyclins); platinum derivatives (e.g. cisplatin, oxaliplatin, carboplatin); alkylation agents (e.g. estramustin, meclorethamine, melphalan, chlorambucil, busulphan, dacarbazin, cyclophosphamide, ifosfamide, temozolomide, nitrosoureas such as for example carmustin and lomustin, thiotepa); antimitotic agents (e.g. Vinca alkaloids such as for example vinblastine, vindesin, vinorelbin and vincristine; and taxanes such as paclitaxel, docetaxel); angiogenesis inhibitors, tubuline inhibitors; DNA synthesis inhibitors, PARP inhibitors, topoisomerase inhibitors (e.g. epipodophyllotoxins such as for example etoposide and etopophos, teniposide, amsacrin, topotecan, irinotecan, mitoxantrone), serine/threonine kinase inhibitors (e.g. PDK1 inhibitors, Raf inhibitors, A-Raf inhibitors, B-Raf inhibitors, C-Raf inhibitors, mTOR inhibitors, mTORC1/2 inhibitors, PI3K inhibitors, PI3Kα inhibitors, dual mTOR/PI3K inhibitors, STK33 inhibitors, AKT inhibitors, PLK1 inhibitors (such as volasertib), inhibitors of CDKs, Aurora kinase inhibitors), tyrosine kinase inhibitors (e.g. PTK2/FAK inhibitors), protein protein interaction inhibitors, MEK inhibitors, ERK inhibitors, FLT3 inhibitors, BRD4 inhibitors, IGF-1R inhibitors, TRAILR2 agonists, Bcl-xL inhibitors, Bcl-2 inhibitors, Bcl-2/Bcl-xL inhibitors, ErbB receptor inhibitors, BCR-ABL inhibitors, ABL inhibitors, Src inhibitors, rapamycin analogs (e.g. everolimus, temsirolimus, ridaforolimus, sirolimus), androgen synthesis inhibitors, androgen receptor inhibitors, DNMT inhibitors, HDAC inhibitors, ANG1/2 inhibitors, CYP17 inhibitors, radiopharmaceuticals, immunotherapeutic agents such as immune checkpoint inhibitors (e.g. CTLA4, PD1, PD-L1, LAG3, and TIM3 binding molecules / immunoglobulins, such as ipilimumab, nivolumab, pembrolizumab), cancer vaccines such as traditional tumor vaccine (cell based vaccines, e.g. Sipuleucel-T for treatment of prostate cancer), personalized neoantigen vaccines, and oncolytic viruses, and various chemotherapeutic agents such as amifostin, anagrelid, clodronat, filgrastin, interferon, interferon

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alpha, leucovorin, rituximab, procarbazine, levamisole, mesna, mitotane, pamidronate and porfimer.

Particularly preferred are methods of treatment including the use of the polypeptides of the invention in combination with a drug selected from the group consisting of:

(i) anti-VEGF antibodies (bevacizumab and other anti-angiogenic substances) with or without chemotherapy combination (including doxorubicin / cyclophosphamide combination and/or capecitabine / docetaxel combination in neoadjuvant setting; taxane / platinum regimen for first and later line treatment) in breast cancer patients;

(ii) EGFR TKIs for EGFR mutant NSCLC or crizotinib for ALK translocated NSCLC with or without chemotherapy combination (platinum based cytotoxic combination therapy, including gemcitabine / cisplatin in first line treatment; docetaxel or pemetrexed in second line treatment in lung cancer patients;

(iii) anti-EGFR antibodies (cetuximab and panitumumab in *KRAS* wild-type tumors) with or without chemotherapy combination (including irinotecan), anti-VEGF antibody combination (bevacizumab and other anti-angiogenic substances) or regorafenib combination, e.g. for the treatment of CRC patients.

(iv) immunotherapeutic agents, including anti-PD-1 agents, such as pembrolizumab and nivolumab, anti-PD-L1 agents, anti-CTLA4 agents, anti-BTLA agents, anti-LAG3 agents, and anti-TIM3 agents, such as anti-PDL1 antibodies etc., e.g. for treatment of breast cancer, lung cancer and CRC patients

(v) chemotherapeutic agents, such as platinium-based antineoplastic agents, or in a combination with a FOLFOX chemotherapy regimen, including folinic acid, 5'-fluorouracil, and oxaliplatin, or in a combination with a FOLFOXIRI chemotherapy regimen, including folinic acid, 5'-fluorouracil, oxaliplatin, and irinotecan, e.g. for treatment of breast cancer or CRC patients.

When two or more substances or principles are to be used as part of a combined treatment regimen, they can be administered via the same route of administration

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or via different routes of administration, at essentially the same time (i.e. simultaneously, concurrently) or at different times (e.g. sequentially, successively, alternately, consecutively, or according to any other sort of alternating regime).

When the substances or principles are to be administered simultaneously via the same route of administration, they may be administered as different pharmaceutical formulations or compositions or as part of a combined pharmaceutical formulation or composition. Also, when two or more active substances or principles are to be used as part of a combined treatment regimen, each of the substances or principles may be administered in the same amount and according to the same regimen as used when the compound or principle is used on its own, and such combined use may or may not lead to a synergistic effect. However, when the combined use of the two or more active substances or principles leads to a synergistic effect, it may also be possible to reduce the amount of one, more or all of the substances or principles to be administered, while still achieving the desired therapeutic action. This may for example be useful for avoiding, limiting or reducing any unwanted side-effects that are associated with the use of one or more of the substances or principles when they are used in their usual amounts, while still obtaining the desired pharmacological or therapeutic effect.

Of course, the above includes the preparation, and methods of preparing, the polypeptides of the invention for the combined use with the above combination partners. Also included are the preparation, and methods of preparing, the above-mentioned combination partners for the combined use with the polypeptides of the invention. Thus, the invention hereby e.g. provides methods of using, or preparing for use, an immune modulator / checkpoint inhibitor, such as an anti-PD1 antibody, such as pembrolizumab or nivolumab, for the administration in combination with a polypeptide of the invention, and more specifically for the administration in a combination therapy regimen with a polypeptide of the invention.

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Furthermore, the invention also encompasses kits comprising at least one polypeptide of the invention and one or more other components selected from the group consisting of other drugs used for the treatment of the diseases and disorders as described above, and devices as described below.

Pharmaceutical compositions, methods of administration, dosages

It will be clear to the skilled person that the above methods of treatment of a disease include the preparation of a medicament for the treatment of said disease. Thus, the invention further relates to pharmaceutical compositions for the treatment of the diseases mentioned hereinabove, wherein such compositions comprise at least one polypeptide of the invention.

The polypeptides of the invention and/or the compositions comprising the same can be administered to a patient in need thereof in any suitable manner, depending on the specific pharmaceutical formulation or composition to be used. Thus, the polypeptides of the invention and/or the compositions comprising the same can for example be administered intravenously (i.v.), subcutaneously (s.c.), intramuscularly (i.m.), intraperitoneally (i.p.), transdermally, orally, sublingually (e.g. in the form of a sublingual tablet, spray or drop placed under the tongue and adsorbed through the mucus membranes into the capillary network under the tongue), (intra-)nasally (e.g. in the form of a nasal spray and/or as an aerosol), topically, by means of a suppository, by inhalation, or any other suitable manner in an effective amount or dose.

The polypeptides of the invention and/or the compositions comprising the same are administered according to a regimen of treatment that is suitable for treating and/or alleviating the disease, disorder or condition to be treated or alleviated. The clinician will generally be able to determine a suitable treatment regimen, depending on factors such as the disease, disorder or condition to be treated or

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alleviated, the severity of the disease, the severity of the symptoms thereof, the specific polypeptide of the invention to be used, the specific route of administration and pharmaceutical formulation or composition to be used, the age, gender, weight, diet, general condition of the patient, and similar factors well known to the clinician. Generally, the treatment regimen will comprise the administration of one or more polypeptides of the invention, or of one or more compositions comprising the same, in therapeutically effective amounts or doses.

Generally, for the treatment and/or alleviation of the diseases, disorders and conditions mentioned herein and depending on the specific disease, disorder or condition to be treated, the potency of the specific polypeptide of the invention to be used, the specific route of administration and the specific pharmaceutical formulation or composition used, the polypeptides of the invention will generally be administered in an amount between 0.005 and 20.0 mg per kilogram of body weight and dose, preferably between 0.05 and 10.0 mg/kg/dose, and more preferably between 0.5 and 10 mg/kg/dose, either continuously (e.g. by infusion) or more preferably as single doses (such as e.g. twice a week, weekly, or monthly doses; cf. below), but can significantly vary, especially, depending on the before-mentioned parameters. Thus, in some cases it may be sufficient to use less than the minimum dose given above, whereas in other cases the upper limit may have to be exceeded. When administering large amounts it may be advisable to divide them up into a number of smaller doses spread over the day.

Depending on the specific polypeptide of the invention and its specific pharmacokinetic and other properties, it may be administered daily, every second, third, fourth, fifth or sixth day, weekly, monthly, and the like. An administration regimen could include long-term, weekly treatment. By "long-term" is meant at least two weeks and preferably months, or years of duration.

The efficacy of the polypeptides of the invention, and of compositions comprising the same, can be tested using any suitable *in vitro* assay, cell-based assay,

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in vivo assay and/or animal model known *per se*, or any combination thereof, depending on the specific disease involved. Suitable assays and animal models will be clear to the skilled person, and for example include the assays and animal models used in the Examples below.

Preferably, the polypeptides of the invention are having better characteristics than conventional antibodies known in the art (such as the LRP6 binders described in the “Background of the Invention” section above) in at least one of these assays or models, and preferably in one or more of the *in vivo* models.

Formulations

For pharmaceutical use, the polypeptides of the invention may be formulated as a pharmaceutical preparation comprising (i) at least one polypeptide of the invention and (ii) at least one pharmaceutically acceptable carrier, diluent, excipient, adjuvant, and/or stabilizer, and (iii) optionally one or more further pharmacologically active polypeptides and/or compounds. By "pharmaceutically acceptable" is meant that the respective material does not show any biological or otherwise undesirable effects when administered to an individual and does not interact in a deleterious manner with any of the other components of the pharmaceutical composition (such as e.g. the pharmaceutically active ingredient) in which it is contained. Specific examples can be found in standard handbooks, such as e.g. Remington's Pharmaceutical Sciences, 18th Ed., Mack Publishing Company, USA (1990). For example, the polypeptides of the invention may be formulated and administered in any manner known *per se* for conventional antibodies and antibody fragments and other pharmaceutically active proteins. Thus, according to a further embodiment, the invention relates to a pharmaceutical composition or preparation that contains at least one polypeptide of the invention and at least one pharmaceutically acceptable carrier, diluent, excipient, adjuvant and/or stabilizer, and optionally one or more further pharmacologically active substances.

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Pharmaceutical preparations for parenteral administration, such as intravenous, intramuscular, subcutaneous injection or intravenous infusion may for example be sterile solutions, suspensions, dispersions, emulsions, or powders which comprise the active ingredient and which are suitable, optionally after a further dissolution or dilution step, for infusion or injection. Suitable carriers or diluents for such preparations for example include, without limitation, sterile water and pharmaceutically acceptable aqueous buffers and solutions such as physiological phosphate-buffered saline, Ringer's solutions, dextrose solution, and Hank's solution; water oils; glycerol; ethanol; glycols such as propylene glycol, as well as mineral oils, animal oils and vegetable oils, for example peanut oil, soybean oil, as well as suitable mixtures thereof.

Solutions of the polypeptides of the invention may also contain a preservative to prevent the growth of microorganisms, such as antibacterial and antifungal agents, for example, p-hydroxybenzoates, parabens, chlorobutanol, phenol, sorbic acid, thiomersal, (alkali metal salts of) ethylenediamine tetraacetic acid, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Optionally, emulsifiers and/or dispersants may be used. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. Other agents delaying absorption, for example, aluminum monostearate and gelatin, may also be added. The solutions may be filled into injection vials, ampoules, infusion bottles, and the like.

In all cases, the ultimate dosage form must be sterile, fluid and stable under the conditions of manufacture and storage. Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of

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sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

Usually, aqueous solutions or suspensions will be preferred. Generally, suitable formulations for therapeutic proteins such as the polypeptides of the invention are buffered protein solutions, such as solutions including the protein in a suitable concentration (such as from 0.001 to 400 mg/ml, preferably from 0.005 to 200 mg/ml, more preferably 0.01 to 200 mg/ml, more preferably 1.0 - 100 mg/ml, such as 1.0 mg/ml (i.v. administration) or 100 mg/ml (s.c. administration) and an aqueous buffer such as:

- phosphate buffered saline, pH 7.4,
- other phosphate buffers, pH 6.2 to 8.2,
- acetate buffers, pH 3.2 to 7.5, preferably pH 4.8 to 5.5
- histidine buffers, pH 5.5 to 7.0,
- succinate buffers, pH 3.2 to 6.6, and
- citrate buffers, pH 2.1 to 6.2,

and, optionally, salts (e.g. NaCl) and/or sugars (such as e.g. sucrose and trehalose) and/or other polyalcohols (such as e.g. mannitol and glycerol) for providing isotonicity of the solution.

Preferred buffered protein solutions are solutions including about 0.05 mg/ml of the polypeptide of the invention dissolved in 25 mM phosphate buffer, pH 6.5, adjusted to isotonicity by adding 220 mM trehalose. In addition, other agents such as a detergent, e.g. 0.02 % Tween-20 or Tween-80, may be included in such solutions. Formulations for subcutaneous application may include significantly higher concentrations of the polypeptide of the invention, such as up to 100 mg/ml or even above 100 mg/ml. However, it will be clear to the person skilled in the art that the ingredients and the amounts thereof as given above do only represent one, preferred option. Alternatives and variations thereof will be

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immediately apparent to the skilled person, or can easily be conceived starting from the above disclosure.

Also, compared to conventional antibodies or antibody fragments, one major advantage of the use of the polypeptides of the invention is that they can also be easily administered via routes other than parenteral administration and can be easily formulated for such administration. For example, as described in international patent application WO2004/041867, such polypeptides may be formulated for oral, intranasal, intrapulmonary and transdermal administration.

According to a further aspect of the invention, a polypeptide of the invention may be used in combination with a device useful for the administration of the polypeptide, such as a syringe, injector pen, micropump, or other device.

Methods of manufacture and purification

The invention further provides methods of manufacturing a polypeptide of the invention, such methods generally comprising the steps of:

- culturing host cells comprising a nucleic acid encoding a polypeptide of the invention (hereinafter: "nucleic acid of the invention") under conditions that allow expression of the polypeptide of the invention; and,
- recovering or isolating the polypeptide expressed by the host cells from the culture; and
- optionally further purifying and/or modifying and/or formulating the polypeptide of the invention.

A nucleic acid of the invention can e.g. be a DNA molecule comprising coding sequences as well as regulatory sequences and optionally natural or artificial introns, or can be a cDNA molecule. It may have its original codons or may have an optimized codon usage that has been specifically adapted for expression in the intended host cell or host organism. According to one embodiment of the

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invention, the nucleic acid of the invention is in essentially isolated form, as defined above.

The nucleic acid of the invention may also be in the form of, be present in and/or be part of a vector, such as for example a plasmid, cosmid or YAC, which again may be in essentially isolated form. The vector may especially be an expression vector, i.e. a vector that can provide for expression of the polypeptide *in vitro* and/or *in vivo* (e.g. in a suitable host cell, host organism and/or expression system). Such expression vector generally comprises at least one nucleic acid of the invention that is operably linked to one or more suitable regulatory element(s), such as promoter(s), enhancer(s), terminator(s), and the like. Specific examples of such regulatory elements and other elements, such as integration factor(s), selection marker(s), signal or leader sequence(s), reporter gene(s), and the like, useful or necessary for expressing polypeptides of the invention, are disclosed e.g. on pp. 131 to 133 of WO2006/040153.

The nucleic acids of the invention can be prepared or obtained in a manner known *per se* (e.g. by automated DNA synthesis and/or recombinant DNA technology), based on the information on the amino acid sequences for the polypeptides of the invention given herein.

According to another embodiment, the invention relates to a host or host cell that expresses or is capable of expressing a polypeptide of the invention; and/or that contains a nucleic acid encoding a polypeptide of the invention. According to a particularly preferred embodiment, said host cells are bacterial cells, yeast cells, fungal cells or mammalian cells.

For production on industrial scale, preferred heterologous hosts for the (industrial) production of immunoglobulin single variable domain polypeptides and protein therapeutics containing them include strains of *E. coli*, *Pichia pastoris*, and *S. cerevisiae* that are suitable for large scale expression, production and

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fermentation, and in particular for large scale (bio-)pharmaceutical expression, production and fermentation.

Polypeptides of the invention produced in a cell as set out above can be produced either intracellularly (e.g. in the cytosol, in the periplasma or in inclusion bodies) and can then be isolated from the host cells and optionally be further purified; or they can be produced extracellularly (secreted into the medium in which the host cells are cultured) and then isolated from the culture medium and optionally further purified.

Further methods and reagents used for the recombinant production of polypeptides, such as suitable expression vectors, transformation or transfection methods, selection markers, methods of induction of protein expression, culture conditions, and the like, are known in the art. Similarly, protein isolation and purification techniques useful in a method of manufacture of a polypeptide of the invention are well known to the skilled person.

Production of the polypeptides of the invention through fermentation in convenient recombinant host organisms such as *E. coli* and yeast is cost-effective, as compared to conventional antibodies which usually require expensive mammalian cell culture facilities. Furthermore, achievable levels of expression are high and yields of the polypeptides of the invention are in the range of 1 to 10 g/l (E. coli) and up to 10 g/l (yeast) and more.

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EXAMPLES

Example 1: Immunization of llamas with LRP5 and LRP6 for the induction of humoral immune responses

Several protocols for the immunization of llamas needed to be worked out and implemented for identification of LRP5/LRP6 cross-reactive binding VHH domains: Llamas were initially immunized with recombinant extracellular domains of LRP6 and LRP5 proteins (human and mouse). However, functional characterization of the above mentioned LRP5 recombinant protein revealed that only the Wnt1 class binding epitope was properly folded. In contrast, there was no indication for proper folding of the LRP5-Wnt3a class binding domain. Thus, further work was required to develop suitable antigens for immunization. As a work-around, llamas were immunized with HEK293 cells stably transfected with human LRP5 or human LRP6. However, also then, only very low expression of human LRP5 could be achieved, by transient or by stable transfection, and using different cell lines (HEK293, CHO and NIH-3T3 cells). Thus, even further work was required to achieve sufficient expression of LRP5. In the end, and after some unsuccessful trial and error, this could be achieved by developing a protocol involving stable co-transfection of HEK293 cells with MesDC-2, a chaperone intended to increase exogenous LRP5 expression. Even then, i.e. upon co-expression of MesDC-2 during the generation of the LRP5 stable transfected cell line, instability of protein expression was repeatedly observed. This resulted in the problem that LRP5 expression could be lost during immunization and selection. To solve this further problem, passaging of the cells expressing LRP5 was limited as much as possible and additional cell sorting was performed to enrich for cells expressing LRP5.

Llamas were additionally immunized with LRP5-coding DNA and LRP6-coding DNA with and without the hMesDC-2 chaperone in opposite flanks. Additional boosts were delivered to several llamas in an attempt to enhance the cross-

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reactive immune response, with the objective to increase chances of identifying LRP5/LRP6 cross-reactive VHH domains.

Immune blood (PBL) samples were taken at regular intervals, serum responses were determined, and total RNA was prepared from the isolated PBL. Medium serum responses to LRP6 were observed, in contrast to low serum responses to LRP5 upon immunization with recombinant protein. A medium LRP5 immune response was observed for llamas immunized with DNA. In contrast, very low immune response was observed for the cell immunizations. Additionally, synthetic libraries were also explored. Nevertheless, finally, sufficient diversity of the repertoire could be achieved for continuing with the next steps, as outlined in Example 2.

Example 2: Isolation of LRP5 and LRP6 binding monovalent VHH domains (VHHs)

Library construction:

Total RNA was extracted immediately following collection of the immune tissues, and RNA integrity and concentration was verified. cDNA samples were made from these RNA preparations. Nucleotide sequences encoding VHHs were amplified from the cDNA samples in a one-step RT-PCR reaction. The 700bp amplicons specifically amplified from the IgG2 and IgG3 cDNAs in the sample were isolated from agarose gel and subsequently used as template in a nested PCR reaction. The PCR products were subsequently digested with *Sfi*I and *BstE*II and ligated into the corresponding restriction sites of phagemid vector pAX50. The ligation mixtures were electroporated into *Escherichia coli* TG-1. The resulting pool of transformants constituted the genetic diversity of the phage display library.

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pAX50 is an expression vector derived from pUC119, which contains a resistance gene for ampicillin and the *lac* promoter followed by the coding sequence of the pIII protein signal peptide in frame with a downstream VHH domain cloning site. In frame with the VHH domain coding sequence, the vector codes for a C-terminal Myc and hexa-histidine tag and a coli phage pIII protein. After infection of the *E. coli* TG-1 library clones with helper phage, the presence of pAX50 allows for production of phage particles from these clones, displaying the individual VHH domains as a fusion protein with the pIII protein.

Selection:

The VHH domain-phagemid libraries were constructed and used for selections. Given the very high species homology across species (between llama and human LRP5 and LRP6), it was uncertain whether the immune response raised in the llamas would raise sufficient diversity of the VHH domains. Therefore, two synthetic libraries were used in parallel with the immune libraries during selections.

Different strategies were used during selections as follows:
- Alternation of LRP5 and LRP6 derived tools to enhance chances of identifying LRP5/LRP6 cross-reactive VHH domains, e.g. selections on libraries from LRP5 immunized llamas with LRP6 derived proteins or the use of both LRP5 and LRP6 proteins during selection on synthetic libraries.
- Alternation of species source to select for human/mouse LRP5/LRP6 cross-reactive VHH domains (mouse cross-reactivity of such LRP5 and LRP6 antagonist allowing to evaluate efficacy, i.e. tumor growth inhibition, and safety profiles, required for assessment of the therapeutic window, in the same pre-clinical models (i.e. in xenograft tumor-mouse models)).
- “In solution” selections with recombinant proteins to keep the epitopes in their native conformation: As an additional obstacle, LRP5 and LRP6 recombinant proteins were found to lose their proper folding if directly coated on ELISA binding plates. Therefore, the recombinant proteins were biotinylated and, after

confirming proper folding in functional assays, were used for selection "in solution".

- Selections using cells overexpressing LRP5 or LRP6, to have native conformation of the receptors. This surprisingly turned out to be an important ruse, especially needed to improve selection of binders to the Wnt3a–class binding domain of LRP5, since functional data of recombinant protein showed lack of proper folding of the Wnt3a binding epitope.

Example 3: Screening of the monovalent VHHs

After selection, clones were grown in 96 deep well plates (1 mL volume), and VHH expression was induced by adding IPTG. Periplasmic extracts of single clones were prepared according to standard methods, as e.g. reported in WO2011/107507, and screened for binding to human LRP6 and LRP5. Initially, the periplasmic extracts were screened in binding ELISA assays using recombinant LRP5 and LRP6, which represent sensitive, robust and high-throughput assays, when compared to FACS-based binding assays. After purification, VHHs identified in ELISA assays were further characterized using binding FACS assay to confirm binding of purified VHHs to the LRP5 and LRP6 receptors in their native conformation.

Usually, a good correlation between ELISA and FACS binding assays is expected. However, in the present case, the best LRP5 and LRP6 binding VHHs in ELISA assays (i.e. with high affinity to recombinant LRP5 or LRP6 ectodomain) did not show any binding or very weak binding to human LRP5 and LRP6 in a FACS binding assay, as shown in Figure 2 for the panel "2" binders. The use of different coating buffers (dPBS vs. bicarbonate buffer) and blocking solutions in the ELISA set-up (Marvel vs. BSA) did not resolve the observed discrepancy. Instead, it was found out that very weak binders in ELISA showed high affinity to LRP5 and LRP6 in binding FACS assays using LRP5 and LRP6 expressing cells, as shown in Figure 2 for the panel "1" binders. These further data and

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experiments thus allowed for selection of high affinity binders recognizing the native conformation of the two receptors. Additionally, confirmation was thereby obtained that these high affinity binders are recognizing a conformation dependent epitope, and not a linear epitope in LRP5 and LRP6 proteins. These further non-routine data and experiments thus allowed for selection of therapeutically relevant LRP5 and LRP6 binders, which should have high affinity towards LRP5 and LRP6 expressed on the plasma membrane in their native conformation.

Thus, despite (i) the low throughput of FACS binding assays, (ii) the less robust assay set-up, and (iii) the above-described difficulties encountered due to the loss of recombinant protein expression upon passaging of the cells over-expressing LRP5, these assays were subsequently used for further selection and characterization of high affinity VHH binders. Briefly, cells were incubated with purified VHH dilutions (1:5 serial dilutions from 1μM to 1pM, final concentration) for 1.5 hours at 4 °C on a plate shaker. After washing the cells 5 x with FACS buffer, consisting of 1x phosphate buffered saline (PBS) + 10% fetal bovine serum (FBS) + 0,05% sodium azide, they were incubated for 30 minute up to 1 hour at 4°C with a polyclonal mouse antibody which binds to the framework regions of the VHHs and, therefore, binds to all the LRP5 and/or LRP6 binders tested. After washing the cells 3X with FACS buffer, the cells were incubated for 30 minutes up to 1 hour at 4 °C with the labeled secondary antibody (anti-mouse PE), followed by 3X washing step with FACS buffer. Fluorescence was measured using FACS Array (BD).

A total of hundred LRP5/LRP6 cross-reactive VHHs families/clusters were identified from immune libraries and from synthetic origin, based on binding FACS data and sequence analysis. Representative examples thereof are shown, and defined by their sequence, further below. The VHHs were expressed in *E.coli* and purified. In case expression in *E.coli* proved insufficient, VHHs were

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produced in *Pichia pastoris*. A brief description of expression and purification of VHHs is reported further below.

Generic expression of VHHs in *E.coli:*

The encoding sequences were cloned into the pAX100 expression vector and expressed in *E.coli* as c-Myc hexa-histidine-tagged proteins. *E.coli* TG-1 cells containing the VHH constructs of interest were grown (37 °C, 250 rpm) in shake flasks in TB medium supplemented with kanamycin and induced by addition of 1mM IPTG for expression. After spinning the cell cultures, periplasmic extracts were prepared by freeze-thawing the pellets and resuspending in dPBS.

Generic expression of VHHs in *Pichia (P.) pastoris:*

The encoding sequences were cloned into the pAX159 expression vector and expressed in *P. pastoris* as c-Myc hexa-histidine-tagged proteins. *P. pastoris* X-33 cells containing VHH constructs of interest were grown (30 °C, 250 rpm) in BGCM (Buffered Glycerol-Complex Medium; Invitrogen). On the third day, the medium was switched to BMCM (Buffered Methanol-Complex Medium; Invitrogen) and the culture was grown further and was regularly induced by addition of 0.5 vol% methanol (100%). After spinning the cell culture, supernatant (containing the secreted VHH) was collected.

VHH purification:

Hexa-histidine-tagged VHHs were purified on the Tecan EVO150 by immobilised metal affinity chromatography (RoboColumns 100ul Nickel Sepharose™ 6 FF, Atoll), eluted from the column with 250mM imidazole and subsequently desalted towards dPBS. The purity and integrity of VHHs was verified by SDS-PAGE and/or western blot using anti-Myc and anti-VHH detection.

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Example 4: *In vitro* characterization of purified monovalent VHHs

After VHH screening, the purified VHHs having high affinity to cells expressing LRP5 and LRP6 were characterized by using several functional and biophysical assays as described below:

4.1 LRP5 and LRP6 binding potency and cross-reactivity: FACS-based DKK1 competition assay

During characterization of LRP5/LRP6 cross-reactive monovalent VHHs, it was observed that data obtained in binding FACS assay did not always correlate with the potency observed in Wnt1 and Wnt3a reporter assays, most likely due to fast off-rate of some of the VHHs. Therefore, this additional assay needed to be established (i.e. a DKK1 competition FACS), which proved to be more reliable for selectivity and binding potency determination and comparison between LRP5 and LRP6 binding. The aim was to select functional VHHs which bind to LRP5 and LRP6 with a similar potency, in order to achieve blockade of both receptors at the same concentration. The identified Wnt1 and Wnt3a functional VHHs were thus characterized in DKK-1 competition FACS as follows:

For FACS-based DKK1 competition assay, HEK293 cells with stable overexpression of human LRP5 or human LRP6 were used. Human recombinant DKK1 (rhDKK1 - R&D Systems, Cat 5439-DK/CF) was added to the cells at the constant final concentration of 1nM. Cells were incubated with rhDKK1 and LRP5 and/or LRP6 binder dilutions (1:5 serial dilution of the purified VHHs) for 1.5 hours at 4 °C on a plate shaker. After washing the cells three times with FACS buffer, they were incubated with biotinylated goat anti-human DKK1 (R&D Systems, Cat BAF1096) for 30 minutes at 4 °C on a plate shaker. After washing the cells three times with FACS buffer, they were incubated with Streptavidin PE (BD Biosciences, Cat 554061) for 30 minute to 1 hour at 4 °C on a plate shaker in the dark. Cells were washed twice with FACS buffer and fluorescence was measured using FACS Array (BD) and MCF values were reported.

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LRP5/LRP6 cross-reactive VHHs are expected to compete with human DKK1 for binding to HEK293 overexpressing human LRP5, as well as for binding to HEK293 overexpressing human LRP6. In contrast, an LRP5 specific VHH would compete with human DKK1 for binding to HEK293 cells overexpressing human LRP5 but not, or with very low potency (>200nM) for binding to HEK293 cells overexpressing human LRP6 (and the same would apply, vice versa, to LRP6 specific VHHs). As a result of this experiment, it could be shown that the present LRP5/LRP6 cross-reactive VHHs competed with human DKK1 for binding to HEK293 cells overexpressing human LRP5, as well as to those overexpressing human LRP6 (i.e. decrease in MCF value with increasing concentration of the binder with complete inhibition of DKK1 binding corresponded to ≤ 60 MCF values at the highest concentration tested).

4.2 Species cross-reactivity: mouse and cynomolgus monkey

To determine whether the selected panel of LRP5/LRP6 cross-reactive VHHs was able to bind to LRP5 and LRP6 of mouse and of cynomolgus monkey origin, DKK1 competition FACS was performed as follows:

Serial dilutions of VHHs were incubated with HEK293 cells stably expressing mouse LRP5, cyno LRP5, mouse LRP6, or cyno LRP6 in the presence of 1 and 0.3 nM hDKK1 (concentration below EC50 value of mouse and cyno, respectively). Binding of DKK1 to the cells was detected using a biotinylated anti-DKK1 antibody with Streptavidin-PE as secondary detection as described above. As a result, such cross-reactivity could be demonstrated.

4.3 Epitope binning

Binning experiments were performed for the most potent Wnt1 signaling blocking LRP5/LRP6 cross-reactive VHHs, to identify different epitope bins. In particular,

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individual VHHs were analyzed for their ability to compete with other biotinylated VHHs (called reference VHHs) for LRP5 and LRP6 receptor binding using FACS based assays. Serial dilutions of the individual VHHs were incubated on HEK293 stably expressing human LRP5 or LRP6 together with 200pM or 500pM biotinylated reference VHH (concentrations below EC50 value). The binding of biotinylated reference VHH to the cells was detected using streptavidin-PE. A VHH competing with the reference VHHs for binding to LRP5 and LRP6 shows a decrease in the fluorescence measured using FACS Array.

As a result of these experiments, the Wnt1 blockers could be categorized into three bins. For the Wnt3a blockers, the lower affinity of the VHHs did not allow to perform epitope binning experiments.

4.4 Wnt1 and Wnt3a reporter assays

The ability of the LRP5/LRP6 cross-reactive VHHs to inhibit Wnt signaling was tested in functional Wnt1 and Wnt3a assays. Also in this regard, no established protocol could be used, but several attempts needed to be tried to establish biochemical functional assays, such as Wnt1/Wnt3a – LRP5 / LRP6 blocking assays: In addition to the difficulties encountered with recombinant LRP5 and LRP6 proteins (see Example 1), a functional recombinant Wnt1 ligand (including commercially available) is not available. Wnt proteins contain many conserved cysteines and are modified by mono-unsaturated fatty acid (palmitoleic acid), attached to a conserved serine. These post-translational modifications are required for efficient signaling and for Wnt secretion. Structural analyses show that one of the domains, containing the palmitoleic acid lipid, is required for binding to the Frizzled receptors, leading to a conformational change that allows the interaction of the Wnt ligands with LRP5 and LRP6 on the cell surface. Thus, it turned out that such post-translational modification is required for functional studies involving this protein, but at the same time such lipid-based post-translational modifications render these proteins very difficult to express and

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purify (low solubility). Thus, this turned out to be a major hurdle for biochemical assays.

Thus, a cell based functional assay was developed for characterization of the purified VHHs: A Wnt beta-lactamase reporter gene assay. In particular for the Wnt1 pathway inhibition, CellSensor LEF/TCF-bla FreeStyle 293F cells (Invitrogen, Cat. K1677) were transfected with human Wnt1, and clones with stable overexpression of human Wnt1 were selected. For testing the Wnt3a pathway inhibition, CellSensor LEF/TCF-bla FreeStyle 293F cells with stable overexpression of human Wnt3a were generated. The CellSensor® LEF/TCF - bla FreeStyle™ 293 cell line contains a beta-lactamase reporter gene under control of the Wnt inducible LEF/TCF promoter, which is stably integrated into FreeStyle™ 293 cells (Invitrogen). The expression of Wnt1 or Wnt3a in these cells thus results in the constitutive expression and, therefore, enzymatic activity of the beta-lactamase. The treatment with LRP5/LRP6 cross-reactive functional VHHs is thus expected to lead to inhibition of Wnt1 and Wnt3a pathway leading to inhibition of beta-lactamase enzymatic activity.

For the assay, 1E06 / ml cells with overexpression of Wnt1 or Wnt3a were seeded into a 384 well tissue culture plate and incubated overnight at 37 °C. The following day, serial dilutions of various LRP5/LRP6 cross-reactive VHH solutions were prepared and added to the cells in the presence of LiCl at the final concentration of 10nM. DKK1, as positive control, was added to the cells at the final concentration of 200nM. DKK1 treatment resulted in a complete inhibition of Wnt1 and Wnt3a pathway, and therefore a complete inhibition of beta-lactamase enzymatic activity. The cells were incubated overnight at 37 °C. The following day, beta-lactamase enzymatic activity was measured according to the manufacturer's instructions (Invitrogen, Cat K1085). For fluorescence emission, values at 460 nm and 530 nm were obtained using a standard fluorescence plate reader and the 460/530 nm emission ratios plotted for the indicated treatment.

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Efficacy was calculated against the positive control (DKK1; 200nM final concentration).

A total of twelve LRP5/LRP6 cross-reactive Wnt1 blockers with full efficacy and potency better than 50nM were selected. Fourteen cross-reactive Wnt3a blockers, mainly with low potencies, were identified. Only one Wnt3a blocker showed good potency (below 5nM).

4.5 Wnt1 and Wnt3a phosphorylation assays

The most potent and efficacious leads from each bin for the Wnt1 blockers and the most potent and efficacious Wnt3a blockers were subsequently tested in Wnt1 and Wnt3a dependent LRP5 and LRP6 phosphorylation assays. Cellsensor LEF/TCF 293F cells from Invitrogen (cat K1677), co-transfected with expression vectors coding for either Wnt1 or Wnt3a, were used in the phosphorylation assays. Since Wnt-Frizzled-LRP5 or -LRP6 complex formation results in LRP5 or LRP6 phosphorylation and subsequent downstream signaling, quantification of phosphorylation can be used to measure such signaling. To obtain a LRP5 and LRP6 specific read-out, the cells were lysed and immuno-precipitation was performed with an LRP6 or LRP5 selective antibody (directed against the intracellular domain of the two receptors). In Western blot, phosphorylated LRP6 or LRP5 was detected using a polyclonal anti-phospho-LRP6 (Ser1490) antibody (Cell Signaling Technology), which detects both LRP6 and LRP5 phosphorylated protein. A selected panel of purified Wnt1 and Wnt3a blocking VHHs, containing at least one representative VHH from each bin, were tested at final concentrations of 10 to 100nM. In particular, cells were incubated overnight in the presence of the blocking VHHs prior cell lysis and LRP5 and LRP6 immuno-precipitation. Efficacy of the Wnt1 and Wnt3a blocking VHHs in blocking LRP5 and LRP6 phosphorylation was calculated via quantification of the Western blot bands against the positive control (DKK1, final concentration of 1 uM).

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4.6 Biophysical characterization

The LRP5/LRP6 cross-reactive VHHs were further characterized for expression and purification in *E. coli* and in *Pichia pastoris,* as reported in Example 3. In particular, expression yields for the monovalent lead panel VHHs was considered acceptable if they were above 0.1 mg/L. The selected LRP5/LRP6 cross-reactive VHHs showed expression ranging between 0.1 and 8.2 mg/L in *E.coli* and higher in *Pichia pastoris* (> 1mg/L). The expression was evaluated by SDS-PPAGE analysis.

Thermal stability of the monovalent LRP5/LRP6 cross-reactive VHHs was determined in a fluorescence-based thermal shift assay (TSA) using the Lightcycler (Roche). VHHs were incubated at different pH values in the presence of Sypro Orange and a temperature gradient was applied. Upon heat-induced unfolding, hydrophobic patches of the proteins are exposed to which the Sypro Orange binds resulting in an increase in fluorescence intensity (Ex/Em = 465/580nm). The inflection point of the first derivative of the fluorescence intensity curve serves as a measure of the melting temperature (Tm). For all VHHs, Tm increased with increasing pH and levels off at pH 6, a typical Tm pattern seen for VHHs. An average of 82 °C at pH 7 was obtained for the LRP5/LRP6 cross-reactive Wnt1 blocker VHHs and Wnt3a blocker VHHs.

Potential occurrence of aggregation and multimerisation for LRP5 and LRP6 VHHs was investigated by analytical size exclusion chromatography (SEC). To this end, 8ug of purified VHH sample at 0,5 mg/mL were injected via the Dionex Ultimate 3000 equipment on an Agilent SEC-3 column. L-arginine buffer (10mM phosphate, 300mM Arg-HCl, pH 6.0) was used as mobile phase and a flow rate of 1mL/min was applied. None of the LRP5/LRP6 VHHs showed major aggregation issues during SEC analysis: profiles indicated more than 95% monomer for most samples.

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Example 5: Generation and characterization of half-life extended biparatopic constructs

The LRP5/LRP6 cross-reactive Wnt1 and Wnt3a VHHs were used as building blocks to generate a biparatopic construct as depicted in Figure 1. A genetic fusion to a serum albumin binding VHH was used as a half-life extension methodology. The three building blocks (Wnt1 blocker, Wnt3a blocker, and the albumin binder) were linked via a flexible linker. VHHs were produced in *P. pastoris* and purified as described in Example 3. The resulting constructs, i.e. biparatopic, half-life extended LRP5/LRP6 cross-reactive VHH constructs, were cloned in *P. pastoris* expression vector pAX159, in the form of C-terminally cMyc-hexa-histidine tagged VHH constructs, according to standard procedures as e.g. reported in WO2012/131078. Different orientation of the building blocks and different linkers, esp. GS-linkers, were explored. A relatively long GS-linker was selected, based on modeling data reflecting an extended surface area between the potential Wnt1 and Wnt3a binding sites in LRP6 (i.e. beta-propellers 1 and 2 not being in close proximity to beta-propeller 3). Best results regarding potency in the combined Wnt1 and Wnt3a reporter assay were obtained by putting the human serum albumin/HSA binding VHH in the middle. A 35 GS linker was used, and Wnt1 and Wnt3a VHH blockers arranged in a preferred order.

For selection of optimal VHH binders and binder combinations, a library was generated where the human serum albumin (HSA) binding VHH was placed in between the LRP5/LRP6 Wnt1-Wnt3a blockers. In particular, the panel of high affinity binders with high potency and efficacy in Wnt1 or Wnt3a assays (reporter and phosphorylation assays) were used in the library to generate half-life extended biparatopic constructs designed as depicted in Figure 1. After expression in *Pichia pastoris* (as reported in Example 3) followed by purification, the half-life extended biparatopic constructs were subsequently screened in the Wnt1 and Wnt3a reporter assays (described in Example 4) in the presence of

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30uM HSA at three dilutions (1/100, 1/1000, 1/7000), to assess efficacy and relative potency. In general, a good correlation was observed between the data in the Wnt1 and Wnt3a reporter assays and high efficacies were measured for numerous formats. A total of 11 half-life extended biparatopic LRP5 and LRP6 constructs were selected for further characterization, taking into account the efficacy in both reporter assays and diversity of the Wnt1 and Wnt3a blockers. This further characterization assays are described below.

Wnt1 / Wnt3a reporter assays:

Wnt1 and Wnt3a reporter assays were performed as described in Example 4.4, in the presence of 30uM HSA final concentration. The purified biparatopic LRP5/LRP6 constructs were tested at 12 dilutions, starting from 2.5 uM.
The majority of the constructs showed high potency - ranging between 1.7 nM and 0.16 nM - and full efficacy in both reporter assays, as shown in Table IV below. The sequences of the individual Wnt1 and Wnt3a inhibiting VHH domains set out therein are provided in Table V below:

Table IV: Potency and efficacy of selected half-life extended biparatopic LRP5/LRP6 cross-reactive VHH constructs in the reporter assays in the presence of HSA

			Wnt1 reporter assay		Wnt3a reporter assay	
Construct	N-term	C-term	IC_{50} (M)	% inh.	IC_{50} (M)	% inh.
F013500053	F0129093A01	F0130333G06	2,3E-10	102	4,1E-10	97
F013500039	F0129093A03	F0130333E06	1,7E-09	102	1,6E-09	82
F013500046	F0130332D03	F0129093A01	5,1E-10	102	6,0E-10	96
F013500016	F0130332D03	F0130367B10	3,1E-10	102	2,7E-10	99
F013500018	F0130332D03	F0130378B05	7,4E-10	102	1,3E-09	98
F013500047	F0130333E06	F0129093A01	8,8E-10	102	9,1E-10	94
F013500026	F0130333E06	F0130367B10	3,3E-10	102	2,6E-10	100
F013500021	F0130333G06	F0130367B10	1,6E-10	102	1,8E-10	102

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F013500032	F0130378A04	F0130333G06	2,4E-10	102	4,3E-10	94
F013500033	F0130378B05	F0130333G06	1,8E-10	102	2,5E-10	88
F013500030	F0130378B05	F0130372C08	1,4E-09	102	1,3E-09	96

Table V: Sequences of the VHH domains set out in Table IV

VHH ID Specificity	Amino Acid Sequence	SEQ ID NO:
F0129093A01 Wnt3a	EVQLVESGGGLVQPGGSLRLSCAASGRTFSSYAMGWFRQAPGKER EFVAAISWSGGSTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDT AVYYCAASPIPYGSLLRRRNNYDYWGQGTLVTVSSAAAEQKLISEED LNGAAHHHHHH	28
F0130333G06 Wnt1	EVQLVESGGGLVQPGGSLRLSCAASGGTFSSYAMGWFRQAPGKER EFVAAIRRSGRRTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTA VYYCAAARRVRSSTRYNTGTWWWEYWGQGTLVTVSSAAAEQKLI SEEDLNGAAHHHHHH	29
F0129093A03 Wnt3a	EVQLVESGGGLVQPGGSLRLSCAASGRTFSTYVMGWFRQAPGKER EFVAAINWSGSRTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDT AVYYCAASRSSYAGRTYYELYDYWGQGTLVTVSSAAAEQKLISEEDL NGAAHHHHHH	30
F0130333E06 Wnt1	EVQLVESGGGLVQPGGSLRLSCAASGRTFSTYTVGWFRQAPGKERE FVAAIRRRGSSTYYSDSVKGRFTISRDNSKNTVYLQMNSLRPEDTAV YYCAADTRTVALLQYRYDYWGQGTLVTVSSAAAEQKLISEEDLNGA AHHHHHH	31
F0130332D03 Wnt1	EVQLVESGGGLVQPGGSLRLSCAASGLTFSRYTMGWFRQAPGKER EFVAAINRSGGSTYYSDSVKGRFTISRDNSKNTVYLQMNSLRPEDTA VYYCAADRRGRGENYSLLYSSNRYEYWGQGTLVTVSSAAAEQKLISE EDLNGAAHHHHHH	32
F0130367B10 Wnt3a	EVQLVESGGGLVQPGGSLRLSCAASGGTFSSYAMGWFRQAPGKER EFVAAISWRSGSTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEGT AVYYCAADPRGYGVAYVSAYYEYWGQGTLVTVSSGAAEQKLISEED LNGAAHHHHHH	33
F0130378B05 Wnt3a	EVQLVESGGGLVQPGGSLRLSCVASGRTFSSYAMGWFRQAPGKER EFVAAISRSGGRTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTA VYYCAADRRVYSTLPPTTSRYNYWGQGTLVTVSSAAAEQKLISEEDL NGAAHHHHHH	34

F0130378A04 Wnt3a	EVQLVESGGGLVQPGGSLRLSCAASGRTFSSYAMGWFRQAPGKER EFVAAITRTGRRTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTA VYYCAADRRGYYYYDSSFYDYWGQGTLVTVSSAAAEQKLISEEDLN GAAHHHHHH	35
F0130372C08 Wnt1	EVQLVESGGGLVQPGGSLRLSCAASGRTFSDYGMGWFRQAPGKE REFVAAISWSGGRTYYADSVKGRFTISRDNSKNTVYLQMNSLRPED TAVYYCAAKRRGRGSVSPNSSSRYNYWGQGTLVTVSSAAAEQKLIS EEDLNGAAHHHHHH	36
F013500016	EVQLVESGGGLVQPGGSLRLSCAASGLTFSRYTMGWFRQAPGKER EFVAAINRSGGSTYYSDSVKGRFTISRDNSKNTVYLQMNSLRPEDTA VYYCAADRRGRGENYSLLYSSNRYEYWGQGTLVTVSSGGGGSGGG GSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGN SLRLSCAASGFTFSSFGMSWVRQAPGKGLEWVSSISGSGSDTLYAD SVKGRFTISRDNAKTTLYLQMNSLRPEDTAVYYCTIGGSLSRSSQGTL VTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEV QLVESGGGLVQPGGSLRLSCAASGGTFSSYAMGWFRQAPGKEREF VAAISWRSGSTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEGTAV YYCAADPRGYGVAYVSAYYEYWGQGTLVTVSSGAAEQKLISEEDLN GAAHHHHHH	37
F013500018	EVQLVESGGGLVQPGGSLRLSCAASGLTFSRYTMGWFRQAPGKER EFVAAINRSGGSTYYSDSVKGRFTISRDNSKNTVYLQMNSLRPEDTA VYYCAADRRGRGENYSLLYSSNRYEYWGQGTLVTVSSGGGGSGGG GSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGN SLRLSCAASGFTFSSFGMSWVRQAPGKGLEWVSSISGSGSDTLYAD SVKGRFTISRDNAKTTLYLQMNSLRPEDTAVYYCTIGGSLSRSSQGTL VTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEV QLVESGGGLVQPGGSLRLSCVASGRTFSSYAMGWFRQAPGKEREF VAAISRSGGRTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVY YCAADRRVYSTLPPTTSRYNYWGQGTLVTVSSGAAEQKLISEEDLN GAAHHHHHH	38
F013500021	EVQLVESGGGLVQPGGSLRLSCAASGGTFSSYAMGWFRQAPGKER EFVAAIRRSGRRTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTA VYYCAAARRVRSSTRYNTGTWWWEYWGQGTLVTVSSGGGGSGG GGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPG NSLRLSCAASGFTFSSFGMSWVRQAPGKGLEWVSSISGSGSDTLYA DSVKGRFTISRDNAKTTLYLQMNSLRPEDTAVYYCTIGGSLSRSSQG TLVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSE VQLVESGGGLVQPGGSLRLSCAASGGTFSSYAMGWFRQAPGKERE FVAAISWRSGSTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEGTA VYYCAADPRGYGVAYVSAYYEYWGQGTLVTVSSGAAEQKLISEEDL NGAAHHHHHH	39

F013500026	EVQLVESGGGLVQPGGSLRLSCAASGRTFSTYTVGWFRQAPGKERE FVAAIRRRGSSTYYSDSVKGRFTISRDNSKNTVYLQMNSLRPEDTAV YYCAADTRTVALLQYRYDYWGQGTLVTVSSGGGGSGGGGSGGGG SGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGNSLRLSCA ASGFTFSSFGMSWVRQAPGKGLEWVSSISGSGSDTLYADSVKGRFT ISRDNAKTTLYLQMNSLRPEDTAVYYCTIGGSLSRSSQGTLVTVSSG GGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESG GGLVQPGGSLRLSCAASGGTFSSYAMGWFRQAPGKEREFVAAISW RSGSTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEGTAVYYCAAD PRGYGVAYVSAYYEYWGQGTLVTVSSGAAEQKLISEEDLNGAAHH HHHH	40
F013500030	EVQLVESGGGLVQPGGSLRLSCVASGRTFSSYAMGWFRQAPGKER EFVAAISRSGGRTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTA VYYCAADRRVYSTLPPTTSRYNYWGQGTLVTVSSGGGGSGGGGSG GGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGNSLR LSCAASGFTFSSFGMSWVRQAPGKGLEWVSSISGSGSDTLYADSVK GRFTISRDNAKTTLYLQMNSLRPEDTAVYYCTIGGSLSRSSQGTLVTV SSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVE SGGGLVQPGGSLRLSCAASGRTFSDYGMGWFRQAPGKEREFVAAI SWSGGRTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVYYCA AKRRGRGSVSPNSSSRYNYWGQGTLVTVSSGAAEQKLISEEDLNGA AHHHHHH	41
F013500032	EVQLVESGGGLVQPGGSLRLSCAASGRTFSSYAMGWFRQAPGKER EFVAAITRTGRRTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTA VYYCAADRRGYYYYDSSFYDYWGQGTLVTVSSGGGGSGGGGSGG GGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGNSLRLS CAASGFTFSSFGMSWVRQAPGKGLEWVSSISGSGSDTLYADSVKG RFTISRDNAKTTLYLQMNSLRPEDTAVYYCTIGGSLSRSSQGTLVTVS SGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVES GGGLVQPGGSLRLSCAASGGTFSSYAMGWFRQAPGKEREFVAAIR RSGRRTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVYYCAA ARRVRSSTRYNTGTWWWEYWGQGTLVTVSSGAAEQKLISEEDLN GAAHHHHHH	42

F013500033	EVQLVESGGGLVQPGGSLRLSCVASGRTFSSYAMGWFRQAPGKER EFVAAISRSGGRTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTA VYYCAADRRVYSTLPPTTSRYNYWGQGTLVTVSSGGGGSGGGGSG GGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGNSLR LSCAASGFTFSSFGMSWVRQAPGKGLEWVSSISGSGSDTLYADSVK GRFTISRDNAKTTLYLQMNSLRPEDTAVYYCTIGGSLSRSSQGTLVTV SSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVE SGGGLVQPGGSLRLSCAASGGTFSSYAMGWFRQAPGKEREFVAAI RRSGRRTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVYYCA AARRVRSSTRYNTGTWWWEYWGQGTLVTVSSGAAEQKLISEEDL NGAAHHHHHH	43
F013500039	EVQLVESGGGLVQPGGSLRLSCAASGRTFSTYVMGWFRQAPGKER EFVAAINWSGSRTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDT AVYYCAASRSSYAGRTYYELYDYWGQGTLVTVSSGGGGSGGGGSG GGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGNSLR LSCAASGFTFSSFGMSWVRQAPGKGLEWVSSISGSGSDTLYADSVK GRFTISRDNAKTTLYLQMNSLRPEDTAVYYCTIGGSLSRSSQGTLVTV SSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVE SGGGLVQPGGSLRLSCAASGRTFSTYTVGWFRQAPGKEREFVAAIR RRGSSTYYSDSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVYYCAAD TRTVALLQYRYDYWGQGTLVTVSSGAAEQKLISEEDLNGAAHHHH HH	44
F013500046	EVQLVESGGGLVQPGGSLRLSCAASGLTFSRYTMGWFRQAPGKER EFVAAINRSGGSTYYSDSVKGRFTISRDNSKNTVYLQMNSLRPEDTA VYYCAADRRGRGENYSLLYSSNRYEYWGQGTLVTVSSGGGGSGGG GSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGN SLRLSCAASGFTFSSFGMSWVRQAPGKGLEWVSSISGSGSDTLYAD SVKGRFTISRDNAKTTLYLQMNSLRPEDTAVYYCTIGGSLSRSSQGTL VTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEV QLVESGGGLVQPGGSLRLSCAASGRTFSSYAMGWFRQAPGKEREF VAAISWSGGSTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAV YYCAASPIPYGSLLRRRNNYDYWGQGTLVTVSSGAAEQKLISEEDLN GAAHHHHHH	45

F013500047	EVQLVESGGGLVQPGGSLRLSCAASGRTFSTYTVGWFRQAPGKERE FVAAIRRRGSSTYYSDSVKGRFTISRDNSKNTVYLQMNSLRPEDTAV YYCAADTRTVALLQYRYDYWGQGTLVTVSSGGGGSGGGGSGGGG SGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGNSLRLSCA ASGFTFSSFGMSWVRQAPGKGLEWVSSISGSGSDTLYADSVKGRFT ISRDNAKTTLYLQMNSLRPEDTAVYYCTIGGSLSRSSQGTLVTVSSG GGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESG GGLVQPGGSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVAAISW SGGSTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVYYCAAS PIPYGSLLRRRNNYDYWGQGTLVTVSSGAAEQKLISEEDLNGAAHH HHHH	46
F013500053	EVQLVESGGGLVQPGGSLRLSCAASGRTFSSYAMGWFRQAPGKER EFVAAISWSGGSTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDT AVYYCAASPIPYGSLLRRRNNYDYWGQGTLVTVSSGGGGSGGGGS GGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGNSL RLSCAASGFTFSSFGMSWVRQAPGKGLEWVSSISGSGSDTLYADSV KGRFTISRDNAKTTLYLQMNSLRPEDTAVYYCTIGGSLSRSSQGTLVT VSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLV ESGGGLVQPGGSLRLSCAASGGTFSSYAMGWFRQAPGKEREFVAA IRRSGRRTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVYYCA AARRVRSSTRYNTGTWWWEYWGQGTLVTVSSGAAEQKLISEE DLNGAAHHHHHH	47

(*Note*: The molecules described in this Table V include a myc-hexa-histidine tag (underlined), to allow for easier purification of the recombinantly expressed polypeptides; this tag is not required for - nor does it usually interfere with - the binding of the molecules to their targets)

Example 6: Sequence optimization of VHHs and VHH constructs

Sequence optimization is a process in which the parental sequence is mutated to make it more identical to the human IGHV3-IGHJ germline consensus sequence. For example, specific amino acids in the framework regions (with the exception of the so-called hallmark residues) are exchanged for their human counterparts, in a way that the protein structure, activity and stability shall be preserved.

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These mutations may be categorized as follows:

1. Standard: Sequence optimization of these positions is not expected to dramatically change the stability or activity or affinity of the VHH and they are therefore altered all at once, yielding a basic variant.
2. Unique: It is not known if sequence optimization of these positions affects the stability or activity or affinity of the VHH and therefore they are investigated on an individual basis on top of the basic variant.

Hallmark residues are known to be critical for the stability, activity and affinity of the VHH and are therefore not mutated.

In addition, the amino acids present in the CDRs for which there is experimental evidence that they are sensitive to post-translational modifications (PTM) were altered in such a way that the PTM site is inactivated while the protein structure, activity and stability shall remain intact. The most common post-translational modifications described for antibodies and VHHs are listed in Table VI below. The sensitivity of the VHHs for post-translational modifications was analysed in accelerated stress studies, applying several standard conditions including H_2O_2 treatment to analyze methionine oxidation, high temperature, high pH and long storage to study asparagine deamidation and aspartate isomerization. The percentage of oxidation, deamidation and isomerization was measured according to standard procedures and compared to the reference samples (VHHs stored at -20°C). Whole protein analysis in Reverse Phase Chromatography (RPC) and peptide mapping using Mass Spectrometry (MS) were performed to identify potentially sensitive residues. In case of post-translational modifications observed in the VHHs after stress test, the corresponding amino acid(s) were mutated.

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Table VI: Potential post-translational modifications, and motifs potentially triggering them

Motif	Modification
M	Met oxidation
N-S/G/H/N/A	Asn deamidation
D-S/G/H	Asp isomerisation
N-X-S/T-X (X ≠ P)	Asn glycosylation
Q/E	pyroglutamate

As a result, several mutations were introduced in the constructs set out above, resulting i.a. in the three constructs shown in Table III above, which were chosen for further *in vitro* and *in vivo* characterization, as set out in the Examples further below.

Example 7: *In vitro* characterization of three half-life extended biparatopic LRP5/LRP6 cross-reactive VHH constructs; Comparison to other LRP6 binding molecules

After VHH sequence optimization, three half-life extended biparatopic LRP5/LRP6 cross-reactive VHH constructs were recombinantly expressed and purified, and were characterized by using several functional and biophysical assays as described below.

7.1 FACS binding assays

Binding to human LRP5 and LRP6 was determined on cells by FACS analysis, as reported in Figures 3A and 3B. In particular, binding to human LRP5 was tested on HEK293 cells with stable overexpression of human LRP5. For human LRP6

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binding, HEK293 cells with stable overexpression of human LRP6 were used. The cells were incubated with the LRP5 and LRP6 binder dilutions (1:5 serial dilution of the binders corresponding to the final concentrations indicated in Figure 3A and Figure 3B) for 1.5 hours at 4°C on a plate shaker. After washing the cells 5 times with FACS buffer (1x PBS (Invitrogen cat.no.141190-094) + 10% FBS (Sigma cat.no. F7524) + 0,05% sodium azide), they were incubated for 1 hour at 4°C with a polyclonal mouse antibody which binds to the framework regions of the VHHs. After washing the cells 3 times with FACS buffer, the cells were incubated for 1 hour at 4°C with the labelled secondary antibody (anti-mouse PE (115-116-071), followed by 3 times washing step with FACS buffer. Fluorescence was measured using FACS Array (BD). Binding to human LRP5 and LRP6 corresponds to ≥ 600 MCF values at the highest concentration tested. Negative control consisted of a non-targeting binder (VHH construct that binds to a bacterial protein which is not expressed in HEK293 cells). As shown in Figure 3A and Figure 3B, respectively, binding to human LRP5 and LRP6 corresponds to ≥ 600 MCF and to ≥ 1600 MCF values, respectively, at the highest tested concentrations of the three half-life extended biparatopic LRP5/LRP6 cross-reactive VHH constructs. These data confirm that the formatted, biparatopic, and sequence-optimized binding molecules bind to both human LRP5 and human LRP6 in their native conformation in a cellular assay system. EC50 values of binding to hLRP5 and hLRP6 are reported in Table VII below.

Table VII: EC_{50} values of binding to human LRP5 and LRP6 determined by FACS binding assays

FACS based binding assay	F013500571	F013500575	F013500720
hLRP5, EC_{50} (nM)	0.01	0.001	0.02
hLRP6, EC_{50} (nM)	0.02	0.01	0.02

7.2 FACS - DKK1 competition assay

Potency and efficacy of the three LRP5/LRP6 cross-reactive VHH constructs were further analysed using the FACS-based DKK1 competition assay, as described in Example 4.1. HEK293 cells with stable overexpression of human LRP5 or human LRP6 were incubated with serial dilution of the LRP5/LRP6 cross-reactive VHH constructs (1:5 serial dilution corresponding to the final concentrations indicated in Figure 4A and Figure 4B). The LRP5/LRP6 cross-reactive VHHs competed with human DKK1 for binding to HEK293 cells overexpressing human LRP5, as well as for binding to HEK293 cells overexpressing human LRP6, as shown in Figures 4A and 4B, respectively. Complete inhibition of DKK1 binding was achieved at the highest tested concentrations (≥ 10 nM) and corresponded to MCF values ≤ 60. In contrast, an LRP5 specific VHH would compete with human DKK1 for binding to HEK293 cells overexpressing human LRP5 but not, or with very low potency (> 200 nM) for binding to HEK293 cells overexpressing human LRP6 (and the same would apply, vice versa, to LRP6 specific VHHs). As a result of this experiment, it could be shown that the present LRP5/LRP6 cross-reactive VHHs competed with human DKK1 for binding to HEK293 cells overexpressing human LRP5, as well as to those overexpressing human LRP6 (i.e. decrease in MCF value with increasing concentration of the binder with complete inhibition of DKK1 binding corresponded to ≤ 60 MCF values at the highest concentration tested). IC50 values of DKK1 competition for binding to hLRP5 and hLRP6 of the three LRP5/LRP6 cross-reactive VHH constructs are reported in Table VIII below. These data confirmed the binding of the three LRP5/LRP6 cross-reactive VHH constructs to human LRP5 and human LRP6 and showed very similar affinity (defined here by the IC_{50} potency values in the DKK1 competition assay) between the two receptors. Furthermore, the data strengthen the notion that the formatted, biparatopic, and sequence-optimized binding molecules are binding to human LRP5 as well as to human LRP6 in their native conformation.

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Table VIII: IC_{50} values of DKK1 competition for binding to human LEP5 and LRP6 determined by FACS binding assays

DKK1 competition assay	F013500571	F013500575	F013500720
hLRP5, IC_{50} (nM)	0.03	0.03	0.3
hLRP6, IC_{50} (nM)	0.01	0.1	0.2

7.3 Combined Wnt1 and Wnt3a reporter assay

Potency and efficacy of the formatted, biparatopic, and sequence-optimized binding molecules were analysed using a combined Wnt1 and Wnt3a reporter assay to allow functional testing of both Wnt1 and Wnt3a blockers in the same assay. The combined Wnt1 and Wnt3a reporter assay is based on the assay described in Example 4.4 with the following changes in the protocol. 1E06 / ml cells with overexpression of Wnt1, seeded into a 384 well tissue culture plate were treated with recombinant human Wnt3a (rec.human Wnt3a: R&D #5036-WN/CF) at the final concentration of 500ng/ml and then the cells were incubated overnight at 37 °C. The following day, serial dilutions of various LRP5/LRP6 biparatopic cross-reactive VHH solutions were prepared and added to the cells in the presence of LiCl at the final concentration of 10nM. DKK1, as positive control, was added to the cells at the final concentration of 200nM. DKK1 treatment resulted in a complete inhibition of the combined Wnt1 and Wnt3a pathway, and therefore a complete inhibition of beta-lactamase enzymatic activity. The cells were incubated overnight at 37 °C. The following day, beta-lactamase enzymatic activity was measured according to the manufacturer's instructions. As reported in Example 4.4., for fluorescence emission, values at 460 nm and 530 nm were obtained using a standard fluorescence plate reader and the 460/530 nm emission ratios plotted for the indicated treatment. The value of the ratio of fluorescence [460/535nm] reported as “baseline” in Figure 5A corresponds to complete inhibition of Wnt1 and Wnt3a pathway, determined by the treatment with the positive control (DKK1; 200nM final concentration). The value of the ratio

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of fluorescence [460/535nm] reported as "Wnt1" corresponds to activation of Wnt1 pathway only, determined from the Wnt1 overexpressing cells (i.e. without treatment with recombinant human Wnt3a). The value of the ratio of fluorescence [460/535nm] reported as "Wnt1 + Wnt3a" corresponds to the combined activation of Wnt1 and Wnt3a pathways, determined by treatment of the Wnt1 overexpressing cells with recombinant human Wnt3a. As shown in Figure 5A, complete inhibition (i.e. ratio of fluorescence [460/535nm] corresponding to the baseline) is achieved by treatment with the three LRP5/LRP6 cross-reactive, formatted, biparatopic, and sequence-optimized binding molecules. Furthermore, high potency is also reported, as shown in Table IX below by the IC50 values.

Table IX: IC_{50} values of Wnt1 and Wnt3a pathway inhibition in combined Wnt1 and Wnt3a reporter assay

Combined Wnt1 and Wnt3a reported assay	F013500571	F013500575	F013500720
IC_{50} (nM)	0.05	0.2	0.06

Next, potency and efficacy of the LRP5/LRP6 cross-reactive, formatted, biparatopic, and sequence-optimized binding molecules were compared to previously disclosed LRP6 binding molecules reported in WO2011/138391 and WO2011/119661:

In WO2011/138391, multivalent antibodies binding to LRP6 and inhibiting both propeller 1 (e.g., Wnt1) and propeller 3 (e.g., Wnt 3) ligand interaction were disclosed. These multivalent LRP6 binding antibodies are biparatopic LRP6 binding molecules consisting of an IgG antibody as a first receptor binding domain and of an scFv fragment as a second receptor binding domain, where the IgG antibody and scFv fragment are linked together by a linker. In WO2011/138391 it is reported that all the LRP6 binding molecules have roughly the same potency in Wnt1 and Wnt3a reporter assay (Fig. 18 of WO2011/138391). Therefore, any of those multivalent LRP6 binding molecules

could be chosen for comparative expriments. Thus, it was decided to use the "901" construct (referred to as MOR08168IgG1LALA 6475 scfv; also shown in Fig. 27 of WO2011/138391) as a first comparative compound.

Derivatives of this "901" construct are shown in WO2013/067355. Specifically, compounds named 801T and 802T are disclosed (cf. disclosure on p.132 of the specification), both having two LRP6 binding scFv domains, plus a half-life extending moiety. As 801T and 802T appear to have the same in vitro potency and biophysical characteristics, only one of them - variant 802T - was included in the experiments described in the following.

In WO2011/119661, bispecific antibodies binding to LRP6 and inhibiting signaling by multiple Wnt isoforms were disclosed. These bispecific anti-LRP6 antibodies bind to two different regions of LRP6 and inhibit signaling induced by Wnt isoforms, among them Wnt1 and Wnt3a. Knobs-into-holes engineering (Atwell *et al.* "Stable heterodimers from remodeling the domain interface of a homodimer using a phage display library". *J Mol Biol*. 1997; 270(1):26-35) was used to build these bispecific anti-LRP6 antibodies. Example 11 of WO2011/119661 discloses an IgG hybrid with YW211.31.62 and YW210.09 heavy chain heterodimers. Thus, for comparative purposes, two bispecific IgG hybrid antibodies with YW211.31.62 and YW210.09 heavy chain heterodimers were generated with the knobs-into-holes engineering technology, i.e. with amino acid changes engineered to create a knob on the CH3 of the heavy chain of YW210.09 and a hole on the CH3 of the heavy chain of YW211.31.62 or vice versa, and referred here as Knob HC YW210.09 and Knob HC YW211.31.62, respectively. These two constructs were characterized in Wnt1 and Wnt3a reporter assays according to Example 4.4. As expected, the two bispecific IgG hybrids with YW211.31.62 and YW210.09 heavy chain heterodimers showed similar potencies in Wnt1 and Wnt3a assays, as reported in Table X below. Thus, for the comparative examples shown further below, Knob HC YW210.09 was selected as a second comparative compound.

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Table X: IC_{50} values of Wnt1 and Wnt3a pathway inhibition in Wnt1 and Wnt3a reporter assays

Wnt reporter assay	Knob HC YW210.09	Knob HC YW211.31.62
Wnt1, IC_{50} (nM)	4.8	4.6
Wnt3a, IC_{50} (nM)	0.7	0.9

Potency and efficacy of the half-life extended biparatopic LRP5/LRP6 cross-reactive VHH constructs were compared to MOR08168IgG1LALA 6475 scfv biparatopic LRP6 binding molecule, to Knob HC YW210.09 bispecific anti-LRP6 molecule and to 802T bispecific anti-LRP6 molecule using the combined Wnt1 and Wnt3a reporter assay. As shown in Figure 5B, complete inhibition (i.e. ratio of fluorescence [460/535nm] corresponding to the baseline in Figure 5B) was achieved by treatment with Knob HC YW210.09 (the bispecific IgG hybrid antibody with YW211.31.62 and YW210.09 heavy chain heterodimers) similar to the LRP5/LRP6 cross-reactive, formatted, biparatopic, and sequence-optimized binding molecule F013500571. However, F013500571 showed higher potency, as reported in Table XI below. Instead, MOR08168IgG1LALA 6475 scfv and 802T biparatopic LRP6 binding molecules showed lack of complete Wnt1 and Wnt3a inhibition (i.e. ratio of fluorescence [460/535nm] significantly higher than the baseline in Figure 5B and in Figure 5C, respectively). These data indicate that both MOR08168IgG1LALA 6475 scfv and 802T biparatopic LRP6 binding molecules have significant lower efficacy in Wnt1 and Wnt3a pathway inhibition when compared to F013500571. Therefore, Knob HC YW210.09 was selected as a comparative compound for *in vivo* experiments as described further below (Example 9; *in vivo* efficacy)

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Table XI: IC_{50} values of Wnt1 and Wnt3a pathway inhibition in combined Wnt1 and Wnt3a reporter assay

Combined Wnt1 and Wnt3a reported assay	F013500571	Knob HC YW210.09	MOR08168IgG1LALA 6475 scfv	802T
IC_{50} (nM)	0.05	1.15	0.19	0.01

Example 8: Effects of three half-life extended biparatopic LRP5/LRP6 cross-reactive VHH constructs on Wnt Signaling and viability in cancer cell lines

The ability of the half-life extended biparatopic LRP5/LRP6 cross-reactive VHH constructs to inhibit active Wnt signaling was further characterized using cancer cell lines with active Wnt signaling, as previously described (Bafico *et al*. "An autocrine mechanism for constitutive Wnt pathway activation in human cancer cells". *Cancer Cell* 2004;6(5):497-506; DeAlmeida *et al*. "The soluble wnt receptor Frizzled8CRD-hFc inhibits the growth of teratocarcinomas in vivo". *Cancer Res*. 2007;67(11):5371-9); Akiri *et al*. "Wnt pathway aberrations including autocrine Wnt activation occur at high frequency in human non-small-cell lung carcinoma". *Oncogene*. 2009; 28(21):2163-72). Briefly, the cancer cell lines with active Wnt signaling, PA-1 and PA-TU-8988S, were seeded in 12-well plates and treated for two days with the LRP5/LRP6 cross-reactive VHH constructs at the final concentration of 1 uM. The ability of inhibiting Wnt signaling was detected by inhibition of mRNA expression of Axin2, the endogenous Wnt target gene. qPCR expression analysis was performed using standard RNA techniques: RNA isolation was performed using the QIAGEN RNeasy Mini Kit according to the protocol provided by QIAGEN; cDNA synthesis using SuperScript VILO cDNA Synthesis Kit (Invitrogen, Cat. No. 11754050) and qPCR using TaqMan Gene Expression Assay with Axin2 TaqMan primers/probe (Hs00610344_m1 AXIN2 FAM, Life Technologies) and with eukaryotic 18s endogenous control VIC-MGB (4319413E-1307061, Applied Biosystems).

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As shown in Figure 6A, both PA-TU8988S and PA-1 cancer cells treated with three half-life extended biparatopic LRP5/LRP6 cross-reactive VHH constructs showed significantly reduced Axin2 relative mRNA levels (i.e. normalized to the endogenous control) when compared to untreated (Control) cells. These data demonstrated the ability of the half-life extended biparatopic LRP5/LRP6 cross-reactive VHH constructs to inhibit Wnt signaling in cancer cell lines with active Wnt signaling. Furthermore, the effect of Wnt signaling blockade on cell viability was investigated in PA-TU8988S and YAPC cancer cell lines, whose proliferation was previously reported to be dependent on active Wnt signaling (Jiang *et al.* "Inactivating mutations of RNF43 confer Wnt dependency in pancreatic ductal adenocarcinoma*". Proc Natl Acad Sci U S A*. 2013; 110(31):12649-54). Cell viability was measured by performing an Alamar Blue assay (Invitrogen, Cat.# DAL1100) after ten days of treatment with the half-life extended biparatopic LRP5/LRP6 cross-reactive VHH constructs (final concentration of 1 uM) or with comparative compound 802T (final concentration 1 uM). As shown in Figure 6B, PA-TU8988S cancer cells treated with three half-life extended biparatopic LRP5/LRP6 cross-reactive VHH constructs showed significantly reduced percentage of viable cells cell ($\geq$ 75% reduction) when compared to untreated (control) cells. Upon treatment with 802T, no effect on cell viability was detected (Figure 6B, diagram on the right-hand side). These data demonstrate the ability of the half-life extended biparatopic LRP5/LRP6 cross-reactive VHH constructs to inhibit cell proliferation of cancer cells which are dependent on active Wnt signaling, and also show a superior effect of these constructs when compared to 802T.

Furthermore, dose dependency of cell viability was assessed for F013500571 in comparison to 802T, in PA-TU8988S (Figure 6C) and YAPC (Figure 6D) cancer cell lines, as described above. Dose dependent decrease in cell viability was detected upon treatment with F013500571. In contrast, no effect on cell viability was shown upon treatment with the comparative compound 802T in both PA-TU8988S and YAPC cancer cell lines. These data show that the half-life

extended biparatopic LRP5/LRP6 cross-reactive VHH constructs have a superior effect when compared to 802T.

Example 9: *In vivo* Efficacy

The LRP5/LRP6 cross-reactive biparatopic half-life extended VHH constructs / binding molecules were further characterized *in vivo* in a Wnt driven tumor model. Experiments were conducted to determine if these binding molecules inhibit tumor growth *in vivo*. Efficacy of the comparative compound Knob HC YW210.09 was also determined using the same Wnt driven tumor model. Transgenic expression of the Wnt ligands using a mouse mammary tumor virus LTR enhancer (MMTV promoter) leads in mice to extensive ductal hyperplasia followed by mammary adenocarcinomas in transgenic (TG) mice by 6 months of age. These mammary tumors are driven by glucocorticoid induced overexpression of Wnt ligands and have characteristics similar to TNBC tumors, including expression of epithelial and mesenchymal markers (basal-like phenotype) and active Wnt signaling as assessed by intracellular beta-catenin localization. In particular, mammary tumors derived from MMTV-Wnt-1 transgenic mice are Wnt1 dependent. Indeed, blocking of Wnt activity using a soluble Wnt receptor comprising the Frizzled8 cysteine-rich domain (CRD) fused to the human Fc domain (F8CRDhFc) (DeAlmeida *et al*. "The soluble wnt receptor Frizzled8CRD-hFc inhibits the growth of teratocarcinomas in vivo". *Cancer Res*. 2007;67(11):5371-9) was reported to inhibit tumor growth *in vivo*. Therefore, tumors isolated from MMTV-Wnt1 transgenic mice were passaged subcutaneously as tumor pieces in nude mice for 2 to 5 passages prior to initiation of the efficacy experiment. Between 14 to 21 days post-implant, when tumors reached a mean volume of approximately 150 to 250 mm^3, mice were randomized into groups with 7 mice per group and dosed *i.v.* with the compounds. The LRP5/LRP6 cross-reactive biparatopic half-life extended VHH constructs were administered to the mice *i.v.* twice per week, with the dosages shown in Figure 7A for F013500571 and in Figure 7B for F013500720. Comparative compound Knob HC YW210.09 was also dosed *i.v.* twice per week,

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but at higher doses, i.e. 30 and 45mg/kg (Figure 7C), due to the data obtained with this compound in the *in vitro* experiments explained above. Tumor volume and body weight were monitored during the efficacy experiment and the median tumor volumes are reported in Figures 7A to 7C. Tumor growth inhibition (TGI) was determined at the end of the efficacy experiment. In particular, TGI was determined for each treatment group as compared to the control group (treatment of mice with histidine buffer - 20mM Histidine pH6.5 buffer - in the experiment shown in Figures 7A and 7B, or with citrate buffer for the experiment shown in Figure 7C). Furthermore, gastro-intestinal (GI) histo-pathological analysis (via H&E staining of sections of the GI tract from the duodenum to the rectum) was performed at the end of the efficacy experiment to evaluate potential toxicity of the LRP5 and LRP6 antagonists. Tumor growth inhibition (TGI), outcome of the GI histo-pathological analysis at the end of the *in vivo* efficacy study, mortality which corresponds to the number of mice that needed to be sacrified due to significant loss of body weight (>18% loss of body weight compared to start of the efficacy experiment) and number of tumor regressions (tumor volume at the end of the experiment smaller than tumor volume measure at the start of the treatment) are reported for each treatment group in Tables XIIA, XIIB, and XIIC, relating to the experiments and data shown also in Figures 7A, 7B and 7C, respectively.

Table XIIA: *In vivo* efficacy of F013500571 administered *i.v.* twice per week. Results of this experiment are also shown in Figure 7A

	Dose [mg/kg]	TGI [%]	Regressions [x/7]	Mortality [x/7]	GI Histopathological evaluation
Control	Histidine buffer	-	-	-	-
F013500571	10	128	7	0	No findings
	4	113	7	0	No findings
	2	61	0	0	n.d.

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Table XIIB: *In vivo* efficacy of F013500720 administered *i.v.* twice per week. Results of this experiment are also shown in Figure 7B

	Dose [mg/kg]	TGI [%]	Regressions [x/7]	Mortality [x/7]	GI Histopathological evaluation
Control	Histidine buffer	-	-	-	-
F013500720	1	128	7	0	No findings
	0.4	60	0	0	No findings
	0.2	17	0	0	n.d.

Table XIIC: *In vivo* efficacy of Knob HC YW210.09 administered *i.v.* twice per week. Results of this experiment are also shown in Figure 7C

i.v.	Dose [mg/kg]	TGI [%]	Regressions [x/7]	Mortality [x/7]	GI Histopathological evaluation
Control	Citrate buffer	-	-	-	-
Knob HC YW210.09	30	80	0	0	-
	45	85	0	0	No findings

As can be taken from Figures 7A to 7C and Tables XIIA to XIIC above, treatment with the LRP5/LRP6 cross-reactive half-life extended biparatopic VHH constructs (F013500571 at 4 and 10 mg/kg and F013500720 at 1mg/kg in a 2x/week schedule) indeed resulted in tumor regression (i.e. tumor growth inhibition (TGI) > 100% which corresponds to tumor shrinkage; decrease of the tumor volume at the end of the efficacy experiment compared to the tumor volume at the start of the experiment), with no significant body weight changes (< 10%) and no findings

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reported after GI histopathological analysis. Importantly, in contrast thereto, no tumor regression could be observed upon treatment with the LRP6 specific binder Knob HC YW210.09, even at the maximum administrable *i.v.* dose/schedule in mice, which correspond to 90 mg/kg with 3x/week schedule.

To further investigate the differences in *in vivo* efficacy as observed in the experiment explained above, a further experiment was set up allowing more frequent administration (three times/week) of an even higher dose of the comparative compound to the mice. In brief, in order to achieve such higher exposure, the comparative compound was administered *i.p.*, as indicated in the following Table XIID:

Table XIID: *In vivo* efficacy of Knob HC YW210.09 administered *i.p.* twice or three times per week, as indicated.

i.p.	Dose [mg/kg]	Schedule	TGI [%]	Regressions [x/5]	Mortality [x/5]
Control	Citrate buffer	Three times/week	-	-	-
Knob HC YW210.09	45	Twice/ week	55	1	0
	90	Twice/ week	85	0	0
	90	Three times/ week	87	0	0

As can be seen from the data shown in Table XIID, also in this setting no significantly stronger effect was obtained in terms of TGI. In other words, these experiments, data and results clearly indicate a higher efficacy of the half-life extended biparatopic VHH constructs when compared to Knob HC YW210.09, and an unprecedented capability of the polypeptides of the invention to not only reduce tumor growth, but to even induce tumor shrinkage. Of course, tumor shrinkage (i.e. tumor regression) is the desired therapeutic effect (i.e. efficacy) for treatment of cancer patients. Indeed, in clinical studies treatments that induce

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tumor regression resulting in pathological complete response (pCR) positively lead to significant improvement of progression free survival and overall survival in high unmet medical need indications such as in breast cancer.

The above comparative examples also show that the LRP5/LRP6 cross-reactive biparatopic half-life extended VHH constructs are not only superior in terms of their binding characteristics, such as affinity or K_D values, but that they have highly advantageous and superior properties in an *in vivo* setting.

Next, it was investigated whether compound MOR08168IgG1LALA 6475 scfv may provide for a similar advantageous effect. For this purpose an in vivo tolerability study was performed in mice as follows: MOR08168IgG1LALA 6475 scfv compound was administered *i.v.* at 3 mg/kg, twice per week (2qw); the same dose/regimen at which in vivo efficacy was detected in a xenograft tumor model in WO2011/138391, as described in Fig. 22 therein. First treatment with MOR08168IgG1LALA 6475 scfv was performed at day 1 and starting from day 6 significant loss of body weight was detected in mice. At day 10, some of the mice treated with MOR08168IgG1LALA 6475 scfv compound showed significant body weight loss (>10%). At day 11 mice were sacrificed and gastro-intestinal (GI) histopathological analysis revealed inflammation with erosion in the colon and in the cecum of the mice. These data suggest that MOR08168IgG1LALA 6475 scfv is not tolerated at the efficacious dose/regimen. Therefore, LRP5/LRP6 cross-reactive biparatopic half-life extended VHH constructs are superior with regard to therapeutic window; i.e. they induce tumor regression with no significant body weight changes (< 10%) and no findings reported after GI histopathological analysis.

Example 10: *In vivo* Wnt pathway inhibition

To further characterize the effect of the LRP5/LRP6 cross-reactive biparatopic half-life extended VHH constructs / binding molecules on Wnt signaling, tumors

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were isolated at the end of the efficacy experiment, described in Example 9. In particular, tumors were isolated 16 hours after the last injection with the compounds or with the control treatment. Wnt signaling inhibition was determined by reduction of mRNA expression of Axin2 in tumors, analysed as described in Example 8. The fold change of Axin2 mRNA expression relative to the control group is reported in Figure 8A for the *in vivo* efficacy with F013500571 and in Figure 8B for the *in vivo* efficacy with F013500720. Quantification of Axin2 mRNA reduction for each treatment group is reported in Tables XIIIA and XIIIB below.

Table XIIIA: Reduction of Axin2 mRNA expression in tumors by treatment with F013500571. The data refers to Figure 7A and 8A.

	Dose [mg/kg]	TGI [%]	Axin2 reduction (%)
Control	Histidine buffer	-	
F013500571	10	128	83
	4	113	77
	2	61	35

Table XIIIB: Reduction of Axin2 mRNA expression in tumors by treatment with F013500720. The data refers to Figure 7B and 8B.

	Dose [mg/kg]	TGI [%]	Axin2 reduction (%)
Control	Histidine buffer	-	
F013500720	1	128	92
	0,4	60	-21
	0,2	17	35

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As can be seen from Figures 8A and 8B and Tables XIIIA and XIIIB, a significant reduction and dose dependent decrease (in particular for treatment with F013500571) of Axin2 mRNA expression was observed in tumors treated with the LRP5/LRP6 cross-reactive binding molecules, compared to the control group. These results suggest that the LRP5/LRP6 cross-reactive binding molecules are indeed able to inhibit tumor growth by suppressing Wnt signaling in the tumor cells.

Example 11: Industrial manufacturing process

11.1 Fermentation: Any of the polypeptides set out in Tables III and V above can be expressed in the cytoplasm of different E. coli strains like W3110, TG1, BL21, BL21(DE3), HMS174, HMS174(DE3), MM294 under control of an inducible promoter. This promoter can be chosen from lacUV5, tac, T7, trp, T5, araB. The cultivation media are preferably fully defined according to Wilms *et al.*, 2001 (Wilms, B., Hauck, A., Reuss, M., Syldatk, C., Mattes, R., Siemann, M., and Altenbuchner, J.: High-Cell-Density Fermentation for Production of L-N-Carbamoylase Using an Expression System Based on the Escherichia coli rhaBAD Promoter. Biotechnology and Bioengineering, 73: 95-103 (2001)), DeLisa *et al.*, 1999 (DeLisa, M. P., Li, J. C., Rao, G., Weigand, W. A., and Bentley, W. E.: Monitoring GFP-operon fusion protein expression during high cell density cultivation of Escherichia coli using an on-line optical sensor. Biotechnology and Bioengineering, 65: 54–64.(1999)) or equivalent. However, supplementation of the medium with amino acids like isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan and valin or complex media components such as soy peptone or yeast extract may be beneficial. The process for fermentation is performed in a fed-batch mode. Conditions: Temperature 30 – 40 °C, pH 6 – 7.5, dissolved oxygen is kept above 20%. After consumption of the initial C-source the culture is fed with the feed media stated above (or equivalent). When a dry cell weight in the fermenter of 40 to 90 g/L is reached the culture is induced with an appropriate inducer corresponding to the used promoter system

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(e.g. IPTG, lactose, arabinose). The induction can either be performed as a pulsed full induction or as a partial induction by feeding the respective inducer into the fermenter over a prolonged time. The production phase should last 4 hours at least. The cells are recovered by centrifugation in bowl centrifuges, tubular bowl centrifuges or disc stack centrifuges, the culture supernatant is discarded.

11.2 Purification: The E. coli cell mass is resuspended in 6- to 8-fold amount of lysis buffer (phosphate or Tris buffer, pH 7-8.5). Cell lysis is preferably performed by high pressure homogenization followed by removing of the cell debris by centrifugation in bowl, tubular bowl or disc stack centrifuges. Supernatant containing the target protein is optionally filtrated using a 0.22-10 µm filter and separated via cation exchange chromatography (e.g. Toyopearl MegaCap® II SP-550EC, Toyopearl GigaCap S-650M, SP Sepharose BB, SP Sepharose FF or S HyperCel™) at pH 7-8.5. Elution is performed by a linear increasing NaCl gradient at pH 7-8.5. Fractions containing the target protein are pooled and subsequently incubated with 5-10 mM DTT in order to prevent dimerization or aggregation mediated by free cysteine residues. After further addition of 0.8-1 M ammonium sulfate or 2-3 M NaCl, solution is separated via hydrophilic interaction chromatography (e.g. Phenyl Sepharose HP, Phenyl Sepharose FF, Butyl Sepharose HP, Butyl Sephrose FF, Butyl Toyopearl 650 (S,M,C), Phenyl Toyopearl 650 (S,M,C)) at pH 7-8.5. Elution is carried out at pH 7-8.5 by a linear decreasing ammonium sulfate or NaCl gradient in presence of 5 mM DTT. Fractions containing the target protein with a purity level of minimally 90% are pooled and desalted by diafiltration in presence of 5 mM DTT followed by concentration to approximately 5 mg/ml. Subsequent refolding is performed by diluting the protein solution 1:5-1:20 with 50 mM Tris, 150 mM NaCl, 4 mM Cystamin, 10 mM CHAPS at pH 8.5 to a final protein concentration of 0.25-1 mg/ml. Refolding solution is incubated under stirring for 12-36 h at room temperature and then separated by cation exchange chromatography (e.g. SP Sepharose FF, SP Sepharose HP, Toyopearl SP-650 (S, M, C)) at pH 7-8.5.

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Elution is performed by a linear increasing NaCl gradient at pH 7-8.5. Fractions containing monomeric target protein are pooled and formulated in 25 mM Na-phosphate, 220 mM endotoxin free trehalose, pH 7.5 via diafiltration. The solution is sterilized by filtration and stored at 2 to 8 °C.

Example 12: Pharmaceutical formulation for s.c. administration

Any of the above biparatopic polypeptide constructs of the invention can be selected for the manufacture of a pharmaceutical formulation for subcutaneous application having a composition as follows:

Drug substance:	100 mg/ml (1 to 3 nmol/ml)
Acetate buffer:	25 mM
Trehalose:	220 mM
Tween-20:	0.02 %

Drug substance is formulated in a solution having the above composition, sterilized and stored at 2 to 8 °C.

Example 13: Pharmaceutical use in humans

The solution as prepared in Example 11.2 above is applied to a patient in need thereof, such as a human being suffering from a cancer sensitive to Wnt signaling inhibitors, by intravenous infusion (dosage of 100 to 200 mg) every two to four weeks.

Example 14: Effect of Wnt3a-signaling inhibition on pro-inflammatory cytokine release by dendritic cells in an *ex-vivo* assay

PBMCs were obtained from healthy donors with informed consent. Human monocyte-derived dendritic cells (Mo-DCs) were generated as follows: PBMCs were cultured in X-VIVO medium supplemented with 50 ng/mL GM-CSF and 50 ng/mL IL-4. After 24 h of culture, the supernatant was carefully removed and

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replaced with X-VIVO medium supplemented with the same GM-CSF and IL-4. On the fourth day, the supernatant was carefully removed and replaced with X-VIVO medium in the presence of LPS only or in combination with human Wnt3a or with human Wnt3a and LRP5/LRP6 cross-reactive binding molecules. On the following day, the supernatants were collected and subjected to analysis of TNF-alpha through ELISA according to the manufacturer's instructions. As previously reported (Oderup *et al*." Canonical and noncanonical Wnt proteins program dendritic cell responses for tolerance". *J Immunol*. 2013;190(12): 6126-34), and as shown in Figure 9A, Wnt3a directly inhibits pro-inflammatory cytokine secretion (i.e. TNF-alpha release) by differentiated dendritic cells (DCs). Wnt3a driven suppression of TNF-alpha release from DCs was restored by addition of LRP5/LRP6 cross-reactive binding molecules.

These data show that the formatted, biparatopic, and sequence-optimized binding molecules are able to restore TNFalpha secretion by Wnt3a treated dendritic cells, thereby suppressing the Wnt inhibitory effect on dendritic cells.

It is important to notice that blocking the Wnt pathway in dendritic cells in the tumor microenviroment might represents a potential therapeutic approach towards breaking tumor-mediated immune suppression and augmenting anti-tumor immunity.

To investigate the effects of DCs on T cells (effector T cells), DCs pre-treated with Wnt3a with or without LRP5/LRP6 cross-reactive binding molecules were co-cultured with T cells, isolated from PBMCs, as previously described (Oderup et al. "Canonical and noncanonical Wnt proteins program dendritic cell responses for tolerance". J Immunol. 2013;190(12): 6126-34). After 3 days of DC/T cells co-culture, the supernatants were collected and subjected to analysis of IFN gamma through ELISA, according to the manufacturer's instructions.

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IFNgamma secretion is a marker of T cell activation. As shown in Figure 9B, Wnt3a mediated DC inhibition leads to reduced IFNgamma secretion by T cells (inhibition of T cell function), which is completely restored by treatment with LRP5/LRP6 cross-reactive binding molecules.

In summary, these data show that LRP5/LRP6 cross-reactive binding molecules suppress the Wnt inhibitory effect on dendritic cells, leading to restoration of T cell function.

It is known that continuous activation/stimulation of T cells induces terminal differentiation, resulting in an exhausted T cell phenotype, a progressive loss of T-cell function. Therefore, it is envisaged that the effect of LRP5/LRP6 cross-reactive binding molecules on T cells, mediated by activation of DCs, might be limited by T cell exhaustion. Combination treatments, combining the administration of LRP5/LRP6 cross-reactive binding molecules with the administration of an immune checkpoint inhibitor which blocks T cell exhaustion, are therefore expected to help to activate and maintain T cell function, thereby changing the tumor microenvironment, and thereby supporting the therapeutic effect of the molecules of the invention.

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Claims:

1. A polypeptide which specifically binds to LRP5 or LRP6, comprising
- a first immunoglobulin single variable domain selected from the group of immunoglobulin single variable domains (i) to (iii) defined by comprising the following CDR sequences:

(i):
CDR1: TYTVG (= SEQ ID NO:1)
CDR2: AIRRRGSSTYYADSVKG (= SEQ ID NO:2)
CDR3: DTRTVALLQYRYDY (= SEQ ID NO:3)
(ii):
CDR1: SYAMG (= SEQ ID NO:4)
CDR2: AIRRSGRRTYYADSVKG (= SEQ ID NO:5)
CDR3: ARRVRSSTRYNTGTWWWEY (= SEQ ID NO:6)
(iii):
CDR1: RYTMG (= SEQ ID NO:7)
CDR2: AIVRSGGSTYYADSVKG (= SEQ ID NO:8)
CDR3: DRRGRGENYILLYSSGRYEY (= SEQ ID NO:9),

and
- a second immunoglobulin single variable domain selected from the group of immunoglobulin single variable domains (iv) and (v) defined by comprising the following CDR sequences:

(iv):
CDR1: SYAMG (= SEQ ID NO:10)
CDR2: AISWSGGSTYYADSVKG (= SEQ ID NO:11)
CDR3: SPIPYGSLLRRRNNYDY (= SEQ ID NO:12)
(v):
CDR1: SYAMG (= SEQ ID NO:13)
CDR2: AISWRSGSTYYADSVKG (= SEQ ID NO:14)
CDR3: DPRGYGVAYVSAYYEY (= SEQ ID NO:15).

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2. The polypeptide of claim 1 wherein

- said first immunoglobulin single variable domain comprises the following CDR sequences:

CDR1: TYTVG (= SEQ ID NO:1)

CDR2: AIRRRGSSTYYADSVKG (= SEQ ID NO:2)

CDR3: DTRTVALLQYRYDY (= SEQ ID NO:3)

and wherein

- said second immunoglobulin single variable domain comprises the following CDR sequences:

CDR1: SYAMG (= SEQ ID NO:10)

CDR2: AISWSGGSTYYADSVKG (= SEQ ID NO:11)

CDR3: SPIPYGSLLRRRNNYDY (= SEQ ID NO:12).

3. The polypeptide of claim 1 wherein

- said first immunoglobulin single variable domain comprises the following CDR sequences:

CDR1: SYAMG (= SEQ ID NO:4)

CDR2: AIRRSGRRTYYADSVKG (= SEQ ID NO:5)

CDR3: ARRVRSSTRYNTGTWWWEY (= SEQ ID NO:6)

and wherein

- said second immunoglobulin single variable domain comprises the following CDR sequences:

CDR1: SYAMG (= SEQ ID NO:13)

CDR2: AISWRSGSTYYADSVKG (= SEQ ID NO:14)

CDR3: DPRGYGVAYVSAYYEY (= SEQ ID NO:15).

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4. The polypeptide of claim 1 wherein
- said first immunoglobulin single variable domain comprises the following CDR sequences:
CDR1: RYTMG (= SEQ ID NO:7)
CDR2: AIVRSGGSTYYADSVKG (= SEQ ID NO:8)
CDR3: DRRGRGENYILLYSSGRYEY (= SEQ ID NO:9)
and wherein
- said second immunoglobulin single variable domain comprises the following CDR sequences:
CDR1: SYAMG (= SEQ ID NO:13)
CDR2: AISWRSGSTYYADSVKG (= SEQ ID NO:14)
CDR3: DPRGYGVAYVSAYYEY (= SEQ ID NO:15).

5. The polypeptide of any of claims 1 to 4, wherein said immunoglobulin single variable domains are VHH domains, and preferably humanized VHH domains.

6. The polypeptide of claim 1, wherein
- said first immunoglobulin single variable domain is selected from the group of immunoglobulin single variable domains (i) to (iii) having the following sequences:
(i):
AVQLVESGGGLVQPGGSLRLSCAASGRTFSTYTVGWFRQAPGKEREF
VAAIRRRGSSTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVYY
CAADTRTVALLQYRYDYWGQGTLVTVSS
(= SEQ ID NO:19),
(ii):
AVQLVESGGGLVQPGGSLRLSCAASGGTFSSYAMGWFRQAPGKERE
FVAAIRRSGRRTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVYY
CAAARRVRSSTRYNTGTWWWEYWGQGTLVTVSS
(= SEQ ID NO:20),

MS&D Exhibit 1008, Page 3111 of 4223

(iii):

AVQLVESGGGLVQPGGSLRLSCAASGLTFSRYTMGWFRQAPGKEREF
VAAIVRSGGSTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVYY
CAADRRGRGENYILLYSSGRYEYWGQGTLVTVSS

(= SEQ ID NO:21),

and wherein

- said second immunoglobulin single variable domain is selected from the group consisting of immunoglobulin single variable domains (iv) and (v) having the following sequences:

(iv):

EVQLVESGGGLVQPGGSLRLSCAASGRTFSSYAMGWFRQAPGKERE
FVAAISWSGGSTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVY
YCAASPIPYGSLLRRRNNYDYWGQGTLVTVSS

(= SEQ ID NO:22),

(v):

EVQLVESGGGLVQPGGSLRLSCAASGGTFSSYAMGWFRQAPGKERE
FVAAISWRSGSTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVY
YCAADPRGYGVAYVSAYYEYWGQGTLVTVSS

(= SEQ ID NO:23).

7. The polypeptide of claim 1 or claim 2, wherein

- said first immunoglobulin single variable domain has the amino acid sequence as shown in SEQ ID NO:19 and
- said second immunoglobulin single variable domain has the amino acid sequence as shown in SEQ ID NO:22.

8. The polypeptide of claim 1 or claim 3, wherein

- said first immunoglobulin single variable domain has the amino acid sequence as shown in SEQ ID NO:20 and
- said second immunoglobulin single variable domain has the amino acid sequence as shown in SEQ ID NO:23.

MS&D Exhibit 1008, Page 3112 of 4223

9. The polypeptide of claim 1 or claim 4, wherein
   - said first immunoglobulin single variable domain has the amino acid sequence as shown in SEQ ID NO:21 and
   - said second immunoglobulin single variable domain has the amino acid sequence as shown in SEQ ID NO:23.

10. The polypeptide according to any of claims 1 to 9, wherein said first and said second immunoglobulin single variable domains are covalently linked by a linker peptide, wherein said linker peptide optionally comprises or consists of a third immunoglobulin single variable domain.

11. The polypeptide according to any of claims 1 to 9, wherein the polypeptide additionally includes a half-life extending moiety, wherein said half-life extending moiety is covalently linked to said polypeptide and is optionally selected from the group consisting of an albumin binding moiety, such as an albumin binding peptide or an albumin binding immunoglobulin domain, a transferrin binding moiety, such as an anti-transferrin immunoglobulin domain, a polyethylene glycol molecule, human serum albumin, and a fragment of human serum albumin.

12. The polypeptide according to claim 11, wherein said half-life extending moiety is an albumin binding immunoglobulin single variable domain, and preferably the Alb11 domain, defined by SEQ ID NO:24.

13. A polypeptide selected from the group of polypeptides comprising or consisting of SEQ ID NO:25, SEQ ID NO:26, and SEQ ID NO:27.

14. A nucleic acid molecule, preferably in isolated form, encoding a polypeptide according to any of claims 1 to 13.

MS&D Exhibit 1008, Page 3113 of 4223

15. An expression vector comprising the nucleic acid of claim 14.

16. A host cell carrying an expression vector according to claim 15.

17. A method of manufacturing a polypeptide according to any of claims 1 to 13, comprising the steps of
- culturing a host cell according to claim 16 under conditions that allow expression of a polypeptide according to any of claims 1 to 13; and
- recovering said polypeptide.

18. The method of claim 17, additionally comprising the step of
- purifying said polypeptide.

19. A pharmaceutical composition comprising (i) as the active ingredient, the polypeptide according to any of claims 1 to 13, and (ii) a pharmaceutically acceptable carrier, and optionally (iii) a diluent, excipient, adjuvant and/or stabilizer.

20. The polypeptide according to any of claims 1 to 13 for use as a medicament in a method for the treatment, prevention or alleviation of a disease, disorder or condition in a human being or an animal.

21. The polypeptide according to any of claims 1 to 13 for use in the treatment of cancer, preferably breast cancer, lung cancer, pancreatic cancer, colorectal cancer, sarcomas, ovarian cancer or hepatocellular carcinoma, or for use in the treatment of idiopathic pulmonary disease, or for use in the treatment of a retinopathy caused by abnormal Wnt signaling.

22. The polypeptide according to any of claims 1 to 13 for use in the treatment of triple negative breast cancer (TNBC).

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23. The polypeptide according to any of claims 1 to 13 for use in combination with a chemotherapeutic agent, a therapeutically active compound that inhibits angiogenesis, a signal transduction pathway inhibitor, an EGFR inhibitor, an immune modulator, an immune checkpoint inhibitor, or a hormonal therapy agent.

24. A therapeutic agent selected from the group consisting of chemotherapeutic agents, therapeutically active compounds that inhibit angiogenesis, signal transduction pathway inhibitors, EGFR inhibitors, immune modulators, immune checkpoint inhibitors, and hormonal therapy agents for use in combination with the polypeptide according to any of claims 1 to 13.

25. A method of treatment of cancer or idiopathic pulmonary disease or a retinopathy in a patient in a need thereof comprising administering to said patient an effective amount of the polypeptide of any one of claims 1 to 13, or the pharmaceutical composition of claim 19.

26. A polypeptide comprising
- a first immunoglobulin binding protein which is able to specifically bind to LRP5 as well as to LRP6 (LRP5/LRP6 cross-reactive) and inhibits Wnt1-driven target gene transcription, and
- a second immunoglobulin binding protein which is able to specifically bind to LRP5 as well as to LRP6 (LRP5/LRP6 cross-reactive) and inhibits Wnt3a-driven target gene transcription.

27. The polypeptide of claim 26, wherein said first and said second immunoglobulin binding proteins are immunoglobulin single variable domains.

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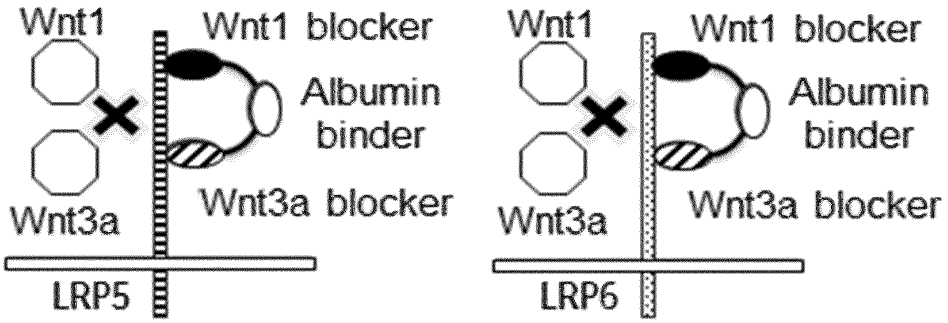
28. Use of a polypeptide of any of claims 1 to 13, 26 or 27 to modify a tumor microenvironment by inhibiting Wnt1- and Wnt3a-driven target gene transcription in dendritic cells.

29. A polypeptide of any of claims 1 to 13, 26 or 27 for use in the treatment of cancer.

30. A polypeptide of any of claims 1 to 13, 26 or 27 for use in the treatment of cancer in combination with an immune checkpoint inhibitor selected from the group consisting of anti-PD1 antibodies, anti-PDL1 antibodies, anti-CTLA4 antibodies, anti-BTLA antibodies, anti-LAG3 antibodies, and anti-TIM3 antibodies, or in combination with a cancer vaccine.

MS&D Exhibit 1008, Page 3116 of 4223

Figure 1



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Figure 2

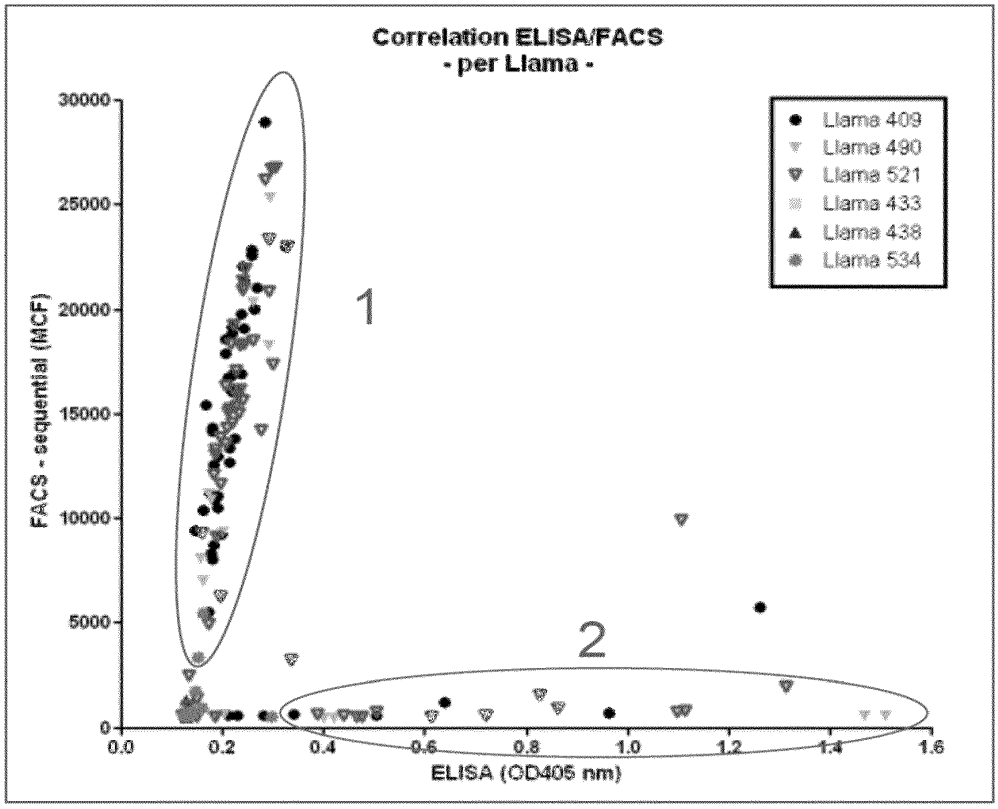

Correlation ELISA/FACS
- per Llama -
Llama 409
Llama 490
Llama 521
Llama 433
Llama 438
Llama 534
1
2
FACS - sequential (MCF)
ELISA (OD405 nm)
30000
25000
20000
15000
10000
5000
0
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6

Figure 3A

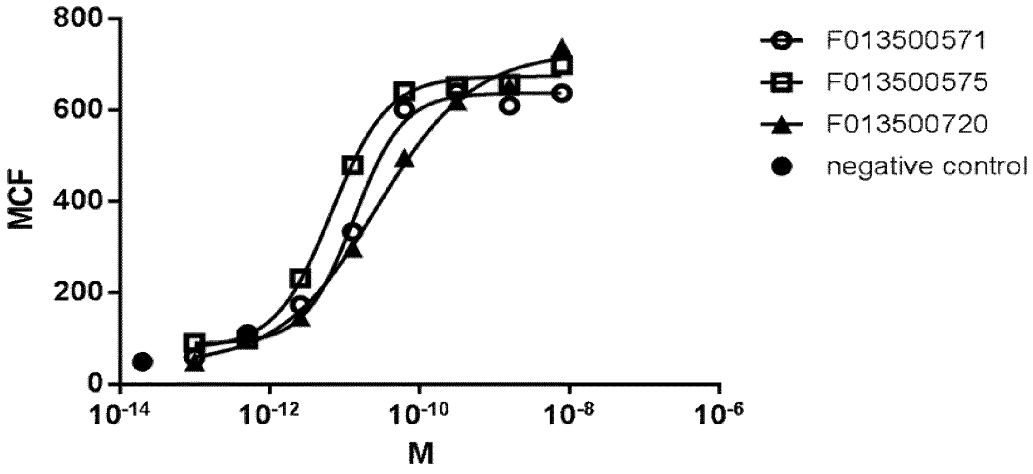


Figure 3B

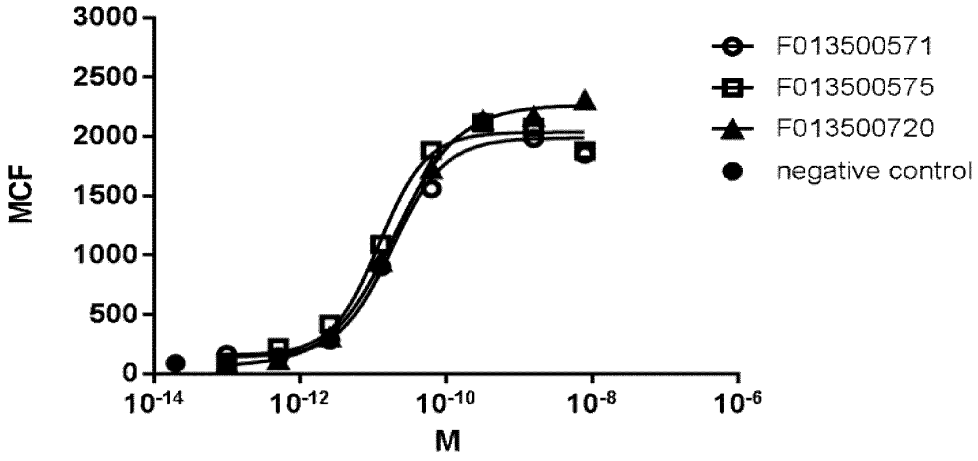


Figure 4A

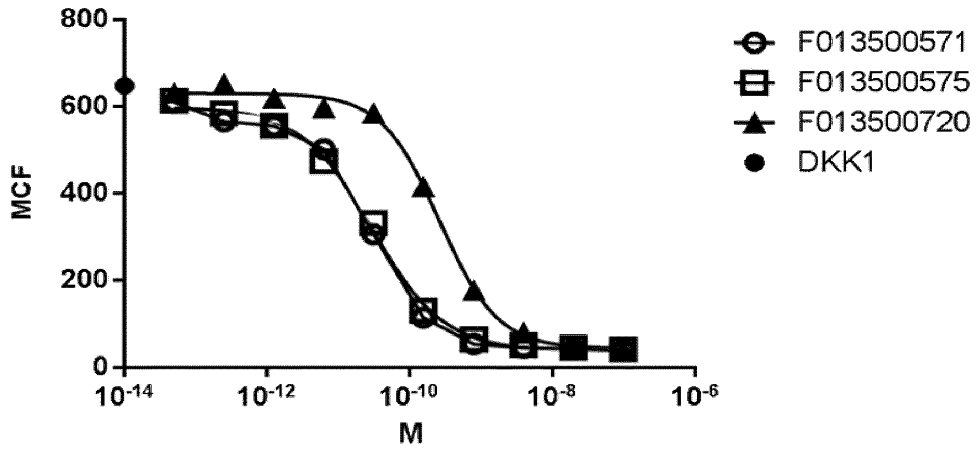


Figure 4B

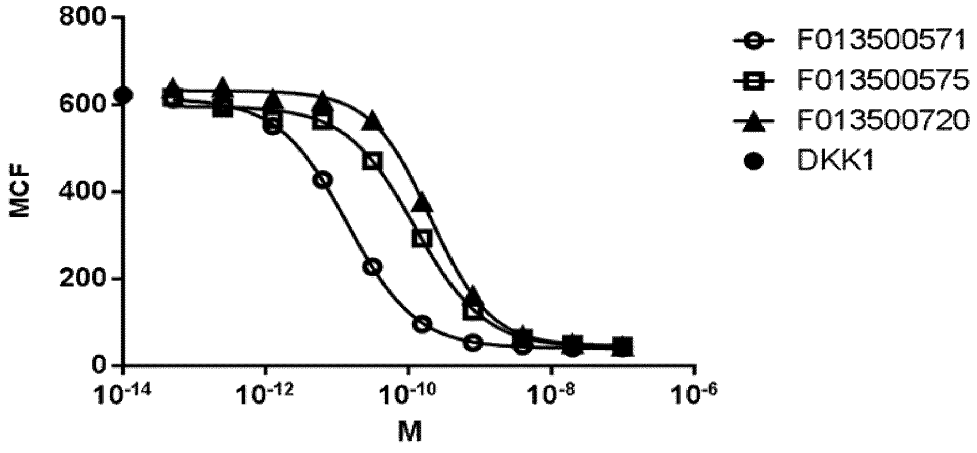


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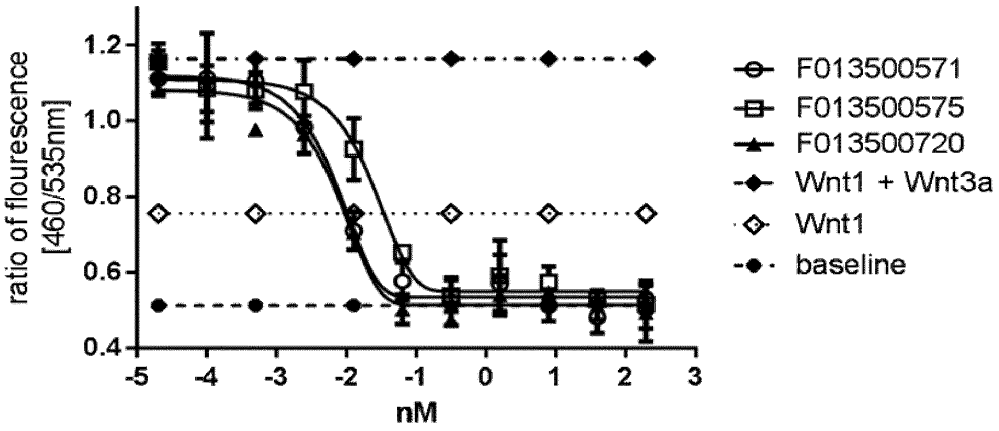


Figure 5B

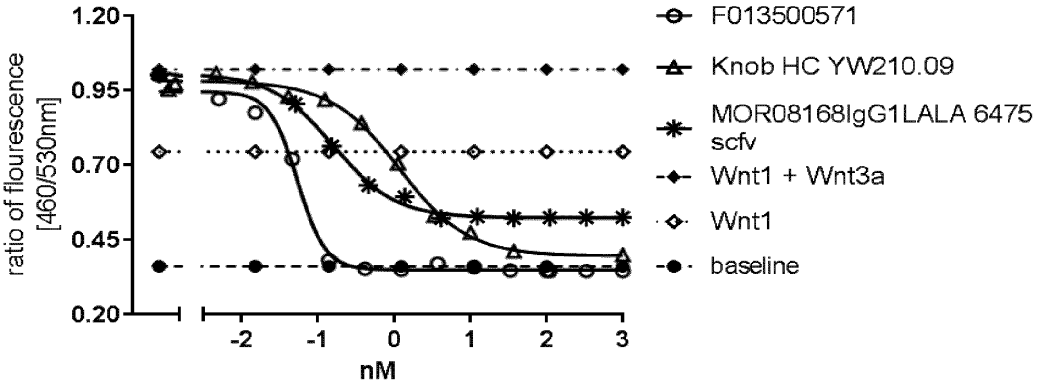


Figure 5C

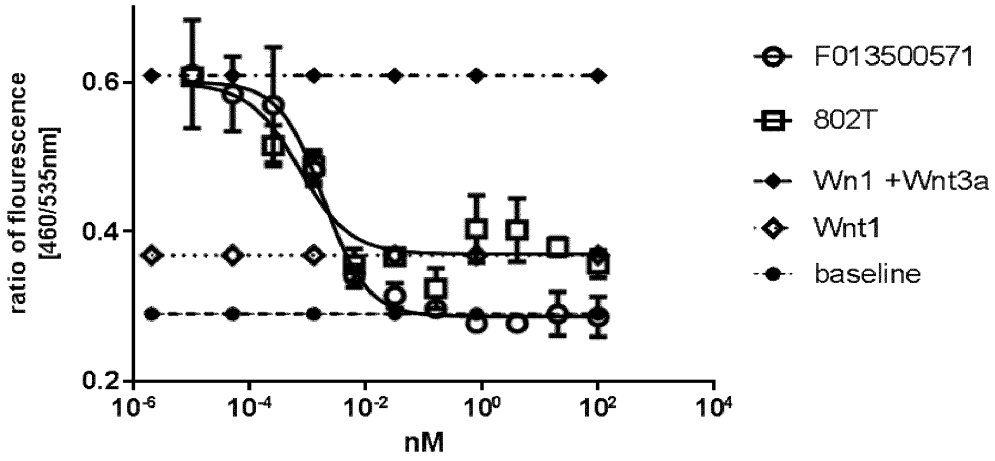

ratio of flourescence [460/535nm]
0.6
0.4
0.2
10^{-6}
10^{-4}
10^{-2}
10^{0}
10^{2}
10^{4}
nM
F013500571
802T
Wn1 +Wnt3a
Wnt1
baseline

Figure 6A

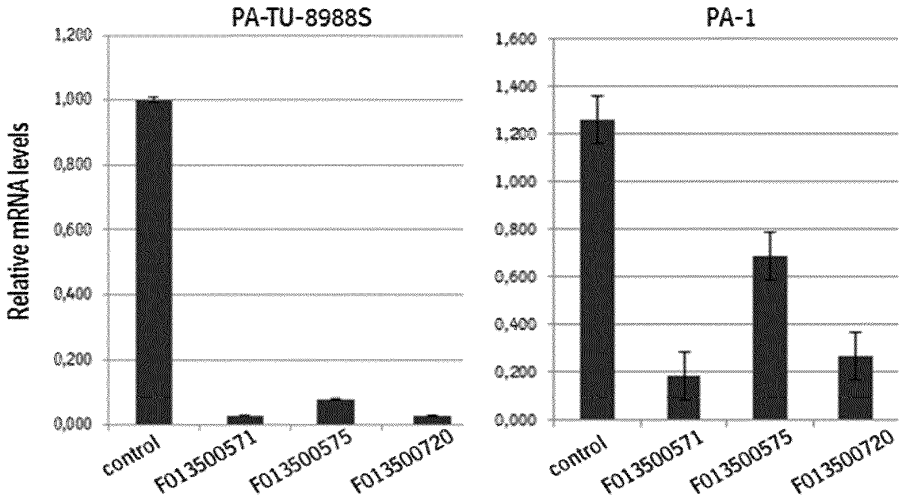


Figure 6B

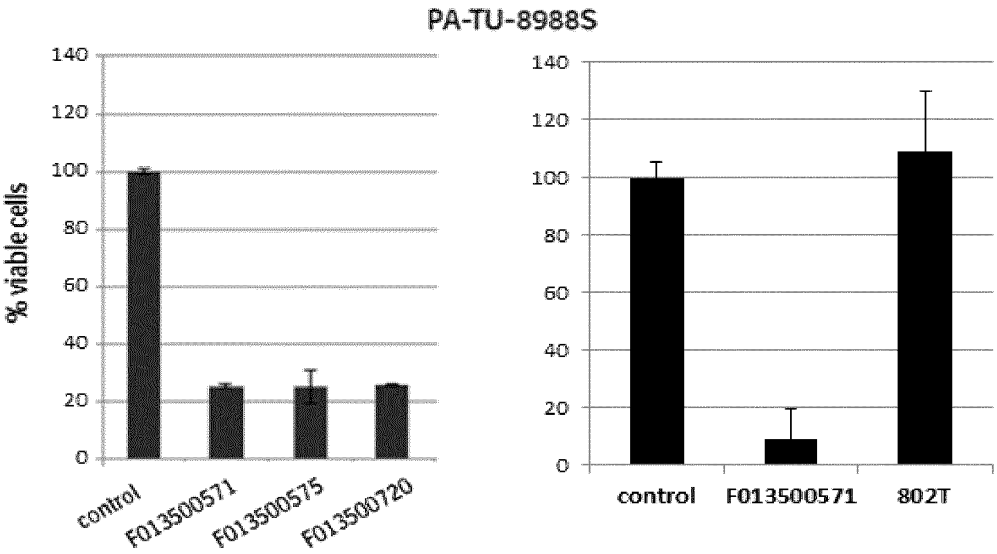


Figure 6C

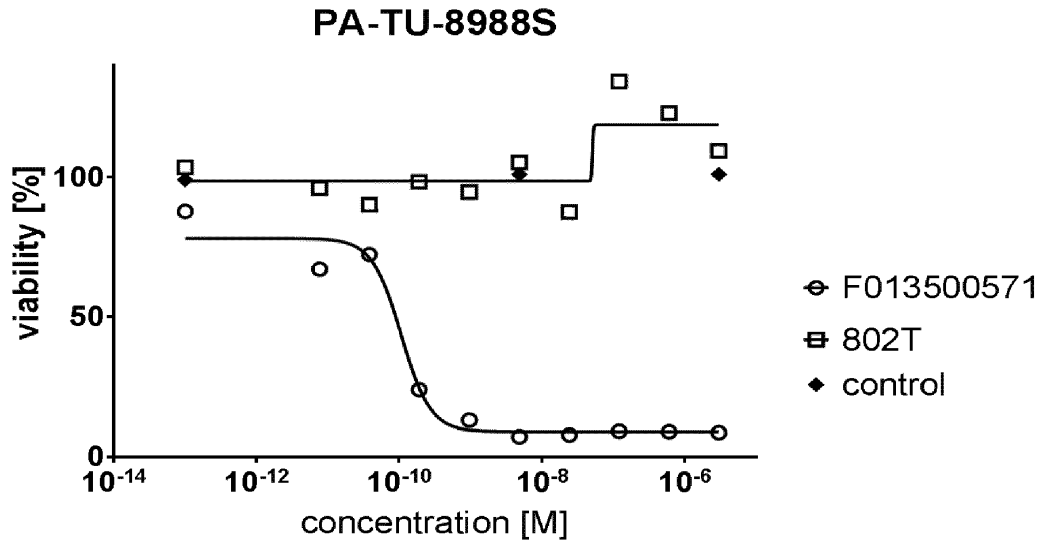


Figure 6D

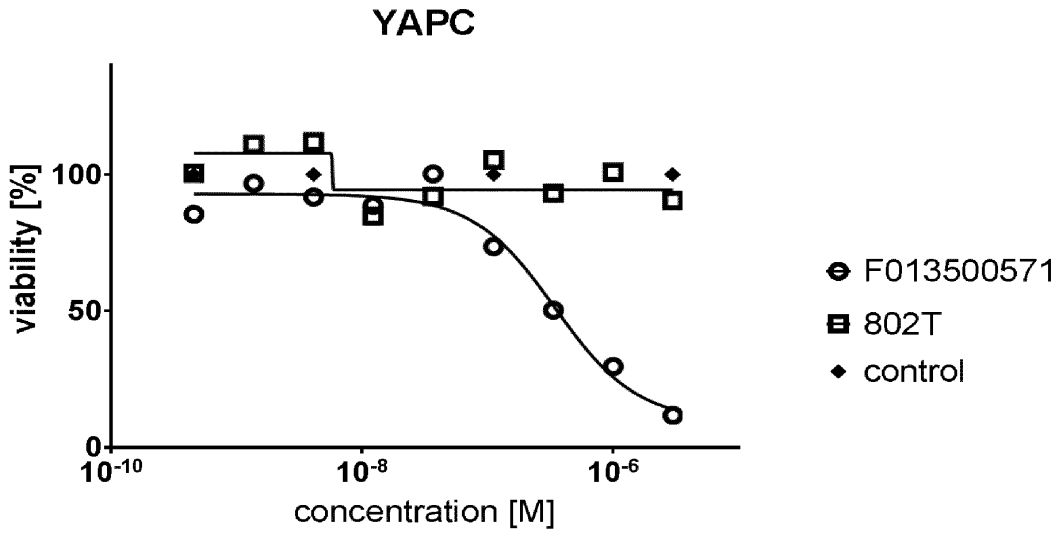


Figure 7A

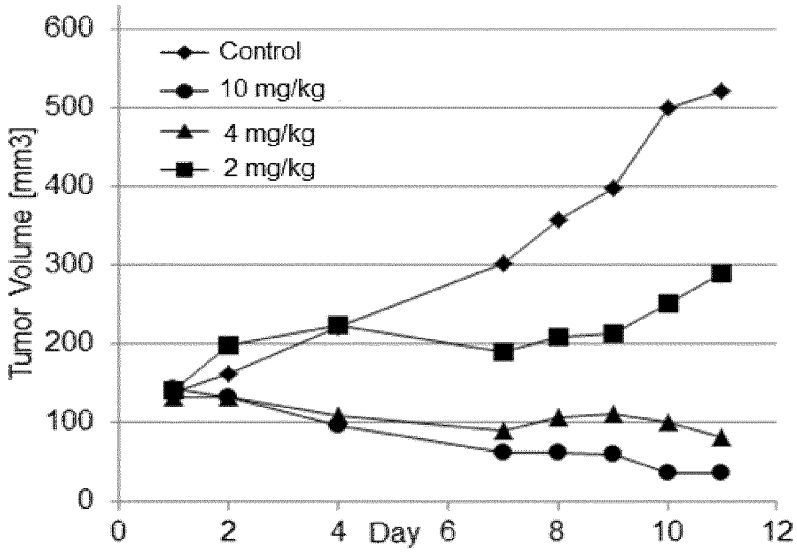


Figure 7B

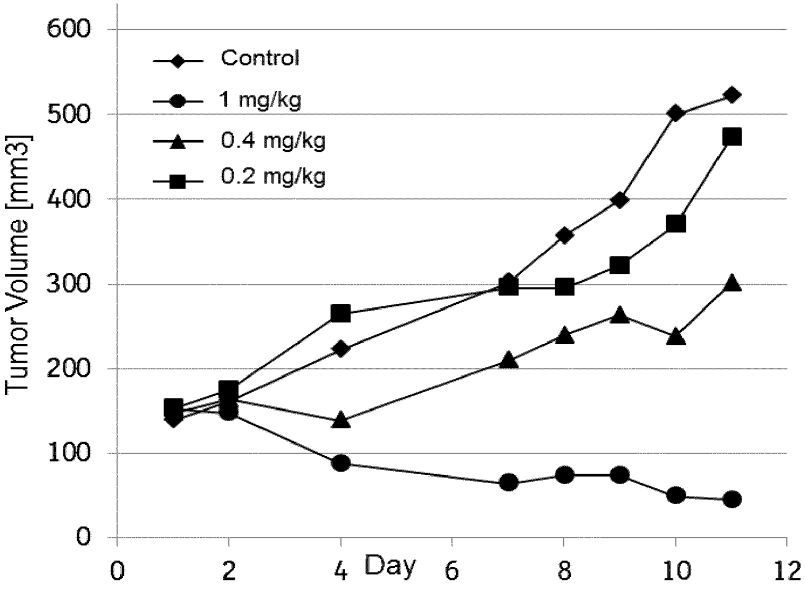


Figure 7C

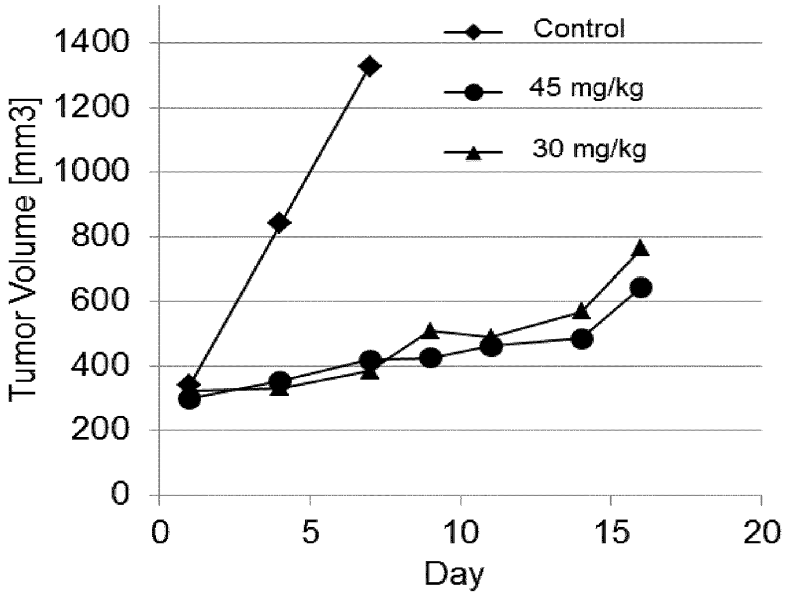

Control
45 mg/kg
30 mg/kg
Tumor Volume [mm3]
1400
1200
1000
800
600
400
200
0
0
5
10
15
20
Day

Figure 8A

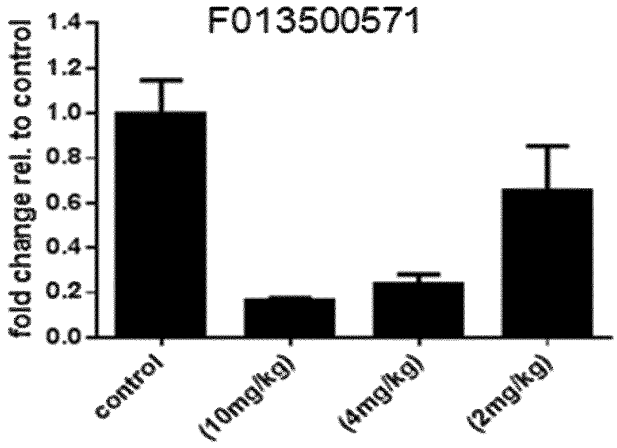


Figure 8B

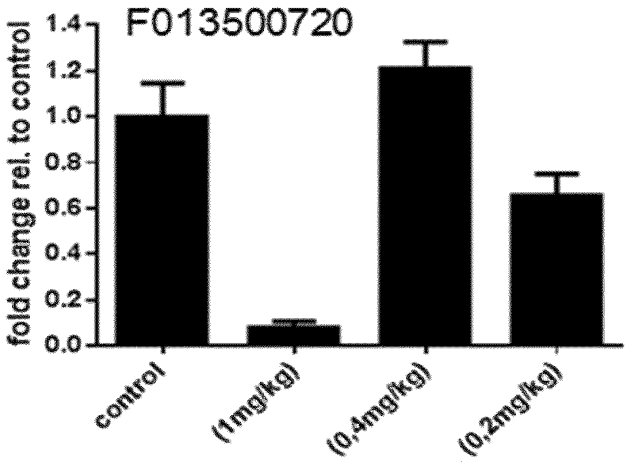


Figure 9A

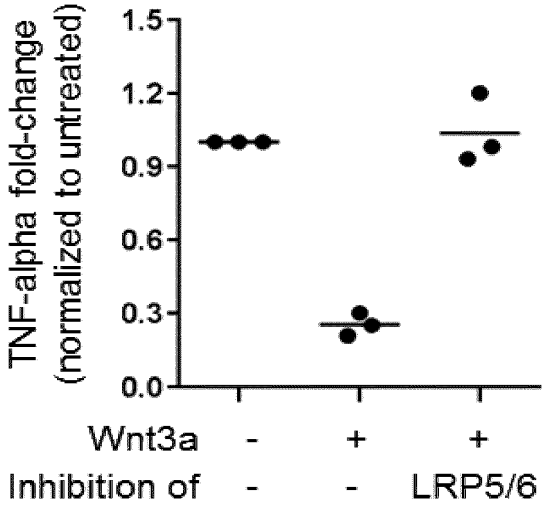
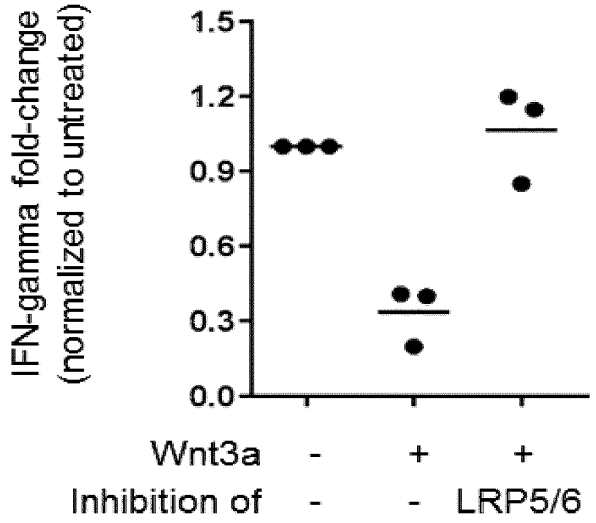


Figure 9B



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/079575

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K39/00 A61P35/00 C07K16/18 C07K16/28 C07K16/46
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/138391 A1 (NOVARTIS AG [CH]; CONG FENG [US]; ETTENBERG SETH [US]; JENKINS DAVID [) 10 November 2011 (2011-11-10) cited in the application examples 1-16	1-30
X	WO 2011/119661 A1 (GENENTECH INC [US]; HOFFMANN LA ROCHE [CH]; BOURHIS ERIC [US]; CARANO) 29 September 2011 (2011-09-29) cited in the application	26,28,29
A	page 2, lines 1-17; examples 1-13	1-25,27, 30
A	WO 2014/029752 A1 (GLAXO GROUP LTD [GB]) 27 February 2014 (2014-02-27) the whole document	1-30

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 February 2017	15/02/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Cilensek, Zoran

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JÄHNICHEN S ET AL: "CXCR4 nanobodies (VHH-based single variable domains) potently inhibit chemotaxis and HIV-1 replication and mobilize stem cells", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, NATIONAL ACADEMY OF SCIENCES, US, vol. 107, no. 47, 23 November 2010 (2010-11-23), pages 20565-20570, XP002611004, ISSN: 0027-8424, DOI: 10.1073/PNAS.1012865107 [retrieved on 2010-11-08] the whole document -----	1-30
A	DANESE M. JOINER ET AL: "LRP5 and LRP6 in development and disease", TRENDS IN ENDOCRINOLOGY AND METABOLISM., vol. 24, no. 1, 1 January 2013 (2013-01-01), pages 31-39, XP055298771, US ISSN: 1043-2760, DOI: 10.1016/j.tem.2012.10.003 figure 2 -----	1-30

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2016/079575

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		CL 2012003093 A1	22-03-2013
		CL 2014001297 A1	03-10-2014
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		CO 6630180 A2	01-03-2013
		EA 201291181 A1	30-05-2013
		EP 2566894 A1	13-03-2013
		GT 201200298 A	08-04-2014
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WO 2014029752 A1	27-02-2014	EP 2888279 A1	01-07-2015
		WO 2014029752 A1	27-02-2014

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 June 2022 (23.06.2022)

WIPO | PCT

(10) International Publication Number
WO 2022/130341 A1

(51) International Patent Classification:
C07K 16/46 (2006.01) *A61P 25/28* (2006.01)
A61K 39/395 (2006.01) *A61P 27/02* (2006.01)

(21) International Application Number:
PCT/IB2021/061971

(22) International Filing Date:
17 December 2021 (17.12.2021)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/127,408 18 December 2020 (18.12.2020) US

(71) Applicant: **ANTLERA THERAPEUTICS INC.** [CA/CA]; 2400-333 Bay Street, P.O. Box 20, Ico Fasken Martineau, Toronto, Ontario M5H 2T6 (CA).

(72) Inventors: **ANGERS, Stephane**; H: 29 Callisto Court, Mississauga, Ontario L5M 0A1 (CA). **SIDHU, Sachdev**; 134 Brunswick Ave., Toronto, Ontario M5S2M3 (CA). **BLAZER, Levi**; 2816 Bloor St. West Apt. 2, Etobicoke, Ontario M8X 1A7 (CA). **ADAMS, Jarrett**; 1801 Bayview Ave Unit 107, Toronto, Ontario M4G4K2 (CA). **SESHAGIRI, Somasekar**; 2400-333 Bay Street, P.O. Box 20, Ico Fasken Martineau, Toronto, Ontario M5H 2T6 (CA).

(74) Agent: **LEDGLEY, Cynthia J.**; Ledgley Law, 724 Annette Street, Toronto, Ontario M6S 2E2 (CA).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(54) Title: TETRAVALENT FZD AND WNT CO-RECEPTOR BINDING ANTIBODY MOLECULES AND USES THEREOF

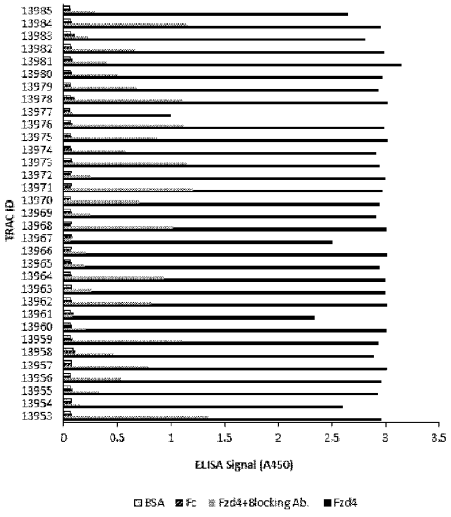


FIG 1A

(57) Abstract: Described herein are tetravalent binding antibody molecules comprising a FZD receptor binding domain and an LRP5/6 co-receptor binding domain on opposite termini of an Fc domain that activate a Wnt beta-catenin signaling pathway and methods for their use.

[Continued on next page]

WO 2022/130341 A1

Published:

— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*
— *with sequence listing part of description (Rule 5.2(a))*
— *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

TETRAVALENT FZD AND WNT CO-RECEPTOR BINDING ANTIBODY MOLECULES AND USES THEREOF

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on December 16, 2021, is named 117946_PD606WO1_FINAL.txt and is 989,433 bytes in size.

BACKGROUND

Wnt signaling pathways are critical for embryonic development and tissue homeostasis in adults. Wnt signaling is initiated when a Frizzled (FZD) receptor on the cell surface membrane binds with a Wnt ligand. Wnt ligands are secreted growth factors that regulate various cellular processes such as proliferation, differentiation, survival and migration.

Nineteen Wnt ligands exist in humans that interact with a network of ten Frizzled cell surface receptors (FZD) and one of several co-receptors that guide the selective engagement of different intracellular signaling branches (Wodarz, A. and Nusse, R. Annu. Rev. Cell Dev. Biol. 14, 59–88 (1998); Angers, S and Moon, R.T., transduction. Nat. Rev. Mol. Cell Biol. 10, 468–477 (2009)). FZDs have conserved structural features including seven hydrophobic transmembrane domains and a cysteine-rich ligand-binding domain. FZDs are known to function in three distinct signaling pathways, known as the Wnt planar cell polarity (PCP) pathway, the canonical Wnt/β-catenin pathway, and the Wnt/calcium pathway. The presence of Wnt co-receptors is also required to direct the differential engagement of the intracellular signaling cascades listed above. For example, Wnt ligands bind to a Frizzled receptor and a member of the low-density lipoprotein receptor-related proteins 5 and 6 (LRP5/6) co-receptor family to activate the Wnt/ β-catenin pathway, or with a receptor tyrosine kinase-like orphan receptors 1 and 2 (ROR1/2), related to receptor tyrosine kinase (RYK) or protein tyrosine kinase 7 (PTK7) co-receptor to activate alternate β- catenin-independent signaling pathways.

Wnt ligands are universally important for the control of tissue stem cells self-renewal and regulation of many progenitor cell populations, but the hydrophobicity and sensitive tertiary structure of Wnt proteins makes their biochemical purification challenging and their use *in*

vitro and *in vivo* inefficient. Described herein are tetravalent binding antibody molecules that activate a Wnt signaling pathway and methods for their use.

SUMMARY OF THE INVENTION

Described herein are tetravalent binding antibody molecules that activate a Wnt signaling pathway and methods for their use. The tetravalent binding antibody molecules bind to both an FZD receptor, e.g., Frizzled Class Receptor 1 (FZD1), Frizzled Class Receptor 2(FZD2), Frizzled Class Receptor 3 (FZD3), Frizzled Class Receptor 4 (FZD4), Frizzled Class Receptor 5 (FZD5), Frizzled Class Receptor 6 (FZD6), Frizzled Class Receptor 7 (FZD7), Frizzled Class Receptor 8 (FZD8), Frizzled Class Receptor 9 (FZD9), or Frizzled Class Receptor 10 (FZD10) and a Wnt co-receptor, e.g., LRP5 or LRP6 (LRP5/6), thereby activating a Wnt signaling pathway. In an embodiment, the tetravalent binding antibody molecules bind to both a FZD4 receptor and LRP5 and/or LRP6 and activate the Wnt/β-catenin signaling pathway. The tetravalent binding antibody molecules of this invention are also referred herein as "FZD Agonists", Frizzled and LRP5/6 Agonist (FLAg), and in some embodiments as "ANTs".

The tetravalent binding antibody molecules include an Fc domain comprised of CH2 and CH3 domains or fragment thereof comprising the CH3 domain, and a first bivalent binding domain that interacts with one or more FZD receptor, e.g., one or more of FZD1, FZD2, FZD3, FZD4, FZD5, FZD6, FZD7, FZD8, FZD9, and FZD10, and a second bivalent binding domain that binds a WNT co-receptor, e.g., LRP5 or LRP6, wherein the FZD binding domain is linked to one terminus of the Fc domain and the co-receptor binding domain is linked to the other terminus of the Fc domain. Thus, the binding domain for the FZD receptor and the binding domain for the WNT co-receptor are not directly linked rather they are separated by the Fc domain, or fragment thereof comprising the CH3 domain.

The Fc domain of the FZD Agonists may be an Fc domain of an immunoglobulin with or without effector function. The immunoglobulin may be an IgG, e.g., an IgG_1. In an embodiment of this invention the tetravalent binding antibody molecule comprises two polypeptides containing an Fc region that dimerize via the intrinsic ability of the Fc region in each polypeptide to dimerize or via a knob-in-holes configuration within the Fc. Thus, the Fc dimer may be a heterodimer or a homodimer. Methods for dimerizing peptides via a knob-in-hole configuration are described in WO2018/026942, inventors Van Dyk et al., Carter P.

(2001) J. Immunol. Methods 248, 7–15; Ridgway et al. (1996) Protein Eng. 9, 617–621; Merchant, et al. (1998) Nat. Biotechnol. 16, 677–681, and; Atwell et al., (1997) J. Mol. Biol. 270, 26–35, all incorporated herein by reference.

In an embodiment, each of the binding domains of the FZD Agonists described herein are bivalent and each may be monospecific, having two binding sites for the same epitope of an FZD receptor, e.g., FZD4, or Wnt co-receptor, e.g. LRP5/6, or bispecific having two binding sites with each site binding a different epitope on an FZD or Wnt co-receptor, e.g., a Wnt1 binding (domain E1-E2 within the extracellular domain of LRP5/6) site and a Wnt3 binding site (domain E3-E4 within the extracellular domain of LRP5/6) within the LRP5/6 co-receptor. In an embodiment, the LRP5/6 binding domain binds to a Wnt3A site (domain E3-E4) on LRP5 and binds to a Wnt3A site (domain E3-E4) on LRP6.

In embodiments of this invention the FZD binding domain linked to the Fc domain of the FZD Agonist comprises one or more immunoglobulin heavy-chain variable domain (VH) fragments and/or one or more immunoglobulin light-chain variable domain (VL) fragments that bind the FZD, e.g., FZD4. In an embodiment of this invention the FZD binding domain may comprise Fabs, a diabody or single chain variable fragments (scFv) single-domain antibody fragments, e.g., V_HH, or combinations thereof that bind to the same or different epitopes on the FZD.

In an embodiment of this invention the VHs and/or VLs of the FZD binding domain binds FZD4 or FZD5 and comprise the light chain CDRs and the heavy chain CDRs of a FZD4 or FZD5 binding antibody of Table 1, Table 2, or Table 6, and/or comprise light chain CDRs and heavy chain CDRs that are 50%, 55%, 60%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to the CDRs of an FZD4 antibody of Table 1, Table 2 or Table 6, and still retain binding to the FZD4 or FZD5 receptor. For example, in an embodiment of the invention, the FZD binding domain may comprise a first heavy chain (CDR-H1), a second heavy chain (CDR-H2), and/or a third heavy chain (CDR-H3), wherein the VH that binds FZD may comprise CDR-H1 of SEQ ID NO: 24, SEQ ID NO: 365, or SEQ ID NO: 893, a CDR-H2 of SEQ ID NO: 51, SEQ ID NO: 61, SEQ ID NO: 462, or SEQ ID NO: 894 and/or CDR-H3 of SEQ ID NO: 79, SEQ ID NO: 90, SEQ ID NO: 484, or SEQ ID NO: 895 and a first light chain (CDR-L1), a second light chain (CDR-L2), and/or a third light chain (CDR-L3), wherein the VL that binds FZD may comprise CDR-L1 of SEQ ID NO: 1, SEQ ID NO:

3 or SEQ ID NO: 12, a CDR-L2 of SEQ ID NO: 2, SEQ ID NO: 3 or SEQ ID NO: 12 and/or a CDR-L3 of SEQ ID NO: 3, SEQ ID NO: 12, SEQ ID NO: 285, or SEQ ID NO: 896.

In an embodiment of this invention the co-receptor (LRP5/6) binding domain linked to the Fc domain of the FZD Agonist comprises one or more immunoglobulin heavy-chain variable domain (VH) fragments and/or one or more immunoglobulin light-chain variable domain (VL) fragments that bind to the Wnt co-receptor, e.g., LRP5 and/or LRP6. For example, in an embodiment of the invention, the LRP binding domain may comprise a first heavy chain (CDR-H1), a second heavy chain (CDR-H2), and/or a third heavy chain (CDR-H3), wherein the VH that binds LRP may comprise a CDR-H1 of SEQ ID NO: 527, SEQ ID NO: 528, SEQ ID NO: 536, SEQ ID NO: 716, or SEQ ID NO: 720, a CDR-H2 of SEQ ID NO: 552, SEQ ID NO: 553, or SEQ ID NO: 566, SEQ ID NO: 785, or SEQ ID NO: 791 and/or a CDR-H3 of SEQ ID NO: 584, SEQ ID NO: 585, SEQ ID NO: 586 or SEQ ID NO: 603, SEQ ID NO: 856 or SEQ ID NO: 862 CDR-H3 and and a first light chain (CDR-L1), a second light chain (CDR-L2), and/or a third light chain (CDR-L3), wherein the VL that binds LRP may comprise CDR-L1 of SEQ ID NO: 1, a CDR-L2 of SEQ ID NO: 2, or SEQ ID NO: 491 and/or a CDR-L3 of SEQ ID NO: 130, SEQ ID NO: 492, SEQ ID NO: 493, SEQ ID NO: 510, SEQ ID NO: 623 or SEQ ID NO: 665.

In an embodiment of this invention, the Wnt co-receptor binding domain is bivalent and may comprise a diabody, or may comprise a Fab, a single chain variable fragment (scFv) or a single domain antibody fragments (V_HH) or combinations thereof for binding to the same or different epitopes on the co-receptor. In embodiments of this invention the VHs and VLs of the Wnt coreceptor binding domain comprise the light chain CDRs and/or the heavy chain CDRs of a LRP5 and/or LRP6 binding antibody of Table 3, Table 4 or Table 6, or comprise light chain CDRs and/or heavy chain CDRs that are 50%, 55%, 60%, 75%. 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to the CDRs of an LRP5 and/or LRP6 antibody of Table 3, Table 4 or Table 6, and still retain binding to the LRP5 and/or LRP6 co-receptor.

In an embodiment of this invention the Wnt co-receptor binding domain linked to the Fc domain of the FZD Agonists described herein comprises a diabody, formed by two peptides each peptide comprising a heavy-chain variable domain (VH or VH domain) linked to a light-chain variable domain (VL or VL domain) wherein the VH and the VL from one peptide pair with the VL and VH of the other peptide forming the diabody. In this configuration, the binding domain has two binding sites that bind to the Wnt co-receptor, e.g., LRP5 or LRP6.

The diabody may be monospecific binding the same site on the co-receptor or may be bispecific (bs) binding two different sites on the co-receptor. By using a knobs-in-holes Fc configuration, the peptides comprising the VH and VL linked to Fc regions, can be non-identical but will still pair to form a bispecific binding domain capable of binding to two different sites on the Wnt co-receptor (e.g. LRP5 or LRP6).

The peptides forming the diabodies, the V_HH, the scFv, and the Fabs that form the binding domains may be derived from an antibody selected for its binding to a desired target, a "source antibody". For the FZD binding domain, the "FZD source antibody" may be an antibody that binds to one or more of the FZD receptor(s), e.g., one or more of FZD1, FZD2, FZD3, FZD4, FZD5, FZD6, FZD7, FZD8, FZD9, and FZD10, and antagonizes Wnt signaling or inhibits Wnt binding to the given FZD receptor(s). Alternatively, the FZD source antibody may be an antibody that binds to the FZD receptor(s) without antagonizing Wnt signaling or without inhibiting Wnt binding to the FZD receptor. Likewise, for the co-receptor binding domain, the "co-receptor source antibody" may be an antibody that binds to the Wnt co-receptor, e.g., LRP5/6, and antagonizes Wnt signaling or inhibits Wnt binding to the Wnt co-receptor. Alternatively, the co-receptor source antibody may be an antibody that binds to a co-receptor, e.g., LRP5/6, without antagonizing Wnt signaling or without inhibiting Wnt binding to the co-receptor.

In an embodiment of this invention the FZD binding domain of the FZD Agonist may bind specifically to a specific FZD, e.g., FZD4, with a higher affinity than to other FZDs, i.e., FZD1, FZD2, FZD3, FZD5, FZD6, FZD7, FZD8, FZD9, and FZD10, or may be pan-specific, binding to one or more other members of the FZD receptor family. In an embodiment the FZD binding domain binds specifically to one FZD with an affinity greater than 10-fold over the binding to any other Frizzled family member.

In an embodiment of this invention the FZD Agonist binds to FZD4, a "FZD4 Agonist". The FZD4 binding domain of the FZD4 Agonist may bind specifically to FZD4, binding with a higher affinity to FZD4 over other FZDs, or may be pan-specific, binding to FZD4 and one or more other members of the FZD receptor family, e.g., Frizzled Class Receptor 1 (FZD1), Frizzled Class Receptor 2(FZD2), Frizzled Class Receptor 3 (FZD3), Frizzled Class Receptor 5 (FZD5), Frizzled Class Receptor 6 (FZD6), Frizzled Class Receptor 7 (FZD7), Frizzled Class Receptor 8 (FZD8), Frizzled Class Receptor 9 (FZD9), or Frizzled Class Receptor 10

(FZD10). In an embodiment the FZD binding domain binds specifically to FZD4 with an affinity greater than 10-fold over any other Frizzled family member listed above.

In an embodiment of this invention the FZD Agonist binds to FZD5, a "FZD5 Agonist." The FZD5 binding domain of the FZD5 Agonist may bind specifically to FZD5, binding with a higher affinity to FZD5 over other FZDs, or may be panspecific, binding to FZD5 and one or more other members of the FZD receptor family, e.g., FZD1, FZD2, FZD3, FZD4, FZD6, FZD7, FZD8, FZD9, or FZD10. In an embodiment the FZD binding domain binds specifically to FZD5 with an affinity greater than 10-fold over any other Frizzled family member listed above.

In an embodiment of the FZD Agonists of this invention the Wnt co-receptor binding domain is a monospecific bivalent LRP5/6 co-receptor binding domain and binds to a single epitope on the LRP5 and/or LRP6 co-receptor, e.g., an epitope of the LRP5 and/or LRP6 coreceptor that binds to Wnt1(E1-E2 domain of LRP5 or LRP6) or binds Wnt3a (E3-E4 domain of LRP5 or LRP6). In an embodiment of this invention the co-receptor binding domain is a bispecific bivalent LRP5/6 binding domain that binds to two epitopes within the LRP5 and/or LRP6 co-receptor extracellular domain, e.g., the co-receptor binding domain interacts with the Wnt1 (E1-E2) and Wnt3 (E3-E4) epitopes of the LRP5 and/or LRP6 co-receptor. In an embodiment of this invention the co-receptor binding domain is a bispecific bivalent binding domain that binds to an extracellular domain of LRP5 and LPR6, e.g., the domain interacts with the Wnt1 (E1-E2) epitope of the LRP5 co-receptor and the Wnt1 (E1-E2) epitope of the LRP6 co-receptor LRP5, or the domain interacts with the Wnt3a (E3-E4) epitope of the LRP5 co-receptor and the Wnt3a (E3-E4) epitope of the LRP6 co-receptor or alternatively the domain interacts with a Wnt1 (E1-E2) epitope or LRP5 co-receptor and a Wnt3a (E3-E4) epitope of LPR6 co-receptor or vis versa.

Various formats of tetravalent binding antibody molecules described herein are depicted in Figure 6. In a particular format, Diabody-Fc-Fab, an LRP5/6 binding diabody is linked to the N-terminus of an Fc domain and two Fabs are linked to the C-terminus of the Fc domain wherein the Fab is linked to the CH3 of the Fc domain via the Fab heavy chain (VH) variable

domain. Alternatively, the Fab is linked to the CH3 of the Fc domain via the variable region (VL) of the light chain.

We previously reported multivalent binding molecules comprising an Fc domain, a FZD binding domain and a Wnt co-receptor (LRP5/6) binding domain on opposite termini of the Fc domain, e.g., a molecule having a FZD4 diabody linked one terminus of an Fc domain and a LRP5/6-binding diabody linked to the other terminus of the Fc domain, see PCT/IB2019/051174 inventors Angers et al. and PCT/IB2020/055463 inventors Angers et al., both incorporated in their entirety by reference.

It has been reported that Wnt-βcatenin signaling, specifically through activation of FZD4, is important for vasculature development and for adult vasculature homeostasis. More specifically, it is critical for barrier function at the blood-retina and blood-brain barriers (BRB and BBB). Defects in FZD4 signaling can lead to endothelial cell permeability defects and genetic mutations within this pathway are known to lead to vascular defects (e.g. Norrie disease, FEVR). At the blood-retina barrier, the extracellular ligand Norrin predominantly activates a FZD4-TSPAN12-LRP5 complex to regulate endothelial cell-cell interactions, barrier functions and permeability (Wang et al. (2012) Norrin/Frizzled4 signaling in retinal vascular development and blood brain barrier plasticity. Cell. 151:1332–1344). At the blood-brain barrier the secreted Wnt7a/b growth factor chiefly activates the FZD4-GPR124-LRP6 receptor complex (Chang et al., (2017). GPR124 is essential for blood-brain barrier integrity in central nervous system disease. (Nat. Med. 23: 450–460). The FZD4 Agonists described herein, e.g., the configurations having a diabody binding domain for a LRP5/6 and an FZD4 binding domain comprised of two Fab fragments that bind FZD4, wherein the binding domains are on opposite termini of an Fc domain, produce a particularly stable and homogenous molecule with an unexpectedly high level of Wnt-βcatenin signaling pathway activation in endothelial cells that translates into increased barrier function and decreased vascular permeability (Figure 11). In essence, the FZD4 Agonists described herein function as Norrin and Wnt7a/b mimetic molecules.

This invention also includes methods for using the FZD Agonists described herein. Described herein are methods to activate a Wnt signaling pathway, e.g., the Wnt/β-catenin signaling pathway, using the tetravalent binding antibody molecules of this invention, which are contemplated to promote the proximity of FZD receptors and Wnt co-receptors, e.g., one or more of FZD1, FZD2, FZD3, FZD4, FZD5, FZD6, FZD7, FZD8, FZD9, and FZD10

receptors and LRP5 and/or LRP6 co-receptors, on a cell wherein binding by the FZD Agonists to both FZD receptor(s) and the LRP5 and/or LPR6 co-receptor(s) activates the Wnt signaling pathway.

Blood-retina barrier (BRB) formation and retinal angiogenesis require βcatenin signaling induced by the ligand norrin (NDP [Norrie disease protein]), the receptor FZD4, co-receptor LRP5, and the TSPAN12 (tetraspanin 12). As such, an aspect of this invention is a method for promoting and/or maintaining retinal vasculature barrier function and angiogenesis by treating eye tissue, e.g., retinal tissue, with an effective amount of a tetravalent FZD4 Agonists of this invention.

Also, an aspect of this invention is a method for promoting, restoring and/or maintaining the BRB and BBB functions by treating the BRB or BBB vasculature with an effective amount of a tetravalent FZD4 Agonist described herein. A further aspect of this invention is a method for treating a subject having a disorder or condition characterized by defective retinal or brain angiogenesis characterized by reduced endothelial cell barrier function leading to vascular leakage by administering to such subject an effective amount of a FZD4 Agonists of this invention. A further aspect of this invention is a FZD4/LRP5 tetravalent binding antibody molecule or pharmaceutical composition for use in the treatment or prevention of a disorder or condition characterized by defective retinal or brain angiogenesis and/or characterized by reduced endothelial cell barrier function and/or vascular leakage. A further aspect of this invention is a method of treating or preventing a disorder or condition characterized by defective retinal or brain angiogenesis and/or reduced endothelial cell barrier function and/or vascular leakage comprising administering to a person in need thereof a therapeutically effective amount of a FZD4/LRP5 tetravalent binding antibody molecule described herein. A further aspect of the invention is the use of a FZD4/LRP5 tetravalent binding antibody molecule for the manufacture of a medicament for the treatment or prevention of a disorder or condition characterized by defective retinal or brain angiogenesis and/or reduced endothelial cell barrier function and/or vascular leakage. Such disorders or conditions include ocular disorders, including but are not limited to disorders of the retina or macula. Such disorders of the retina or macula include, but are not limited to diabetic retinopathy, retinipathy of prematurity, Coats' disease, FEVR, Norrie disease, macular degeneration, diabetic macular edema, and pediatric vitreoretinopathies. Additional disorders or conditions

included in embodiments of this invention include but are not limited to Alzheimer's disease, epilepsy, multiple sclerosis, ischemia, and stroke.

An embodiment of this invention includes methods for producing vascularized cerebral organoids by promoting the barrier function of the vasculature network throughout the organoids, and thereby mimicking blood-brain-barrier function using an effective amount of a tetravalent FZD4 Agonist described herein.

Also, an embodiment of this invention is a method of treating a subject suffering from a gastrointestinal disorder, including a subject having inflammation of all or part of the intestines, also known as inflammatory bowel disease, by administering to such subject an effective amount of a pharmaceutical composition of this invention, e.g., a composition comprising a FZD5 Agonist. Examples of inflammatory bowel disease include, but are not limited to, Crohn's disease, and ulcerative colitis.

Also, an embodiment of this invention are methods for directing differentiation of iPS or other pluripotent stem cells (PSCs) towards various lineages by culturing these cells in the presence of an effective amount of a tetravalent binding antibody molecule of this invention.

Also described herein are methods for making the tetravalent binding antibody molecules of this invention.

The modular aspects of this invention allow for mixing and matching binding domains derived from FZD-binding antibodies and LRP5/6-binding antibodies on opposite termini of the Fc domain to generate a tetravalent binding antibody molecule that can engage a FZD-LRP5/6 co-receptor complexes to selectively activate Wnt signaling. The modularity and effectiveness of the tetravalent binding antibody molecules for activating Wnt signaling pathways described herein contrasts with the Wnt surrogates described in the prior art that consists of monovalent FZD and Wnt co-receptor binding ligands, or FZD and Wnt co-receptor binding ligands wherein the binding ligands are not attached to opposite ends of an Fc domain.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1A and Figure 1B. Single point ELISAs. FZD4-binding antibodies isolated from affinity matured libraries of the known FZD4-binding antibodies 5044 (Figure 1A) and 5027 (Figure 1B) bind to FZD4 sites that compete with their parental antibody. The reaction was

stopped by adding 1M H_3PO_4 and the absorbance was measured spectrophotometrically at 450 nm in a microtiter plate reader; white=BSA; black and white stripe=Fc; gray=FZD4 + blocking antibody; and black=FZD4.

Figure 2. Epitope mapping of FZD4 antibodies. FZD4 and 5027 and 5044 have overlapping epitopes. The pan-FZD binder 5016 is a positive control showing that the antigens are functional, with the exception of "FZD4_Swap10". Both FZD4-specific antibodies 5027 and 5044 are unable to bind to "FZD4 Swap 7" suggesting that these molecules bind to this region of the FZD ECD.

Figure 3A. Size-exclusion chromatography (SEC). Analysis of FZD4 antibodies as compared to Trastuzumab. Protein elution was monitored using absorbance at 280 nM.

Figure 3B. ELISA specificity. Measurements of the FZD4 antibodies determined against FZD4 and against FZD1 and FZD10, two members of the FZD family most-closely related to FZD4. The reaction was stopped by adding 1M H3PO4 and the absorbance was measured spectrophotometrically at 450 nm in a microtiter plate reader.

Figure 4. Phage clonal ELISA of synthetic antibodies targeting LRP5. The results demonstrate that the synthetic antibodies bound to LRP5. The absorbance was measured spectrophotometrically at 450 nm in a microtiter plate reader; gray=BSA; light gray=his-Fc; dark gray=LRP5

Figures 5A and 5B. Phage clonal ELISA of synthetic antibodies targeting LRP6. The results demonstrate the synthetic antibodies bound to LRP6. The absorbance was measured spectrophotometrically at 450 nm in a microtiter plate reader; black=BSA; gray=Fc; light gray=LRP6-Fc.

Figure 6. Modalities of tetravalent binding antibody molecules. Illustrated are: a diabody-Fc-diabody format having an FZD-binding monospecific diabody on the N-terminal of the Fc domain and a LPR5/6-binding bispecific diabody on the C-terminal of the Fc domain; a Diabody-Fc-scFv format having an N-terminal LPR5/6-binding bispecific diabody and two C-terminal FZD binding scFv; an IgG-diabody format having two FZD-binding Fabs forming an N-terminal binding domain and a bispecific LRP5/6 binding diabody forming the C-terminal binding domain; an IgG-scFv format having two FZD-binding Fabs forming an N-terminal binding domain and two LRP5/6 binding scFvs forming the C-terminal binding

domain, and; a diabody-Fc-Fab format having a bispecific LRP5/6 binding diabody forming the N-terminal binding domain and two FZD-binding Fabs forming the C-terminal binding domain, wherein the Fabs are linked to the CH3 of the Fc domain via the Fab variable heavy region. It is specifically contemplated that in an alternate diabody-Fc-Fab format the Fabs are linked to the CH3 of the Fc domain via the Fab variable light region. The various domains of the tetravalent molecules, VL, VH, CH1, CH2, CH3, CL1 and Fc, are joined via linkers, e.g., peptide linkers. The Fc domain, is formed by the dimerization of the CH2 and CH3 domains of the Hole construct Fc region and Knob construct Fc region. The various domains of the tetravalent molecules, VL, VH, CH1, CH2, CH3, CL1 and Fc, are joined via linkers, e.g., peptide linkers.

Figure 7. FZD4 Agonist having a Diabody-Fc-Fab format. The Diabody-Fc-Fab format having an LRP5-binding bispecific diabody forming a bivalent bispecific N-terminal LRP5-binding domain and two FZD4-binding Fabs forming a bivalent monospecific C-terminal FZD4-binding domain and an Fc region with attenuated effector functions due to amino acid mutations, e.g., N297G (NG) and D265A, (DANG) variants. The various domains of the tetravalent molecules, VL, VH, CH1, CH2, CH3, CL1 and Fc, are joined via linkers, e.g., peptide linkers.

Figure 8. FZD4 Agonists having a Diabody-Fc-Fab format (ANT) bind FZD4 with high selectivity. Figure 8A depicts the apparent selectivity of the FZD4 Agonists for the recombinant extracellular domain (ECD) of 9 of the 10 FZD as determined by biolayer interferometry (BLI). Figure 8B demonstrates FZD agonists do not recognize common non-specific antigens. The FZD Agonists were tested at 100 nM for binding to a panel of antigens as described in Mouquet et al. Polyreactivity increases the apparent affinity of anti-HIV antibodies by heteroligation. Nature. 2010 Sep;467(7315):591-595. DOI: 10.1038/nature09385, PMC3699875, and Jain T. et al. Biophysical properties of the clinical-stage antibody landscape. Proceedings of the National Academy of Sciences of the United States of America. 2017 Jan;114(5):944-949. DOI: 10.1073/pnas.1616408114, PMC5293111.

Figure 9. FZD4 Agonists (ANT) having a Diabody-Fc-Fab format (having a LRP-binding bispecific diabody and two FZD4-binding Fabs) are stable and monomeric in solution. Figure 9A presents the results of an analytical SEC analysis of FZD agonists as compared to trastuzumab IgG. Figure 9B presents the results of differential scanning fluorimetry demonstrating that the FZD4 Agonists in the Diabody-Fc-Fab format have thermal

denaturation profiles similar to that of trastuzumab, whereas a first generation diabody-Fc-diabody FZD4 modality (CM0199) is less optimal.

Figure 10. FZD4-LRP5 specific FZD4 Agonists having the Diabody-Fc-Fab format (ANT). FZD4-LRP5 specific FZD4 Agonists in this format stimulate FZD4 in mouse endothelial cell line (bEND3.1) and lead to an increase in Axin2 (beta catenin target gene) gene transcription in a concentration-dependent manner.

Figure 11A and Figure 11B depicts a FZD4-LRP5 specific agonist having the diabody-fc-diabody format promotes endothelial cell barrier functions in a mechanism opposing VEGF-induced permeability. Figure 11A depicts Immunofluoresence of ZO-1/CLDN3 and ZO-1/CLDN5 localization on bEnd.3 cell junctions. bEnd.3 cells were treated or not with 30nM of F4L5.13 (aka CM0199) and Norrin (NDP) in the presence or absence of VEGF (100ng/ml) for 1h. Starting from the top row and working downward: NT (non-treated) show no change in permeability; VEGF treatment of bEND3.1 cells leads to junction disassembly as seen by loss of plasma membrane staining of CLDN3, CLDN5 and ZO-1; Co-treatment of cells with VEGF and the FZD4 agonist CM0199 (F4L5.13) leads to a near-complete rescue of the effect of VEGF alone; the last row of Figure 11A shows co-treatment of cells with VEGF and NDP and similarly leads to a near-complete rescue of the effect of VEGF alone, suggesting that the FZD4 Agonists described herein function as Norrin and Wnt7a/b mimetic molecules. Figure 11B shows a transendothelial permeability assay quantifying the passage of FITC-dextran through a monolayer of bEnd.3 cells. Passage of FITC-dextran was measured after exposure of bEnd.3 cells to 100 ng/ml VEGF, 30 nM F4L5.13 or both or pretreated with VEGF for 1 h before treating with F4L5.13 for 1 h. Data are presented as mean ± SD, n = 5 independent experiments. Significance was calculated by one-way ANOVA with Bonferroni's multiple comparisons test (*$P < 0.05$ as compared to VEGF treatment).

Figure 12. Single point ELISA. FZD5 antibodies that bind the extracellular domain of FZD5 at a site overlapping with 2919 identified from affinity maturation libraries. New FZD5 antibodies bind FZD5 at a site overlapping with 2919 identified from affinity maturation libraries. Single point ELISAs were performed on 96-well Maxisorp plates coated with the ECDs of human FZD5 protein in the presence or absence of a saturating concentration of 2919 IgG. The absorbance was measured spectrophotometrically at 450 nm in a microtiter

plate reader; white with black stripes=BSA; black with white stripes=Fc; gray=FZD5 + blocking antibody; black=FZD5.

Figure 13. Single point ELISA. demonstrates new FZD5 antibodies from 2928 affinity maturation library selectively bind FZD5. New FZD5 antibodies from 2928 affinity maturation library selectively bind FZD5. Single point ELISAs were performed on 96-well Maxisorp plates coated with the ECDs of human FZD2, FZD5, or FZD8 protein. The absorbance was measured spectrophotometrically at 450 nm in a microtiter plate reader; black with white stripes=Fc; white with black stripes=FZD2; gray=FZD8; black=FZD5.

Figure 14. Luciferase assay. Pan-FZD/LRP6 ANT9 and FZD5-specific/LRP6 ANT59 activate Wnt signaling in cells. TOPFLASH cells were treated overnight with varying concentrations of FZD agonist or a non-targeting control molecule (CM0156) and TCF/LEF-driven luciferase expression was measured using a standard luciferase assay. Both molecules are able to activate FZD-mediated luciferase expression in a concentration-responsive manner. ANT9, which is able to bind to 7 of the 10 FZD receptor subtypes produces a higher maximal activation signal than the FZD5-specific ANT59.

Figure 15. Original format ANT39 and inverted format ANT39i. The FZD4 Agonist ANT39 having a Diabody-Fc-Fab format and FZD4 Agonist ANT39i having an IgG-Diabody format (having two FZD-binding Fabs forming an N-terminal binding domain and a bispecific LRP5/6 binding diabody forming the C-terminal binding domain) and an Fc domain. The FZD binding domain of ANT39i comprises two Fab fragments attached to the N- terminus of the Fc domain and each Fab binds an FZD. The LRP5/6 co-receptor binding domain is attached to the C- terminus of the Fc domain and is composed of a diabody that binds two different sites on the co-receptor, e.g., a Wnt1 site (E1-E2) and a Wnt3 site (E3-E4) on LRP5/6. The Fabs may be specific for a particular FZD, e.g. FZD4, or may be pan-specific, binding to more than one FZD, e.g., to FZD4 and one or more other FZD. The Fc region may have attenuated effector functions due to amino acid mutations, e.g., N297G (NG) and D265A, (DANG) variants. The various domains of the tetravalent molecules, VL, VH, CH1, CH2, CH3, CL1 and Fc, are joined via linkers, e.g., peptide linkers.

Figure 16A depicts FZD4 Agonist ANT39 having a Diabody-Fc-Fab format (having an LRP5-binding bispecific diabody forming a bivalent bispecific N-terminal LRP5-binding domain and two FZD4-binding Fabs forming a bivalent monospecific C-terminal FZD4-

binding domain) with the Fc region having attenuated effector functions due amino acid mutations to N297G and D265A (DANG) variants or L234A, L235A, P331S (LALAPS) variants, and with the Fc region further comprising knob-in-hole heterodimerization variants Merrimack, Merchant or Merchant S:S (Merrimack CH3 mutations as described in WO2018/026942A1, Merchant CH3 mutations as described in Merchant A.M. et al Nature Biothechnology 1998 vol 16 p677-681). Figure 16A discloses SEQ ID NOS 886, 892, 891, 886, 892, 891, 886, 892, 891, 886, 892, and 891, respectively, in order of appearance. Figure 16B depicts FZD4 Agonist ANT39i having an IgG-Fc-Diabody format (having two Fab fragments attached to the N- terminus of the Fc domain, each Fab binding to an FZD, and a LRP5/6 co-receptor binding domain attached to the C- terminus of the Fc domain that is composed of a diabody that binds two different sites on the co-receptor) and an Fc region with attenuated effector functions due to DANG or LALAPS variants, and Merrimack, Merchant or Merchant S:S heterodimerization variants. Figure 16B discloses SEQ ID NOS 891, 886, 891, 886, 891, 886, 891, and 886, respectively, in order of appearance.

Figure 17. Thermostability of ANT39 variants. Figure 17 presents the results of differential scanning fluorimetry experiments demonstrating that the LALA variant of FZD4 agonist ANT39 (ANT39 LALA) has improved thermal stability relative to the parental ANT39 (containing DANG mutations in the Fc). Specifically, the LALA variant showed an improved thermal stability that is closer to the profile of a variant of Trastuzumab that contains the same Knob/Hole Fc mutations as the ANT.

Figure 18. FZD4 Agonist ANT42 having a Diabody-Fc-Fab format. FZD4 Agonist ANT42 having an LRP5-binding bispecific diabody forming a bivalent bispecific N-terminal LRP5-binding domain and two FZD4-binding Fabs forming a bivalent monospecific C-terminal FZD4-binding domain with the Fc region having attenuated effector functions due amino acid mutations to N297G and D265A (DANG) variants or L234A, L235A, P331S (LALAPS) variants, and with the Fc region further comprising knob-in-hole heterodimerization variants Merrimack, Merchant or Merchant S:S (Merrimack CH3 mutations as described in WO2018/026942A1, Merchant CH3 mutations as described in Merchant A.M. et al Nature Biothechnology 1998 vol 16 p677-681). And FZD4 Agonist ANT42i having an IgG-Fc-Diabody format (having two Fab fragments attached to the N- terminus of the Fc domain, each Fab binding to an FZD, and a LRP5/6 co-receptor binding domain attached to the C-terminus of the Fc domain that is composed of a diabody that binds two different sites on the

co-receptor) and an Fc region with attenuated effector functions due to DANG or LALAPS variants, and Merrimack, Merchant or Merchant S:S heterodimerization variants. Figure 18 discloses SEQ ID NOS 886, 892, 891, 891, 886, 886, 892, 891, 891, 886, 886, 892, 891, 891, 886, 886, 892, 891, 891, and 886, respectively, in order of appearance.

Figure 19. Antibody modalities tested for FZD agonism. A) Diabody-Fc-Diabody, VH and VL were tested both FZD or LRP binding variable domains; B) Diabody-Fc-scFv; C) scFv-Fc-Diabody; D) scFv-Fc-scFv; E) IgG-Diabody; F) IgG-scFv; G) Diabody-Fc-Fab; H) Diabody-CH3-Diabody; I) Fab-Diabody. In figure 19, molecules B-F, H-I, comprise N-terminal variable domains that bind LRP and the C-terminal variable domains bind FZD. In figure 19, molecule G comprises a variable domain at the N-terminal that binds FZD and a variable domain at the C-terminal that binds LRP. These antibody formats marked with an * were tested using a Knobs-in-Holes Fc.

Figure 20. Multiple antibody architectures are able to elicit potent FZD agonism. Paratopes targeting pan-FZD and LRP6 were configured in various arrangements as described in table 14. Canonical Wnt pathway stimulation by each antibody was determined on wild-type HEK cells expressing the TOPFLASH reporter in a blinded manner by two different scientists. Data are presented as mean ± SD and are representative of 4 different experiments.

Figure 21. Expression Titers of various FZD agonist modalities. Various FZD agonist modalities were expressed in HEK cells, purified via protein A chromatography, and expression titer was determined based on the absorbance at 280 nm. EC50 for FZD activation was determined on wild-type HEK cells expressing the TOPFLASH reporter in a blinded manner by two different scientists.

Figure 22. Organoid viability Assay. Mouse small intestine organoids were grown in the presence of 1 μM LGK-974 to block endogenous Wnt secretion and treated with PBS, Wnt3a conditioned media or FLAg molecules as indicated. Left, representative images from n=3 independent experiments. Right, quantification of organoid viability via CellTiter-Glo luminescence assay. Bars represent mean +/- standard error from 3 independent experiments.

Figure 23. Mouse colon histology. Histological appearance of the mouse colon following DSS treatment cycle (7 days 2% DSS, 3 days 0.5% DSS) with intraperitoneal injection of either control IgG or ANT59 (10 mg/kg) on days 4 and 7. (A) Images captured at 20X

magnification showing overall architecture. (B) Images captured at 100X showing rescue of mucosal integrity with ANT59 treatment.

Figure 24. (A) Body weight changes in mice throughout DSS treatment cycle (7 days 2% DSS, 3 days 0.5% DSS) with intraperitoneal injection of either control CM0156, PanFZD agonist or ANT59 (10 mg/kg) on days 4 and 7. (B) Left: Representative images of dissected colons from 6-8 mice per treatment group with centimeter scale for comparison. Right: colon length from each treatment group with bar representing mean colon length +/- S.D. and individual data points displayed. *** indicates $p < 0.0001$ in one-way ANOVA, H2O indicates normal water (no DSS).

Figure 25. Characterization of FZD5/LRP6 ANTs. ANTs were expressed in HEK cells, purified via protein A chromatography, and expression titer was determined based on the absorbance at 280 nm. Using biolayer interferometry, the apparent affinity (avidity) of each molecule for recombinant Fc-fused human FZD5 was determined and selectivity against other human FZDs was measured. Dose–response curves for the activation of a LEF/TCF reporter gene in FZD-knockout (1,2,4,5,7) HEK293 cells overexpressing FZD5. Cells were seeded in 96-well dishes for 24 hours, then treated as indicated for 17 hours. Reporter activation was assessed using the Dual-Luciferase Reporter Assay System (Promega). Data are presented as mean ± SD for technical duplicates and representative of n=3 independent experiments.

DETAILED DESCRIPTION OF THE INVENTION

Described herein are tetravalent binding antibody molecules comprising an Fc domain, with or without effector function, a bivalent FZD binding domain and a bivalent LRP-binding domain, wherein the binding domains are attached to opposite ends of the Fc domain. In an embodiment, the FZD binding domain is attached to the carboxy terminus of the Fc region and the LRP co-receptor binding domain is attached to the amino terminus of the Fc domain. Alternatively, the FZD binding domain is attached to the amino terminus of the Fc region and the co-receptor binding domain is attached to the carboxy terminus of the Fc domain. The binding domains may be attached directly to the Fc domain or attached to the Fc domain via a linker. The FZD binding domain may bind to one or to more than one FZD receptor, i.e., one or more of FZD1, FZD2, FZD3, FZD4, FZD5, FZD6, FZD7, FZD8, FZD9, and FZD10.

In an embodiment of the invention the FZD binding domain is bivalent and comprises a diabody or comprises a scfv, a V_HH fragment, or an Fab fragment or combinations thereof

that bind FZD, and the co-receptor binding domain is bivalent and comprises a diabody or a V_HH fragment, an Fab, or a scFv or combinations thereof that bind the LRP5/6 co-receptor. In an embodiment of the invention the FZD binding domain is attached to the carboxy-terminus of the Fc domain and comprises two scfv, two V_HH fragments, two Fab fragments or a diabody that bind FZD, and the co-receptor binding domain attached to the amino terminus of the Fc domain comprises a diabody, two V_HH fragments or two scFvs that binds to the LRP5/6 co-receptor. When attached to the carboxy terminus of the Fc domain the FZD-binding Fabs are linked to the CH3 of the Fc domain via the Fab variable heavy region or variable light region. In other embodiments the FZD binding domain is attached to the amino terminus of the Fc domain and is comprised of two Fabs and the LRP5/6 co-receptor binding domain is attached to the carboxy terminus of the Fc domain and is comprised of a diabody or two scFvs that bind the co-receptor.

Figure 6 illustrates a tetravalent binding antibody molecule of this invention in the Diabody-Fc-scFv format having a LRP5/6 co-receptor binding domain, an Fc domain, and a FZD binding domain. The Diabody-Fc-sFv comprises (i) an Fc domain, (ii) a bispecific diabody attached to the N-terminal of the Fc domain that binds two different sites on the co-receptor, e.g., a Wnt1 (E1-E2) site on LRP5/6, and a Wnt3 site (E3-E4) on LRP5/6, and (iii) a FZD binding domain comprising two FZD-binding scFv fragments attached to the carboxy terminus of the Fc domain. The scFv may be specific for a particular FZD, e.g. FZD4, or may be pan-specific, binding to more than one FZD, e.g. to FZD4 and one or more other FZD.

An embodiment of this invention is a tetravalent binding antibody molecule in a Diabody-Fc-scFv format having (i) an Fc domain, (ii) a LRP5/6 co-receptor binding domain that comprises a bispecific diabody that binds two different sites on the co-receptor, e.g., a Wnt1 (E1-E2) site on LRP5/6, and a Wnt3 site (E3-E4) on LRP5/6, wherein the diabody is attached to the amino terminus of the Fc domain and (iii) a FZD binding domain, attached to the carboxy terminus of the Fc domain comprising two scFv fragments each binding FZD. The scFv may be specific for the FZD, or may be pan-specific, binding to the FZD and one or more other FZD.

Figure 6 also illustrates a tetravalent binding antibody molecule of this invention in the IgG-diabody format having (i) an Fc domain, (ii) a FZD binding domain that comprises of two Fab fragments attached to the N- terminus of the Fc domain, each Fab binding to an FZD,

and (iii) a LRP5/6 co-receptor binding domain attached to the C- terminus of the Fc domain that is composed of a diabody that binds two different sites on the co-receptor, e.g., a Wnt1 site (E1-E2) and a Wnt3 site (E3-E4) on LRP5/6. The Fabs may be specific for a particular FZD, e.g. FZD4, or may be pan-specific, binding to more than one FZD, e.g., to FZD4 and one or more other FZD.

An embodiment of this invention is a tetravalent binding antibody molecule in an IgG-Diabody format comprising (i) an Fc domain, (ii) an N-terminal binding domain for a FZD, comprising two FZD-binding Fabs and (ii) a C-terminal binding domain for a LRP5 and/or LRP6 co-receptor, comprising a LRP5/6 coreceptor-binding diabody. This FZD Agonist in the IgG-Diabody format comprises,

(1) a first and second heavy chain monomer, wherein each heavy chain monomer comprises a single-chain polypeptide comprising from N-terminus to C-terminus:

(a) a heavy chain variable domain (VH) that binds a FZD, linked to

(b) a heavy chain constant region domain 1 (CH1 domain), linked to

(c) an Fc region (or fragment thereof comprising a constant heavy chain domain 3 (CH3 domain)), linked to

(d) a peptide comprising a VH that binds a LRP5/6 co-receptor, linked to a light chain variable domain (VL) that binds a LRP5/6 co-receptor, and

(2) a first and second light chain monomer, each light chain monomer comprising from N terminus to C terminus a VL that binds the FZD, linked to a constant light chain domain 1 (CL1 domain).

The first and second heavy chain monomers dimerize via their Fc regions, or fragments thereof. The linker between the VH and VL that bind the LRP5/6 is of a length that promotes the pairing of the VH and VL of the first heavy chain monomer with the VL and VH of the second heavy chain monomer thereby forming a LRP5/6 co-receptor binding diabody. The FZD-binding Fabs are formed by the pairing of each heavy chain monomer with a light chain monomer such that the VH that binds FZD4 and CH1 of each of the heavy chain monomer, pairs with the VL that binds FZD4 and CL1 of the light chain monomers. In this IgG-Diabody format, the Fabs

form the FZD4-binding domain on the N-terminus of the Fc domain and the diabody forms the co-receptor-binding domain on the C-terminus of the Fc domain. The Fabs may be specific for one FZD, e.g., FZD4 or FZD5, or may be pan-specific, binding to more than one FZD, e.g., to FZD4 and/or FZD5, and in some cases more FZD. The Fc regions may dimerize via a knob-in-hole configuration. Methods for dimerizing peptides via a knob-in-hole configuration are described in WO2018/026942, inventors Van Dyk et al., Carter P. (2001) J. Immunol. Methods 248, 7–15; Ridgway et al. (1996) Protein Eng. 9, 617–621; Merchant, et al. (1998) Nat. Biotechnol. 16, 677–681, and; Atwell et al., (1997) J. Mol. Biol. 270, 26–35. The Fc regions may be Merrimack (knob chain: Q347M, Y349F, T350D, T366W and L368M; hole chain: S354I, E357L, T366S, L368A and Y407V), Merchant (knob chain: T366W; hole chain: T336S, L368A and Y407V) or Merchant S:S (Merchant mutations with additional S354C variant in the knob chain and Y349C in the hole chain). The Fc regions may also contain mutations that alter their effector function, e.g., the Fc region may have attenuated effector functions due to amino acid mutations, e.g., DANG variants and LALAPS variants.

Although in Figure 6 the peptides forming the diabody in the IgG-Diabody format are linked to the C-terminal of the Fc domain via their VH domain in a VH-VL orientation (N terminal to C terminal), in some embodiments, the peptides forming the diabody are linked to the C-terminal of the Fc domain via their VL domains in a VL-VH orientation (N-terminal to C-terminal). And, although the heavy chains are depicted as comprising a VH domain and a CH1 domain linked to the N-terminal of the Fc domain and the light chains are depicted as comprising a VL domain and CL1 domain to form the Fabs, in some embodiments (Diabody-Fc-Fab in Fig.6 and Fig. 7A) the diabodies are fused to the N-terminus of the Fc and the Fabs are fused to the C-terminus of the Fc. In order to do this, the CH3 domain of the Fc is fused directly to the heavy chain of the Fab via its VH domain (VH-CH1) or directly to the light chain via its VL domain (VL-CL) and where the light and heavy chains still associate to form the Fabs.

Figure 6 illustrates a tetravalent binding antibody molecule in a Diabody-Fc-Fab configuration having an LRP5/6-binding bispecific bivalent diabody forming the N-terminal binding domain, and two FZD-binding Fabs forming the C-terminal binding domain. The Fabs may be specific for a particular FZD, e.g. FZD4, or may be pan-specific, binding to

more than one FZD, e.g. FZD4 and one or more other FZD. See also Figure 7A, which illustrates a tetravalent binding antibody molecule in the Diabody-Fc-Fab format having an Fc in a knob-in-hole (KiH) configuration and an LRP5-binding bispecific bivalent diabody forming the N-terminal binding domain, and two FZD4-binding Fabs forming the C-terminal binding domain. Although Figures 6 and 7A illustrates the Fabs linked to the CH3 of the Fc domain (at the C-terminus) via the Fab variable heavy domain (VH), it is specifically contemplated that in an alternate diabody-Fc-Fab format the Fabs are linked to the CH3 of the Fc domain via the Fab variable light domain (VL). The various domains of the tetravalent molecules, VL, VH, CH1, CH2, CH3, CL1 and Fc, are joined via linkers, e.g., peptide linkers.

Also an embodiment of this invention is a tetravalent binding antibody molecule in the Diabody-Fc-Fab format comprising (i) an Fc domain, (ii) an N-terminal binding domain comprising a diabody that binds to the co-receptor, e.g., LRP5 and/or LRP6 co-receptor and (ii) a C-terminal binding domain comprising two Fab that bind to one or more FZD, e.g., FZD4 or FZD5. This FZD Agonist in the Diabody-Fc-Fab format comprises,

(1) a first and second heavy chain monomer, wherein each heavy chain monomer comprises a single-chain polypeptide comprising, from N-terminus to C-terminus:

(a) a peptide comprising a heavy chain variable (VH) domain that binds a LRP5/6 co-receptor and a light chain variable (VL) domain that binds a LRP5/6 co-receptor, linked to

(b) an Fc region (or fragment thereof comprising a constant heavy chain domain 3 (CH3 domain)), linked to

(c) a VH domain that binds a FZD, linked to

(d) a CH1 domain, and

(2) a first and second light chain monomer each light chain monomer comprising from N-terminus to C-terminus a VL domain that binds FZD, and a constant light chain domain 1 (CL1).

The first and second heavy chain monomers dimerize via the Fc regions or fragments thereof and a bivalent LRP5/6-binding diabody is formed by the pairing of the VH domain and VL

domain that bind LRP5/6 of the first heavy chain monomer with the VL domain and VH domain that bind LRP5/6 of the second heavy chain monomer. The two FZD-binding Fabs are formed by the pairing of each heavy chain monomer with a light chain monomer such that the VL that binds the FZD and the CL1 of a light chain monomer pairs with the VH that binds the FZD and the CH1 of each of the heavy chain monomers. In this Diabody-Fc-Fab format, the diabody forms the LRP5/6 co-receptor binding domain on the amino terminus of the tetravalent molecule and the two Fabs form the FZD binding domain on the C-terminus of the tetravalent binding antibody molecule. The Fc regions may dimerize via a knob-in-hole configuration.

Methods for dimerizing peptides via a knob-in-hole configuration are described in WO2018/026942, inventors Van Dyk et al., Carter P. (2001) J. Immunol. Methods 248, 7–15; Ridgway et al. (1996) Protein Eng. 9, 617–621; Merchant, et al. (1998) Nat. Biotechnol. 16, 677–681, and; Atwell et al., (1997) J. Mol. Biol. 270, 26–35. The Fc regions may be Merrimack (knob chain: Q347M, Y349F, T350D, T366W and L368M; hole chain: S354I, E357L, T366S, L368A and Y407V), Merchant (knob chain: T366W; hole chain: T336S, L368A and Y407V) or Merchant S:S (Merchant mutations with additional S354C variant in the knob chain and Y349C in the hole chain). The Fc regions may also contain mutations that alter their effector function, e.g., the Fc region may have attenuated effector functions due to amino acid mutations, e.g., DANG variants and LALAPS variants.

Although in Figures 6 and 7A the peptides forming the diabody in the Diabody-Fc-Fab format are linked to the Fc domain via their VL domains, thus in a VH -VL orientation (from N-terminal to C-terminal), in some embodiments the orientation can be switched such that the peptides forming the diabody are linked to the N-terminal of the Fc domain via their VH domains, thus in a VL-VH orientation (from N-terminal to C-terminal). Also, although the heavy chains in the Diabody-Fc-Fab format are depicted as comprising a VH domain and a CH1 domain, which pair with the light chain comprising a VL and CL1 domain to form the Fabs, it is also contemplated that in some embodiments the variable and constant domains are switched such that the heavy chains comprise a VL domain and a CL1 domain and the light chains comprises the VH domain and CH1 domain and the heavy and light chains still pair to form the Fabs.

In an embodiment of this invention the binding moiety of the FZD binding domain is derived from an antibody, or an antibody fragment, that binds specifically to one FZD, e.g. FZD4 or

FZD5, or is pan-specific interacting with a specific FZD, e.g. FZD4 or FZD5, and one or more additional FZD receptors (an FZD source antibody), and the co-receptor binding domain comprises a binding moiety that is derived from an antibody or antibody fragment that binds to a LPR5 and/or LRP6 (a LRP5/6 coreceptor source antibody). In an embodiment of the invention the FZD-binding antibodies bind to an extracellular cysteine rich domain (CRD) of the FZD receptor. The antibody that binds FZD may be an antibody that binds the FZD receptor and antagonizes Wnt signaling or inhibits binding of a Wnt ligand to the FZD receptor. The antibody that binds FZD may be an antibody that binds the FZD receptor without antagonizing or inhibiting binding of a Wnt ligand to the FZD receptor. The antibody that binds FZD may be an antibody that binds FZD and enhances Wnt signaling. The antibody that binds the LRP5/6 co-receptor may be an antibody that binds the LRP5/6 co-receptor and antagonizes Wnt signaling or inhibits binding of a Wnt ligand to the co-receptor, or the antibody that binds the LRP5/6 co-receptor may be an antibody that binds the co-receptor without antagonizing Wnt or Norrin signaling or inhibiting binding of a Wnt or Norrin ligand to the co-receptor.

In an embodiment of this invention the LRP5/6 co-receptor binding domain binds to a single epitope on a co-receptor, e.g., an epitope that binds to the Wnt1 (E1-E2) or Wnt3 (E3-E4) interacting domain of LRP5/6. In an embodiment of this invention the LRP5/6 co-receptor binding domain binds to two epitopes within the co-receptor, e.g., a paratope that binds to the Wnt1 (E1-E2) interacting epitope and a paratope that binds to Wnt3 (E3-E4) epitope of LRP5/6. In an embodiment of this invention the multivalent binding molecule comprises a Fc domain, wherein the Fc domain is the Fc domain of an immunoglobulin or a fragment thereof comprising the CH3 domain. In an embodiment of the invention the immunoglobulin is an IgG. In an embodiment of this invention the IgG is an IgG_1.

In an embodiment of this invention the LRP5/6 binding domain comprises a diabody comprising two peptides each comprising a heavy chain variable domain (VH) that binds to LRP5/6 linked to a light-chain variable domain (VL) that binds LRP5/6 wherein the binding domain is formed by pairing of the VH and the VL from one peptide to the VL and VH of the other peptide thereby forming the LRP5/6 binding domain.

In the tetravalent binding antibody molecules of this invention both of the binding domains are bivalent and one or both of the bivalent binding domains may be bispecific for the respective FZD receptor, e.g., FZD4 or FZD5, or LRP5/6 co-receptor. For example, the

binding molecule may comprise an FZD binding domain that is bivalent and monospecific (each binding site binding to the same epitope) and the LRP 5/6 binding domain is bivalent and bispecific, binding to two different epitopes (the Wnt1 (E1-E2) and Wnt3 (E3-E4) sites on the LRP5/6 ectodomain). In an embodiment of this invention both binding domains are bivalent and bispecific, each binding domain binding to two different epitopes on their respective target FZD receptor or LRP 5/6 co-receptor.

The VH and VL domains of the FZD binding domain of the tetravalent molecules of this invention may comprise the three light chain CDRs and three heavy chain CDRs of a FZD source antibody, e.g. the FZD4 or FZD5, binding antibodies of Table 1, Table 2 or Table 6, or three light chain CDRs and three heavy chain CDRs that are at least 50%, at least 55%, at least 60%, at least 75, at least. 80%, at least 85%, at least 90%, at least at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to the CDRs of the FZD source antibody, e.g., the FZD4 antibodies of Table 1, Table 2 or Table 6, and still retain binding to the FZD or FZD5 receptor bound by the source antibody.

The VH and VL domains of the LRP5/6 co-receptor binding domain of the tetravalent molecules of this invention may comprise the three light chain CDRs and three heavy chain CDRs of an LRP5/6 co-receptor source antibody, e.g., the LRP5/6 binding antibodies of Table 3, Table 4 or Table 6, or three light chain CDRs and three heavy chain CDRs that are at least 50%, at least 55%, at least 60%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to the VH and VL of the Wnt co-receptor source antibody, e.g., the LRP5/6 binding antibodies of Table 3, Table 4 or Table 6, and still bind to the LRP5/6 co-receptor.

In an embodiment of this invention the FZD binding domain of the tetravalent binding molecule of this invention binds FZD4 (an FZD4 Agonist) or FZD5 (FZD5 Agonist) or FZD4 and/or FZD5 and one or more other FZDs (a pan-FZD Agonist) and comprises

the CDR-H1, CDR-H2 and CDR-H3 and the CDR-L1, CDR-L2 and CDR-L3 of the antibodies of Table 1, Table 2 or Table 6, or CDRs that are at least 50%, at least 55%, at least 60%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to the CDR-H1, CDR-H2 and CDR-H3 and CDR-L1, CDR-L2 and CDR-L3 of the antibodies of Table 1, Table 2 or Table 6, and still bind to FZD4 or FZD5,

and the LRP5/6 binding domain of the FZD4 Agonist or FZD5 Agonist or pan-FZD Agonist comprises

the CDR-H1, CDR-H2 and CDR-H3 and CDR-L1, CDR-L2 and CDR-L3 of the antibodies of Table 3, Table 4 or Table 6 or the CDRs are at least 50%, at least 55%, at least 60%, at least 75%. at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to the CDR-H1, CDR-H2 and CDR-H3 and CDR-L1, CDR-L2 and CDR-L3 of the antibodies in Table 3, Table 4 or Table 6, and still bind to LRP5 or LRP6.

In an embodiment, the tetravalent binding antibody molecule's FZD binding domain does not comprise a diabody, scFv, or Fab comprising the three heavy chain CDRs or three light chain CDRs of the FZD4-binding antibody 5044 in combination with a Wnt co-receptor binding domain comprising a diabody, scFv, or Fab comprising the three heavy chain CDRs and three light chain CDRs of LRP6-binding antibody 2542 and/or antibody 2539. In an embodiment, the tetravalent binding molecule does not comprise a diabody, scFv, or Fab, comprising the three heavy chain CDRs and three light chain CDRs of the FZD4-binding antibody 5027 in combination with a Wnt co-receptor binding domain comprising a diabody, scFv, or Fab comprising the three heavy chain CDRs and three light chain CDRs of LRP6-binding antibody 2542 and/or antibody 2539.

Also, an embodiment of this invention are the nucleic acid molecules encoding the tetravalent binding molecules described herein. An embodiment of this invention are the nucleic acid molecules encoding the polypeptides of the tetravalent binding molecules described herein comprising the heavy chain and light chain CDRs set forth in Tables 1, 2, 3, 4, 6. Also an embodiment of this invention are the nucleic acid molecules that encode the polypeptides of the tetravalent binding molecules, e.g., FZD5 Agonists or FZD4 Agonists, of Figure 7A and 7B that comprise the CDRs of Table 6. Also, an embodiment of this invention are the nucleic acid molecules that encode VH and VL domains comprising respectively the heavy chain and light chain CDRs set forth in Tables 1, 2, 3, 4, and 6. The nucleic acid molecules can be inserted into a vector and expressed in an appropriate host cell and then the tetravalent binding antibody molecules may be isolated from the cells using methods well known in the art. As such, also an aspect of this invention are expression cassettes and vectors comprising the nucleic acid molecules that encode the polypeptides of the tetravalent binding molecules, e.g., FZD4 or FZD5 Agonists, described herein, the VL and VH domains, the Fabs and the

diabodies comprising the CDRs of set forth in Tables 1, 2, 3, 4, and 6, and the Fc domains described herein. An aspect of this invention are the host cells expressing these expression cassettes and vectors.

As used in this invention, the term "vector" refers to a nucleic acid delivery vehicle or plasmid that can be engineered to contain a nucleic acid molecule, e.g., a nucleic acid sequence encoding the tetravalent binding antibody molecules described herein. The vector that can express protein when inserted with a polynucleotide is called an expression vector. Vectors can be inserted into the host cell by transformation, transduction, or transfection, so that the carried genetic substances can be expressed in the host cell. Vectors are well known to the technical personnel in the field, including but not limited to: plasmid; phagemid; cosmid; artificial chromosome such as yeast artificial chromosome (YAC), bacterial artificial chromosome (BAC), or P1 derived artificial chromosome (PAC); phage such as λphage or M13 phage and animal viruses etc. Animal viruses may include but not limited to, reverse transcriptase virus (including lentivirus), adenovirus, adeno-associated virus, herpes virus (e. g. herpes simplex virus), chicken pox virus, baculovirus, papilloma virus, and papova virus (such as SV40). A vector can contain multiple components that control expression of the tetravalent binding antibody molecules described herein, including but not limited to, promoters, e.g., viral or eukaryotic promoters, e.g., a CMV promoter, signal peptides, e.g., TRYP2 signal peptide, transcription initiation factor, enhancer, selection element, and reporter gene. In addition, the vector may also contain replication initiation site(s).

As used in this invention, the term "host cell" refers to cells that can import expression cassettes and vectors, including but not limited to, prokaryotic cells such as Escherichia coli and Bacillus subtilis, fungal cells such as yeast and Aspergillus, insect cells such as S2 drosophila cells and Sf9, or animal cells, including human cells, e.g., fibroblast cells, CHO cells, COS cells, NSO cells, HeLa cells, BHK cells, or HEK293 cells.

An embodiment of this invention is a pharmaceutical composition comprising a FZD Agonist or a nucleic acid molecule, expression cassette and vector encoding a FZD Agonist described herein and a pharmaceutically acceptable carrier, diluent or excipient. The pharmaceutical composition may further comprise an additional agent, e.g., a second therapeutic antibody e.g. an anti-VEGF antibody (aflibercept, ranibizumab and bevacizumab), a growth factor, e.g., VEGF, or an agent that activates a Wnt pathway, e.g., the small molecule CHIR99021, a Norrin or R-Spondin, or a nucleic acid molecule, expression cassettes and vectors that encode

the agent. The pharmaceutical composition may consist of or consist essentially of a FZD Agonist, or a nucleic acid molecule, an expression cassette or vector encoding an FZD Agonist described herein, and a pharmaceutically acceptable diluent, carrier or excipient. Suitable carriers, diluents and excipients, and their formulations are described in Remington: The Science and Practice of Pharmacy (19th ed.) ed. A. R. Gennaro, Mack Publishing Company, Easton, Pa. 1995. Typically, an appropriate amount of a pharmaceutically-acceptable salt is used in the formulation to render the formulation isotonic. Examples of the pharmaceutically-acceptable carrier include, but are not limited to, saline, Ringer's solution and dextrose solution. The pH of the solution may be e.g., from about 5 to about 8, from about 5 to 7.5 or from about 6 to 7. Further carriers include sustained release preparations such as semipermeable matrices of solid hydrophobic polymers containing the agonist, which matrices are in the form of shaped articles, e.g., films, liposomes or microparticles. It will be apparent to those persons skilled in the art that certain carriers may be more preferable depending upon, for instance, the route of administration and concentration of the FZD Agonists being administered.

This invention also includes methods for using the FZD Agonists, described herein. An embodiment of this invention is a method for activating a Wnt signaling pathway in a cell, comprising contacting a cell having an FZD receptor and a LRP5/6 co-receptor, with a tetravalent binding antibody molecule of this invention that binds the FZD, e.g., FZD4, and the LRP5/6 in an amount effective to activate Wnt signaling. It has been reported that the Norrin-FZD4 pathway plays a role in retinal angiogenesis (see Wang et al. Cell. 2012;151(6):1332–1344.; Braunger BM, Tamm ER. Adv Exp Med Biol. 2012; 723:679–683; Ohlmann A, Tamm ER. Prog Retin Eye Res. 2012;31(3):243–257 and; Ye et al. Trends Mol Med. 2010;16(9):417–425). Signaling through Norrin-FZD4 pathway is necessary for development and maintenance of retinal vasculature. Mutations affecting genes of this pathway may result in several vitreoretinopathies, such as Norrie Disease, Familial Exudative Vitreoretinopathy (FEVR), and Pseudoglioma and Osteoporosis Syndrome. Additionally, Retinopathy of Prematurity (ROP) has been associated with mutations in this Norrin-FZD4 pathway, and Wnt-pathway mutations have been reported in Coats Disease and Persistent Fetal Vasculature (PFV). FZD4 signaling activated by Norrin and/or WNT7A/B pathway is also associated with CNS blood brain barrier development and homeostasis. Genetic ablation of the Norrin, *FZD4*, *LRP5*, *LRP6* and the co-receptor Tetraspanin-12 (Tspan-12) result in defective angiogenesis and barrier disruption in the retinal and/or cerebellar vessels (Cho et

al. (2017) Neuron 95, 1056-1073; Zhou et al., (2014) J Clin Invest 124:3825–3846). Thus, a functional Wnt signaling system plays a key fundamental role in the development of a sufficient vascular and neural network in the eye and retina to support vision and in the CNS to support BBB development and homeostasis.

An aspect of this invention is a method for promoting and/or maintaining retinal vasculature by treating eye tissue, e.g., retinal tissue, with an effective amount of a pharmaceutical compositions comprising the tetravalent antibody molecules of this invention, e.g., tetravalent antibody molecules that binds FZD4 and LRP5/6, a FZD4 Agonists, having the structures illustrated in Figure 6 through local or systemic administration. Also, an aspect of this invention is a method for promoting and/or maintaining BBB vasculature by treating a subject in need thereof with an effective amount of a pharmaceutical compositions of this invention, e.g., a composition comprising a FZD4 Agonists having the structures depicted in Figure 6. The BBB is initiated during development and its integrity remains vital for homeostasis and neural protection throughout life. A subject in need thereof includes a subject having a neurological condition associated with BBB dysfunction, e.g., neurodegenerative diseases such as Alzheimer's disease, as well epilepsy, multiple sclerosis, and stroke.

A further aspect of this invention is a method for treating a subject having a disorder characterized by vascular leakage, particularly retinal vascular leakage, and/or endothelial cell leakage, and disorders characterized by reduced retinal or brain endothelial cell barrier functions or a compromised BBB or BRB, e.g., diabetic retinopathy, retinipathy of prematurity, Coat's disease, FEVR, Norrie disease, macular degeneration, diabetic macular edema, and pediatric vitreoretinopathies, by administering to such subject an effective amount of a pharmaceutical compositions of this invention, e.g., a composition comprising a FZD4 Agonist having the structures depicted in Figure 6. An effective amount of such composition is an amount sufficient, e.g., to increase or restore endothelial cell barrier functions and thereby reducing vascular leakage in such subject. The subject may be a fetus. The FZD4 Agonists of this invention particularly the FZD4 Agonist in the diabody-Fc-Fab format comprising two Fab fragments forming the FZD4 binding domain on the carboxy terminal of the Fc receptor and a binding domain for LRP5 and/or LRP6 composed of a diabody on the amino terminal of the Fc domain, e.g., as illustrated in Figure 6, activates FZD4 and β-catenin signaling in endothelial cells, promotes barrier functions and thereby

reduces endothelial cell permeability and significantly enhance angiogenesis. In particular, treatment of endothelial cells, in vivo, ex vivo or in vitro, with these FZD4 Agonists, preferably those with the diabody-Fc-Fab format, enhance the development and maintenance of retinal vasculature and/or the BRB and the BBB far more effectively than other molecules that do not have this structure.

A further aspect of the invention is a method for treating a subject having inflammation of all or part of the intestines, also known as inflammatory bowel disease, by administering to such subject an effective amount of a pharmaceutical composition of this invention, e.g., a composition comprising a FZD5 Agonist. Examples of inflammatory bowel disease include, but are not limited to, Crohn's disease, and ulcerative colitis. An effective amount of such composition is an amount sufficient to reduce, ameliorate, eliminate, or treat the inflammation. A subject in need thereof includes a subject having inflammation of the mucosal of the gastrointestinal tract. The methods disclosed herein may be practiced to reduce inflammation (e.g., inflammation associated with IBD or in a tissue affected by IBD, such as gastrointenstinal tract tissue, e.g., small intestine, large intestine, or colon), activate WNT signaling, or reduce any of the histological symptoms of IBD (e.g., those disclosed herein).

The FZD Agonists of the present invention may be administered systemically or locally, e.g., by injection (e.g. subcutaneous, intravenous, intraperitoneal, intrathecal, intraocular, intravitreal, etc.), implantation, topically, or orally. Depending on the route of administration, the FZD Agonists may be coated in a material to protect the agonists from conditions that may inactivate the agonists. The tetravalent binding antibody molecules described herein may be dissolved or suspended in a pharmaceutically acceptable, preferably aqueous carrier. In addition, the composition comprising the FZD Agonists can contain excipients, such as buffers, binding agents, blasting agents, diluents, flavors, lubricants, etc. An extensive listing of excipients that can be used in such a composition, can be, for example, taken from A. Kibbe, Handbook of Pharmaceutical Excipients (Kibbe, 2000). The tetravalent binding antibody molecules can also be administered together with immune stimulating substances, such as cytokines.

An embodiment of this invention includes a method for deriving cerebral organoids with a vascular network exhibiting barrier functions by using the tetravalent antibody molecules described herein. The tetravalent binding antibody molecules described herein that activate

FZD4 signaling are envisioned to promote barrier function within endothelial cells cultured with cerebral organoids and thereby promoting angiogenesis.

An embodiment of this invention includes a method for directed differentiation of multipotent or pluripotent stem cells (PSC) or induced pluripotent stem (iPS) cells comprising culturing the cells under conditions suitable for directed differentiation wherein said culturing conditions further comprise an effective amount of a tetravalent binding antibody molecule described herein. Studies in mouse and human PSCs have identified specific approaches to the addition of growth factors, including Wnt, which can induce PSC differentiation into different lineages. Methods for directed differentiation of PSCs comprising the activation of Wnt signaling are known in the art see e.g. Lam et al. (2014) Semin Nephol 34(4); 445-461; Yucer et al. (September 6, 2017) Scientific Reports 7, Article number 10741. It is contemplated that the FZD Agonists, e.g. FZD4 Agonists, described herein can be used in an amount sufficient to effect activation of Wnt signaling pathways to direct differentiation of the PSCs to certain mesodermal lineages such as cardiomyocytes (cite Yoon et al. FZD4 Marks Lateral Plate Mesoderm and Signals with NORRIN to Increase Cardiomyocyte Induction from Pluripotent Stem Cell-Derived Cardiac Progenitors. Stem Cell Reports. 2018 Jan;10(1):87-100. DOI: 10.1016/j.stemcr.2017.11.008.PMID: 29249665).

An embodiment of this invention is a method for enhancing tissue regeneration in a subject in need thereof by activating Wnt signaling in such subject by administering to the subject in need thereof an effective amount of a FZD Agonists described herein.

An embodiment of this invention includes a method for promoting endothelial cell barrier functions in eye tissue, e.g., retinal tissue, in a subject in need thereof, by administering an effective amount of a tetravalent binding molecule of this invention that binds FZD4 and LPR5/6, an FZD4 Agonist. In a particular embodiment the FZD4 Agonist of this invention that binds to FZD4 and a binding domain that binds to LRP5 or/and LRP6 has a diabody-Fc-Fab structure depicted in Figure 6 and 7. In an embodiment of this invention the FZD4 Agonists for enhancing retinal angiogenesis comprise the light chain CDRs, i.e., CDR-L1, CDR-L2, and CDR-L3 and heavy chain CDRs, i.e., CDR-H1, CDR-H2 and CDR-H3 of the

FZD4-binding antibodies set forth in Tables 1, 2, and 6 and the LRP5/6-binding antibodies set forth in Tables 3, 4, and 6.

A subject as used herein may be any animal (e.g., a mammal), including, but not limited to, humans, non-human primates, horses, cows, dogs, cats, rodents, and the like. The subject may be a fetus. Typically, the subject is human.

Effective dosages and schedules for administering the FZD Agonists and nucleic acids that encode them described herein may be determined empirically, and making such determinations is within the skill in the art. Those skilled in the art will understand that the dosage of such FZD Agonists that must be administered will vary depending on, for example, the subject who will receive the antibody, the route of administration, the particular type of FZD Agonists used and other drugs being administered. Guidance in selecting appropriate doses for FZD Agonists is found in the literature on therapeutic uses of antibodies, e.g., Handbook of Monoclonal Antibodies, Ferrone, eds., Noges Publications, Park Ridge, N.J., (1985) ch. 22 and pp. 303-357; Smith, Antibodies in Human Diagnosis and Therapy, Haber, eds., Raven Press, New York (1977) pp. 365-389. The dosage ranges for the administration of the compositions are those large enough to produce the desired effect, e.g., promote endothelial cell barrier functions, vascular homeostasis, or enhance Wnt signaling. The dosage should not be so large as to cause adverse side effects, such as unwanted cross-reactions, anaphylactic reactions, and the like. Generally, the dosage will vary with the age, condition, gender and the extent of the disease or disorder, in the patient and can be determined by one of skill in the art. The dosage can be adjusted by the individual physician in the event of any contraindications. Dosage can vary, and can be administered in one or more dose administrations daily, for one or several days. While individual needs vary, determination of optimal ranges of effective amounts of the vector is within the skill of the art.

Also, an aspect of this invention is a method for making the tetravalent binding antibody molecules described herein. The amino acid sequences of FZD receptors, e.g. FZD4, and the Wnt co-receptors LRP5/6, and nucleotide sequences encoding FZD receptors and the Wnt co-receptors LRP5/6, as well as antibodies and libraries of antibodies that bind FZD, e.g., FZD4, or the Wnt co-receptors LRP5/6, are readily available or can be generated using methods well known in the art (see e.g., U.S. publication no. 2015/0232554, inventors Gurney et al. and US publication no. 2016/0194394, inventors Sidhu et al. and US 20190040144, inventors Pan et

al.; U.S. publication no. 2017/0166636, inventors Wu et al.; U.S. publication no. 2016/0208018, inventors Chen et al.; U.S. publication no. 2016/0053022, inventors Macheda et al.; U.S. publication no. 2015/031293, inventors Damelin et al.). And a variety of methods are known in the art for generating and screening such phage display libraries for antibodies, and antibody fragments, scFv, Fab, VL, and VH possessing the desired binding characteristics. Such methods are reviewed, e.g., in Hoogenboom et al. in Methods in Molecular Biology 178:1-37 (O'Brien et al., ed., Human Press, Totowa, N.J., 2001) and further described, e.g., in the McCafferty et al., Nature 348:552-554; Clackson et al., Nature 352: 624-628 (1991); Marks et al., J. Mol. Biol. 222: 581-597 (1992); Marks and Bradbury, in Methods in Molecular Biology 248:161-175 (Lo, ed., Human Press, Totowa, N.J., 2003); Sidhu et al., J. Mol. Biol. 338(2): 299-310 (2004); Lee et al., J. Mol. Biol. 340(5): 1073-1093 (2004); Fellouse, Proc. Natl. Acad. Sci. USA 101(34): 12467-12472 (2004); and Lee et al., J. Immunol. Methods 284(1-2): 119-132(2004), all incorporated herein by reference. In certain phage display methods, repertoires of VH and VL genes are separately cloned by polymerase chain reaction (PCR) and recombined randomly in phage libraries, which can then be screened for antigen-binding phage as described in Winter et al., Ann. Rev. Immunol., 12: 433-455 (1994). Phage typically display antibody fragments, either as single-chain Fv (scFv) fragments or as Fab fragments. Libraries from immunized sources provide high-affinity antibodies to the immunogen without the requirement of constructing hybridomas. Alternatively, the naive repertoire can be cloned (e.g., from human) to provide a single source of antibodies to a wide range of non-self and also self antigens without any immunization as described by Griffiths et al., EMBO J, 12: 725-734 (1993). Finally, naive libraries can also be made synthetically by cloning unrearranged V-gene segments from stem cells, and using PCR primers containing random sequence to encode the highly variable CDR3 regions and to accomplish rearrangement in vitro, as described by Hoogenboom and Winter, J. Mol. Biol., 227: 381-388 (1992). Patent publications describing human antibody phage libraries include, for example: U.S. Pat. No. 5,750,373, and US Patent Publication Nos. 2005/0079574, 2005/0119455, 2005/0266000, 2007/0117126, 2007/0160598, 2007/0237764, 2007/0292936, and 2009/0002360, all incorporated herein by reference. Antibodies or antibody fragments

isolated from human antibody libraries are considered human antibodies or human antibody fragments herein.

In an embodiment of this invention a tetravalent binding antibody molecule in a diabody-Fc-scFv format comprising a LRP5/6 coreceptor binding domain comprising LRP5/6 -binding diabody and an FZD-binding domain comprising two FZD-binding scFvs is generated by,

(a) selecting an Fc domain having a C-terminus and an N-terminus

(b) identifying an antibody that binds to an FZD receptor (the "FZD source antibody"), and

(c) identifying an antibody that binds LRP 5/6 co-receptor ("coreceptor source antibody" or "LRP 5/6 source antibody"),

(d) generating a nucleic acid molecule comprising a nucleotide sequence that encodes a polypeptide monomer comprising

(i) a peptide comprising a VL domain linked to a VH domain, the domains comprising the heavy chain and/or light chain CDRs of the antibody of step b that bind the FZD receptor, or comprising heavy chain and/or light chain CDRs derived from the antibody of step b that still bind the FZD, linked to

(ii) an Fc domain of step a, linked to

(iii) a peptide comprising VL domain linked to a VH domain comprising the light chain and/or heavy chain CDRs of the antibody of step c, or comprising CDRs derived from the antibody of step c and that still bind LRP 5/6 co-receptor,

(e) expressing the nucleic acid molecule of step d to produce the polypeptide monomer and then dimerizing the polypeptide,

wherein the VH and VL that bind the FZD of each monomer form a scFv that binds FZD, and the VH and VL domains that bind the LRP 5/6 coreceptor of one monomer bind the VL and VH that binds the Wnt coreceptor of another monomer forming a LRP5/6 co-receptor-binding diabody, and

wherein the polypeptide monomer dimerizes via the Fc regions to form a tetravalent binding antibody molecule comprising an Fc domain, a FZD-binding domain comprised of two FZD-binding scFvs, and a LRP5/6 coreceptor binding domain comprised of the diabody,

wherein the FZD binding domain and the LRP5/6 co-receptor binding domain are on opposite termini of Fc domain. It is contemplated that the peptides comprising the VL and VH domains that bind the FZD or the LRP may be linked to either the N or C terminus of the Fc domain via the VL domain or the VH domain provided the FZD binding domain and LRP binding domain are on opposite termini of the Fc domain. The FZD may be one or more of FZD1, FZD2, FZD3, FZD4, FZD5, FZD6, FZD7, FZD8, FZD9, and FZD10.

In an embodiment of this invention, the tetravalent binding antibody molecule has two FZD-binding Fabs, e.g., FZD4-binding Fabs, linked to one terminus of the Fc domain and two LRP5/6-binding scFvs or a LRP5/6-binding diabody linked to the other terminus of the Fc domain and is generated by,

(a) identifying the light chain complementary determining regions (CDR-L1, CDR-L2, and CDR-L3) and/or heavy chains complementary determining regions (CDR-H1, CDR-H2, and CDR-H3) of an antibody that binds to the FZD, e.g., FZD4 or FZD5, (the "FZD source antibody") and

(b) identifying the CDR-L1, CDR-L2, and CDR-L3 and/or the CDR-H1, CDR-H2, and CDR-H3 of one or more antibodies that binds to LRP5 or LRP6, (the "LRP5/6 source antibody"),

(c) generating a nucleic acid molecule encoding a "heavy chain" polypeptide comprising

(i) a peptide comprising an immunoglobulin constant heavy chain region 1 (CH1 domain) linked to a VH domain comprising the CDR-H1, H2 and H3 of the antibody of step a), or a CDR-H1, CDR-H2 and CDR-H3 derived from the antibody of step a) that still binds the FZD4, linked to

(ii) an Fc region, linked to

(iii) a peptide comprising a VL domain comprising the CDR-L1, CDR-L2 and CDR-L3 of an antibody of step b) linked to a VH domain comprising

the CDR-H1, CDR-H2 and CDR-H3 of an antibody of step b), or CDR-H1, CDR-H2 and CDR-H3 derived from the antibody of step b) that binds to LRP5 or LRP6,

(d) generating a nucleic acid molecule comprising a nucleic acid sequence that encodes a "light chain" polypeptide comprising an immunoglobulin constant light region 1 (CL1) linked to a VL domain wherein the VL domain comprises the FZD light chain CDR-L1, CDR-L2 and CDR-L3 of the antibody in step a),

(e) expressing the nucleic acid molecules of (c) and (d) to produce the heavy chain polypeptide and the light chain polypeptide,

wherein two heavy chain polypeptides dimerize via their Fc regions and the VH that binds the FZD and CH1 domains of the heavy chain polypeptide pair with the VL that binds the FZD and CL1 domains of the light chain polypeptide forming two FZD Fabs and

wherein the VH and VL that binds LRP5/6 in each heavy chain polypeptide pair to form an scFv that binds LRP5/6, or the VH and VL that bind LRP5/6 of one heavy chain polypeptide in the dimer pair with the VL and VH that bind the LRP5/6 of the other heavy chain polypeptide in the dimer to form a diabody, thereby forming the tetravalent binding antibody molecule comprising an Fc domain, two FZD Fabs linked to either the N or C terminus of the Fc domain and two LRP5/6-binding scFvs or a LRP5/6-binding diabody linked to the other terminus of the Fc domain.

The FZD source antibody may be an antibody that binds specifically to one FZD, e.g., FZD4, or is a pan-specific antibody binding FZD, e.g., FZD4 or FZD5, and one or more other FZD receptors and antagonizes Wnt signaling or inhibits Wnt binding to the receptor. Alternatively, the FZD source antibody may be an antibody that binds specifically to one FZD, e.g., FZD4 or FZD5, or is a pan-specific antibody binding one FZD, e.g., FZD4 or FZD5, and one or more other FZD receptors without antagonizing Wnt signaling or inhibiting Wnt binding to the receptor. The LRP source antibody may be an antibody that binds specifically to LRP5/6, or is panspecific binding to LRP5/6 and to one or more of the Wnt co-receptors, and antagonizes Wnt signaling or inhibits Wnt binding to the co-receptor. Alternatively, the LRP5/6 source antibody may be an antibody that binds to the LRP 5/6 co-

receptor, or is panspecific binding to LRP5/6 and to one or more of the Wnt co-receptors, without antagonizing Wnt signaling or inhibiting Wnt binding to the LRP5/6 co-receptor.

The FZD source antibody may be an antibody fragment that binds the FZD receptor, e.g., an Fab, a VL or VH. The light chain and heavy chain CDRs, the VH and/or VL in the FZD binding domain of the FZD Agonists may be identical to the CDRs, the VH and/or VL of the FZD source antibody or may be at least 50%, at least 55%, at least 60%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to the CDRs, VH or VL of the source antibody and still retain binding to the FZD receptor. The CDRs, the VH and/or VL in the FZD binding domain of the FZD Agonists may be identical to the CDRs, the VH and/or VL of a FZD4-binding or FZD5-binding antibody of Table 1, Table 2 or Table 6, or may be at least 50%, at least 55%, at least 60%, 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to the CDRs, VH or VL of a FZD4-binding or FZD5-binding antibody of Table 1 or Table 2 or Table 6 and still retain binding to the FZD receptor.

Likewise, the Wnt co-receptor source antibody may be an antibody fragment, e.g. an Fab, a VL or a VH, that binds the LRP co-receptor, e.g., LRP5/6. The light chain CDRs and heavy chain CDRs, the VH and/or VL in the Wnt co-receptor binding domain of the FZD4 Agonists may be identical to the CDRs, the VH and/or VL of the Wnt co-receptor source antibody or may be at least at least 50%, at least 55%, at least 60%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to the CDRs, VHs or VLs of the source antibody and still retain binding to the LRP co-receptor. The light chain CDRs and heavy chain CDRs, the VH and/or VL in the LRP5/6 binding domain of the FZD Agonists may be identical to the light chain CDRs and heavy chain CDRs, the VH and/or VL of a LRP-binding antibody of Table 3, Table 4 or Table 6 or may be at least at least 50%, at least 55%, at least 60%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to the light chain CDRs and heavy chain CDRs, VH or VL of a LRP-binding antibody of Table 3, Table 4 or Table 6 and still retain binding to the LRP co- receptor.

In an embodiment of this invention, two polypeptides of the tetravalent binding antibody molecule dimerize via knob-in-hole configuration of their Fc sequences. The tetravalent binding antibody molecules of this invention may be generated by dimerizing two

polypeptides in a "knob-in-hole" configuration. The knob-in-hole configuration increases the modularity of this invention by facilitating the association of peptides that comprise binding moieties that bind different epitopes on a FZD receptor or LRP5/6 co-receptor or to epitopes on different members of the FZD receptor or co-receptor family, see e.g., Figure 6. Methods for engineering Fc molecules via the knobs into holes design are well known in the art, see e.g., WO2018/026942, inventors Van Dyk et al., Carter P. (2001) J. Immunol. Methods 248, 7–15; Ridgway et al. (1996) Protein Eng. 9, 617–621; Merchant, et al. (1998) Nat. Biotechnol. 16, 677–681, and; Atwell et al., (1997) J. Mol. Biol. 270, 26–35.

Without wishing to be bound by theory, it is contemplated that the tetravalent binding antibody molecules of this invention facilitate the interaction of a FZD receptor and an LRP5/6 co-receptor on a cell by promoting their proximity and stabilizing conformations of the receptor proteins that are favorable for activating Wnt signaling pathways. Another embodiment of this invention is a method for facilitating the interaction of a FZD receptor and an LRP5/6 co-receptor on a cell thereby activating a Wnt signaling pathway in the cell comprising, a) selecting an Fc domain, or fragment thereof comprising a CH3 domain, having a C-terminus and an N-terminus b) linking a first bivalent binding domain, which binds the FZD receptor, on one terminus of the Fc domain and linking a second bivalent binding domain, which binds to the Wnt co-receptor, on the other terminus of the Fc domain thereby forming a tetravalent binding antibody molecule; c) contacting said tetravalent binding antibody molecule with the cell expressing said FZD receptor and Wnt co-receptor under conditions wherein the FZD receptor and co-receptor both bind to the tetravalent binding antibody molecule thereby activating the Wnt signaling pathway. The Wnt co-receptor binding domain and FZD binding domain are bivalent and each comprise a VL and/or a VH, or V_HH domain and one or both of the binding domains may be monospecific. In an embodiment of the invention one or both the Wnt co-receptor binding domain and FZD binding domain are bispecific. In an embodiment of the invention the Wnt co-receptor binding domain is bivalent and bispecific. The FZD binding domain may comprise a scFV that binds FZD, a V_HH that binds FZD, or an Fab that binds FZD, or combinations thereof, or a diabody that binds FZD. The Wnt co-receptor binding domain may comprise a scFV that binds the LRP5/6 co-receptor, a V_HH that binds LRP5/6, an Fab that binds the LRP5/6 co-receptor, or combinations thereof, or a diabody that binds the LRP5/6 co-receptor. In an embodiment of the invention the FZD binding domain comprises two FZD-binding Fabs and

the Wnt co-receptor binding domain comprises a bispecific bivalent diabody that binds LRP5/6 on two different epitopes.

The tetravalent binding antibody molecules of this invention initiate the Wnt signaling pathway(s) that are stimulated by the FZD-co-receptor complexes, e.g., the β-catenin pathway stimulated by FZD-LRP5/6 complexes. Wnt ligands function by promoting the clustering of FZD receptors with co- receptors. Without wishing to be bound by theory, it is contemplated that the FZD Agonists described herein bind both the FZD receptor and its LRP5/6 co-receptor thereby forming a complex that mimics the binding of a Wnt molecule to the FZD receptor and LRP 5/6 co-receptor(s), which in turn activates Wnt signaling pathways, the Wnt β-catenin pathway.

An embodiment of this invention is a method for activating a Wnt signaling pathway comprising contacting a cell expressing a FZD receptor and its LRP5/6 co-receptor with an effective amount of the FZD Agonists of this invention comprising a FZD binding domain and a LRP5/6 co-receptor binding domain.

The FZD Agonists of this invention may be made recombinantly, e.g., by Gibson assembly (see Gibson et al. (2009) Nature Methods 6 (5): 343–345 and Gibson DG. (2011) Methods in Enzymology 498: 349–361), or the molecules may be made synthetically e.g., using commercial synthetic apparatuses, for example, automated synthesizers by Applied Biosystems, Inc., Beckman, etc. By using synthesizers, naturally occurring amino acids may be substituted with unnatural amino acids. The particular sequence and the manner of preparation will be determined by convenience, economics, purity required, and the like. If desired, various groups may be introduced into the peptide during synthesis or during expression, which allow for linking to other molecules or to a surface.

The binding domains of the FZD Agonists may be linked to the Fc domain via a linker. In some embodiments, adjacent VH and VL domains may be attached to each other via a peptide linker. In some embodiements adjacent constant domains and variable domains are attached via a peptide linker. The linker may be, e.g. a polypeptide linker, or a non-peptidic linker. In some embodiments the constant domains and variable domains of the FZD Agonists are attached to the Fc domain via a peptide linker. Suitable linkers are well known in the art, e.g., an XTEN linker (see WO2013120683, inventors Schellenberger et al.) In some embodiments, the peptide linker comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13,

14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or at least 100 amino acids. In some embodiments, the peptide linker is between 1 to 100, 5 to 75, 1 to 50, 5 to 50, 1 to 30, 1 to 25, 5 to 25, 5 to 20, 5 to 15, 5 to 10, 1-10 or 1-5 amino acids in length. The modular aspects of this invention allow for mixing and matching of binding domains derived from antibodies that bind to FZD receptor or antibodies that bind LRP5/6 co-receptor on the opposite termini of the Fc domain to generate a tetravalent binding antibody molecule that can engage FZD receptor – LRP5/6 co-receptor complexes to activate Wnt signaling.

The Fc domain of the FZD Agonists, with or without the linker, is of a length and flexibility that allows for the tetravalent binding antibody molecule of this invention to bind both the FZD receptor and its LRP5/6 co-receptor thereby stabilizing receptor conformations that are compatible with activation of downstream Wnt signaling pathways. In an embodiment of this invention the Fc domain, or fragment thereof comprising the CH3 domain, with or without the linker is greater than 100 amino acids spanning up to 300Å, greater than 125 amino acids spanning up to 375Å, greater than 150 amino acids spanning up to 450Å, greater than 175 amino acids spanning up to 525Å, or greater than 300 amino acids spanning up to 900Å. Preferably the Fc domain is about 200 amino acids to about 300 amino acids in length.

As used herein and in the appended claims, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a cell" includes a plurality of such cells and reference to "the peptide" includes reference to one or more peptides and equivalents thereof, e.g. polypeptides, known to those skilled in the art, and so forth.

An "affinity matured" antibody or “maturation of an antibody” refers to an antibody with one or more alterations in one or more hypervariable regions (HVRs), compared to a parent or source antibody which does not possess such alterations, such alterations resulting in an improvement in the affinity of the antibody for antigen or to other desired properties of the molecule.

By "comprising" it is meant that the recited elements are required in the composition/method/kit, but other elements may be included to form the

composition/method/kit etc. within the scope of the claim. For example, a composition comprising tetravalent binding antibody molecules is a composition that may comprise other elements in addition to the tetravalent binding antibody molecules, e.g. functional moieties such as polypeptides, small molecules, or nucleic acids bound, e.g. covalently bound, to the tetravalent binding antibody molecules; agents that promote the stability of the tetravalent binding antibody molecule composition, agents that promote the solubility of the tetravalent binding antibody molecule composition, adjuvants, etc. as will be readily understood in the art, with the exception of elements that are encompassed by any negative provisos.

By "consisting essentially of", it is meant a limitation of the scope of composition or method described to the specified materials or steps that do not materially affect the basic and novel characteristic(s) of the subject invention. For example, a tetravalent binding antibody molecule "consisting essentially of" a disclosed sequence has the amino acid sequence of the disclosed sequence plus or minus about 5 amino acid residues at the boundaries of the sequence based upon the sequence from which it was derived, e.g. about 5 residues, 4 residues, 3 residues, 2 residues or about 1 residue less than the recited bounding amino acid residue, or about 1 residue, 2 residues, 3 residues, 4 residues, or 5 residues more than the recited bounding amino acid residue.

By "consisting of", it is meant the exclusion from the composition, method, or kit of any element, step, or ingredient not specified in the claim. For example, a tetravalent binding antibody molecule "consisting of" a disclosed sequence consists only of the disclosed amino acid sequence.

Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limits of that range is also specifically disclosed. Each smaller range between any stated value or intervening value in a stated range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included or excluded in the range, and each range where either, neither or both limits are included in the smaller ranges is also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the

stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

The basic antibody structural unit is known to comprise a tetramer. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector functions, e.g., binding Fc receptors and activation of antibody-dependent cellular cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC). Methods for dimerizing peptides via a knob-in-hole configuration are described in WO2018/026942, inventors Van Dyk et al., Carter P. (2001) J. Immunol. Methods 248, 7–15; Ridgway et al. (1996) Protein Eng. 9, 617–621; Merchant, et al. (1998) Nat. Biotechnol. 16, 677–681, and; Atwell et al., (1997) J. Mol. Biol. 270, 26–35. The Fc regions may be Merrimack (knob chain: Q347M, Y349F, T350D, T366W and L368M; hole chain: S354I, E357L, T366S, L368A and Y407V), Merchant (knob chain: T366W; hole chain: T336S, L368A and Y407V) or Merchant S:S (Merchant mutations with additional S354C variant in the knob chain and Y349C in the hole chain). The Fc regions may also contain mutations that alter their effector function, e.g., the Fc region may have attenuated effector functions due to amino acid mutations, e.g., DANG variants and LALAPS variants. Methods are well known in the art for mitigating antibody effector function, including for example amino acid substitutions in the Fc regions, e.g., the N297G and D265A, N297G (DANG) variants, L234A, L235A, P331S (LALAPS), LALAPS Merchant, LALAPS Merchant S-S (Merchant A.M. et al Nature Biothechnol 1998 vol 16 p677-681) variants, or L234A, L235A, P329G (LALA-PG) substitutions, see e.g., Lo et al. "Effector Attenuating Substitutions that Maintain Antibody Stability and Reduce Toxicity in Mice. The Journal of Biological Chemistry Vol. 292, No. 9, pp. 3900 –3908, March 3, 2017, incorporated herein by reference. In general, antibody molecules obtained from humans relate to any of the classes IgG, IgM, IgA, IgE and IgD, which differ from one another by the nature of the heavy chain present in the molecule. Certain classes have subclasses as well, such as IgG_1, IgG_2, and others. Furthermore, in humans, the light chain may be a kappa chain or a lambda chain.

Three highly divergent stretches within each of the heavy chain variable domain, VH or VH domain, and light chain variable domain, VL or VL domain, referred to as complementarity

determining regions (CDRs), are interposed between more conserved flanking stretches known as "framework regions", or "FRs". Thus, the term "FR" refers to amino acid sequences which are naturally found between, and adjacent to, CDRs in immunoglobulins. A VH domain typically has four FRs, referred to herein as VH framework region 1 (FR1), VH framework region 2 (FR2), VH framework region 3 (FR3), and VH framework region 4 (FR4). Similarly, a VL domain typically has four FRs, referred to herein as VL framework region 1 (FR1), VL framework region 2 (FR2), VL framework region 3 (FR3), and VL framework region 4 (FR4). In an antibody molecule, the three CDRs of a VL domain (CDR-L1, CDR-L2 and CDR-L3) and the three CDRs of a VH domain (CDR-H1, CDR-H2 and CDR-H3) are disposed relative to each other in three-dimensional space to form an antigen-binding site within the antibody variable region. The surface of the antigen-binding site is complementary to a three-dimensional surface of a bound antigen. The amino acid sequences of VL and VH domains may be numbered, and CDRs and FRs therein identified/defined, according to the Kabat numbering system (Kabat et al., 1991, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md.) or the INTERNATIONAL IMMUNOGENETICS INFORMATION SYSTEM (IMGT numbering system; Lefranc et al., 2003, Development and Comparative Immunology 27:55-77), both incorporated herein by reference. One of ordinary skill in the art would possess the knowledge for numbering amino acid residues of a VL domain and of a VH domain, and identifying CDRs and FRs therein, according to a routinely employed numbering system such as the IMGT numbering system, the Kabat numbering system, and the like.

The term “antibody” as referred to herein includes whole antibodies and any antigen binding fragment (i.e., “antigen-binding portion”) or single chain thereof. A “whole antibody” or full-length refers to a glycoprotein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, or an antigen binding portion thereof. Each heavy chain is comprised of a heavy chain variable region or domain (abbreviated herein as VH) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region or domain (abbreviated herein as VL) and a light chain constant region. The light chain constant region is comprised of one domain, CL or CL1. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions

(FR). Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (e.g., effector cells) and the first component (Clq) of the classical complement system.

The term "antigen-binding portion" or "antigen-binding fragment" of an antibody (or simply "antibody portion" or "antibody fragment"), as used herein, refers to one or more fragments, portions or domains of an antibody that retain the ability to specifically bind to an antigen. It has been shown that fragments of a full-length antibody can perform the antigen-binding function of an antibody. Examples of binding fragments encompassed within the term "antigen-binding portion" of an antibody include (i) an Fab fragment, a monovalent fragment consisting of the VL, VH, CL1 and CH1 domains; (ii) an $F(ab')_2$ fragment, a bivalent fragment comprising two F(ab)' fragments linked by a disulfide bridge at the hinge region; (iii) an Fd fragment consisting of the VH and CH1 domains; (iv) an Fv fragment consisting of the VL and VH domains of a single arm of an antibody; (v) a dAb fragment (Ward et al. (1989) Nature 241:544-546), which consists of a VH domain; and (vi) an isolated complementary determining region (CDR). Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single contiguous chain in which the VL and VH regions pair to form monovalent molecules (known as single chain Fv (scFv); see e.g., Bird et al. (1988) Science 242:423-426; and Huston et al. (1988) Proc. Natl. Acad. Sci. USA 85:5879-5883). Such single chain antibodies are also intended to be encompassed within the term "antigen-binding portion" of an antibody. Other forms of single chain antibodies, such as diabodies, are also encompassed (see e.g., Holliger et al. (1993) PNAS. USA 90:6444-6448).

"Diabodies," or sometimes referred to herein as "Dia," as used herein are dimeric antibody fragments. In each polypeptide of the diabody, a heavy-chain variable domain (VH) is linked to a light-chain variable domain (VL) but unlike single-chain Fv fragments, the linker between the VL and VH is too short for intramolecular pairing and as such each antigen-binding site is formed by pairing of the VH and VL of one polypeptide with the VH and VL of the other polypeptide. Diabodies thus have two antigen-binding sites, and can be

monospecific or bispecific. (see, e.g., Holliger, P., et al. (1993) Proc. Natl. Acad. Sci. USA 90:6444-6448; Poljak, R. J., et al. (1994) Structure 2:1121-1123; Kontermann and Dubel eds., Antibody Engineering (2001) Springer-Verlag. New York. 790 pp. (ISBN 3-540-41354-5) incorporated herein by reference.

As used herein an "effective amount" of an agent, e.g., the tetravalent binding antibody molecules or a pharmaceutical composition comprising the molecules, refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired result. In some embodiments, a therapeutically effective amount is one that reduces the incidence and/or severity of, stabilizes one or more characteristics of, and/or delays onset of, one or more symptoms of the disease, disorder, and/or condition. In some embodiments, the amount of a FZD Agonists administered to the subject is in the range of about 0.001mg/kg to 10mg/kg, 0.5 mg/kg to about 10 mg/kg, or about 0.5 mg/kg to about 1mg/kg of the subject's body weight. For example, in some embodiments the FZD4 Agonist may be applied to the eye in an amount of, e.g., about 0.02 -1.5 mg, about 0.05-1.0mg, or about 0.1-0.5 mg per eye.

As used herein, the term "epitope" includes any protein determinant capable of specific binding to an immunoglobulin or fragment thereof, or a T-cell receptor. The term "epitope" includes any protein determinant capable of specific binding to an immunoglobulin or T-cell receptor. Epitopic determinants usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three-dimensional structural characteristics, as well as specific charge characteristics. An antibody is said to specifically bind an antigen when the dissociation constant is $\leq 10\mu M$; e.g., ≤ 100 nM, preferably ≤ 10 nM and more preferably ≤ 1 nM.

The constant region of immunoglobulin molecules is also called the fragment crystallizable region, the “Fc region” or “Fc domain.” The Fc domain is composed of two identical protein fragments, derived from the second and third constant domains of the antibody's two heavy chains and the Fc domains of IgGs bear a highly conserved N-glycosylation site. Glycosylation of the Fc fragment is essential for Fc receptor-mediated activity. In an embodiment of the invention the Fc domain of the tetravalent binding antibody molecule is engineered such that it does not target the cell that binds the tetravalent binding antibody molecule for ADCC or CDC-dependent death. In an embodiment of the invention the Fc

domain of the tetravalent binding antibody molecule is a peptide dimer in a knob-in-hole configuration. The peptide dimer may be a heterodimer.

The terms "individual," "subject," "host," and "patient," are used interchangeably herein and refer to any mammalian subject for whom diagnosis, treatment, or therapy is desired, particularly humans.

"LRP", "LRP proteins" and "LRP receptors" is used herein to refer to members of the low density lipoprotein receptor-related protein family. These receptors are single-pass transmembrane proteins that bind and internalize ligands in the process of receptor-mediated endocytosis. LRP proteins LRP5 (e.g., LRP5: NP_002326.2) and LRP6 (e.g., LRP6: NP_002327.2) are included in a Wnt receptor complex required for activation on the Wnt-ßcatenin signaling pathway. See also, for human/mouse LRP5 and LRP6: https :// www.uniprot. org/uniprot/O75197, https :// www.uniprot. org/uniprot/Q91VN0, https :// www.uniprot. org/uniprot/O75581, https :// www.uniprot .org/uniprot/O88572.

The term "polypeptide fragment" as used herein refers to a polypeptide that has an amino terminal and/or carboxy-terminal deletion, but where the remaining amino acid sequence is identical to the corresponding positions in the naturally-occurring sequence deduced, for example, from a full-length cDNA sequence.

As used herein the term “paratope” includes the antigen binding site in the variable region of an antibody that binds to an epitope.

"Single-chain Fv" or "scFv" antibody fragments comprise the VH and VL domains of an antibody, wherein these domains are present in a single polypeptide chain. Generally, the Fv polypeptide further comprises a polypeptide linker between the VH and VL domains which enables the scFv to form the desired structure for antigen binding. For a review of scFv and other antibody fragments, see James D. Marks, Antibody Engineering, Chapter 2, Oxford University Press (1995) (Carl K. Borrebaeck, Ed.).

“Single-domain antibody” (sdAb), or “nanobody”, is an antibody fragment consisting of a single monomeric variable antibody domain. “VHH” or “VHH fragment” as used herein refers to a human VH that has been engineered to be independent of the light chain

(Nilvebrant et al. Curr Pharm Des. (2016) 22(43):6527-6537; Barthelemy et al., Journal of Biological Chemistry (2007) 283:3639-3654).

The terms "treatment", "treating" and the like are used herein to generally mean obtaining a desired pharmacologic and/or physiologic effect. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof and/or may be therapeutic in terms of a partial or complete cure for a disease and/or adverse effect attributable to the disease. "Treatment" as used herein covers any treatment of a disease in a mammal, and includes: (a) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it; (b) inhibiting the disease, i.e., slowing or arresting its development; or (c) relieving the disease, i.e., causing regression of the disease. The therapeutic agent may be administered before, during or after the onset of disease or injury. The treatment of ongoing disease, where the treatment stabilizes or reduces the undesirable clinical symptoms of the patient, is of particular interest. Such treatment is desirably performed prior to complete loss of function in the affected tissues. The subject therapy may be administered during the symptomatic stage of the disease, and in some cases after the symptomatic stage of the disease.

The ability of the tetravalent binding antibody molecules of this invention to activate Wnt signaling can be confirmed by a number of assays. The tetravalent binding antibody molecules of this invention typically initiate a reaction or activity that is similar to or the same as that initiated by the FZD receptor's natural ligand. The tetravalent binding antibody molecules of this invention activates the Wnt signaling pathways, e.g., the canonical Wnt-βcatenin signaling pathway. As used herein, the term "activates" refers to a measurable increase in the intracellular level of a Wnt signaling pathway, e.g., the Wnt-βcatenin signaling pathway, compared with the level in the absence of a FZD Agonist of the invention.

Various methods are known in the art for measuring the level of Wnt-βcatenin activation. These include but are not limited to assays that measure: Wnt-βcatenin target gene expression; LEF/TCF reporter gene expression (such as TopFLASH, superTopFLASH, pBAR); βcatenin stabilization; LRP5/6 phosphorylation; Dishevelled phosphorylation; Axin translocation from cytoplasm to cell membrane and binding to LRP5/6. The canonical Wnt-βcatenin signaling pathway ultimately leads to changes in gene expression through the transcription factors TCF1, TCF7L1, TCF7L2 and LEF1. The transcriptional response to Wnt

activation has been characterized in a number of cells and tissues. As such, global transcriptional profiling by methods well known in the art can be used to assess Wnt-βcatenin signaling activation.

Changes in Wnt-responsive gene expression are generally mediated by TCF and LEF transcription factors. A TCF reporter assay assesses changes in the transcription of TCF/LEF controlled genes to determine the level of Wnt-βcatenin signaling. A TCF reporter assay was first described by Korinek, V. et al., 1997. Also known as TOP/FOP this method involves the use of three copies of the optimal TCF motif CCTTTGATC, or three copies of the mutant motif CCTTTGGCC, upstream of a minimal c-Fos promoter driving luciferase expression (pTOPFLASH and pFOPFLASH, respectively) to determine the transactivational activity of endogenous βcatenin/TCF. A higher ratio of these two reporter activities (TOP/FOP) indicates higher βcatenin/TCF activity. A newer and more sensitive version of this reporter is called pBAR and contains 12 repeats of the TCF motifs (Biechele and Moon, Methods Mol Biol. 2008;468:99-110, PMID: 19099249).

General methods in molecular and cellular biochemistry can be found in such standard textbooks as Molecular Cloning: A Laboratory Manual, 3rd Ed. (Sambrook et al., CSH Laboratory Press 2001); Short Protocols in Molecular Biology, 4th Ed. (Ausubel et al. eds., John Wiley & Sons 1999); Protein Methods (Bollag et al., John Wiley & Sons 1996); Nonviral Vectors for Gene Therapy (Wagner et al. eds., Academic Press 1999); Viral Vectors (Kaplift & Loewy eds., Academic Press 1995); Immunology Methods Manual (I. Lefkovits ed., Academic Press 1997); and Cell and Tissue Culture: Laboratory Procedures in Biotechnology (Doyle & Griffiths, John Wiley & Sons 1998).

Unless otherwise defined, scientific and technical terms used in connection with the present invention shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Generally, nomenclatures utilized in connection with, and techniques of, cell and tissue culture, molecular biology, and protein and oligo- or polynucleotide chemistry and hybridization described herein are those well-known and commonly used in the art. Standard techniques are used for recombinant DNA, oligonucleotide synthesis, and tissue culture and transformation (e.g., electroporation, lipofection). Enzymatic reactions and purification techniques are performed according to manufacturer's specifications or as commonly accomplished in the art or as described herein. The foregoing techniques and procedures are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification. See e.g., Sambrook et al. Molecular Cloning: A Laboratory Manual (2d ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989)). The nomenclatures utilized in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well-known and commonly used in the art. Standard techniques are used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

EXAMPLES

EXAMPLE I Identification and characterization of FZD4 binding or FZD5 binding Fab-phage.

A. FZD4 antibodies from affinity matured libraries of FZD4-binding antibody 5027 and 5044; FZD5 antibodies from affinity matured libraries of FZD5-binding antibody 2919 and 2928.

Affinity matured libraries of known FZD4-binding antibodies 5027 and 5044 and known FZD5-binding antibodies 2919 and 2928 were prepared using routine methods, essentially as described in US publication no. 2016/0194394, inventors Sidhu et al., see also Persson et al.

J. Mol. Biol., 2013 Feb 22; 425(4):803-11 https ://pubmed. ncbi.nlm.nih. gov/23219464/, both incorporated herein in their entirety by reference.

The 6 CDRs of the heavy chain (CDR-H1, CDR-H2 and CDR-H3) and light chains (CDR-L1, CDR-L2 and CDR-L3) of antibodies 5044, 5027, 2919, and 2928 antibodies isolated from the affinity matured libraries are set forth in Table 1 and Table 2.

Single point ELISAs were performed on 96-well Maxisorp plates coated with the extracellular domains (ECDs) of human FZD4 protein in the presence or absence of a saturating concentration of 5027 diabody-Fc (a diabody comprising the VL and VH of 5027 linked to an Fc domain). The plates were incubated with monoclonal Fab-phage followed by incubation with horseradish peroxidase (HRP)-conjugated anti-M13 antibody. Wells were subsequently washed 8 times followed by incubations with 3,3,'5,5'-tetramethylbenidine/H_2O_2 peroxidase (TMB) substrate for 5-10 min. The reaction was stopped by adding 1M H_3PO_4 and the absorbance was measured spectrophotometrically at 450 nm in a microtiter plate reader. The results of the assay are depicted in Figure 1 and Figure 2 and demonstrate that the newly identified FZD4 antibodies bind FZD4 at a site overlapping with the site recognized by antibody 5027. FZD4 binding antibodies 5027 and 5044 are described in US provisional application no. 62/885,781, incorporated herein by reference.

B. Epitope mapping of Lead FZD4 antibodies.

ELISA assays were performed in 384-well Maxisorp plates coated with FZD4 ECD wild-type (FZD4) or mutant FZD4 proteins (FZD_swap1-18) that replace segments of the FZD4 ECD with corresponding regions from FZD5. The plates were incubated with 10 nM IgG known to bind specifically to FZD4, i.e., 5044 and 5027, or to be panspecific, i.e., 5016 (binds FZD4, FZD5, and other FZD receptors), followed by incubation with horseradish peroxidase (HRP)-conjugated anti-Kappa light chain antibody. Phosphate buffered saline (PBS) and IgG 4275 which does not bind FZD4 or FZD5 were used as controls. The wells were washed 6 times followed by incubations with 3,3,'5,5'-tetramethylbenidine/H_2O_2 peroxidase (TMB) substrate for 3-5 min. The reaction was stopped by adding 1M H_3PO_4 and the absorbance was measured spectrophotometrically at 450 nm in a microtiter plate reader, see Figure 2. The pan-FZD binder 5016 is a positive control showing that the antigens are functional, with the exception of "FZD4_Swap10". Both FZD4-specific antibodies 5027 and 5044 are unable

to bind to "FZD4 Swap 7", suggesting that these molecules bind to this region of the FZD ECD.

C. Characterization of FZD4 IgG.

FZD4-binding full length IgGs were expressed via transient transfection in an Expi293 cell culture system, essentially as described in Tao et al., Tailored tetravalent antibodies potently and specifically activate Wnt/Frizzled pathways in cells, organoids and mice. Elife. 2019 Aug 27;8:e46134. doi: 10.7554/eLife.46134; PMID: 31452509. and purified via Protein A affinity chromatography. Briefly, cells were grown to a density of approximately 2.5 x 10^6 cells/ml in Expi293 Expression Media (Gibco) in baffled cell culture flasks and transfected with the appropriate vectors using FectoPRO transfection reagent (Polyplus-transfection) using standard manufacture protocols (ThermoFisher). Expression was allowed to proceed for 5 days at 37 °C and 8% CO_2 with shaking at 125 rpm. After expression, cells were removed by centrifugation and protein was purified from the conditioned media using rProtein A Sepharose (GE Healthcare). Purified protein was buffer exchanged into either PBS or a formulated stabilization buffer (36.8 mM citric acid, 63.2 mM Na_2HPO_4, 10% trehalose, 0.2 M L-arginine, 0.01% Tween-80, pH 6.0) for storage. Proteins concentrations were determined by absorbance at 280 nm and purity was confirmed by SDS-PAGE analysis.

Expression titers were determined as mg of purified protein per liter of mammalian cell culture. Size exclusion chromatography (SEC) results in Table A below are defined as "-": evidence of multiple peaks on SEC trace, <50% monomeric species; "+": >50% monomeric species, delayed retention time (>14 min.); "++": >90% of major peak at/near expected retention time for a monomeric IgG. Standard retention time was determined by comparison to Trastuzumab.

Table A

TRAC ID	Expression Titer (mg/l)	SEC Result
13980	58	-
13981	40	-
13982	43	-
13983	65	++
13984	52	-
13985	61	++
13956	47	+
13957	52	+
13958	58	-
13959	46	+
13962	38	-
13963	56	-
13964	47	-
13965	74	++
13966	86	-
13967	87	-
13968	89	+
13969	72	-
13970	36	-
13971	46	++
13972	27	+
13973	41	+
13974	41	+
13975	41	++
13979	49	-

Trac ID corresponds to the antibody number in Table 1 and Table 2.

D. Size-exclusion chromatography analysis and ELISA specificity measurements of the FZD4 IgGs.

Twenty micrograms of the FZD4 binding IgGs were separated over an AdvanceBio SEC, 300Å, 2.7 µm, 4.6 x 300 mm column in a mobile phase of PBS using an Agilent Bio-Inert HPLC. Protein elution was monitored using absorbance at 280 nM. The results are presented in Figure 3A.

ELISA specificity measurements of the FZD4 antibodies were determined against FZD1 and FZD10, the two FZD family member most closely related to FZD4. ELISA assays were performed in 384-well Maxisorp plates coated with FZD ECD wild-type or mutant proteins at a concentration of 1 µg/ml and excess binding sites were blocked with 0.5% BSA. The plates

were incubated with 10 nM of the FZD4 binding IgGs followed by incubation with horseradish peroxidase (HRP)-conjugated anti-Kappa light chain antibody. The wells were washed 6 times followed by incubations with 3,3,'5,5'-tetramethylbenidine/H_2O_2 peroxidase (TMB) substrate for 3-5 min. The reaction was stopped by adding 1M H_3PO_4 and the absorbance was measured spectrophotometrically at 450 nm in a microtiter plate reader. The results are presented in Figure 3B.

E. Identification of the CDRs of the FZD4 or FZD5 binding antibodies.

The amino acid sequences of the CDRs of the FZD4-binding and FZD5-binding immunoglobulins are set forth in Tables 1 and 2. The CDRs were identified according to the INTERNATIONAL IMMUNOGENETICS INFORMATION SYSTEM (IMGT numbering system; Lefranc et al., 2003, Development and Comparative Immunology 27:55-77), and annotated as described in Persson et al. J Mol Biol. 2013 Feb 22;425(4):803-11, both incorporated herein by reference.

Table 1	FZD4 binding antibodies CDRs													
Antibody ID	Library	L1	SEQ ID NO:	L2	SEQ ID NO:	L3	SEQ ID NO:	H1	SEQ ID NO:	H2	SEQ ID NO:	H3	SEQ ID NO:
5044	F	SVSSA	1	SASSLYS	2	WYYAPI	3	LSSYSM	24	YISSYYGYTY	51	PAPGHWGF	79
13953	5044AM	SVSSA	1	SASSLYS	2	GNYGPI	4	IAFYSI	25	YISPFSGITH	52	PAVGHLAM	80
13954	5044AM	SVSSA	1	SASSLYS	2	GYYAPI	5	IYSYSI	26	YISSYYGYTY	51	STVGHGGM	81
13955	5044AM	SVSSA	1	SASSLYS	2	WYYAPI	3	ISSYSI	27	YISPYYSYTY	53	PAPAHWGF	82
13956	5044AM	SVSSA	1	SASSLYS	2	GYYALI	6	LSSYSM	24	YISSYAGYTS	54	PALGHAGM	83
13957	5044AM	SVSSA	1	SASSLYS	2	WYFAPI	7	ISAYSI	28	YISPYFGLTG	55	PAPGHWGM	84
13958	5044AM	SVSSA	1	SASSLYS	2	WYYAPI	3	LSSYSI	29	YISSYYGYTY	51	PVAGHGGM	85
13959	5044AM	SVSSA	1	SASSLYS	2	GYNAPI	8	LYSYSM	30	FISSFYGYTD	56	PAVGHLAL	86
13960	5044AM	SVSSA	1	SASSLYS	2	WYYAPI	3	LTSYSM	31	YISSYYGSTY	57	PAPGHWGM	84
13961	5044AM	SVSSA	1	SASSLYS	2	WYYAPI	3	ISSYSM	32	YISSYYSYTY	58	PAPGYGAL	87
13962	5044AM	SVSSA	1	SASSLYS	2	GYFAPI	9	LFSYPM	33	YISPYYGYTN	59	QTAGHAGM	88
13963	5044AM	SVSSA	1	SASSLYS	2	WFNAPI	10	LSAYSM	34	YISSYYGYTY	51	PAPGHWGF	79
13964	5044AM	SVSSA	1	SASSLYS	2	SNYAPI	11	ISSHSM	35	YISPFFSFTH	60	QAPGVSGI	89
13965	5044AM	SVSSA	1	SASSLYS	2	WYNAPI	12	LSSYSM	24	YISSYDSITD	61	PAVGHMAF	90
13966	5044AM	SVSSA	1	SASSLYS	2	GFYAPI	13	LSSYSM	24	YISSYYSYTA	62	PTPGHGGL	91
13967	5044AM	SVSSA	1	SASSLYS	2	WYYAPI	3	ISAYAM	36	YISPYYGYTF	63	PAPGHGGM	92
13968	5044AM	SVSSA	1	SASSLYS	2	GYSAPI	14	ISTYSM	37	YISPHYGFTS	64	PAVGHLGM	93
13969	5044AM	SVSSA	1	SASSLYS	2	WYFAPI	7	LHAFSM	38	YISPYYGYTY	65	PAPGHWGL	94
13970	5044AM	SVSSA	1	SASSLYS	2	GFYAPI	13	ISGYSI	39	YISSYYGYTF	66	TAPGHGAF	95
13971	5044AM	SVSSA	1	SASSLYS	2	GFYAPI	13	ISNYSI	40	IISSNFGYTS	67	PALGHLAM	96
13972	5044AM	SVSSA	1	SASSLYS	2	GYAGLI	15	ISAYSM	41	SISSYYGFTS	68	LAPGHPAL	97
13973	5044AM	SVSSA	1	SASSLYS	2	GFSSPI	16	LTSYAM	42	YISPYYGYTY	65	PAAGHLAL	98
13974	5044AM	SVSSA	1	SASSLYS	2	GYYAPI	5	LYSYSI	43	YISPSYGSTY	69	PIPGHLAF	99
13975	5044AM	SVSSA	1	SASSLYS	2	GHYAPI	17	LSSFSM	44	YISSFNGSTF	70	PTWAHGAF	100
13976	5044AM	SVSSA	1	SASSLYS	2	SFYAPI	18	IASYSI	45	YISSYYGSTY	57	PVLAHSAF	101
13977	5044AM	SVSSA	1	SASSLYS	2	GYRAPI	19	IHSNSM	46	YISPYYSFTS	71	QTPGHSGM	102
13978	5044AM	SVSSA	1	SASSLYS	2	WHRAPI	20	LSTNSM	47	YISPYYSFTY	72	QAPGPWGM	103
13979	5044AM	SVSSA	1	SASSLYS	2	SFYAPI	18	LHSFSM	48	FISSYYGYTY	73	PAPGHGAF	104

Table 1 cont'		FZD4 binding antibodies CDRs											
Antibody ID	Library	L1	SEQ ID NO:	L2	SEQ ID NO:	L3	SEQ ID NO:	H1	SEQ ID NO:	H2	SEQ ID NO:	H3	SEQ ID NO:
13980	5044AM	SVSSA	1	SASSLYS	2	GYYAPI	5	LTSYSM	31	SISPYYSYTN	74	PTTAHMAL	105
13981	5044AM	SVSSA	1	SASSLYS	2	WYYAPI	3	ISSFSI	49	FINPYYSYTY	75	PAPGHWGM	84
13982	5044AM	SVSSA	1	SASSLYS	2	GYYAPI	5	ISSYSM	32	YISSYYDYTY	76	PTPGHSGF	106
13983	5044AM	SVSSA	1	SASSLYS	2	GDFAPF	21	LPYYSM	50	IISSYFGFTY	77	PAVGHGAL	107
13984	5044AM	SVSSA	1	SASSLYS	2	GYSSPI	22	ISSHSM	35	YISPYYSYTY	53	TAPGHPAM	108
13985	5044AM	SVSSA	1	SASSLYS	2	WFYAPI	23	ISSYSI	27	YISSNFGSTY	78	PVPAHGAF	109

Table 2A		FZD4 binding antibodies CDRs											
Antibody ID	Library	L1	SEQ ID NO:	L2	SEQ ID NO:	L3	SEQ ID NO:	H1	SEQ ID NO:	H2	SEQ ID NO:	H3	SEQ ID NO:
5027	**F**	**SVSSA**	**1**	**SASSLYS**	**2**	**SSYSLI**	**130**	**SSFYFM**	**148**	**TVYPYLDYTY**	**985**	**AFPGSYHPM**	**199**
13986	5027AM	SVSSA	1	SASSLYS	2	ASYYLI	110	STYFFI	139	TIYPYLNSTY	166	AYPGSYHPL	198
13987	5027AM	SVSSA	1	SASSLYS	2	SNYALI	111	TSFYFM	140	SVYPYLDNTY	167	AFPGSYHPM	199
13988	5027AM	SVSSA	1	SASSLYS	2	SSSFLI	112	SSFYFI	141	TVYSYIDITY	168	AFPFSYHPM	200
13989	5027AM	SVSSA	1	SASSLYS	2	SSDSLI	113	SAYYFI	142	TVYPYRGYTY	169	GYPLAYTPL	201
13990	5027AM	SVSSA	1	SASSLYS	2	STHFLI	114	SYFYFM	143	SVYPYLSYTY	170	AFPGSYHPM	199
13991	5027AM	SVSSA	1	SASSLYS	2	ASYSLI	115	SSFYFI	141	SVYPYLDFTY	171	ALQGHYHPM	202
13992	5027AM	SVSSA	1	SASSLYS	2	SAYTLI	116	TSFYYM	144	AIYPYLDYTY	172	AFPGSYLPM	203
13993	5027AM	SVSSA	1	SASSLYS	2	SSVSLI	117	FTFYFM	145	SIYPYLNYTF	173	AFPGSYHPM	199
13994	5027AM	SVSSA	1	SASSLYS	2	SYYSLI	118	SSYYFI	146	TIYPYSDNTY	174	GFPGRYHPL	204
13995	5027AM	SVSSA	1	SASSLYS	2	SSYYLI	119	SSFYVM	147	SIYSYGNITY	175	AFPLSYHPM	205
13996	5027AM	SVSSA	1	SASSLYS	2	ASYYLI	110	SSFYFM	148	AIYPYLSYTY	176	AFPGRYHGM	206
13997	5027AM	SVSSA	1	SASSLYS	2	AYYFLI	120	SSFYYI	149	TVFPYLGRTY	177	AFPFSYTPL	207

Table 2A – cont'	FZD4 binding antibodies CDRs													
Antibody ID	Library	L1	SEQ ID NO:	L2	SEQ ID NO:	L3	SEQ ID NO:	H1	SEQ ID NO:	H2	SEQ ID NO:	H3	SEQ ID NO:
13998	5027AM	SVSSA	1	SASSLYS	2	SSFSLI	121	STFYFM	150	SVYPYLNYTY	178	AFPGAYSPM	208
13999	5027AM	SVSSA	1	SASSLYS	2	SAYSLI	122	SAFYYM	151	TVYPYLSYTY	179	AFPGAYHPM	209
14000	5027AM	SVSSA	1	SASSLYS	2	SSYALI	123	ASFYFM	152	TVYPYLNHTY	180	AFPGAYHPF	210
14001	5027AM	SVSSA	1	SASSLYS	2	SYFSLI	124	SAFYFI	153	SIYPYLSYTY	181	AFPGAYHPM	209
14002	5027AM	SVSSA	1	SASSLYS	2	SRFTLI	125	FPFYFM	154	SVYPYLNDTY	182	AYPGFYHPI	211
14003	5027AM	SVSSA	1	SASSLYS	2	SSNTLI	126	SAFYFM	155	SVYSSLSHTY	183	AYPLSYHPM	212
14004	5027AM	SVSSA	1	SASSLYS	2	SSFSLI	121	ASYYFM	156	SVYPYLDFTY	171	ALPGFYHPF	213
14005	5027AM	SVSSA	1	SASSLYS	2	SSFALI	127	SVFYFM	157	SVYPYNDITY	184	GFPGTYHPL	214
14006	5027AM	SVSSA	1	SASSLYS	2	ANYALI	128	SSLYYM	158	SVYPYLDNTH	185	AIPGFYHPI	215
14008	5027AM	SVSSA	1	SASSLYS	2	ASYSLI	115	SNFYLM	159	SIYSYLNYTF	186	AFPGSYHPM	199
14009	5027AM	SVSSA	1	SASSLYS	2	SSASLI	129	FSFYFI	160	SIYPYLDFTH	187	AFPGSYHPL	216
14010	5027AM	SVSSA	1	SASSLYS	2	SSYSLI	130	SAFYFM	155	AIYPYIGYTY	188	PFPASYHPL	217
14011	5027AM	SVSSA	1	SASSLYS	2	SSYSLI	130	SSLYFM	161	TIYPFRGTTY	189	AYPGRYHPL	218
14012	5027AM	SVSSA	1	SASSLYS	2	SAFYLI	131	YYFYYM	162	AIYPYLGYTY	190	AFPGSYHPL	216
14013	5027AM	SVSSA	1	SASSLYS	2	SAYFLI	132	SSFYFI	141	SVYPYLGDTY	191	AFPGFYHPF	219
14015	5027AM	SVSSA	1	SASSLYS	2	ASSSLI	133	TSYYFI	163	SVYSYLGYTF	192	AFPGSYHPL	216
14016	5027AM	SVSSA	1	SASSLYS	2	SIYSLI	134	SYFYFM	143	AIYPYLSYTY	176	AFPGSYHPM	199
14018	5027AM	SVSSA	1	SASSLYS	2	ASYYLI	110	FSFYFI	160	TVYPYLSHTY	193	AFPGSYHPM	199
14019	5027AM	SVSSA	1	SASSLYS	2	STGSLI	135	SDFYFI	164	TIYPFIGNTY	194	AFPGSYHPF	220
14020	5027AM	SVSSA	1	SASSLYS	2	SSHSLI	136	SSFYFM	148	SVYPYVDYTY	195	AFPGFYHPM	221
14021	5027AM	SVSSA	1	SASSLYS	2	SSYTLI	137	SSFYYM	165	TVYPYLSFTY	196	ALPGSYHPF	222
14022	5027AM	SVSSA	1	SASSLYS	2	SYHYLI	138	STFYFM	150	SVYPYLDDTY	197	AYPGSYHPL	198

Table 2B **FZD5 binding antibodies CDRs**

Antibody ID	Antigen Name	Selection ID	L1	SEQ ID NO:	L2	SEQ ID NO:	L3	SEQ ID NO:	H1	SEQ ID NO:	H2	SEQ ID NO:	H3	SEQ ID NO:
14023	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYSGVHGLI	223	LIYTYI	308	TIYPASSSTS	381	GAM	
14024	FZD5	2919AM	SVSSA	1	SASSLYS	2	WFSSAHVPF	224	ITYPGM	309	TIFSSHGSTS	382	FGM	
14025	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYSYGHHLI	225	ISYSYM	310	SIYSSSSSTS	383	GAL	
14026	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYTSGHVLI	226	ISFFYM	311	TIDSSTGSTT	384	GAL	
14027	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYASDHGLI	227	IPYFYM	312	SIYSSSGSTS	385	GAM	
14028	FZD5	2919AM	SVSSA	1	SASSLYS	2	WFSPGNVLI	228	ISYYYI	313	SIYPSSSSTT	386	AAF	
14029	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYSTRNILI	229	ISYAYM	314	SIYPSSSSTA	387	YAF	
14030	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYFSDHDLF	230	ITYFYM	315	SIYPSFGSTS	388	GGM	
14031	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYSSGDVLI	231	IYYSYI	316	SIYSSNGGTS	389	GAM	
14032	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYSSADVLF	232	ILNTYM	317	SIYPSSSSTA	387	GGL	
14033	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYSSGHGLI	233	ISFYYI	318	SIYPASSSTS	390	GGI	
14034	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYSSGHALI	234	LAYSYM	319	SIYPSSGDTS	391	GAM	
14035	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYSSNHIPI	235	IRYSYI	320	AIYSSSSSTS	392	GAM	
14036	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYSSSNVLI	236	ITYSYM	321	TIYPSSGSTA	393	FAM	
14037	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYFSDRVLI	237	IINTYM	322	SIYSAPSSTA	394	GAI	
14038	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYPSSHVLI	238	ISYSYM	310	TIYPSSGSTA	393	GGM	
14039	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYSSRHHLI	239	LANSYM	323	TIYSSSGSTS	395	GAM	
14040	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYSTGRVLF	240	LSYTYM	324	SIDPSSGSTS	396	FGM	
14041	FZD5	2919AM	SVSSA	1	SASSLYS	2	WFPTGHVLF	241	ISYSYI	325	TIYPSSGSTG	397	FGM	
14042	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYAPRHVLI	242	ISYSYI	325	SIYSSSSSTS	383	GAM	
14043	FZD5	2919AM	SVSSA	1	SASSLYS	2	WFTSGLVLF	243	LSYLYI	326	SIYPSSSSTS	398	GGM	
14044	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYSSGHVLF	244	ISYAYI	327	SIYSSPSSTS	399	GAM	
14045	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYPGAPVLI	245	IAYSYM	328	SIYPSSSSTS	398	GAM	
14046	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYSSSNVLI	236	FIWESLLVS	329	TIYPSSGSTA	393	FAM	
14047	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYSSANALF	246	ISHSYM	330	SIDSSSGSTS	400	GAL	
14048	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYSSGDVLI	231	LRYSYI	331	TIYSASGSTT	401	GAL	

Table 2B **FZD5 binding antibodies CDRs**

Antibody ID	Antigen Name	Selection ID	L1	SEQ ID NO:	L2	SEQ ID NO:	L3	SEQ ID NO:	H1	SEQ ID NO:	H2	SEQ ID NO:	H3	SEQ ID NO:
14049	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYSSNHVLI	247	ISYAYM	314	SISPSDSSTS	402	GAL	
14050	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYSAAHILF	248	ISYSYM	310	SIDPSSGLTS	403	GAL	
14051	FZD5	2919AM	SVSSA	1	SASSLYS	2	WFASGHVLI	249	IRYAYM	332	TIDSFSGSTS	404	YAM	
14052	FZD5	2919AM	SVSSA	1	SASSLYS	2	WFSSGDSLI	250	ITHLYM	333	SIYPSSGSTS	405	AAL	
14053	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYASGNVLI	251	LSIFYM	334	TIYPSSSSTS	406	GAF	
14054	FZD5	2919AM	SVSSA	1	SASSLYS	2	WFSPGHLLI	252	LSYSYI	335	AIYPSPSSTS	407	GAM	
14055	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYPSGHVLF	253	ISYSFM	336	SIYSTSGSTS	408	GGL	
14056	FZD5	2919AM	SVSSA	1	SASSLYS	2	WFAAGHVLI	254	IAYVGI	337	AITPSSSNTS	409	FGF	
14057	FZD5	2919AM	SVSSA	1	SASSLYS	2	WFRSAHVLI	255	LSYSYM	338	SIDPSSSSTA	410	FGF	
14058	FZD5	2919AM	SVSSA	1	SASSLYS	2	WFASGHILI	256	ISYSFM	336	SIYSRSGSTA	411	GAM	
14059	FZD5	2919AM	SVSSA	1	SASSLYS	2	WFSGGHALI	257	IAYFYI	339	TIDPSSGSTS	412	GGL	
14060	FZD5	2919AM	SVSSA	1	SASSLYS	2	WFASAHVLF	258	LSSSYM	340	SIGPSSGSTS	413	FGF	
14061	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYSPGHVLI	259	LSYSYM	338	SIYPSSSSTS	398	GGI	
14062	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYASGLVLI	260	IYYSYM	341	SIDPSSSSTS	414	GGM	
14063	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYTSGHVLF	261	ITYSYM	321	SIYPSPSSTS	415	GGM	
14064	FZD5	2919AM	SVSSA	1	SASSLYS	2	WFSFPHALI	262	LHYGGI	342	SISSSFSSTS	416	FGF	
14066	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYASGTDLI	263	ISYSYM	310	TIYSSSSSTA	417	GGM	
14067	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYSSGRLLI	264	IGYAYM	343	SIYSSPGSTA	418	GAL	
14068	FZD5	2919AM	SVSSA	1	SASSLYS	2	WFSSPHVLF	265	LSYSSI	344	SICPFCSSTS	419	FGF	
14069	FZD5	2919AM	SVSSA	1	SASSLYS	2	WFASASSLF	266	LSYDGI	345	TIYSSSGSTS	395	FGL	
14070	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYPSSHVLF	267	LSYAYM	346	SIHPFDGSTS	420	GAL	
14071	FZD5	2919AM	SVSSA	1	SASSLYS	2	WFPAHHVLF	268	ISYSGI	347	SISSSSGSTA	421	FGM	
14072	FZD5	2919AM	SVSSA	1	SASSLYS	2	WFPSGNVLF	269	ISSSYM	348	TIDPYAGSTS	422	FAM	
14073	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYSSNNVLI	270	LSYSYM	338	SIYPSSGSTA	423	GGM	
14074	FZD5	2919AM	SVSSA	1	SASSLYS	2	WFSSRHVLF	271	LSYSGM	349	TIYPSSSSTS	406	FGM	
14075	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYFSDHDLI	272	GFTISYFFM	350	SIYPSDSSTS	424	GAM	

Table 2B **FZD5 binding antibodies CDRs**

Antibody ID	Antigen Name	Selection ID	L1	SEQ ID NO:	L2	SEQ ID NO:	L3	SEQ ID NO:	H1	SEQ ID NO:	H2	SEQ ID NO:	H3	SEQ ID NO:
14076	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYSSGGVLI	273	ISYSFI	351	SIYPSSGHTS	425	GAL	
14077	FZD5	2919AM	SVSSA	1	SASSLYS	2	WFPSGHVLF	274	ISYSYM	310	SIDPSSGSTS	396	FGM	
14078	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYSSTHVLF	275	LSYTYM	324	SIYSSPGSTS	426	GGM	
14079	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYSSGSALI	276	ISHAYM	352	SIYSSPGSTA	418	FAL	
14080	FZD5	2919AM	SVSSA	1	SASSLYS	2	WFSPGSVLI	277	LLFFYM	353	SIDPSSGFTS	427	GAM	
14081	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYPSAHILF	278	IAYSYM	328	SIYPASSSTS	390	GGM	
14082	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYGSGGILI	279	LSYFYM	354	SIFSSSSSTS	428	GAM	
14083	FZD5	2919AM	SVSSA	1	SASSLYS	2	WFTSGRDLF	280	GFTLISSSI	355	SIYPAPSSTP	429	GGM	
14084	FZD5	2919AM	SVSSA	1	SASSLYS	2	WYLSRNILI	281	LSYSYI	335	SIYSSSSSTS	383	GAM	
14085	FZD5	2919AM	SVSSA	1	SASSLYS	2	WFSGRDALF	282	ITNSYM	356	SIYSSPSSTS	399	GGL	
14369	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFFYPI	283	ISFSSI	357	SIYPSYGSSF	430	YYAF	483
14370	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYFPI	284	ISYSSM	358	TIYPYYSSTL	431	YYAF	483
14371	FZD5	2928AM	SVSSA	1	SASSLYS	2	AHYFPI	285	ISYSSM	358	SIYSSYSSTY	432	YYAM	484
14372	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYFPI	284	ISYSSM	358	SIYPSYSVTY	433	YYGM	485
14373	FZD5	2928AM	SVSSA	1	SASSLYS	2	SHYYPI	286	LSFSSM	359	SIYPYYGSTF	434	YYAM	484
14374	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYFPI	284	ISYSSM	358	SIYSSYSSTY	432	YYGF	486
14375	FZD5	2928AM	SVSSA	1	SASSLYS	2	GFYYPI	287	ISFGSI	360	SIYPSYSSTF	435	YYAM	484
14376	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYYPI	288	ITYSSI	361	SIYPAYSSTY	436	YYAF	483
14377	FZD5	2928AM	SVSSA	1	SASSLYS	2	SFYFPI	289	ISYSAI	362	SIYSSYSSTF	437	YYAM	484
14378	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYFPI	284	ISYSSM	358	SIYSSYGSTY	438	YYAM	484
14379	FZD5	2928AM	SVSSA	1	SASSLYS	2	ADYFPI	290	ISYSSM	358	SIYPSYSSTY	439	YYGM	485
14380	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYYPI	288	ISYSSI	363	SIYSYYGSTY	440	YYAM	484
14381	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYFPI	284	ISFSSI	357	TIYSLFGATF	441	YYGF	486
14382	FZD5	2928AM	SVSSA	1	SASSLYS	2	SFYFPI	289	ISYSSM	358	SIYPSYSSTY	439	YYAF	483
14383	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFHYPI	291	ISFSSI	357	SIYPSYSSTY	439	YYAM	484
14384	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYYPI	288	ISFSSI	357	SIYPAYGATF	442	YYGM	485

Table 2B **FZD5 binding antibodies CDRs**

Antibody ID	Antigen Name	Selection ID	L1	SEQ ID NO:	L2	SEQ ID NO:	L3	SEQ ID NO:	H1	SEQ ID NO:	H2	SEQ ID NO:	H3	SEQ ID NO:
14385	FZD5	2928AM	SVSSA	1	SASSLYS	2	AYYYPI	292	ISYSSI	363	SIYSSYSSTF	437	YYAF	483
14386	FZD5	2928AM	SVSSA	1	SASSLYS	2	VFYYPI	293	ISYSSM	358	SIYSSYSSTY	432	YYAF	483
14387	FZD5	2928AM	SVSSA	1	SASSLYS	2	SFYFPI	289	ISYSSM	358	SIYPYYSSTY	443	YYAM	484
14388	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYFPI	284	LSYSSM	364	SIYPAYSSTY	436	YYGM	485
14389	FZD5	2928AM	SVSSA	1	SASSLYS	2	ANYFPI	294	ISFGSI	360	SIYSSYSSTY	432	YYAM	484
14390	FZD5	2928AM	SVSSA	1	SASSLYS	2	GFYFPI	295	ISYSSI	363	SIYPSFGSTY	444	YYAM	484
14391	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYFPI	284	ISYSSM	358	SIYPSFSPTY	445	YYGM	485
14392	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYFPI	284	IAYSSM	365	SIYSSYGSTF	446	YYAF	483
14393	FZD5	2928AM	SVSSA	1	SASSLYS	2	AYYFPI	296	ISYSSI	363	SIYPAYSPTY	447	YYAF	483
14394	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFIFPI	297	ISYSAM	366	SIYPSYSSTY	439	YYAL	487
14395	FZD5	2928AM	SVSSA	1	SASSLYS	2	AYYYPI	292	ISYGVI	367	SIYSAYSSTF	448	YYAF	483
14396	FZD5	2928AM	SVSSA	1	SASSLYS	2	SFYFPI	289	ISYSSI	363	TIYPYYDPTY	449	YYAF	483
14397	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYFPI	284	LSYSSM	364	SIYSSYGSTY	438	YYAM	484
14398	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYYPI	288	ISYSSI	363	SIYPSYGSTY	450	YYGM	485
14399	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYFPI	284	ISYSSM	358	SIYPHYGATF	451	YYGM	485
14400	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYYPI	288	ISYSSI	363	SIYPSYGSTF	452	YYAM	484
14401	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFFFPI	298	ISYSSI	363	SIYSSYSATY	453	YYAM	484
14402	FZD5	2928AM	SVSSA	1	SASSLYS	2	SFYYPI	299	ISYSSM	358	SIYPSYSSTY	439	YYAF	483
14403	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYFPI	284	IPYGSM	368	SIYPSYGSTF	452	YYAM	484
14404	FZD5	2928AM	SVSSA	1	SASSLYS	2	ALYYPI	300	ISYSSM	358	SIYPSYSSTF	435	YYAM	484
14405	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYFPI	284	ISYSAM	366	SIYPYYGPTY	454	YYAF	483
14406	FZD5	2928AM	SVSSA	1	SASSLYS	2	VFYYPI	293	ISYSSI	363	SIYPFYGSTF	455	FYAF	488
14407	FZD5	2928AM	SVSSA	1	SASSLYS	2	RFYFPI	301	ISYSSI	363	AIYPSYSSTN	456	YYAM	484
14408	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYYPI	288	ISYSSI	363	SIYPYYSSTH	457	YYAM	484
14409	FZD5	2928AM	SVSSA	1	SASSLYS	2	LYYFPI	302	IAYSAM	369	SIYPSYSTTY	458	YYAM	484
14410	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYFPI	284	LSFSSI	370	SIYPSYSSTF	435	YYAF	483

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Table 2B **FZD5 binding antibodies CDRs**

Antibody ID	Antigen Name	Selection ID	L1	SEQ ID NO:	L2	SEQ ID NO:	L3	SEQ ID NO:	H1	SEQ ID NO:	H2	SEQ ID NO:	H3	SEQ ID NO:
14411	FZD5	2928AM	SVSSA	1	SASSLYS	2	AYYFPI	296	ISYSSM	358	SIYSSYGSTY	438	YYGM	485
14412	FZD5	2928AM	SVSSA	1	SASSLYS	2	SSYFPI	303	ISYSSM	358	SIYSNYSSSY	459	YYAM	484
14413	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYFPI	284	LTYSSI	371	TIYPSYGSTY	460	YYAM	484
14414	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYFPI	284	ISYSSM	358	SIYPSFGSTF	461	YYAI	489
14415	FZD5	2928AM	SVSSA	1	SASSLYS	2	AHYFPI	285	LSYGSI	372	SIYPSYGSTY	450	YYGM	485
14416	FZD5	2928AM	SVSSA	1	SASSLYS	2	ASYFPI	304	ISYSSM	358	TIYPSYSSTY	462	YYAM	484
14417	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYFPI	284	IAYSSM	365	TIYSSYGATS	463	YYAF	483
14418	FZD5	2928AM	SVSSA	1	SASSLYS	2	AHYYPI	305	ISYSSI	363	SIYPSYSSTI	464	YYAM	484
14419	FZD5	2928AM	SVSSA	1	SASSLYS	2	AGFFPI	306	ISYSSI	363	TIYPYYGATY	465	YYGF	486
14420	FZD5	2928AM	SVSSA	1	SASSLYS	2	SSYYPI	307	ISYSSI	363	SIYSGYSATY	466	YYAM	484
14421	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYFPI	284	ITYSSM	373	SIYPSYGSTY	450	YYGF	486
14422	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYFPI	284	ISYSSI	363	TIYPSYSSTY	462	YYAM	484
14423	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYFPI	284	LGYGSM	374	SIYPSYGSTY	450	YYAM	484
14424	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYFPI	284	ISYSSM	358	SIYPSYSATF	467	YFAL	490
14425	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYYPI	288	IGYSSI	375	TIYPSYSSTF	468	YYAF	483
14426	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYYPI	288	ITYGSI	376	AIYSSYGSTY	469	YYAF	483
14427	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYYPI	288	ISYSSM	358	SIFPYYGSTY	470	YYGF	486
14428	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYFPI	284	ISYSSM	358	SIYPFYSTTF	471	YYAM	484
14429	FZD5	2928AM	SVSSA	1	SASSLYS	2	SSYYPI	307	ISYGSM	377	SIYPSYSATF	467	YYGM	485
14430	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYYPI	288	ISYSSM	358	SIYPSYGSTS	472	YYGM	485
14431	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYFPI	284	IYYSSM	378	SIYPTYGSTV	473	YYGM	485
14432	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYFPI	284	ISYSSI	363	TIYPNYSSTY	474	YYAM	484
14433	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYFPI	284	IFYSSM	379	SIYPSYSATY	475	YYAM	484
14434	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYYPI	288	ISYSSM	358	SIYPGYSSTY	476	YYAM	484
14435	FZD5	2928AM	SVSSA	1	SASSLYS	2	AHYFPI	285	IAYSSM	365	TIYPSYSSTY	462	YYAM	484
14436	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYYPI	288	ISYSSI	363	SIYPSYSSTS	477	YYGM	485

Table 2B **FZD5 binding antibodies CDRs**

Antibody ID	Antigen Name	Selection ID	L1	SEQ ID NO:	L2	SEQ ID NO:	L3	SEQ ID NO:	H1	SEQ ID NO:	H2	SEQ ID NO:	H3	SEQ ID NO:
14437	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYFPI	284	ISYSSM	358	SIYSGYGSTY	478	YYGM	485
14438	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYFPI	284	ISYSSM	358	SIYPSYGSTY	450	YYGM	485
14439	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYFPI	284	LSFSSM	359	SIYSGYSATY	466	YYAL	487
14440	FZD5	2928AM	SVSSA	1	SASSLYS	2	AYYFPI	296	ISYSSM	358	SIYPSYGSTN	479	YYAF	483
14441	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYFPI	284	LSYSSI	344	SIYPTYGSAY	480	YYGM	485
14442	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYFPI	284	ITYSSM	373	TIYSSYGSTY	481	YYAM	484
14443	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYFPI	284	ISFSSM	380	AIYPYYGSTY	482	YYGF	486
14444	FZD5	2928AM	SVSSA	1	SASSLYS	2	AHYFPI	285	ISYSSM	358	SIYSSYGSTY	438	YYGM	485
14445	FZD5	2928AM	SVSSA	1	SASSLYS	2	ASYFPI	304	LSYSSM	364	SIYPSYSSTF	435	YYAM	484
14446	FZD5	2928AM	SVSSA	1	SASSLYS	2	AFYYPI	288	ISYGSM	377	SIYPSYGSTY	450	YYGM	485

EXAMPLE 2: Identification and characterization of LRP binding synthetic antibodies

A. Phage Clonal ELISA of Synthetic Antibodies targeting LRP5 and LRP6.

Single point ELISAs were performed on 96-well Maxisorp plates coated with the ECDs of mouse LRP5-his protein or human Fc and blocked with BSA (0.5%). The plates were incubated with monoclonal Fab-phage, or VH-phage and titers $>10^9$ phage/ml followed by incubation with horseradish peroxidase (HRP)-conjugated anti-M13 antibody. The wells were washed 8 times followed by incubations with 3,3,'5,5'-tetramethylbenidine/H_2O_2 peroxidase (TMB) substrate for 5-10 min. the reaction was stopped by adding 1M H_3PO_4 and the absorbance was measured spectrophotometrically at 450 nm in a microtiter plate reader. The results are presented in Figure 4. The results demonstrate that the synthetic antibodies bound to LRP5. LRP5 binding antibodies, 2459, 2460 and 8716, are described in US provisional application no. 62/886,913, incorporated herein by reference.

Single point ELISAs were performed on 96-well Maxisorp plates coated with the ECDs of human LRP6-Fc protein chimeras. The plates were incubated with the monoclonal Fab-phage, or VH-phage and titers >109 phage/ml followed by incubation with horseradish peroxidase (HRP)-conjugated anti-M13 antibody. The wells were washed 8 times followed by incubations with 3,3,'5,5'-tetramethylbenidine/H_2O_2 peroxidase (TMB) substrate for 5-10 min. the reaction was stopped by adding 1M H_3PO_4 and the absorbance was measured spectrophotometrically at 450 nm in a microtiter plate reader. The results are presented in Figures 5A and 5B. The results demonstrate the synthetic antibodies bound to LRP6. LRP6 binding antibodies, 2539, 2540, and 2542 are described in US provisional application no. 62/886,918, incorporated herein by reference.

B. Identification of the CDRs of the synthetic antibodies targeting LRP5 and LRP6.

The CDRs of the LRP5-binding and LRP6-binding immunoglobulins set forth in Tables 3 and 4 were identified according to the INTERNATIONAL IMMUNOGENETICS INFORMATION SYSTEM (IMGT numbering system; Lefranc et al., 2003, Development and Comparative Immunology 27:55-77) and annotated as described in Persson et al. J Mol Biol. 2013 Feb 22;425(4):803-11, both incorporated herein by reference.

Table 3	LRP5 – antibody		LRP5-binding antibodies CDRs											
Antibody ID	Library	Antigen	L1	SEQ ID NO:	L2	SEQ ID NO:	L3	SEQ ID NO:	H1	SEQ ID NO:	H2	SEQ ID NO:	H3	SEQ ID NO:
2459	F	mLRP5-his	SVSSA1	2	SASSLYS	2	ASYAPI	492	LSYYYM	527	SIYSSYGYTY	552	WSHVSGHYSGM	584
2460	F	mLRP5-his	SVSSA1	2	SASSLYS	2	SSYSLI	130	FSSSSI	528	SISSSYGYTY	553	GGSGVSHYGSVYYSWWAL	585
8716	F	mLRP5-his	SVSSA1	2	SASSLYS	2	YWAYYSPI	493	FSSSSI	528	SISSSYGYTY	553	SWAM	586
9931	F	mLRP5-his	SVSSA1	2	SASSLYS	2	SSSGHLI	494	LYYYSM	529	YISSYYSYTS	554	WSHVVGAHYGWAI	587
9932	F	mLRP5-his	SVSSA1	2	SASSLYS	2	PYGYPI	495	IYYYSM	530	SISSYYGYTS	555	SWWYWSYHGYAAM	588
9933	F	mLRP5-his	SVSSA1	2	SASSLYS	2	FHGLI	496	ISSSYM	348	SIYSYSSYTS	556	GYSYVWYGVYYHGYGAM	589
9934	F	mLRP5-his	SVSSA1	2	SASSLYS	2	YWFLI	497	LYYYYI	531	SISPYYGYTS	557	SGYGWYAM	590
9935	F	mLRP5-his	SVSSA1	2	SASSLYS	2	HSYGYPI	498	ISYSYM	310	SISSSYGYTY	553	SYYWGYWAAL	591
9936	F	mLRP5-his	SVSSA1	2	SASSLYS	2	YYAWYLI	499	ISYYSM	532	SIYSSYGYTY	552	GGVYYYPSYAGWPYGM	592
9937	F	mLRP5-his	SVSSA1	2	SASSLYS	2	AAYSPI	500	ISSSYM	348	SIYPSYGYTY	558	HYAWWVGAF	593
9938	F	mLRP5-his	SVSSA1	2	SASSLYS	2	YYSWYPPF	501	ISYSYM	310	SIYSYYSYTS	559	GGGAHGWGYSL	594
9939	F	mLRP5-his	SVSSA1	2	SASSLYS	2	SFYPI	502	LSSYSI	29	SIYPYYGYTS	560	SGPVYASYSWAWYYYGAL	595
9940	F	mLRP5-his	SVSSA1	2	SASSLYS	2	YYWYPF	503	LSYYY1	533	SIYSYYSSTY	561	YSWGAYGYGAM	596
9941	F	mLRP5-his	SVSSA1	2	SASSLYS	2	WGSPI	504	FSSSSI	528	SIYPSSGSTY	562	YYYHYSVPVYAAL	597
9942	F	mLRP5-his	SVSSA1	2	SASSLYS	2	YSSWYLI	505	LYYYSM	529	SIYPSSGSTY	562	SPYYGFYYSGFYHWVFYGF	598
9943	F	mLRP5-his	SVSSA1	2	SASSLYS	2	GAYLI	506	LYYSSM	534	YIYSYYGYTY	563	AAWGWHPAF	599
9944	F	mLRP5-his	SVSSA1	2	SASSLYS	2	HFYYYPI	507	IYSSYI	535	YISSYYGSTY	57	GGGFYYAGGWPYASYAWAF	600
9945	F	mLRP5-his	SVSSA1	2	SASSLYS	2	AFHSPI	508	LYYSSM	534	YIYPYYGYTS	564	AWYSYYVGL	601
9946	F	mLRP5-his	SVSSA1	2	SASSLYS	2	AWYPI	509	ISYSSM	358	SIYPYYGSTY	565	GVYYGGGYWAGGYYPAAL	602
12600	H	mLRP5-his	SVSSA1	491	SASDLYS	491	YAGAGLI	510	FTAYAM	536	SIYPSGGYTA	566	RSYYFAL	603
12601	H	mLRP5-his	SVSSA1	491	SASDLYS	491	SYSYPI	511	LGGYGI	537	GIYPSGGYTA	567	SSTYSSYYYHFYAL	604
12602	H	mLRP5-his	SVSSA1	491	SASDLYS	491	YYRSRLI	512	FASAWM	538	RISPSGGYTA	568	STRWHSAYAYYYSHAM	605
12603	H	mLRP5-his	SVSSA1	491	SASDLYS	491	SYFYPI	513	IGGAAM	539	GISASGGATA	569	SRPSWYWSYHYFAL	606
12604	H	mLRP5-his	SVSSA1	491	SASDLYS	491	GFFPI	514	FSSSSI	528	GISTSGGATA	570	SYYGYSRGF	607
12605	H	mLRP5-his	SVSSA1	491	SASDLYS	491	SHSYPI	515	FASYGM	540	SIYPSGGYTA	566	SYSFHYAWPRYHYGAL	608

Table 3

LRP5 – antibody			LRP5-binding antibodies CDRs											
Antibody ID	**Library**	**Antigen**	**L1**	**SEQ ID NO:**	**L2**	**SEQ ID NO:**	**L3**	**SEQ ID NO:**	**H1**	**SEQ ID NO:**	**H2**	**SEQ ID NO:**	**H3**	**SEQ ID NO:**
12606	H	mLRP5-his	SVSSA	1	SASDLYS	491	SHYYPI	286	IAGSSI	541	GISASGGYTA	571	YDSGYYAWYYHDRAM	609
12607	H	mLRP5-his	SVSSA	1	SASDLYS	491	RGSGPI	516	LTGDW M	542	GIYPSGGATA	572	FGSPHYGM	610
12608	H	mLRP5-his	SVSSA	1	SASDLYS	491	RYSGGLI	517	FTSYSM	543	GIYPSGGSTA	573	PRYYAYYSGGF	611
12609	H	mLRP5-his	SVSSA	1	SASDLYS	491	SARYYYLI	518	LNAAAM	544	GISASRGATA	574	SHSSGSRSRGL	612
12610	H	mLRP5-his	SVSSA	1	SASDLYS	491	SSYSLI	130	LAGAGM	545	RISTSGGYTA	575	YSFRYPSYAM	613
12611	H	mLRP5-his	SVSSA	1	SASDLYS	491	SYRGYYLI	519	IGGAAM	539	GIYASGGATA	576	GSRYSGF	614
13218	2539AM	mLRP5-his	SVSSA	1	SASSLYS	2	FSWGLI	520	ISYYPM	546	YISPYSGYTF	577	HYYFRWSRGM	615
13219	2539AM	mLRP5-his	SVSSA	1	SASSLYS	2	YSWLPI	521	IVFGSI	547	HIAPYYGFTY	578	VNFIRRFRGM	616
13378	2542AM	mLRP5-his	SVSSA	1	SASSLYS	2	FFRPI	522	ISSNYI	548	SINPSYSYTF	579	AVRRSQGI	617
13379	2539AM	mLRP5-his	SVSSA	1	SASSLYS	2	YSRRLF	523	LTYTSM	549	SISPFHGHTF	580	FPYFAWVGGM	618
13380	2539AM	mLRP5-his	SVSSA	1	SASSLYS	2	FIRVPI	524	ITYYSM	550	SITSYYGNTD	581	SHYFPWTVAL	619
13558	2540AM	mLRP5-his	SVSSA	1	SASSLYS	2	FYVPF	525	*N.D.*		SIYPYYGFTD	582	ASYHASFDGL	620
13559	2540AM	mLRP5-his	SVSSA	1	SASSLYS	2	GYSFGQ	526	IADSSI	551	SISPYFSYTR	583	TSIFKRFAGM	621

Table 4

LRP6 – antibody			LRP6 binding antibodies CDRs											
Antibody ID	**Library**	**Antigen**	**L1**	**SEQ ID NO:**	**L2**	**SEQ ID NO:**	**L3**	**SEQ ID NO:**	**H1**	**SEQ ID NO:**	**H2**	**SEQ ID NO:**	**H3**	**SEQ ID NO:**
2539	F	LRP6-Fc	SVSSA	1	SASSLYS	2	YSWGPF	622	ISYSSI	363	YISSYYGYTY	51	AHYFPWAGAM	813
2542	F	LRP6-Fc	SVSSA	1	SASSLYS	2	YYWPI	623	ISSYYI	683	SIYSSYGYTS	741	TVRGSKKPYFSGWAM	814
2540	F	LRP6-Fc	SVSSA	1	SASSLYS	2	YYFLI	624	ISYSSI	363	SISPYYGYTY	742	SSYFPWFSAM	815
12612	H	LRP6-Fc	SVSSA	1	SASDLYS	491	YRYYWRPI	625	FSGDAM	684	RISSSGGYTA	743	ASYYSNYYYGPAM	816
12613	H	LRP6-Fc	SVSSA	1	SASDLYS	491	GPWGLI	626	ISGAWM	685	RIYPSGGTTD	744	GWFSFRSYYRSYYYYSA L	817

Table 4 LRP6 – antibody			LRP6 binding antibodies CDRs											
Antibody ID	Library	Antigen	L1	SEQ ID NO:	L2	SEQ ID NO:	L3	SEQ ID NO:	H1	SEQ ID NO:	H2	SEQ ID NO:	H3	SEQ ID NO:
12614	H	LRP6-Fc	SVSSA	1	SASDLYS	491	RYSSPI	627	FTTYSI	686	GISTSGGYTD	745	SGHPRYYSRRHSYGM	818
12615	H	LRP6-Fc	SVSSA	1	SASDLYS	491	YRYWYGPI	628	FAASGI	687	YISPSGGYTD	746	SYYSNYYYYYDAM	819
12979	2539AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YSWALF	629	IFFSSM	688	GISSYYGFTY	747	AHYFPWAGAL	820
12980	2539AM	LRP6-Fc	SVSSA	1	SASSLYS	2	ISWGLI	630	IRYSSI	689	GIFSNYGPTT	748	AHYFRRARGL	821
12981	2539AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YFSYPI	631	LSYSSI	344	FISSYYSFTH	749	SHYFPWAGAM	822
12982	2539AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YRWALF	632	LAYSSI	690	SISSYYGFTY	750	AHYFPWAGGM	823
12983	2539AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YSRILF	633	LRYASM	691	YIASFYGDTY	751	SYYYPRSRGM	824
12984	2539AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YSLRPI	634	LSFSSI	370	HISPYYGYTH	752	SHYFPWAVAM	825
12985	2539AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YSRGLI	635	IFYSSI	692	YISSYYSYTY	58	SHYFPWAVAM	825
12986	2539AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YFWGLI	636	LSYSSM	364	NITPYYGYTS	753	SHYFPWFAAM	826
12987	2539AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YSWGLI	637	INYSSI	693	GISSYYSYTY	754	ANYFPWAYAM	827
12988	2539AM	LRP6-Fc	SVSSA	1	SASSLYS	2	DSWGLF	638	ISYSSM	358	LITSYYGYTT	755	AHYFPWVVGM	828
12989	2539AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYWGLI	639	LSYSSI	344	FISSYYGYTY	73	SHYFPWAGAL	829
13002	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYYLI	640	IAFSSI	694	SISSYYGYTS	555	SSYFPWFSAL	830
13003	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYILI	641	LFYSSM	695	FISPYYSFTN	756	SSYFPWLSDM	831
13004	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	HSFPI	642	ISYSSM	358	NITSYYGYTT	757	SSYFPWVSGM	832
13005	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YHHLI	643	ISFASM	696	SISPYYSYTS	758	SSYFPWFSAM	815
13006	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYSPI	644	IFYSSI	692	SISPYYGYTD	759	SSYLPWFSAL	833
13007	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYYPI	645	ISFYSI	697	SISSYYSYTD	760	SSYFPWFTAL	834
13008	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YHFLI	646	ISYSSI	363	AIYSYYSYTI	761	SSYFPWVGGF	835
13009	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYFPI	647	LSYSSI	344	SISPYYSYTS	758	SSRFPWFYGL	836
13010	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YDFLI	648	ISYSSM	358	SISSYYGYTS	555	SSYFPWFSAL	830
13394	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYILI	641	LFYASM	698	SISSYYGYTS	555	SSYFPWFSAM	815
13395	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYYLI	640	ISYSSI	363	SISPYYGFTL	762	SSYFPWFSAM	815
13396	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYFPI	647	IAYASI	699	SISSYYSYTY	763	SSYFPWFSAM	815
13397	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYFPI	647	ITYSSI	361	SISSYYGYTA	764	SSYFPWSSAM	837
13398	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	NSFLI	649	ISRSSI	700	GISSYYGYTR	765	SHYFPWLSAL	838

Table 4
LRP6 – antibody

			LRP6 binding antibodies CDRs											
Antibody ID	**Library**	**Antigen**	**L1**	**SEQ ID NO:**	**L2**	**SEQ ID NO:**	**L3**	**SEQ ID NO:**	**H1**	**SEQ ID NO:**	**H2**	**SEQ ID NO:**	**H3**	**SEQ ID NO:**
13399	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYNPI	650	ISYASI	701	SISPYYGYTR	766	ASYYPWFSAM	839
13400	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YGFLI	651	LDYSSI	702	SISPYYSYTT	767	SSYIPWRYAI	840
13401	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYFLI	624	ISYSSI	363	SISPYYSYTN	74	SSYFPWISAM	841
13402	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYFPI	647	IYYYSM	530	GISSYYSYTS	768	SSYFPWISAL	842
13403	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYFPI	647	ISYSSM	358	SISPYYSFTS	769	SSRFPWISGM	843
13404	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YNFLI	652	ISYSSI	363	SISSYYGFTS	68	SSYFPWFSAL	830
13405	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYFPI	647	ISYSSI	363	SISSYYGFTS	68	SPYFPWSSAL	844
13406	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYFPI	647	LSYSAI	703	YISPYYGYTY	65	ASYLPWFSAM	845
13407	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	SSFLI	653	LSGFGI	704	FISSYYGYTA	770	SSYLPWITAM	846
13408	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YVFLI	654	LSFASM	705	SISSYYGYTP	771	SAYFPWFAAL	847
13409	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYFPI	647	LAYNSI	706	SIFSYYSYTN	772	SSYFPWFSAM	815
13410	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	FYGPI	655	ISFSSI	357	SISSYYGYTL	773	SSYFPWFFAM	848
13411	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YFFLI	656	LYYSNI	707	YISSYYGYTS	774	SSYFPWFSAL	830
13412	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYGPI	657	IHYYSI	708	SISPYYSFTD	775	SSYFPWFSAM	815
13413	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YDFLI	648	ISFASI	709	SIYSYYSFTN	776	SSHFPWVSAL	849
13414	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYSPI	644	IYYSSM	378	SISPYYGYTS	557	SSYFPWVSAM	850
13415	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYFLI	624	LSYFSM	710	SIYSYYGFTN	777	SSHFPWFSAM	851
13422	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	FYGPI	655	LFYSSM	695	TISPYYGYTS	778	SSYFPWFSAL	830
13428	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YTLPI	658	ISFSSM	380	HISSYYGFTS	779	SSYFPWFSAL	830
13430	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YRFPI	659	ISYFSI	711	SISPYYSYTN	74	SSYFPWFSAI	852
13431	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YHLLI	660	LYYNSI	712	AIHPYYGYTS	780	SSRFPWFPAM	853
13432	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YSFPI	661	LSYASI	713	SISSYYGYTG	781	SSYFPWFSAM	815
13435	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YFLPI	662	LSYSSM	364	SISPYYGFTY	782	SSYFPWFSAL	830
13436	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYFPI	647	ISYASM	714	SISSYYGYTD	783	SSYVPWFYAL	854
13437	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YDNLI	663	ITYSSI	361	SISSYYGFTS	68	SSYFPWFSAM	815

Table 4
LRP6 – antibody

			LRP6 binding antibodies CDRs												
Antibody ID	**Library**	**Antigen**	**L1**	**SEQ ID NO:**	**L2**	**SEQ ID NO:**	**L3**	**SEQ ID NO:**	**H1**	**SEQ ID NO:**	**H2**	**SEQ ID NO:**	**H3**	**SEQ ID NO:**
13438	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YLFPI	664	ISYYSI	715	SIYSYYGYTT	784	ASYFPWFPAM	855
13439	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YFFPI	665	LSHSSI	716	SISSHYGYTH	785	SSYFPWFFAL	856
13440	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYIPI	666	IAYNSM	717	SISSYYSYTD	760	SSYFPWFSAL	830
13441	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	FNFLI	667	LSYSSI	344	YISSYYGYTA	786	SSYYPWFSAL	857
13442	2540AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YNYLI	668	LAYSSI	690	SISSYYGYTY	787	SSYLPWVSAL	858
12990	2542AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYWPI	623	ISLFFM	718	SIYSSYSYTS	788	SFNGAKKPYFSGWAM	859
12991	2542AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYWPI	623	IPSYFM	719	SIYSSYSYTA	789	NVVVSRKPYFFRSAM	860
12992	2542AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYWPI	623	ISSSYM	348	SIYSSYSYTG	790	TVPGSKRPYFASLAI	861
12993	2542AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYWPI	623	ISSYFI	720	SIYPSYSYTS	791	NVRGFRKPYFSRWAM	862
12994	2542AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYWPI	623	LSSYYM	721	SIYSRFSYTA	792	NVPGIKRPYFTAWAM	863
12995	2542AM	LRP6-Fc	SVSSA	1	SASSLYS	2	SYWPI	669	LHSYYI	722	NIYSSYGYTS	793	TIRGSKRPYFAASGL	864
12996	2542AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYWPI	623	LSSYYM	721	SIYSSYSYTS	788	TARENKKPYFSGWAM	865
12997	2542AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYRPI	670	IGSYYM	723	AIYSPYGYTS	794	TLPLSKKPYFSLWAF	866
12998	2542AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYWPI	623	LGSYYI	724	TIYSYYSYTS	795	TFHGSKKPYFSGRAM	867
12999	2542AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYWPI	623	LTSYYI	725	SIYPSYSYTS	791	SIRGSKKPYFSRLAL	868
13000	2542AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYWPI	623	ISTYYM	726	SIYPSYSYTS	791	SVRGSKKPYFSHWAM	869
13001	2542AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YYWPI	623	ISSNYI	548	SIYSSFGYTS	796	NVRTSKKPYFPLWAM	870
13011	2460AM	LRP6-Fc	SVSSA	1	SASSLYS	2	ASNNLI	671	IPLYTI	727	SISPSYSYTY	797	GVSGGSNYISIFRNSSGM	871
13012	2460AM	LRP6-Fc	SVSSA	1	SASSLYS	2	SSYSLI	130	IFSTSI	728	SITSAYSYTY	798	GGLSVSHYNYVVHSFKWG L	872
13013	2460AM	LRP6-Fc	SVSSA	1	SASSLYS	2	SAITPI	672	ISYSTM	729	SIVSSYSRTY	799	SCSSFCNYVSNYNARRA L	873
13014	2460AM	LRP6-Fc	SVSSA	1	SASSLYS	2	FSYSPF	673	LSSSGM	730	AIYPFDGYTY	800	GNARVSNYISSYYAWRA M	874
13015	2460AM	LRP6-Fc	SVSSA	1	SASSLYS	2	SSYNLI	674	FSSSSI	528	GIFSYFSYTY	801	GGYGFSYYNSVTFYRWA F	875

Table 4
LRP6 – antibody

			LRP6 binding antibodies CDRs											
Antibody ID	**Library**	**Antigen**	**L1**	**SEQ ID NO:**	**L2**	**SEQ ID NO:**	**L3**	**SEQ ID NO:**	**H1**	**SEQ ID NO:**	**H2**	**SEQ ID NO:**	**H3**	**SEQ ID NO:**
13016	2460AM	LRP6-Fc	SVSSA	1	SASSLYS	2	SYNFPF	675	IRGPSI	731	SISPFCGFTY	802	VGSGVCNSLHNYFYKRG M	876
13017	2460AM	LRP6-Fc	SVSSA	1	SASSLYS	2	SSTVPF	676	FSSTYM	732	SITPSYGYTN	803	SSSDISIDNSIRYTWGAM	877
13018	2460AM	LRP6-Fc	SVSSA	1	SASSLYS	2	SSYSLI	130	INSSFM	733	SISPSYGYTY	804	GHSGVTNFISFYYRRRA M	878
13019	2460AM	LRP6-Fc	SVSSA	1	SASSLYS	2	SNYSLF	677	IFGYSM	734	SIFPCCSNTY	805	GVSGLDNNRTASYSRMG M	879
13020	2460AM	LRP6-Fc	SVSSA	1	SASSLYS	2	STYSLI	678	FSSSTI	735	SIAPSFGHTY	806	GAASVNHIGSLYVSWRG L	880
13021	2460AM	LRP6-Fc	SVSSA	1	SASSLYS	2	SAFSLI	679	LSSSTM	736	SISPYYSYTR	807	HGSGLSHNATTSYYRSAI	881
13022	2460AM	LRP6-Fc	SVSSA	1	SASSLYS	2	SSYSLI	130	ISYTSI	737	SIFSTYSYTY	808	SSSAVSRNSIVYYSRTAM	882
13023	2460AM	LRP6-Fc	SVSSA	1	SASSLYS	2	SSYTPI	680	FSSSVM	738	SIAPSYSFTY	809	GVCRVSNYSSYFYSRGA M	883
13024	2460AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YSNSLI	681	ISYSTM	729	SITPYYSTTS	810	AISHVAHYDNVIYSKWGI	884
13025	2460AM	LRP6-Fc	SVSSA	1	SASSLYS	2	SSYSLI	130	IASYSM	739	FISPYHSYTD	811	GHSVLSNYVSIHYYWAG F	885
13026	8716AM	LRP6-Fc	SVSSA	1	SASSLYS	2	YWAYFSPI	682	FSYSSM	740	SISSRYGYTY	812	SWAM	586

EXAMPLE 3: Tetravalent binding antibody molecule formats

A. We generated various formats of tetravalent binding antibody molecules comprising pan-FZD and LRP5/6 antibody fragments, e.g., scFv, diabodies and Fab, on either end of an Fc domain, see Table 5 and Figure 6, and assayed their Wnt agonist activity. DNA fragments encoding antibody variable domains were either amplified by PCR from phagemid DNA template or were constructed by chemical synthesis (Twist Biosciences). The DNA fragments were cloned into mammalian expression vectors (pSCSTa). Bispecific diabodies and IgGs contained an optimized version of a "knobs-in-holes" heterodimeric Fc (Ridgway et al. Protein Eng. 9, 617–621 (1996)). Diabody domains were arranged in a VH-VL orientation with the variable domains separated by a short GGGGS linker (SEQ ID NO: 886), which favors intermolecular association between VH and VL domains and thus favors diabody formation. To produce diabody fusion constructs, the diabody chains were fused to human IgG1 Fc. Diabody-fc-diabody proteins were constructed as VH-x-VL-y-[human IgG1 Fc]-z-VH-x-VL where linkers are x= GGGGS (SEQ ID NO: 886), y= LEDKTHTKVEPKSS (SEQ ID NO: 887), and z= SGSETPGTSESATPESGGG (SEQ ID NO: 888). In this format, the human IgG1 Fc or knob-in-hole IgG1 Fc fragments spanned from position 234-478 (Kabat numbering). For scFv-Fc fusions, the variable domains were arranged in a VL-VH orientation and were connected by a long GTTAASGSSGGSSSGA linker (SEQ ID NO: 889), which favors intramolecular association between VH and VL domains and thus favors scFv formation. Variants with a Fab domain fused to the C-terminus of the Fc were generated via chemical synthesis (Twist Biosciences). For all constructs, the entire coding region was cloned into a mammalian expression vector in frame with the secretion signal peptide.

These various of tetravalent binding antibody molecules comprising pan-specific FZD and LRP5/6 antibody fragments were tested in a TOPFLASH assay to monitor beta catenin-mediated gene reporter activity. Proteins were compared against the native ligand Wnt3a. Assays were performed by plating TOPFLASH cells to ~70% confluency in a 96-well tissue culture treated plate. Agonists were diluted in DMEM to provide a final assay concentration of 0.046 nM – 100 nM and cells were treated overnight at 37°C under 5% CO_2. Luciferase expression was quantified using the Dual-Luciferase Reporter Assay System (Promega) in 96-well black plates in accordance with the manufacturer's instructions. Briefly, HEK293T cells were transduced with lentivirus coding for the pBARls reporter (Biechele and Moon in *Wnt Signaling: Pathway Methods and Mammalian Models*, E. Vincan, Ed. (Humana Press, Totowa,

NJ, 2008), pp. 99–110) and with Renilla Luciferase as a control to generate a Wnt-βcatenin signaling reporter cell line. 1-2 x 10^3 cells in 120 µl were seeded in each well of 96-well plates for 24 hours prior to transfection or stimulation. The following day, FZD Agonists or Ab protein was added, and following 15-20 hours of stimulation, cells were lysed and luminescence was measured in accordance with the dual luciferase protocol (Promega) using an Envision plate reader (PerkinElmer). For the FZD4 Agonist assay, FZD4 cDNA was transfected for 6 hours prior to adding the FZD Agonist. For the Wnt inhibition assays, Wnt1 was introduced by cDNA transfection or WNT3A protein was applied for 6 hours prior to the addition of Ab protein. All assays were repeated at least three times. The results are presented in Table 5. As shown in Table 5, each of the tetravalent formats activate FZD signaling to differing degrees when clustering FZD4 and LRP5. These formats were also evaluated for stability, homogeneity and yield production from Expi293 (Figures 3 and 9). From these analyses, the Diabody-Fc-Fab format provides the best balance of activity, expression, stability. Finally, we applied the same modality arrangement for FZD5 and LRP6 and we observed potent agonist activity. The results in Table 5 show that the various tetravalent modalities elicit WNT agonism and that engagement of 2 LRP5/6 epitopes produces WNT signaling activity (maxima) higher than with 1 LRP5/6 epitope.

Table 5

Molecule	Modality	Paratopes	Binding specificity (Paratope Stoichiometry)	Topflash EC50 (nM) Avg	Stdev	% Wnt Maxima Avg	Stdev
Wnt3a	Recombinantly produced ligand	NA	FZD/LRP	6	3	100%	ND
CM0011	FZD Diabody-Fc-LRP Diabody	5019 (FZD Diabody); 2539, 2542 (LRP diabody)	FZD1/2/4/5/7/8, LRP6[1], LRP6[3] (2:1:1)	0.3	0.1	63%	10%
ANT-4	FZD Diabody-Fc-LRP Fab	5016(FZD Diabody); 2540,2542 (LRP Fab)	FZD1/2/4/5/7/8, LRP6[1], LRP6[3] (2:1:1)	0.5	0.1	63%	6%
ANT-5	FZD Diabody-Fc-LRP Fab	5016(FZD Diabody); 2540,2542 (LRP Fab)	FZD1/2/4/5/7/8, LRP6[1], LRP6[3] (2:1:1)	0.5	0.1	59%	8%
CT0001	FZD IgG-LRP Diabody	5016(FZD IgG); 2539,2542 (LRP Diabody)	FZD1/2/4/5/7/8, LRP6[1], LRP6[3] (2:1:1)	0.3	0.1	57%	17%
CT0002	LRP Diabody-Fc-FZD scFv (VL-VH)	2539, 2542 (LRP Diabody); 5016 (FZD scFv)	FZD1/2/4/5/7/8, LRP6[1], LRP6[3] (2:1:1)	0.5	0.1	55%	22%
CM0126	FZD Diabody-Fc-LRP Diabody	5016(FZD Diabody); 2539, 2542 (LRP Diabody)	FZD1/2/4/5/7/8, LRP6[1], LRP6[3] (2:1:1)	0.3	0.2	52%	1%
ANT-1	LRP Diabody-Fc-FZD Fab	2540, 2542 (LRP Diabody); 5016 (FZD Fab)	FZD1/2/4/5/7/8, LRP6[1], LRP6[3] (2:1:1)	0.7	0.5	49%	22%
CT0003	FZD Diabody-Fc-LRP scFv	5016 (FZD Diabody); 2539, 2542 (LRP scFv)	FZD1/2/4/5/7/8, LRP6[1], LRP6[3] (2:1:1)	0.4	0.1	42%	16%
ANT-2	LRP Diabody-Fc-FZD Fab	2540, 2542(LRP Diabody); 5016(FZD Fab)	FZD1/2/4/5/7/8, LRP6[1], LRP6[3] (2:1:1)	0.3	0.1	38%	25%
CM0042	FZD Diabody-Fc-LRP Diabody	5019(FZD Diabody); 2539 (LRP Diabody)	FZD1/2/4/5/7/8, LRP6[3] (2:2)	0.9	0.8	33%	22%
CM0302	FZD IgG-LRP Diabody	5056(FZD IgG)-2539(LRP Diabody)	FZD1/2/4/5/7/8/10, LRP6[3] (2:2)	0.3	0.2	18%	8%
CM0303	FZD IgG-LRP scFv	5056(FZD IgG); 2539(LRP scFv)	FZD1/2/4/5/7/8/10, LRP6[3] (2:2)	3.7	2.1	17%	13%
CM0299	FZD IgG-LRP Diabody	5016(FZD IgG)-, 2539(LRP Diabody)	FZD1/2/4/5/7/8, LRP6[3] (2:2)	0.1	0.1	14%	5%

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Table 5 Cont'

Molecule	Modality	Paratopes	Binding specificity (Paratope Stoichiometry)	Topflash EC_{50} (nM) Avg Stdev		% Wnt Maxima Avg	Stdev
Wnt3a	Recombinantly produced ligand	NA	FZD/LRP	6	3	100%	ND
CM0300	FZD IgG-LRP scFv	5016(FZD IgG)-, 2539(LRP scFv)	FZD1/2/4/5/7/8, $LRP6^3$ (2:2)	0.3	0.2	5%	2%
CM0301	FZD IgG-LRP scFv	5016(FZD IgG)-, 2542(LRP scFv)	FZD1/2/4/5/7/8, $LRP6^1$ (2:2)	0.2	0.2	1%	1%
CM0156	Diabody-Fc-Diabody	4275	no FZD/LRP binding	NA	NA	NA	NA
4275	IgG	4275	no FZD/LRP binding	NA	NA	NA	NA

B. Diabody-Fc-Fab format FZD4 Agonists.

FZD Agonists having a bispecific LRP5-binding diabody and a FZD4 binding domain comprising FZD4-binding Fabs (FZD4 Agonists), a FZD5 binding domain comprising FZD5-binding Fabs (FZD5 Agonists), or a FZD binding domain that binds multiple FZD (pan-FZD Agonist) were generated using a knob-in-holes system. Briefly, the constructs were generated by chemical synthesis (Twist Biosciences) or by standard molecular biology techniques in a mammalian expression vector (pSCSTa). Diabody constructs were arranged in a VH-VL manner with a short (GGGGS (SEQ ID NO: 886)) linker linking the VH and VL to favor intermolecular pairing. For bispecific diabody arrangements, the variable domains for paratopes A and B, respectively, were arranged as VH(A) – VL(B) on the Hole Fc chain and VH(B)-VL(A) on the Knob Fc chain to facilitate proper paratope formation. Diabodies were fused to the N-terminus of an optimized knob-in-holes heterodimeric Fc (Ridgway et al. Protein Eng. 9, 617–621 (1996) via a GGGGSGGGGSEPKSS linker (SEQ ID NO: 890). The Fc region also contains the effector-null mutations D278A and N314G (Kabat numbering), corresponding to D655A/N297G (EU numbering). Fab domains were fused to the C-terminus of the heterodimeric Fc via a GGGSGGGSGGGSGGGSGSTG linker (SEQ ID NO: 891). Directly to this linker was fused the N-terminus of the Fab VH domain followed by CH1, terminating at T238 (Kabat numbering). This Fab pairs with a standard kappa light chain which was cloned as described above. For all constructs, the entire coding region was cloned into a mammalian expression vector in frame with the secretion signal peptide.

In addition, Diabody-fc-Fab formats were constructed as VH-x-VL-y-[human IgG1 Fc]-z-VH where linkers are x= GGGGS (SEQ ID NO: 886), y= GGGGSGGGGSEPKSSDKTHT (SEQ ID NO: 892), and z= GGGSGGGSGGGSGGGSGSTG (SEQ ID NO: 891). Diabody domains were arranged in a VH-VL orientation with the variable domains separated by a short GGGGS linker (SEQ ID NO: 886), which favors intermolecular association between VH and VL domains and thus favors diabody formation. Further, the Fc region may exhibit attenuated effector functions due amino acid mutations to N297G and D265A (DANG) variants or L234A, L235A, P331S (LALAPS) variants, and with the Fc region further comprising knob-in-hole heterodimerization variants Merrimack, Merchant or Merchant S:S.

Figure 7 is an illustration of the Diabody-Fc-Fab format FZD4 Agonists having a LRP5 binding domain comprised of a diabody that is bivalent and bispecific for LRP5 and a FZD4

binding domain comprised of two FZD4 binding Fab fragments formed by a VL and CL1 of the light chain construct pairing with the VH and CH1 of each of the heavy chain hole and heavy chain knob constructs. Table 12 presents the amino acid sequences of heavy chains and light chains of FZD4 Agonists ANT's (Diabody-Fc-Fab format): the heavy chain knob construct (ANT16 knob), the heavy chain hole construct (ANT hole) and the light chain construct. The light chain and heavy chain variable CDRs are in bold underlined italics.

Figure 16A depicts Diabody-Fc-Fab format FZD4 Agonists having Fc regions with attenuated effector functions due to amino acid mutations, e.g., N297G (NG) and D265A, (DANG) variants, and/or LALAPS variants, and with the Fc region further comprising knob-in-hole heterodimerization variants Merrimack, Merchant or Merchant S:S

B. IgG-Diabody format FZD4 Agonists.

FZD Agonists having two FZD-binding Fabs forming an N-terminal binding domain and a bispecific LRP5/6 binding diabody forming the C-terminal binding domain and an Fc domain were generated using a knob-in-holes system. IgG-Diabody proteins were constructed as VH-[human IgG1 Fc]-y- VH-x-VL where linkers are x= GGGGS (SEQ ID NO: 886) and y= GGGSGGGSGGGSGGGSGSTG (SEQ ID NO: 891).

Figure 15 presents an illustration of the IgG-Diabody format FZD4 Agonists having an FZD binding domain comprising two Fab fragments attached to the N- terminus of the Fc domain with each Fab binding an FZD. The LRP5/6 co-receptor binding domain is attached to the C-terminus of the Fc domain and is composed of a diabody that binds two different sites on the co-receptor, e.g., a Wnt1 site (E1-E2) and a Wnt3 site (E3-E4) on LRP5/6. The Fabs may be specific for a particular FZD, e.g. FZD4, or may be pan-specific, binding to more than one FZD, e.g., to FZD4 and one or more other FZD.

Figure 16B depicts IgG-Diabody FZD4 Agonists having Fc regions with attenuated effector functions due to amino acid mutations, e.g., N297G (NG) and D265A, (DANG) variants, and/or LALAPS variants, and with the Fc region further comprising knob-in-hole heterodimerization variants Merrimack, Merchant or Merchant S:S. Table 13 presents the amino acid sequences of heavy chains and light chains of FZD4 Agonist, ANT39 (Diabody-Fc-Fab format) and ANT39wi (IgG-Diabody format): the heavy chain knob construct (ANT39 and ANT39i knob), the heavy chain hole construct (ANT39 and ANT39i hole) and the light chain construct. Also included in Table 13 are amino acid sequences of heavy chains

and light chains of FZD4 Agonist, ANT39 and ANT39i variants DANG, LALAPS, LALAPS Merchant and LALAPS Merchant S-S. The light chain and heavy chain variable CDRs are in bold underlined italics.

Table 6A	LRP5 Diabody Site 1						LRP5 Diabody Site 2				
Molecule	[1]	[2]	SEQ ID NO	[3]	SEQ ID NO	[4]	SEQ ID NO	[5]	SEQ ID NO	[6]	SEQ ID NO
		CDR-H1		CDR-H2		CDR-H3		CDR-L2		CDR-L3	
ANT16-Hole	D	FSSSSI	528	SISSSYGYTY	553	SWAM	586	SASDLYS	491	YAGAGLI	510
ANT16-Knob	D	FTAYAM	536	SIYPSGGYTA	566	RSYYFAL	603	SASSLYS	2	YWAYYSPI	493
ANT18-Hole	N	LSYYYM	527	SIYSSYGYTY	552	WSHVSGHYSGM	584	SASSLYS	2	SSYSLI	130
ANT18-Knob	N	FSSSSI	528	SISSSYGYTY	553	GGSGVSHYGSVYYSWWAL	585	SASSLYS	2	ASYAPI	492
ANT20-Hole	N	LSYYYM	527	SIYSSYGYTY	552	WSHVSGHYSGM	584	SASDLYS	491	YAGAGLI	510
ANT20-Knob	D	FTAYAM	536	SIYPSGGYTA	566	RSYYFAL	603	SASSLYS	2	ASYAPI	492
ANT21-Hole	N	FSSSSI	528	SISSSYGYTY	553	SWAM	586	SASSLYS	2	SSYSLI	130
ANT21-Knob	N	FSSSSI	528	SISSSYGYTY	553	GGSGVSHYGSVYYSWWAL	585	SASSLYS	2	YWAYYSPI	493
ANT36-Hole	N	LSYYYM	527	SIYSSYGYTY	552	WSHVSGHYSGM	584	SASSLYS	2	SSYSLI	130
ANT36-Knob	N	FSSSSI	528	SISSSYGYTY	553	GGSGVSHYGSVYYSWWAL	585	SASSLYS	2	ASYAPI	492
ANT39-Hole	D	FSSSSI	528	SISSSYGYTY	553	SWAM	586	SASDLYS	491	YAGAGLI	510
ANT39-Knob	D	FTAYAM	536	SIYPSGGYTA	566	RSYYFAL	603	SASSLYS	2	YWAYYSPI	493
ANT42-Hole	D	FSSSSI	528	SISSSYGYTY	553	SWAM	586	SASDLYS	491	YAGAGLI	510
ANT42-Knob	D	FTAYAM	536	SIYPSGGYTA	566	RSYYFAL	603	SASSLYS	2	YWAYYSPI	493

In all the molecules the LRP5 Diabody site 2 CDR-L1 is SVSSA (SEQ ID NO: 1)

Table 6B		FZD4 FAb							
Molecule	[7]	[8]	SEQ ID NO:	[9]	SEQ ID NO:	[10]	SEQ ID NO:	[11]	SEQ ID NO:
		CDR-H1		CDR-H2		CDR-H3		CDR-L3	
ANT16-Hole	T	LSSYSM	24	YISSYYGYTY	51	PAPGHWGF	79	WYYAPI	3
ANT16-Knob	T	LSSYSM	24	YISSYYGYTY	51	PAPGHWGF	79	WYYAPI	3
ANT18-Hole	T	LSSYSM	24	YISSYYGYTY	51	PAPGHWGF	79	WYYAPI	3
ANT18-Knob	T	LSSYSM	24	YISSYYGYTY	51	PAPGHWGF	79	WYYAPI	3
ANT20-Hole	T	LSSYSM	24	YISSYYGYTY	51	PAPGHWGF	79	WYYAPI	3
ANT20-Knob	T	LSSYSM	24	YISSYYGYTY	51	PAPGHWGF	79	WYYAPI	3
ANT21-Hole	T	LSSYSM	24	YISSYYGYTY	51	PAPGHWGF	79	WYYAPI	3
ANT21-Knob	T	LSSYSM	24	YISSYYGYTY	51	PAPGHWGF	79	WYYAPI	3
ANT36-Hole	T	LSSYSM	24	YISSYDSITD	61	PAVGHMAF	90	WYNAPI	12
ANT36-Knob	T	LSSYSM	24	YISSYDSITD	61	PAVGHMAF	90	WYNAPI	12
ANT39-Hole	T	LSSYSM	24	YISSYDSITD	61	PAVGHMAF	90	WYNAPI	12
ANT39-Knob	T	LSSYSM	24	YISSYDSITD	61	PAVGHMAF	90	WYNAPI	12
ANT42-Hole	T	SDFYFI	164	TIYPFIGNTY	194	AFPGSYHPF	220	STGSLI	135
ANT42-Knob	T	SDFYFI	164	TIYPFIGNTY	194	AFPGSYHPF	220	STGSLI	135

In all the molecules the FZD FAB CDR-L1 and CDR-L2 are respectively SVSSA (SEQ ID NO: 1) and SASSLYS (SEQ ID NO: 2)

Table 6C	LRP6 Diabody Site 1						LRP6 Diabody Site 2				
Molecule	[1]	[2]	SEQ ID NO	[3]	SEQ ID NO	[4]	SEQ ID NO	[5]	SEQ ID NO	[6]	SEQ ID NO
		CDR-H1		CDR-H2		CDR-H3		CDR-L2		CDR-L3	
ANT59-Hole	D	ISSYFI	720	SIYPSYSYTS	791	NVRGFRKPYFSRWAM	862	SASSLYS	2	YFFPI	665
ANT59-Knob	D	LSHSSI	716	SISSHYGYTH	785	SSYFPWFFAL	856	SASSLYS	2	YYWPI	623
ANT9-Hole	D	ISSYFI	720	SIYPSYSYTS	791	NVRGFRKPYFSRWAM	862	SASSLYS	2	YFFPI	665
ANT9-Knob	D	LSHSSI	716	SISSHYGYTH	785	SSYFPWFFAL	856	SASSLYS	2	YYWPI	623

In all the molecules the CDR-L1 of all LRP abs are SVSSA (SEQ ID NO: 1)

Table 6D	FZD Paratope											
Molecule	FZD Specificity		7	H1 (8)	SEQ ID NO	H2 (9)	SEQ ID NO	H3 (10)	SEQ ID NO	L3 (11)	SEQ ID NO
				CDR-H1		CDR-H2		CDR-H3		CDR-L3	
ANT59-Hole	5		N	IAYSSM	365	TIYPSYSSTY	462	YYAM	484	AHYFPI	285
ANT59-Knob	5		N	IAYSSM	365	TIYPSYSSTY	462	YYAM	484	AHYFPI	285
ANT9-Hole	1,2,4,5,7,8		N	IHSSSI	893	ATYSSFGSIT	894	YHHPFGYAL	895	GVYLF	896
ANT9-Knob	1,2,4,5,7,8		N	IHSSSI	893	ATYSSFGSIT	894	YHHPFGYAL	895	GVYLF	896

In all molecules the CDR-L1 for FZD FAB are SVSSA (SEQ ID NO: 1) and CDR-L2 are SASSLYS (SEQ ID NO: 2)

C. FZD Agonists are highly specific for FZD4, bind with high specificity and are stable in solution.

Using biolayer interferometry (BLI) we have found that FZD4 Agonists described herein are highly specific for FZD4 over other FZD receptors. Recombinant FZD ECD proteins were immobilized on BLI sensors. The FZD4 Agonists in the Diabody-Fc-Fab format, having a LRP5 binding domain comprised of a diabody that is bivalent and bispecific for LRP5 and a FZD4 binding domain comprised of two FZD4 binding Fab fragments, were tested at a concentration of 100 nM in a buffer of PBS+0.05% Tween-20 and 1% BSA for binding to the ECD proteins. The results are presented in Figure 8A. Controls in the assay included CM0199, a diabody-Fc-diabody format FZD agonist that recognizes FZD4 and LRP5 and Immunoglobulin 4275, which is an IgG that does not bind FZD or LRP.

The FZD4 Agonists also did not recognize common non-specific antigens. The FZD4 Agonists were tested at 100 nM for binding to a panel of antigens essentially as described in Monquet et al. "Polyreactivity increases the apparent affinity of anti-HIV antibodies by heteroligation" Nature 2010 Sep 30;467(7315):591-5(PMC3699875), and Jain et al., "Biophysical properties of the clinical-stage antibody landscape" Proc Natl Acad Sci 2017 Jan 31;114(5):944-949. (PMC5293111). Controls in the assay included CM0199, a diabody-Fc-diabody format FZD agonist that recognizes FZD4 and LRP5 and immunoglobulin 6606, which is an IgG that is particularly prone to non-specific binding in this assay. The results are presented in Figures 8B.

The FZD4 Agonists comprising binding domains for FZD4 and LRP5 bind both FZD4 and LRP5 with high affinity. The apparent affinity of the FZD4 Agonists for recombinant ECD of FZD4 were determined by biolayer interferometry essentially as described in Elife. 2019 Aug 27; 8: e46134., Briefly, BLI assays were performed using an Octet HTX instrument (ForteBio). For measuring binding to antigen, FZD-Fc proteins were captured on AHQ BLI sensors (18–5001, ForteBio) to achieve a BLI response of 0.6–1 nm and remaining Fc-binding sites were saturated with human Fc (009-000-008, Jackson ImmunoResearch). FZD-coated or control (Fc-coated) sensors were transferred into 100-0.1 nM tetravalent FZD agonist in assay buffer (PBS, 1% BSA, 0.05% Tween20) and association was monitored for 300 s. Sensors were then transferred into assay buffer and dissociation was monitored for an

additional 300 s. Shake speed was 1000 rpm and temperature was 25°C. The results are presented in Table 7.

Table 7		
Molecule	FZD4 KD (nM)	LRP5 EC50 (nM)
CM0199	0.7	7.5
ANT16	0.6	1.4
ANT18	2.6	ND
ANT20	0.7	ND
ANT21	2.2	ND
ANT36	<0.1*	ND
ANT39	0.3	ND

The FZD4 Agonists were also analyzed by SEC as compared to trastuzumab IgG. The results are presented in Figure 9A and demonstrate that the diabody-Fc-Fab format Agonists are stable and homogenous in solution.

The FZD4 Agonists are also stable in solution. Purified FZD4 Agonists, ANT16, ANT18, ANT20, ANT21 and ANT 36 were resuspended to 1 mg/ml (except for ANT18, which was resuspended at 0.34 mg/ml) in 10 mM Histidine, 140 mM NaCl, 0.9% sucrose, pH 6 and stored either at 4°C or 40°C for a period of 6 days. Samples were removed at various time points, centrifuged to remove precipitated protein and residual protein concentration was measured. The results are presented in Tables 8 and 9.

Table 8

	Soluble Protein Remaining (%)			
Time at 40 degrees (days)	**0**	**1**	**2**	**6**
CM0199	100%	60%	64%	40%
ANT-16	100%	102%	104%	104%
ANT-18	100%	92%	83%	105%
ANT-20	100%	97%	67%	104%
ANT-21	100%	102%	75%	102%
ANT-36	100%	100%	149%	106%

Table 9		
	Active Protein Remaining (%)	
Time at 40 degrees (days)	0	6
CM0199	100%	42%
ANT-16	100%	34%
ANT-18	100%	42%
ANT-20	100%	30%
ANT-21	100%	25%

On Day 6, the amount of FZD4-specific binding sites remaining in the samples were quantified using BLI. Analysis by differential scanning fluorimetry showed that the FZD4 Agonists having a Diabody-Fc-Fab formats with an LRP-binding diabody on the N-terminal of the Fc domain and two FZD4-binding Fabs on the C-terminal of the Fc domain, have thermal denaturation profiles similar to that of Trastuzumab. IgGs generally display two peaks in a thermal stability assay, the first corresponding to CH2, the later to the Fab domain and CH3, see Figure 9B.

The FZD4 Agonists were also assayed for induction of the beta-catenin target gene *AXIN2* in a mouse endothelial cell line (bEND3.1) and were shown to induce transcription in a concentration dependent manner. These results are presented in Figure 10.

TABLE 10			
Antibody No.		FZD recognized	Co-Receptor recognized
5019		FZD1, FZD2, FZD4, FZD5, FZD7, FZD8	
5027		FZD4	
5044		FZD4	
5016		FZD1, FZD2, FZD4, FZD5, FZD7, FZD8	
5056		FZD1, FZD 2, FZD 4, FZD5, FZD7, FZD8, FZD10	
2459			LRP5-W3
2460			LRP5-W1
8716			LRP5-W3

TABLE 10

Antibody No.		FZD recognized	Co-Receptor recognized
12600			LRP5-W1
12608			LPR5-W1
2539			LRP6-W3
2540			LRP6-W3
2542			LRP6-W1
CM0199		FZD4	LRP5
6066		N/A Positive control for non-specificity assay	
4275		no FZD/LRP binding	

EXAMPLE 4. The FZD4 agonist was assayed for its ability to oppose the effect on cell junction disassembly and increased permeability mediated by VEGF, a cytokine released during tissue hypoxia. VEGF treatment of bEND3.1 cells leads to junction disassembly as seen by loss of plasma membrane staining of CLDN3, CLDN5 and ZO-1. Co-treatment of cells with VEGF and the FZD4 agonist leads to a near-complete rescue of this effect (Fig. 11). This decrease cell-cell junction stability mediated by VEGF treatment translates into increase endothelial cell permeability as monitor in a transendothelial permeability assay measuring the passage of 40-kDa FITC-dextran across a confluent endothelial monolayer of bEnd.3 grown on transwell filters. Co-treatment of cells with VEGF and the FZD4 agonist completely rescues that VEGF-mediated increase in cell permeability. These results indicate that the FZD4 agonist promotes endothelial cell barrier functions in a mechanism independent of VEGF.

A) Immunofluoresence of ZO-1 (green)/CLDN3(red) and ZO-1 (green)/CLDN5(red) localization on bEnd.3 cell junctions. bEnd.3 cells were treated or not with 30nM of F4L5.13 (aka CM0199) and Norrin in the presence or absence of VEGF (100ng/ml) for 1h. DAPI (blue) stain the nucleus. B) Transendothelial permeability was determined by measuring the passage of FITC-dextran through the bEnd.3 monolayer. Passage of FITC-dextran was measured after bEnd.3 treatment with VEGF (100ng/ml) and F4L5.13 (30nM) alone or

simultaneously or upon pre-treatment with VEGF for 1h followed by F4L5.13 treatment for 1h. Error bar indicate SEM, n=5. The results are presented in Figure 11.

EXAMPLE 5. New FZD5 antibodies bind FZD5 at a site overlapping with 2919 identified from affinity maturation libraries.

Single point ELISAs were performed on 96-well Maxisorp plates coated with the ECDs of human FZD5 protein in the presence or absence of a saturating concentration of 2919 IgG. The plates were incubated with the monoclonal Fab-phage followed by incubation with horseradish peroxidase (HRP)-conjugated anti-M13 antibody. Wells were subsequently washed 8 times followed by incubations with 3,3,'5,5'-tetramethylbenidine/H_2O_2 peroxidase (TMB) substrate for 5-10 min. the reaction was stopped by adding 1M H_3PO_4 and the absorbance was measured spectrophotometrically at 450 nm in a microtiter plate reader. The results are presented in Figure 12.

EXAMPLE 6. New FZD5 antibodies from 2928 affinity maturation library selectively bind FZD5.

Single point ELISAs were performed on 96-well Maxisorp plates coated with the ECDs of human FZD2, FZD5, or FZD8 protein. The plates were incubated with the monoclonal Fab-phage followed by incubation with horseradish peroxidase (HRP)-conjugated anti-M13 antibody. Wells were subsequently washed 8 times followed by incubations with 3,3,'5,5'-tetramethylbenidine/H_2O_2 peroxidase (TMB) substrate for 5-10 min. the reaction was stopped by adding 1M H_3PO_4 and the absorbance was measured spectrophotometrically at 450 nm in a microtiter plate reader. The results are presented in Figure 13.

EXAMPLE 7. Pan-FZD/LRP6 ANT9 and FZD5-specific/LRP6 ANT9 activate Wnt signaling in cells.

TOPFLASH HEK293 cells were treated overnight with varying concentrations of FZD agonist or a non-targeting control molecule (CM0156) and TCF/LEF-driven luciferase expression was measured using a standard luciferase assay. Both molecules are able to activate FZD-mediated luciferase expression in a concentration-responsive manner. ANT9,

which is able to bind to 7 of the 10 FZD receptor subtypes produces a higher maximal activation signal than the FZD5-specific ANT59.

In vivo Experiments

DSS induced colitis model

In figure 24, C57/BL6 mice were given 2% DSS in the drinking water for 7 days and 0.5% DSS for an additional 3 days to induce colitis. Control-FLAg, Pan-FLAg and ANT59 were administered via intraperitoneal injection on days 4 and 7 at a dosage of 10 mg/kg. Mice were weighed daily. On day 10 mice were euthanized and tissues were harvested for measurement of colon length and histology.

Histology

For histological analysis, harvested tissues were fixed in 4% paraformaldehyde and embedded in paraffin. Sections of 5 μm were stained with haematoxylin and eosin (H&E). Images were captured using a Nikon Eclipse microscope (figure 23).

Organoid Culture and Viability Measurement

Small intestine crypts were harvested from 8-week-old, female, C57BL/6 mice and cultured as previously described (O'Rourke et al., 2016). Organoid cultures were passaged and embedded in 25 μl Growth Factor Reduced Matrigel (Corning, 356231) and plated in triplicates in a 48-well plate. Organoid cultures were treated with DMSO, 1 μM LGK974, 1 μM LGK974 +50% WNT3A conditioned media, 1 μM LGK974 +30 nM Pan-FLAg, 1 μM LGK974 +30 nM FZD2-FLAg, 1 μM LGK974 +30 nM FZD4-FLAg, 1 μM LGK974 +30 nM FZD5-FLAg, 1 μM LGK974 +30 nM FZD7-FLAg. Treatments were prepared in 250 μl of complete media, added to each well on day of passaging and changed every 2–3 days. At the endpoint (7 days), 150 μl Cell Titer-Glo3D (Promega) was added to 150 μl media in each well. Organoids were lysed on a rocking platform for 30 min at room temperature. The luminescence reading was measured in duplicates for 20 μl lysate from each well on the Envision multilabel plate reader. The average luminescence reading for each condition was normalized to the control condition to calculate relative viability (figure 22).

EXAMPLE 8. Transient expression of 8 ANT39 variants. A series of eight ANT39 variants (Figures 16A and 16B) were transiently expressed in CHO cells using standard manufacture

lipid based protocols (ThermoFisher). Briefly cells were grown to a density of approximately 2.0 x106 cells/ml in growth media and relevant DNAs were transfected with appropriate transfection reagent. For each variant two alternate input plasmid ratios were tested, either 1:1:2 or 2:1:3 (knob heavy chain : hole heavy chain : light chain). Conditioned media was harvested 7 days later, purified by Protein A Sepharose and the titre measured.

Table 11

Molecule	**DNA Ratio (Knob:Hole:LC)**	**Titer (mg/L)**
ANT39	1:1:2	390
	2:1:3	290
ANT39i	1:1:2	260
	2:1:3	250
ANT39 LALAPS	1:1:2	330
	2:1:3	250
ANT39i LALAPS	1:1:2	300
	2:1:3	270
ANT39 LALAPS Merchant	1:1:2	340
	2:1:3	280
ANT39i LALAPS Merchant	1:1:2	240
	2:1:3	280
ANT39 LALAPS Merchant S:S	1:1:2	320
	2:1:3	190
ANT39i LALAPS Merchant S:S	1:1:2	300
	2:1:3	250
ANT42*	1:1:2	107
ANT42 LALA*	1:1:2	287
ANT42 LALAPS*	1:1:2	95
ANT42i LALAPS*	1:1:2	49

*Variants were transiently expressed in HEK293 cells

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, numerous equivalents to the specific procedures described herein. Such

equivalents are considered to be within the scope of the inventions. Various substitutions, alterations and modifications may be made to the invention without departing from the spirit and scope of the invention. Other aspects, advantages, and modifications are within the scope of the invention.

The contents of all references, issued patents, and published patent applications cited through this application are hereby incorporated by reference. The appropriate component, process and methods of those patents, applications and other documents may be selected for the invention and embodiments thereof.

Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer, step, group of integers or group of steps but not to the exclusion of any other integer, step, group of integers or group of steps.

To clarify the use of and to hereby provide notice to the public, the phrases "at least one of <A>, <B>, ... and <N>" or "at least one of <A>, <B>, ... or <N>" or "at least one of <A>, <B>, ... <N>, or combinations thereof" or "<A>, <B>, ... and/or <N>" are defined by the Applicant in the broadest sense, superseding any other implied definitions hereinbefore or hereinafter unless expressly asserted by the Applicant to the contrary, to mean one or more elements selected from the group comprising A, B, ... and N. In other words, the phrases mean any combination of one or more of the elements A, B, ... or N including any one element alone or the one element in combination with one or more of the other elements which may also include, in combination, additional elements not listed. Unless otherwise indicated or the context suggests otherwise, as used herein, "a" or "an" means "at least one" or "one or more."

Table 12
Diabody-Fc-Fab amino acid sequences of the "heavy chain" hole construct, "heavy chain" knob construct and the "light chain" construct of the FZD4 Agonists, ANT16, ANT18, ANT20, ANT21, ANT39, and ANT42.

The CDRs of the chains are underlined, italicized. The CDRs may be replaced with the CDRs of another antibody to alter the binding specificity, e.g., the specificity could be altered to bind another site on the FZD or LPR5/6, or to another FZD or LPR.

FZD4 Agonist ANT16	
Knob Hc construct	EVQLVESGGGLVQPGGSLRLSCAASGF***DFTAYAM***HWVRQAPGKGLEWVA***SIYPSGGYTA***YADSVKGRFTISADTSKNTAYLQ MNSLRAEDTAVYYCAR***RSYYFAL***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGK APKLLIY***SASSLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YWAYYSPT***FGQGTKVEIKGGGSGGGGSEPKTSDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPMVFDLPPSREEMTKNQVSLWCMVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGGSGSTGEVQLVES GGGLVQPGGSLRLSCAASGF***TLSSYSM***HWVRQAPGKGLEWVA***YISSYYGYTY***YADSVKGRFTISADTSKNTAYLQMNSLRAED TAVYYCAR***PAPGHWGFD***YWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 897)
Hole Hc construct	EVQLVESGGGLVQPGGSLRLSCAASGF***DFSSSSY***HWVRQAPGKGLEWVA***SISSSYGYTY***YADSVKGRFTISADTSKNTAYLQMN SLRAEDTAVYYCAR***SWAMD***YWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKL LIY***SASDLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLT***FGQGTKVEIKGGGSGGGGSEPKSSDKTHTCPPCP APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDW LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPIRELMTSNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGGSTGEVQLVESGGGLVQ PGGSLRLSCAASGF***TLSSYSM***HWVRQAPGKGLEWVA***YISSYYGYTY***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYC AR***PAPGHWGFD***YWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 898)
Light Chain	DIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SASSLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYY CQQ***WYYAPT***FGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS TYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 899)

FZD4 Agonist ANT18	
Knob Hc construct	MNLLLILTFVAAAVAEVQLVESGGGMVQPGGSLRLSCAASGF***NFSSSSYH***WVRQAPGKGLEWVA***SYSSSYGYTY***YADSVKGR FTISADTSKNTAYLQMNSLRAEDTAVYYCAR***GGSGVSHYGSVYYSWWALD***YWGQGTLVTVSSGGGGSDIQMTQSPSSLSAS VGDRVTITCRASQ***SVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***ASYAPT***TFG QGTKVEIKGGGSGGGGSEPKTSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKN QVSLWCMVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SLSPGKGGGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF***TLSSYSM***HWVRQAPGKGLEWVA***YISSYY*** ***GYTTY***ADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***PAPGHWGF***DYWGQGTLVTVSSASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP KSCDKTHT (SEQ ID NO: 900)
Hole Hc construct	MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***NLSYYYM***HWVRQAPGKGLEWVA***SYTSSYGYTY***YADSVKG RFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***WSHVSGHYSGM***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVT ITCRASQ***SVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***SSYSLT***FGQGTKVEI KGGGGSGGGGSEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPIRELMTSNQVSLSCA VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGG GSGGGSGGGGSGGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF***TLSSYSM***HWVRQAPGKGLEWVA***YISSYYGYTY***YADS VKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***PAPGHWGF***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTH T (SEQ ID NO: 901)
Light Chain	MNLLLILTFVAAAVADIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGT DFTLTISSLQPEDFATYYCQQ***WYYAPT***TFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 902)

FZD4 Agonist ANT20	
Knob Hc construct	MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***DFTAYAM***HWVRQAPGKGLEWVA***SIYPSGGYTA***YADSVKGR FTISADTSKNTAYLQMNSLRAEDTAVYYCAR***RSYYFALD***YWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***S*** ***VSS4***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***ASYAPT***FGQGTKVEIKGGGSGG GGSEPKTSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY GSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPMVFDLPPSREEMTKNQVSLWCMVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGG GSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF***TLSSYSM***HWVRQAPGKGLEWVA***YISSYYGYTY***YADSVKGRFTISADTSKNT AYLQMNSLRAEDTAVYYCAR***PAPGHWGF***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 903)
Hole Hc construct	MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***NLSYYVM***HWVRQAPGKGLEWVA***SIYSSYGYTY***YADSVKGRF TISADTSKNTAYLQMNSLRAEDTAVYYCAR***WSHWSGHYSGM***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCR ASQ***SVSSA***VAWYQQKPGKAPKLLIY***SASDLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLT***FGQGTKVEIKGG GGSGGGGSEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPIRELMTSNQVSLSCAVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGG GSGGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF***TLSSYSM***HWVRQAPGKGLEWVA***YISSYYGYTY***YADSVKGRFTISADT SKNTAYLQMNSLRAEDTAVYYCAR***PAPGHWGF***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 904)
Light Chain	MNLLLILTFVAAAVADIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SASSLY***SGVPSRFSGSRSGTDF TLTISSLQPEDFATYYCQQ***WTYAPT***FGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 902)

FZD4 Agonist ANT21	
Knob He construct	MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***NFSSSSI***HWVRQAPGKGLEWVA***SISSSYGYTY***YADSVKGR FTISADTSKNTAYLQMNSLRAEDTAVYYCAR***GGSGVSHYGSVTYSWWAL***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSAS VGDRVTITCRASQ***SVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YWAYYSPT***T FGQGTKVEIKGGGGSGGGGSEPKTSDKTHTCPPCP*APELAGGPSVFLFPPKPKDTLAISRTPEVTCVVVAVSHEDPEVKFNWYVD* *GVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ*PREPMVFDLPPSREEMTKNQVSL WCMVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG KGGGSGGGGSGGGGSGGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF***TLSSYSM***HWVRQAPGKGLEWVA***YISSYYGYTY***Y ADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***P4PGHWGF***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCD KTHT (SEQ ID NO: 905)
Hole He construct	MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***NFSSSSI***HWVRQAPGKGLEWVA***SISSSYGYTY***YADSVKGR FTISADTSKNTAYLQMNSLRAEDTAVYYCAR***SWAM***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***S*** ***VSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***SSYSLT***FGQGTKVEIKGGGGSG GGGSEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPIRELMTSNQVSLSCAVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGG GSGGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF***TLSSYSM***HWVRQAPGKGLEWVA***YISSYYGYTTY***YADSVKGRFTISA DTSKNTAYLQMNSLRAEDTAVYYCAR***P4PGHWGF***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 906)
Light Chain	MNLLLILTFVAAAVADIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGT DFTLTISSLQPEDFATYYCQQ***WYYAPT***FGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 902)

FZD4 Agonist ANT39	
Knob Hc construct	MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***DFTAYAM***HWVRQAPGKGLEWVA***SIYPSGGYTA***YADSVK GRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***RSYYFAL***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITC RAS***QSVSSA***VAWYQQKPGKAPKLLIY***SASSLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YWAYYSPT***FGQGTKVE IKGGGGSGGGGSEPKTSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPMVFDLPPSREEMTKNQVSL WCMVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GKGGGSGGGSGGGSGGGSGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF***TLSSYSM***HWVRQAPGKGLEWVA***YISSYDSITD*** YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***P4VGHM4F***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS CDKTHT (SEQ ID NO: 907)
Hole Hc construct	MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***DFSSSSH***HWVRQAPGKGLEWVA***SISSSYGYTTY***ADSVKGR FTISADTSKNTAYLQMNSLRAEDTAVYYCAR***SWAM***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRAS***QS*** ***VSSA***VAWYQQKPGKAPKLLIY***SASDLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLT***FGQGTKVEIKGGG GSGGGGSEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPIRELMTSNQVSLSCAVKGF YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGG GSGGGSGGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF***TLSSYSM***HWVRQAPGKGLEWVA***YISSYDSITD***YADSVKGR FTISADTSKNTAYLQMNSLRAEDTAVYYCAR***P4VGHM4F***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 908)
Light Chain	MNLLLILTFVAAAVADIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SASSLY***SGVPSRFSGSRSG TDFTLTISSLQPEDFATYYCQQ***WYNAPT***FGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD NALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 909)

FZD4 Agonist ANT42

Knob Hc construct	MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAAASGF***DFTAYAM***HWVRQAPGKGLEWVA***SIYPSGGYTA***YADSVK GRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***RSYYFAL***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCR AS***QSVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YWAYYSPPT***FGQGTKVEIK GGGGSGGGGSEPKTSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLWCM VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGG GSGGGSGGGSGGGSGGSTGEVQLVESGGGLVQPGGSLRLSCAAASGF***TSDFYFI***HWVRQAPGKGLEWVA***TIYPFIGNTY***YADS VKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***AFPGSYHPF***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTH T (SEQ ID NO: 910)
Hole Hc construct	MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAAASGF***DFSSSSI***HWVRQAPGKGLEWVA***SISSSYGYTY***YADSVKGR FTISADTSKNTAYLQMNSLRAEDTAVYYCAR***SWAM***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***S VSSA***VAWYQQKPGKAPKLLIY***SASDLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLT***FGQGTKVEIKGGGG SGGGGSEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPIRELMTSNQVSLSCAVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGG SGGGSGGGSGGSTGEVQLVESGGGLVQPGGSLRLSCAAASGF***TSDFYFI***HWVRQAPGKGLEWVA***TIYPFIGNTY***YADSVKGRFT ISADTSKNTAYLQMNSLRAEDTAVYYCAR***AFPGSYHPF***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 911)
Light Chain	MNLLLILTFVAAAVADIQMTQSPSSLSASVGDRVTITCRASQ***SVSSAVA***WYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGT DFTLTISSLQPEDFATYYCQQ***STGSLI***TFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 912)

FZD5-LRP6 ANT 59	
Knob Hc construct	EVQLVESGGGLVQPGGSLRLSCAASGF***DLSHSSI***HWVRQAPGKGLEWVA***SISSHHYGYTHY***ADSVKGRFTISADTSKNTAYLQM NSLRAEDTAVYYCAR***SSYFPWFFAL***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***VAWYQQKP GKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YYWPT***TFGQGTKVEIKGGGGSGGGGSEPKTSDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPMVFDLPPSREEMTKNQVSLWCMVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGGSTGEVQLVES GGGLVQPGGSLRLSCAASGF***NIAYSSM***HWVRQAPGKGLEWVA***TTYPSYSSTY***YADSVKGRFTISADTSKNTAYLQMNSLRAED TAVYYCAR***YYAM***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 913)
Hole Hc construct	EVQLVESGGGLVQPGGSLRLSCAASGF***DISSYFH***HWVRQAPGKGLEWVA***SIYPSYSYTS***YADSVKGRFTISADTSKNTAYLQMN SLRAEDTAVYYCAR***NVRGFRKPYFSRWAMD***YWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***VAW YQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YFFPT***TFGQGTKVEIKGGGGSGGGGSEPKSS DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVV SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPIRELMTSNQVSLSCAVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGGSTGEV QLVESGGGLVQPGGSLRLSCAASGF***NIAYSSM***HWVRQAPGKGLEWVA***TIYPSYSSTY***YADSVKGRFTISADTSKNTAYLQMNS LRAEDTAVYYCAR***YYAM***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 914)
Light Chain	DIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYY CQQ***AHYFPT***TFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS TYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 915)

pFZD-LRP6 ANT9	
Knob Hc construct	EVQLVESGGGLVQPGGSLRLSCAASGF***DLSHSSI***HWVRQAPGKGLEWVA***SISSHHYGYTHY***ADSVKGRFTISADTSKNTAYLQM NSLRAEDTAVYYCAR***SSYFPWFFAL***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***VAWYQQKP GKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YYWPT***TFGQGTKVEIKGGGGSGGGGSEPKTSDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPMVFDLPPSREEMTKNQVSLWCMVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGGGSGSTGEVQLVES GGGLVQPGGSLRLSCAASGF***NIHSSSI***HWVRQAPGKGLEWVA***TYSSFGSIT***YADSVKGRFTISADTSKNTAYLQMNSLRAEDT AVYYCAR***YHHPFGYAL***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 916)
Hole Hc construct	EVQLVESGGGLVQPGGSLRLSCAASGF***DISSYFI***HWVRQAPGKGLEWVA***SIYPSYSYTS***YADSVKGRFTISADTSKNTAYLQMN SLRAEDTAVYYCAR***NVRGFRKPYFSRWAMD***YWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***VAW YQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YFFPT***FGQGTKVEIKGGGGSGGGGSEPKSS DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVV SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPIRELMTSNQVSLSCAVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGGGSGSTGEV QLVESGGGLVQPGGSLRLSCAASGF***NIHSSSI***HWVRQAPGKGLEWVA***ATYSSFGSIT***YADSVKGRFTISADTSKNTAYLQMNSL RAEDTAVYYCAR***YHHIPFGYAL***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 917)
Light Chain	DIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYY CQQ***GVYLF***TFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 918)

diabody-Fc-diabody FZD4 CM0199	
Knob Hc construct	EFEVQLVESGGGLVQPGGSLRLSCAASGF*NSSFYFM*HWVRQAPGKGLEWVA*TVYPYLDYTY*YADSVKGRFTISADTSKNTAYL QMNSLRAEDTAVYYCAR*AFPGSYHPM*DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ*SVSSA*VAWYQQ KPGKAPKLLIY*SASSLYS*GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ*SSYSLT*FGQGTKVEIKLEDKTHTKVEPKTSDKTH TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPMVFDLPPSREEMTKNQVSLWCMVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATPESGGGEVQLVESG GGLVQPGGSLRLSCAASGF*NFSSSSSI*HWVRQAPGKGLEWVA*SISSSYGYTY*YADSVKGRFTISADTSKNTAYLQMNSLRAEDTA VYYCAR*GGSGVSHYGSVYYSWWAL*DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ*SVSSA*VAWYQQKP GKAPKLLIY*SASSLYS*GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ*ASYAPT*TFGQGTKVEIK (SEQ ID NO: 919)
Hole Hc construct	EFEVQLVESGGGLVQPGGSLRLSCAASGF*NSSFYFM*HWVRQAPGKGLEWV*ATVYPYLDYTY*YADSVKGRFTISADTSKNTAYL QMNSLRAEDTAVYYCAR*AFPGSYHPM*DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ*SVSSA*VAWYQQ KPGKAPKLLIY*SASSLYS*GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ*SSYSLT*FGQGTKVEIKLEDKTHTKVEPKSSDKTH NCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPIRELMTSNQVSLSCAVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATPESGGGEVQLVESGG GLVQPGGSLRLSCAASGF*NLSYYYM*HWVRQAPGKGLEWVA*SIYSSYGYTY*YADSVKGRFTISADTSKNTAYLQMNSLRAEDTA VYYCAR*WSHIVSGHIYSGM*DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ*SVSSA*VAWYQQKPGKAPKLL IY*SASSLYS*GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ*SSYSLT*FGQGTKVEIK (SEQ ID NO: 920)

Table 13

Diabody-Fc-Fab and IgG-Diabody amino acid sequences of the "heavy chain" hole construct, "heavy chain" knob construct and the "light chain" construct of the FZD4 Agonists, ANT39 and ANT42, ANT39 and ANT42, and ANT39i and ANT42i having Fc domain amino acid mutations DANG, LALAPS, LALAPS and Merchant or LALAPS and Merchant S-S. Mature sequences do not include the 5' leader peptide. The V-region CDRs of the chains are underlined, italicized and bolded, Fc null mutations are italicized, CH3 heterodimerisation mutations are underlined and italicized, CH3 cys disulphide bridges are bolded, and linkers are underlined.

ANT39i HC hole DANG

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***TLSSYSM***HWVRQAPGKGLEWVA***YISSYDSITD***YADSVKGRFTISAD
TSKNTAYLQMNSLRAEDTAVYYCAR***PAVGHMAF***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS
WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKP
KDTLMISRTPEVTCVVV*A*VSHEDPEVKFNWYVDGVEVHNAKTKPREEQY*G*STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
KTISKAKGQPREPQVYTLPP*I*RE*L*MT*S*NQVSL*S*C*A*VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL*V*SKLTVDKSRWQQGNV
FSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF***DFSSSSI***HWVRQAPG
KGLEWVA***SISSSYGYTY***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***SWAM***DYWGQGTLVTVSSGGGGSDIQMTQSPS
SLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SASDLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLI***TFG
QGTKVEIK* (SEQ ID NO: 921)

ANT39i HC hole LALAPS

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***TLSSYSM***HWVRQAPGKGLEWVA***YISSYDSITD***YADSVKGRFTISAD
TSKNTAYLQMNSLRAEDTAVYYCAR***PAVGHMAF***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS
WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE*AA*GGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA*S*IE
KTISKAKGQPREPQVYTLPP*I*RE*L*MT*S*NQVSL*S*C*A*VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL*V*SKLTVDKSRWQQGNV
FSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF***DFSSSSI***HWVRQAPG
KGLEWVA***SISSSYGYTY***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***SWAM***DYWGQGTLVTVSSGGGGSDIQMTQSPS
SLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SASDLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLI***TFG
QGTKVEIK* (SEQ ID NO: 922)

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ANT39i HC hole LALAPS Merchant

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***TLSSYSM***HWVRQAPGKGLEWVA***YISSYDSITD***YADSVKGRFTISAD
TSKNTAYLQMNSLRAEDTAVYYCAR***P4VGHM4F***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS
WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE*A4*GGPSVFLFPPKP
5 KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
KTISKAKGQPREPQVYTLPPSREEMTKNQVSL*S*C*A*VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL*I*SKLTVDKSRWQQGN
VFSCSVMHEALHNHYTQKSLSLSPGK*G*GGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF***DFSSSSI***HWVRQAP
GKGLEWVA***SISSSYGYTT***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***SWAM***DYWGQGTLVTVSSGGGGSDIQMTQS
10 PSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SASDLI***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLIT***
FGQGTKVEIK* (SEQ ID NO: 923)

ANT39i HC hole LALAPS Merchant S-S

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***TLSSYSM***HWVRQAPGKGLEWVA***YISSYDSITD***YADSVKGRFTISAD
TSKNTAYLQMNSLRAEDTAVYYCAR***P4VGHM4F***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS
WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE*A4*GGPSVFLFPPKP
15 KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
KTISKAKGQPREPQVCTLPPSREEMTKNQVSL*S*C*A*VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL*I*SKLTVDKSRWQQGN
VFSCSVMHEALHNHYTQKSLSLSPGK*G*GGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF***DFSSSSI***HWVRQAP
GKGLEWVA***SISSSYGYTT***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***SWAM***DYWGQGTLVTVSSGGGGSDIQMTQS
20 PSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SASDLI***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLIT***
FGQGTKVEIK* (SEQ ID NO: 924)

Mature ANT39i HC hole DANG

EVQLVESGGGLVQPGGSLRLSCAASGF***TLSSYSM***HWVRQAPGKGLEWVA***YISSYDSITD***YADSVKGRFTISADTSKNTAYLQMNSLRA
EDTAVYYCAR***P4VGHM4F***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV
VAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY
TLPPSREEMTSNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLISKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPGKGGGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF***DFSSSSI***HWVRQAPGKGLEWVA***SISSSYGYTT***

FYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***SWAM***DYWGQGTLVTVSS**GGGGS**DIQMTQSPSSLSASVGDRVTITCRA
S***QSVSSA***VAWYQQKPGKAPKLLIY***SASDLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLI***TFGQGTKVEIK* (SEQ ID NO: 925)

Mature ANT39i HC hole LALAPS

EVQLVESGGGLVQPGGSLRLSCAASGF***TLSSYSM***HWVRQAPGKGLEWVA***YISSYDSSITD***YADSVKGRFTISADTSKNTAYLQMNSLRA
EDTAVYYCAR***PAVGHMAF***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE*AA*GGPSVFLFPPKPKDTLMISRTPEVTCVV
VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA*S*IEKTISKAKGQPREPQVY
TLPP*S*RE*E*MT*K*NQVSL*S*C*A*VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL*Y*SKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPGK**G**GGSGGGSGGGSGGSGGS**T**GEVQLVESGGGLVQPGGSLRLSCAASGF***DFSSSSS***HWVRQAPGKGLEWVA***SISSSYGYT***
YYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***SWAM***DYWGQGTLVTVSS**GGGGS**DIQMTQSPSSLSASVGDRVTITCRA
S***QSVSSA***VAWYQQKPGKAPKLLIY***SASDLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLI***TFGQGTKVEIK* (SEQ ID NO: 926)

Mature ANT39i HC hole LALAPS Merchant

EVQLVESGGGLVQPGGSLRLSCAASGF***TLSSYSM***HWVRQAPGKGLEWVA***YISSYDSSITD***YADSVKGRFTISADTSKNTAYLQMNSLRA
EDTAVYYCAR***PAVGHMAF***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE*AA*GGPSVFLFPPKPKDTLMISRTPEVTCVV
VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA*S*IEKTISKAKGQPREPQVY
TLPPSREEMTKNQVSL*S*C*A*VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL*Y*SKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPGK**G**GGSGGGSGGGSGGSGGS**T**GEVQLVESGGGLVQPGGSLRLSCAASGF***DFSSSSS***HWVRQAPGKGLEWVA***SISSSYGYT***
YYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***SWAM***DYWGQGTLVTVSS**GGGGS**DIQMTQSPSSLSASVGDRVTITCRA
S***QSVSSA***VAWYQQKPGKAPKLLIY***SASDLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLI***TFGQGTKVEIK* (SEQ ID NO: 927)

Mature ANT39i HC hole LALAPS Merchant S-S

EVQLVESGGGLVQPGGSLRLSCAASGF***TLSSYSM***HWVRQAPGKGLEWVA***YISSYDSSITD***YADSVKGRFTISADTSKNTAYLQMNSLRA
EDTAVYYCAR***PAVGHMAF***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE*AA*GGPSVFLFPPKPKDTLMISRTPEVTCVV

VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPASIEKTISKAKGQPREPQVC
TLPPSREEMTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPGKGGGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF***DFSSSSS****HWVRQAPGKGLEWVA***SISSSYGYT***
YYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***SWAM***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRA
S***QSVSSA***VAWYQQKPGKAPKLLIY***SASDLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLT***FGQGTKVEIK* (SEQ ID
NO: 928)

ANT39i HC knob DANG

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***TLSSYSM***HWVRQAPGKGLEWVA***YISSYDSITD***YADSVKGRFTISAD
TSKNTAYLQMNSLRAEDTAVYYCAR***PAVGHMAF***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS
WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKP
KDTLMISRTPEVTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
KTISKAKGQPREPMVEDLPPSREEMTKNQVSLWCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF***DFTAYAMH***WVRQ
APGKGLEWVA***SIYPSGGYTA***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***RSYYFAL***DYWGQGTLVTVSSGGGGSDIQ
MTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SASSLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YWA***
YYSPITFGQGTKVEIK* (SEQ ID NO: 929)

ANT39i HC Knob LALAPS

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***TLSSYSM***HWVRQAPGKGLEWVA***YISSYDSITD***YADSVKGRFTISAD
TSKNTAYLQMNSLRAEDTAVYYCAR***PAVGHMAF***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS
WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE*AA*GGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA*S*IE
KTISKAKGQPREPMVEDLPPSREEMTKNQVSLWCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF***DFTAYAMH***WVRQ
APGKGLEWVA***SIYPSGGYTA***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***RSYYFAL***DYWGQGTLVTVSSGGGGSDIQ
MTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SASSLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YWA***
YYSPITFGQGTKVEIK* (SEQ ID NO: 930)

ANT39i HC Knob LALAPS Merchant

MNLLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***TLSSYSM***HWVRQAPGKGLEWVA***YISSYDSITD***YADSVKGRFTISAD
TSKNTAYLQMNSLRAEDTAVYYCAR***PAVGIIMAF***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS
WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE*AA*GGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA*S*IE
KTISKAKGQPREPQVYTLPPSR*E*EMTKNQVSL*W*CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN
VFSCSVMHEALHNHYTQKSLSLSPGK**G**GGSGGGSGGGSGGGSGGSTGEVQLVESGGGLVQPGGSLRLSCAASGF***DFTAYAM***HWVRQA
PGKGLEWVA***SIYPSGGYTA***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***RSYYFAL***DYWGQGTLVTVSSGGGGSDIQM
TQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SASSLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YWAIY***
SPTTFGQGTKVEIK* (SEQ ID NO: 931)

ANT39i HC Knob LALAPS Merchant S-S

MNLLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***TLSSYSM***HWVRQAPGKGLEWVA***YISSYDSITD***YADSVKGRFTISAD
TSKNTAYLQMNSLRAEDTAVYYCAR***PAVGIIMAF***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS
WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE*AA*GGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA*S*IE
KTISKAKGQPREPQVYTLPP**C**REEMTKNQVSL*W*CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN
VFSCSVMHEALHNHYTQKSLSLSPGK**G**GGSGGGSGGGSGGGSGGSTGEVQLVESGGGLVQPGGSLRLSCAASGF***DFTAYAM***HWVRQA
PGKGLEWVA***SIYPSGGYTA***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***RSYYFAL***DYWGQGTLVTVSSGGGGSDIQM
TQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SASSLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YWAIY***
SPTTFGQGTKVEIK* (SEQ ID NO: 932)

Mature ANT39i HC knob DANG

EVQLVESGGGLVQPGGSLRLSCAASGF***TLSSYSM***HWVRQAPGKGLEWVA***YISSYDSITD***YADSVKGRFTISADTSKNTAYLQMNSLRA
EDTAVYYCAR***PAVGIIMAF***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV
VAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP*M*V*F*
*D*LPPSREEMTKNQVSL*W*C*M*VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK**G**GGSGGGSGGGSGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF***DFTAYAM***HWVRQAPGKGLEWVA***SIYPSGG***
YTAYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***RSYYFAL***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTI

TCRASQSVSSA4VAWYQQKPGKAPKLLIYSASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYWATYSPTTFGQGTKVEIK* (SEQ ID NO: 933)

Mature ANT39i HC Knob LALAPS

EVQLVESGGGLVQPGGSLRLSCAASGFTLSSYSMHWVRQAPGKGLEWVAYISSYDSITDYADSVKGRFTISADTSKNTAYLQMNSLRA
EDTAVYYCARP4VGHM4FDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE4AGGPSVFLFPPKPKDTLMISRTPEVTCVV
VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPASIEKTISKAKGQPREPMVF
DLPPSREEMTKNQVSLWCMVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGKGGGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGFDFTAYAMHWVRQAPGKGLEWVASIYPSGG
YTA4YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRSYYFALDYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTI
TCRASQSVSSA4VAWYQQKPGKAPKLLIYSASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYWATYSPTTFGQGTKVEIK* (SEQ ID NO: 934)

Mature ANT39i HC Knob LALAPS Merchant

EVQLVESGGGLVQPGGSLRLSCAASGFTLSSYSMHWVRQAPGKGLEWVAYISSYDSITDYADSVKGRFTISADTSKNTAYLQMNSLRA
EDTAVYYCARP4VGHM4FDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE4AGGPSVFLFPPKPKDTLMISRTPEVTCVV
VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPASIEKTISKAKGQPREPQVY
TLPPSREEMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGKGGGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGFDFTAYAMHWVRQAPGKGLEWVASIYPSGG
YTA4YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRSYYFALDYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTI
TCRASQSVSSA4VAWYQQKPGKAPKLLIYSASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYWATYSPTTFGQGTKVEIK* (SEQ ID NO: 935)

Mature ANT39i HC Knob LALAPS Merchant S-S

EVQLVESGGGLVQPGGSLRLSCAASGFTLSSYSMHWVRQAPGKGLEWVAYISSYDSITDYADSVKGRFTISADTSKNTAYLQMNSLRA
EDTAVYYCARP4VGHM4FDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE4AGGPSVFLFPPKPKDTLMISRTPEVTCVV

VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPASIEKTISKAKGQPREPQVY
TLPPCREEMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGKGGGSGGGSGGGSGGGSGGGSGTGEVQLVESGGGLVQPGGSLRLSCAASGF***DFTFAYAM***HWVRQAPGKGLEWVA***SIYPSGG***
YTAYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***RSYYFALD***YWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTI
TCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YWAYYSPT***TFGQGTKVEIK*
(SEQ ID NO: 936)

ANT39 Hc Hole DANG

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***DFSSSSS***HWVRQAPGKGLEWVA***SISSSYGYTY***YADSVKGRFTISADT
SKNTAYLQMNSLRAEDTAVYYCAR***SWAMD***YWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKP
GKAPKLLIY***SASDLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLT***TFGQGTKVEIKGGGGSGGGGSEPKSSDKTHTCPP
CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLN
GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRELMTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF
LVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGGGSGTGEVQLVESGGGLVQPGGSLRLSCAAS
GF***TLSSYSM***HWVRQAPGKGLEWVA***YISSYDSITD***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***PAVGHMAF***DYWGQ
GTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI
CNVNHKPSNTKVDKKVEPKSCDKTHT* (SEQ ID NO: 908)

ANT39 Hc Hole LALAPS

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***DFSSSSS***HWVRQAPGKGLEWVA***SISSSYGYTY***YADSVKGRFTISADT
SKNTAYLQMNSLRAEDTAVYYCAR***SWAMD***YWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKP
GKAPKLLIY***SASDLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLT***TFGQGTKVEIKGGGGSGGGGSEPKSSDKTHTCPP
CPAPE***AA***GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN
GKEYKCKVSNKALPA**A**IEKTISKAKGQPREPQVYTLPP**A**RELMTKNQVSL**A**C**A**VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF
LVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGTGEVQLVESGGGLVQPGGSLRLSCAAS
GF***TLSSYSM***HWVRQAPGKGLEWVA***YISSYDSITD***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***PAVGHMAF***DYWGQ
GTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI
CNVNHKPSNTKVDKKVEPKSCDKTHT* (SEQ ID NO: 937)

ANT39 Hc Hole LALAPS Merchant

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***DFSSSSI***HWVRQAPGKGLEWVA***SISSSYGYTY***YADSVKGRFTISADT
SKNTAYLQMNSLRAEDTAVYYCAR***SWAM***DYWGQGTLVTVSS**G**GGG**S**DIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKP
GKAPKLLIY***SASDLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLI***TFGQGTKVEIK**G**GGG**S**GGG**S**EPKSSDKTHTCPP
CPAPE***AA***GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG**V**EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN
GKEYKCKVSNKALPA**P**IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL**S**C***A***VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF
FL***Y***SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK**G**GGG**S**GGG**S**GGG**S**GGG**S**GS**T**GEVQLVESGGGLVQPGGSLRLSCAA
SGF***TLSSYSM***HWVRQAPGKGLEWVA***YISSYDSITD***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***PAVGHMAF***DYWG
QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY
ICNVNHKPSNTKVDKKVEPKSCDKTHT* (SEQ ID NO: 938)

ANT39 Hc Hole LALAPS Merchant S-S

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***DFSSSSI***HWVRQAPGKGLEWVA***SISSSYGYTY***YADSVKGRFTISADT
SKNTAYLQMNSLRAEDTAVYYCAR***SWAM***DYWGQGTLVTVSS**G**GGG**S**DIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKP
GKAPKLLIY***SASDLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLI***TFGQGTKVEIK**G**GGG**S**GGG**S**EPKSSDKTHTCPP
CPAPE***AA***GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG**V**EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN
GKEYKCKVSNKALPA**P**IEKTISKAKGQPREPQV**C**TLPPSREEMTKNQVSL**S**C***A***VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF
FL***Y***SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK**G**GGG**S**GGG**S**GGG**S**GGG**S**GS**T**GEVQLVESGGGLVQPGGSLRLSCAA
SGF***TLSSYSM***HWVRQAPGKGLEWVA***YISSYDSITD***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***PAVGHMAF***DYWG
QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY
ICNVNHKPSNTKVDKKVEPKSCDKTHT* (SEQ ID NO: 939)

Mature ANT39 Hc Hole DANG

EVQLVESGGGLVQPGGSLRLSCAASGF***DFSSSSI***HWVRQAPGKGLEWVA***SISSSYGYTY***YADSVKGRFTISADTSKNTAYLQMNSLRA
EDTAVYYCAR***SWAM***DYWGQGTLVTVSS**G**GGG**S**DIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SASDLY***
SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLI***TFGQGTKVEIK**G**GGG**S**GGG**S**EPKSSDKTHTCPPCPAPELLGGPSVFLF
PPKPKDTLMISRTPEVTCVVVA**V**SHEDPEVKFNWYVDG**V**EVHNAKTKPREEQYG**S**TYRVVSVLTVLHQDWLNGKEYKCKVSNKALP
APIEKTISKAKGQPREPQVYTLPP**R**E**L**MT**K**NQVSL**S**C***A***VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL***Y***SKLTVDKSRWQQ
GNVFSCSVMHEALHNHYTQKSLSLSPGK**G**GGG**S**GGG**S**GGG**S**GGG**S**GS**T**GEVQLVESGGGLVQPGGSLRLSCAASGF***TLSSYSM***HWVRQ

APGKGLEWVA***YISSYDSITD***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***PAVGHMAF***DYWGQGTLVTVSSASTKGPS
VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK
KVEPKSCDKTHT* (SEQ ID NO: 940)

Mature ANT39 Hc Hole LALAPS

EVQLVESGGGLVQPGGSLRLSCAASGF***DFSSSSI***HWVRQAPGKGLEWVA***SISSSYGYTY***YADSVKGRFTISADTSKNTAYLQMNSLRA
EDTAVYYCAR***SWAMD***YWGQGTLVTVSS**G**GGGS**D**IQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SASDLY***
SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLT***FGQGTKVEIK**G**GGGSGGGGSEPKSSDKTHTCPPCPAPE*AA*GGPSVFLF
PPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP
A**S**IEKTISKAKGQPREPQVYTLPP**J**RE**L**MT**K**NQVSL**S**C*A*VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY**S**KLTVDKSRWQQ
GNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF***TLSSYSM***HWVRQ
APGKGLEWVA***YISSYDSITD***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***PAVGHMAF***DYWGQGTLVTVSSASTKGPS
VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK
KVEPKSCDKTHT* (SEQ ID NO: 941)

Mature ANT39 Hc Hole LALAPS Merchant

EVQLVESGGGLVQPGGSLRLSCAASGF***DFSSSSI***HWVRQAPGKGLEWVA***SISSSYGYTY***YADSVKGRFTISADTSKNTAYLQMNSLRA
EDTAVYYCAR***SWAMD***YWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SASDLY***
SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLT***FGQGTKVEIK**G**GGGSGGGGSEPKSSDKTHTCPPCPAPE*AA*GGPSVFLF
PPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP
A**S**IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL**S**C*A*VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY**S**KLTVDKSRWQ
QGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF***TLSSYSM***HWVR
QAPGKGLEWVA***YISSYDSITD***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***PAVGHMAF***DYWGQGTLVTVSSASTKGP
SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD
KKVEPKSCDKTHT* (SEQ ID NO: 942)

Mature ANT39 Hc Hole LALAPS Merchant S-S

EVQLVESGGGLVQPGGSLRLSCAASGF***DFSSSSI***HWVRQAPGKGLEWVA***SISSSYGYTY***YADSVKGRFTISADTSKNTAYLQMNSLRA
EDTAVYYCAR***SWAMD***YWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SASDLY***
SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLT***FGQGTKVEIK**G**GGGSGGGGSEPKSSDKTHTCPPCPAPE*AA*GGPSVFLF

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PPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP
ASIEKTISKAKGQPREPQVCTLPPSREEMTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLISKLTVDKSRWQ
QGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGGGSGSTGEVQLVQPGGSLRLSCAASGFTLSSYSMHWVR
QAPGKGLEWVAVISSYDSITDYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARPAVGHMAFDYWGQGTLVTVSSASTKGP
5 SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD
KKVEPKSCDKTHT* (SEQ ID NO: 943)

ANT39 Hc knob DANG

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGFDFTAYAMHWVRQAPGKGLEWVASIYPSGGYTAYADSVKGRFTISA
DTSKNTAYLQMNSLRAEDTAVYYCARRSYYFALDYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWY
10 QQKPGKAPKLLIYSASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYWAYYSPTTFGQGTKVEIKGGGGSGGGGSEPKSSDKT
HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQ
DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPMVFDLPPSREEMTKNQVSLWCMVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSL
RLSCAASGFTLSSYSMHWVRQAPGKGLEWVAYISSYDSITDYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARPAVGHMA
15 FDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS
LGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT* (SEQ ID NO: 944)

ANT39 Hc knob LALAPS

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGFDFTAYAMHWVRQAPGKGLEWVASIYPSGGYTAYADSVKGRFTISA
DTSKNTAYLQMNSLRAEDTAVYYCARRSYYFALDYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWY
20 QQKPGKAPKLLIYSASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYWAYYSPTTFGQGTKVEIKGGGGSGGGGSEPKSSDKT
HTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ
DWLNGKEYKCKVSNKALPASIEKTISKAKGQPREPMVFDLPPSREEMTKNQVSLWCMVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSL
RLSCAASGFTLSSYSMHWVRQAPGKGLEWVAYISSYDSITDYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARPAVGHMA
25 FDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS
LGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT* (SEQ ID NO: 945)

ANT39 Hc knob LALAPS Merchant

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***DFTAYAM***HWVRQAPGKGLEWVA***SIYPSGGYTA***YADSVKGRFTISA
DTSKNTAYLQMNSLRAEDTAVYYCAR***RSYYFAL***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWY
QQKPGKAPKLLIY***SASSLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YWAYYSPI***TFGQGTKVEIKGGGGSGGGGSEPKSSDKT
HTCPPCPAPE*AA*GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ
DWLNGKEYKCKVSNKALPA*S*IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL*W*CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSLR
LSCAASGF***TLSSYSM***HWVRQAPGKGLEWVA***YISSYDSITD***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***PAVGHMAF***
DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL
GTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT* (SEQ ID NO: 946)

ANT39 Hc knob LALAPS Merchant S-S

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***DFTAYAM***HWVRQAPGKGLEWVA***SIYPSGGYTA***YADSVKGRFTISA
DTSKNTAYLQMNSLRAEDTAVYYCAR***RSYYFAL***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWY
QQKPGKAPKLLIY***SASSLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YWAYYSPI***TFGQGTKVEIKGGGGSGGGGSEPKSSDKT
HTCPPCPAPE*AA*GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ
DWLNGKEYKCKVSNKALPA*S*IEKTISKAKGQPREPQVYTLPP**C**REEMTKNQVSL*W*CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSLR
LSCAASGF***TLSSYSM***HWVRQAPGKGLEWVA***YISSYDSITD***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***PAVGHMAF***
DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVIITFPAVLQSSGLYSLSSVVTVPSSSL
GTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT*(SEQ ID NO: 947)

Mature ANT39 Hc knob DANG

EVQLVESGGGLVQPGGSLRLSCAASGF***DFTAYAM***HWVRQAPGKGLEWVA***SIYPSGGYTA***YADSVKGRFTISADTSKNTAYLQMNSLR
AEDTAVYYCAR***RSYYFAL***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SAS***
SLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YWAYYSPI***TFGQGTKVEIKGGGGSGGGGSEPKSSDKTHTCPPCPAPELLGGPS
VFLFPPKPKDTLMISRTPEVTCVVV*A*VSHEDPEVKFNWYVDGVEVHNAKTKPREEQY*G*STYRVVSVLTVLHQDWLNGKEYKCKVSN
KALPAPIEKTISKAKGQPREP*M*V*FD*LPPSREEMTKNQVSL*WCM*VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK
SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF***TLSSYSM***

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HWVRQAPGKGLEWVA***YISSYDSITDY***ADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***PAVGHMAF***DYWGQGTLVTVSSA
STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN
TKVDKKVEPKSCDKTHT* (SEQ ID NO: 948)

Mature ANT39 Hc knob LALAPS

EVQLVESGGGLVQPGGSLRLSCAASGF***DFTAYAM***HWVRQAPGKGLEWVA***SIYPSGGYTA***YADSVKGRFTISADTSKNTAYLQMNSLR
AEDTAVYYCAR***RSYYFALD***YWGQGTLVTVSS<u>GGGGS</u>DIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SAS***
SLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YWAYYSPT***TFGQGTKVEIK<u>GGGGSGGGGSEPKSSDKTHTCPPCPAPE</u>*AAGGPS*
VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN
KALPASIEKTISKAKGQPREP*MVED*LPPSREEMTKNQVSL*WCM*VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK
SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK<u>GGGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF***TLSSYSM***</u>
HWVRQAPGKGLEWVA***YISSYDSITDY***ADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***PAVGHMAF***DYWGQGTLVTVSSA
STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN
TKVDKKVEPKSCDKTHT* (SEQ ID NO: 949)

Mature ANT39 Hc knob LALAPS Merchant

EVQLVESGGGLVQPGGSLRLSCAASGF***DFTAYAM***HWVRQAPGKGLEWVA***SIYPSGGYTA***YADSVKGRFTISADTSKNTAYLQMNSLR
AEDTAVYYCAR***RSYYFALD***YWGQGTLVTVSS<u>GGGGS</u>DIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SAS***
SLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YWAYYSPT***TFGQGTKVEIK<u>GGGGSGGGGSEPKSSDKTHTCPPCPAPE</u>*AAGGPS*
VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN
KALPASIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL*WCL*VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK
SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK<u>GGGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF***TLSSYSM***</u>
HWVRQAPGKGLEWVA***YISSYDSITDY***ADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***PAVGHMAF***DYWGQGTLVTVSSA
STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN
TKVDKKVEPKSCDKTHT* (SEQ ID NO: 950)

Mature ANT39 Hc knob LALAPS Merchant

EVQLVESGGGLVQPGGSLRLSCAASGF***DFTAYAM***HWVRQAPGKGLEWVA***SIYPSGGYTA***YADSVKGRFTISADTSKNTAYLQMNSLR
AEDTAVYYCAR***RSYYFALD***YWGQGTLVTVSS<u>GGGGS</u>DIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SAS***
SLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YWAYYSPT***TFGQGTKVEIK<u>GGGGSGGGGSEPKSSDKTHTCPPCPAPE</u>*AAGGPS*

VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN
KALPASIEKTISKAKGQPREPQVYTLPPCREEMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK
SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGGSTGEVQLVESGGGLVQPGGSLRLSCAASGFTLSSYSM
HWVRQAPGKGLEWVAYISSYDSITDYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARPAVGHMAFDYWGQGTLVTVSSA
STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN
TKVDKKVEPKSCDKTHT* (SEQ ID NO: 951)

ANT39 LC

MNLLLILTFVAAAVADIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIYSASSLYSGVPSRFSGSRSGTDFTLTIS
SLQPEDFATYYCQQWYNAPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVT
EQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC* (SEQ ID NO: 909)

Mature ANT39 LC

DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIYSASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQWY
NAPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTL
SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 952)

ANT42i HC hole DANG

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGFTSDFYEIHWVRQAPGKGLEWVATIYPFIGNTYYADSVKGRFTISAD
TSKNTAYLQMNSLRAEDTAVYYCARAFPGSYHPFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS
WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKP
KDTLMISRTPEVTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
KTISKAKGQPREPQVYTLPPCREEMTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNV
FSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGGSTGEVQLVESGGGLVQPGGSLRLSCAASGFDFSSSSYIHWVRQAPG
KGLEWVASISSSSYGYTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARSWAMDYWGQGTLVTVSSGGGGSDIQMTQSPS
SLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIYSASDLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYAGAGLITFG
QGTKVEIK* (SEQ ID NO: 953)

ANT42i HC hole LALAPS

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***TSDFYFI***HWVRQAPGKGLEWVA***TIYPFIGNTY***YADSVKGRFTISAD
TSKNTAYLQMNSLRAEDTAVYYCAR***AFPGSYHPF***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS
WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE*AA*GGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA*S*IE
KTISKAKGQPREPQVYTLPP*I*RE*L*MT*S*NQVSL*S*C*A*VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL*V*SKLTVDKSRWQQGNV
FSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF***DFSSSSI***HWVRQAPG
KGLEWVA***SISSSYGYTY***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***SWAM***DYWGQGTLVTVSSGGGGSDIQMTQSPS
SLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SASDLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLI***TFG
QGTKVEIK* (SEQ ID NO: 954)

ANT42i HC hole LALAPS Merchant

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***TSDFYFI***HWVRQAPGKGLEWVA***TIYPFIGNTY***YADSVKGRFTISAD
TSKNTAYLQMNSLRAEDTAVYYCAR***AFPGSYHPF***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS
WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE*AA*GGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA*S*IE
KTISKAKGQPREPQVYTLPPSREEMTKNQVSL*S*C*A*VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL*V*SKLTVDKSRWQQGN
VFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF***DFSSSSI***HWVRQAP
GKGLEWVA***SISSSYGYTY***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***SWAM***DYWGQGTLVTVSSGGGGSDIQMTQS
PSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SASDLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLI***T
FGQGTKVEIK* (SEQ ID NO: 955)

ANT42i HC hole LALAPS Merchant S-S

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***TSDFYFI***HWVRQAPGKGLEWVA***TIYPFIGNTY***YADSVKGRFTISAD
TSKNTAYLQMNSLRAEDTAVYYCAR***AFPGSYHPF***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS
WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE*AA*GGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA*S*IE
KTISKAKGQPREPQV**C**TLPPSREEMTKNQVSL*S*C*A*VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL*V*SKLTVDKSRWQQGN
VFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF***DFSSSSI***HWVRQAP

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GKGLEWVA***SISSSYGYTY***ADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***SWAM***DYWGQGTLVTVSSGGGGSDIQMTQS
PSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SASDLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLI***T
FGQGTKVEIK* (SEQ ID NO: 956)

Mature ANT42i HC hole DANG

EVQLVESGGGLVQPGGSLRLSCAASGF***TSDFYFI***HWVRQAPGKGLEWVA***TIYPFIGNTY***YADSVKGRFTISADTSKNTAYLQMNSLRA
EDTAVYYCAR***AFPGSYHIPF***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV
VAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY
TLPPSRE*L*MTKNQVSL*S*C*A*VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL*Y*SKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPGK***GGGSGGGSGGGSGGGSGGS***TGEVQLVESGGGLVQPGGSLRLSCAASGF***DFSSSSI***HWVRQAPGKGLEWVA***SISSSYGYT***
YYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***SWAM***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRA
S***QSVSSA***VAWYQQKPGKAPKLLIY***SASDLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLI***TFGQGTKVEIK* (SEQ ID
NO: 957)

Mature ANT42i HC hole LALAPS

EVQLVESGGGLVQPGGSLRLSCAASGF***TSDFYFI***HWVRQAPGKGLEWVA***TIYPFIGNTY***YADSVKGRFTISADTSKNTAYLQMNSLRA
EDTAVYYCAR***AFPGSYHIPF***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE*A*GGPSVFLFPPKPKDTLMISRTPEVTCVV
VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA*P*IEKTISKAKGQPREPQVY
TLPPSRE*L*MTKNQVSL*S*C*A*VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL*Y*SKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPGK***GGGSGGGSGGGSGGGSGGS***TGEVQLVESGGGLVQPGGSLRLSCAASGF***DFSSSSI***HWVRQAPGKGLEWVA***SISSSYGYT***
YYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***SWAM***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRA
S***QSVSSA***VAWYQQKPGKAPKLLIY***SASDLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLI***TFGQGTKVEIK* (SEQ ID
NO: 958)

Mature ANT42i HC hole LALAPS Merchant

EVQLVESGGGLVQPGGSLRLSCAASGF***TSDFYFI***HWVRQAPGKGLEWVA***TIYPFIGNTY***YADSVKGRFTISADTSKNTAYLQMNSLRA
EDTAVYYCAR***AFPGSYHIPF***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE*A*GGPSVFLFPPKPKDTLMISRTPEVTCVV

VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPASIEKTISKAKGQPREPQVY
TLPPSREEMTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPGKGGGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF***DFSSSSIHWVRQAPGKGLEWVA******SISSSYGYT***
IYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***SWAMD***YWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRA
S***QSVSSA***VAWYQQKPGKAPKLLIY***SASDLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLI***TFGQGTKVEIK* (SEQ ID
NO: 959)

Mature ANT42i HC hole LALAPS Merchant S-S

EVQLVESGGGLVQPGGSLRLSCAASGF***TSDFYFI***HWVRQAPGKGLEWVA***TIYPFIGNTY***YADSVKGRFTISADTSKNTAYLQMNSLRA
EDTAVYYCAR***AFPGSYHIPF***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE***AA***GGPSVFLFPPKPKDTLMISRTPEVTCVV
VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA**I**EKTISKAKGQPREPQV**C**
TLPPSREEMTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPGKGGGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF***DFSSSSIHWVRQAPGKGLEWVA******SISSSYGYT***
IYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***SWAMD***YWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRA
S***QSVSSA***VAWYQQKPGKAPKLLIY***SASDLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLI***TFGQGTKVEIK* (SEQ ID
NO: 960)

ANT42i HC knob DANG

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***TSDFYFI***HWVRQAPGKGLEWVA***TIYPFIGNTY***YADSVKGRFTISAD
TSKNTAYLQMNSLRAEDTAVYYCAR***AFPGSYHIPF***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS
WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKP
KDTLMISRTPEVTCVVV*A*VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYG*S*TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
KTISKAKGQPREPM*V*F*D*LPPSREEMTKNQVSL*W*C*M*VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF***DFTAYAMH***WVRQ
APGKGLEWVA***SIYPSGGYTA***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***RSYYFAL***DYWGQGTLVTVSSGGGGSDIQ
MTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SASSLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YWA***
YSSPTTFGQGTKVEIK* (SEQ ID NO: 961)

ANT42i HC Knob LALAPS

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF*TSDFYFI*HWVRQAPGKGLEWVA*TIYPFIGNTY*YADSVKGRFTISAD
TSKNTAYLQMNSLRAEDTAVYYCAR*AFPGSYHPF*DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS
WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE*AA*GGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA*S*IE
KTISKAKGQPREP*MVED*LPPSREEMTKNQVSL*WCM*VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPGK*G*GGSGGGSGGGSGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF*DFTAYAMH*WVRQ
APGKGLEWVA*SIYPSGGYTA*YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR*RSYYFAL*DYWGQGTLVTVSSGGGGSDIQ
MTQSPSSLSASVGDRVTITCRAS*QSVSSA*VAWYQQKPGKAPKLLIY*SASSLY*SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ*YWA*
YYSPITFGQGTKVEIK* (SEQ ID NO: 962)

ANT42i HC Knob LALAPS Merchant

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF*TSDFYFI*HWVRQAPGKGLEWVA*TIYPFIGNTY*YADSVKGRFTISAD
TSKNTAYLQMNSLRAEDTAVYYCAR*AFPGSYHPF*DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS
WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE*AA*GGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA*S*IE
KTISKAKGQPREPQVYTLPPSREEMTKNQVSL*W*CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN
VFSCSVMHEALHNHYTQKSLSLSPGK*G*GGSGGGSGGGSGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF*DFTAYAM*HWVRQA
PGKGLEWVA*SIYPSGGYTA*YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR*RSYYFAL*DYWGQGTLVTVSSGGGGSDIQM
TQSPSSLSASVGDRVTITCRAS*QSVSSA*VAWYQQKPGKAPKLLIY*SASSLY*SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ*YWAYY*
SPITFGQGTKVEIK* (SEQ ID NO: 963)

ANT42i HC Knob LALAPS Merchant S-S

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF*TSDFYFI*HWVRQAPGKGLEWVA*TIYPFIGNTY*YADSVKGRFTISAD
TSKNTAYLQMNSLRAEDTAVYYCAR*AFPGSYHPF*DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS
WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE*AA*GGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA*S*IE
KTISKAKGQPREPQVYTLPPC*C*REEMTKNQVSL*W*CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN
VFSCSVMHEALHNHYTQKSLSLSPGK*G*GGSGGGSGGGSGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF*DFTAYAM*HWVRQA

PGKGLEWVA***SIYPSGGYTA***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***RSYYFALD***YWGQGTLVTVSSGGGGSDIQM
TQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SASSLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YWAYY***
SPTTFGQGTKVEIK* (SEQ ID NO: 964)

Mature ANT42i HC knob DANG

EVQLVESGGGLVQPGGSLRLSCAASGF***TSDFYFI***HWVRQAPGKGLEWVA***TIYPFIGNTY***YADSVKGRFTISADTSKNTAYLQMNSLRA
EDTAVYYCAR***AFPGSYHIPF***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV
VAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYT
LPPSREEMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGKGGGSGGGGSGGGSGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF***DFTAYAM***HWVRQAPGKGLEWVA***SIYPSGG***
YTAYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***RSYYFAL***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTI
TCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SASSLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YWAYYSPT***TFGQGTKVEIK*
(SEQ ID NO: 965)

Mature ANT42i HC Knob LALAPS

EVQLVESGGGLVQPGGSLRLSCAASGF***TSDFYFI***HWVRQAPGKGLEWVA***TIYPFIGNTY***YADSVKGRFTISADTSKNTAYLQMNSLRA
EDTAVYYCAR***AFPGSYHIPF***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE*AA*GGPSVFLFPPKPKDTLMISRTPEVTCVV
VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA*P*IEKTISKAKGQPREPQVYT
LPPSREEMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGKGGGSGGGGSGGGSGGSGSTGEVQLVESGGGLVQPGGSLRLSCAASGF***DFTAYAM***HWVRQAPGKGLEWVA***SIYPSGG***
YTAYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***RSYYFAL***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTI
TCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SASSLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YWAYYSPT***TFGQGTKVEIK*
(SEQ ID NO: 966)

Mature ANT42i HC Knob LALAPS Merchant

EVQLVESGGGLVQPGGSLRLSCAASGF***TSDFYFI***HWVRQAPGKGLEWVA***TIYPFIGNTY***YADSVKGRFTISADTSKNTAYLQMNSLRA
EDTAVYYCAR***AFPGSYHIPF***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE*AA*GGPSVFLFPPKPKDTLMISRTPEVTCVV

VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPASIEKTISKAKGQPREPQVY
TLPPSREEMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGKGGGSGGGSGGGSGGGSGGGSGTGEVQLVESGGGLVQPGGSLRLSCAASGF*DFTAYAM*HWVRQAPGKGLEWVA*SIYPSGG*
*YTA*YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR*RSYYFAL*DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTI
TCRAS*QSVSSA*VAWYQQKPGKAPKLLIY*SASSLY*SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ*YWAYYSPT*TFGQGTKVEIK*
(SEQ ID NO: 967)

Mature ANT42i HC Knob LALAPS Merchant S-S

EVQLVESGGGLVQPGGSLRLSCAASGF*TSDFYFI*HWVRQAPGKGLEWVA*TIYPFIGNTY*YADSVKGRFTISADTSKNTAYLQMNSLRA
EDTAVYYCAR*AFPGSYHIPF*DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE*AA*GGPSVFLFPPKPKDTLMISRTPEVTCVV
VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPASIEKTISKAKGQPREPQVY
TLPPCREEMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGKGGGSGGGSGGGSGGGSGTGEVQLVESGGGLVQPGGSLRLSCAASGF*DFTAYAM*HWVRQAPGKGLEWVA*SIYPSGG*
*YTA*YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR*RSYYFAL*DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTI
TCRAS*QSVSSA*VAWYQQKPGKAPKLLIY*SASSLY*SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ*YWAYYSPT*TFGQGTKVEIK*
(SEQ ID NO: 968)

ANT42 Hc Hole DANG

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF*DFSSSSI*HWVRQAPGKGLEWVA*SISSSYGYTY*YADSVKGRFTISADT
SKNTAYLQMNSLRAEDTAVYYCAR*SWAM*DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRAS*QSVSSA*VAWYQQKP
GKAPKLLIY*SASDLY*SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ*YAGAGLI*TFGQGTKVEIKGGGGSGGGGSEPKSSDKTHTCPP
CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVA*V*SHEDPEVKFNWYVDGVEVHNAKTKPREEQYG*S*TYRVVSVLTVLHQDWLN
GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP*J*RE*L*MT*N*QVSL*SC*A*V*KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF
L*V*SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGGGSGTGEVQLVESGGGLVQPGGSLRLSCAAS
GF*TSDFYFI*HWVRQAPGKGLEWVA*TIYPFIGNTY*YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR*AFPGSYHIPF*DYWGQ
GTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI
CNVNHKPSNTKVDKKVEPKSCDKTHT* (SEQ ID NO: 911)

ANT42 Hc Hole LALAPS

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***DFSSSSS***HWVRQAPGKGLEWVA***SISSSYGYTY***YADSVKGRFTISADT
SKNTAYLQMNSLRAEDTAVYYCAR***SWAM***DYWGQGTLVTVSS**GGGGS**DIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKP
GKAPKLLIY***SASDLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLI***TFGQGTKVEIK**GGGGSGGGGSEPKSSDKTHT**CPP
CPAPE*AA***GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN
GKEYKCKVSNKALPA**S**IEKTISKAKGQPREPQVYTLPP**S**RE**L**MT**K**NQVSL**S**C*A*VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF
L**Y**SKLTVDKSRWQQGNVFSCSVMHE*A*LHNHYTQKSLSLSPGK**GGGSGGGGSGGGGSGGGGS**GSTGEVQLVESGGGLVQPGGSLRLSCAAS
GF***TSDFYFI***HWVRQAPGKGLEWVA***TTYPFIGNTY***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***AFPGSWHPF***DYWGQ
GTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI
CNVNHKPSNTKVDKKVEPKSCDKTHT* (SEQ ID NO: 969)

ANT42 Hc Hole LALAPS Merchant

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***DFSSSSS***HWVRQAPGKGLEWVA***SISSSYGYTY***YADSVKGRFTISADT
SKNTAYLQMNSLRAEDTAVYYCAR***SWAM***DYWGQGTLVTVSS**GGGGS**DIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKP
GKAPKLLIY***SASDLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLI***TFGQGTKVEIK**GGGGSGGGGSEPKSSDKTHT**CPP
CPAPE*AA***GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN
GKEYKCKVSNKALPA**S**IEKTISKAKGQPREPQVYTLPP**S**RE**L**MT**K**NQVSL**S**C*A*VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF
FL**Y**SKLTVDKSRWQQGNVFSCSVMHE*A*LHNHYTQKSLSLSPGK**GGGSGGGGSGGGGSGGGGS**GSTGEVQLVESGGGLVQPGGSLRLSCAA
SGF***TSDFYFI***HWVRQAPGKGLEWVA***TTYPFIGNTY***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***AFPGSWHPF***DYWG
QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY
ICNVNHKPSNTKVDKKVEPKSCDKTHT* (SEQ ID NO: 970)

ANT42 Hc Hole LALAPS Merchant S-S

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***DFSSSSS***HWVRQAPGKGLEWVA***SISSSYGYTY***YADSVKGRFTISADT
SKNTAYLQMNSLRAEDTAVYYCAR***SWAM***DYWGQGTLVTVSS**GGGGS**DIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKP
GKAPKLLIY***SASDLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLI***TFGQGTKVEIK**GGGGSGGGGSEPKSSDKTHT**CPP
CPAPE*AA***GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN
GKEYKCKVSNKALPA**S**IEKTISKAKGQPREPQVC**T**LPP**S**REEMTKNQVSL**S**C*A*VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF
FL**Y**SKLTVDKSRWQQGNVFSCSVMHE*A*LHNHYTQKSLSLSPGK**GGGSGGGGSGGGGSGGGGS**GSTGEVQLVESGGGLVQPGGSLRLSCAA

SGF***TSDFYFH***WVRQAPGKGLEWVA***TIYPFIGNTY***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***AFPGSYHPF***DYWG
QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY
ICNVNHKPSNTKVDKKVEPKSCDKTHT* (SEQ ID NO: 971)

Mature ANT42 Hc Hole DANG

EVQLVESGGGLVQPGGSLRLSCAASGF***DFSSSSI***HWVRQAPGKGLEWVA***SISSSYGYTY***YADSVKGRFTISADTSKNTAYLQMNSLRA
EDTAVYYCAR***SWAMD***YWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SASDLY***
SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLI***TFGQGTKVEIKGGGGSGGGGSEPKSSDKTHTCPPCPAPELLGGPSVFLF
PPKPKDTLMISRTPEVTCVVV***A***VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYG***S***TYRVVSVLTVLHQDWLNGKEYKCKVSNKALP
APIEKTISKAKGQPREPQVYTLPP***R***EEMTKNQVSL***S***C***A***VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY***S***KLTVDKSRWQQ
GNVFSCSVMHEALHNHYTQKSLSLSPGK***G***GGSGGGGSGGGSGGSG***S***TGEVQLVESGGGLVQPGGSLRLSCAASGF***TSDFYFH***WVRQ
APGKGLEWVA***TIYPFIGNTY***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***AFPGSYHPF***DYWGQGTLVTVSSASTKGP
SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD
KKVEPKSCDKTHT* (SEQ ID NO: 972)

Mature ANT42 Hc Hole LALAPS

EVQLVESGGGLVQPGGSLRLSCAASGF***DFSSSSI***HWVRQAPGKGLEWVA***SISSSYGYTY***YADSVKGRFTISADTSKNTAYLQMNSLRA
EDTAVYYCAR***SWAMD***YWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SASDLY***
SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLI***TFGQGTKVEIKGGGGSGGGGSEPKSSDKTHTCPPCPAPE***AA***GGPSVFLF
PPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP
ASIEKTISKAKGQPREPQVYTLPP***R***EEMTKNQVSL***S***C***A***VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY***S***KLTVDKSRWQQ
GNVFSCSVMHEALHNHYTQKSLSLSPGK***G***GGSGGGGSGGGSGGSG***S***TGEVQLVESGGGLVQPGGSLRLSCAASGF***TSDFYFH***WVRQ
APGKGLEWVA***TIYPFIGNTY***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***AFPGSYHPF***DYWGQGTLVTVSSASTKGP
SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD
KKVEPKSCDKTHT* (SEQ ID NO: 973)

Mature ANT42 Hc Hole LALAPS Merchant

EVQLVESGGGLVQPGGSLRLSCAASGF***DFSSSSI***HWVRQAPGKGLEWVA***SISSSYGYTY***YADSVKGRFTISADTSKNTAYLQMNSLRA
EDTAVYYCAR***SWAMD***YWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SASDLY***
SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YAGAGLI***TFGQGTKVEIKGGGGSGGGGSEPKSSDKTHTCPPCPAPE***AA***GGPSVFLF

PPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP
ASIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQ
QGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGGGSGSTGEVQLVQPGGSLRLSCAASGFTSDFYFEHWVR
QAPGKGLEWVATIYPFIGNTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARAFPGSYHIPFDYWGQGTLVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD
KKVEPKSCDKTHT* (SEQ ID NO: 974)

Mature ANT42 Hc Hole LALAPS Merchant S-S

EVQLVESGGGLVQPGGSLRLSCAASGFDFSSSSIHWVRQAPGKGLEWVASISSSYGYTYYADSVKGRFTISADTSKNTAYLQMNSLRA
EDTAVYYCARSWAMDYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIYSASDLY
SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYAGAGLTFGQGTKVEIKGGGGSGGGGSEPKSSDKTHTCPPCPAPEAAGGPSVFLF
PPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP
ASIEKTISKAKGQPREPQVCTLPPSREEMTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQ
QGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGGGSGSTGEVQLVQPGGSLRLSCAASGFTSDFYFEHWVR
QAPGKGLEWVATIYPFIGNTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARAFPGSYHIPFDYWGQGTLVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD
KKVEPKSCDKTHT* (SEQ ID NO: 975)

ANT42 Hc knob DANG

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGFDFTAYAMHWVRQAPGKGLEWVASIYPSGGYTAYADSVKGRFTISA
DTSKNTAYLQMNSLRAEDTAVYYCARRSYYFALDYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWY
QQKPGKAPKLLIYSASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYWAYYSPITFGQGTKVEIKGGGGSGGGGSEPKSSDKT
HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQ
DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPMVEDLPPSREEMTKNQVSLWCMVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSL
RLSCAASGFTSDFYFEHWVRQAPGKGLEWVATIYPFIGNTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARAFPGSYHIP
FDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS
LGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT* (SEQ ID NO: 976)

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ANT42 Hc knob LALAPS

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***DFTAYAM***HWVRQAPGKGLEWVA***SIYPSGGYTA***YADSVKGRFTISA
DTSKNTAYLQMNSLRAEDTAVYYCAR***RSYYFAL***DYWGQGTLVTVSS**GGGGS**DIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWY
QQKPGKAPKLLIY***SASSLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YWAYYSPT***FGQGTKVEIK**GGGSGGGGSGGGGS**EPKSSDKT
HTCPPCPAPE***AAGGPSVFLFPPKPK***DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ
DWLNGKEYKCKVSNKALPA**S**IEKTISKAKGQPREP***MVFD***LPPSR**E**EMTKNQVSL***W***C***M***VKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK**G**GGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSL
RLSCAASGF***TSDFYFT***HWVRQAPGKGLEWVA***TIYPFIGNTY***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***AFPGSYHIP***
FDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS
LGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT* (SEQ ID NO: 977)

ANT42 Hc knob LALAPS Merchant

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***DFTAYAM***HWVRQAPGKGLEWVA***SIYPSGGYTA***YADSVKGRFTISA
DTSKNTAYLQMNSLRAEDTAVYYCAR***RSYYFAL***DYWGQGTLVTVSS**GGGGS**DIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWY
QQKPGKAPKLLIY***SASSLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YWAYYSPT***FGQGTKVEIK**GGGSGGGGSGGGGS**EPKSSDKT
HTCPPCPAPE***AAGGPSVFLFPPKPK***DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ
DWLNGKEYKCKVSNKALPA**S**IEKTISKAKGQPREP***MVFD***LPPSR**E**EMTKNQVSL***W***C***M***VKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK**G**GGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSLR
LSCAASGF***TSDFYFT***HWVRQAPGKGLEWVA***TIYPFIGNTY***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***AFPGSYHIPF***
DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL
GTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT* (SEQ ID NO: 978)

ANT42 Hc knob LALAPS Merchant S-S

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***DFTAYAM***HWVRQAPGKGLEWVA***SIYPSGGYTA***YADSVKGRFTISA
DTSKNTAYLQMNSLRAEDTAVYYCAR***RSYYFAL***DYWGQGTLVTVSS**GGGGS**DIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWY
QQKPGKAPKLLIY***SASSLY***SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YWAYYSPT***FGQGTKVEIK**GGGSGGGGSGGGGS**EPKSSDKT
HTCPPCPAPE***AAGGPSVFLFPPKPK***DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ
DWLNGKEYKCKVSNKALPA**S**IEKTISKAKGQPREPQVYTLPP**C**REEMTKNQVSL***W***CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK**G**GGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSLR

LSCAASGF***TSDFYFI***HWVRQAPGKGLEWVA***TIYPFIGNTY***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***AFPGSYHPF***
DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL
GTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT* (SEQ ID NO: 979)

Mature ANT42 Hc knob DANG

EVQLVESGGGLVQPGGSLRLSCAASGF***DFTAYAM***HWVRQAPGKGLEWVA***SIYPSGGYTA***YADSVKGRFTISADTSKNTAYLQMNSLR
AEDTAVYYCAR***RSYYFAL***DYWGQGTLVTVSS<u>GGGGS</u>DIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SAS***
SLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YWAYYSPT***TFGQGTKVEIK<u>GGGGSGGGGSEPKSSDKTHTCPPCPAPELLGGPS</u>
VFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSN
KALPAPIEKTISKAKGQPREP<u>MVFD</u>LPPSREEMTKNQVSL***WCM***VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK
SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK<u>GGGSGGGSGGGSGGGSGSTG</u>EVQLVESGGGLVQPGGSLRLSCAASGF***TSDFYFI***
HWVRQAPGKGLEWVA***TIYPFIGNTY***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***AFPGSYHPF***DYWGQGTLVTVSS
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS
NTKVDKKVEPKSCDKTHT* (SEQ ID NO: 980)

Mature ANT42 Hc knob LALAPS

EVQLVESGGGLVQPGGSLRLSCAASGF***DFTAYAM***HWVRQAPGKGLEWVA***SIYPSGGYTA***YADSVKGRFTISADTSKNTAYLQMNSLR
AEDTAVYYCAR***RSYYFAL***DYWGQGTLVTVSS<u>GGGGS</u>DIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SAS***
SLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YWAYYSPT***TFGQGTKVEIK<u>GGGGSGGGGSEPKSSDKTHTCPPCPAPE*AA*GGPS</u>
VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN
KALPASIEKTISKAKGQPREP<u>MVFD</u>LPPSREEMTKNQVSL***WCM***VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK
SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK<u>GGGSGGGSGGGSGGGSGSTG</u>EVQLVESGGGLVQPGGSLRLSCAASGF***TSDFYFI***
HWVRQAPGKGLEWVA***TIYPFIGNTY***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***AFPGSYHPF***DYWGQGTLVTVSS
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS
NTKVDKKVEPKSCDKTHT* (SEQ ID NO: 981)

Mature ANT42 Hc knob LALAPS Merchant

EVQLVESGGGLVQPGGSLRLSCAASGF***DFTAYAM***HWVRQAPGKGLEWVA***SIYPSGGYTA***YADSVKGRFTISADTSKNTAYLQMNSLR
AEDTAVYYCAR***RSYYFAL***DYWGQGTLVTVSS<u>GGGGS</u>DIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VAWYQQKPGKAPKLLIY***SAS***
SLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YWAYYSPT***TFGQGTKVEIK<u>GGGGSGGGGSEPKSSDKTHTCPPCPAPE*AA*GGPS</u>

VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN
KALPASIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK
SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSLRLSCAAASGF*TSDFYFI*
HWVRQAPGKGLEWVA*TTYPFIGNTYY*ADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR*AFPGSYHPFD*YWGQGTLVTVSS
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS
NTKVDKKVEPKSCDKTHT* (SEQ ID NO: 982)

Mature ANT42 Hc knob LALAPS Merchant S-S

EVQLVESGGGLVQPGGSLRLSCAASGF*DFTAYAM*HWVRQAPGKGLEWVA*SYPSGGYTA*YADSVKGRFTISADTSKNTAYLQMNSLR
AEDTAVYYCAR*RSYYFALD*YWGQGTLVTVSS<u>GGGGS</u>DIQMTQSPSSLSASVGDRVTITCRAS*QSVSSA*VAWYQQKPGKAPKLLIY*SAS*
*SLY*SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ*YWAYYSPT*TFGQGTKVEIK<u>GGGSGGGGSGGGGS</u>EPKSSDKTHTCPPCPAPE*AA*GGPS
VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN
KALPA*S*IEKTISKAKGQPREPQVYTLPP<u>C</u>REEMTKNQVSL<u>#</u>CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK
SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK<u>GGGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSLRLSCAAASGF*TSDFYFI*</u>
HWVRQAPGKGLEWVA*TTYPFIGNTYY*ADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR*AFPGSYHPFD*YWGQGTLVTVSS
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS
NTKVDKKVEPKSCDKTHT* (SEQ ID NO: 983)

ANT42 LC

MNLLLLTFVAAAVADIQMTQSPSSLSASVGDRVTITCRAS*QSVSSA*VAWYQQKPGKAPKLLIY*SASSLY*SGVPSRFSGSRSGTDFTLTIS
SLQPEDFATYYCQQ*STGSLI*TFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE
QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC* (SEQ ID NO: 912)

Mature ANT42 LC

DIQMTQSPSSLSASVGDRVTITCRAS*QSVSSA*VAWYQQKPGKAPKLLIY*SASSLY*SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ*S*
*TGSLI*TFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTL
SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 984)

ANT80-1 Hole

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***TLSYSYI***HWVRQAPGKGLEWVA***SIYSYTGATD***YADSVKGRFTISADT
SKNTAYLQMNSLRAEDTAVYYCAR***YWSTNRILSYGGMD***YWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***
VAWYQQKPGKAPKLLIYSASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YFDPIT***FGQGTKVEIKGGGGSGGGGSEPKSSD
KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPIRELMTSNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSL
RLSCAASGF***NIAYSSM***HWVRQAPGKGLEWVA***TIYPSYSSTY***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***YYAMD***YW
GQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT
YICNVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 986)

ANT80-2 Knob

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***DLSHSSI***HWVRQAPGKGLEWVA***SISSHYGYTH***YADSVKGRFTISAD
TSKNTAYLQMNSLRAEDTAVYYCAR***SSYFPWFFAL***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***DVSTA***VA
WYQQKPGKAPKLLIY***SASFLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***HYTTPPT***FGQGTKVEIKGGGGSGGGGSEPKTSDK
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPMVFDLPPSREEMTKNQVSLWCMVKGFYPSDIAVEWESNGQPENNYKTTPPV
LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGS
LRLSCAASGF***NIAYSSM***HWVRQAPGKGLEWVA***TIYPSYSSTY***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***YYAMD***DY
WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
QTYICNVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 987)

ANT98-1 Hole

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***TLSYSYI***HWVRQAPGKGLEWVA***SIYSYTGATD***YADSVKGRFTISADT
SKNTAYLQMNSLRAEDTAVYYCAR***YWSTNRILSYGGMD***YWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***
VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YFDPT***FGQGTKVEIKGGGGSGGGGSEPKSSD
KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPIRELMTSNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSL

RLSCAASGF***NIAYSSM***HWVRQAPGKGLEWVA***TIYPSYSSTI***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***DYAMD***DYW
GQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT
YICNVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 988)

ANT98-2 Knob

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***DLSHSSI***HWVRQAPGKGLEWVA***SISSHYGTTHY***ADSVKGRFTISAD
TSKNTAYLQMNSLRAEDTAVYYCAR***SSYFPWFFAL***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***DVSTA***VA
WYQQKPGKAPKLLIY***SASFLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***HYTTPP***TFGQGTKVEIKGGGGSGGGGSEPKTSDK
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPMVFDLPPSREEMTKNQVSLWCMVKGFYPSDIAVEWESNGQPENNYKTTPPV
LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGS
LRLSCAASGF***NIAYSSM***HWVRQAPGKGLEWVA***TIYPSYSSTY***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***DYAMD***DY
WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
QTYICNVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 989)

ANT99-1 Hole

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***TLSYSYI***HWVRQAPGKGLEWVA***SIYSYTGATD***YADSVKGRFTISADT
SKNTAYLQMNSLRAEDTAVYYCAR***YWSTNRILSYGGM***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***
VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YFDPT***TFGQGTKVEIKGGGGSGGGGSEPKSSD
KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPIRELMTSNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGSL
RLSCAASGF***NIAYSSM***HWVRQAPGKGLEWVA***TIYPSYSSTY***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***YYDM***DYW

GQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT
YICNVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 990)

ANT99-2 Knob

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***DLSHSSH***HWVRQAPGKGLEWVA***SISSHHYGYTHY***YADSVKGRFTISAD
TSKNTAYLQMNSLRAEDTAVYYCAR***SSYFPWFFAL***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRAS***QDVSTA***VA
WYQQKPGKAPKLLIY***SASFLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***HYTTPP***TFGQGTKVEIKGGGSGGGGSEPKTSDK
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPMVFDLPPSREEMTKNQVSLWCMVKGFYPSDIAVEWESNGQPENNYKTTPPV
LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSGGGSGSTGEVQLVESGGGLVQPGGS
LRLSCAASGF***NIAYSSMH***WVRQAPGKGLEWVA***TIYPSYSSTY***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***YYDMD***Y
WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
QTYICNVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 991)

ANT80 ANT98 ANT99 LC

MNLLLILTFVAAAVADIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTIS
SLQPEDFATYYCQQ***AHYEPT***TFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE
QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 992)

CM0042 (Dia-Fc-Dia)

MNLLLILTFVAAAVAEFEVQLVESGGGLVQPGGSLRLSCAASGF***NIGSSSI***HWVRQAPGKGLEWVA***SIYSAFASTS***YADSVKGRFTISA
DTSKNTAYLQMNSLRAEDTAVYYCAR***YHFPFGFAL***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VA
WYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***GYYLF***TFGQGTKVEIKLEDKTHTKVEPKSSDKTH
TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS
DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATPESGGGEVQLVESGGGLVQPGGSLRLSC
AASGF***NISYSSH***WVRQAPGKGLEWVA***YISSYYGYTY***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***AHYFPWAGAMD***
YWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTL
TISSLQPEDFATYYCQQ***YSWGPFT***FGQGTKVEIK (SEQ ID NO: 993)

CM0011 Hole (Dia-Fc-Dia)

MNLLLILTFVAAAVAEFEVQLVESGGGLVQPGGSLRLSCAASGF***NIGSSSI***HWVRQAPGKGLEWVA***SIYSAFASTS***YADSVKGRFTISA
DTSKNTAYLQMNSLRAEDTAVYYCAR***YHFPFGFAL***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***VA
WYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***GVYLF***TFGQGTKVEIKLEDKTHTKVEPKSSDKTH
NCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPIRELMTSNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
GSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATPESGGGEVQLVESGGGLVQPGGSLRLSCA
ASGF***NISSYYI***HWVRQAPGKGLEWVA***SIYSSYGYTSY***ADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***TVRGSKKPYFSGW***
AMDYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGT
DFTLTISSLQPEDFATYYCQQ***YSWGPF***TFGQGTKVEIK (SEQ ID NO: 994)

CM0011 Knob (Dia-Fc-Dia)

MNLLLILTFVAAAVAEFEVQLVESGGGLVQPGGSLRLSCAASGF***NIGSSSI***HWVRQAPGKGLEWVA***SIYSAFASTS***YADSVKGRFTISA
DTSKNTAYLQMNSLRAEDTAVYYCAR***YHFPFGFAL***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***VA
WYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***GVYLF***TFGQGTKVEIKLEDKTHTKVEPKTSDKTH
TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPMVFDLPPSREEMTKNQVSLWCMVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATPESGGGEVQLVESGGGLVQPGGSLRLS
CAASGF***NISYSSI***HWVRQAPGKGLEWVA***YISSYYGYTTY***ADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***AHYFPWAGAM***
DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDF
TLTISSLQPEDFATYYCQQ***YYWPT***TFGQGTKVEIK (SEQ ID NO: 995)

CM0126 Hole (Dia-Fc-Dia)

MNLLLILTFVAAAVAEFEVQLVESGGGLVQPGGSLRLSCAASGF***NIHSSSI***HWVRQAPGKGLEWVA***ATYSSFGSIT***YADSVKGRFTISA
DTSKNTAYLQMNSLRAEDTAVYYCAR***YHHPFGYALD***YWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***VA
WYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***GVYLF***TFGQGTKVEIKLEDKTHTKVEPKSSDKTH
NCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPIRELMTSNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
GSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATPESGGGEVQLVESGGGLVQPGGSLRLSCA
ASGF***NISSYYI***HWVRQAPGKGLEWVA***SIYSSYGYTSY***ADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***TVRGSKKPYFSGW***

AMDYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSS4***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGT
DFTLTISSLQPEDFATYYCQQ***YSWGPF***TFGQGTKVEIK (SEQ ID NO: 996)

CM0126 Knob (Dia-Fc-Dia)

MNLLLILTFVAAAVAEFEVQLVESGGGLVQPGGSLRLSCAASGF***NIHSSSI***HWVRQAPGKGLEWVA***ATYSSFGSITY***ADSVKGRFTISA
DTSKNTAYLQMNSLRAEDTAVYYCAR***YHIIPFGYALD***YWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSS4***VA
WYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***GVYLF***TFGQGTKVEIKLEDKTHTKVEPKTSDKTH
TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPMVFDLPPSREEMTKNQVSLWCMVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATPESGGGEVQLVESGGGLVQPGGSLRLS
CAASGF***NISYSSI***HWVRQAPGKGLEWVA***YISSYYGYTTY***ADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***AHYFPWAGAM***
DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSS4***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDF
TLTISSLQPEDFATYYCQQ***YYWPT***TFGQGTKVEIK (SEQ ID NO: 997)

CM0107 Hole (Dia-Fc-scFv)

MNLLLILTFVAAAVAEFEVQLVESGGGLVQPGGSLRLSCAASGF***NIGSSSI***HWVRQAPGKGLEWVA***SIYS4FASTS***YADSVKGRFTISA
DTSKNTAYLQMNSLRAEDTAVYYCAR***YHFPFGFAL***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSS4***VA
WYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***GVYLF***TFGQGTKVEIKLEDKTHTKVEPKSSDKTH
NCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPIRELMTSNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
GSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATPESGGGDIQMTQSPSSLSASVGDRVTITCR
ASQ***SVSS4***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YSWGPF***TFGQGTKVEIKGTTAASG
SSGGSSSGAEVQLVESGGGLVQPGGSLRLSCAASGF***NISYSSI***HWVRQAPGKGLEWVA***YISSYYGYTTY***ADSVKGRFTISADTSKNTAY
LQMNSLRAEDTAVYYCAR***AHYFPWAG4***MDYWGQGTLVTVSS (SEQ ID NO: 998)

CM0107 Knob (Dia-Fc-scFv)

MNLLLILTFVAAAVAEFEVQLVESGGGLVQPGGSLRLSCAASGF***NIGSSSI***HWVRQAPGKGLEWVA***SIYS4FASTS***YADSVKGRFTISA
DTSKNTAYLQMNSLRAEDTAVYYCAR***YHFPFGFAL***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSS4***VA
WYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***GVYLF***TFGQGTKVEIKLEDKTHTKVEPKTSDKTH
TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD

WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPMVFDLPPSREEMTKNQVSLWCMVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATPESGGGDIQMTQSPSSLSASVGDRVTIT
CRASQ***SVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YSWGPF***TFGQGTKVEIKGTTAA
SGSSGGSSSGAEVQLVESGGGLVQPGGSLRLSCAASGF***NISYSSI***HWVRQAPGKGLEWVA***YISSYYGYTY***YADSVKGRFTISADTSKNT
AYLQMNSLRAEDTAVYYCAR***AHYFPWAGAMD***YWGQGTLVTVSS (SEQ ID NO: 999)

CM0108 Hole (Dia-Fc-scFv)

MNLLLILTFVAAAVAEFEVQLVESGGGLVQPGGSLRLSCAASGF***NIGSSSI***HWVRQAPGKGLEWVA***SIYSAFASTSY***YADSVKGRFTISA
DTSKNTAYLQMNSLRAEDTAVYYCAR***YHFPFGFAL***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***VA
WYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***GVYLF***TFGQGTKVEIKLEDKTHTKVEPKSSDKTH
NCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPIRELMTSNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
GSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATPESGGGDIQMTQSPSSLSASVGDRVTITCR
ASQ***SVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YYWPT***TFGQGTKVEIKGTTAASGSS
GGSSSGAEVQLVESGGGLVQPGGSLRLSCAASGF***NISSYYI***HWVRQAPGKGLEWVA***SIYSSYGYTS***YADSVKGRFTISADTSKNTAYLQ
MNSLRAEDTAVYYCAR***TVRGSKKPYFSGWAMD***YWGQGTLVTVSS (SEQ ID NO: 1000)

CM0108 Knob (Dia-Fc-scFv)

MNLLLILTFVAAAVAEFEVQLVESGGGLVQPGGSLRLSCAASGF***NIGSSSI***HWVRQAPGKGLEWVA***SIYSAFASTSY***YADSVKGRFTISA
DTSKNTAYLQMNSLRAEDTAVYYCAR***YHFPFGFAL***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***VA
WYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***GVYLF***TFGQGTKVEIKLEDKTHTKVEPKTSDKTH
TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPMVFDLPPSREEMTKNQVSLWCMVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATPESGGGDIQMTQSPSSLSASVGDRVTIT
CRASQ***SVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YYWPT***TFGQGTKVEIKGTTAAS
GSSGGSSSGAEVQLVESGGGLVQPGGSLRLSCAASGF***NISSYYI***HWVRQAPGKGLEWVA***SIYSSYGYTS***YADSVKGRFTISADTSKNTA
YLQMNSLRAEDTAVYYCAR***TVRGSKKPYFSGWAMD***YWGQGTLVTVSS (SEQ ID NO: 1001)

CM0108 Hole (Dia-Fc-scFv)

MNLLLILTFVAAAVAEFEVQLVESGGGLVQPGGSLRLSCAASGF***NIGSSSI***HWVRQAPGKGLEWVA***SIYSAFASTS***YADSVKGRFTISA
DTSKNTAYLQMNSLRAEDTAVYYCAR***YHFPFGFAL***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VA
WYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***GVYLF***TFGQGTKVEIKLEDKTHTKVEPKSSDKTH
NCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPIRELMTSNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
GSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATPESGGGDIQMTQSPSSLSASVGDRVTITCR
ASQ***SVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YYWPT***TFGQGTKVEIKGTTAASGSS
GGSSSGAEVQLVESGGGLVQPGGSLRLSCAASGF***NISSYYI***HWVRQAPGKGLEWVA***SIYSSYGYTS***YADSVKGRFTISADTSKNTAYLQ
MNSLRAEDTAVYYCAR***TVRGSKKPYFSGWAMD***YWGQGTLVTVSS (SEQ ID NO: 1000)

CM0108 Knob (Dia-Fc-scFv)

MNLLLILTFVAAAVAEFEVQLVESGGGLVQPGGSLRLSCAASGF***NIGSSSI***HWVRQAPGKGLEWVA***SIYSAFASTS***YADSVKGRFTISA
DTSKNTAYLQMNSLRAEDTAVYYCAR***YHFPFGFAL***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VA
WYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***GVYLF***TFGQGTKVEIKLEDKTHTKVEPKTSDKTH
TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPMVFDLPPSREEMTKNQVSLWCMVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATPESGGGDIQMTQSPSSLSASVGDRVTIT
CRASQ***SVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YYWPT***TFGQGTKVEIKGTTAAS
GSSGGSSSGAEVQLVESGGGLVQPGGSLRLSCAASGF***NISSYYI***HWVRQAPGKGLEWVA***SIYSSYGYTS***YADSVKGRFTISADTSKNTA
YLQMNSLRAEDTAVYYCAR***TVRGSKKPYFSGWAMD***YWGQGTLVTVSS (SEQ ID NO: 1001)

CM0109 Hole (Dia-Fc-scFv)

MNLLLILTFVAAAVAEFEVQLVESGGGLVQPGGSLRLSCAASGF***NIGSSSI***HWVRQAPGKGLEWVA***SIYSAFASTS***YADSVKGRFTISA
DTSKNTAYLQMNSLRAEDTAVYYCAR***YHFPFGFAL***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VA
WYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***GVYLF***TFGQGTKVEIKLEDKTHTKVEPKSSDKTH
NCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPIRELMTSNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
GSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATPESGGGDIQMTQSPSSLSASVGDRVTITCR
ASQ***SVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YYWPT***TFGQGTKVEIKGTTAASGSS

GGSSSGAEVQLVESGGGLVQPGGSLRLSCAASGF***NISSYYI***HWVRQAPGKGLEWVA***SIYSSYGYTS***YADSVKGRFTISADTSKNTAYLQ
MNSLRAEDTAVYYCAR***TVRGSKKPYFSGWAMD***YWGQGTLVTVSS (SEQ ID NO: 1000)

CM0109 Knob (Dia-Fc-scFv)

MNLLLILTFVAAAVAEFEVQLVESGGGLVQPGGSLRLSCAASGF***NIGSSSI***HWVRQAPGKGLEWVA***SIYSAFASTS***YADSVKGRFTISA
DTSKNTAYLQMNSLRAEDTAVYYCAR***YHFPFGFALD***YWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***VA
WYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***GVYLF***TFGQGTKVEIKLEDKTHTKVEPKTSDKTH
TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPMVFDLPPSREEMTKNQVSLWCMVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATPESGGGDIQMTQSPSSLSASVGDRVTIT
CRASQ***SVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YSWGPF***TFGQGTKVEIKGTTAA
SGSSGGSSSGAEVQLVESGGGLVQPGGSLRLSCAASGF***NISYSSI***HWVRQAPGKGLEWVA***YISSYYGYTT***YADSVKGRFTISADTSKNT
AYLQMNSLRAEDTAVYYCAR***AIIYFPWAGAMD***YWGQGTLVTVSS (SEQ ID NO: 999)

CT003 Hole (Dia-Fc-scFv)

MNLLLILTFVAAAVAEFEVQLVESGGGLVQPGGSLRLSCAASGF***NISSYYI***HWVRQAPGKGLEWVA***SIYSSYGYTS***YADSVKGRFTISA
DTSKNTAYLQMNSLRAEDTAVYYCAR***TVRGSKKPYFSGWAMD***YWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***S***
VSSAVAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YSWGPF***TFGQGTKVEIKLEDKTHTKVEP
KSSDKTHNCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV
LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPIRELMTSNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATPESGGGEVQLVESGGGLVQPG
GSLRLSCAASGF***NIHSSSI***HWVRQAPGKGLEWVA***ATYSSFGSITY***ADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***YIIIIPF***
GYALDYWGQGTLVTVSSGTTAASGSSGGSSSGADIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***
GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***GVYLF***TFGQGTKVEIK (SEQ ID NO: 1002)

CT003 Knob (Dia-Fc-scFv)

MNLLLILTFVAAAVAEFEVQLVESGGGLVQPGGSLRLSCAASGF***NISYSSI***HWVRQAPGKGLEWVA***YISSYYGYTT***YADSVKGRFTISA
DTSKNTAYLQMNSLRAEDTAVYYCAR***AIIYFPWAGAMD***YWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***V
AWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YYWPT***TFGQGTKVEIKLEDKTHTKVEPKTSDKT
HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ

DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPMVFDLPPSREEMTKNQVSLWCMVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATPESGGGEVQLVESGGGLVQPGGSLRL
SCAASGF*NIHSSSI*HWVRQAPGKGLEWVA*ATYSSFGSITY*ADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR*YHHPFGYA*LD
YWGQGTLVTVSSGTTAASGSSGGSSSGADIQMTQSPSSLSASVGDRVTITCRASQ*SVSSA*VAWYQQKPGKAPKLLIY*SASSLYS*GVPSRF
SGSRSGTDFTLTISSLQPEDFATYYCQQ*GVYLF*TFGQGTKVEIK (SEQ ID NO: 1003)

CM0112 Hole (scFv-Fc-Dia)

MNLLLILTFVAAAVAEFDIQMTQSPSSLSASVGDRVTITCRASQ*SVSSA*VAWYQQKPGKAPKLLIY*SASSLYS*GVPSRFSGSRSGTDFTLT
ISSLQPEDFATYYCQQ*GVYLF*TFGQGTKVEIKGTTAASGSSGGSSSGAEVQLVESGGGLVQPGGSLRLSCAASGF*NIGSSSI*HWVRQAP
GKGLEWVA*SIYSAFASTS*YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR*YHFPFGFAL*DYWGQGTLVTVSSLEDKTHTK
VEPKSSDKTHNCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV
VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPIRELMTSNQVSLSCAVKGFYPSDIAVEWESNGQPENN
YKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATPESGGGEVQLVESGGGLV
QPGGSLRLSCAASGF*NISSYIH*HWVRQAPGKGLEWVA*SIYSSYGYTS*YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR*TV*
RGSKKPYFSGWAMDYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ*SVSSA*VAWYQQKPGKAPKLLIY*SASSLYS*G
VPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ*YSWGPF*TFGQGTKVEIK (SEQ ID NO: 1004)

CM0112 Knob (scFv-Fc-Dia)

MNLLLILTFVAAAVAEFDIQMTQSPSSLSASVGDRVTITCRASQ*SVSSA*VAWYQQKPGKAPKLLIY*SASSLYS*GVPSRFSGSRSGTDFTLT
ISSLQPEDFATYYCQQ*GVYLF*TFGQGTKVEIKGTTAASGSSGGSSSGAEVQLVESGGGLVQPGGSLRLSCAASGF*NIGSSSI*HWVRQAP
GKGLEWVA*SIYSAFASTS*YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR*YHFPFGFAL*DYWGQGTLVTVSSLEDKTHTK
VEPKTSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV
VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPMVFDLPPSREEMTKNQVSLWCMVKGFYPSDIAVEWESNGQPEN
NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATPESGGGEVQLVESGGGL
VQPGGSLRLSCAASGF*NISSYIH*HWVRQAPGKGLEWVA*YISSYYGYTT*YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR*A*
HYFPWAGAMDYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ*SVSSA*VAWYQQKPGKAPKLLIY*SASSLYS*GVPSR
FSGSRSGTDFTLTISSLQPEDFATYYCQQ*YYWPT*TFGQGTKVEIK (SEQ ID NO: 1005)

CM0110 Hole (scFv-Fc-scFv)

MNLLLILTFVAAAVAEFDIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLT
ISSLQPEDFATYYCQQ***GVYLF***TFGQGTKVEIKGTTAASGSSGGSSSGAEVQLVESGGGLVQPGGSLRLSCAASGF***NIGSSSI***HWVRQAP
GKGLEWVA***SIYSAFASTS***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***YHFPFGFAL***DYWGQGTLVTVSSLEDKTHTK
VEPKSSDKTHNCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV
VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPIRELMTSNQVSLSCAVKGFYPSDIAVEWESNGQPENN
YKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATPESGGGDIQMTQSPSSLSA
SVGDRVTITCRASQ***SVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YYWPT***TFGQGTKV
EIKGTTAASGSSGGSSSGAEVQLVESGGGLVQPGGS**LRLSCAASGF*NISSYYI*HWVRQAPGKGLEWVA***SIYSSYGYTS***YADSVKGRFTIS
ADTSKNTAYLQMNSLRAEDTAVYYCAR***TVRGSKKPYFSGWAMD***YWGQGTLVTVSS (SEQ ID NO: 1006)

CM0110 Knob (scFv-Fc-scFv)

MNLLLILTFVAAAVAEFDIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLT
ISSLQPEDFATYYCQQ***GVYLF***TFGQGTKVEIKGTTAASGSSGGSSSGAEVQLVESGGGLVQPGGSLRLSCAASGF***NIGSSSI***HWVRQAP
GKGLEWVA***SIYSAFASTS***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***YHFPFGFAL***DYWGQGTLVTVSSLEDKTHTK
VEPKTSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV
VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPMVFDLPPSREEMTKNQVSLWCMVKGFYPSDIAVEWESNGQPEN
NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATPESGGGDIQMTQSPSSLS
ASVGDRVTITCRASQ***SVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YSWGPF***TFGQGT
KVEIKGTTAASGSSGGSSSGAEVQLVESGGGLVQPGGSLRLSCAASGF***NISYSSI***HWVRQAPGKGLEWVA***YISSYYGYTY***YADSVKGRF
TISADTSKNTAYLQMNSLRAEDTAVYYCAR***AHYFPIWAGAMD***YWGQGTLVTVSS (SEQ ID NO: 1007)

CT001 CM0299 CM0300 CM0301 ANT1 LC

MNLLLILTFVAAAVADIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTIS
SLQPEDFATYYCQQ***GVYLF***TFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE
QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 1008)

CT001 Hole (bsIgG-dia)

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***NIHSSSI***HWVRQAPGKGLEWVA***ATYSSFGSIT***YADSVKGRFTISADT
SKNTAYLQMNSLRAEDTAVYYCAR***YHHPFGYAL***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW
NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK
TISKAKGQPREPQVYTLPPIRELMTSNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVF
SCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATPESGGGEVQLVESGGGLVQPGGSLRLSCAASGF***NISYYIH***HWVRQAPGKGLE
WVA***SIYSSYGYTS***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***TVRGSKKPYFSGWAMD***YWGQGTLVTVSSGGGGSDI
QMTQSPSSLSASVGDRVTITCRASQ***SVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YS***
WGPFTFGQGTKVEIK (SEQ ID NO: 1009)

CT001 Knob (bsIgG-dia)

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***NIHSSSI***HWVRQAPGKGLEWVA***ATYSSFGSIT***YADSVKGRFTISADT
SKNTAYLQMNSLRAEDTAVYYCAR***YHHPFGYAL***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW
NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK
TISKAKGQPREPMVFDLPPSREEMTKNQVSLWCMVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN
VFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATPESGGGEVQLVESGGGLVQPGGSLRLSCAASGF***NISYSSI***HWVRQAPGKG
LEWVA***YISSYYGYTY***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***AHYFPWAGAMD***YWGQGTLVTVSSGGGGSDIQM
TQSPSSLSASVGDRVTITCRASQ***SVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YYWPT***
TFGQGTKVEIK (SEQ ID NO: 1010)

CM0299 Hc (IgG-Dia)

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***NIHSSSI***HWVRQAPGKGLEWVA***ATYSSFGSIT***YADSVKGRFTISADT
SKNTAYLQMNSLRAEDTAVYYCAR***YHHPFGYAL***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW
NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK
TISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV
FSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATPESGGGEVQLVESGGGLVQPGGSLRLSCAASGF***NISYSSI***HWVRQAPGKGL
EWVA***YISSYYGYTY***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***AHYFPWAGAMD***YWGQGTLVTVSSGGGGSDIQMT

QSPSSLSASVGDRVTITCRASQ***SVSS4***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YSWGPF***
TFGQGTKVEIK (SEQ ID NO: 1011)

CM0300 Hc (IgG-scFv)

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***NIHSSSI***HWVRQAPGKGLEWVA***ATYSSFGSITY***ADSVKGRFTISADT
SKNTAYLQMNSLRAEDTAVYYCAR***YHHPFGYALD***YWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW
NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK
TISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV
FSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATPESGGGDIQMTQSPSSLSASVGDRVTITCRASQ***SVSS4***VAWYQQKPGKAPK
LLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YSWGPF***TFGQGTKVEIKGTTAASGSSGGSSSGAEVQLVESGGGLVQ
PGGSLRLSCAASGF***NISYSSI***HWVRQAPGKGLEWVA***YISSYYGYTY***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***AHY***
FPWAGAMDYWGQGTLVTVSS (SEQ ID NO: 1012)

CM0301 Hc (IgG-scFv)

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***NIHSSSI***HWVRQAPGKGLEWVA***ATYSSFGSITY***ADSVKGRFTISADT
SKNTAYLQMNSLRAEDTAVYYCAR***YHHIPFGYAL***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW
NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK
TISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV
FSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATPESGGGDIQMTQSPSSLSASVGDRVTITCRASQ***SVSS4***VAWYQQKPGKAPK
LLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YYWPT***TFGQGTKVEIKGTTAASGSSGGSSSGAEVQLVESGGGLVQP
GGSLRLSCAASGF***NISSYYI***HWVRQAPGKGLEWVA***SIYSSYGYTS***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***TVRG***
SKKPYFSGWAMDYWGQGTLVTVSS (SEQ ID NO: 1013)

ANT1 Hole (Dia-Fc-Fab)

MNLLLILTFVAAAVAEFEVQLVESGGGLVQPGGSLRLSCAASGF***NISSYYI***HWVRQAPGKGLEWVA***SIYSSYGYTSY***ADSVKGRFTISA
DTSKNTAYLQMNSLRAEDTAVYYCAR***TVRGSKKPYFSGWAMD***YWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***S***
VSS4VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YYFLT***FGQGTKVEIKLEDKTHTKVEPKS
SDKTHNCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT

VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPIRELMTSNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPP
VLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATPESGGGEVQLVESGGGLVQPGGSL
RLSCAASGF***NIHSSSI***HWVRQAPGKGLEWVA***ATYSSFGSITY***ADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***YHHPFGYA***
LDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS
LGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 1014)

ANT1 Knob (Dia-Fc-Fab)

MNLLLILTFVAAAVAEFEVQLVESGGGLVQPGGSLRLSCAASGF***NISYSSI***HWVRQAPGKGLEWVA***SISPYYGYTTY***ADSVKGRFTISA
DTSKNTAYLQMNSLRAEDTAVYYCAR***SSYFPWFSAMD***YWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***V
AWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YYWPT***TFGQGTKVEIKLEDKTHTKVEPKTSDKT
HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ
DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPMVFDLPPSREEMTKNQVSLWCMVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATPESGGGEVQLVESGGGLVQPGGSLRL
SCAASGF***NIHSSSI***HWVRQAPGKGLEWVA***ATYSSFGSITY***ADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCA***RYHHPFGYALD***
YWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TQTYICNVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 1015)

Fab-Dia Hc (Fab-Dia)

MNLLLILTFVAAAVAEVQLVESGGGLVQPGGSLRLSCAASGF***NIHSSSI***HWVRQAPGKGLEWVA***ATYSSFGSITY***ADSVKGRFTISADT
SKNTAYLQMNSLRAEDTAVYYCAR***YHHPFGYAL***DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW
NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTGGSGGEVQLVESGGGLVQPGG
SLRLSCAASGF***TISYSSI***HWVRQAPGKGLEWVA***SISPYYGYTTY***ADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***SSYFPWF***
SAMDYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSG
TDFTLTISSLQPEDFATYYCQQ***YYWPT***TFGQGTKVEIK (SEQ ID NO: 1016)

Fab-Dia LC (Fab-Dia)

MNLLLILTFVAAAVADIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTIS
SLQPEDFATYYCQQ***GVYLF***TFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE
QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECGGGGSEVQLVESGGGLVQPGGSLRLSCAASGF***TISSYYI***H
WVRQAPGKGLEWVA***SIYSSYGYTTS***YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***TYRGSKKPYFSGWAMD***YWGQGTL

VTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPE
DFATYYCQQ***YYFLI***TFGQGTKVEIK (SEQ ID NO: 1017)

CH3 (Dia-CH3-Dia)

MNLLLLITFVAAAVAEFEVQLVESGGGLVQPGGSLRLSCAASGF***NIGSSSI***HWVRQAPGKGLEWVA***SIYSAFASTSY***ADSVKGRFTISA
DTSKNTAYLQMNSLRAEDTAVYYCAR***YHFPFGFALD***YWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***VA
WYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***GVYLF***TFGQGTKVEIKDKTHTKVEPKTSDKTHTC
PPCPGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS
CSVMHEALHNHYTQKSLSLSPGKGTTAASGSSGGSSSGAGRTEVQLVESGGGLVQPGGSLRLSCAASGF***NISYSSI***HWVRQAPGKGLE
WVA***YISSYYGYTYY***ADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***AHYFPWAGAMD***YWGQGTLVTVSSGGGGSDIQMTQ
SPSSLSASVGDRVTITCRASQ***SVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YSWGPFT***
FGQGTKVEIK (SEQ ID NO: 1018)

CM0156

EVQLVESGGGLVQPGGSLRLSCAASGF***NISYSYM***HWVRQAPGKGLEWVA***SISPYYSYTSY***ADSVKGRFTISADTSKNTAYLQMNSLRA
EDTAVYYCAR***PSAWSHIYYPSSSSSAF***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***VAWYQQKPGKAP
KLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***SSYSLI***TFGQGTKVEIKLEDKTHTKVEPKSSDKTHTCPPCPAPELLG
GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK
VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV
DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATPESGGGEVQLVESGGGLVQPGGSLRLSCAASGF***NISYSYM***
HWVRQAPGKGLEWVA***SISPYYSYTSY***ADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***PSAWSHIYYPSSSSSAF***DYWGQGT
LVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQP
EDFATYYCQQ***SSYSLI***TFGQGTKVEIK (SEQ ID NO: 1019)

Table 14

Comparison of expression titers and monodispersity of FZD agonists following Protein A purification. See corresponding figure 21.

Molecule	Format	N-term Paratope	C-term Paratope	Expression titer mg/l	% Monomer	Monomer Yield (mg/l)
CM0042	Dia – Fc – Dia	5019	2539	8±4	43	3
CM0011	Dia – Fc – Dia	5019	2539/2542	12±3	81±5	10
CM0126	Dia – Fc – Dia	5016	2539/2542	8±0.7	ND	ND
CM0107	Dia – Fc - scFv	5019	2539	90	87	80
CM0108	Dia – Fc - scFv	5019	2542	47	89	40
CM0109	Dia – Fc - scFv	5019	2539/2542	79	86	70
CT003	Dia – Fc - scFv	2539/2542	5016	47	67	30
CM0112	scFv – Fc – Dia	5019	2539/2542	15	79	10
CM0110	scFv - Fc - scFv	5019	2539/2542	82	81	70
CT001	bsIgG-dia	5016	2539/2542	47±21	44±11	30
CM0299	IgG-dia	5016	2539	20±8	ND	ND
CM0300	IgG – scFv	5016	2539	134±38	66±7	100
CM0301	IgG – scFv	5016	2542	134±27	71±8	90
ANT1	Dia-Fc-Fab	5016	2539/2542	294±75	53±9	150
CH3	Dia-CH3-Dia	5019	2539	<1	ND	ND
Fab-Dia	FAb-Dia	5016	2540/2542	1	ND	ND

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Table 15

Functional comparison of FZD agonists. Concentration-response curves of each FZD agonist were generated using the TOPFLASH assay. Figure 20 shows representative traces of the A) Diabody-Fc-Diabody and B) Diabody-Fc-Fab format overlaid with Wnt3a for comparison. Calculated EC50 and maximum efficacy relative to recombinant Wnt3a control were derived and are presented as the average ± SD.

Name	Format	N-term Paratope	C-term Paratope	EC_{50} (nM)	Maximal Signal (% Wnt3a maxima)
Wnt3a	Recombinant Protein	NA	NA	6±3	100
CM0042	Dia – Fc – Dia	5019	2539	0.9±0.8	33±22
CM0011	Dia – Fc – Dia	5019	2539/2542	0.3±0.1	63±10
CM0126	Dia – Fc –Dia	5016	2539/2542	0.3±0.2	52±1
CM0107	Dia-Fc-scFv	5019	2539	ND	ND
CM0108	Dia-Fc-scFv	5019	2542	ND	ND
CM0109	Dia-Fc-scFv	5019	2539/2542	ND	ND
CT003	Dia-Fc-scFv	2539/2542	5016	0.4±0.1	42±16
CM0112	scFv-Fc-Dia	5019	2539/2542	ND	ND
CM0110	scFv-Fc-scFv	5019	2539/2542	ND	ND
CT001	bsIgG-dia	5016	2539/2542	0.3±0.1	57±17
CM0299	IgG-dia	5016	2539	0.1±0.1	14±5
CM0300	IgG-scFv	5016	2539	0.3±0.2	5±2
CM0301	IgG-scFv	5016	2542	0.2±0.2	1±1
ANT1	Dia-Fc-Fab	5016	2539/2542	0.7±0.5	50±18
CH3	Dia-CH3-Dia	5019	2539	ND	22±10
FAb-Dia	Fab-Dia	5016	2540/2542	0.4±0.2	42±16

Table 16

FZD2-LRP6 CM0072	
Knob construct	MNLLLILTFVAAAVAEFEVQLVESGGGLVQPGGSLRLSCAASGF***NIYYSSI***HWVRQAPGKGLEWVA***SIYPYYGYTY***YADSVKGR FTISADTSKNTAYLQMNSLRAEDTAVYYCAR***YYHYGL***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***S*** ***VSS4***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***SYWHHSYLL***TFGQGTKVEIKLEDKT HTKVEPKTSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPMVFDLPPSREEMTKNQVSLWCMVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESAT PESGGGEVQLVESGGGLVQPGGSLRLSCAASGF***NISYSSI***HWVRQAPGKGLEWVA***YISSYYGYTY***YADSVKGRFTISADTSKNT AYLQMNSLRAEDTAVYYCAR***AHYFPWAGAMD***YWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***VA WYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YYWTP***TFGQGTKVEIK (SEQ ID NO: 1020)
Hole construct	MNLLLILTFVAAAVAEFEVQLVESGGGLVQPGGSLRLSCAASGF***NIYYSSI***HWVRQAPGKGLEWVA***SIYPYYGYTY***YADSVKGR FTISADTSKNTAYLQMNSLRAEDTAVYYCAR***YYHYGL***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***S*** ***VSS4***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***SYWHHSYLL***TFGQGTKVEIKLEDKT HTKVEPKSSDKTHNCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPIRELMTSNQVSLSCAVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATPES GGGEVQLVESGGGLVQPGGSLRLSCAASGF***NISSYYI***HWVRQAPGKGLEWVA***SIYSSYGYTSY***YADSVKGRFTISADTSKNTAYL QMNSLRAEDTAVYYCAR***TVRGSKKPYFSGWAMD***YWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA*** VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YSWGPF***TFGQGTKVEIK (SEQ ID NO: 1021)

FZD5-LRP6 CM0024	
Knob construct	MNLLLILTFVAAAVAEFEVQLVESGGGLVQPGGSLRLSCAASGF***NISYSSIH***WVRQAPGKGLEWVA***SIYPSYSSTTY***YADSVKGR FTISADTSKNTAYLQMNSLRAEDTAVYYCAR***YYAM***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVS*** ***S4***VAWYQQKPGKAPKLLIY***S4SSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***4FYYPT***TFGQGTKVEIKLEDKTHTKV EPKTSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPMVFDLPPSREEMTKNQVSLWCMVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATPESGG GEVQLVESGGGLVQPGGSLRLSCAASGF***NISYSSIH***WVRQAPGKGLEWVA***YISSYYGYTY***YADSVKGRFTISADTSKNTAYLQM NSLRAEDTAVYYCAR***4HYFPW4GAM***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSS4***VAWYQQKP GKAPKLLIY***S4SSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YYWPT***TFGQGTKVEIK (SEQ ID NO: 1022)
Hole construct	MNLLLILTFVAAAVAEFEVQLVESGGGLVQPGGSLRLSCAASGF***NISYSSIH***WVRQAPGKGLEWVA***SIYPSYSSTTY***YADSVKGR FTISADTSKNTAYLQMNSLRAEDTAVYYCAR***YYAM***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVS*** ***S4***VAWYQQKPGKAPKLLIY***S4SSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***4FYYPT***TFGQGTKVEIKLEDKTIITKV EPKSSDKTHNCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPIRELMTSNQVSLSCAVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATPESGG EVQLVESGGGLVQPGGSLRLSCAASGF***NISSYYH***WVRQAPGKGLEWVA***SIYSSYGYTS***YADSVKGRFTISADTSKNTAYLQMN SLRAEDTAVYYCAR***TYRGSKKPYFSGW4AM***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSS4***VAWYQ QKPGKAPKLLIY***S4SSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YSWGPT***TFGQGTKVEIK (SEQ ID NO: 1023)

FZD7-LRP6 CM0172
Knob construct
MNLLLILTFVAAAVAEFEVQLVESGGGLVQPGGSLRLSCAASGF***NISSSSSM***HWVRQAPGKGLEWVA***SIISYYGSTY***YADSVKG RFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***WTGM***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***S*** ***VSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***PGSWYFPPT***TFGQGTKVEIKLEDK THTKVEPKTSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPMVFDLPPSREEMTKNQVSLWCMVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESA TPESGGGEVQLVESGGGLVQPGGSLRLSCAASGF***NISYSSSI***HWVRQAPGKGLEWVA***YISSYYGYTY***YADSVKGRFTISADTSKN TAYLQMNSLRAEDTAVYYCAR***AHYFPWAGAM***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***VA WYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YYWPT***TFGQGTKVEIK (SEQ ID NO: 1024)
Hole construct
MNLLLILTFVAAAVAEFEVQLVESGGGLVQPGGSLRLSCAASGF***NISSSSSM***HWVRQAPGKGLEWVA***SIISYYGSTY***YADSVKG RFTISADTSKNTAYLQMNSLRAEDTAVYYCAR***WTGM***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***S*** ***VSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***PGSWYFPPT***TFGQGTKVEIKLEDK THTKVEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPIRELMTSNQVSLSCAVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESAT PESGGGEVQLVESGGGLVQPGGSLRLSCAASGF***NISSYYI***HWVRQAPGKGLEWVA***SIISSYGYTS***YADSVKGRFTISADTSKNTA YLQMNSLRAEDTAVYYCAR***TTRGSKKPYFSGWAM***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA*** VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YSWGPT***TFGQGTKVEIK (SEQ ID NO: 1025)

PanFZD-LRP6 CM0011	
Knob construct	MNLLLILTFVAAAVAEFEVQLVESGGGLVQPGGSLRLSCAASGF***NIGSSSIH***WVRQAPGKGLEWVA***SIYSAFASTSY***ADSVKGR FTISADTSKNTAYLQMNSLRAEDTAVYYCAR***YHFPFGFAL***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRA SQ***SVSS4***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***GVYLF***TFGQGTKVEIKLEDKT HTKVEPKTSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPMVFDLPPSREEMTKNQVSLWCMVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESA TPESGGGEVQLVESGGGLVQPGGSLRLSCAASGF***NISYSSSIH***WVRQAPGKGLEWVA***YISSYYGYTY***YADSVKGRFTISADTSKN TAYLQMNSLRAEDTAVYYCAR***AHYFPWAGAM***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRAS***QSVSSA***VA WYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YYWPT***TFGQGTKVEIK (SEQ ID NO: 1026)
Hole construct	MNLLLILTFVAAAVAEFEVQLVESGGGLVQPGGSLRLSCAASGF***NIGSSSIH***WVRQAPGKGLEWVA***SIYSAFASTSY***ADSVKGR FTISADTSKNTAYLQMNSLRAEDTAVYYCAR***YHFPFGFAL***DYWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRA SQ***SVSS4***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***GVYLF***TFGQGTKVEIKLEDKT HTKVEPKSSDKTHNCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPIRELMTSNQVSLSCAVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATP ESGGGEVQLVESGGGLVQPGGSLRLSCAASGF***NISSYYH***WVRQAPGKGLEWVA***SIYSSYGYTS***YADSVKGRFTISADTSKNTA YLQMNSLRAEDTAVYYCAR***TTRGSKKPYFSGWAMD***YWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSS4*** VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YSWGPF***TFGQGTKVEIK (SEQ ID NO: 1027)

FZD4-LRP6 CM0016	
Knob construct	MNLLLILTFVAAAVAEFEVQLVESGGGLVQPGGSLRLSCAASGF***NISYYYIH***WVRQAPGKGLEWVA***SIYPSSGYTT***YADSVKGR FTISADTSKNTAYLQMNSLRAEDTAVYYCAR***SSFYWAMD***YWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ ***SVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***SYAAVLF***TFGQGTKVEIKLEDKT HTKVEPKSSDKTHNCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPIRELMTSNQVSLSCAVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESATP ESGGGEVQLVESGGGLVQPGGSLRLSCAASGF***NISYYYIH***WVRQAPGKGLEWVA***SIYSSYGYTS***YADSVKGRFTISADTSKNTA YLQMNSLRAEDTAVYYCAR***TVRGSKKPYFSGWAMD***YWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA*** VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YSWGPF***TFGQGTKVEIK (SEQ ID NO: 1028)
Hole construct	MNLLLILTFVAAAVAEFEVQLVESGGGLVQPGGSLRLSCAASGF***NISYYYIH***WVRQAPGKGLEWVA***SIYPSSGYTT***YADSVKGR FTISADTSKNTAYLQMNSLRAEDTAVYYCAR***SSFYWAMD***YWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ ***SVSSA***VAWYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***SYAAVLF***TFGQGTKVEIKLEDKT HTKVEPKTSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPMVFDLPPSREEMTKNQVSLWCMVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKSGSETPGTSESA TPESGGGEVQLVESGGGLVQPGGSLRLSCAASGF***NISYSSI***HWVRQAPGKGLEWVA***YISSYYGYTT***YADSVKGRFTISADTSKN TAYLQMNSLRAEDTAVYYCAR***AHYFPWAGAMD***YWGQGTLVTVSSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQ***SVSSA***VA WYQQKPGKAPKLLIY***SASSLYS***GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ***YYWPT***TFGQGTKVEIK (SEQ ID NO: 1029)

WE CLAIM

1. A tetravalent binding antibody molecule comprising:

(a) an Fc domain or fragment thereof comprising a constant heavy chain domain 3 (CH3),

(b) a bivalent low-density lipoprotein receptor-related protein (LRP) binding domain, and

(c) a bivalent Frizzled (FZD) binding domain,

wherein the LRP binding domain is attached to one terminus of the Fc domain and the FZD binding domain is attached to the other end of the Fc domain,

wherein the LRP binding domain is selected from the group consisting of: a diabody that binds LRP5, a diabody that binds LRP6, two scFv that bind LRP5, two scFv that bind LRP6, two Fab that bind LRP5, and two Fab that bind LRP6 and combinations thereof; and

wherein the FZD binding domain is selected from the group consisting of: a diabody that binds one or more FZD, two scFv that bind one or more FZD, two Fab that bind one or more FZD

wherein the FZD is a Frizzled Class Receptor 1 (FZD1), Frizzled Class Receptor 2 (FZD2), Frizzled Class Receptor 3 (FZD3), Frizzled Class Receptor 5 (FZD4), Frizzled Class Receptor 5 (FZD5), Frizzled Class Receptor 6 (FZD6), Frizzled Class Receptor 7 (FZD7), Frizzled Class Receptor 8 (FZD8), Frizzled Class Receptor 9 (FZD9), or Frizzled Class Receptor 10 (FZD10)

wherein when the LRP binding domain binds only LRP5, the FZD binding domain binds a FZD selected from the group consisting of FZD1, FZD2, FZD3, FZD5, FZD6, FZD7, FZD8, FZD9, FZD10, and combinations thereof .

2. The tetravalent binding antibody molecule of claim 1, wherein

(a) the LRP binding domain diabody is attached to the N-terminal of the Fc domain, and

(b) the FZD binding domain is attached to the C-terminal of the Fc domain.

3. The tetravalent binding antibody molecule of claim 2, wherein

(a) the LRP binding domain diabody is attached to the N-terminal of the Fc domain via a VL or VH of the diabody, and

(b) the FZD binding domain comprises two FZD binding Fab fused to the C-terminal of the Fc, wherein each Fab is attached to the Fc domain via a heavy or light chain variable domain (VH or VL) of the Fab linked to the CH3 domain of the Fc domain.

4. The tetravalent binding antibody molecule of claim 1, wherein the FZD binding domain is attached to the N-terminal of the Fc domain and the LRP binding domain is attached to the C-terminal of the Fc domain.

5. The tetravalent binding antibody molecule of claim 4, wherein

(a) the FZD binding domain comprises two Fabs that bind the FZD, wherein each Fab is attached to N-terminal of the Fc domain via a heavy or light chain variable domain (VH or VL) of the Fab linked to the CH2 domain of the Fc domain, and

(b) the LRP binding domain comprises a diabody or two scFv that bind LRP5 and/or LRP6, wherein the diabody or two scFv are attached to the C-terminal of the Fc domain via a VL or VH of the diabody or scFv linked to the CH3 of the Fc domain.

6. The tetravalent binding antibody molecule of claim 1, wherein the LRP binding domain and/or the FZD binding domain is bispecific.

7. The tetravalent binding antibody molecule of claim 6 wherein the LPR binding domain binds to LRP5 and LRP6.

8. The tetravalent binding antibody molecule of claim 7 wherein the LPR binding domain binds to a Wnt3A site (E3E4 domains) on LRP5 and a Wnt3A site (E3E4 domains) on LRP6.

9. The tetravalent binding antibody molecule of claim 1, wherein

(a) the diabody of the LRP binding domain binds LRP5 and comprises heavy chain complementary determining regions CDR-H1, CDR-H2 and CDR-H3 and light chain

complementary determining regions CDR-L1, CDR-L2 and CDR-L3, of an antibody of Table 3 or Table 6, or

(b) the diabody of the LRP binding domain binds LRP6 and comprises heavy chain complementary determining regions CDR-H1, CDR-H2 and CDR-H3 and light chain complementary determining regions CDR-L1, CDR-L2 and CDR-L3 of an antibody of Table 4 or Table 6, or

(c) the diabody of the LRP binding domain binds LRP5 and LRP6, the diabody comprising CDR-H1, CDR-H2 and CDR-H3 and CDR-L1, CDR-L2 and CDR-L3 of an antibody of Table 3 or Table 6 and CDR-H1, CDR-H2 and CDR-H3 and CDR-L1, CDR-L2 and CDR-L3 of an antibody of Table 4.

10. The tetravalent binding antibody molecule of claim 1 wherein the Fc domain or fragment thereof is in a knob-in-hole configuration.

11. The tetravalent binding antibody molecule of claim 1, wherein the Fc domain lacks one or more effector functions.

12. The tetravalent binding antibody molecule of claim 1, wherein the LRP binding domain and FZD binding domain are each attached to the Fc domain by a linker.

13. The tetravalent binding antibody molecule of claim 12, wherein the linker comprises 1 to 100, 1 to 50, 1-30, 1-25, 1- 10, 1-6 amino acids, 1-5 amino acids, or 2-4 amino acids.

14. The tetravalent binding antibody molecule of claim 1, wherein the LRP binding domain binds LRP6 or binds LRP5 and LRP6, and the FZD binding domain binds a FZD selected from the group consisting of: FZD1, FZD2, FZD3, FZD4, FZD5, FZD6, FZD7, FZD8, FZD9, and FZD10.

15. The tetravalent binding antibody molecule of claim 14, wherein the FZD binding domain binds FZD4 or FZD5.

16. The tetravalent binding antibody molecule of claim 15, wherein the FZD binding domain comprises two Fabs that bind FZD4 or FZD5 or multiple FZD.

17. The tetravalent binding antibody molecule of claim 16, wherein the FZD-binding Fab comprise light chain complementary determining regions CDR-L1, CDR-L2 and CDR-L3 and heavy chain CDRs, CDR-H1, CDR-H2 and CDR-H3 of an antibody of Table 1, Table 2 or Table 6.

18. The tetravalent binding antibody molecule of claim 15, wherein the LRP binding diabody binds to a Wnt3A site on LRP5 and a Wnt 3A site on LRP6.

19. The tetravalent binding antibody molecule of claim 1, wherein

(a) the diabody of the LRP binding domain binds LRP5 comprises heavy chain complementary determining regions CDR-H1, CDR-H2 and CDR-H3 and light chain complementary determining regions CDR-L1, CDR-L2 and CDR-L3, of an antibody of Table 3 or Table 6, or

(b) the diabody of the LRP binding domain binds LRP6 and comprises heavy chain complementary determining regions CDR-H1, CDR-H2 and CDR-H3 and light chain complementary determining regions CDR-L1, CDR-L2 and CDR-L3 of an antibody of Table 4 or Table 6, or

(c) the diabody of the LRP binding domain binds LRP5 and LRP6, the diabody comprising

(i) CDR-H1, CDR-H2 and CDR-H3 and CDR-L1, CDR-L2 and CDR-L3 of an antibody of Table 3 or Table 6, and

(ii) CDR-H1, CDR-H2 and CDR-H3 and CDR-L1, CDR-L2 and CDR-L3 of an antibody of Table 4 or Table 6.

20. The tetravalent binding antibody molecule of claim 3 comprising,

(a) a dimer of a first and second heavy chain monomer, each monomer comprising a single-chain polypeptide comprising, from N-terminus to C-terminus:

(1) a peptide comprising a heavy chain variable domain (VH) that binds LRP5 and/or LRP6 and a light chain variable domain (VL) that binds LRP5 and/or LRP6

(2) an Fc region, or fragment thereof comprising the CH3,

(3) a VH that binds FZD4, FZD5, or FZD4 and/or FZD5 and one or more other FZD, and

(4) a constant heavy chain domain 1 (CH1),

wherein

(5) the VH that binds LRP5 comprises heavy chain CDRs (CDR-H1, CDR-H2 and CDR-H3), of an antibody of Table 3 or Table 6, or

the VH that binds LRP6 comprises the CDR-H1, CDR-H2 and CDR-H3 of an antibody of Table 4 or Table 6, and

(b) the VL that binds LRP5 comprises light chain CDRs (CDR-L1, CDR-L2 and CDR-L3), of an antibody of Table 3 or Table 6, or

the VL that binds LRP6 comprises the CDR-L1, CDR-L2 and CDR-L3 of an antibody of Table 4 or Table 6, and

(c) the VH that binds FZD4, FZD5, or FZD4 and/or FZD5 and one or more other FZD comprises the heavy chain CDRs (CDR-H1, CDR-H2 and CDR-H3), of an antibody of Table 1, Table 2 or Table 6,

and

(d) a third and fourth light chain monomer each comprising from N terminus to C terminus a VL that binds FZD4, FZD5, or FZD4 and/or FZD5 and one or more other FZD and a constant light chain domain 1 (CL1), the VL that binds FZD4, FZD5, or FZD4 and/or FZD5 and one or more other FZD comprises the light chain CDRs (CDR-L1, CDR-L2 and CDR-L3), of an antibody of Table 1, Table 2 or Table 6,

wherein the first and second heavy chain monomer dimerize via their Fc regions and the VL and VH that bind LRP5 or LRP6 of the first monomer pair with the VH and VL that bind LRP5 or LRP6 of the second monomer forming a bivalent diabody that binds LRP5 or LRP6, and

the CL1 and VLs that bind FZD4, FZD5, or FZD4 and/or FZD5 and one or more other FZD of the third and fourth light chain monomers pair with the CH1 and VHs that bind FZD4, FZD5, or FZD4 and/or FZD5 and one or more other FZD of the first and second heavy chain monomers forming two Fabs that bind FZD4, FZD5, or FZD4 and/or FZD5 and one or more other FZD, wherein the diabody forms the N-terminal bivalent LRP5 or LRP6 binding domain and the two Fab form the C-terminal bivalent FZD4, FZD5, or FZD4 and/or FZD5 and one or more other FZD binding domain.

21. The tetravalent binding antibody molecule of claim 20, wherein the LRP binding diabody is bispecific, wherein

the CDRs of the VHs that bind LRP5 or LRP6 of the first heavy chain monomer and the CDRs of the VHs that bind LRP5 or LRP6 of the second heavy chain monomer are non-identical, and

the CDRs of the VLs that bind LRP5 and LRP6 of the first heavy chain monomer and the CDRs of the VLs that bind LRP5 and LRP6 second heavy chain monomer are non-identical.

22. The tetravalent binding antibody molecule of claim 20, wherein the first and second monomers dimerize via a knob-in-hole configuration of the Fc regions or fragments thereof.

23. The tetravalent binding antibody molecule of claim 20, wherein the Fc domain lacks one or more effector functions.

24. The tetravalent binding antibody molecule of claim 20, wherein the peptide of (a)(1) is linked to the Fc region by a first peptide linker, and the Fc region is linked to the VH that binds FZD4 or FZD5 or to multiple FZD (pan-FZD) by a second peptide linker and the VH that binds FZD4 or FZD5 or to multiple FZD (pan-FZD) is linked to the CH1 by a third peptide linker,

and the VL that binds FZD4 or FZD5 or to multiple FZD (pan-FZD) is linked to the CL1 domain by a peptide linker.

25. The tetravalent binding antibody molecule of claim 24, wherein one or more of the second, third or fourth peptide linker comprises 1 to 100, 1 to 50, 1-30, 1-25, 1- 10 or 1-5 amino acids.

26. The tetravalent binding antibody molecule of claim 20, wherein in each first and second heavy chain monomer, the VH that binds to LRP5 or LRP6 is linked to the VL that binds to LRP5 or LRP6 by a peptide linker.

27. The tetravalent binding antibody molecule of claim 26, wherein the peptide linker comprises 1-6 amino acids, 1-5 amino acids, or 2-4 amino acids.

28. The tetravalent binding antibody molecule of claim 20 wherein the tetravalent binding antibody molecule does not comprise a FZD binding domain comprising the CDRs of the FZD-binding antibody 5044 in combination with the Wnt co-receptor binding domain comprising the CDRs of LRP6-binding antibody 2542 and/or antibody 2539.

29. The tetravalent binding antibody molecule of claim 20, wherein the tetravalent binding antibody molecule comprises

(a) a first heavy chain comprising the amino acid sequence of the hole heavy chain construct of FZD5-LRP6 of Table 11, a second heavy chain comprising the amino acid sequence of the knob heavy chain construct of FZD5-LRP6 of Table 11 and a light chain comprising the amino acid sequence of the light chain construct of LRP6 of Table 11 wherein the amino acid sequence of the CDRs are the amino acid sequence of the CDRs of ANT59, or

(b) a first heavy chain comprising the amino acid sequence of the hole heavy chain construct of pFZD-LRP6 of Table 11, a second heavy chain comprising the amino acid a knob heavy chain construct of pFZD-LRP6 of Table 11and a light chain comprising the amino acid sequence of the light chain construct of pFZD-LRP6 of Table 11 wherein the amino acid sequence of the CDRs are the amino acid sequence of the CDRs of ANT9.

30. A tetravalent binding antibody molecule having an N-terminal FZD4 or FZD5 binding domain comprising two FZD4-binding or two FZD5-binding Fabs and a C-terminal LRP binding domain comprising two LRP binding scFvs, the tetravalent binding antibody molecule comprising

(a) a dimer of a first and second heavy chain monomer, wherein each monomer comprises a single-chain polypeptide comprising, from N-terminus to C-terminus:

(i) a first heavy chain variable domain (VH) that binds FZD 4 or 5

(ii) a heavy chain constant region domain 1 (CH1 domain)

(ii) an Fc region or fragment thereof comprising a constant heavy chain domain 3 (CH3 domain),

(iv) a peptide comprising a VH that binds LRP5 or LRP6, and a first light chain variable domain (VL) that binds LRP5 or LRP6, and

(b) a third and fourth light chain monomer each monomer comprising from N terminus to C terminus a second VL that binds the FZD and a constant light chain domain 1 (CL1 domain),

wherein the first and second heavy chain monomers dimerize via the Fc regions or fragments thereof,

wherein the first VH that binds FZD4 or FZD5 and CH1 domain of the first and second monomer pairs with the second VL and CL1 domain of the third and fourth monomers forming two Fabs that bind FZD4 or FZD5,

and the second VH and first VL of each heavy chain monomer pair to form a scFv that binds LRP5 or LRP6,

wherein the LRP binding scFvs form a C-terminal LRP binding domain of the tetravalent binding antibody molecule and the FZD4 or FZD5 binding Fabs form an N-terminus FZD4 or FZD5-binding domain of the tetravalent binding antibody molecule,

wherein when the LRP binding domain binds only LRP5, the FZD binding domain binds FZD5.

31. The tetravalent binding antibody molecule of claim 30, wherein

the VH that binds FZD4 or FZD5 comprises the heavy chain CDRs (CDR-H1, CDR-H2 and CDR-H3), of an antibody of Table 1, Table 2 or Table 6,

the VH that binds LRP5 comprises heavy chain CDRs (CDR-H1, CDR-H2 and CDR-H3), of an antibody of Table 3 or Table 6, or the VH that binds LRP6 comprises the CDR-H1, CDR-H2 and CDR-H3 of an antibody of Table 4, and

the VL that binds LRP5 comprises light chain CDRs (CDR-L1, CDR-L2 and CDR-L3), of an antibody of Table 3 or Table 6, or the VL that binds LRP6 comprises the CDR-L1, CDR-L2 and CDR-L3 of an antibody of Table 4.

32. A tetravalent binding antibody molecule comprising an N-terminal LRP binding diabody and a C-terminal domain comprising two FZD4-binding or FZD5-binding scFv, the tetravalent binding antibody molecule comprising

a dimer of a first and second monomer, wherein each monomer comprises a single-chain polypeptide comprising, from N-terminus to C-terminus:

(a) a first peptide, said first peptide comprising a first heavy chain variable domain (VH) and a first light chain variable (VL) domain that bind LRP5 or LRP6,

(b) an Fc region, or fragment thereof comprising a constant heavy chain domain 3 (CH3), and

(c) a second peptide, said second peptide comprising a second VL and a second VH that bind a FZD4 or FZD5,

wherein the first and second monomers dimerize via the Fc regions or fragments thereof, the first VH and VL of each monomer pairs with the first VH and VL of the other monomer forming a diabody that binds LRP5 or LRP6 and the second VL and VH of each monomer pair to form a scFvs that bind FZD4 or FZD5,

wherein the LRP binding diabody forms the N-terminal LRP binding domain of the tetravalent binding antibody molecule and the two FZD4-binding or FZD5-binding scFvs form the C-terminal FZD-binding domain of the tetravalent binding antibody molecule

wherein when the LRP binding domain binds only LRP5, the FZD binding domain binds FZD5.

33. The tetravalent binding antibody molecule of claim 32, wherein

the VH that binds LRP5 comprises heavy chain CDRs (CDR-H1, CDR-H2 and CDR-H3), of an antibody of Table 3 or Table 6, or the VH that binds LRP6 comprises the CDR-H1, CDR-H2 and CDR-H3 of an antibody of Table 4,

the VL that binds LRP5 comprises light chain CDRs (CDR-L1, CDR-L2 and CDR-L3), of an antibody of Table 3 or Table 6, or the VL that binds LRP6 comprises the CDR-L1, CDR-L2 and CDR-L3 of an antibody of Table 4, and

the VH that binds FZD comprises the heavy chain CDRs (CDR-H1, CDR-H2 and CDR-H3), of an antibody of Table 1, Table 2 or Table 6.

34. A tetravalent binding antibody molecule in a Diabody-Fc-scFv format comprising an Fc domain, a LRP5/6 co-receptor binding domain including a bispecific diabody that binds at least two sites on the co-receptor,

wherein the diabody is attached to the amino terminus of the Fc domain and a FZD binding domain is attached to the carboxy terminus of the Fc domain comprising two scFv fragments each binding FZD wherein the scFv is specific for FZD5, or pan-specific binding to FZD5 and one or more other FZD.

35. A tetravalent binding antibody molecule in an IgG-diabody format having an Fc domain, a FZD binding domain that comprises of two Fab fragments attached to the N-terminus of the Fc domain, each Fab binding to an FZD5, or FZD4 and FZD5 and a LRP5/6 co-receptor binding domain attached to the C- terminus of the Fc domain that is composed of a diabody that binds at least two sites on the co-receptor LRP5/6, wherein the Fabs are specific for FZD5 or pan-specific, binding to FZD5 and one or more FZD.

36. A tetravalent binding antibody molecule in an IgG-Diabody format comprising an Fc domain, an N-terminal binding domain for a FZD, wherein the FZD-binding Fabs bind FZD5 or FZD5 and at least one other FZD and a C-terminal binding domain for a LRP5/6 co-receptor and including a LRP5/6 coreceptor-binding diabody.

37. The tetravalent binding antibody molecule of claim 36, comprising:

a first and second heavy chain monomer, wherein each heavy chain monomer includes a single-chain polypeptide from N-terminus to C-terminus:

(a) a heavy chain variable domain (VH) that binds FZD5 or FZD4 and FZD5, linked to

(b) a heavy chain constant region domain 1 (CH1 domain), linked to

(c) an Fc region (or fragment thereof comprising a constant heavy chain domain 3 (CH3 domain)), linked to

(d) a peptide comprising a VH that binds a LRP5/6 co-receptor, linked to a light chain variable domain (VL) that binds a LRP5/6 co-receptor, and

a first and second light chain monomer, wherein each light chain monomer includes from N terminus to C terminus a VL that binds the FZD, linked to a constant light chain domain 1 (CL1 domain).

38. The tetravalent binding antibody molecule of any one of claims 1 to 37, wherein the tetravalent binding antibody molecule comprises

(a) a first heavy chain comprising the amino acid sequence of the hole heavy chain construct of SEQ ID NO: 986, a second heavy chain comprising the amino acid a knob heavy chain construct of SEQ ID NO: 987 and a light chain comprising the amino acid sequence of the light chain construct of SEQ ID NO: 992 wherein the amino acid sequence of the CDRs are the amino acid sequence of the CDRs of ANT80; or

(b) a first heavy chain comprising the amino acid sequence of the hole heavy chain construct of SEQ ID NO: 988, a second heavy chain comprising the amino acid a knob heavy chain construct

of SEQ ID NO: 989 and a light chain comprising the amino acid sequence of the light chain construct of SEQ ID NO: 992 wherein the amino acid sequence of the CDRs are the amino acid sequence of the CDRs of ANT 98; or

(c) a first heavy chain comprising the amino acid sequence of the hole heavy chain construct of SEQ ID NO: 990, a second heavy chain comprising the amino acid a knob heavy chain construct of SEQ ID NO: 991 and a light chain comprising the amino acid sequence of the light chain construct of SEQ ID NO: 992 wherein the amino acid sequence of the CDRs are the amino acid sequence of the CDRs of ANT99; or

(d) a first heavy chain comprising the amino acid sequence of the hole heavy chain construct selected from the group consisting of SEQ ID NO: 986, SEQ ID NO: 988, and SEQ ID NO: 990; a second heavy chain comprising the amino acid of a knob heavy chain construct selected from the group consisting of SEQ ID NO: 987, SEQ ID NO: 989, and SEQ ID NO: 991; and a light chain comprising the amino acid sequence of the light chain construct of SEQ ID NO: 992.

39. A pharmaceutical composition comprising a tetravalent binding antibody molecule of any one claims 1 to 38 and a pharmaceutically acceptable carrier.

40. A method for promoting endothelial cell barrier functions in a tissue comprising administering an effective amount of a tetravalent binding antibody molecule of any one of claims 1 to 38 to a tissue.

41. The method of claim 40, wherein the tissue is brain, kidney or eye tissue.

42. The method of claim 41, wherein the tetravalent binding antibody molecule is administered to eye tissue by intravitreal injection.

43. A method for treating inflammatory bowel disease in a subject in need thereof comprising administering an effective amount of a tetravalent binding molecule of any one of claims 1 to 38 to said subject.

44. A method for increasing retinal or brain endothelial cell barrier functions, decreasing endothelial cell permeability, enhancing or restoring blood retina and blood brain barrier maintenance in a subject in need thereof comprising contacting an endothelial cell comprising an

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FZD4 receptor and an LRP5 and/or LRP6 in a subject in need thereof with an effective amount of a tetravalent binding antibody molecule of any one of claim 1 to 38.

45. The method of claim 43 or 44, wherein the tetravalent binding antibody molecule is administered to the subject in need thereof by injection, topically, or orally.

46. The method of claim 43 or 44, wherein the tetravalent binding antibody molecule is administered subcutaneously, intravenously, intraperitoneally, intrathecally, intravitreously or intraocularly.

MS&D Exhibit 1008, Page 3286 of 4223

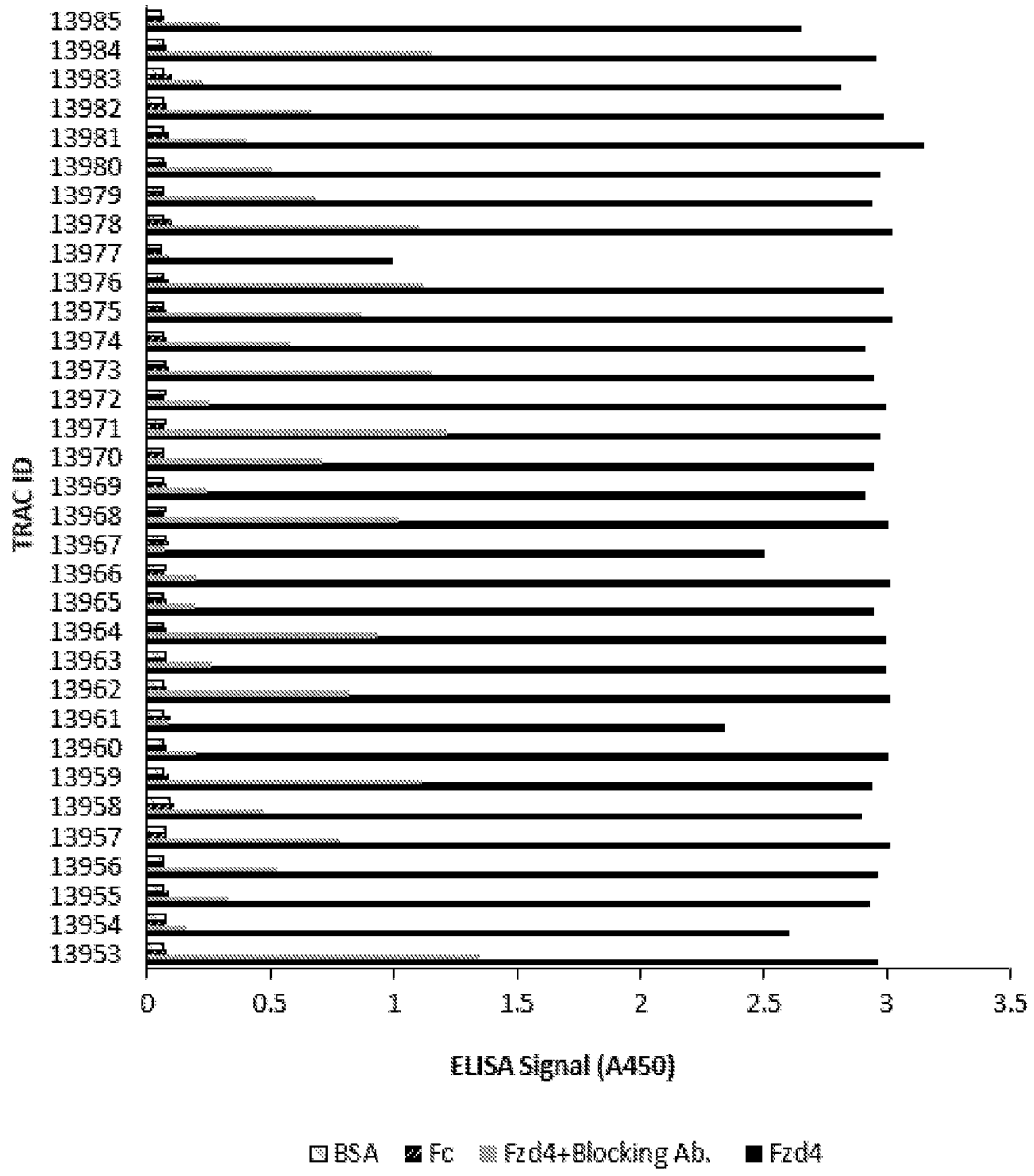

TRAC ID
13985
13984
13983
13982
13981
13980
13979
13978
13977
13976
13975
13974
13973
13972
13971
13970
13969
13968
13967
13966
13965
13964
13963
13962
13961
13960
13959
13958
13957
13956
13955
13954
13953
0
0.5
1
1.5
2
2.5
3
3.5
ELISA Signal (A450)
BSA
Fc
Fzd4+Blocking Ab.
Fzd4

FIG 1A

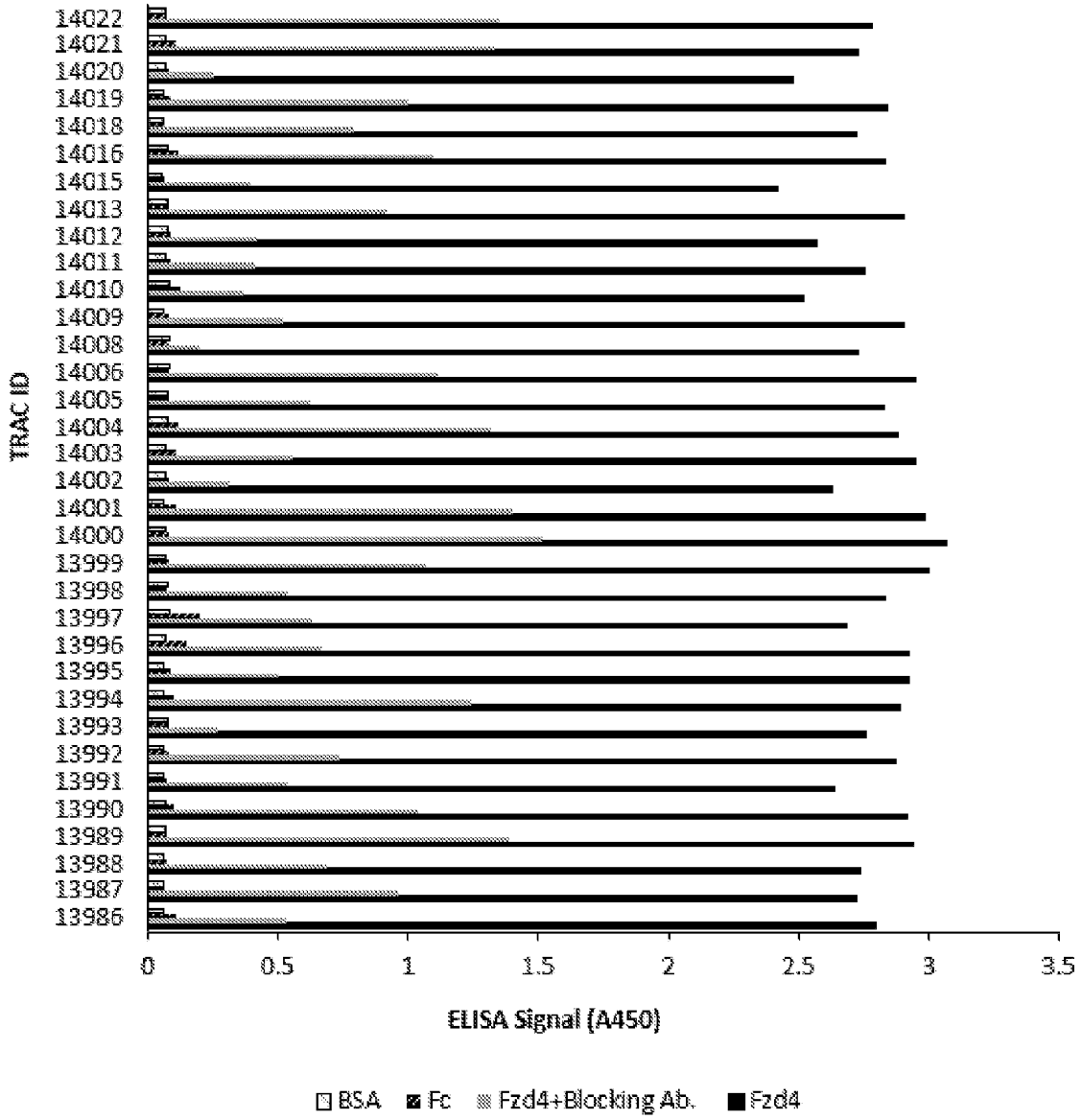

TRAC ID
14022
14021
14020
14019
14018
14016
14015
14013
14012
14011
14010
14009
14008
14006
14005
14004
14003
14002
14001
14000
13999
13998
13997
13996
13995
13994
13993
13992
13991
13990
13989
13988
13987
13986
0
0.5
1
1.5
2
2.5
3
3.5
ELISA Signal (A450)
BSA
Fc
Fzd4+Blocking Ab.
Fzd4

FIG 1B

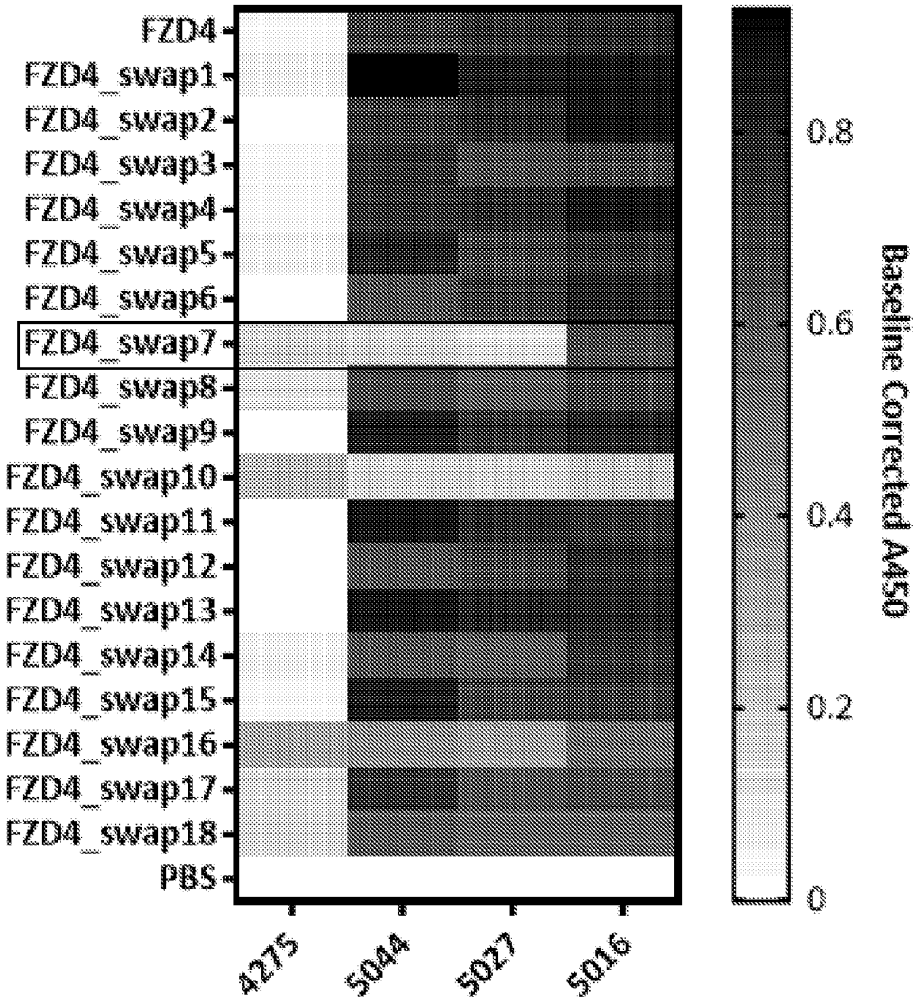

FZD4
FZD4_swap1
FZD4_swap2
FZD4_swap3
FZD4_swap4
FZD4_swap5
FZD4_swap6
FZD4_swap7
FZD4_swap8
FZD4_swap9
FZD4_swap10
FZD4_swap11
FZD4_swap12
FZD4_swap13
FZD4_swap14
FZD4_swap15
FZD4_swap16
FZD4_swap17
FZD4_swap18
PBS
4275
5044
5027
5016
0.8
0.6
0.4
0.2
0
Baseline Corrected A450

FIG 2

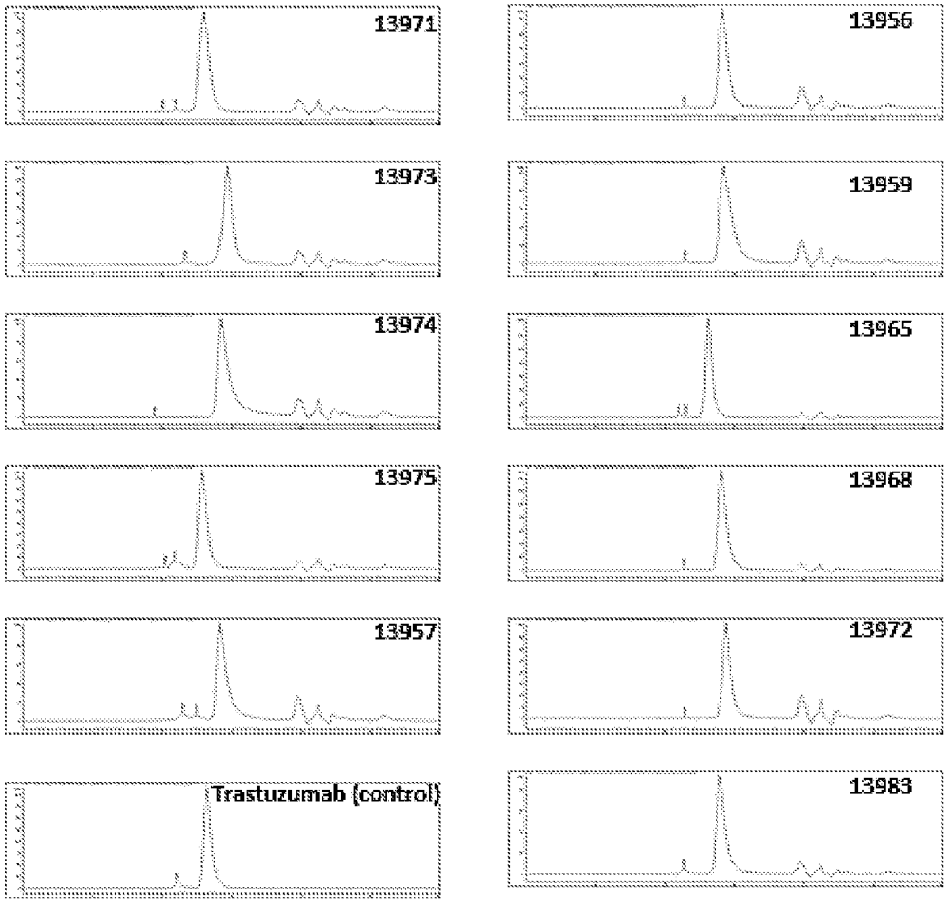

13971
13956
13973
13959
13974
13965
13975
13968
13957
13972
Trastuzumab (control)
13983

FIG 3A

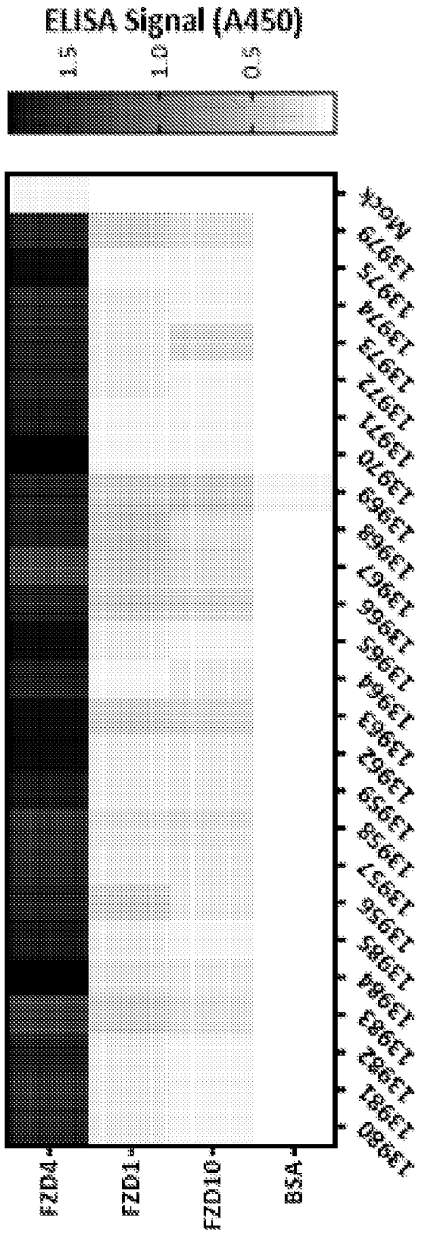

ELISA Signal (A450)
1.5
1.0
0.5
FZD4
FZD1
FZD10
BSA
Mock
13979
13975
13974
13973
13972
13971
13970
13969
13968
13967
13966
13965
13964
13963
13962
13959
13958
13957
13956
13985
13984
13983
13982
13981
13980

FIG 3B

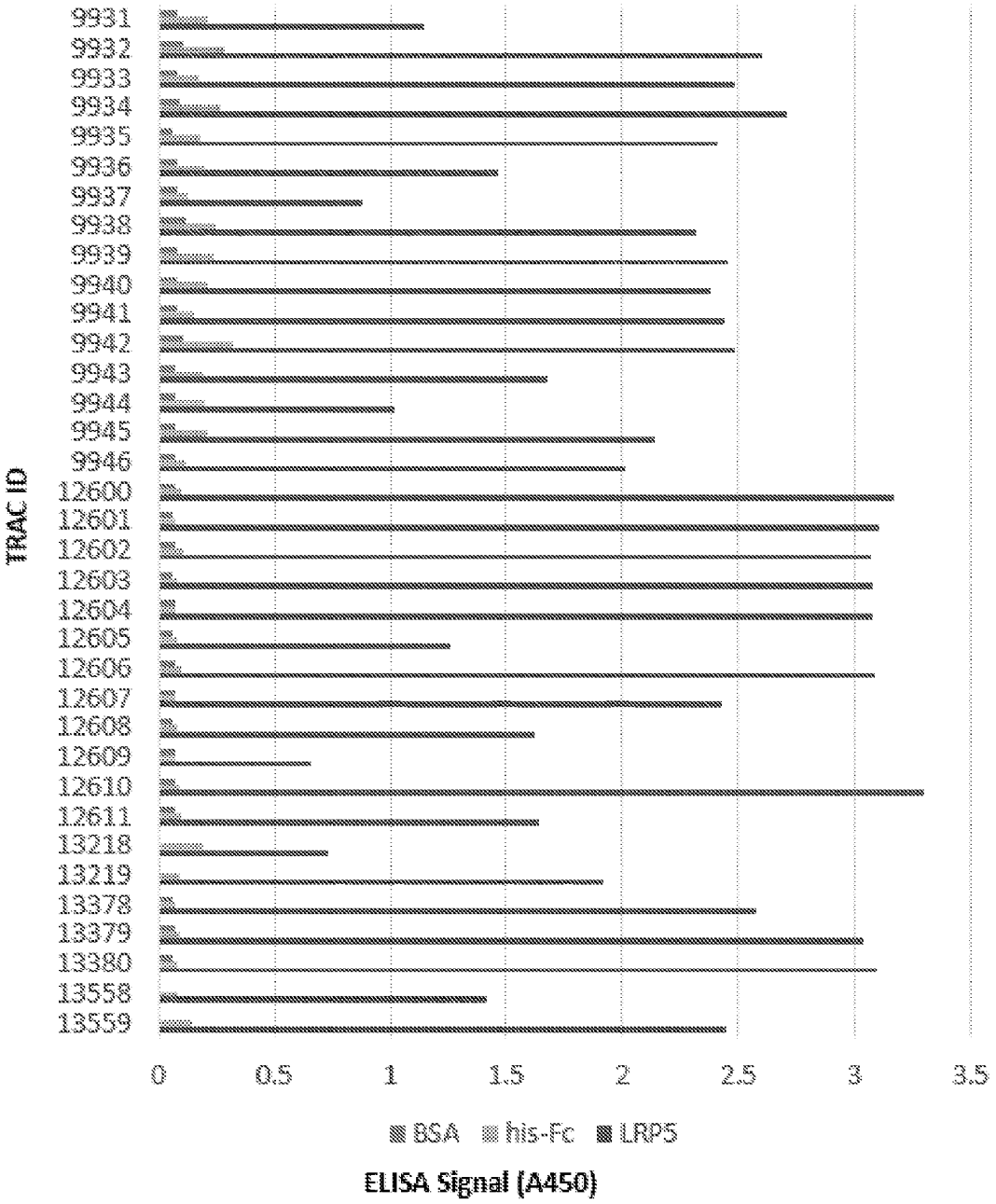

TRAC ID
9931
9932
9933
9934
9935
9936
9937
9938
9939
9940
9941
9942
9943
9944
9945
9946
12600
12601
12602
12603
12604
12605
12606
12607
12608
12609
12610
12611
13218
13219
13378
13379
13380
13558
13559
0
0.5
1
1.5
2
2.5
3
3.5
BSA
his-Fc
LRP5
ELISA Signal (A450)

FIG 4

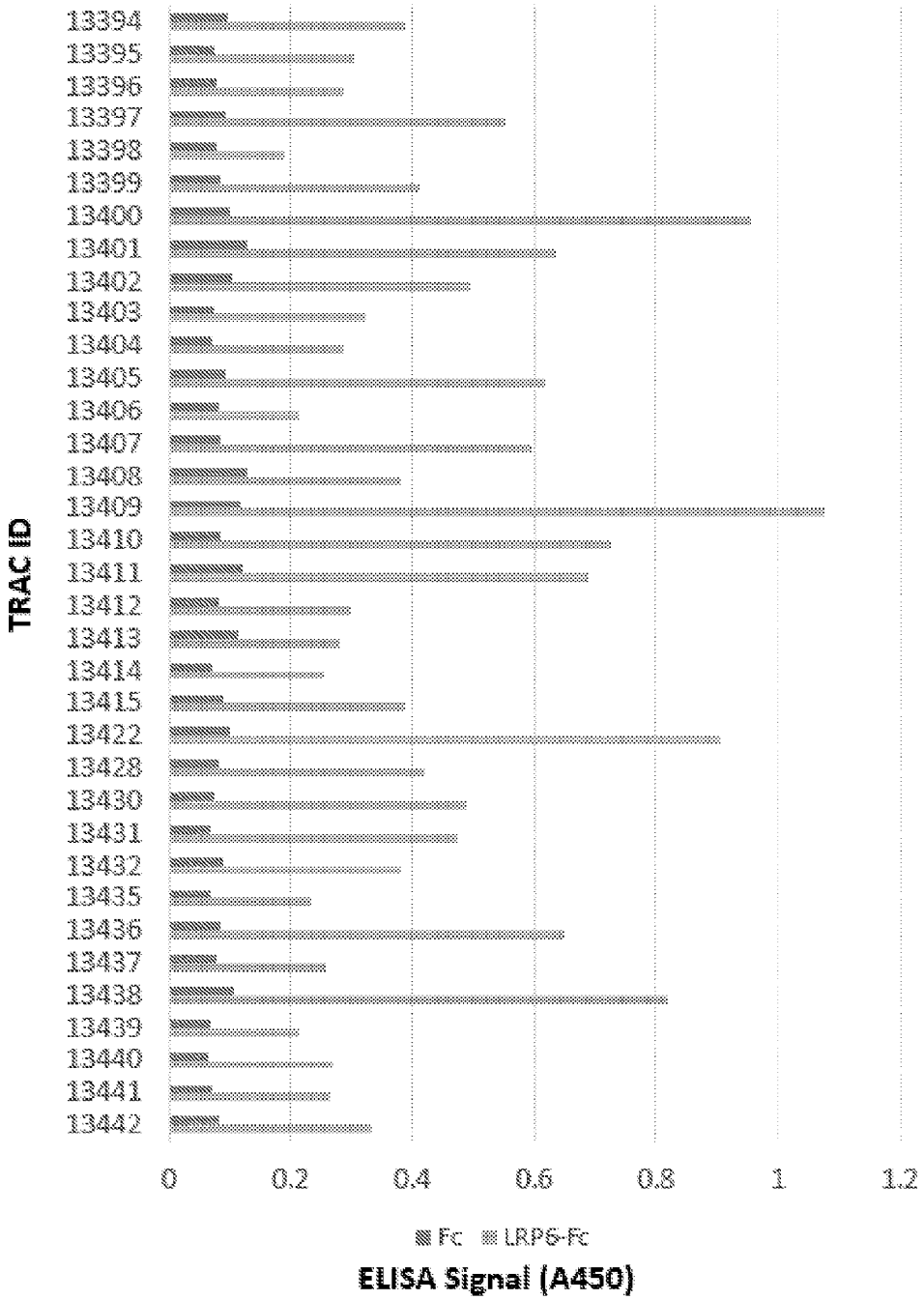

TRAC ID
13394
13395
13396
13397
13398
13399
13400
13401
13402
13403
13404
13405
13406
13407
13408
13409
13410
13411
13412
13413
13414
13415
13422
13428
13430
13431
13432
13435
13436
13437
13438
13439
13440
13441
13442
0
0.2
0.4
0.6
0.8
1
1.2
Fc
LRP6-Fc
ELISA Signal (A450)

FIG 5A

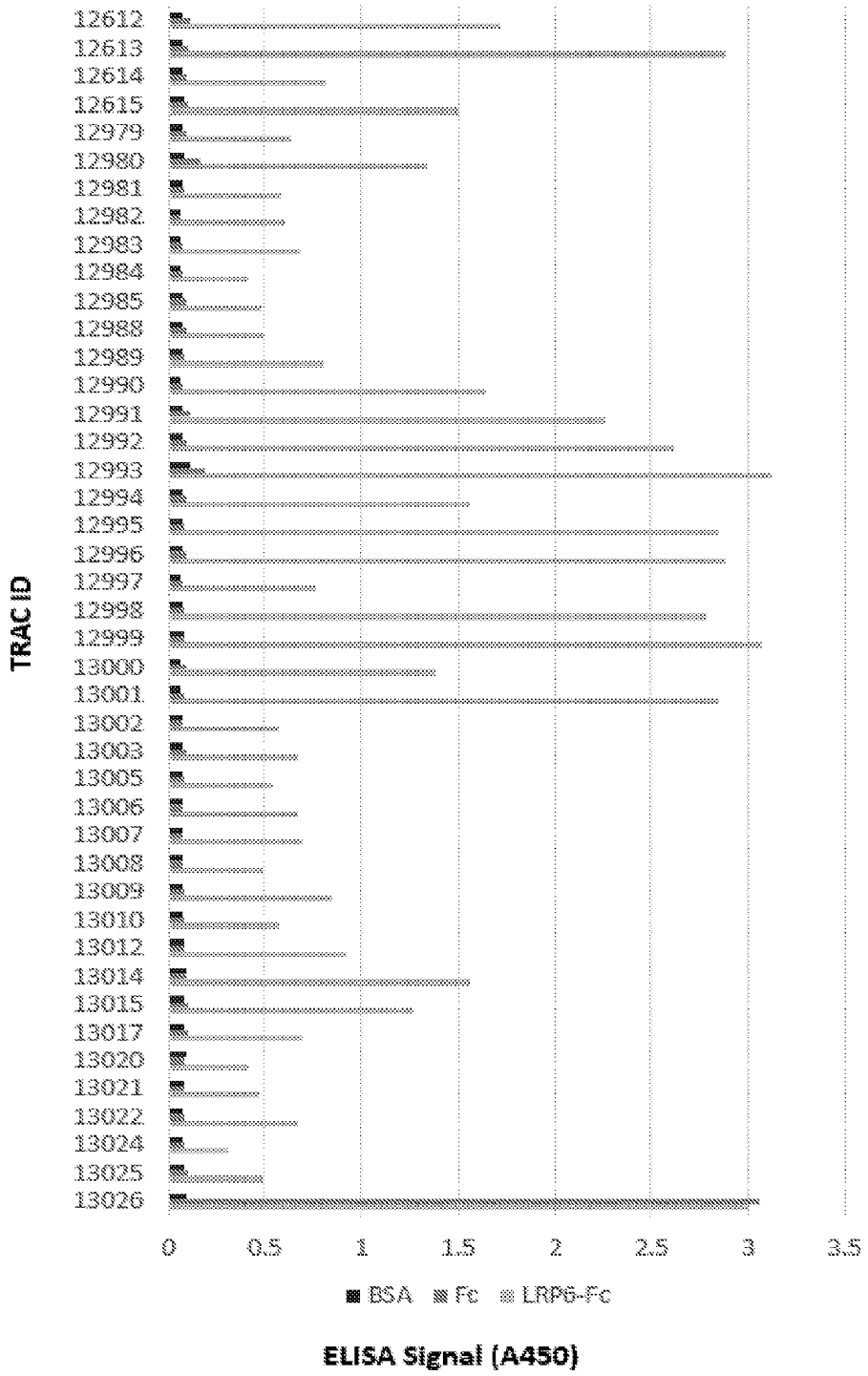

TRAC ID
12612
12613
12614
12615
12979
12980
12981
12982
12983
12984
12985
12988
12989
12990
12991
12992
12993
12994
12995
12996
12997
12998
12999
13000
13001
13002
13003
13005
13006
13007
13008
13009
13010
13012
13014
13015
13017
13020
13021
13022
13024
13025
13026
0
0.5
1
1.5
2
2.5
3
3.5
BSA
Fc
LRP6-Fc
ELISA Signal (A450)

FIG 5B

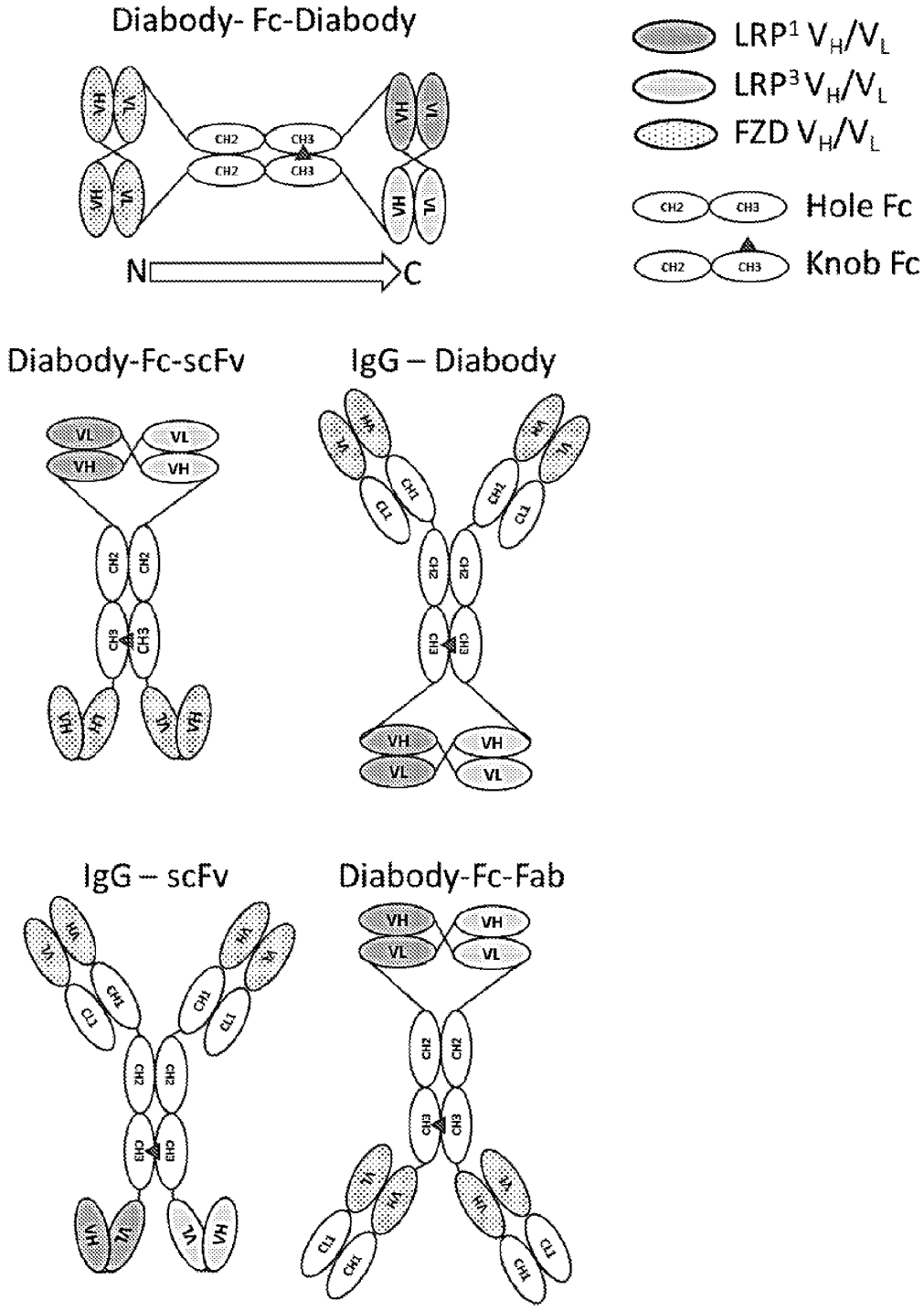

Diabody- Fc-Diabody
LRP1 VH/VL
LRP3 VH/VL
FZD VH/VL
Hole Fc
Knob Fc
N
C
Diabody-Fc-scFv
IgG – Diabody
IgG – scFv
Diabody-Fc-Fab

FIG 6

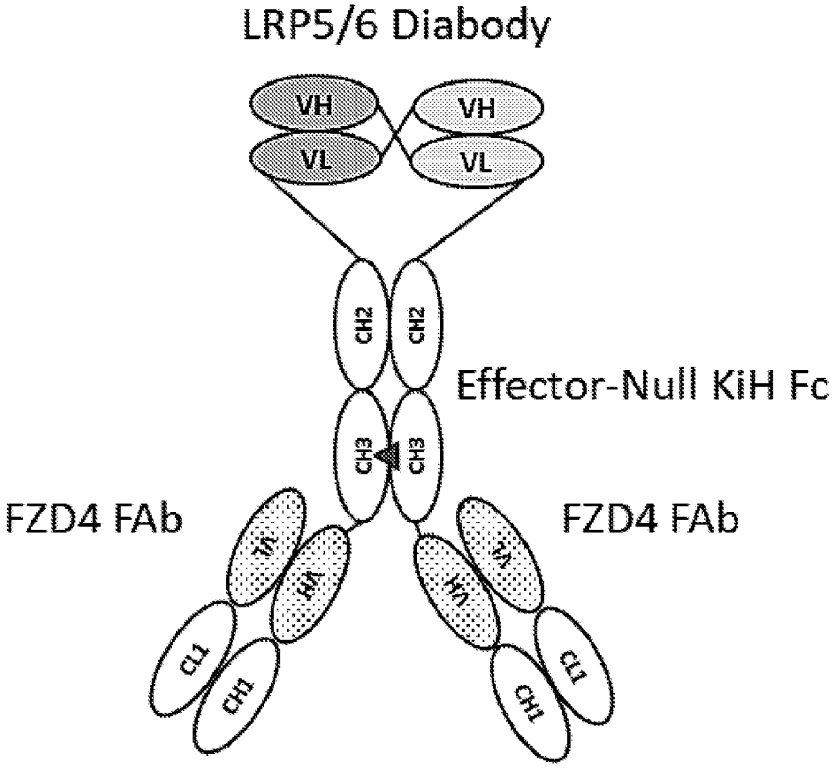

LRP5/6 Diabody
VH
VL
VH
VL
CH2
CH2
Effector-Null KiH Fc
CH3
CH3
FZD4 FAb
FZD4 FAb
VL
VH
CL1
CH1
VL
VH
CL1
CH1

FIG 7

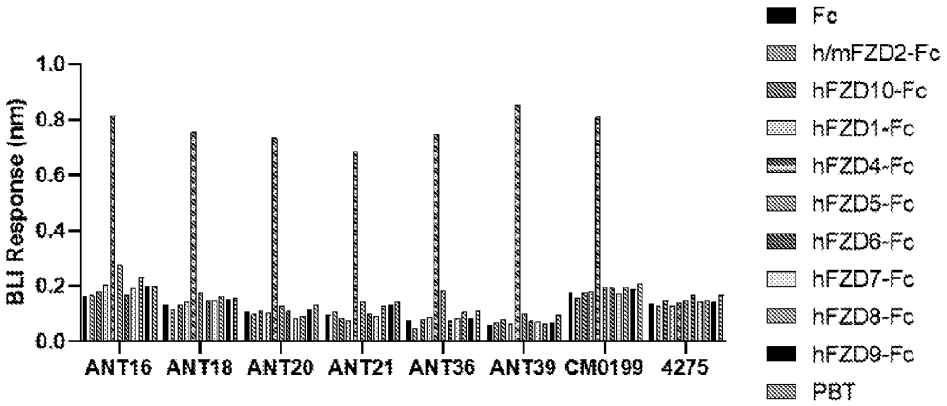

BLI Response (nm)
1.0
0.8
0.6
0.4
0.2
0.0
ANT16 ANT18 ANT20 ANT21 ANT36 ANT39 CM0199 4275
Fc
h/mFZD2-Fc
hFZD10-Fc
hFZD1-Fc
hFZD4-Fc
hFZD5-Fc
hFZD6-Fc
hFZD7-Fc
hFZD8-Fc
hFZD9-Fc
PBT

FIG 8A

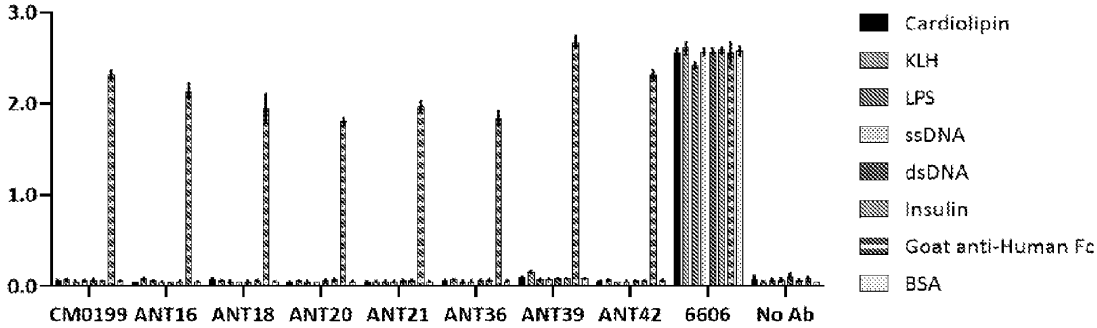

3.0
2.0
1.0
0.0
CM0199 ANT16 ANT18 ANT20 ANT21 ANT36 ANT39 ANT42 6606 No Ab
Cardiolipin
KLH
LPS
ssDNA
dsDNA
Insulin
Goat anti-Human Fc
BSA

FIG 8B

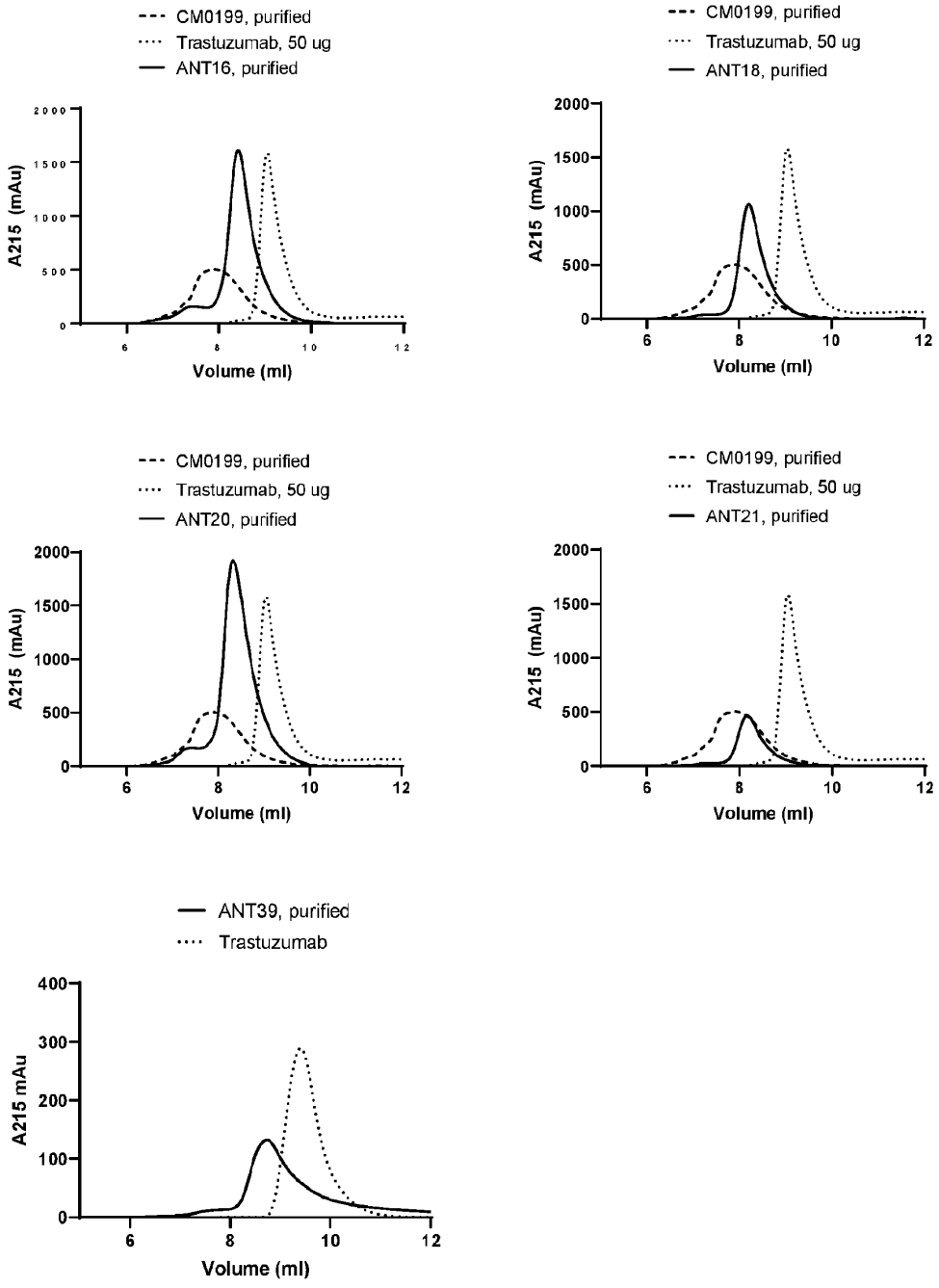

CM0199, purified
Trastuzumab, 50 ug
ANT16, purified
A215 (mAu)
Volume (ml)
CM0199, purified
Trastuzumab, 50 ug
ANT18, purified
A215 (mAu)
Volume (ml)
CM0199, purified
Trastuzumab, 50 ug
ANT20, purified
A215 (mAu)
Volume (ml)
CM0199, purified
Trastuzumab, 50 ug
ANT21, purified
A215 (mAu)
Volume (ml)
ANT39, purified
Trastuzumab
A215 mAu
Volume (ml)

FIG 9A

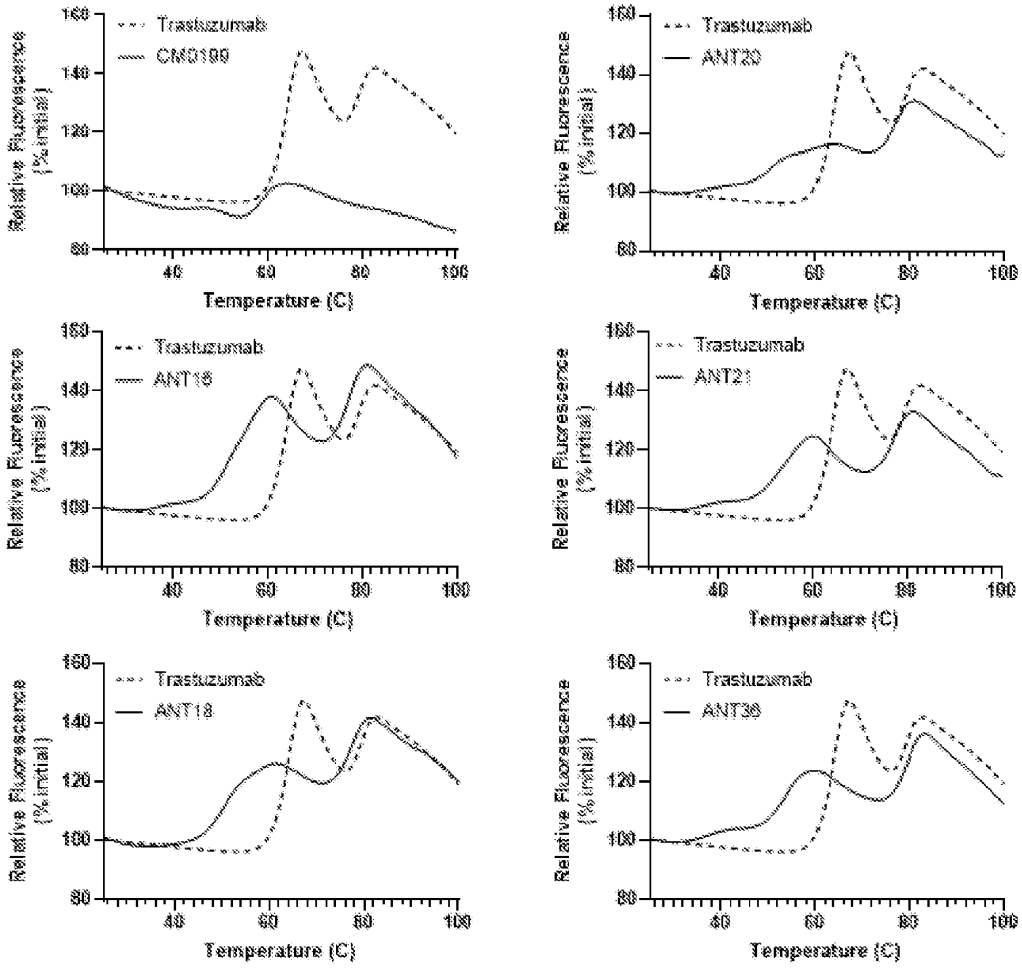

Trastuzumab
CNO199
ANT20
ANT16
ANT21
ANT18
ANT30
Relative Fluorescence (% initial)
Temperature (C)
80
100
120
140
160
40
60
80
100

FIG 9B

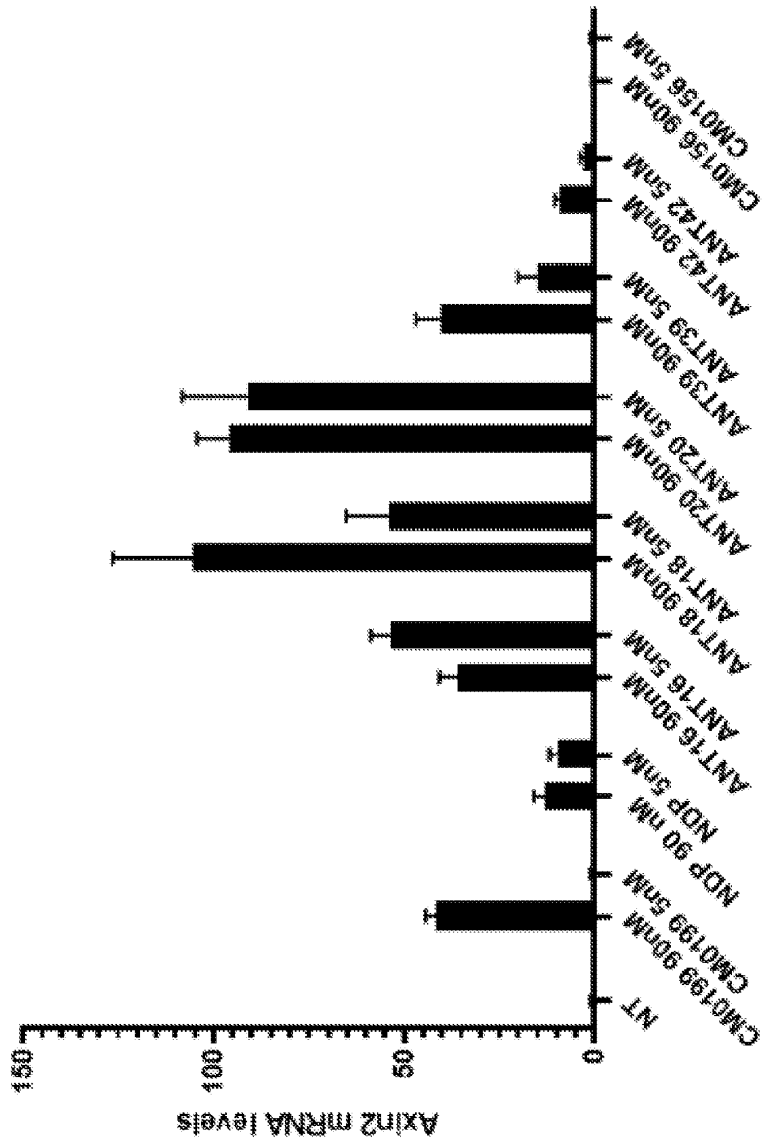
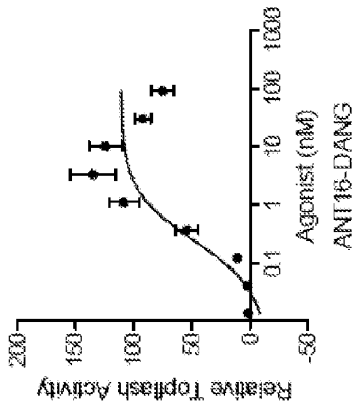
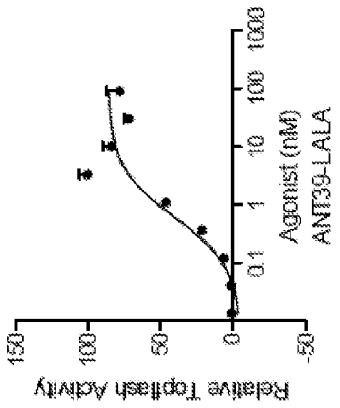
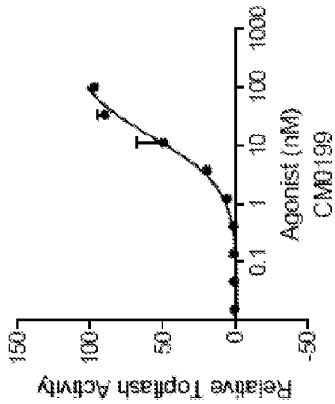
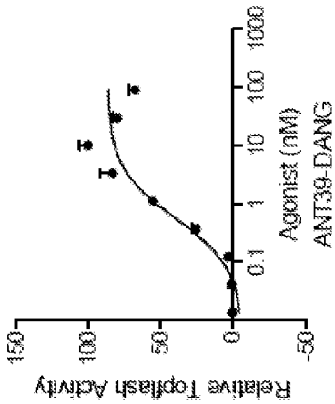

Axin2 mRNA levels
150
100
50
0
NT
CM0199 90nM
CM0199 5nM
NDP 90 nM
NDP 5nM
ANT16 90nM
ANT16 5nM
ANT18 90nM
ANT18 5nM
ANT20 90nM
ANT20 5nM
ANT39 90nM
ANT39 5nM
ANT42 90nM
ANT42 5nM
CM0156 90nM
CM0156 5nM

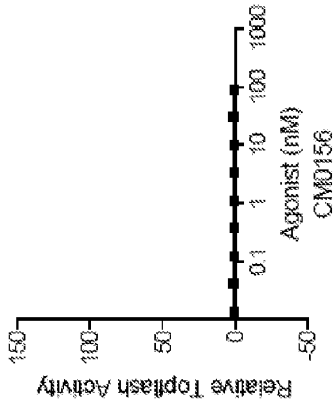
FIG 10


Relative Topflash Activity
200
150
100
50
0
-50
0.1
1
10
100
1000
Agonist (nM)
ANT16-DANG


Relative Topflash Activity
150
100
50
0
-50
0.1
1
10
100
1000
Agonist (nM)
ANT39-LALA


Relative Topflash Activity
150
100
50
0
-50
0.1
1
10
100
1000
Agonist (nM)
CM0199


Relative Topflash Activity
150
100
50
0
-50
0.1
1
10
100
1000
Agonist (nM)
ANT39-DANG


Relative Topflash Activity
150
100
50
0
-50
0.1
1
10
100
1000
Agonist (nM)
CM0156

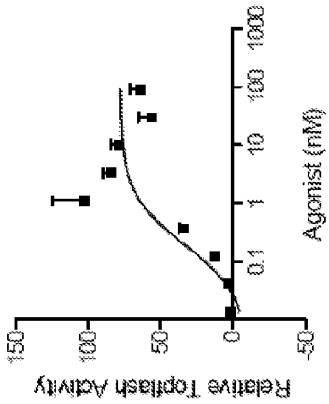

Relative Topflash Activity
150
100
50
0
-50
0.1
1
10
100
1000
Agonist (nM)
ANT16-LALA

FIG 10 cont.

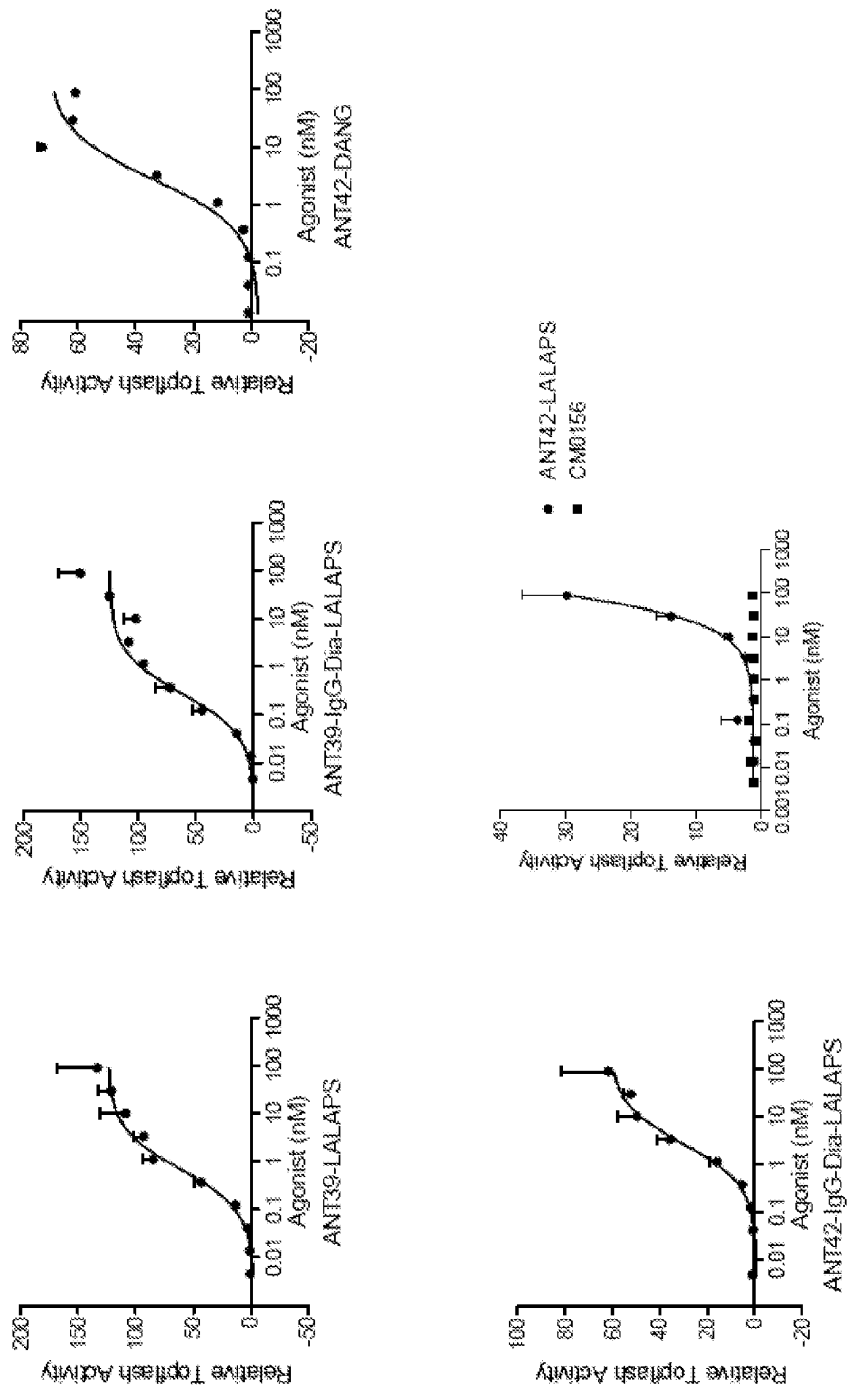

Relative Topflash Activity
Agonist (nM)
ANT42-DANG
ANT39-IgG-Dia-LALAPS
ANT39-LALAPS
ANT42-LALAPS
CM8156
ANT42-IgG-Dia-LALAPS

FIG 10 cont.

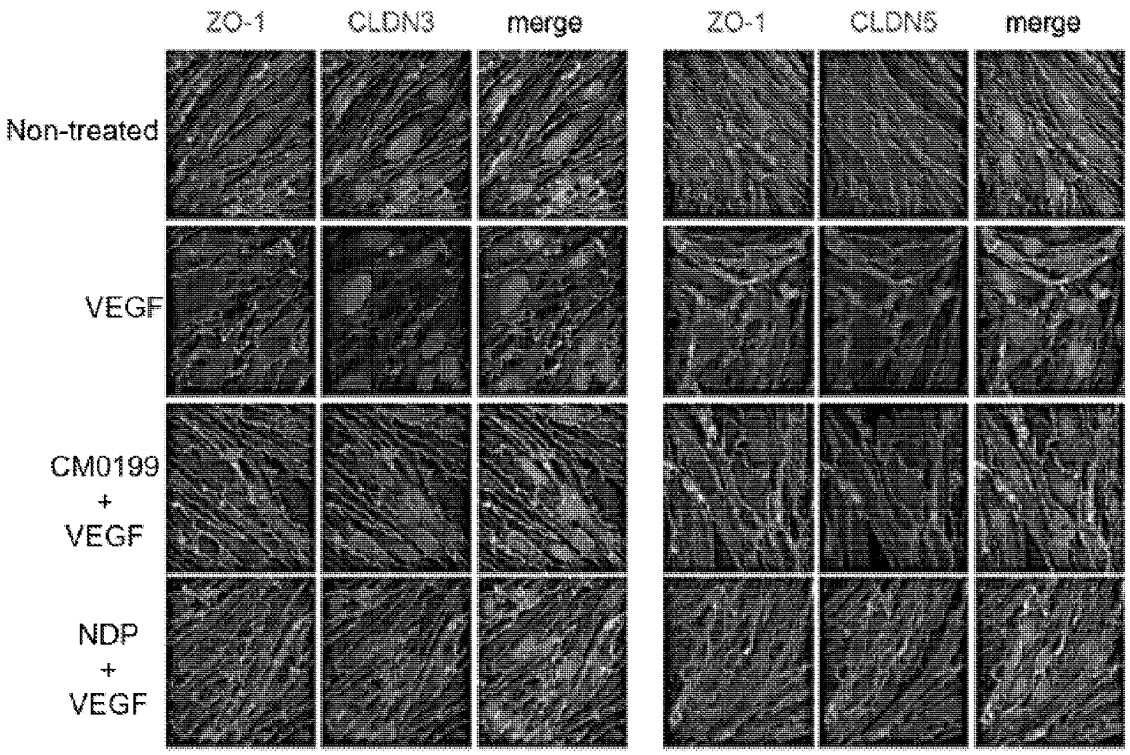

ZO-1
CLDN3
merge
ZO-1
CLDN5
merge
Non-treated
VEGF
CM0199
+
VEGF
NDP
+
VEGF

FIG 11A

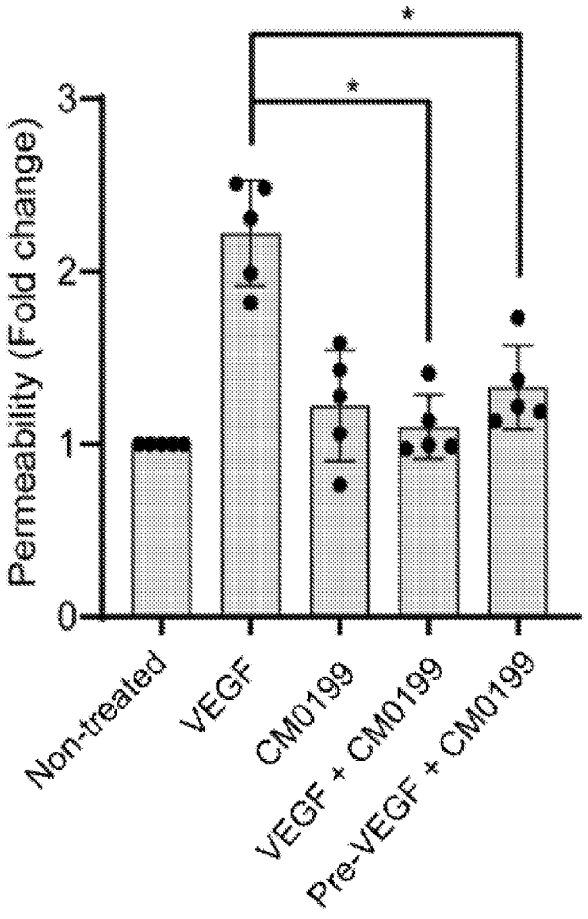

*
*
Permeability (Fold change)
0
1
2
3
Non-treated
VEGF
CM0199
VEGF + CM0199
Pre-VEGF + CM0199

FIG 11B

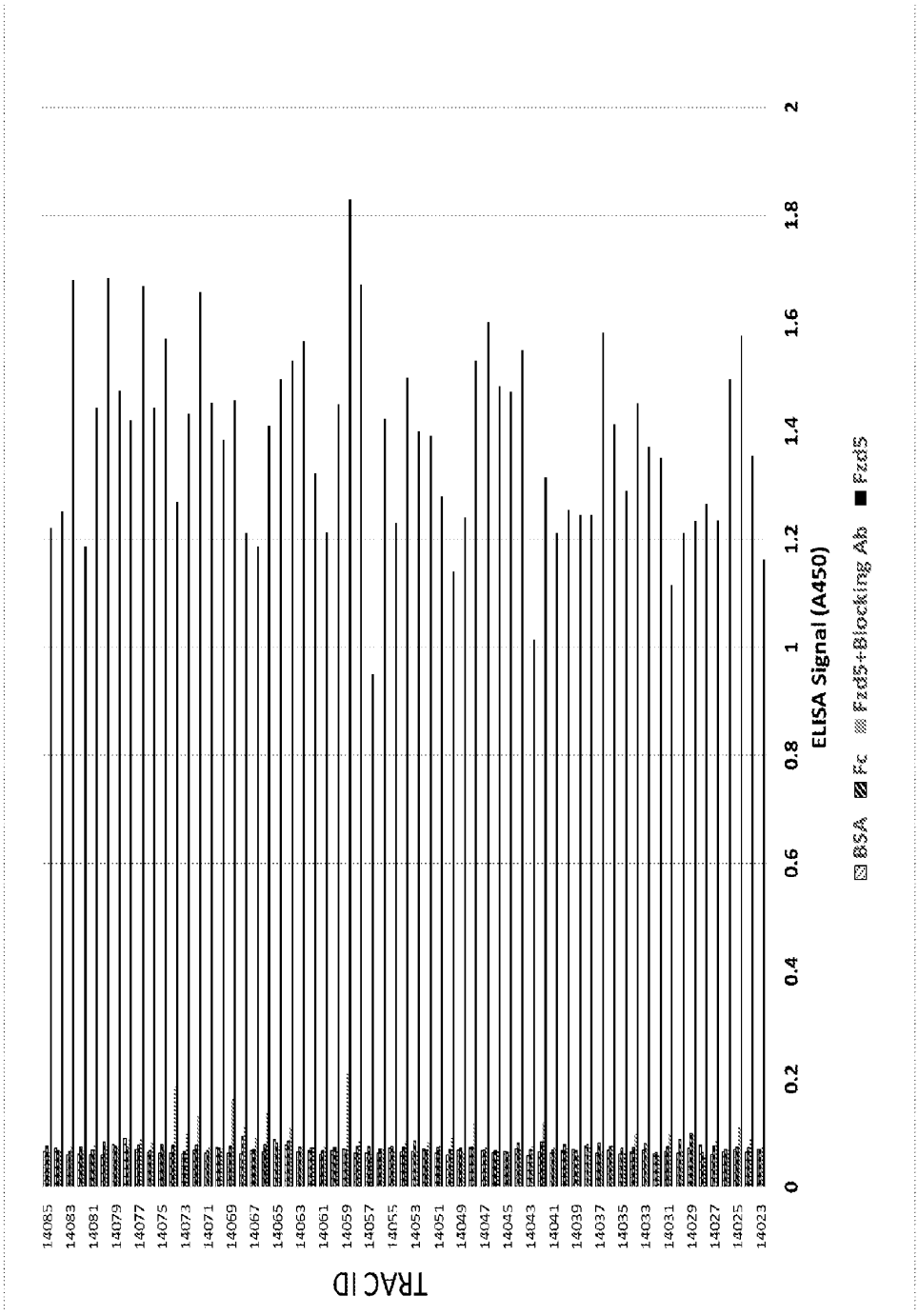

TRAC ID
14085
14083
14081
14079
14077
14075
14073
14071
14069
14067
14065
14063
14061
14059
14057
14055
14053
14051
14049
14047
14045
14043
14041
14039
14037
14035
14033
14031
14029
14027
14025
14023
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
ELISA Signal (A450)
BSA
Fc
Fc05+Blocking Ab
Fc05

FIG 12

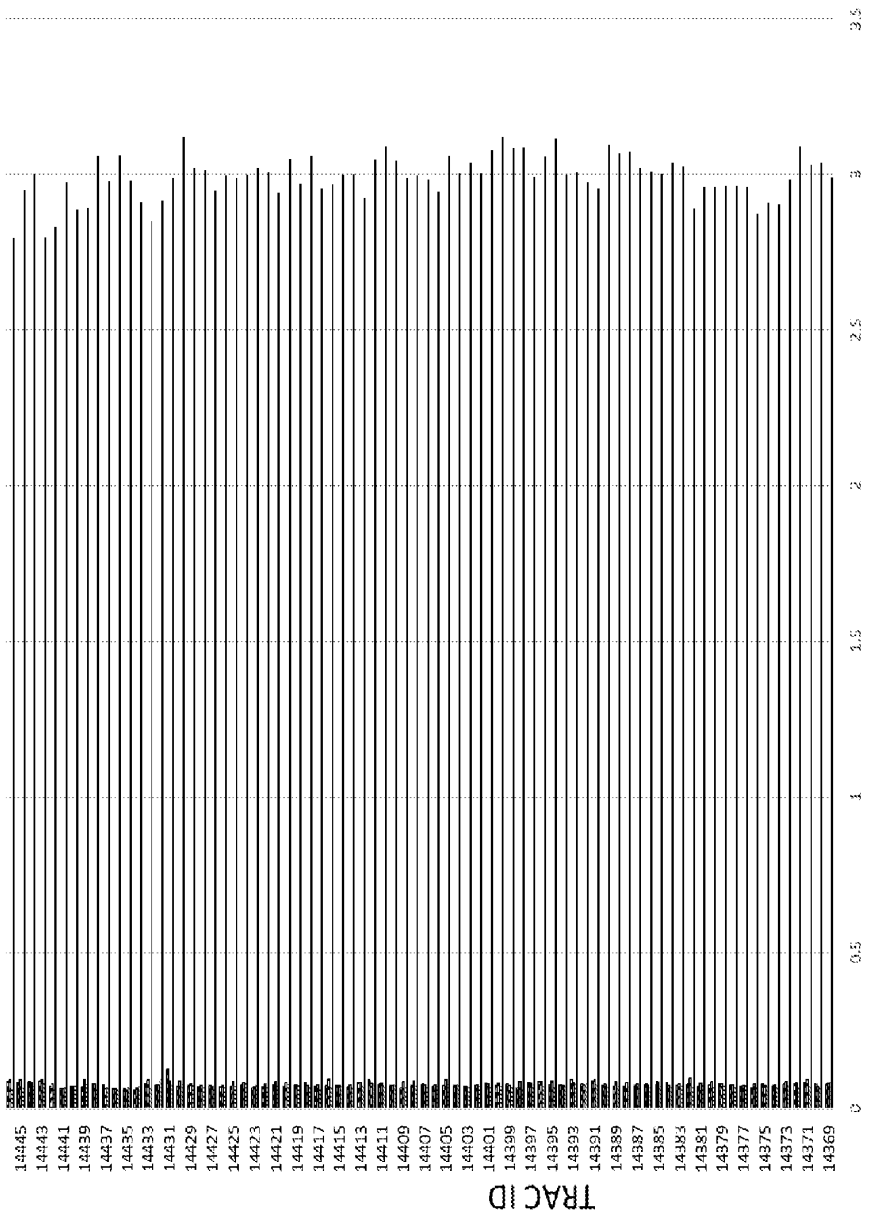

TRAC ID
14445
14443
14441
14439
14437
14435
14433
14431
14429
14427
14425
14423
14421
14419
14417
14415
14413
14411
14409
14407
14405
14403
14401
14399
14397
14395
14393
14391
14389
14387
14385
14383
14381
14379
14377
14375
14373
14371
14369
0
0.5
1
1.5
2
2.5
3
3.5
ELISA Signal (A450)
Fc
Fzd2
Fzd8
Fzd5

FIG 13

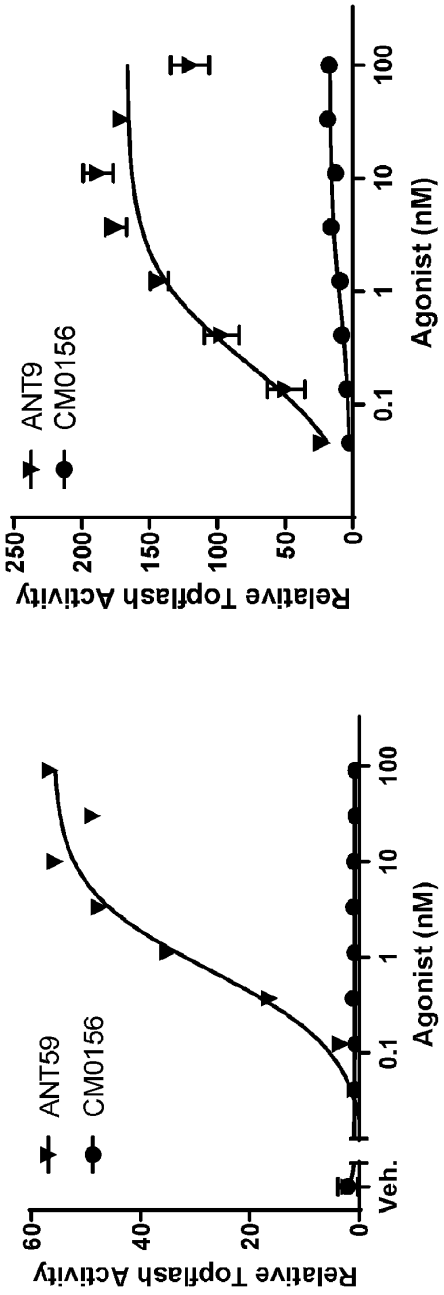

Relative Topflash Activity
250
200
150
100
50
0
ANT9
CM0156
0.1
1
10
100
Agonist (nM)
Relative Topflash Activity
60
40
20
0
ANT59
CM0156
Veh.
0.1
1
10
100
Agonist (nM)

FIG 14

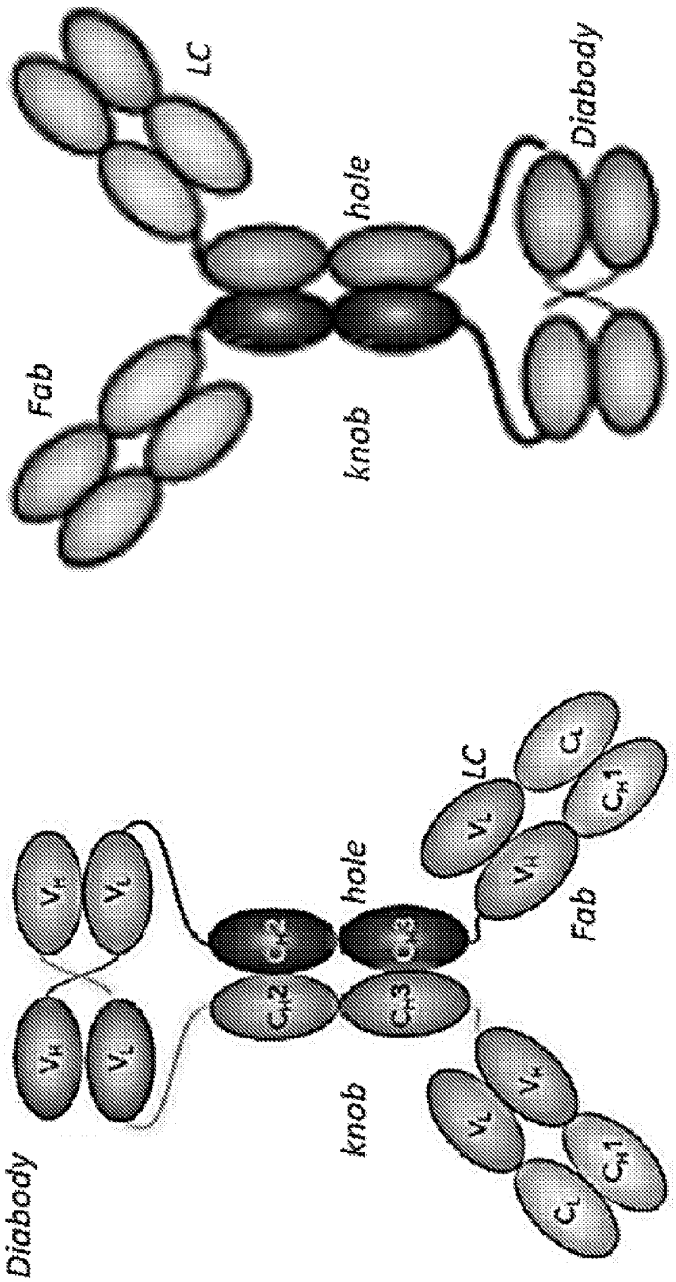

LC
Fab
hole
knob
Diabody
ANT39i
Diabody
Fab
hole
knob
LC
ANT39

FIG 15

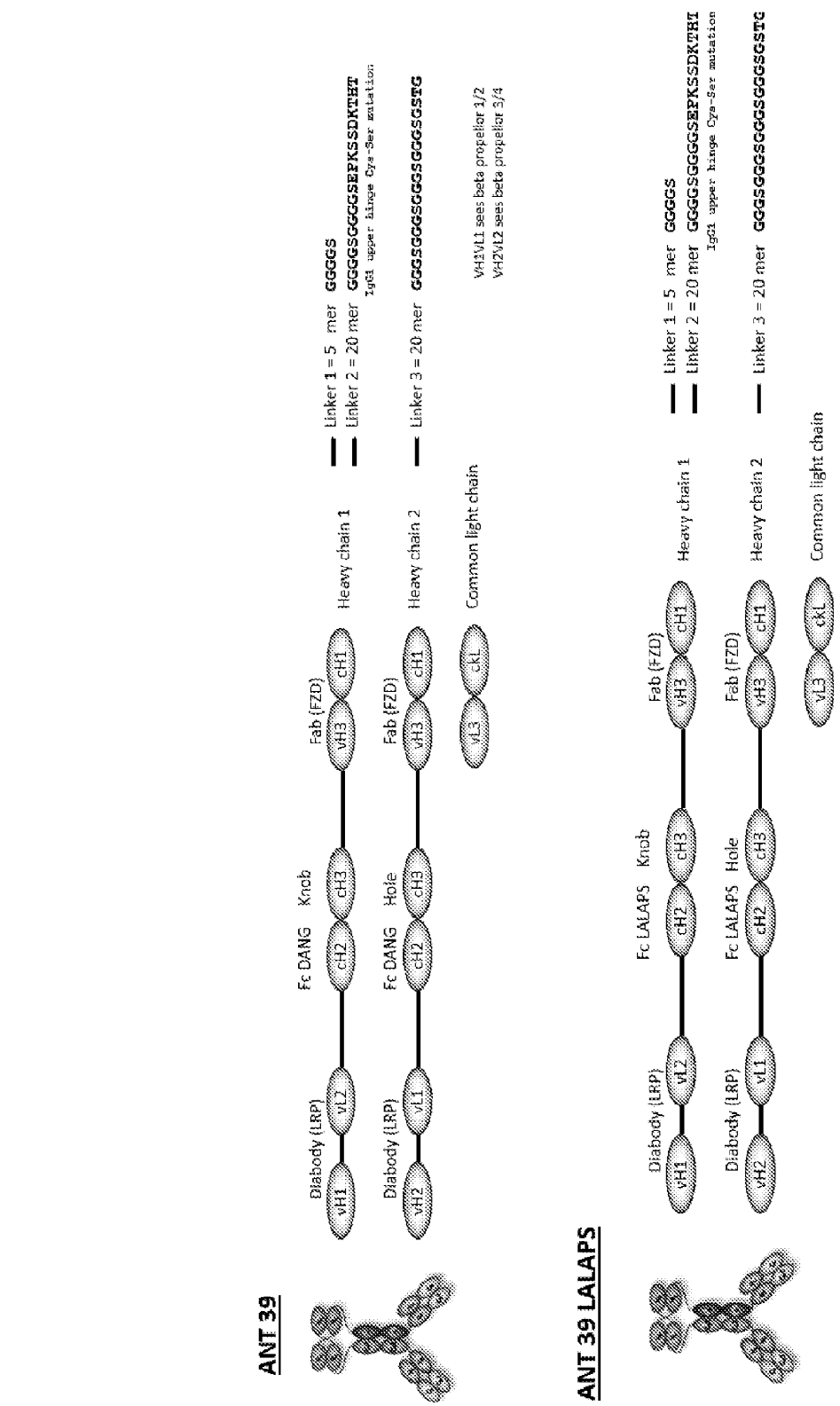

ANT 39
Diabody (LRP)
vH1
vL2
Fc DANG
Knob
cH2
cH3
Fab (FZD)
vH3
cH1
Heavy chain 1
Linker 1 = 5 mer GGGGS
Linker 2 = 20 mer GGGGSGGGGSEPKSSDKTHT
IgG1 upper hinge Cys-Ser mutation
Diabody (LRP)
vH2
vL1
Fc DANG
Hole
Fab (FZD)
Heavy chain 2
Linker 3 = 20 mer GGGSGGGSGGGSGGGSGSTG
Common light chain
vL3
cKL
VH3VL1 sees beta propellor 1/2
VH2VL2 sees beta propellor 3/4
ANT 39 LALAPS
Diabody (LRP)
vH1
vL2
Fc LALAPS
Knob
cH2
cH3
Fab (FZD)
vH3
cH1
Heavy chain 1
Linker 1 = 5 mer GGGGS
Linker 2 = 20 mer GGGGSGGGGSEPKSSDKTHT
IgG1 upper hinge Cys-Ser mutation
Diabody (LRP)
vH2
vL1
Fc LALAPS
Hole
Fab (FZD)
vH3
cH1
Heavy chain 2
Linker 3 = 20 mer GGGSGGGSGGGSGGGSGSTG
Common light chain
vL3
cKL

FIG 16A

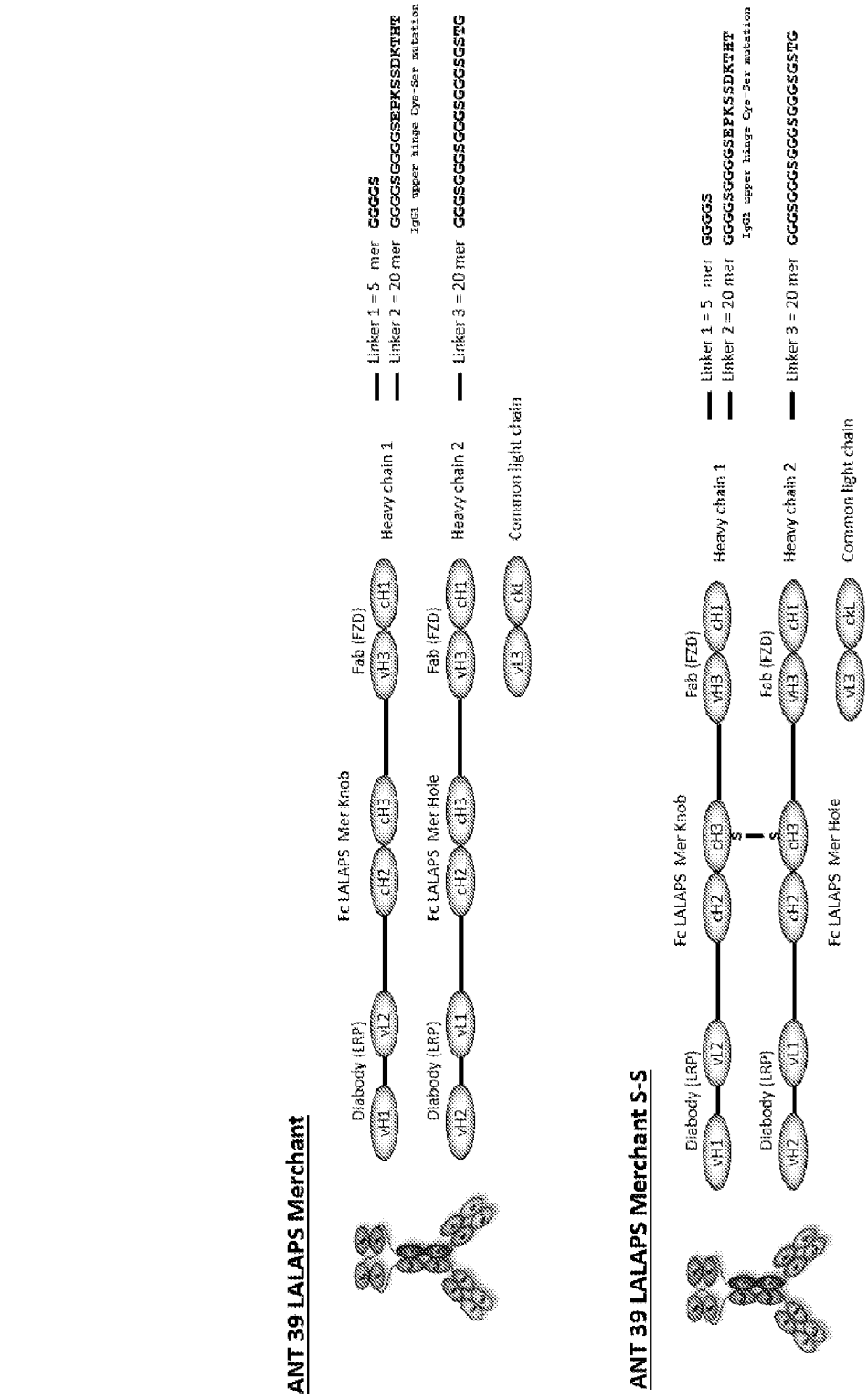

ANT 39 LALAPS Merchant
Diabody (LRP)
VH1
VL2
Diabody (LRP)
VH2
VL1
Fc LALAPS Mer Knob
CH2
CH3
Fc LALAPS Mer Hole
CH2
CH3
Fab (FZD)
VH3
CH1
Heavy chain 1
Fab (FZD)
VH3
CH1
Heavy chain 2
VL3
CKL
Common light chain
Linker 1 = 5 mer GGGGS
Linker 2 = 20 mer GGGGSGGGGSEPKSSDKTHT
IgG1 upper hinge Cys-Ser mutation
Linker 3 = 20 mer GGGSGGGSGGGSGGGSGSTG
ANT 39 LALAPS Merchant S-S
Diabody (LRP)
VH1
VL2
Diabody (LRP)
VH2
VL1
Fc LALAPS Mer Knob
CH2
CH3
Fc LALAPS Mer Hole
CH2
CH3
Fab (FZD)
VH3
CH1
Heavy chain 1
Fab (FZD)
VH3
CH1
Heavy chain 2
VL3
CKL
Common light chain
Linker 1 = 5 mer GGGGS
Linker 2 = 20 mer GGGGSGGGGSEPKSSDKTHT
IgG1 upper hinge Cys-Ser mutation
Linker 3 = 20 mer GGGSGGGSGGGSGGGSGSTG

FIG 16A cont.

ANT 39i
Fab (FZD)
Fc DANG
Knob
Hole
Diabody (LRP)
Heavy chain 1
Heavy chain 2
Common light chain
Linker 1 = 20 mer GGGSGGGSGGGSGGGSGGGTG
Linker 2 = 5 mer GGGGS
ANT 39i LALAPS
Fc LALAPS
Linker 1 = 20 mer GGGSGGGSGGGSGGGSGGGTG
Linker 2 = 5 mer GGGGS

FIG 16B

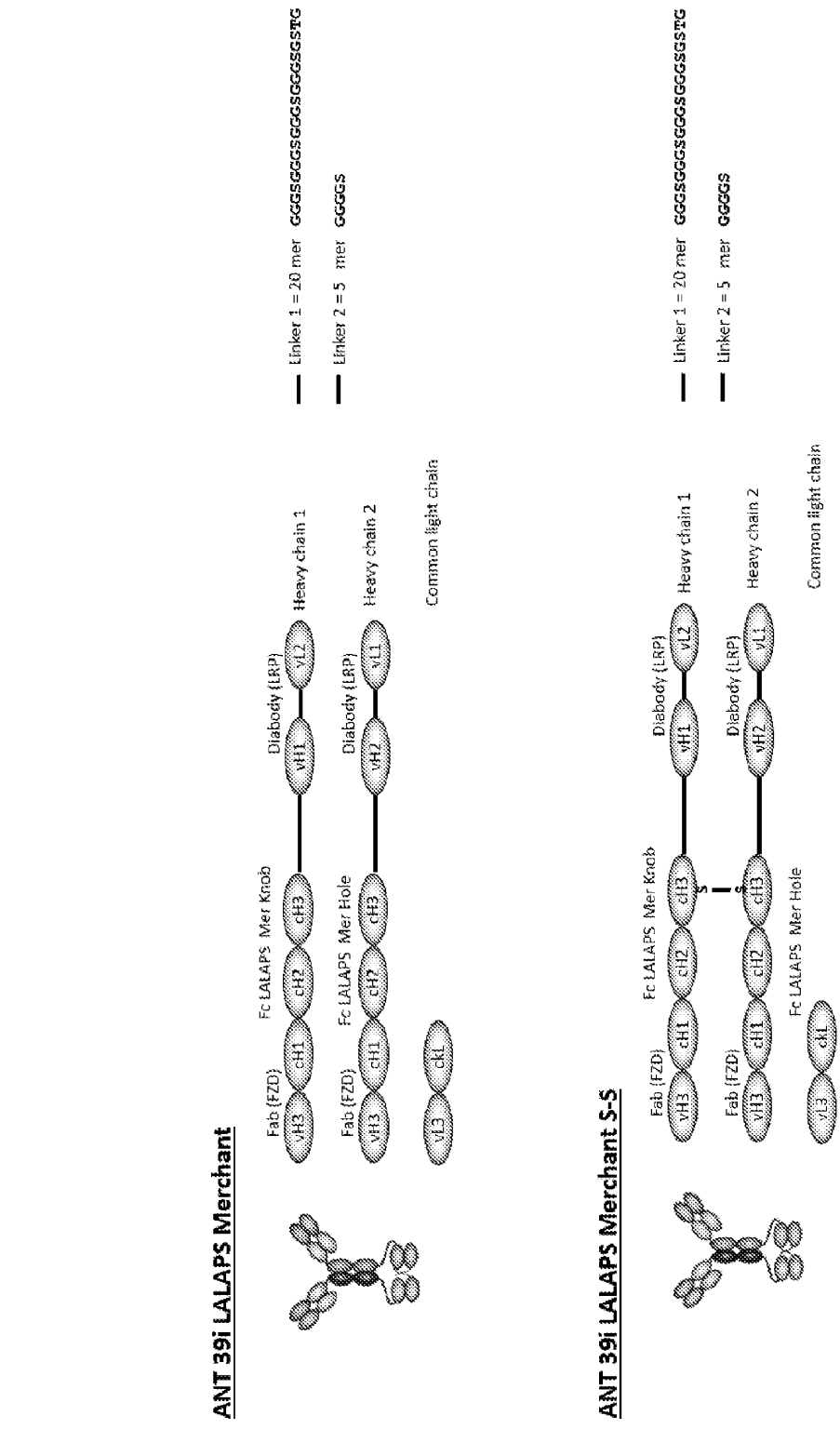

ANT 39i LALAPS Merchant
Fab (FZD)
Fc LALAPS Mer Knob
Diabody (LRP)
Heavy chain 1
Fab (FZD)
Fc LALAPS Mer Hole
Diabody (LRP)
Heavy chain 2
Common light chain
Linker 1 = 20 mer GGGSGGGSGGGSGGGSGGGSTG
Linker 2 = 5 mer GGGGS
ANT 39i LALAPS Merchant S-S
Fab (FZD)
Fc LALAPS Mer Knob
Diabody (LRP)
Heavy chain 1
Fab (FZD)
Fc LALAPS Mer Hole
Diabody (LRP)
Heavy chain 2
Common light chain
Linker 1 = 20 mer GGGSGGGSGGGSGGGSGGGSTG
Linker 2 = 5 mer GGGGS

FIG 16B cont.

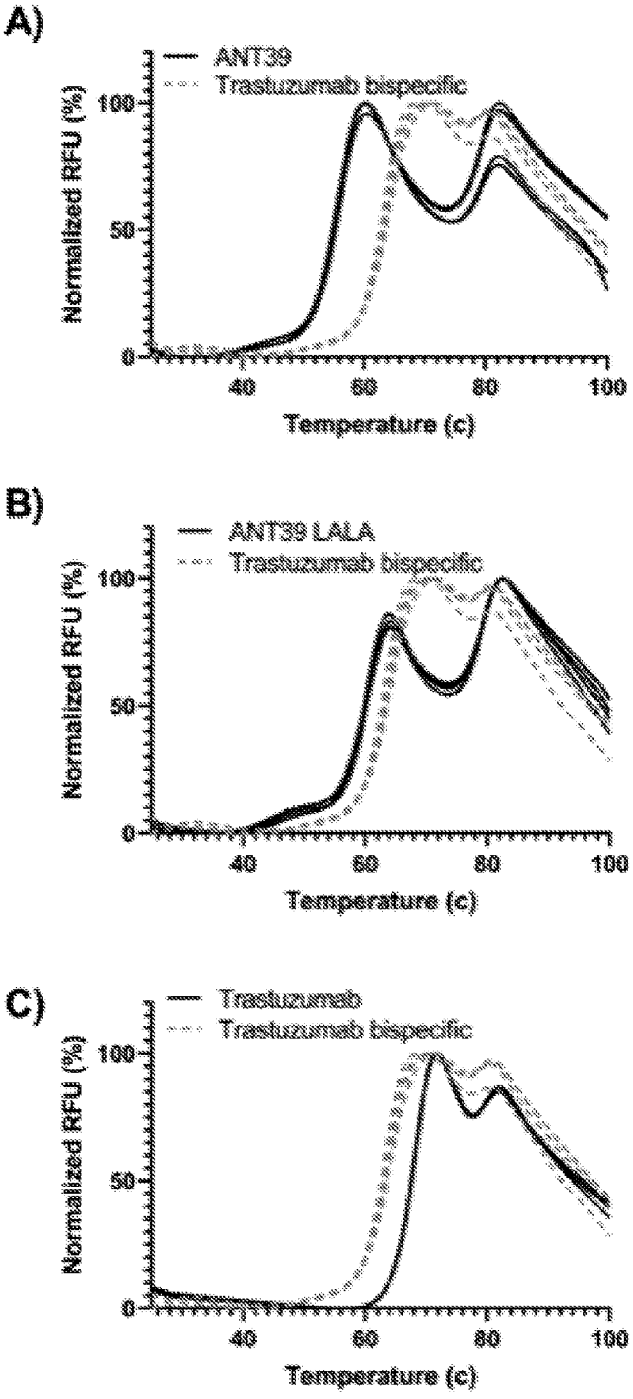

A)
ANT39
Trastuzumab bispecific
Normalized RFU (%)
100
50
0
40
60
80
100
Temperature (c)
B)
ANT39 LALA
Trastuzumab bispecific
Normalized RFU (%)
100
50
0
40
60
80
100
Temperature (c)
C)
Trastuzumab
Trastuzumab bispecific
Normalized RFU (%)
100
50
0
40
60
80
100
Temperature (c)

FIG 17

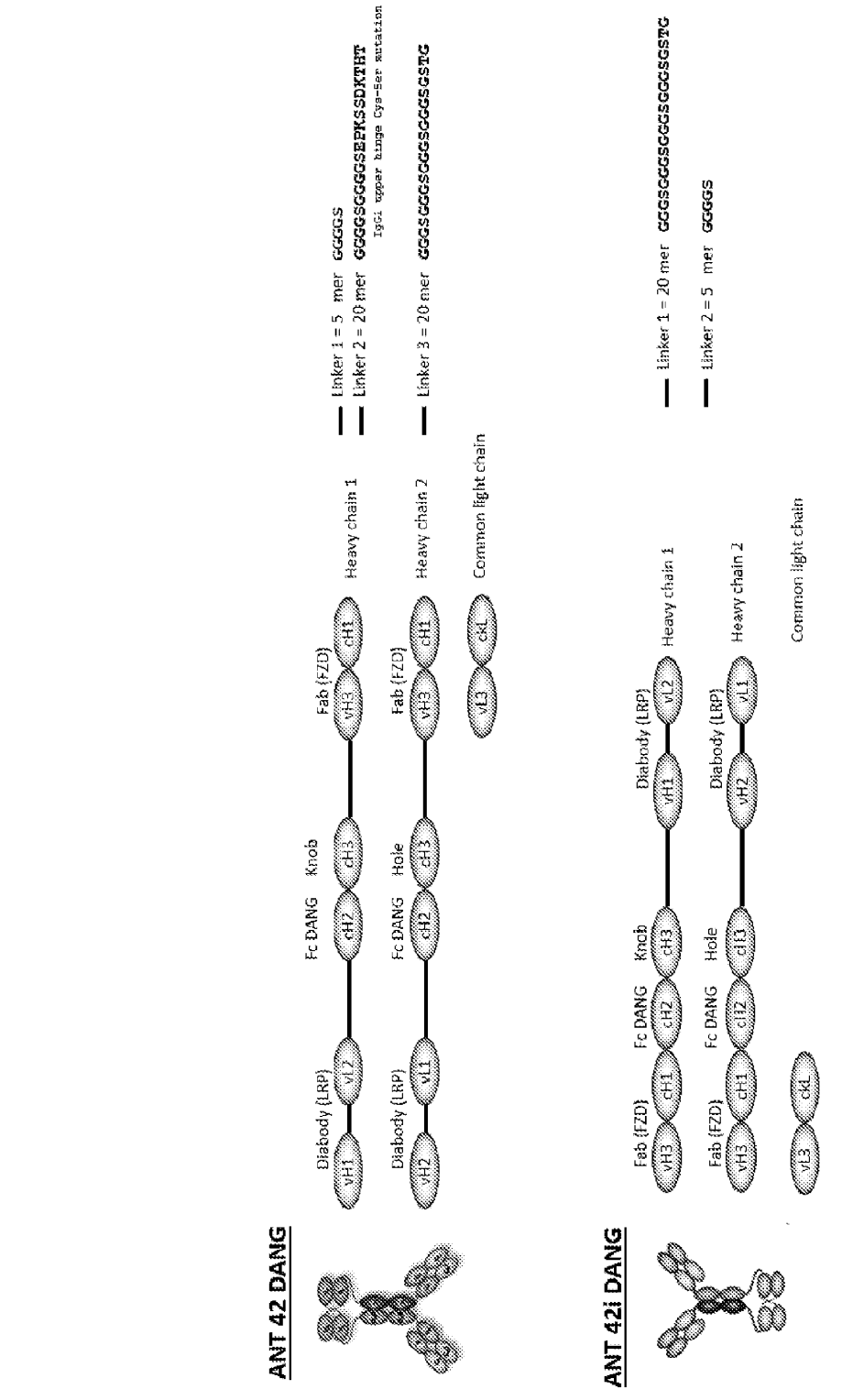

ANT 42 DANG
Diabody (LRP)
vH1
vL2
Fc DANG
cH2
Knob
cH3
Fab (FZD)
vH3
cH1
Heavy chain 1
Diabody (LRP)
vH2
vL1
Fc DANG
cH2
Hole
cH3
Fab (FZD)
vH3
cH1
Heavy chain 2
vL3
cKL
Common light chain
Linker 1 = 5 mer GGGGS
Linker 2 = 20 mer GGGGSGGGGSGGGGSEPKSSDKTHT
IgG1 upper hinge Cys-Ser mutation
Linker 3 = 20 mer GGGSGGGSGGGSGGGSGGTG
ANT 42i DANG
Fab (FZD)
vH3
cH1
Fc DANG
cH2
Knob
cH3
Diabody (LRP)
vH1
vL2
Heavy chain 1
Fab (FZD)
vH3
cH1
Fc DANG
cH2
Hole
cH3
Diabody (LRP)
vH2
vL1
Heavy chain 2
vL3
cKL
Common light chain
Linker 1 = 20 mer GGGSGGGSGGGSGGGSGGTG
Linker 2 = 5 mer GGGGS

FIG 18

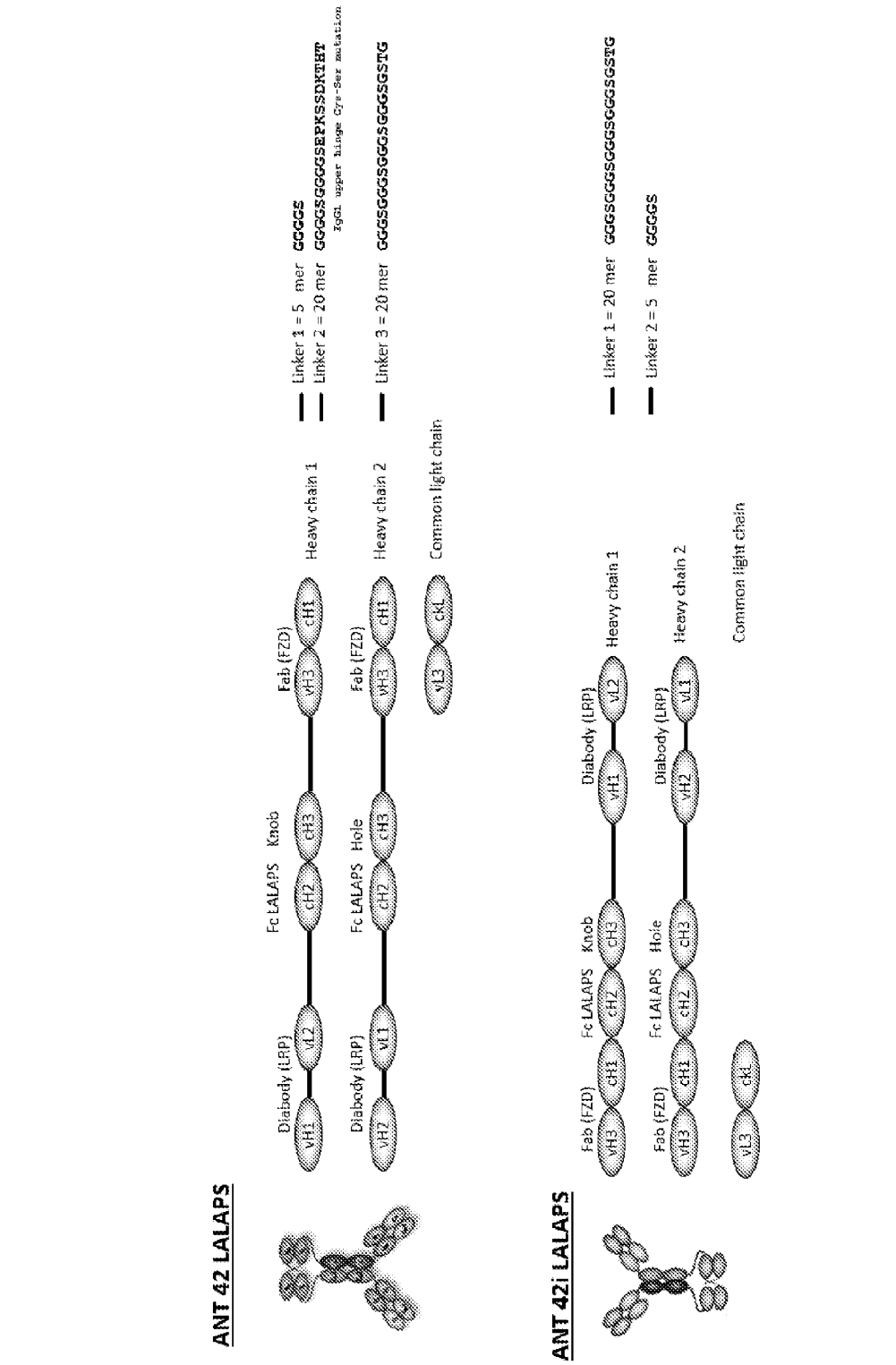

ANT 42 LALAPS
Diabody (LRP)
Fc LALAPS Knob
Fab (FZD)
Heavy chain 1
Linker 1 = 5 mer GGGGS
Linker 2 = 20 mer GGGGSGGGGSGGGGSEPKSSDKTHT
IgG1 upper hinge Cys-Ser mutation
Diabody (LRP)
Fc LALAPS Hole
Fab (FZD)
Heavy chain 2
Linker 3 = 20 mer GGGSGGGSGGGSGGGSGGGTG
Common light chain
ANT 42i LALAPS
Fab (FZD)
Fc LALAPS Knob
Diabody (LRP)
Heavy chain 1
Linker 1 = 20 mer GGGSGGGSGGGSGGGSGGGTG
Fab (FZD)
Fc LALAPS Hole
Diabody (LRP)
Heavy chain 2
Linker 2 = 5 mer GGGGS
Common light chain

FIG 18

ANT 42 LALAPS Merchant
Diabody (LRP)
Fc LALAPS Mer Knob
Fab (FZD)
Heavy chain 1
Diabody (LRP)
Fc LALAPS Mer Hole
Fab (FZD)
Heavy chain 2
Common light chain
Linker 1 = 5 mer GGGGS
Linker 2 = 20 mer GGGGSGGGGSGGPKSSDKTHT
IgG1 upper hinge Cys-Ser mutation
Linker 3 = 20 mer GGGSGGGSGGGSGGGSGGTG
ANT 42i LALAPS Merchant
Linker 1 = 20 mer GGGSGGGSGGGSGGGSGGTG
Linker 2 = 5 mer GGGGS

FIG 18

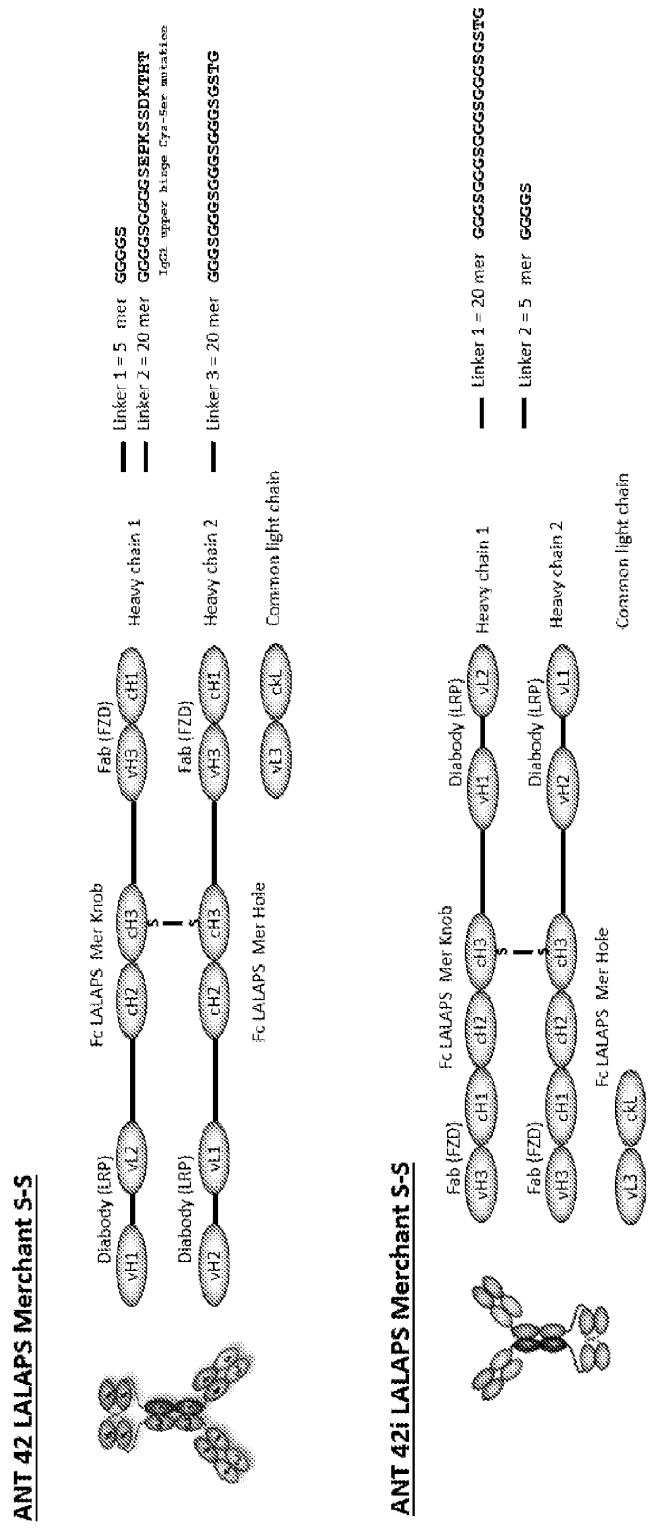

ANT 42 LALAPS Merchant S-S
Diabody (LRP)
Fc LALAPS Mer Knob
Fab (FZD)
Heavy chain 1
Linker 1 = 5 mer GGGGS
Linker 2 = 20 mer GGGGSGGGGSGGGGSEPKSSDKTHT
IgG1 upper hinge Cys-Ser mutation
Linker 3 = 20 mer GGGSGGGSGGGSGGGSGGGTG
Heavy chain 2
Common light chain
Fc LALAPS Mer Hole
ANT 42i LALAPS Merchant S-S
Linker 1 = 20 mer GGGSGGGSGGGSGGGSGGGTG
Linker 2 = 5 mer GGGGS

FIG 18

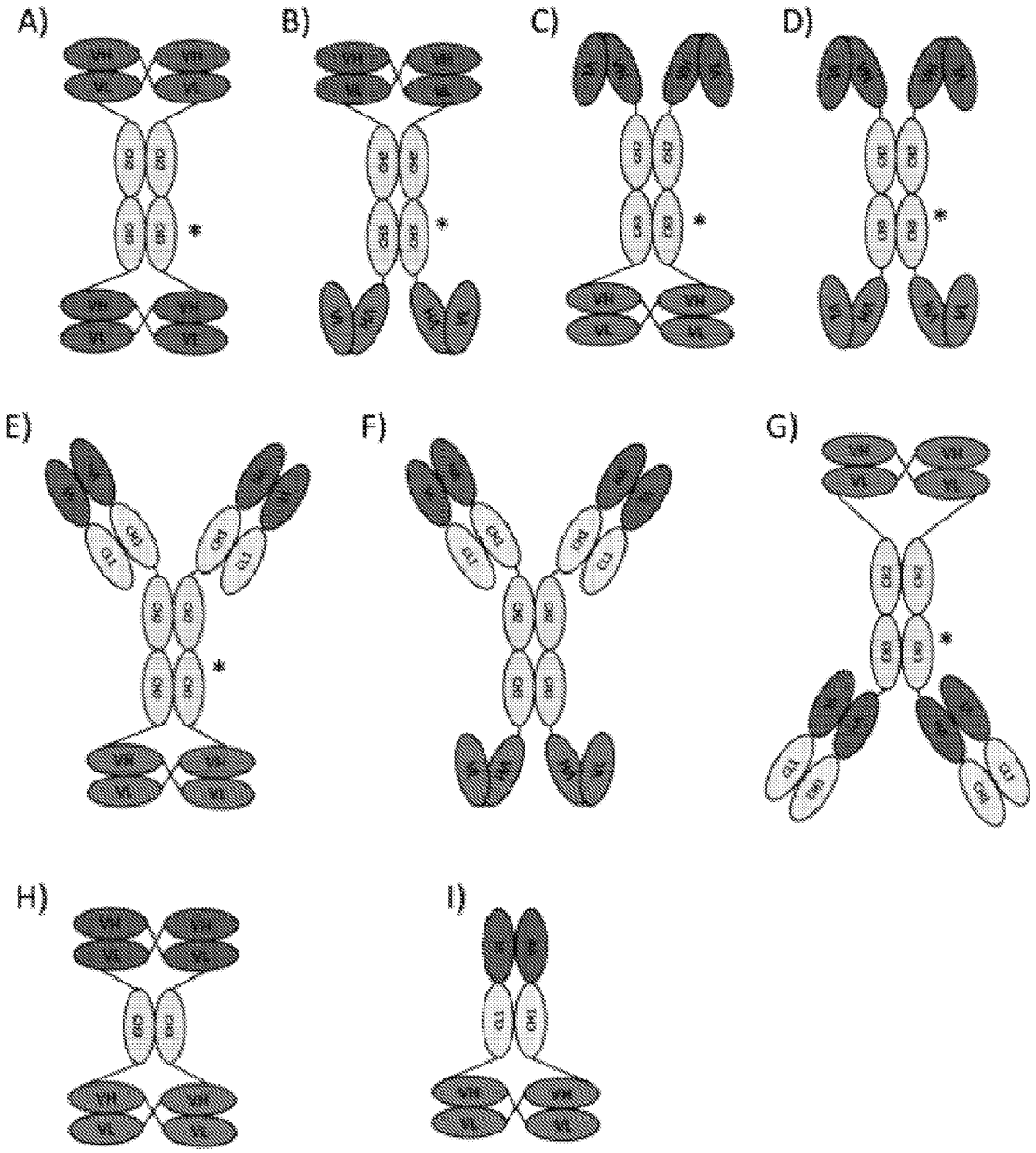


FIG 19

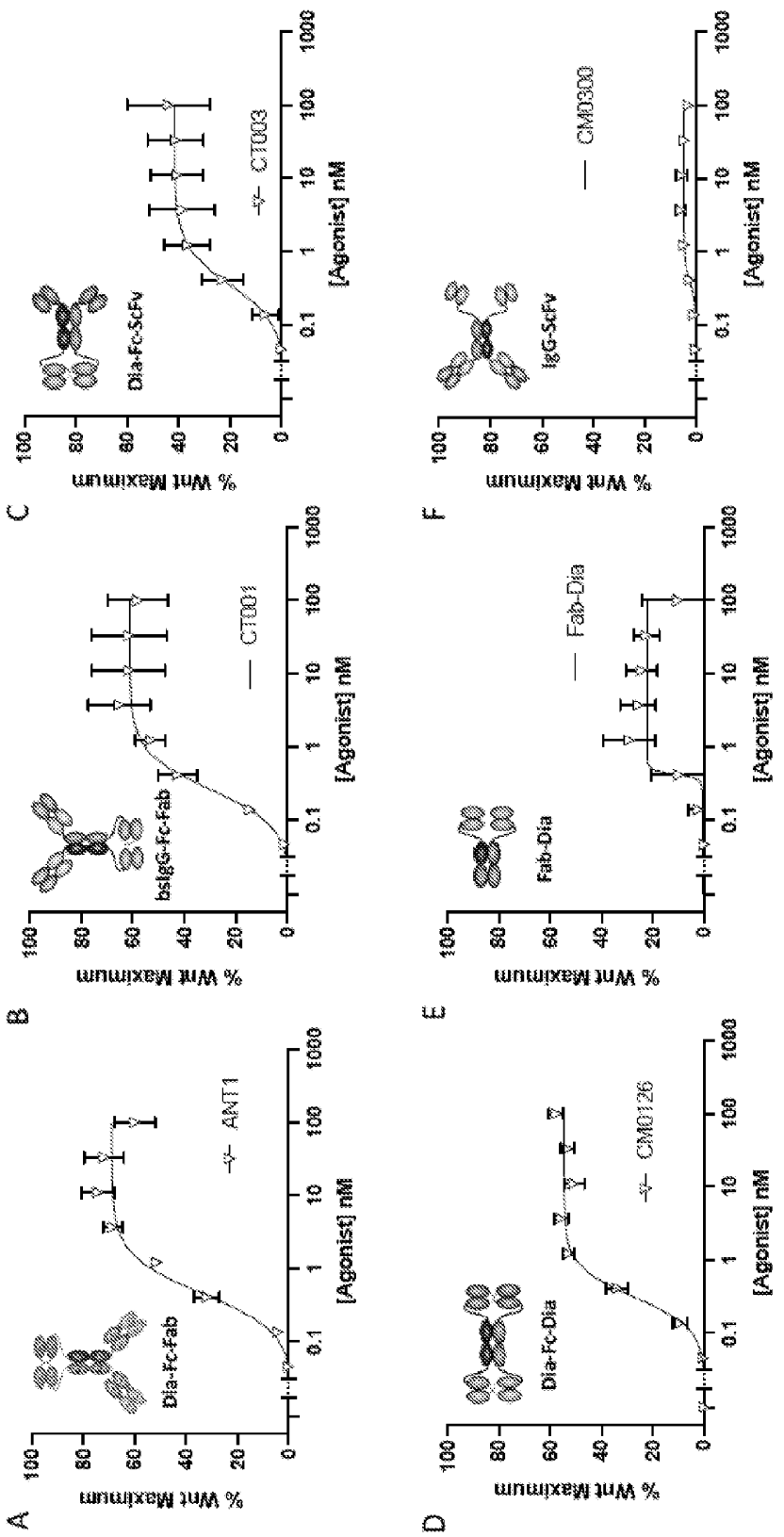

A
B
C
D
E
F
% Wnt Maximum
[Agonist] nM
Dia-Fc-Fab
ANT1
bsIgG-Fc-Fab
CT001
Dia-Fc-ScFv
CT003
Dia-Fc-Dia
CM0126
Fab-Dia
IgG-ScFv
CM0300

FIG 20

#	Format	Expression [Monomer] (mg/l)*	EC50 (nM)	Alternate Names/Alternate Variant Names
1	Dia-Fc-Fab	97	0.45	ANT#, Ant#, ANT #, Ant #, Diabody-Fc-Fab, ANT#LALAPS, ANT# LALAPS, ANT# LALALPS Merchant, ANT# LALALPS Merchant_S:S, ANT#LALA, ANT# LALA, ANT#DANG, ANT# DANG,
2	bsIgG-Dia	50	0.26	ANT#i, Ant#i, IgG-Diabody, IgG-Dia, bsIgG-Dia, CT#, CM#, ANT#iLALAPS, ANT#i LALAPS, ANT#i LALALPS Merchant, ANT#i LALALPS Merchant_S:S
3	Dia-Fc-ScFv	50	0.60	Diabody-Fc-ScFv, CM#, CT#
4	Dia-Fc-Dia	20	0.31	FLAg, CM#, Diabody-Fc-Diabody, CM#
5	Fab-Dia	25	0.42	Fab-Diabody, CM#
6	IgG-ScFv	100	NA	CM#

- number; Dia = Diabody

FIG 21

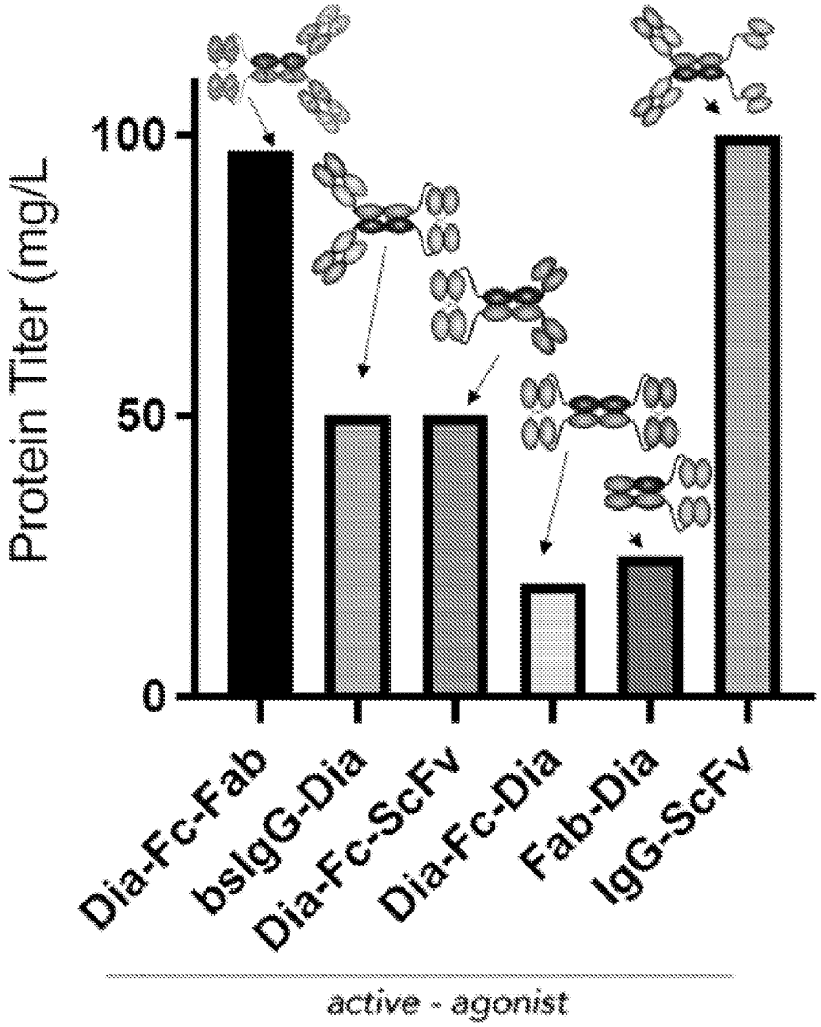

Protein Titer (mg/L
100
50
0
Dia-Fc-Fab
bsIgG-Dia
Dia-Fc-ScFv
Dia-Fc-Dia
Fab-Dia
IgG-ScFv
active - agonist

FIG 21 cont.

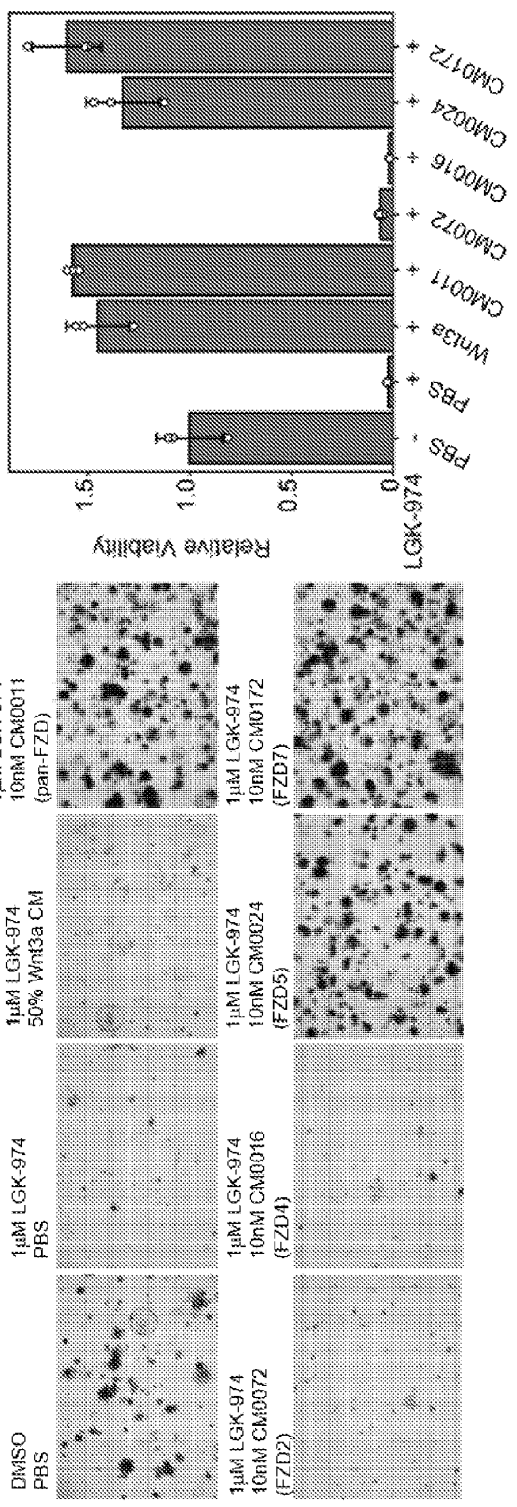

Relative Viability
1.5
1.0
0.5
0
LGK-974
PBS
PBS
Wnt3a
CM0011
CM0072
CM0016
CM0024
CM0172
DMSO
PBS
1μM LGK-974
PBS
1μM LGK-974
50% Wnt3a CM
1μM LGK-974
10nM CM0011
(pan-FZD)
1μM LGK-974
10nM CM0072
(FZD2)
1μM LGK-974
10nM CM0016
(FZD4)
1μM LGK-974
10nM CM0024
(FZD5)
1μM LGK-974
10nM CM0172
(FZD7)

FIG 22

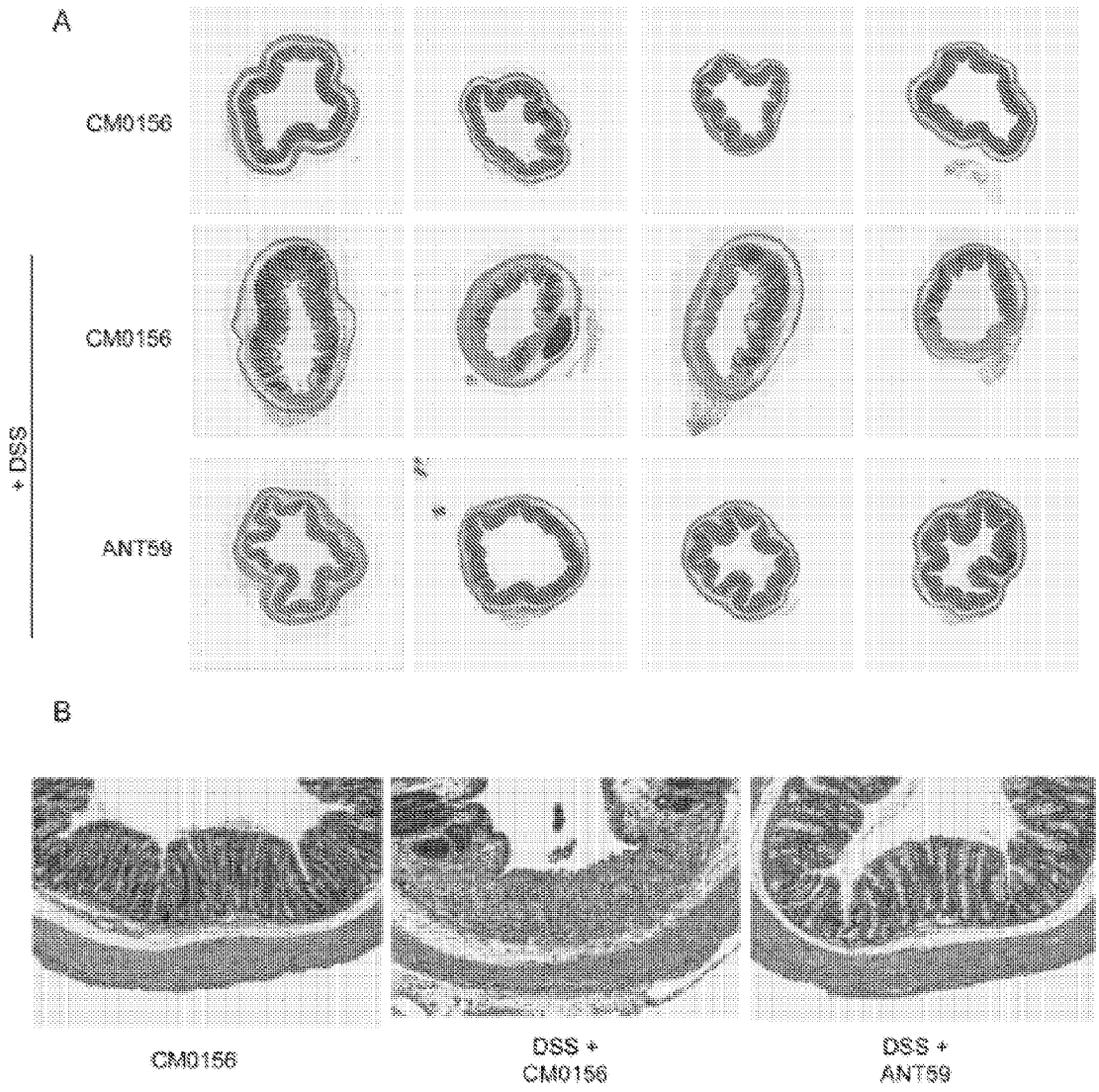


FIG 23

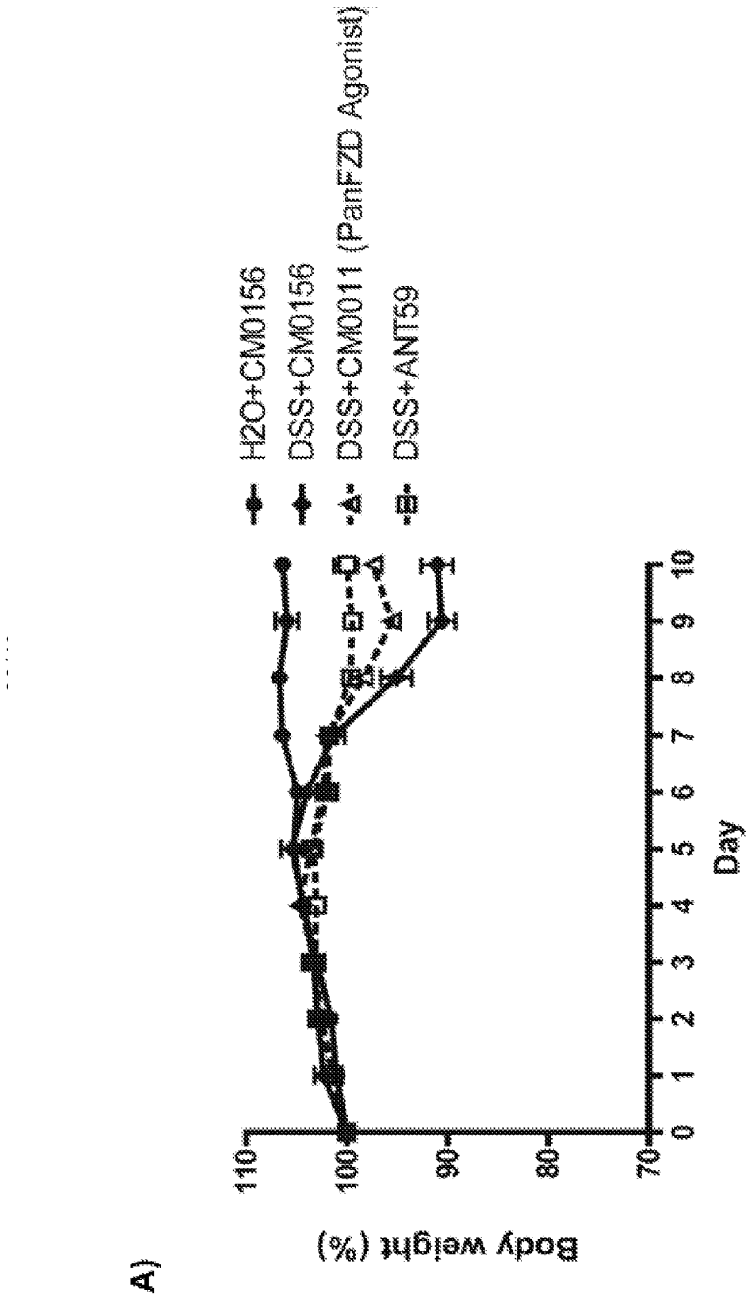
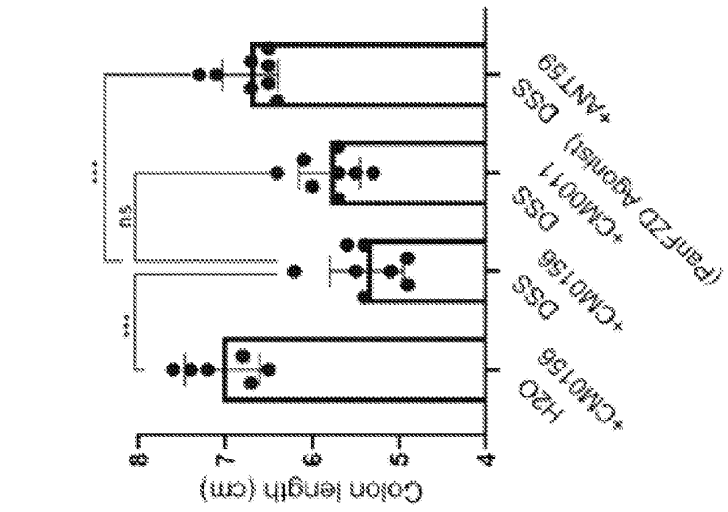

A)
Body weight (%)
110
100
90
80
70
0 1 2 3 4 5 6 7 8 9 10
Day
H2O+CM0156
DSS+CM0156
DSS+CM0011 (PanFZD Agonist)
DSS+ANT59

FIG 24


Colon length (cm)
8
7
6
5
4
H2O
+CM0156
DSS
+CM0156
DSS
+CM0111
(PanFZD Aptamer)
DSS
+ANT59
***
n.s.
***

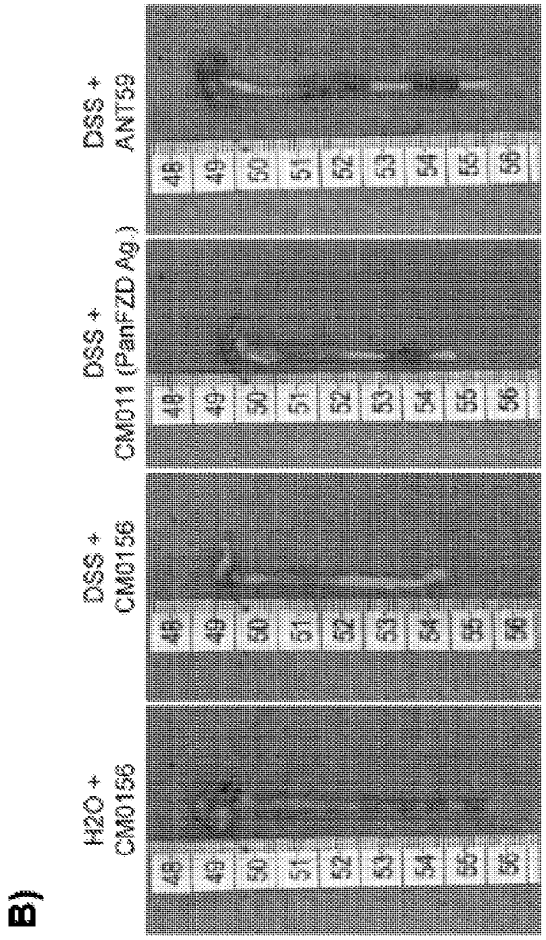
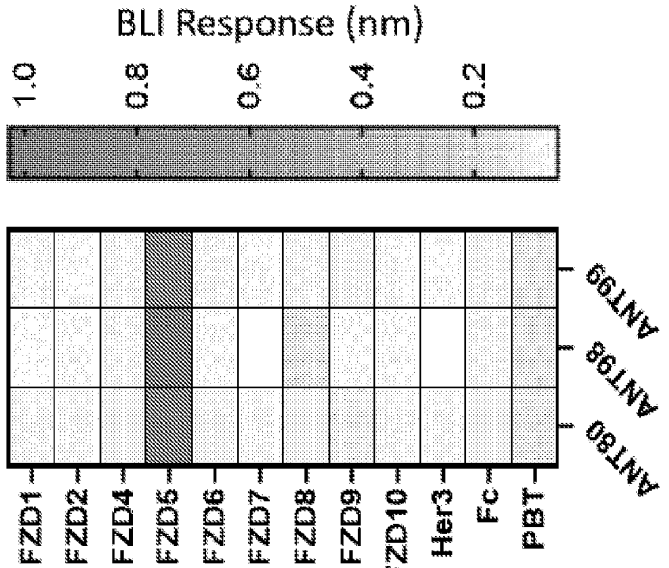

B)
H2O +
CM0156
DSS +
CM0156
DSS +
CM011 (PanFZD Ag.)
DSS +
ANT59
48
49
50
51
52
53
54
55
56

FIG 24 cont.



ANT	Exp. Titer (mg/l)	FZD5 avidity (nM)
80	121	0.05
98	81	2
99	234	0.4

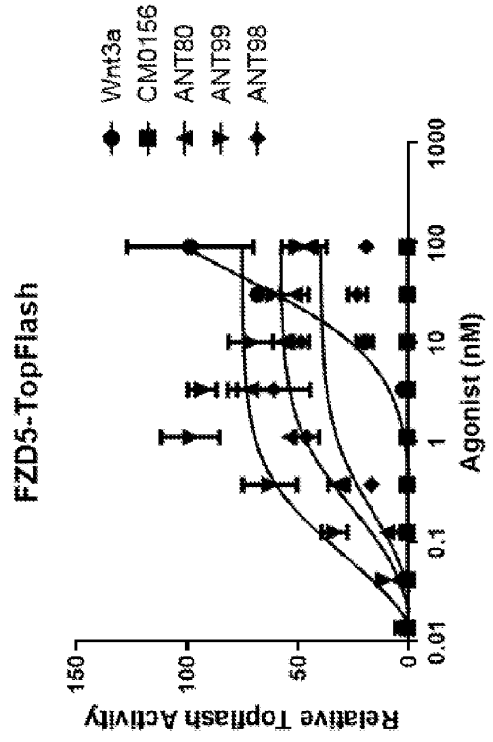


FIG 25

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2021/061971

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***C07K 16/46*** (2006.01), ***A61K 39/395*** (2006.01), ***A61P 25/28*** (2006.01), ***A61P 27/02*** (2006.01)

CPC: **C07K 16/468** (2020.01), A61K 39/395 (2020.01), A61P 25/28 (2020.01), A61P 27/02 (2020.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Keywords used across the whole IPC

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Databases: GQ Pat, Genbank, GB SET, Protein Data Bank, Questel, Google, Scopus, Protein Data Bank, Genpept, STM Source, Derwent Biotechnology Abstracts
Keywords: LRP6, FZD5, antibody; Sequences: SEQ ID NO:990, 991, 992

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2020/250156 A1 (ANGERS, S. et al.) 17 December 2020 (17-12-2020)	
X	WO 2019/159084 A1 (ANGERS, S. et al.) 22 August 2019 (22-08-2019)	1-16, 18-28, 30, 32, 34-37, 39, 43, 45 and 46
X	TAO, Y. et al. Tailored tetravalent antibodies potently and specifically activate Wnt/Frizzled pathways in cells, organoids and mice. Elife. 27 August 2019 (27-08-2019), Vol. 8, Article e46134.	1-8, 10-16, 18, 20-28, 30, 32, 34-37 and 39

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"D"	document cited by the applicant in the international application	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"E"	earlier application or patent but published on or after the international filing date	"&"	document member of the same patent family
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)		
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 25 February 2022 (25-02-2022)	Date of mailing of the international search report 26 April 2022 (26-04-2022)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 819-953-2476	Authorized officer Rena Oulton (819) 639-6855

Form PCT/ISA/210 (second sheet) (July 2019)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2021/061971

Box No. I **Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)**

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

a. ☒ forming part of the international application as filed:

☒ in the form of an Annex C/ST.25 text file.

☐ on paper or in the form of an image file.

b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2021/061971

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
See extra sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos.:
claims 1-28 and 30-46 (all partially).

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2021/061971

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
WO2019159084A1	22 August 2019 (22-08-2019)	CA3129736A1	22 August 2019 (22-08-2019)
		CN111989345A	24 November 2020 (24-11-2020)
		EP3752537A1	23 December 2020 (23-12-2020)
		EP3752537A4	01 December 2021 (01-12-2021)
		IL276646D0	30 September 2020 (30-09-2020)
		JP2021519574A	12 August 2021 (12-08-2021)
		SG11202007675VA	29 September 2020 (29-09-2020)
		US2021032352A1	04 February 2021 (04-02-2021)
WO2020250156A1	17 December 2020 (17-12-2020)	AU2020291208A1	06 January 2022 (06-01-2022)
		CA3140580A1	17 December 2020 (17-12-2020)

Form PCT/ISA/210 (patent family annex) (July 2019)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2021/061971

Continuation of Box No. III:

Documents cited:

D1: WO 2020/250156 A1 (ANGERS, S. et al.) 17 December 2020 (17-12-2020)
D2 : WO 2019/159084 A1 (ANGERS, S. et al.) 22 August 2019 (22-08-2019)

D1 discloses tetravalent binding molecules (claim 16) comprising an Fc domain, a bivalent Wnt co-receptor binding domain (linked to one terminus of the Fc domain), and a bivalent FZD2 or FZD7 receptor binding domain (linked to the other Fc domain terminus). The co-receptor binding domain may bind to any Wnt co-receptor, such as LRP5/6 (paragraph rool8l). The Wnt co-receptor binding domain and the FZD2 or FZD7 receptor binding domain may include two scFv or diabodies (paragraphs [0013] to [0017]).

D2 discloses tetravalent binding molecules comprising an Fc domain, a bivalent LRP binding domain (linked to one terminus of the Fc domain), and a bivalent FZD binding domain (linked to the other Fc domain terminus); see claims 9 and 14. Further disclosed are FZD binding domain antibodies (5019, 5027, 5044, 5056; Tables 1 and 2, and paragraph [0175]), as well as LRP5 (2459 and 2460; paragraph [0174]) and LRP6 antibodies (2539, 2540, 2542; Table 2 and paragraph [0155]). Binding domain formats including Fab, scFv and diabodies are contemplated (paragraphs [0015] and [0136]). Specifically disclosed is the antibody 5019-K/II-2459:2460 (paragraph [0174]) which binds to FZD1 (pan-FZD diabody 5019) and LRP5 (2459 and 2460).

The claims are directed to a plurality of inventive concepts as follows:

The claims relate to tetravalent binding antibody molecules comprising:
(a) an Fc domain or fragment thereof comprising a constant heavy chain domain 3 (CH3),
(b) a bivalent low-density lipoprotein receptor-related protein (LRP) binding domain, and
(c) a bivalent Frizzled (FZD) binding domain.

With regard to feature (b), the following structurally distinct embodiments are contemplated: anti-LRP5 antibodies having CDR regions from Tables 3 and 6; anti-LRP6 antibodies having CDR regions from Tables 4 and 6; and combinations thereof.

With regard to feature (c), the following structurally distinct embodiments are contemplated: binding domains for 10 types of Frizzled Class Receptors, FZD1-FZD10, and anti-FZD antibodies having CDR regions from Tables 1, 2, 6 and 10.

Further, it appears that tetravalent binding antibody molecules comprising features (a) to (c) are known; see D1 or D2 as described above. In addition, D2 discloses all combinations of FZD binding domains selected from one or more binding domains to FZD 1-FZD 10, and LRP binding domains selected from binding domains to LRP5, LRP6 and LRP5/6 (claim 14). D2 also discloses the anti-FZD4 antibody 5044 (Tables 1 and 2) which is the first antibody listed in Table 1 of the instant application. Moreover D2 discloses the anti-LRP5 antibody 2459 (Tables 1 and 2) which is the first antibody listed in Table 3 of the instant application.

In view of the structurally distinct embodiments and the prior art, the claims lack unity *a priori* and *a posteriori*.

Therefore each tetravalent binding antibody molecule is considered a separate inventive concept wherein each FZD binding domain is defined by a specific antibody (for example, one of the antibodies listed in Tables 1 (34 FZD4 antibodies), 2A (35 FZD4 antibodies), 2B (140 FZD5 antibodies), 6 or 10 (3 pan-FZD antibodies)), and each LRP binding domain is defined by a specific antibody (for example, one of the antibodies listed in Tables 3 (38 LRP5 antibodies), 4 (90 LRP6 antibodies) or 6).

The claims must be limited to one inventive concept as set out in PCT Rule 13.

The International Searching Authority has established the international search report on those parts of the international application which relate to the following groups:

(i) the invention first mentioned, specifically wherein the LRP binding domain binds LRP5 and is antibody 2459 (the first antibody listed in Table 3), and wherein the FZD binding domain binds FZD1 and is antibody 5019 (the first FZD1 antibody listed in Table 10; Tables 1, 2 and 6 do not explicitly identify FZD1 antibodies): claims 1-14, 16, 19, 34-36 and 39-46 (all partially), and
(ii) the tetravalent binding antibody molecule wherein the LRP binding domain binds LRP6, and wherein the FZD binding domain binds FZD5, wherein the antibody is ANT99 (identified in Table 13): claims 1-28, 30-39, 43, 45 and 46 (all partially).

UNITED STATES
PATENT AND TRADEMARK OFFICE

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/361,782	**10/11/2024 06:00:48 PM Z ET**	**SRZN-006/04US 328202-2203**

Title of Invention

WNT SURROGATE MOLECULES AND USES THEREOF

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	9001	FILED BY	MaxVal Group
PATENT CENTER #	67499875	FILING DATE	07/28/2023
CUSTOMER #	157070	FIRST NAMED INVENTOR	Yang LI
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Ashley Sherrid

Documents

TOTAL DOCUMENTS: 52

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
SRZN-006_04US_328202-2203_IDS_Transmittal_2024-10-09.pdf	2	Transmittal Letter	105 KB
SRZN-006_04US_328202-2203_IDS_SB08_20241008171740.pdf	6	Information Disclosure Statement (IDS) Form (SB08)	147 KB
Warning: This is not a USPTO supplied IDS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.			
FOR_WO2011138391A1_EFS.pdf	239	Foreign Reference	11140 KB
FOR_WO2017093478A1_EFS.pdf	125	Foreign Reference	5197 KB
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FOR_WO2022130341A1_EFS.pdf	200	Foreign Reference	11168 KB
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Digest

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

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New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 6

Complete if Known	
Application Number	18/361,782
Filing Date	07-28-2023
First Named Inventor	LI; Yang
Art Unit	1645
Examiner Name	CHEONG, CHEOM-GIL
Attorney Docket Number	SRZN-006/04US 328202-2203

U. S. PATENT DOCUMENTS

Examiner Initials*		Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		001	US-12006368	06-11-2024	LI; Yang et al.	
		002	US-20210032352	02-04-2021	ANGERS; Stephane et al.	
		003	US-20210309704	10-07-2021	VANHOLLEBEKE; Benoit	
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		007	WO-2011138391-A1	11-10-2011	NOVARTIS AG., et al.		☐
		008	WO-2017093478-A1	06-08-2017	BOEHRINGER INGELHEIM INT.		☐
		009	WO-2019093342-A1	05-16-2019	KYOWA HAKKO KIRIN CO LTD.		☒
		010	WO-2022130341-A1	06-23-2022	ANTLERA THERAPEUTICS INC.		☐
		011	WO-2024040118-A2	02-22-2024	SURROZEN OPERATING INC.		☐

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Sheet 2 of 6

Complete if Known	
Application Number	18/361,782
Filing Date	07-28-2023
First Named Inventor	LI; Yang
Art Unit	1645
Examiner Name	CHEONG, CHEOM-GIL
Attorney Docket Number	SRZN-006/04US 328202-2203

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*		Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
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		052	US Patent Application No. 18/691,419 filed March 12, 2024, by Russell FLETCHER, et al.	☐
		053	US Patent Application No. 18/719,798 filed June 13, 2024, by Yang LI, et al.	☐
		054	US Patent Application No. 18/888,027, filed September 17, 2024, by Kenan Christopher GARCIA, et al.	☐
		055	US Patent Application No. 18/893,740, filed September 23, 2024, by Kenan Christopher GARCIA, et al.	☐
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(54) **Title**: COMPOSITIONS AND METHODS OF USE FOR THERAPEUTIC LOW DENSITY LIPOPROTEIN - RELATED PROTEIN 6 (LRP6) MULTIVALENT ANTIBODIES

(57) **Abstract**: The present disclosure relates to an antibody or antigen binding fragment having at least two receptor binding domains for two different binding sites of LRP6 and compositions and methods of use thereof.

COMPOSITIONS AND METHODS OF USE FOR THERAPEUTIC LOW DENSITY LIPOPROTEIN – RELATED PROTEIN 6 (LRP6) MULTIVALENT ANTIBODIES

Related Applications

This application claims priority to U.S. Provisional Application Serial No. 61/331,993 filed May 6, 2010, the contents of which are incorporated herein by reference in its entirety.

Field of the Invention

The present invention relates to multivalent antibodies comprising at least two receptor binding domains for two different binding sites on LRP6. The invention more specifically relates to multivalent antibodies that are LRP6 antagonists.

Background of the Invention

The Wnt/β-catenin pathway regulates diverse biological processes during development and tissue homeostasis through modulating the protein stability of β-catenin (Clevers *et al.*, (2006) Cell 127:469-480; and Logan *et al.*, (2004) Annu. Rev Cell Dev. Biol 20:781-810). In the absence of Wnt signaling, cytoplasmic β-catenin is associated with the β-catenin destruction complex that contains multiple proteins including adenomatous polyposis coli (APC), Axin, and glycogen synthase kinase 3 (GSK3). In this complex, β-catenin is constitutively phosphorylated by GSK3 and degraded by the proteasome pathway. The Wnt signal is transduced across the plasma membrane through two distinct receptors, the serpentine receptor Frizzled, and the single-transmembrane protein LRP5 or LRP6. The Wnt proteins promote the assembly of the Frizzled-LRP5/6 signaling complex, and induce phosphorylation of the cytoplasmic PPPSPxS motifs of LRP5/6 by GSK3 and Casein Kinase I. Phosphorylated LRP5/6 bind to Axin and inactivate the β-catenin degradation complex. Stabilized β-catenin enters the nucleus, binds to the TCF family transcription factors, and turns on transcription.

The large extracellular domain of LRP5/6 contains four YWTD-type β-propeller regions that are each followed by an EGF-like domain, and the LDLR domain. Each propeller region contains six YWTD motifs that form a six-bladed β-propeller structure. Biochemical studies suggest that Wnt proteins physically interact with both Frizzled and

LRP6 and induce formation of Frizzled-LRP6 signaling complex (Semenov *et al.*, (2001) Curr. Biol 11, 951-961; and Tamai, *et al.* (2000) Nature 407, 530-535). Besides Wnt proteins, the large extracellular domain of LRP5/6 binds to multiple secreted Wnt modulators, including Wnt antagonist, DKK1 and Sclerostin (SOST), and Wnt agonist R-Spondins.

Mutations in pathway components such as APC and β-catenin have been associated with human cancers. Recent studies suggest that overexpression of Wnt proteins and/or silencing of Wnt antagonists such as DKK1, WISP and sFRPs promote cancer development and progression (Akiri *et al.*, (2009) Oncogene 28:2163-2172; Bafico *et al.*, (2004) Cancer Cell 6:497-506; Suzuki *et al.*, (2004) Nat Genet. 36:417-422; Taniguchi *et al.*, (2005) Oncogene. 24:7946-7952; Veeck *et al.*, (2006) Oncogene. 25:3479-3488; Zeng *et al.*, (2007) Hum. Pathol. 38:120-133). In addition, Wnt signaling has been implicated for the maintenance of cancer stem cells (Jamieson *et al.*, (2004) Cancer Cell 6:531-533 and Zhao *et al.*, (2007) Cancer Cell 12:528-541).

Antibody therapy has been used as a means to treat certain cancers. Efforts to increase the valency or the number of antigenic determinants that an individual antibody molecule can bind have lead to the development of bispecific antibodies (for examples see Jimenez *et al.*, Molecular Cancer Therapeutics 2005:4427-434, Lu *et al.*, J. of Immun. Methods 1999:230, 159-171 and U.S. Patent Publication Nos. 20070014794 and 20050100543). Bispecific antibodies are immunoglobulin (Ig)-based molecules that bind to two different epitopes on either the same or distinct antigens. The antibodies, for example, could be specific for a tumor cell antigen and an effector cell such as an activated T-cell or two functional targets or epitopes.

A major obstacle in the development of bispecific antibodies as therapeutics has been difficulty in producing the antibodies in sufficient quantity and quality for clinical studies. In particular, traditional methods, including hybrid hybridoma, in which two distinct hybridomas are fused to create a cell expressing two sets of heavy and light chains, and chemical conjugation (Carter *et al.*, (1995) J. Hematotherapy 4:463-70) have been inadequate. For example, coexpression of two different sets of IgG light and heavy chains in a hybrid hybridoma may produce up to 10 light- and heavy-chain pairs, with only one of these pairs forming the functional bispecific heterodimer (Suresh *et al.* (1986) Methods Enzymol. 121:210-28). In addition, purification of the antibodies from the non-

functional species, such as homodimers and mispaired heterodimers of non-cognate Ig light and heavy chains produced by the hybrid hybridoma is cumbersome and inefficient.

Chemical crosslinking of two IgGs or their fragments is also inefficient and can lead to the loss of antibody activity (Zhu *et al.* (1994) Cancer Lett. 86:127-34). Multimeric aggregates resulting from chemical conjugationresult in a poor yield (Cao *et al.* (1998) Bioconj. Chem. 9:635-44).

Accordingly, a need exists for functional multivalent antibodies capable of binding at least two or more epitopes with high affinity. In particular, there is need for functional multivalent antibodies that modify receptors with more then one modifying ligand, such as the canonical Wnt signaling co-receptor, LRP6.

Summary of the Invention

The present invention provides novel multivalent antibodies that bind to multiple binding sites on the LRP6 receptor. In particular, the invention provides LRP6 multivalent antibodies that inhibit thecanonical Wnt signaling pathway.

The present invention is based on the discovery that the multivalent antibodies (e.g., a single LRP6 biparatopic antibody) have the ability to inhibit both propeller 1 (e.g., Wnt1) and propeller 3 (e.g., Wnt 3) ligands. Furthermore, and unexpectedly, the multivalent antibody (e.g., a single LRP6 biparatopic antibody) display no significant potentiation (enhancement) of a Wnt signal. The multivalent antibody binds to distinct LRP6 β-propeller domains. Propeller 1 antibodies bind to the β-propeller 1 domain and block propeller1-dependent Wnts such as Wnt1, Wnt2, Wnt6, Wnt7A, Wnt7B, Wnt9, Wnt10A, Wnt10B. Propeller 3 antibodies bind to the β-propeller 3 domain and block propeller3-dependent Wnts such as Wnt3a and Wnt3. LRP6 antibodies differentiate propeller 1 and propeller 3 ligands into two separate classes and bind to distinct binding sites of the LRP6 target receptor. Conversion of fragments of the LRP6 antibodies (e.g., Fabs) to full length IgG antibody results in an antibody that potentiates (enhances) a Wnt signal in the presence of another protein such as a Wnt 1 or Wnt 3 ligand. Multivalent antibodies inhibit both propeller 1 (e.g., Wnt1) and propeller 3 (e.g., Wnt 3) ligands but without potentation. In addition to Wnt ligands LRP6 Propeller 1 antibodies are expected to inhibit the interaction with other Propeller 1 binding ligands (e.g. Sclerostin, Dkk1).

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Similarly, Propeller 3 antibodies are expected to inhibit the interaction with other propeller 3 binding ligands (e.g. Dkk1). Furthermore, propeller 1 and 3 binding antibodies may be expected to affect the activity of other Wnt signaling modulators e.g. R-spondins.

Multivalent antibodies provide advantages over traditional antibodies for example, expanding the repertoire of targets, having new binding specificities, increased potency, and no signal potentiation. A single LRP6 multivalent antibody can bind to multiple β-propeller domains on a single LRP6 target receptor on the same cell, and inhibit Wnt signaling. In one embodiment, the multivalent antibody binds to any combination of a β-propeller domains selected from the group consisting of propeller 1, propeller 2, propeller 3, and propeller 4. In one embodiment, the multivalent antibody binds to propeller 1 and propeller 3 domains of LRP6. Thus, a single LRP6 multivalent antibody has increased potency of action by binding to multiple β-propeller domains and inhibiting Wnt signaling mediated by each domain. For example, a single LRP6 multivalent antibody inhibits both propeller 1 and propeller 3 mediated Wnt signaling binding to both propeller 1 and propeller 3 domains, respectively. The increased potency of action may be due to increased avidity or better binding of the LRP6 multivalent antibody.

Accordingly, in one aspect, the invention pertains to an isolated multivalent antibody having at least two receptor binding domains for two different binding sites of a target receptor, wherein the first receptor binding domain binds to a first binding site on the target receptor and the second receptor binding domain binds to a second binding site on the same target receptor, wherein the first and second receptor binding domains are linked together such that the binding of the first and second receptor binding domains to the first and second binding sites of the target receptor inhibits a canonical Wnt signal transduction pathway; and wherein the antibody or antigen binding fragment displays no significant potentiation of a Wnt signal.

The multivalent antibody has an affinity for target receptor of approximately nanomolar affinity, or of approximately 1 picomolar affinity. The multivalent antibody is a multivalent antibody, a bivalent antibody, a bispecific antibody, or a biparatopic antibody. In one embodiment, the first and second receptor binding domains is an IgG antibody, an scFv fragment, a single chain diabody, an antibody mimetic, or an antibody variable domain. The first and second receptor binding domains are linked together by a linker with a spatial distribution that permits the first and second receptor binding domains to

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bind to the first and second binding sites, respectively. In one embodiment, the linker is a Gly-Ser linker. In one embodiment, the multivalent antibody has the functional activity of inhibiting a canonical Wnt signal transduction pathway such as the Wnt1 signal pathway and/or the Wnt3 signal transduction pathway. In one embodiment, the multivalent antibody has the functional activity of depleting a cell population, inhibiting or reducing proliferation of a cell population, inhibiting or reducing secretion of inflammatory mediators from a cell population, inhibiting or reducing secretion of cytoplasmic granules from a cell population, wherein the cell population is selected from the group consisting of tumor cells, T cells B cells, and Wnt dependent cells.

In another aspect, the invention pertains to an isolated multivalent antibody having at least two receptor binding domains for two different binding sites of an LRP6 target receptor, where the first receptor binding domain binds to a first binding site on the target receptor and the second receptor binding domain binds to a second binding site on the same LRP6 target receptor. The first and second receptor binding domains are linked together such that the binding of the first and second receptor binding domains to the first and second binding sites of the LRP6 target receptor inhibits a canonical Wnt signal transduction pathway, and the antibody or antigen binding fragment displays no significant potentiation of a Wnt signal.

In one embodiment, the antibody has an affinity for target receptor of approximately nanomolar affinity. In another embodiment, the antibody has an affinity for target receptor of approximately 1 picomolar affinity.

In one embodiment, the first receptor binding domain is an IgG antibody and the second receptor binding domain is an scFv fragment, where the IgG antibody and scFv fragment are linked together by a linker with a spatial distribution that permits the IgG antibody and scFv fragment to bind to the first and second epitopes of LRP6, respectively. In one embodiment, the linker is a Gly-Ser linker selected from the group consisting of $(Gly_4Ser)_4$, and $(Gly_4Ser)_3$.

In one embodiment, the first epitope of the LRP6 target receptor is a β-propeller 1 domain and the second epitope of the LRP6 target receptor is a β-propeller 3 domain. In one embodiment, the antibody or antigen binding fragment binds to the LPR6 β-propeller 1 domain and comprises a heavy chain CDR1 selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 21, and SEQ ID NO: 47; a CDR2 selected from the group consisting

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of SEQ ID NO: 2, SEQ ID NO: 22, and SEQ ID NO: 48; and a CDR3 selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 23, and SEQ ID NO: 49; and a light chain CDR1 selected from the group consisting of SEQ ID NO: 4, SEQ ID NO: 24, and SEQ ID NO: 50; a CDR2 selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 25, and SEQ ID NO: 51; and a CDR3 selected from the group consisting of SEQ ID NO: 6, SEQ ID NO: 26, and SEQ ID NO: 52.

In one embodiment, the antibody or antigen binding fragment binds to the LPR6 β-propeller 3 domain and comprises a heavy chain CDR1 selected from the group consisting of SEQ ID NO: 69, SEQ ID NO: 93, and SEQ ID NO: 115; a CDR2 selected from the group consisting of SEQ ID NO: 70, SEQ ID NO: 94, and SEQ ID NO: 116; and a CDR3 selected from the group consisting of SEQ ID NO: 71, SEQ ID NO: 95, and SEQ ID NO: 117; and a light chain CDR1 selected from the group consisting of SEQ ID NO: 72, SEQ ID NO: 96, and SEQ ID NO: 118; a CDR2 selected from the group consisting of SEQ ID NO: 73, SEQ ID NO: 97, and SEQ ID NO: 119; and a CDR3 selected from the group consisting of SEQ ID NO: 74, SEQ ID NO: 98, and SEQ ID NO: 120. In one embodiment, the IgG heavy chain antibody is selected from the group consisting of SEQ ID NO: 18, 66, and 101 and the light chain is selected from the group consisting of SEQ ID NO: 17, 86, and 85. In one embodiment, the scFv is selected from the group consisting of SEQ ID NO: 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, and 164. In one embodiment, the scFv fragment comprises at least one amino acid mutation that improves stability of the scFv compared with the unmutated scFv fragment, wherein the amino acid mutation is selected from Figures 29-32. In one embodiment, the multivalent antibody has the functional activity of inhibiting a canonical Wnt signal transduction pathway selected from the group consisting of Wnt1 signal pathway and Wnt3 signal transduction pathway. In another embodiment, the multivalent antibody has the functional activity of depleting a cell population, inhibiting or reducing proliferation of a cell population, inhibiting or reducing secretion of inflammatory mediators from a cell population, inhibiting or reducing secretion of cytoplasmic granules from a cell population, wherein the cell population is selected from the group consisting of tumor cells, T cells B cells, and Wnt dependent cells.

In another aspect, the invention pertains to an isolated biparatopic antibody comprising an IgG antibody that binds to a β-propeller 1 domain on an LRP6 target receptor and a scFv that binds to a β-propeller 3 domain on the LRP6 target, where the IgG antibody and

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the scFv are linked by a linker such that the binding of the IgG antibody and the scFv to the β-propeller 1 domain and the β-propeller 3 domains, respectively inhibits a canonical Wnt signal transduction pathway, and where the biparatopic antibody displays no significant potentiation of a Wnt signal.

In one embodiment, the antibody has an affinity for target receptor of approximately nanomolar affinity. In another embodiment, the antibody has an affinity for target receptor of approximately 1 picomolar affinity.

In one embodiment, the linker comprises a spatial distribution that permits binding of the IgG antibody and the scFv fragment to bind the β-propeller 1 domain of LRP6 and the β-propeller 3 domain of LRP6, respectively. In one embodiment, the scFv is linked by a Ser-Gly linker to the Fc binding site of the IgG antibody, where the Ser-Gly linker is selected from the group consisting of $(Gly_4Ser)_4$, and $(Gly_4Ser)_3$. In another embodiment, the Fc binding site of the IgG antibody is a CH3 domain. In another embodiment, the scFv is linked by a Ser-Gly linker to the light chain of the IgG antibody, where the Ser-Gly linker is selected from the group consisting of $(Gly_4Ser)_4$, and $(Gly_4Ser)_3$. In one emdodiment, the scFv comprises at least one amino acid mutation that improves stability of the scFv compared with the unmutated scFv fragment, wherein the amino acid mutation is selected from Figures 29-32.

In one embodiment, the antibody comprises a heavy chain variable region CDR1 of SEQ ID NO: 1; a heavy chain variable region CDR2 of SEQ ID NO: 2; a heavy chain variable region CDR3 of SEQ ID NO: 3; a light chain variable region CDR1 of SEQ ID NO: 4; a light chain variable region CDR2 of SEQ ID NO: 5; and a light chain variable region CDR3 of SEQ ID NO: 6, wherein the antibody binds to a β-propeller 1 domain of LRP6; and a scFv heavy chain variable region CDR1 of SEQ ID NO: 69; a heavy chain variable region CDR2 of SEQ ID NO: 70; a heavy chain variable region CDR3 of SEQ ID NO: 71; a light chain variable region CDR1 of SEQ ID NO: 72; a light chain variable region CDR2 of SEQ ID NO: 73; and a light chain variable region CDR3 of SEQ ID NO: 74, wherein the scFv binds to a β-propeller 3 domain of LRP6. In one embodiment, the antibody further comprises a Lys deletion from position 454 of SEQ ID NO: 166. In one embodiment, the antibody further comprises a Pro to Ala mutation at position 677 of SEQ ID NO: 166.

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In one embodiment, the antibody comprises a heavy chain sequence selected from the group consisting of SEQ ID NOs: 166, 171, 173, 175, 195, 201 and 207 in combination with a light chain sequence selected from the group consisting of SEQ ID NOs: 170, 193, 199, and 205. In one embodiment, the antibody comprises a combination of heavy and light chain sequences selected from the group consisting of SEQ ID NOs: 166/170, 171/170, 173/170, 175/170, 201/199, 207/205, and 195/193. In one embodiment, the antibody comprises heavy and light chain sequences with SEQ ID NOs: 166/170. In one embodiment, the antibody comprising heavy and light chain sequences with SEQ ID NOs; 177/ 181.

In one embodiment, the antibody has the functional activity of inhibiting a canonical Wnt signal transduction pathway selected from the group consisting of Wnt1 signal pathway and Wnt3 signal transduction pathway. In another embodiment, the antibody has the functional activity of depleting a cell population, inhibiting or reducing proliferation of a cell population, inhibiting or reducing secretion of inflammatory mediators from a cell population, inhibiting or reducing secretion of cytoplasmic granules from a cell population, wherein the cell population is selected from the group consisting of tumor cells, T cells B cells, and Wnt dependent cells.

In another aspect, the invention pertains to an isolated biparatopic antibody comprising an IgG antibody that binds to a β-propeller 3 domain on an LRP6 target receptor and a scFv that binds to a β-propeller 1 domain on the LRP6 target, wherein the IgG antibody and the scFv are linked by a linker such that the binding of the IgG antibody and the scFv to the β-propeller 3 domain and the β-propeller 1 domains, respectively inhibits a canonical Wnt signal transduction pathway, and wherein the biparatopic antibody displays no significant potentiation of a Wnt signal.

In one embodiment, the antibody has an affinity for target receptor of approximately nanomolar affinity. In another embodiment, the antibody has an affinity for target receptor of approximately 1 picomolar affinity.

In one embodiment, the linker comprises a spatial distribution that permits binding of the IgG antibody and the scFv to bind the β-propeller 3 domain of LRP6 and the β-propeller 1 domain of LRP6, respectively. In one embodiment, the scFv is linked by a Ser-Gly linker to the Fc binding site of the IgG antibody, wherein the Ser-Gly linker is selected from the group consisting of $(Gly_4Ser)_4$, and $(Gly_4Ser)_3$. In one embodiment, the Fc

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binding site of the IgG antibody is a CH3 domain. In one embodiment, the scFv comprises at least one amino acid mutation that improves stability of the scFv compared with the unmutated scFv fragment, wherein the amino acid mutation is selected from Figures 29-32.

In one embodiment, the antibody comprises a heavy chain variable region CDR1 of SEQ ID NO: 69; a heavy chain variable region CDR2 of SEQ ID NO: 70; a heavy chain variable region CDR3 of SEQ ID NO: 71; a light chain variable region CDR1 of SEQ ID NO: 72; a light chain variable region CDR2 of SEQ ID NO: 73; and a light chain variable region CDR3 of SEQ ID NO: 74, wherein the antibody binds to a β-propeller 3 domain of LRP6; and an scFv with a heavy chain variable region CDR1 of SEQ ID NO: 1; a heavy chain variable region CDR2 of SEQ ID NO: 2; a heavy chain variable region CDR3 of SEQ ID NO: 3; a light chain variable region CDR1 of SEQ ID NO: 4; a light chain variable region CDR2 of SEQ ID NO: 5; and a light chain variable region CDR3 of SEQ ID NO: 6, wherein the scFv thereof binds to a β-propeller 1 domain of LRP6. In one embodiment, the scFv VH and VL are linked with a linker comprising 3 amino acids. In another embodiment, the scFv VH and VL are linked with a linker comprising 4 amino acids. In one embodiment, the antibody comprises a heavy chain sequence selected from the group consisting of SEQ ID NO:, 187, and 189; and a light chain sequence comprising SEQ ID NO: 185. In one embodiment, the antibody has the functional activity of inhibiting a canonical Wnt signal transduction pathway selected from the group consisting of Wnt1 signal pathway and Wnt3 signal transduction pathway. In another embodiment, the antibody has the functional activity of depleting a cell population, inhibiting or reducing proliferation of a cell population, inhibiting or reducing secretion of inflammatory mediators from a cell population, inhibiting or reducing secretion of cytoplasmic granules from a cell population, wherein the cell population is selected from the group consisting of tumor cells, T cells B cells, and Wnt dependent cells.

In another aspect, the invention pertains to nucleic acid comprising a nucleotide sequence encoding a multivalent antibody.

In one aspect, the invention pertains to a nucleic acid comprising a nucleotide sequence encoding a multivalent antibody comprising a heavy chain sequence selected from the group consisting of SEQ ID NOs: 166, 171, 173, 175, 195, 201, and 207; and light chain sequences selected from the group consisting of SEQ ID NOs: 170, 193, 199, and 205.

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In another aspect, the invention pertains to a nucleic acid comprising a nucleotide sequence encoding multivalent antibody comprising a heavy chain sequence selected from the group consisting of SEQ ID NOs: 166, 171, 173, 175, 193, 199, 201, and 207; and light chain sequences selected from the group consisting of SEQ ID NOs: 170, 195, and 205 least, where the antibody or antigen binding fragment has 98% sequence identity to SEQ ID NOs: 166, 171, 173, 175, 195, 201, and 207; and light chain sequences selected from the group consisting of SEQ ID NOs: 170, 193, 199, and 205.

In another aspect, the invention pertains to a nucleic acid comprising a nucleotide sequence encoding a multivalent antibody comprising a SEQ ID NO: 166 and SEQ ID NO: 170.

In another aspect, the invention pertains to a nucleic acid comprising a nucleotide sequence encoding a multivalent antibody comprising at least 98% sequence identity to a SEQ ID NO: 166 and SEQ ID NO: 170.

In another aspect, the invention pertains to a nucleic acid comprising a nucleotide sequence encoding a multivalent antibody comprising a sequence selected from the group consisting of SEQ ID NOs: 177, and; and a light chain sequence of SEQ ID NO: 181.

In another aspect, the invention pertains to a nucleic acid comprising a nucleotide sequence encoding a multivalent antibody comprising at least 98% sequence identity to SEQ ID NOs: 177; and a light chain sequence of SEQ ID NO: 181.

In another aspect, the invention pertains to a nucleic acid comprising a nucleotide sequence encoding a multivalent antibody comprising a sequence selected from the group consisting of SEQ ID NOs: 187, and 189; and a light chain sequence of SEQ ID NO: 185.

In another aspect, the invention pertains to a nucleotide sequence encoding a multivalent antibody comprising at least 98% sequence identity to SEQ ID NOs: 187, and 189; and a light chain sequence of SEQ ID NO: 185. In another aspect, the invention pertains to a vector comprising the nucleic acid of the invention.

In another aspect, the invention pertains to a pharmaceutical composition comprising a multivalent antibody having at least two receptor binding domains for two different binding sites of a target receptor and a pharmaceutically acceptable carrier.

In another aspect, the invention pertains to a method of obtaining a multivalent antibody of the invention by a) providing a first receptor binding domain which binds to a first binding site of an LRP6 target receptor; (b) providing a second receptor binding domain which binds to a second binding site of an LRP6 target receptor; and (c) linking the first receptor binding domain to the second receptor binding domain. In one embodiment, the first or second receptor binding domain are selected from the group consisting of an IgG antibody, an scFv fragment, a single chain diabody, an antibody mimetic, and an antibody variable domain. In one embodiment, the first and second receptor binding domains are linked together by a linker with a spatial distribution that permits the first and second receptor binding domains to bind to the first and second epitopes of LRP6, respectively. In one embodiment, the linker is a Gly-Ser linker selected from the group consisting of $(Gly_4Ser)_4$, and $(Gly_4Ser)_3$. In one emdodiment, the method further comprises introducing at least one amino acid mutation to the first or second receptor binding domain, such that the amino acid mutation improves stability of the first or second receptor binding domain compared with the unmutated first or second receptor binding domain.

In one aspect, the invention pertains to a method of treating a cancer comprising selecting a subject (e.g., human) having an LRP6 expressing cancer, administering to a subject in need thereof an effective amount of a composition comprising a multivalent antibody having at least two receptor binding domains for two different binding sites of a target receptor.

In one aspect, the invention pertains to a method of treating a cancer comprising selecting a subject having an LRP6 expressing cancer, administering to a subject in need thereof an effective amount of a composition comprising a multivalent antibody having at least two receptor binding domains for two different binding sites of a target receptor, where the cancer is selected from the group consisting of breast cancer, lung cancer, multiple myeloma, ovarian cancer, liver cancer, bladder cancer, gastric cancer, prostate cancer, acute myeloid leukemia, chronic myeloid leukemia, osteosarcoma, squamous cell carcinoma, and melanoma. In one embodiment, the cancer is breast cancer.

In another aspect, the invention pertains to a method of treating a disease mediated by a canonical Wnt signaling pathway using a biparatopic antibody to LRP6.

In another aspect, the invention pertains to a method of treating a cancer comprising selecting a subject having an LRP6 expressing cancer, administering to said subject an

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effective amount of a composition comprising a antibody with heavy and light chain sequences selected from the group consisting of SEQ ID NOs: 166/170, 171/170, 173/170, 175/170, 201/199, 207/205, and 195/193 in combination with any standard of care cancer therapies.

In another aspect, the invention pertains to use of a multivalent antibody in the manufacture of a medicament for the treatment of a cancer selected from the group consiting of breast cancer, lung cancer, multiple myeloma, ovarian cancer, liver cancer, bladder cancer gastric cancer, prostate cancer, acute myeloid leukemia, chronic myeloid leukemia, osteosarcoma, squamous cell carcinoma, and melanoma.

In another aspect, the invention pertains to a multivalent antibody having VH of SEQ ID NO: 14; VL of SEQ ID NO: 13; VH of SEQ ID NO: 82; VL of SEQ ID NO: 81 for use in treating a cancer mediated by a canonical Wnt signaling pathway.

In another aspect, the invention pertains to a multivalent antibody having VH of SEQ ID NO: 14; VL of SEQ ID NO: 13; VH of SEQ ID NO: 82; VL of SEQ ID NO: 81 for use as a drug.

In another aspect, the invention pertains to a multivalent antibody having SEQ ID NO: 166 and SEQ ID NO: 170 for use in treating a cancer mediated by a canonical Wnt signaling pathway.

In another aspect, the invention pertains to a multivalent antibody having SEQ ID NO: 166 and SEQ ID NO: 170 for use as a drug.

In another aspect, the invention pertains to a multivalent antibody for use as a medicament. In another aspect, the invention pertains to a multivalent antibody for use as a medicament for treatment of an LRP6 expressing cancer. In another aspect, the invention pertains a multivalent antibody for use as a medicament for treatment of an LRP6 expressing cancer, wherein the cancer is selected from the group consisting of breast cancer, lung cancer, multiple myeloma, ovarian cancer, liver cancer, bladder cancer, gastric cancer, prostate cancer, acute myeloid leukemia, chronic myeloid leukemia, osteosarcoma, squamous cell carcinoma, and melanoma.

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Brief Description of Figures

Figure 1 is a graph showing FACS EC_{50} determination of selected Fabs on PA1 cells, U266 cells and Daudi cells and the corresponding mRNA expression data (A) and knockdown of LRP6 by shRNA and the corresponding mRNA expression data B;

Figure 2A-L are graphs showing anti-LRP6 Fab fragments activity in HEK293T/17 STF cells (gene reporter assay) expressing Wnt1 or Wnt3A ligands The data shows that anti-LRP6 Fabs selectively block Wnt1 or Wnt3 signaling;

Figure 3 shows the cross-reactivity values of anti-LRP6 β-propeller 1 and β-propeller 3 antibodies for human, mouse and cymologous monkey;

Figure 4 is a graph showing transient expression of various WNT ligands in HEK293T/17 STF cells (gene reporter assay) and treatment with anti-LRP6 antibodies, showing activity inhibition of particular WNTs based on antibody binding/blocking to specific β-propeller regions of LRP6;

Figure 5 is a bar chart showing that Fab conversion to IgG results in potentiation of signal from the non-blocked Wnt ligand;

Figure 6 is a western blot showing selective target inhibition of LRP6 in cellular systems;

Figure 7 is a graph showing a single i.v. dose of an LRP6 antibody that binds to β-propeller 1 region at 5mg/kg in a rodent;

Figure 8A is a table that shows genes in MMTV-Wnt1 tumors that were upregulated >2-fold relative to t=0 control with an adjusted P-value of <0.01 and Figure 8B is a table that shows genes that were downregulated >2-fold relative to t=0 control with an adjusted P-value of <0.01 8 h after administartion of a single dose of MOR08168 (5 mg/kg) to MMTV-Wnt1 tumors bearing mice;

Figure 9A is a graph showing Propeller 1, but not Propeller 3 mAb, causes in vivo tumor regression in MMTV-Wnt1 model. Figure 9B is a graph showing the effect of different doses of the Propeller 1 mAb on the growth of the MMTV-Wnt1 tumor model;

Figure 10 is a graph showing Propeller 3, but not Propeller 1 mAb, causes inhibition of tumor growth in a MMTV-Wnt3 model;

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Figure 11 is a graph showing Propeller 3, but not Propeller 1 mAb causes inhibition of Wnt3A-induced Super Top Flash activity in PA-1 cells *in vivo*;

Figure 12 is a figure showing solvent protected regions of LRP6 PD3-4 by MOR06475 by HDx MS (A) and that mutations of specific residues result in loss of binding of scFv MOR06475 (B);

Figure 13 is a schematic showing the β-propeller regions of LRP6;

Figure 14 is a photograph of an SDS-PAGE gel showing that all scFv molecules successfully expressed and purified from *E. coli*;

Figure 15 A-D are schematic example of multivalent antibodies. (15A) scFv scFv attached to the C-terminus of full IgG (15B) scFv scFv attached to the N-terminus of Fc (15C) scFv scFv attached to the C-terminus of Fc (15D) scFv scFv attached to the N and C terminus of Fc;

Figure 16 is a photograph of an SDS-PAGE gel showing purified biparatopic anti-LRP6 IgG scFv under non-reduced (lane 1) and reduced (lane 2) conditions;

Figure 17 shows activity in STF assay of a biparatopic antibody and respective component parts separately;

Figure 18 shows activity in STF assay of linker length comparisons in scFv molecules;

Figure 19 is a table showing the binding activity a biparatopic antibody;

Figure 20 shows the activity of a biparatopic antibody and a Prop3 antibody but not a Prop1 antibody in a PA-1/Wnt3a L-cell co-culture model;

Figure 21 is a graph showing a comparison between single i.v. doses of a Prop1 LRP6 antibody and a Prop1/3 biparatopic antibody at 5mg/kg in a rodent;

Figure 22 is a graph showing both Propeller 1 and biparatopic propeller 1/3 antibodies cause *in vivo* tumor regression in MMTV-Wnt1 model;

Figure 23 is a graph showing dose-response relationship of a Prop1/3 binding biparatopic antibody in MMTV-Wnt1 model;

Figure 24 shows that differentiation of murine MMTV-Wnt1 mammary tumors is induced by antagonistic LRP6 antibodies. A-B) Fragments of MMTV-Wnt1 tumors were

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implanted subcutaneously into nude mice. Tumor-bearing mice were treated with either a single dose of PBS (control) or 5mg/kg MOR08168IgG1LALA 6475 scfv. A) Representative images of Oil Red O staining for lipid. B) Quantification of Oil Red O staining. Graph represents mean±SEM values. n=4 in the 72 hour group, n=3 in 24 hour group, n=2 in the 5 Day group, and n=1 for PBS (control);

Figure 25 is a graph showing activity of Prop1/3 binding biparatopic antibody in the E-Cadherin negative MDA-MB231 xenograft model;

Figure 26 shows the affinity and binding kinetics of MOR08168, MOR06475 and MOR08168IgG1LALA 6475 scfv to recombinant LRP6 PD1/2 and PD3/4. A) summary table of the affinities and on/off rates as determined by Biacore analysis. B) representative binding curves of the anti-LRP6 molecules for corresponding LRP6 receptor domains, PD1/2 and PD3/4. C) sequential binding of LRP6 PD1/2 and PD3/4 to MOR08168IgG1LALA 6475 scfv;

Figure 27 shows a schematic drawing of IgG based biparatopic antibodies;

Figure 28 are photographs of SDS-PAGE gels showing the optimization of anti-LRP6 scFv expression in *E. coli*;

Figure 29 is a table showing the effect of single mutations in MOR06475 scFv on Tm.
Figure 30 is a table showing the effect of single mutations in MOR08168 scfv on Tm;

Figure 31 is a table showing the effect of double mutations in MOR08168 scFv on Tm in material expressed in both bacterial and mammalian systems;

Figure 32 is a table summarizing the binding and functional activities of the WILD TYPE and single/double mutated versions of MOR06475 and MOR08168 scFvs in ELISA, Proteon affinity and STF reporter gene assays;

Figure 33 is an illustration of selected examples of the designed mutations. In all figures, the protein backbone is rendered in ribbon diagram while selected side chains are rendered as sticks. (a): In the homology model of scFv6475, VH:I37 is close to two aromatic residues, which were VL:F98 and VH:W103. (b) In the VH:I37F mutant of scFv6475, VH:F37 and VH:W103 could form a perpendicular pi-pi stacking interaction, while VH:F37 and VL:F98 could form another perpendicular pi-pi stacking interaction. (c) In the homology model of scFv8168, the hydrophobic residue VH:V33 is close to a

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polar residue VH:N100a. (d) In the VH:V33N mutant of scFv8168, the VH:N33 side chain could form a hydrogen bond with VH:N100a, suggested by homology modeling. The hydrogen bond between the two residues is illustrated by a bond. (e): In the homology model of scFv8168, the charged residue VH:K43 did not form a salt bridge with the hydrophobic residue VH:V85. (f): The two charged side chains of VH:K43 and VH:E85 could form a salt bridge due to the VH:V85E mutation on scFv8168. The distance between the two charge groups could be 2.61Å; and

Figure 34 is a table showing thermostability measurements of biparatopic antibodies.

Detailed Description of the Invention

Definitions

In order that the present invention may be more readily understood, certain terms are first defined. Additional definitions are set forth throughout the detailed description.

The phrase "immune response" as used herein refers to the action of, for example, lymphocytes, antigen presenting cells, phagocytic cells, granulocytes, and soluble macromolecules produced by the above cells or the liver (including antibodies, cytokines, and complement) that results in selective damage to, destruction of, or elimination from the human body of invading pathogens, cells or tissues infected with pathogens, cancerous cells, or, in cases of autoimmunity or pathological inflammation, normal human cells or tissues.

The phrase "signal transduction pathway" or "signaling activity" as used herein refers to a biochemical causal relationship generally initiated by a protein-protein interaction such as binding of a growth factor to a receptor, resulting in transmission of a signal from one portion of a cell to another portion of a cell. For LRP6, the transmission involves specific phosphorylation of one or more tyrosine, serine, or threonine residues on one or more proteins in the series of reactions causing signal transduction. Penultimate processes typically include nuclear events, resulting in a change in gene expression.

The phrase "Wnt signaling pathway" as used herein refers to the canonical Wnt pathway in which members of the Wnt family of secreted protein ligands bind a receptor complex of LRP and Frizzled (FZD) allowing β-catenin to be translocated into the nucleus, interact with the LEF/TCF transcription factors and activate target gene expression. The Wnt

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signaling pathway can be measured using a Wnt reporter gene assay or other measure of Wnt directed signaling (e.g., LRP6 phosphorylation, β-catenin stabilization and nuclear translocation, cellular proliferation/ survival) as described herein.

The phrase "Wnt 1 signaling pathway" refers to a canonical Wnt pathway that is activated by LRP6 interacting with the Wnt1 ligand and the class of Wnt1 binding ligands, such as Wnt2, Wnt6, Wnt7a, Wnt7b, Wnt9a, Wnt10a, or Wnt10b.

The phrase "Wnt 3 signaling pathway" refers to a canonical Wnt pathway that is activated by LRP6 interacting with the Wnt3 or a Wnt3a ligand.

The term "LRP6" refers to human LRP6 as defined in Accession No. NP002327.

The term "antibody" as used herein refers to whole antibodies that interact with (e.g., by binding, steric hinderance, stabilizing/destabilizing, spatial distribution) an LRP6 epitope and inhibit signal transduction. A naturally occurring "antibody" is a glycoprotein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as VL) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The VH and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (e.g., effector cells) and the first component (Clq) of the classical complement system. The term "antibody" includes for example, monoclonal antibodies, human antibodies, humanized antibodies, camelised antibodies, chimeric antibodies, Fab fragments, F(ab') fragments, and anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the invention), and epitope-binding fragments of any of the above. The antibodies can be of any isotype (e.g., IgG,

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IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass.

Both the light and heavy chains are divided into regions of structural and functional homology. The terms "constant" and "variable" are used functionally. In this regard, it will be appreciated that the variable domains of both the light (VL) and heavy (VH) chain portions determine antigen recognition and specificity. Conversely, the constant domains of the light chain (CL) and the heavy chain (CH1, CH2 or CH3) confer important biological properties such as secretion, transplacental mobility, Fc receptor binding, complement binding, and the like. By convention the numbering of the constant region domains increases as they become more distal from the antigen binding site or amino-terminus of the antibody. The N-terminus is a variable region and at the C-terminus is a constant region; the CH3 and CL domains actually comprise the carboxy-terminus of the heavy and light chain, respectively. In particular, the term "antibody" specifically includes an IgG-scFv formats as shown in Fig 12A-D.

The term "receptor binding domain" or "RBD" refers to portions of a binding molecule (e.g., an antibody), that specifically interacts with (e.g., by binding, steric hinderance, stabilizing/destabilizing, spatial distribution) a binding site on a target receptor. RBD also refers to one or more fragments of an antibody that retain the ability to specifically interact with (e.g., by binding, steric hinderance, stabilizing/destabilizing, spatial distribution) an LRP6 epitope and inhibit signal transduction. Examples of antibody fragments include, but are not limited to, an scFv, a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; a $F(ab)_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment consisting of the VH and CH1 domains; a Fv fragment consisting of the VL and VH domains of a single arm of an antibody; a dAb fragment (Ward *et al.*, (1989) Nature 341:544-546), which consists of a VH domain; and an isolated complementarity determining region (CDR).

Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules (known as single chain Fv (scFv); see e.g., Bird *et al.*, (1988) Science 242:423-426; and Huston *et al.*, (1988) Proc. Natl. Acad. Sci. 85:5879-5883).

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Such single chain antibodies are also intended to be encompassed within the term "antibody fragment". These antibody fragments are obtained using conventional techniques known to those of skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies.

Antibody fragments can also be incorporated into "single domain antibodies", "maxibodies", "minibodies", "diabodies", "triabodies", "tetrabodies", "v-NAR" and "bis-scFv" (see, *e.g.*, Hollinger and Hudson, (2005) Nature Biotechnology 23: 1126-1136). Antibody fragments can be grafted into scaffolds based on polypeptides such as Fibronectin type III (Fn3) (see U.S. Pat. No. 6,703,199, which describes fibronectin polypeptide monobodies).

Antibody fragments can be incorporated into single chain molecules comprising a pair of tandem Fv segments (VH-CH1-VH-CH1) which, together with complementary light chain polypeptides, form a pair of antigen binding regions (Zapata *et al.*, (1995) Protein Eng. 8:1057-1062; and U.S. Pat. No. 5,641,870).

RBDs also include single domain antibodies, maxibodies, unibodies, minibodies, , diabodies, triabodies, tetrabodies, v-NAR and bis-scFv (see, *e.g.*, Hollinger and Hudson, (2005) Nature Biotechnology 23: 1126-1136), bispecific single chain diabodies, or single chain diabodies designed to bind two distinct epitopes. RBDs also include antibody-like molecules or antibody mimetics, which include, but not limited to minibodies, maxybodies, Fn3 based protein scaffolds, Ankrin repeats (also known as DARpins), VASP polypeptides, Avian pancreatic polypeptide (aPP), Tetranectin, Affililin, Knottins, SH3 domains, PDZ domains, Tendamistat, Neocarzinostatin, Protein A domains, Lipocalins, Transferrin, and Kunitz domains that specifically bind epitopes, which are within the scope of the invention.

The term "multivalent antibody" refers to a single binding molecule with more than one valency, where "valency" is described as the number of antigen-binding moieties present per molecule of an antibody construct. As such, the single binding molecule can bind to more than one binding site on a target receptor. Examples of multivalent antibodies include, but are not limited to bivalent antibodies, trivalent antibodies, tetravalent antibodies, pentavalent antibodies, and the like, as well as bispecific antibodies and biparatopic antibodies. For example, for the LRP6 receptor, the mutivalent antibody (e.g., an LRP6 biparatopic antibody) has a binding moiety for the β-propeller 1 domain

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binding site and a binding moiety for the β-propeller 3 domain binding site of LRP6, respectively.

The term "multivalent antibody" also refers to a single binding molecule that has more than one antigen-binding moieties for two separate target receptors. For example, an antibody that binds to both an LRP6 target receptor and a second target receptor that is not LRP6 (such as ErbB, cmet, IGFR1, Smoothened, Notch receptors). In one embodiment, a multivalent antibody is a tetravalent antibody that has four receptor binding domains. A tetravalent molecule may be bispecific and bivalent for each binding site on that target receptor.

The multivalent antibody mediates biological effect (e.g., which modulates cellular activation (e.g., by binding to a cell surface receptor and resulting in transmission or inhibition of an activating or inhibitory signal), which results in death of the cell (e.g., by a cell signal induced pathway), or which modulates a disease or disorder in a subject (e.g., by mediating or promoting cell killing, or by modulating the amount of a substance which is bioavailable.

The phrase "isolated antibody", as used herein, refers to antibody that is substantially free of other antibodies having different antigenic specificities (e.g., an isolated antibody that specifically binds LRP6 is substantially free of antibodies that specifically bind antigens other than LRP6). An isolated antibody that specifically binds LRP6 may, however, have cross-reactivity to other antigens, such as LRP6 molecules from other species. Moreover, an isolated antibody may be substantially free of other cellular material and/or chemicals.

The term "monovalent antibody" as used herein, refers to an antibody that binds to a single epitope on a target receptor such as LRP6.

The term "bivalent antibody" as used herein, refers to an antibody that binds to two epitopes on at least two identical target receptors (e.g., an antibody that binds to the β-propeller 1 domain of two LRP6 receptors, or an antibody that binds to the β-propeller 3 domain of two LRP6 receptors). The bivalent antibody may also crosslink the target receptors to one another. A "bivalent antibody" also refers to an antibody thatbind to two different epitopes on at least two identical target receptors.

The term "biparatopic antibody" as used herein, refers to an antibody that binds to two different epitopes on the same target receptor, e.g., an antibody that binds to the β-

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propeller 1 domain and the β-propeller 3 domain of a single LRP6 receptor. The term also includes an antibody, which binds to both the β-propeller 1 and β-propeller 3 domains of at least two LRP6 receptor(s) e.g., a tetravalent biparatopic antibody.

The term "bispecific antibody" as used herein, refers to an antibody that binds to two or more different epitopes on at least two different target receptors (e.g., an LRP6 receptor and a receptor that is not a LRP6 receptor).

The phrases "monoclonal antibody" or "monoclonal antibody composition" as used herein refers to polypeptides, including antibodies, antibody fragements, bisepcific antibodies, etc. that have ubstantially identical to amino acid sequence or are derived from the same genetic source. This term also includes preparations of antibody molecules of single molecular composition. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope.

The phrase "human antibody", as used herein, includes antibodies having variable regions in which both the framework and CDR regions are derived from sequences of human origin. Furthermore, if the antibody contains a constant region, the constant region also is derived from such human sequences, e.g., human germline sequences, or mutated versions of human germline sequences or antibody containing consensus framework sequences derived from human framework sequences analysis, for example, as described in Knappik, et al. (2000. J Mol Biol 296, 57-86). The structures and locations of immunoglobulin variable domains, e.g., CDRs, may be defined using well known numbering schemes, e.g., the Kabat numbering scheme, the Chothia numbering scheme, or a combination of Kabat and Chothia (see, e.g., Sequences of Proteins of Immunological Interest, U.S. Department of Health and Human Services (1991), eds. Kabat *et al.;* Al Lazikani *et al.,* (1997) J. Mol. Bio. 273:927 948); Kabat *et al.,* (1991) Sequences of Proteins of Immunological Interest, 5th edit., NIH Publication no. 91-3242 U.S. Department of Health and Human Services; Chothia *et al.,* (1987) J. Mol. Biol. 196:901-917; Chothia *et al.,* (1989) Nature 342:877-883; and Al-Lazikani *et al.,* (1997) J. Mol. Biol. 273:927-948.

The human antibodies of the invention may include amino acid residues not encoded by human sequences (e.g., mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation in vivo, or a conservative substitution to promote stability or manufacturing). However, the term "human antibody" as used herein, is not intended to

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include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

The phrase "recombinant human antibody" as used herein, includes all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies isolated from an animal (e.g., a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom, antibodies isolated from a host cell transformed to express the human antibody, e.g., from a transfectoma, antibodies isolated from a recombinant, combinatorial human antibody library, and antibodies prepared, expressed, created or isolated by any other means that involve splicing of all or a portion of a human immunoglobulin gene, sequences to other DNA sequences. Such recombinant human antibodies have variable regions in which the framework and CDR regions are derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies can be subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the VH and VL regions of the recombinant antibodies are sequences that, while derived from and related to human germline VH and VL sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

The term "linker" as used herein refers to a peptide linker that consists of glycine and serine residues used to link an scFv to an IgG. An exemplary Gly/Ser linker comprises the amino acid sequence $(Gly\text{-}Gly\text{-}Ser)_2$, i.e., $(Gly_2\ Ser)_n$ where n is a positive integer equal to or greater than 1. For example, n=1, n=2, n=3. n=4, n=5 and n=6, n=7, n=8, n=9 and n=10. In one embodiment, the linkers include, but are not limited to, $(Gly_4\ Ser)_4$ or $(Gly_4\ Ser)_3$. In another embodiment, the linkers Glu and Lys residues interspersed within the Gly-Ser linkers for better solubility. In another embodiment, the linkers include multiple repeats of (Gly_2Ser), (GlySer) or (Gly_3Ser). In anther embodiment, the linkers include combinations and multiples of $(Gly_3Ser)+(Gly_4Ser)+(GlySer)$. In another embodiment, Ser can be replaced with Ala e.g., (Gly_4Ala) or (Gly_3Ala). In another embodiment, the linker comprises any combination of Gly, Ser and Pro. In yet another embodiment, the linker comprises the motif $(GluAlaAlaAlaLys)_n$, where n is a positive integer equal to or greater than 1.

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The term "Fc region" as used herein refers to a polypeptide comprising the CH3, CH2 and at least a portion of the hinge region of a constant domain of an antibody. Optionally, an Fc region may include a CH4 domain, present in some antibody classes. An Fc region, may comprise the entire hinge region of a constant domain of an antibody. In one embodiment, the invention comprises an Fc region and a CH1 region of an antibody. In one embodiment, the invention comprises an Fc region CH3 region of an antibody. In another embodiment, the invention comprises an Fc region, a CH1 region and a Ckappa/lambda region from the constant domain of an antibody. In one embodiment, a binding molecule of the invention comprises a constant region, e.g., a heavy chain constant region. In one embodiment, such a constant region is modified compared to a wild-type constant region. That is, the polypeptides of the invention disclosed herein may comprise alterations or modifications to one or more of the three heavy chain constant domains (CH1, CH2 or CH3) and/or to the light chain constant region domain (CL). Exemplary modifications include additions, deletions or substitutions of one or more amino acids in one or more domains. Such changes may be included to optimize effector function, half-life, etc.

The term "binding site" as used herein comprises an area on a target receptor to which an antibody or antigen binding fragment selectively binds. For example, the binding sites on LRP6 include the β- propeller 1 binding domain, β- propeller 2 binding domain, β- propeller 3 binding domain, and β- propeller 4 binding domain.

The term "epitope" as used herein refers to any determinant capable of binding with high affinity to an immunoglobulin. An epitope is a region of an antigen that is bound by an antibody that specifically targets that antigen, and when the antigen is a protein, includes specific amino acids that directly contact the antibody. Most often, epitopes reside on proteins, but in some instances, may reside on other kinds of molecules, such as nucleic acids. Epitope determinants may include chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl or sulfonyl groups, and may have specific three dimensional structura l characteristics, and/or specific charge characteristics.

Generally, antibodies specific for a particular target antigen will bind to an epitope on the target antigen in a complex mixture of proteins and/or macromolecules.

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Regions of a given polypeptide that include an epitope can be identified using any number of epitope mapping techniques, well known in the art. See, e.g., Epitope Mapping Protocols in Methods in Molecular Biology, Vol. 66 (Glenn E.Morris, Ed., 1996) Humana Press, Totowa, New Jersey. For example, linear epitopes may be determined by e.g., concurrently synthesizing large numbers of peptides on solid supports, the peptides corresponding to portions of the protein molecule, and reacting the peptides with antibodies while the peptides are still attached to the supports. Such techniques are known in the art and described in, e.g., U.S. Patent No. 4,708,871 ; Geysen *et al.*, (1984) Proc. Natl. Acad. Sci. USA 8:3998-4002; Geysen *et al.*, (1985) Proc. Natl. Acad. Sci. USA 82:78-182; Geysen *et al.*, (1986) Mol. Immunol. 23:709-715. Similarly, conformational epitopes are readily identified by determining spatial conformation of amino acids such as by, e.g., x-ray crystallography and two-dimensional nuclear magnetic resonance. See, e.g., Epitope Mapping Protocols, supra. Antigenic regions of proteins can also be identified using standard antigenicity and hydropathy plots, such as those calculated using, e.g., the Omiga version 1.0 software program available from the Oxford Molecular Group. This computer program employs the Hopp/Woods method, Hopp *et al., (1981)* Proc. Natl. Acad. Sci USA 78:3824-3828; for determining antigenicity profiles, and the Kyte-Doolittle technique, Kyte *et al.*, (1982) J.Mol. Biol. 157:105-132; for hydropathy plots.

The term "specific binding" between two entities means a binding with an equilibrium constant (K_A) (k_{on}/k_{off}) of at least 10^2M^{-1}, at least $5x10^2M^{-1}$, at least 10^3M^{-1}, at least $5x10^3M^{-1}$, at least 10^4M^{-1}, at least $5x10^4M^{-1}$, at least 10^5M^{-1}, at least $5x10^5M^{-1}$, at least 10^6M^{-1}, at least $5x10^6M^{-1}$, at least 10^7M^{-1}, at least $5x10^7M^{-1}$, at least 10^8M^{-1}, at least $5x10^8M^{-1}$, at least 10^9M^{-1}, at least $5x10^9M^{-1}$, at least $10^{10}M^{-1}$, at least $5x10^{10}M^{-1}$, at least $10^{11}M^{-1}$, at least $5x10^{11}M^{-1}$, at least $10^{12}M^{-1}$, at least $5x10^{12}M^{-1}$, at least $10^{13}M^{-1}$, at least $5x10^{13}$ M^{-1}, at least $10^{14}M^{-1}$, at least $5x10^{14}M^{-1}$, at least $10^{15}M^{-1}$, or at least $5x10^{15}M^{-1}$

The phrase "specifically (or selectively) binds" to a LRP6 multivalent antibody (e.g., a biparatopic antibody) refers to a binding reaction that is determinative of the presence of a cognate antigen (*e.g.*, a human LRP6) in a heterogeneous population of proteins and other biologics. In addition to the equilibrium constant (K_A), an LRP6 multivalent antibody of the invention typically also has a dissociation rate constant (K_D) of about (k_{off}/k_{on}) of less than $5x10^{-2}M$, less than $10^{-2}M$, less than $5x10^{-3}M$, less than $10^{-3}M$, less than $5x10^{-4}M$, less than $10^{-4}M$, less than $5x10^{-5}M$, less than $10^{-5}M$, less than $5x10^{-6}M$, less than $10^{-6}M$, less

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than $5x10^{-7}$M, less than 10^{-7}M, less than $5x10^{-8}$M, less than 10^{-8}M, less than $5x10^{-9}$M, less than 10^{-9}M, less than $5x10^{-10}$M, less than 10^{-10}M, less than $5x10^{-11}$M, less than 10^{-11}M, less than $5x10^{-12}$M, less than 10^{-12}M, less than $5x10^{-13}$M, less than 10^{-13}M, less than $5x10^{-14}$M, less than 10^{-14}M, less than $5x10^{-15}$M, or less than 10^{-15}M or lower, and binds to LRP6 with an affinity that is at least two-fold greater than its affinity for binding to a non-specific antigen (*e.g.*, HSA). In one embodiment, the LRP6 multivalent antibody has dissociation constant (K_d) of less than 3000 pM, less than 2500 pM, less than 2000 pM, less than 1500 pM, less than 1000 pM, less than 750 pM, less than 500 pM, less than 250 pM, less than 200 pM, less than 150 pM, less than 100 pM, less than 75 pM, less than 10 pM, less than 1 pM as assessed using a method described herein or known to one of skill in the art (e.g., a BIAcore assay, ELISA, FACS, SET) (Biacore International AB, Uppsala, Sweden).

The term "K_{assoc}" or "K_a", as used herein, refers to the association rate of a particular antibody-antigen interaction, whereas the term "K_{dis}" or "K_d," as used herein, refers to the dissociation rate of a particular antibody-antigen interaction. The term "K_D", as used herein, refers to the dissociation constant, which is obtained from the ratio of K_d to K_a (i.e. K_d/K_a) and is expressed as a molar concentration (M). K_D values for antibodies can be determined using methods well established in the art. A method for determining the K_D of an antibody is by using surface plasmon resonance, or using a biosensor system such as a Biacore® system.

The term "affinity" as used herein refers to the strength of interaction between antibody and antigen at single antigenic sites. Within each antigenic site, the variable region of the antibody "arm" interacts through weak non-covalent forces with antigen at numerous sites; the more interactions, the stronger the affinity.

The term "avidity" as used herein refers to an informative measure of the overall stability or strength of the antibody-antigen complex. It is controlled by three major factors: antibody epitope affinity; the valence of both the antigen and antibody; and the structural arrangement of the interacting parts. Ultimately these factors define the specificity of the antibody, that is, the likelihood that the particular antibody is binding to a precise antigen epitope.

The term "Wnt 1" as used herein refers to Wnt1, Wnt2, Wnt6, Wnt7a, Wnt7b, Wnt9a, Wnt10a, or Wnt10b

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The term "Wnt 3a" as used herein refers to Wnt3a and Wnt3.

The term "potentiate" as used herein refers to a process whereby the Wnt signal is activated and enhanced upon conversion of a fragment of an antibody to a full length IgG LRP6 antibody in the presence of a Wnt ligand.

The term "no significant potentiation" or "avoids potentiation" refers to a Wnt signal that is not activated or enhanced compared with an control antibody or fragment thereof that binds to the same epitope. No significant potentiation can be at least 10% less than control antibody or fragment thereof, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 100% less than then control antibody or fragment thereof.

The term "cluster" as used herein refers to any protein that gathers or groups together LRP6 receptors and potentiates Wnt signaling. Examples of such proteins include, but are not limited to, Wnt1 ligands, Wnt3a ligands and Wnt3 ligands. These proteins can cause multimerization, e.g., dimerization of two endogenous LRP6 receptors. This dimerization may result in increased avidity due to increased interactions of LRP6, which in the presence of a Wnt ligand can potentiate a Wnt signal.

The phrase "conservatively modified variant" applies to both amino acid and nucleic acid sequences. With respect to particular nucleic acid sequences, conservatively modified variants refers to those nucleic acids which encode identical or essentially identical amino acid sequences, or where the nucleic acid does not encode an amino acid sequence, to essentially identical sequences. Because of the degeneracy of the genetic code, a large number of functionally identical nucleic acids encode any given protein. For instance, the codons GCA, GCC, GCG and GCU all encode the amino acid alanine. Thus, at every position where an alanine is specified by a codon, the codon can be altered to any of the corresponding codons described without altering the encoded polypeptide. Such nucleic acid variations are "silent variations," which are one species of conservatively modified variations. Every nucleic acid sequence herein which encodes a polypeptide also describes every possible silent variation of the nucleic acid. One of skill will recognize that each codon in a nucleic acid (except AUG, which is ordinarily the only codon for methionine, and TGG, which is ordinarily the only codon for tryptophan) can be modified to yield a functionally identical molecule. Accordingly, each silent variation of a nucleic acid that encodes a polypeptide is implicit in each described sequence.

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For polypeptide sequences, "conservatively modified variants" include individual substitutions, deletions or additions to a polypeptide sequence which result in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are well known in the art. Such conservatively modified variants are in addition to and do not exclude polymorphic variants, interspecies homologs, and alleles of the invention. The following eight groups contain amino acids that are conservative substitutions for one another: 1) Alanine (A), Glycine (G); 2) Aspartic acid (D), Glutamic acid (E); 3) Asparagine (N), Glutamine (Q); 4) Arginine (R), Lysine (K); 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W); 7) Serine (S), Threonine (T); and 8) Cysteine (C), Methionine (M) (see, *e.g.*, Creighton, Proteins (1984)). In some embodiments, the term "conservative sequence modifications" are used to refer to amino acid modifications that do not significantly affect or alter the binding characteristics of the antibody containing the amino acid sequence.

The terms "cross-block", "cross-blocked" and "cross-blocking" are used interchangeably herein to mean the ability of the multivalent antibody, to interfere with the binding of other antibodies or binding agents to LRP6 in a standard competitive binding assay.

The ability or extent to which an multivalent antibody is able to interfere with the binding of another antibody or binding molecule to LRP6, and therefore whether it can be said to cross-block according to the invention, can be determined using standard competition binding assays. One suitable assay involves the use of the Biacore technology (*e.g.* by using the BIAcore 3000 instrument (Biacore, Uppsala, Sweden)), which can measure the extent of interactions using surface plasmon resonance technology. Another assay for measuring cross-blocking uses an ELISA-based approach.

The term "optimized" as used herein refers to a nucleotide sequence has been altered to encode an amino acid sequence using codons that are preferred in the production cell or organism, generally a eukaryotic cell, for example, a cell of *Pichia*, a cell of *Trichoderma*, a Chinese Hamster Ovary cell (CHO) or a human cell. The optimized nucleotide sequence is engineered to retain completely or as much as possible the amino acid sequence originally encoded by the starting nucleotide sequence, which is also known as the "parental" sequence.

Standard assays to evaluate the binding ability of the multivalent antibodies toward LRP6 of various species are known in the art, including for example, ELISAs, western blots and RIAs. Suitable assays are described in detail in the Examples. The binding kinetics (e.g., binding affinity) of the multivalent antibodies also can be assessed by standard assays known in the art, such as by Biacore™ analysis. Assays to evaluate the effects of the multivalent antibodies on functional properties of LRP6 (e.g., receptor binding assays, modulating the Wnt pathway, or IgG production) are described in further detail in the Examples.

Accordingly, a multivalent antibody that "inhibits" one or more of these LRP6 functional properties (e.g., biochemical, immunochemical, cellular, physiological or other biological activities, or the like) as determined according to methodologies known to the art and described herein, will be understood to relate to a statistically significant decrease in the particular activity relative to that seen in the absence of the multivalent antibody (e.g., or when a control antibody of irrelevant specificity is present). A multivalent antibody that inhibits LRP6 activity effects such a statistically significant decrease by at least 10% of the measured parameter, by at least 50%, 80% or 90%, and in certain embodiments an antibody of the invention may inhibit greater than 95%, 98% or 99% of LRP6 functional activity.

The phrases "percent identical" or "percent identity," in the context of two or more nucleic acids or polypeptide sequences, refers to two or more sequences or subsequences that are the same. Two sequences are "substantially identical" if two sequences have a specified percentage of amino acid residues or nucleotides that are the same (*i.e.*, 60% identity, optionally 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% over a specified region, or, when not specified, over the entire sequence), when compared and aligned for maximum correspondence over a comparison window, or designated region as measured using one of the following sequence comparison algorithms or by manual alignment and visual inspection. Optionally, the identity exists over a region that is at least about 50 nucleotides (or 10 amino acids) in length, or more preferably over a region that is 100 to 500 or 1000 or more nucleotides (or 20, 50, 200 or more amino acids) in length.

For sequence comparison, typically one sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are entered into a computer, subsequence coordinates are designated,

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if necessary, and sequence algorithm program parameters are designated. Default program parameters can be used, or alternative parameters can be designated. The sequence comparison algorithm then calculates the percent sequence identities for the test sequences relative to the reference sequence, based on the program parameters.

A "comparison window", as used herein, includes reference to a segment of any one of the number of contiguous positions selected from the group consisting of from 20 to 600, usually about 50 to about 200, more usually about 100 to about 150 in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned. Methods of alignment of sequences for comparison are well known in the art. Optimal alignment of sequences for comparison can be conducted, *e.g.*, by the local homology algorithm of Smith and Waterman (1970) Adv. Appl. Math. 2:482c, by the homology alignment algorithm of Needleman and Wunsch (1970) J. Mol. Biol. 48:443, by the search for similarity method of Pearson and Lipman, (1988) Proc. Nat'l. Acad. Sci. USA 85:2444, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by manual alignment and visual inspection (see, *e.g.*, Brent *et al.*, (2003) Current Protocols in Molecular Biology).

Two examples of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul *et al.*, (1977) Nuc. Acids Res. 25:3389-3402; and Altschul *et al.*, (1990) J. Mol. Biol. 215:403-410, respectively. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul *et al.*, *supra*). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always > 0) and N (penalty score for mismatching residues; always < 0). For amino acid sequences, a scoring matrix is used to calculate the

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cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, an expectation (E) or 10, M=5, N=-4 and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a wordlength of 3, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff, (1989) Proc. Natl. Acad. Sci. USA 89:10915) alignments (B) of 50, expectation (E) of 10, M=5, N=-4, and a comparison of both strands.

The BLAST algorithm also performs a statistical analysis of the similarity between two sequences (see, *e.g.*, Karlin and Altschul (1993) Proc. Natl. Acad. Sci. USA 90:5873-5787). One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic acid to the reference nucleic acid is less than about 0.2, more preferably less than about 0.01, and most preferably less than about 0.001.

The percent identity between two amino acid sequences can also be determined using the algorithm of E. Meyers and W. Miller (Comput. Appl. Biosci. 4:11-17 (1988)) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. In addition, the percent identity between two amino acid sequences can be determined using the Needleman and Wunsch (J. Mol, Biol. 48:444-453 (1970)) algorithm which has been incorporated into the GAP program in the GCG software package (available at www.gcg.com), using either a Blossom 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6.

Other than percentage of sequence identity noted above, another indication that two nucleic acid sequences or polypeptides are substantially identical is that the polypeptide encoded by the first nucleic acid is immunologically cross reactive with the antibodies raised against the polypeptide encoded by the second nucleic acid, as described below.

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Thus, a polypeptide is typically substantially identical to a second polypeptide, for example, where the two peptides differ only by conservative substitutions. Another indication that two nucleic acid sequences are substantially identical is that the two molecules or their complements hybridize to each other under stringent conditions, as described below. Yet another indication that two nucleic acid sequences are substantially identical is that the same primers can be used to amplify the sequence.

The phrase "nucleic acid" is used herein interchangeably with the term "polynucleotide"and refers to deoxyribonucleotides or ribonucleotides and polymers thereof in either single- or double-stranded form. The term encompasses nucleic acids containing known nucleotide analogs or modified backbone residues or linkages, which are synthetic, naturally occurring, and non-naturally occurring, which have similar binding properties as the reference nucleic acid, and which are metabolized in a manner similar to the reference nucleotides. Examples of such analogs include, without limitation, phosphorothioates, phosphoramidates, methyl phosphonates, chiral-methyl phosphonates, 2-O-methyl ribonucleotides, peptide-nucleic acids (PNAs).

Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (*e.g.*, degenerate codon substitutions) and complementary sequences, as well as the sequence explicitly indicated. Specifically, as detailed below, degenerate codon substitutions may be achieved by generating sequences in which the third position of one or more selected (or all) codons is substituted with mixed-base and/or deoxyinosine residues (Batzer *et al.*, (1991) Nucleic Acid Res. 19:5081; Ohtsuka *et al.*, (1985) J. Biol. Chem. 260:2605-2608; and Rossolini *et al.*, (1994) Mol. Cell. Probes 8:91-98).

The phrase "operably linked" refers to a functional relationship between two or more polynucleotide (*e.g.*, DNA) segments. Typically, it refers to the functional relationship of a transcriptional regulatory sequence to a transcribed sequence. For example, a promoter or enhancer sequence is operably linked to a coding sequence if it stimulates or modulates the transcription of the coding sequence in an appropriate host cell or other expression system. Generally, promoter transcriptional regulatory sequences that are operably linked to a transcribed sequence are physically contiguous to the transcribed sequence, *i.e.*, they are cis-acting. However, some transcriptional regulatory sequences, such as enhancers,

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need not be physically contiguous or located in close proximity to the coding sequences whose transcription they enhance.

The terms "polypeptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer. Unless otherwise indicated, a particular polypeptide sequence also implicitly encompasses conservatively modified variants thereof.

The term "subject" includes human and non-human animals. Non-human animals include all vertebrates, *e.g.*, mammals and non-mammals, such as non-human primates, sheep, dog, cow, chickens, amphibians, and reptiles. Except when noted, the terms "patient" or "subject" are used herein interchangeably.

The term "anti-cancer agent" means any agent that can be used to treat a cell proliferative disorder such as cancer, including cytotoxic agents, chemotherapeutic agents, radiotherapy and radiotherapeutic agents, targeted anti-cancer agents, and immunotherapeutic agents.

"Tumor" refers to neoplastic cell growth and proliferation, whether malignant or benign, and all pre-cancerous and cancerous cells and tissues.

The term "anti-tumor activity" means a reduction in the rate of tumor cell proliferation, viability, or metastatic activity. A possible way of showing anti-tumor acitivey is show a decline in growth rate of abnormal cells that arises during therapy or tumor size stability or reduction. Such activity can be assessed using accepted in vitro or in vivo tumor models, including but not limited to xenograft models.

The term "malignancy" refers to a non-benign tumor or a cancer. As used herein, the term "cancer" includes a malignancy characterized by deregulated or uncontrolled cell growth. Exemplary cancers include: carcinomas, sarcomas, leukemias, and lymphomas. The term "cancer" includes primary malignant tumors (e.g., those whose cells have not migrated to sites in the subject's body other than the site of the original tumor) and secondary malignant tumors (e.g., those arising from metastasis, the migration of tumor cells to secondary sites that are different from the site of the original tumor).

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Various aspects of the invention are described in further detail in the following sections and subsections.

LRP6 and the Wnt-Signaling Pathway

The invention pertains to LRP6 multivalent antibodies and uses thereof. Inhibition of Wnt signaling by molecules directed to LRP6 lead to a loss of canonical Wnt signaling. Therefore, antagonism of LRP6 receptor function with a multivalent antibody will inhibit Wnt ligand signaling and aid in diseases associated with aberrant canonical Wnt signaling, e.g., cancer. In particular, the LRP6 multivalent antibodies can specifically increase or decrease signaling mediated by Wnt1 or Wnt3a class proteins in different disease settings.

Misregulation of the Wnt/β-catenin signaling pathway has been linked to various human diseases such as cancer and bone disorders. Molecules that restore the balance of Wnt signaling in these diseases might have therapeutic potential. Using phage-based panning, LRP6 antibodies have been identified that either inhibit or enhance Wnt signaling. Remarkably, two classes of LRP6 antagonistic antibodies have been identified. One class of antibodies specifically inhibits Wnt proteins represented by Wnt1, while the second class specifically inhibits Wnt proteins represented by Wnt3a. Epitope mapping experiments indicate that Wnt1-specific and Wnt3a-specific LRP6 antibodies bind to the first β-propeller and the third β-propeller of LRP6 respectively, suggesting that Wnt1 and Wnt3a proteins bind to different β-propeller regions of LRP6 (See International Serial No. PCT/EP2008/064821 filed October 31, 2008, the contents of which are incorporated herein by reference in their entirety).

Additional characterization of the Propeller 3 domain of LRP6 identified residues in this domain responsible for interaction with the antibodies. Antibody binding sites within YWTD-EGF region of Propeller 3 were identified using hydrogen-deuterium exchange (HDx) mass spectrometry (MS) and correspond to a concave surface between blade 1 and 6 of Propeller 3 domain.

The Wnt signaling pathway is important in embryonic development and postnatal tissue maintenance. This is achieved by directing a specific set of genes that control temporal and spatial regulation of cell growth, movement and cell survival (reviewed in Barker and Clevers (2006) Nature Rev. 5:997). Proper regulation of this pathway is important for maintaining tissue homeostasis. Chronic activation of this pathway promotes uncontrolled

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cell growth and survival and can consequently drive the development of cell proliferative diseases, such as cancer. Altematively, abnormal inhibition of this pathway can result in many disease states, for example loss of bone mass and other bone diseases. Wnt proteins initiate downstream signaling by interacting with a Frizzled receptor and one of two cell-surface receptors, which are members of the low-density-lipoprotein receptor (LDLR)-related proteins (LRPs): LRP5 and LRP6 (reviewed in He *et al.*,(2004) Development 31:1663-1677).

The role of LRP6 in canonical Wnt signaling was discovered via genetic studies. Mutant mice lacking LRP6 exhibited composite phenotypes similar to mutations in several individual Wnt genes (Pinson *et al.*, (2000) Nature 407:535-538). In Xenopus embryos, dominant-negative LRP6 blocked signaling by several Wnt proteins, whereas overexpression of LRP6 activated Wnt/ β-catenin signaling (Tamai *et al.*, (2000) Nature 407:530-535). Furthermore, it has been shown that expression of either LRP6 or LRP5 is necessary for cells to respond to canonical Wnt signaling (reviewed in He *et al.*, *supra,* 2004).

LRP5 and LRP6 are highly homologous and share 73% and 64% identity in their extra- and intracellular domains, respectively. They are widely co-expressed during embryogenesis and in adult tissues and share some functional redundancy.

The extracellular domains of LRP5 and LRP6 comprise three basic domains: 1) a YWTD (tyrosine, tryptophan, threonine, aspartic acid)-type β-propeller region, 2) an EGF (epidermal growth factor)-like domain, and 3) an LDLR type A (LA) domain.

The YWTD-type β-propeller region contains six YWTD repeats of 43-50 amino acid residues each and forms a six-bladed β-propeller structure. In LRP5 and LRP6, there are four YWTD-type β-propeller regions that are each followed by an EGF- like domain, which comprises about 40 amino acid residues with conserved cysteine residues, which in turn are followed by three LA domains. (Springer *et al.*, (1998) J. Mol. Biol. 283:837-862; Jeon *et al.*, (2001) Nat. Struct. Biol. 8:499-504). The β- propeller-EGF-like domains appear to bind extracellular ligands. The extracellular domain of LRP6 is defined by amino acid residues 19 to 1246 and contains four β-propeller domains at amino acid residues 43-324, 352-627, 654-929, and 957-1250, which correspond to β-propeller regions 1, 2, 3 and 4, respectively. Propeller domains 1-2 include amino acids 19-629, and Propeller domains 3-4 include amino acids 631-1246.

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LRP6 Antibodies

The present invention provides antibodies that specifically bind to LRP6 (*e.g.*, human LRP6, cynomologus LRP6). In some embodiments, the present invention provides antibodies that specifically bind to both human and cynomologus LRP6.

The Wnt proteins capable of activating β-catenin signaling can be divided into two classes and they require different β-propeller regions of LRP6 for signaling as described in International Serial No. PCT/EP2008/064821 filed October 31, 2008, the contents of which are incorporated herein by reference in their entirety. In addition, dimeric LRP6 antibodies (e.g., IgG) strongly sensitize cells to Wnt signaling, for example through dimerization of endogenous LRP6. These results suggest that β-propeller 1 and β-propeller 3 are differentially required for signaling activity of Wnt1 and Wnt 3. These findings provide new insights on Wnt-induced LRP6 activation and pave the way for the development of LRP6 antibodies to modulate Wnt signaling in different diseases. Furthermore, conversion of fragments of the LRP6 antibodies into an IgG format results in an antibody that clusters LRP6 receptors and in the presence of a ligand protein can potentiate a Wnt signal.

In one embodiment, the antibodies potentiate a Wnt signal with the proviso that potentiation does not occur with biparatopic antibodies of the invention. In such an embodiment, the Wnt signal is activated and enhanced upon conversion of a fragment of an antibody to a full length IgG LRP6 antibody in the presence of a Wnt ligand. For example, a Wnt 1 Fab binds to the β-propeller 1 domain of the LRP6 receptor and blocks the Wnt 1 pathway in absence of a Wnt ligand, e.g., Wnt 3. In the presence of a Wnt ligand, e.g., Wnt 3, the Wnt 1 Fab blocks signaling through the Wnt 1 pathway, but signal activation may occur through the Wnt 3 pathway, thereby producing a signal. When the Wnt 1 Fab is converted to a full length Wnt 1 IgG, the Wnt 1 IgG binds to the β-propeller 1 domains of two LRP6 receptors and blocks the Wnt 1 pathway, however, in the presence of a Wnt ligand, e.g., Wnt 3; signal activation occurs through the Wnt 3 pathway and is also enhanced. While not required to provide a theory of action, one possible mechanism is that the IgG clusters together two or more LRP6 receptors by binding to the β-propeller 1 domains of each LRP6 receptor, which in the presence of a Wnt 3 ligand results in a stronger signal through the Wnt 3 pathway. Dimerization of the LRP6

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receptors promotes Wnt signaling, perhaps through the increases avidity of the various interactions involving LRP6.

The reverse results are obtained with a Wnt 3 Fab that binds to the β-propeller 3 domain of the LRP6 receptor and blocks the Wnt 3 pathway. In the presence of a Wnt 1 ligand, the Wnt 3 Fab blocks the Wnt 3 pathway, but activates the Wnt 1 pathway to generate a signal. When the Wnt 3 Fab is converted to a full length Wnt 3 IgG, the Wnt 3 IgG binds to the β-propeller 3 regions of two LRP6 receptors, and in the presence of a Wnt 1 ligand, inhibits signaling through the Wnt 1 pathway. In one embodiment, the antibodies avoid potentiating a Wnt signal. In some embodiments, the present invention provides antibodies that specifically bind to both human and cynomologus LRP6. In one embodiment, the LRP6 antibodies are antagonistic antibodies. In another embodiment, the LRP6 antibodies are agonistic antibodies.

As different Wnt proteins require different β-propellers domains of LRP6 for signaling, and as clustering or dimerization of LRP6 potentiates Wnt signaling, therapy using the LRP6 antibodies can be regulated and "fine tuned" by using different combinations of antibodies.

In one embodiment, the LRP6 antibodies are used as monomeric antibodies or fragments thereof such as single chain antibodies, unibodies, and the like. In one embodiment, a monomeric LRP6 antibody that binds to the β-propeller 1 region of LRP6 is used in combination with a monomeric LRP6 antibody that binds to the β-propeller 3 region of LRP6. In another embodiment, the LRP6 antibodies are used as multimeric antibodies or fragments thereof such as bispecific, biparatopic LRP6 antibodies.

In addition to Wnt ligands LRP6 Propeller 1 antibodies are expected to inhibit the interaction with other Propeller 1 binding ligands (e.g. Sclerostin, Dkk1). Similarly, Propeller 3 antibodies are expected to inhibit the interaction with other propeller 3 binding ligands (e.g. Dkk1). Furthermore, propeller 1 and 3 binding antibodies may be expected to affect the activity of other Wnt signaling modulators e.g. R-spondins

The present invention also provides antibodies that specifically bind to a LRP6 protein (*e.g.*, human and/or cynomologus LRP6), the antibodies comprising a VH CDR having an amino acid sequence of any one of the VH CDRs listed in Table 1, *infra*. In particular, the invention provides antibodies that specifically bind to a LRP6 protein (*e.g.*, human

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and/or cynomologus LRP6), the antibodies comprising (or alternatively, consisting of) one, two, three, four, five or more VH CDRs having an amino acid sequence of any of the VH CDRs listed in Table 1, *infra*.

The present invention provides antibodies that specifically bind a LRP6 protein (*e.g.*, human and/or cynomologus LRP6), the antibodies comprising a VH domain having an amino acid sequence of SEQ ID NOs: 14, 34, 36, 44, 60 and 62. The present invention provides antibodies that specifically bind to a LRP6 protein (*e.g.*, human and/or cynomologus LRP6), the antibodies comprising a VL domain having an amino acid sequence of SEQ ID NOs: 13, 33, 35, 43, 59, and 61.

The present invention provides antibodies that specifically bind a LRP6 protein (*e.g.*, human and/or cynomologus LRP6), the antibodies comprising a VH domain having an amino acid sequence of SEQ ID NOs: 82, 89, 106, 108, 128, 130, and 138. The present invention provides antibodies that specifically bind to a LRP6 protein (*e.g.*, human and/or cynomologus LRP6), the antibodies comprising a VL domain having an amino acid sequence of SEQ ID NOs: 81, 90, 105, 107, 127, and 129.

Other antibodies of the invention include amino acids that have been mutated, yet have at least 60%, 70%, 80%, 90%, 95% or 98% identity in the CDR regions with the CDR regions depicted in the sequences described in Table 1. In some embodiments, it includes mutant amino acid sequences wherein no more than 1, 2, 3, 4 or 5 amino acids have been mutated in the CDR regions when compared with the CDR regions depicted in the sequence described in Table 1, while still maintaining their specifity for the the orignal antibody's epitope .

Other antibodies of the invention include amino acids that have been mutated, yet have at least 60%, 70%, 80%, 90%, 95% or 98% identity in the framework regions with the framework regions depicted in the sequences described in Table 1. In some embodiments, it includes mutant amino acid sequences wherein no more than 1, 2, 3, 4, 5, 6, or 7 amino acids have been mutated in the framework regions when compared with the framework regions depicted in the sequence described Table 1, while still maintaining their specifity for the the orignal antibody's epitope

The present invention also provides nucleic acid sequences that encode VH, VL, the full length heavy chain, and the full length light chain of the antibodies that specifically bind

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to a LRP6 protein (*e.g.*, human and/or cynomologus LRP6). Such nucleic acid sequences can be optimized for expression in mammalian cells (for example, Table 1 for MOR08168, MOR08545, and MOR06706 for β-propeller 1 antibodies and MOR06475, MOR08193, and MOR08473 for β-propeller 3 antibodies).

The LRP6 antibodies of the invention bind to distinct LRP6 β-propeller regions. Propeller 1 antibodies bind to the β-propeller 1 domain and block Propeller1-dependent Wnts such as Wnt1, Wnt2, Wnt6, Wnt7A, Wnt7B, Wnt9, Wnt10A, Wnt10B. Propeller 3 antibodies bind to the β-propeller 3 domain and block Propeller 3-dependent Wnts such as Wnt3a and Wnt3.

Table 1: Examples of LRP6 Antibodies of the Present Invention

SEQ ID NUMBER	Ab region	Sequence
MOR08168 Prop1		
SEQ ID NO:1 (Kabat)	HCDR1	DYVIN
SEQ ID NO:2 (Kabat)	HCDR2	GISWSGVNTHYADSVKG
SEQ ID NO:3 (Kabat)	HCDR3	LGATANNIRYKFMDV
SEQ ID NO:4 (Kabat)	LCDR1	SGDSLRNKVY
SEQ ID NO:5 (Kabat)	LCDR2	KNNRPS
SEQ ID NO:6 (Kabat)	LCDR3	QSYDGQKSLV
SEQ ID NO:7 (Chothia)	HCDR1	GFTFSDY
SEQ ID NO:8 (Chothia)	HCDR2	SW5GVN
SEQ ID NO:9 (Chothia)	HCDR3	LGATANNIRYKFMDV
SEQ ID NO:10 (Chothia)	LCDR1	DSLRNK
SEQ ID NO:11 (Chothia)	LCDR2	KN
SEQ ID NO:12 (Chothia)	LCDR3	YDGQKSL

SEQ ID ND:13	VL	DIELTQPPSVSVAPGQTARISCSGDSLRNKVYWYQQKPGQAPVLVIYKNNRPSGIPERFSGSNSGNTATLTISGTQA EDEADYYCQSYDGQKSLVFGGGTKLTVL
SEQ ID ND:14	VH	QVQLVESGGGLVQPGGSLRLSCAASGFTFSDYVINWVRQAPGKGLEWVSGISWSGVNTHYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARLGATANNIRYKFMDVWGQGTLVTVSS
SEQ ID ND:1S	DNA VL	GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGGC GATTCTCTTCGTAATAAGGTTTATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAAGA ATAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGACCATTAG CGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGTCTTATGATGGTCAGAAGTCTCTTGTGTTTGGC GGCGGCACGAAGTTAACCGTCCTA
SEQ ID NO:16	DNA VH	CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCTGCGCGGC CTCCGGATTTACCTTTTCTGATTATGTTATTAATTGGGTGCGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGTG AGCGGTATTTCTTGGTCTGGTGTTAATACTCATTATGCTGATTCTGTTAAGGGTCGTTTTACCATTTCACGTGAT AATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCGCGC GTCTTGGTGCTACTGCTAATAATATTCGTTATAAGTTTATGGATGTTTGGGGCCAAGGCACCCTGGTGACGGT TAGCTCA
SEQ ID NO:17	Light Lambda	DIELTQPPSVSVAPGQTARISCSGDSLRNKVYWYQQKPGQAPVLVIYKNNRPSGIPERFSGSNSGNTATLTISGTQA EDEADYYCQSYDGQKSLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSP VKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
SEQ ID NO:18	Heavy IgG1 LALA	QVQLVESGGGLVQPGGSLRLSCAASGFTFSDYVINWVRQAPGKGLEWVSGISWSGVNTHYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARLGATANNIRYKFMDVWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK
SEQ ID NO: 19	DNA Light Lambda	GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGGC GATTCTCTTCGTAATAAGGTTTATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAAGA ATAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGACCATTAG CGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGTCTTATGATGGTCAGAAGTCTCTTGTGTTTGGC GGCGGCACGAAGTTAACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTG AGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGG CCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAAC AAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAG GTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCA
SEQ ID NO: 20	DNA Heavy IgG1 LALA	CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCTGCGCGGC CTCCGGATTTACCTTTTCTGATTATGTTATTAATTGGGTGCGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGTG AGCGGTATTTCTTGGTCTGGTGTTAATACTCATTATGCTGATTCTGTTAAGGGTCGTTTTACCATTTCACGTGAT AATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCGCGC GTCTTGGTGCTACTGCTAATAATATTCGTTATAAGTTTATGGATGTTTGGGGCCAAGGCACCCTGGTGACGGT TAGCTCAGCCTCCACCAAGGGTCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACA GCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTG ACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCG TGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGG ACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAGCAGCGG GGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCAC ATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGG TGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCCTCACC GTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCC ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGG GAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTG GAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTC CTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTG ATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

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MOR08545 Prop1		
SEQ ID ND:21 (Kabat)	HCDR1	VNGMH
SEQ ID NO:22 (Kabat)	HCDR2	VIDGMGHTYYADSVKG
SEQ ID ND:23 (Kabat)	HCDR3	YDYIKYGAFDP
SEQ ID NO:24 (Kabat)	LCDR1	SGDNIGSKYVH
SEQ ID NO:25 (Kabat)	LDCR2	GDSNRPS
SEQ ID NO:26 (Kabat)	LCDR3	TRTSTPISGV
SEQ ID NO:27 (Chothia)	HCDR1	GFTFSVN
SEQ ID NO:28 (Chothia)	HCDR2	DGMGH
SEQ ID NO:29 (Chothia)	HCDR3	YDYIKYGAFDP
SEQ ID NO:30 (Chothia)	LCDR1	DNIGSKY
SEQ ID NO:31 (Chothia)	LDCR2	GDS
SEQ ID NO:32 (Chothia)	LCDR3	TSTPISG
SEQ ID NO:33	VL	DIELTQPPSVSVAPGQTARISCSGDNIGSKYVHWYQQKPGQAPVLVIYGDSNRPSGIPERFSGSN5GNTATLTISGT QAEDEADYYCTRTSTPISGVFGGGTKLTVL
SEQ ID NO:34	VH	QVQLVE5GGGLVQPGG5LRLSCAASGFTFSVNGMHWVRQAPGKGLEWV5VIDGMGHTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARYDYIKYGAFDPWGQGTLVTV5S
SEQ ID NO:35	VL Germlined	SYELTQPPSVSVSPGQTASITCSGDNIGSKYVHWYQQKPGQSPVLVIYGDSNRPSGIPERFSGSNSGNTATLTISGT QAMDEADYYCTRTSTPISGVFGGGTKLTVL
SEQ ID NO:36	VH Germlined	EVQLVESGGGLVQPGGSLRLSCAASGFTFSVNGMHWVRQAPGKGLEWVSVIDGMGHTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARYDYIKYGAFDPWGQGTLVTVSS
SEQ ID NO:37	DNA VL	GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGGC GATAATATTGGTTCTAAGTATGTTCATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATG GTGATTCTAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCACTCGTACTTCTACTCCTATTTCTGGTGTGT TTGGCGGCGGCACGAAGTTAACCGTTCTT
SEQ ID NO:38	DNA VH	CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCTGCGCGGC CTCCGGATTTACCTTTTCTGTTAATGGTATGCATTGGGTGCGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGTG AGCGTTATTGATGGTATGGGTCATACTTATTATGCTGATTCTGTTAAGGGTCGTTTTACCATTTCACGTGATAA TTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCGCGCGT TATGATTATATTAAGTATGGTGCTTTTGATCCTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA

SEQ ID NO:39	Light lambda	DIELTQPPSVSVAPGQTARISCSGDNIGSKYVHWYQQKPGQAPVLVIYGDSNRPSGIPERFSGSNSGNTATLTISGT QAEDEADYYCTRTSTPISGVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSS PVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEA
SEQ ID NO:40	Heavy Fab	QVQLVESGGGLVQPGGSLRLSCAASGFTFSVNGMHWVRQAPGKGLEWVSVIDGMGHTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARYDYIKYGAFDPWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS
SEQ ID NO:41	DNA Light lambda	GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGGC GATAATATTGGTTCTAAGTATGTTCATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATG GTGATTCTAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCACTCGTACTTCTACTCCTATTTCTGGTGTGT TTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAGCCGAAAGCCGCACCGAGTGTGACGCTGTTTCCGCCGA GCAGCGAAGAATTGCAGGCGAACAAAGCGACCCTGGTGTGCCTGATTAGCGACTTTTATCCGGGAGCCGTGA CAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGC AACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGC TGCCAGGTCACGCATGAGGGGAGCACCGTGGAAAAAACCGTTGCGCCGACTGAGGCC
SEQ ID NO:42	DNA Heavy Fab	CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCTGCGCGGC CTCCGGATTTACCTTTTCTGTTAATGGTATGCATTGGGTGCGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGTG AGCGTTATTGATGGTATGGGTCATACTTATTATGCTGATTCTGTTAAGGGTCGTTTTACCATTTCACGTGATAA TTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCGCGCGT TATGATTATATTAAGTATGGTGCTTTTGATCCTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCAGCGTCGA CCAAAGGTCCAAGCGTGTTTCCGCTGGCTCCGAGCAGCAAAAGCACCAGCGGCGGCACGGCTGCCCTGGGCT GCCTGGTTAAAGATTATTTCCCGGAACCAGTCACCGTGAGCTGGAACAGCGGGGCGCTGACCAGCGGCGTGC ATACCTTTCCGGCGGTGCTGCAAAGCAGCGGCCTGTATAGCCTGAGCAGCGTTGTGACCGTGCCGAGCAGCA GCTTAGGCACTCAGACCTATATTTGCAACGTGAACCATAAACCGAGCAACACCAAAGTGGATAAAAAAGTGG AACCGAAAAGC
SEQ ID NO:43	VL Germlined	SYELTQPLSVSVALGQTARITCGGDNIGSKYVHWYQQKPGQAPVLVIYGDSNRPSGIPERFSGSNSGNTATLTISRA QAGDEADYYCTRTSTPISGVFGGGTKLTVL
SEQ ID NO:44	VH Germlined	EVQLLESGGGLVQPGGSLRLSCAASGFTFSVNGMHWVRQAPGKGLEWVSVIDGMGHTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARYDYIKYGAFDPWGQGTLVTVSS
SEQ ID NO:45	DNA VL Germlined	AGCTATGAACTGACCCAGCCGCTGTCTGTGAGCGTGGCGCTGGGCCAGACCGCGCGTATTACCTGCGGTGGC GATAACATTGGCAGCAAATATGTGCATTGGTATCAGCAGAAACCGGGCCAGGCGCCGGTGCTGGTGATTTAT GGCGATAGCAACCGTCCGAGCGGCATTCCGGAACGTTTTAGCGGCAGCAACAGCGGCAACACCGCGACCCTG ACCATTTCTCGCGCGCAGGCGGGTGATGAAGCGGATTATTATTGCACCCGTACCAGCACCCCGATTAGCGGC GTGTTTGGCGGCGGTACGAAGTTAACCGTTCTT
SEQ ID ND:46	DNA VH Germlined	GAGGTGCAATTGCTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCTGCGCGGC CTCCGGATTTACCTTTTCTGTTAATGGTATGCATTGGGTGCGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGTG AGCGTTATTGATGGTATGGGTCATACTTATTATGCTGATTCTGTTAAGGGTCGTTTTACCATTTCACGTGATAA TTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCGCGCGT TATGATTATATTAAGTATGGTGCTTTTGATCCTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
MOR06706 Prop1		
SEQ ID NO:47 (Kabat)	HCDR1	DYAIH
SEQ ID ND:48 (Kabat)	HCDR2	GISYSGSSTHYAD5VKG
SEQ ID NO:49 (Kabat)	HCDR3	GSHGNIMAKRYFDF
SEQ ID NO:50	LCDR1	SGDNIRKKYVY

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(Kabat)		
SEQ ID NO:51 (Kabat)	LDCR2	EDSKRPS
SEQ ID NO:52 (Kabat)	LCDR3	STADSGINNGV
SEQ ID NO:53 (Chothia)	HCDR1	GFTFSDY
SEQ ID NO:54 (Chothia)	HCDR2	SYSGSS
SEQ ID NO:55 (Chothia)	HCDR3	GSHGNIMAKRYFDF
SEQ ID NO:56 (Chothia)	LCDR1	DNIRKKY
SEQ ID NO:57 (Chothia)	LDCR2	EDS
SEQ ID NO:58 (Chothia)	LCDR3	ADSGINNG
SEQ ID NO:59	VL	DIELTQPPSVSVAPGQTARISCSGDNIRKKYVYWYQQKPGQAPVLVIYEDSKRPSGIPERFSGSNSGNTATLTISGTQ AEDEADYYCSTADSGINNGVFGGGTKLTVL
SEQ ID NO:60	VH	QVQLVESGGGLVQPGGSLRLSCAASGFTFSDYAIHWVRQAPGKGLEWVSGISYSGSSTHYADSVKGRFTISRDNSK NTLYLQMNSLRAEDTAVYYCARGSHGNIMAKRYFDFWGQGTLVTVSS
SEQ ID NO:61	VL Germlined	SYELTQPPSVSVSPGQTASITCSGDNIRKKYVYWYQQKPGQSPVLVIYEDSKRPSGIPERFSGSNSGNTATLTISGTQ AMDEADYYCSTADSGINNGVFGGGTKLTVL
SEQ ID NO:62	VH Germlined	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYAIHWVRQAPGKGLEWVSGISYSGSSTHYADSVKGRFTISRDNSK NTLYLQMNSLRAEDTAVYYCARGSHGNIMAKRYFDFWGQGTLVTVSS
SEQ ID NO:63	DNA VL	GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGGC GATAATATTCGTAAGAAGTATGTTTATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATG AGGATTCTAAGCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGA CCATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCTCTACTGCTGATTCTGGTATTAATAATGG TGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTT
SEQ ID NO:64	DNA VH	CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCTGCGCGGC CTCCGGATTTACCTTTTCTGATTATGCTATTCATTGGGTGCGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGTG AGCGGTATCTCTTATTCTGGTAGCTCTACCCATTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCACGTGA TAATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCGCG CGTGGTTCTCATGGTAATATTATGGCTAAGCGTTATTTTGATTTTTGGGGCCAAGGCACCCTGGTGACGGTTA GCTCA
SEQ ID NO:65	Light Lambda	DIELTQPPSVSVAPGQTARISCSGDNIRKKYVYWYQQKPGQAPVLVIYEDSKRPSGIPERFSGSNSGNTATLTISGTQ AEDEADYYCSTADSGINNGVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKAD5 SPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
SEQ ID NO:66	Heavy IgG1 LALA	QVQLVESGGGLVQPGGSLRLSCAASGFTFSDYAIHWVRQAPGKGLEWVSGISYSGSSTHYADSVKGRFTISRDNSK NTLYLQMNSLRAEDTAVYYCARGSHGNIMAKRYFDFWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDK THTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVV5VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLD5DGSFFLYSKLTVDKSRWQQGNVF5CSVMHEALHNHYTQKSLSLSPGK

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SEQ ID ND:67	DNA hlamda	GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGGC GATAATATTCGTAAGAAGTATGTTTATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATG AGGATTCTAAGCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGA CCATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCTCTACTGCTGATTCTGGTATTAATAATGG TGTGTTTGGCGGCGGCACGAAGTTAACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCG CCCTCCTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCG TGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAA AGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTAC AGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCA
SEQ ID ND:68	DNA Heavy IgG1 LALA	CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCTGCGCGGC CTCCGGATTTACCTTTTCTGATTATGCTATTCATTGGGTGCGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGTG AGCGGTATCTCTTATTCTGGTAGCTCTACCCATTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCACGTGA TAATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCGCG CGTGGTTCTCATGGTAATATTATGGCCAAGCGTTATTTTGATTTTTGGGGCCAAGGCACCCTGGTGACGGTTA GCTCAGCCTCCACCAAGGGTCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGC GGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGAC CAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTG CCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGAC AAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAGCAGCGGGG GGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATG CGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGC ATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCCTCACCGTCC TGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCG AGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGG AGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGT GGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCT TCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGC ATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA
MOR06475 Prop3		
SEQ ID NO:69 (Kabat)	HCDR1	NRGGGVG
SEQ ID NO:70 (Kabat)	HCDR2	WIDWDDDKSYSTSLKT
SEQ ID NO:71 (Kabat)	HCDR3	MHLPLVFDS
SEQ ID NO:72 (Kabat)	LCDR1	RASQFIGSRYLA
SEQ ID NO:73 (Kabat)	LDCR2	GASNRAT
SEQ ID ND:74 (Kabat)	LCDR3	QQYYDYPQT
SEQ ID ND:75 (Chothia)	HCDR1	GFSLSNRGG
SEQ ID ND:76 (Chothia)	HCDR2	DWDDD
SEQ ID NO:77 (Chothia)	HCDR3	MHLPLVFDS
SEQ ID NO:78 (Chothia)	LCDR1	SQFIGSRY

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SEQ ID ND:79 (Chothia)	LDCR2	GAS
SEQ ID NO:80 (Chothia)	LCDR3	YYDYPQ
SEQ ID NO:81	VL	DIVLTQSPATLSLSPGERATLSCRASQFIGSRYLAWYQQKPGQAPRLLIYGASNRATGVPARFSGSGSGTDFTLTISSL EPEDFATYYCQQYYDYPQTFGQGTKVEIK
SEQ ID NO:82	VH	QVQLKESGPALVKPTQTLTLTCTFSGFSLSNRGGGVGWIRQPPGKALEWLAWIDWDDDKSYSTSLKTRLTISKDTS KNQVVLTMTNMDPVDTATYYCARMHLPLVFDSWGQGTLVTVSS
SEQ ID NO:83	DNA VL	GATATCGTGCTGACCCAGAGCCCGGCGACCCTGAGCCTGTCTCCGGGCGAACGTGCGACCCTGAGCTGCAGA GCGAGCCAGTTTATTGGTTCTCGTTATCTGGCTTGGTACCAGCAGAAACCAGGTCAAGCACCGCGTCTATTAA TTTATGGTGCTTCTAATCGTGCAACTGGGGTCCCGGCGCGTTTTAGCGGCTCTGGATCCGGCACGGATTTTAC CCTGACCATTAGCAGCCTGGAACCTGAAGACTTTGCGACTTATTATTGCCAGCAGTATTATGATTATCCTCAGA CCTTTGGCCAGGGTACGAAAGTTGAAATTAAA
SEQ ID NO:84	DNA VH	CAGGTGCAATTGAAAGAAAGCGGCCCGGCCCTGGTGAAACCGACCCAAACCCTGACCCTGACCTGTACCTTTT CCGGATTTAGCCTGTCTAATCGTGGTGGTGGTGTGGGTTGGATTCGCCAGCCGCCTGGGAAAGCCCTCGAGT GGCTGGCTTGGATCGATTGGGATGATGATAAGTCTTATAGCACCAGCCTGAAAACGCGTCTGACCATTAGCA AAGATACTTCGAAAAATCAGGTGGTGCTGACTATGACCAACATGGACCCGGTGGATACGGCCACCTATTATTG CGCGCGTATGCATCTTCCTCTTGTTTTTGATTCTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
SEQ ID NO:8S	Light kappa	DIVLTQSPATLSLSPGERATLSCRASQFIGSRYLAWYQQKPGQAPRLLIYGASNRATGVPARFSGSGSGTDFTLTISSL EPEDFATYYCQQYYDYPQTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNAL QSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO:86	Heavy IgG1 LALA	QVQLKESGPALVKPTQTLTLTCTFSGFSLSNRGGGVGWIRQPPGKALEWLAWIDWDDDKSYSTSLKTRLTISKDTS KNQVVLTMTNMDPVDTATYYCARMHLPLVFDSWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHT CPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
SEQ ID NO:87	DNA Light kappa	GATATCGTGCTGACCCAGAGCCCGGCGACCCTGAGCCTGTCTCCGGGCGAACGTGCGACCCTGAGCTGCAGA GCGAGCCAGTTTATTGGTTCTCGTTATCTGGCTTGGTACCAGCAGAAACCAGGTCAAGCACCGCGTCTATTAA TTTATGGTGCTTCTAATCGTGCAACTGGGGTCCCGGCGCGTTTTAGCGGCTCTGGATCCGGCACGGATTTTAC CCTGACCATTAGCAGCCTGGAACCTGAAGACTTTGCGACTTATTATTGCCAGCAGTATTATGATTATCCTCAGA CCTTTGGCCAGGGTACGAAAGTTGAAATTAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCT GATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAG TACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAG GACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCC TGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT
SEQ ID NO:88	DNA Heavy IgG1 LALA	CAGGTGCAATTGAAAGAAAGCGGCCCGGCCCTGGTGAAACCGACCCAAACCCTGACCCTGACCTGTACCTTTT CCGGATTTAGCCTGTCTAATCGTGGTGGTGGTGTGGGTTGGATTCGCCAGCCGCCTGGGAAAGCCCTCGAGT GGCTGGCTTGGATCGATTGGGATGATGATAAGTCTTATAGCACCAGCCTGAAAACGCGTCTGACCATTAGCA AAGATACTTCGAAAAATCAGGTGGTGCTGACTATGACCAACATGGACCCGGTGGATACGGCCACCTATTATTG CGCGCGTATGCATCTTCCTCTTGTTTTTGATTCTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCAGCCTCCA CCAAGGGTCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTG CCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCA CACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCT TGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGC CCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAGCAGCGGGGGGACCGTCAGTCTT CCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGAC GTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGAC AAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACT GGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCT CCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAG AACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAAT GGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCA AGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGC

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		ACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA
SEQ ID NO:89	VH Germlined	QVTLKESGPALVKPTQTLTLTCTFSGFSLSNRGGGVGWIRQPPGKALEWLAWIDWDDDKSYSTSLKTRLTISKDTS KNQVVLTMTNMDPVDTATYYCARMHLPLVFDSWGQGTLVTVSS
SEQ ID NO:90	VL Germlined	EIVLTQSPATLSLSPGERATLSCRASQFIGSRYLAWYQQKPGQAPRLLIYGASNRATGIPARFSGSGSGTDFTLTISSLE PEDFAVYYCQQYYDYPQTFGQGTKVEIK
SEQ ID NO:91	DNA VH Germlined	CAGGTCACACTGAAAGAGTCCGGCCCTGCCCTGGTCAAACCCACCCAGACCCTGACCCTGACATGCACCTTCA GCGGCTTCAGCCTGAGCAACAGAGGCGGCGGAGTGGGCTGGATCAGACAGCCTCCCGGCAAGGCCCTGGAA TGGCTGGCCTGGATCGACTGGGACGACGACAAGAGCTACAGCACCAGCCTGAAAACCCGGCTGACCATCAGC AAGGACACCAGCAAGAACCAGGTGGTGCTGACCATGACCAACATGGACCCCGTGGACACCGCCACCTACTAC TGCGCCCGGATGCATCTGCCCCTGGTGTTCGATAGCTGGGGCCAGGGCACCCTGGTCACCGTCAGCTCA
SEQ ID NO:92	DNA VL Germlined	GAAATCGTGCTGACCCAGAGCCCCGCCACCCTGTCTCTGAGCCCTGGCGAGAGAGCCACCCTGAGCTGCCGG GCCAGCCAGTTCATCGGCAGCAGATACCTGGCTTGGTATCAGCAGAAGCCCGGCCAGGCCCCCAGACTGCTG ATCTACGGCGCCAGCAACCGGGCCACCGGCATCCCTGCCAGATTTTCTGGCAGCGGCAGCGGCACCGACTTC ACCCTGACCATCAGCAGCCTGGAACCCGAGGACTTCGCCGTGTACTACTGCCAGCAGTACTACGACTACCCCC AGACCTTCGGCCAGGGCACCAAGGTGGAAATCAAG
MOR08193 Prop3		
SEQ ID ND:93 (Kabat)	HCDR1	NRGGGVG
SEQ ID NO:94 (Kabat)	HCDR2	WIDWDDDKSYSTSLKT
SEQ ID NO:95 (Kabat)	HCDR3	MHLPLVFDS
SEQ ID NO:96 (Kabat)	LCDR1	RASQFIGSRYLA
SEQ ID ND:97 (Kabat)	LDCR2	GASNRAT
SEQ ID NO:98 (Kabat)	LCDR3	QQYWSIPIT
SEQ ID ND:99 (Chothia)	HCDR1	GFSLSNRGG
SEQ ID NO:100 (Chothia)	HCDR2	DWDDD
SEQ ID ND:101 (Chothia)	HCDR3	MHLPLVFDS
SEQ ID NO:102 (Chothia)	LCDR1	SQFIGSRY
SEQ ID NO:103 (Chothia)	LDCR2	GAS
SEQ ID NO:104 (Chothia)	LCDR3	YWSIPI

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SEQ ID NO:105	VL	DIVLTQSPATLSLSPGERATLSCRASQFIGSRYLAWYQQKPGQAPRLLIYGASNRATGVPARFSGSGSGTDFTLTISSL EPEDFAVYYCQQYWSIPITFGQGTKVEIK
SEQ ID NO:106	VH	QVQLKESGPALVKPTQTLTLTCTFSGFSLSNRGGGVGWIRQPPGKALEWLAWIDWDDDKSYSTSLKTRLTISKDTS KNQVVLTMTNMDPVDTATYYCARMHLPLVFDSWGQGTLVTVSS
SEQ ID NO:107	VL Germlined	EIVLTQSPATLSLSPGERATLSCRASQFIGSRYLAWYQQKPGQAPRLLIYGASNRATGIPARFSGSGSGTDFTLTISSLE PEDFAVYYCQQYWSIPITFGQGTKVEIK
SEQ ID NO:108	VH Germlined	QVTLKESGPALVKPTQTLTLTCTFSGFSLSNRGGGVGWIRQPPGKALEWLAWIDWDDDKSYSTSLKTRLTISKDTS KNQVVLTMTNMDPVDTATYYCARMHLPLVFDSWGQGTLVTVSS
SEQ ID NO:109	DNA VL	GATATCGTGCTGACCCAGAGCCCGGCGACCCTGAGCCTGTCTCCGGGCGAACGTGCGACCCTGAGCTGCAGA GCGAGCCAGTTTATTGGTTCTCGTTATCTGGCTTGGTACCAGCAGAAACCAGGTCAAGCACCGCGTCTATTAA TTTATGGTGCTTCTAATCGTGCAACTGGGGTCCCGGCGCGTTTTAGCGGCTCTGGATCCGGCACGGATTTTAC CCTGACCATTAGCAGCCTGGAACCTGAAGACTTTGCGGTGTATTATTGCCAGCAGTATTGGTCTATTCCTATTA CCTTTGGCCAGGGTACGAAAGTTGAAATTAAA
SEQ ID NO:110	DNA VH	CAGGTGCAATTGAAAGAAAGCGGCCCGGCCCTGGTGAAACCGACCCAAACCCTGACCCTGACCTGTACCTTTT CCGGATTTAGCCTGTCTAATCGTGGTGGTGGTGTGGGTTGGATTCGCCAGCCGCCTGGGAAAGCCCTCGAGT GGCTGGCTTGGATCGATTGGGATGATGATAAGTCTTATAGCACCAGCCTGAAAACGCGTCTGACCATTAGCA AAGATACTTCGAAAAATCAGGTGGTGCTGACTATGACCAACATGGACCCGGTGGATACGGCCACCTATTATTG CGCGCGTATGCATCTTCCTCTTGTTTTTGATTCTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
SEQ ID NO:111	Light kappa	DIVLTQSPATLSLSPGERATLSCRASQFIGSRYLAWYQQKPGQAPRLLIYGASNRATGVPARFSGSGSGTDFTLTISSL EPEDFAVYYCQQYWSIPITFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNAL QSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEA
SEQ ID NO:112	Heavy Fab	QVQLKESGPALVKPTQTLTLTCTFSGFSLSNRGGGVGWIRQPPGKALEWLAWIDWDDDKSYSTSLKTRLTISKDTS KNQVVLTMTNMDPVDTATYYCARMHLPLVFDSWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS
SEQ ID NO:113	DNA Light kappa	GATATCGTGCTGACCCAGAGCCCGGCGACCCTGAGCCTGTCTCCGGGCGAACGTGCGACCCTGAGCTGCAGA GCGAGCCAGTTTATTGGTTCTCGTTATCTGGCTTGGTACCAGCAGAAACCAGGTCAAGCACCGCGTCTATTAA TTTATGGTGCTTCTAATCGTGCAACTGGGGTCCCGGCGCGTTTTAGCGGCTCTGGATCCGGCACGGATTTTAC CCTGACCATTAGCAGCCTGGAACCTGAAGACTTTGCGGTGTATTATTGCCAGCAGTATTGGTCTATTCCTATTA CCTTTGGCCAGGGTACGAAAGTTGAAATTAAACGTACGGTGGCTGCTCCGAGCGTGTTTATTTTTCCGCCGAG CGATGAACAACTGAAAAGCGGCACGGCGAGCGTGGTGTGCCTGCTGAACAACTTTTATCCGCGTGAAGCGAA AGTTCAGTGGAAAGTAGACAACGCGCTGCAAAGCGGCAACAGCCAGGAAAGCGTGACCGAACAGGATAGCA AAGATAGCACCTATTCTCTGAGCAGCACCCTGACCCTGAGCAAAGCGGATTATGAAAAACATAAAGTGTATGC GTGCGAAGTGACCCATCAAGGTCTGAGCAGCCCGGTGACTAAATCTTTTAATCGTGGCGAGGCC
SEQ ID NO:114	DNA Heavy Fab	CAGGTGCAATTGAAAGAAAGCGGCCCGGCCCTGGTGAAACCGACCCAAACCCTGACCCTGACCTGTACCTTTT CCGGATTTAGCCTGTCTAATCGTGGTGGTGGTGTGGGTTGGATTCGCCAGCCGCCTGGGAAAGCCCTCGAGT GGCTGGCTTGGATCGATTGGGATGATGATAAGTCTTATAGCACCAGCCTGAAAACGCGTCTGACCATTAGCA AAGATACTTCGAAAAATCAGGTGGTGCTGACTATGACCAACATGGACCCGGTGGATACGGCCACCTATTATTG CGCGCGTATGCATCTTCCTCTTGTTTTTGATTCTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCAGCGTCGA CCAAAGGTCCAAGCGTGTTTCCGCTGGCTCCGAGCAGCAAAAGCACCAGCGGCGGCACGGCTGCCCTGGGCT GCCTGGTTAAAGATTATTTCCCGGAACCAGTCACCGTGAGCTGGAACAGCGGGGCGCTGACCAGCGGCGTGC ATACCTTTCCGGCGGTGCTGCAAAGCAGCGGCCTGTATAGCCTGAGCAGCGTTGTGACCGTGCCGAGCAGCA GCTTAGGCACTCAGACCTATATTTGCAACGTGAACCATAAACCGAGCAACACCAAAGTGGATAAAAAAGTGG AACCGAAAAGC
MOR08473 Prop3		
SEQ ID NO:115 (Kabat)	HCDR1	SYGMS
SEQ ID NO:116 (Kabat)	HCDR2	NISNDGHYTYYADSVKG

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SEQ ID ND:117 (Kabat)	HCDR3	FQASYLDIMDY
SEQ ID ND:118 (Kabat)	LCDR1	SGDNIGSKYVH
SEQ ID NO:119 (Kabat)	LDCR2	NDSNRPS
SEQ ID NO:120 (Kabat)	LCDR3	QAWGDNGTRV
SEQ ID ND:121 (Chothia)	HCDR1	GFTFSSY
SEQ ID NO:122 (Chothia)	HCDR2	SNDGHY
SEQ ID NO:123 (Chothia)	HCDR3	FQASYLDIMDY
SEQ ID ND:124 (Chothia)	LCDR1	DNIGSKY
SEQ ID ND:125 (Chothia)	LDCR2	NDS
SEQ ID NO:126 (Chothia)	LCDR3	WGDNGTR
SEQ ID ND:127	VL	DIELTQPPSVSVAPGQSITISCSGDNIGSKYVHWYQQKPGQAPVLVIYNDSNRPSGIPERFSGSNSGNTATLTISGTQ AEDEADYYCQAWGDNGTRVFGGGTKLTVL
SEQ ID NO:128	VH	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYGMSWVRQAPGKGLEWVSNISNDGHYTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARFQASYLDIMDYWGQGTLVTVSS
SEQ ID NO:129	VL Germlined	SYELTQPPSVSVSPGQTASITCSGDNIGSKYVHWYQQKPGQSPVLVIYNDSNRPSGIPERFSGSNSGNTATLTISGT QAMDEADYYCQAWGDNGTRVFGGGTKLTVL
SEQ ID ND:130	VH Germlined	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYGMSWVRQAPGKGLEWVSNISNDGHYTYYADSVKGRFTISRDNS KNTLYLQMNSLRAEDTAVYYCARFQASYLDIMDYWGQGTLVTVSS
SEQ ID ND:131	DNA VL	GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGAGCATTACCATCTCGTGTAGCGGCG ATAATATTGGTTCTAAGTATGTTCATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAAT GATTCTAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGACCA TTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGGCTTGGGGTGATAATGGTACTCGTGTGT TTGGCGGCGGCACGAAGTTAACCGTTCTT
SEQ ID ND:132	DNA VH	CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCTGCGCGGC CTCCGGATTTACCTTTTCTTCTTATGGTATGTCTTGGGTGCGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGTG AGCAATATTTCTAATGATGGTCATTATACTTATTATGCTGATTCTGTTAAGGGTCGTTTTACCATTTCACGTGAT AATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCGCGC GTTTTCAGGCTTCTTATCTTGATATTATGGATTATTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
SEQ ID ND:133	Light lambda	DIELTQPPSVSVAPGQSITISCSGDNIGSKYVHWYQQKPGQAPVLVIYNDSNRPSGIPERFSGSNSGNTATLTISGTQ AEDEADYYCQAWGDNGTRVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADS SPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEA
SEQ ID NO:134	Heavy Fab	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYGMSWVRQAPGKGLEWVSNISNDGHYTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARFQASYLDIMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS

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SEQ ID ND:135	DNA Light lambda	GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGAGCATTACCATCTCGTGTAGCGGCG ATAATATTGGTTCTAAGTATGTTCATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAAT GATTCTAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGACCA TTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGGCTTGGGGTGATAATGGTACTCGTGTGT TTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAGCCGAAAGCCGCACCGAGTGTGACGCTGTTTCCGCCGA GCAGCGAAGAATTGCAGGCGAACAAAGCGACCCTGGTGTGCCTGATTAGCGACTTTTATCCGGGAGCCGTGA CAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGC AACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGC TGCCAGGTCACGCATGAGGGGAGCACCGTGGAAAAAACCGTTGCGCCGACTGAGGCC
SEQ ID ND:136	DNA Heavy Fab	CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCTGCGCGGC CTCCGGATTTACCTTTTCTTCTTATGGTATGTCTTGGGTGCGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGTG AGCAATATTTCTAATGATGGTCATTATACTTATTATGCTGATTCTGTTAAGGGTCGTTTTACCATTTCACGTGAT AATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCGCGC GTTTTCAGGCTTCTTATCTTGATATTATGGATTATTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCAGCGTC GACCAAAGGTCCAAGCGTGTTTCCGCTGGCTCCGAGCAGCAAAAGCACCAGCGGCGGCACGGCTGCCCTGG GCTGCCTGGTTAAAGATTATTTCCCGGAACCAGTCACCGTGAGCTGGAACAGCGGGGCGCTGACCAGCGGCG TGCATACCTTTCCGGCGGTGCTGCAAAGCAGCGGCCTGTATAGCCTGAGCAGCGTTGTGACCGTGCCGAGCA GCAGCTTAGGCACTCAGACCTATATTTGCAACGTGAACCATAAACCGAGCAACACCAAAGTGGATAAAAAAG TGGAACCGAAAAGC
SEQ ID ND:137	VL Germlined	SYELTQPLSVSVALGQTARITCGGDNIGSKYVHWYQQKPGQAPVLVIYNDSNRPSGIPERFSGSNSGNTATLTISRA QAGDEADYYCQAWGDNGTRVFGGGTKLTVL
SEQ ID NO:138	VH Germlined	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMSWVRQAPGKGLEWVSNISNDGHYTYYADSVKGRFTISRDNS KNTLYLQMNSLRAEDTAVYYCARFQASYLDIMDYWGQGTLVTVSS
SEQ ID NO:139	DNA VL Germlined	AGCTATGAACTGACCCAGCCGCTGAGTGTTAGCGTTGCGCTGGGTCAGACCGCGCGTATTACCTGCGGCGGT GATAACATTGGCAGCAAATATGTGCATTGGTATCAGCAGAAACCGGGCCAGGCGCCGGTGCTGGTGATTTAT AACGATAGCAACCGTCCGAGCGGCATTCCGGAACGTTTTAGCGGCAGCAACAGCGGCAATACCGCGACCCTG ACCATTAGCCGTGCGCAGGCGGGTGATGAAGCGGATTATTATTGCCAGGCGTGGGGCGATAATGGTACGCG TGTGTTTGGCGGTGGTACGAAGTTAACCGTTCTT
SEQ ID NO:140	DNA VH Germlined	GAGGTGCAATTGCTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCTGCGCGGC CTCCGGATTTACCTTTTCTTCTTATGGTATGTCTTGGGTGCGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGTG AGCAATATTTCTAATGATGGTCATTATACTTATTATGCTGATTCTGTTAAGGGTCGTTTTACCATTTCACGTGAT AATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCGCGC GTTTTCAGGCTTCTTATCTTGATATTATGGATTATTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
Biparatopic construction **MOR06475**		
SEQ ID NO:141	DNA VL-(GGGGS)3-VH scFv	Gatatcgttctgacccagagtccggcaaccctgagcctgagtccgggtgaacgtgccaccctgagctgtcgtgcaagccagtttattggtagccg ttatctggcatggtatcagcagaaaccgggtcaggcaccgcgtctgctgatttatggtgcaagcaatcgtgcaaccggtgttccggcacgttttag cggtagcggtagtggcaccgattttaccctgaccattagcagcctggaaccggaagattttgcaacctattattgccagcagtattatgattatcc gcagacctttggtcagggcaccaaggtggaaattaaaggtggtggtggtagcggtggtggtggctcaggtggtggcggtagtcaggttcaattg aaagaaagcggtccggcactggttaaaccgacccagaccctgaccctgacatgtaccttttagcggttttagcctgagcaatcgtggtggtggtgt tggttggattcgtcagcctccgggtaaagcactggaatggctggcatggattgattgggatgatgataaaagctatagcaccagcctgaaaacc cgtctgaccattagtaaagataccagcaaaaatcaggtggttctgaccatgaccaatatggatccggttgataccgccacctattattgtgcacgt atgcatctgccgctggttttgatagctggggtcagggtacactagttaccgttagcagc
SEQ ID NO:142	VL-(GGGGS)3-VH scFv	DIVLTQSPATLSLSPGERATLSCRASQFIGSRYLAWYQQKPGQAPRLLIYGASNRATGVPARFSGSGSGTDFTLTISSL EPEDFATYYCQQYYDYPQTFGQGTKVEIKGGGGSGGGGSGGGGSQVQLKESGPALVKPTQTLTLTCTFSGFSLSN RGGGVGWIRQPPGKALEWLAWIDWDDDKSYSTSLKTRLTISKDTSKNQVVLTMTNMDPVDTATYYCARMHLPL VFDSWGQGTLVTVSS

SEQ ID ND:143	DNA VL-(GGGGS)4-VH scFv	Gatatcgtgctgacacagagccctgccaccctgtctctgagccctggcgagagagccaccctgagctgccgggccagccagttcatcggctccc gctacctggcctggtatcagcagaagcccggacaggctcccagactgctgatctacggcgccagcaacagagctacggcgtgcccgccagatt ttctggcagcggcagcggcaccgacttcaccctgaccatcagcagcctggaacccgaggacttcgccacctactactgccagcagtactacgac tacccccagacctt cggccagggcaccaaggtggagatcaagggcggaggcggatccgggggtggcggaagtggaggcggaggaagcggag ggggcggaagccaggtgcaattgaaagagtccggccctgccctggtgaagcctacccagaccctgaccctgacatgcaccttcagcggcttcag cctgagcaacagaggcggcggagtgggctggatcagacagcctcccggcaaggccctggaatggctggcctggatcgactgggacgacgaca agagctacagcaccagcctgaaaacccggctgaccatctccaaggacaccagcaagaaccaggtggtgctcaccatgaccaacatggacccc gtggacaccgccacctattattgcgcccggatgcatctgcccctggtgttcgatagctgggggccagggaaccctggtgacagtgtccagc
SEQ ID ND:144	VL-(GGGGS)4-VH scFv	DIVLTQSPATLSLSPGERATLSCRASQFIGSRYLAWYQQKPGQAPRLLIYGASNRATGVPARFSGSGSGTDFTLTISSL EPEDFATYYCQQYYDYPQTFGQGTKVEIKGGGGSGGGGSGGGGSGGGGSGGGGSQVQLKESGPALVKPTQTLTLTCTFS GFSLSNRGGGVGWIRQPPGKALEWLAWIDWDDDKSYSTSLKTRLTISKDTSKNQVVLTMTNMDPVDTATYYCAR MHLPLVFDSWGQGTLVTVSS
SEQ ID NO:145	DNA VH-(GGGGS)3-VL scFv	Caggttcaattgaaagaaagcggtccggcactggttaaaccgacccagaccctgaccctgacatgtacctttagcggttttagcctgagcaatc gtggtggtggtgttggttggattcgtcagcctccgggtaaagcactggaatggctggcatggattgatttgggatgatgataaaagctatagcacc agcctgaaaacccgtctgaccattagcaaagataccagcaaaaatcaggttgttctgaccatgaccaatatggatccggttgataccgcaacct attattgtgcacgtatgcatctgccgctggtttttgatagctggggtcagggtacactagttaccgttagcagcggtggtggtggtagcggtggtg gcggttcaggtggtggtggcagtgatatcgttctgacccagagtccggcaaccctgagcctgagtccgggtgaacgtgccacccctgagctgtcgt gcaagccagtttattggtagccgttatctggcatggtatcagcagaaaccgggtcaggcaccgcgtctgctgatttatggtgcaagcaatcgtgc aaccggtgttccggcacgttttagcggtagcggtagtggcaccgattttaccctgaccattagtagcctggaaccggaagattttgccacctatta ttgccagcagtattatgattatccgcagacctttggtcagggcaccaaggtggaaattaaa
SEQ ID NO:146	VH-(GGGGS)3-VL scFv	QVQLKESGPALVKPTQTLTLTCTFSGFSLSNRGGGVGWIRQPPGKALEWLAWIDWDDDKSYSTSLKTRLTISKDTS KNQVVLTMTNMDPVDTATYYCARMHLPLVFDSWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIVLTQSPATLSLSP GERATLSCRASQFIGSRYLAWYQQKPGQAPRLLIYGASNRATGVPARFSGSGSGTDFTLTISSLEPEDFATYYCQQY YDYPQTFGQGTKVEIK
SEQ ID NO:147	DNA VH-(GGGGS)4-VL scFv	Caggttcaattgaaagaaagcggtccggcactggttaaaccgacccagaccctgaccctgacatgtacctttagcggttttagcctgagcaatc gtggtggtggtgttggttggattcgtcagcctccgggtaaagcactggaatggctggcatggattgatttgggatgatgataaaagctatagcacc agcctgaaaacccgtctgaccattagcaaagataccagcaaaaatcaggttgttctgaccatgaccaatatggatccggttgataccgcaacct attattgtgcacgtatgcatctgccgctggtttttgatagctggggtcagggtacactagttaccgttagcagcggtggtggtggtagcggtggtg gcggttcaggtggtggtggcagtggcggtggtggtagtgatatcgttctgacccagagtccggcaaccctgagcctgagtccgggtgaacgtgcc accctgagctgtcgtgcaagccagtttattggtagccgttatctggcatggtatcagcagaaaccgggtcaggcaccgcgtctgctgatttatggt gcaagcaatcgtgcaaccggtgttccggcacgttttagcggtagcggtagtggcaccgattttaccctgaccattagtagcctggaaccggaaga ttttgccacctattattgccagcagtattatgattatccgcagacctttggtcagggcaccaaggtggaaattaaa
SEQ ID NO:148	VH-(GGGGS)4-VL scFv	QVQLKESGPALVKPTQTLTLTCTFSGFSLSNRGGGVGWIRQPPGKALEWLAWIDWDDDKSYSTSLKTRLTISKDTS KNQVVLTMTNMDPVDTATYYCARMHLPLVFDSWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIVLTQSPA TLSLSPGERATLSCRASQFIGSRYLAWYQQKPGQAPRLLIYGASNRATGVPARFSGSGSGTDFTLTISSLEPEDFATYY CQQYYDYPQTFGQGTKVEIK
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SEQ ID NO:150	VL-(GGGGS)3-VH scFv	DIELTQPPSVSVAPGQTARISCSGDSLRNKVYWYQQKPGQAPVLVIYKNNRPSGIPERFSGSNSGNTATLTISGTQA EDEADYYCQSYDGQKSLVFGGGTKLTVLGGGGSGGGGSGGGGSQVQLVESGGGLVQPGGSLRLSCAASGFTFSD YVINWVRQAPGKGLEWVSGISWSGVNTHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARLGATANN IRYKFMDVWGQGTLVTVSS

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SEQ ID ND:151	DNA VL-(GGGGS)4-VH scFv	Gatatcgaactgacccagcctccgagcgttagcgttgcaccgggtcagaccgcacgtattagctgtagcggtgatagcctgcgtaataaagttta ttggtatcagcagaaaccgggtcaggcaccggttctggttatttataaaaataatcgtccgagcggtattccggaacgttttagcggtagcaata gcggtaataccgcaaccctgaccattagcggcacccaggcagaagatgaagcagattattattgccagagctatgatggtcagaaaagcctgg tttttggtggtggcaccaagcttaccgttctgggtggtggtggtagcggtggtggtggctcaggtggtggcggttctggtggcggtggttcacaggt tcaattggttgaaagtggtggtggtctggttcagcctggtggtagcctgcgtctgagctgtgcagcaagcggttttacctttagcgattatgtgatt aattgggttcgccaggcaccgggtaaaggtctggaatgggttagcggtattagctggtcaggtgttaatacccattatgcagatagcgtgaaag gtcgttttaccattagccgtgataatagcaaaaataccctgtatctgcagatgaatagcctgcgtgcagaagataccgcagtttattattgtgcac gtctgggtgcaaccgcaaataatattcgctataaatttatggatgtgtggggtcagggtacactagttaccgttagcagc
SEQ ID ND:152	VL-(GGGGS)4-VH scFv	DIELTQPPSVSVAPGQTARISCSGDSLRNKVYWYQQKPGQAPVLVIYKNNRPSGIPERFSGSNSGNTATLTISGTQA EDEADYYCQSYDGQKSLVFGGGTKLTVLGGGGSGGGG5GGGGSGGGGSQVQLVESGGGLVQPGGSLRLSCAAS GFTFSDYVINWVRQAPGKGLEWVSGISWSGVNTHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARL GATANNIRYKFMDVWGQGTLVTVSS
SEQ ID NO:153	DNA VH-(GGGGS)3-VL scFv	Caggttcaattggttgaaagcggtggtggtctggttcagcctggtggtagcctgcgtctgagctgtgcagcaagcggttttacctttagcgattat gtgattaattgggttcgtcaggcaccgggtaaaggtctggaatgggttagcggtattagctggtcaggtgttaatacccattatgcagatagcgtg aaaggtcgttttaccattagccgtgataatagcaaaaataccctgtatctgcagatgaatagcctgcgtgcagaagataccgcagtttattattgt gcacgtctgggtgcaaccgcaaataatattcgctataaatttatggatgtgtggggtcagggtacactagttaccgttagcagtggtggtggtggt agcggtggtggcggatctggtggcggtggcagtgatatcgaactgacccagcctccgagcgttagcgttgcaccgggtcagaccgcacgtatta gctgtagcggtgatagtctgcgtaataaagtttattggtatcagcagaaaccgggtcaggctccggttctggttatttataaaaataatcgtccga gcggtattccggaacgttttagcggtagcaatagcggtaataccgcaaccctgaccattagcggcacccaggcagaagatgaagccgattatta ttgtcagagctatgatggtcagaaaagcctggtttttggtggtggcaccaagcttaccgttctg
SEQ ID ND:154	VH-(GGGGS)3-VL scFv	QVQLVESGGGLVQPGGSLRLSCAASGFTFSDYVINWVRQAPGKGLEWVSGISWSGVNTHYADSVKGRFTISRDN 5KNTLYLQMN5LRAEDTAVYYCARLGATANNIRYKFMDVWGQGTLVTVSSGGGG5GGGG5GGGGSDIELTQPPS VSVAPGQTARISCSGDSLRNKVYWYQQKPGQAPVLVIYKNNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYC QSYDGQKSLVFGGGTKLTVL
SEQ ID NO:155	DNA VH-(GGGGS)4-VL scFv	Caggttcaattggttgaaagcggtggtggtctggttcagcctggtggtagcctgcgtctgagctgtgcagcaagcggttttacctttagcgattat gtgattaattgggttcgtcaggcaccgggtaaaggtctggaatgggttagcggtattagctggtcaggtgttaatacccattatgcagatagcgtg aaaggtcgttttaccattagccgtgataatagcaaaaataccctgtatctgcagatgaatagcctgcgtgcagaagataccgcagtttattattgt gcacgtctgggtgcaaccgcaaataatattcgctataaatttatggatgtgtggggtcagggtacactagttaccgttagcagtggtggtggtggt agcggtggtggcggatctggtggcggtggcagtgatatcgaactgacccagcctccgagcgttagcgttgcaccgggtc agaccgcacgtattagctgtagcggtgatagtctgcgtaataaagtttattggtatcagcagaaaccgggtcaggctccggttctggttatttata aaaataatcgtccgagcggtattccggaacgttttagcggtagcaatagcggtaataccgcaaccctgaccattagcggcacccaggcagaag atgaagccgattattattgtcagagctatgatggtcagaaaagcctggtttttggtggtggcaccaagcttaccgttctg
SEQ ID NO:156	VH-(GGGGS)4-VL scFv	QVQLVESGGGLVQPGGSLRLSCAASGFTFSDYVINWVRQAPGKGLEWVSGISW5GVNTHYADSVKGRFTISRDN SKNTLYLQMN5LRAEDTAVYYCARLGATANNIRYKFMDVWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIE LTQPPSVSVAPGQTARISCSGDSLRNKVYWYQQKPGQAPVLVIYKNNRPSGIPERFSGSN5GNTATLTISGTQAED EADYYCQSYDGQKSLVFGGGTKLTVL
MOR08545		
SEQ ID NO:157	DNA VL-(GGGGS)3-VH scFv	Gatatcgaactgacccagcctccgagcgttagcgttgcaccgggtcagaccgcacgtattagctgtagcggtgataatattggcagcaaatatg tgcattggtatcagcagaaaccgggtcaggcaccggttctggttatttatggtgatagcaatcgtccgagcggtattccggaacgttttagcggta gcaatagcggtaataccgcaaccctgaccattagcggcacccaggcagaagatgaagcagattattattgtacccgtaccagcaccccgattag cggtgtttttggtggtggcaccaagcttaccgttctgggtggtggtggtggtagcggtggtggtggctcaggtggtggtggttcacaggttcaattggtt gaaagtggtggtggtctggttcagcctggtggtagcctgcgtctgagctgtgcagcaagcggttttacctttagcgttaatggtatgcattgggttc gccaggcaccgggtaaaggtctggaatgggttagcgttattgatggtatgggccatacctattatgccgatagcgttaaaggtcgttttaccatta gccgtgataatagcaaaaatacccgtatctgcagatgaatagcctgcgtgcagaagatgaccgcagtttattattgcgcacgctatgattatatta aatatggtgcctttgatccgtggggtcagggtacactagttaccgttagcagc
SEQ ID NO:158	VL-(GGGGS)3-VH scFv	DIELTQPPSVSVAPGQTARISCSGDNIGSKYVHWYQQKPGQAPVLVIYGDSNRPSGIPERFSGSNSGNTATLTI5GT QAEDEADYYCTRTSTPISGVFGGGTKLTVLGGGGSGGGGSGGGG5QVQLVE5GGGLVQPGGSLRLSCAASGFTFS VNGMHWVRQAPGKGLEWVSVIDGMGHTYYADSVKGRFTI5RDNSKNTLYLQMNSLRAEDTAVYYCARYDYIKY GAFDPWGQGTLVTVSS

SEQ ID NO:159	DNA VL-(GGGGS)4-VH scFv	Gatatcgaactgacccagcctccgagcgttagcgttgcaccgggtcagaccgcacgtattagctgtagcggtgataatattggcagcaaatatg tgcattggtatcagcagaaaccgggtcaggcaccggttctggttatttatggtgatagcaatcgtccgagcggtattccggaacgttttagcggta gcaatagcggtaataccgcaaccctgaccattagcggcacccaggcagaagatgaagcagattattattgtacccgtaccagcaccccgattag cggtgtttttggtggtggcaccaagcttaccgttctgggtggtggtggtagcggtggtggtggctcaggtggtggcggttctggtggcggtggttca caggttcaattggttgaaagtggtggtggtctggttcagcctggtggtagcctgcgtctgagctgtgcagcaagcggttttaccttagcgttaatg gtatgcattgggttcgccaggcaccgggtaaaggtctggaatgggttagcgttattgatggtatgggccatacctattatgccgatagcgttaaa ggtcgttttaccattagccgtgataatagcaaaaataccctgtatctgcagatgaatagcctgcgtgcagaagatacccgcagtttattattgcgca cgctatgattatattaaatatggtgcctttgatccgtggggtcagggtacactagttaccgttagcagtggtggtggtggtagcggtggtggcgga tctggtggcggtggttcagatatcgaactgacccagcctccgagcgttagcgttgcaccgggtcagaccgcacgtattagctgtagcggtgataa tattggcagcaaatatgtgcattggtatcagcagaaaccgggtcaggctccggttctggttatttatggtgatagcaatcgtccgagcggtattcc ggaacgttttagcggtagcaatagcggtaataccgcaaccctgaccattagcggcacccaggcagaagatgaagccgattattattgcacccgt accagcaccccgattagcggtgtttttggtggtggcaccaagcttaccgttctg
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SEQ ID ND:162	VH-(GGGGS)3-VL scFv	QVQLVESGGGLVQPGGSLRLSCAASGFTFSVNGMHWVRQAPGKGLEWVSVIDGMGHTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARYDYIKYGAFDPWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIELTQPPSVSVA PGQTARISCSGDNIGSKYVHWYQQKPGQAPVLVIYGDSNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCTR TSTPISGVFGGGTKLTVL
SEQ ID NO:163	DNA VH-(GGGGS)4-VL scFv	Caggttcaattggttgaaagcggtggtggtctggttcagcctggtggtagcctgcgtctgagctgtgcagcaagcggttttaccttagcgttaat ggtatgcattgggttcgtcaggcaccgggtaaaggtctggaatgggttagcgttattgatggtatgggccatacctattatgccgatagcgttaaa ggtcgttttaccattagccgtgataatagcaaaaataccctgtatctgcagatgaatagcctgcgtgcagaagatacccgcagtttattattgtgcc cgttatgattatattaaatatggtgcctttgatccgtggggtcagggtacactagttaccgttagcagtggtggtggtggtagcggtggtggcgga tctggtggcggtggttcaggtggtggtggcagtgatatcgaactgacccagcctccgagcgttagcgttgcaccgggtcagaccgcacgtattag ctgtagcggtgataatattggcagcaaatatgtgcattggtatcagcagaaaccgggtcaggctccggttctggttatttatggtgatagcaatcg tccgagcggtattccggaacgttttagcggtagcaatagcggtaataccgcaaccctgaccattagcggcacccaggcagaagatgaagccga ttattattgcacccgtaccagcaccccgattagcggtgtttttggtggtggcaccaagcttaccgttctg
SEQ ID ND:164	VH-(GGGGS)4-VL scFv	QVQLVESGGGLVQPGGSLRLSCAASGFTFSVNGMHWVRQAPGKGLEWVSVIDGMGHTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARYDYIKYGAFDPWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIELTQPP SVSVAPGQTARISCSGDNIGSKYVHWYQQKPGQAPVLVIYGDSNRPSGIPERFSGSNSGNTATLTISGTQAEDEAD YYCTRTSTPISGVFGGGTKLTVL
Biparatopic MOR08168/ MOR06475		
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		cagcagaagcccggacaggctcccagactgctgatctacggcgccagcaacagagctaccggcgtgcccgccagattttctggcagcggcagc ggcaccgacttcaccctgaccatcagcagcctggaacccgaggacttcgccacctactactgccagcagtactacgactacccccagaccttcg gccagggcaccaaggtggagatcaaggcggaggcggatccgggggtggcggaagtggaggcggaggaagcggaggggcggaagccag gtgcaattgaaagagtccggccctgccctggtgaagcctacccagaccctgaccctgacatcgaccttcagcggcttcagcctgagcaacagag gcggcggagtgggctggatcagacagcctcccggcaaggccctggaatggctggcctggatcgactgggacgacgacaagagctacagcacc agcctgaaaacccggctgaccatctccaaggacaccagcaagaaccaggtggtgctcaccatgaccaacatggacccccgtggacaccgccac ctattattgcgcccggatgcatctgcccctggtgttcgatagctggggccagggaaccctggtgacagtgtccagc
SEQ ID NO:166	Heavy MDR08168 hIgG1 LALA MDR06475 scFv	QVQLVESGGGLVQPGGSLRLSCAASGFTFSDYVINWVRQAPGKGLEWVSGISWSGVNTHYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARLGATANNIRYKFMDVWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GKGGSGGSDIVLTQSPATLSLSPGERATLSCRASQFIGSRYLAWYQQKPGQAPRLLIYGASNRATGVPARFSGSGSG TDFTLTISSLEPEDFATYYCQQYYDYPQTFGQGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLKESGPALVKPTQ TLTLTCTFSGFSLSNRGGGVGWIRQPPGKALEWLAWIDWDDDKSYSTSLKTRLTISKDTSKNQVVLTMTNMDPV DTATYYCARMHLPLVFDSWGQGTLVTVSS
SEQ ID NO:167	VL MDR08168	DIELTQPPSVSVAPGQTARISCSGDSLRNKVYWYQQKPGQAPVLVIYKNNRPSGIPERFSGSNSGNTATLTISGTQA EDEADYYCQSYDGQKSLVFGGGTKLTVL
SEQ ID ND:168	DNA VL MOR08168	GACATCGAGCTGACCCAGCCCCCTTCTGTGTCTGTGGCCCCTGGCCAGACCGCCAGAATCAGCTGCAGCGGC GACAGCCTGCGGAACAAGGTGTACTGGTATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTACAAG AACAACCGGCCCAGCGGCATCCCTGAGCGGTTCAGCGGCAGCAACAGCGGCAATACCGCCACCCTGACCATC AGCGGCACCCAGGCCGAAGATGAGGCCGACTACTACTGCCAGAGCTACGACGGCCAGAAAAGCCTGGTGTT CGGCGGAGGCACCAAGCTTACCGTGCTG
SEQ ID NO:169	DNA Light lambda MOR08168	Gacatcgagctgacccagccccttctgtgtctgtggccccctggccagaccgccagaatcagctgcagcggcgacagcctgcggaacaaggtg tactggtatcagcagaagcccggccaggctcccgtgctggtgatctacaagaacaaccggcccagcggcatccctgagcggttcagcggcagc aacagcggcaataccgccaccctgaccatcagcggcacccaggccgaagatgaggccgactactactgccagagctacgacggccagaaaag cctggtgttcggcggaggcaccaagcttaccgtgctgggccagcccaaagccgcccctagcgtgaccctgttcccccccagcagcgaggaactg caggccaacaaggccaccctggtctgcctgatcagcgacttctaccctggcgccgtgaccgtggcctggaaggccgacagcagccccgtgaag gccggcgtggagacaaccaccccagcaagcagagcaacaacaagtacgccgccagcagctacctgagcctgaccccgagcagtggaaga gccacagaagctacagctgccaggtcacccacgagggcagcaccgtggagaaaaccgtggcccccaccgagtgcagc
SEQ ID NO:170	Light lambda MOR08168	DIELTQPPSVSVAPGQTARISCSGDSLRNKVYWYQQKPGQAPVLVIYKNNRPSGIPERFSGSNSGNTATLTISGTQA EDEADYYCQSYDGQKSLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSP VKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
SEQ ID NO:171	Heavy MOR08168 hIgG1 LALA (w/o K) MOR06475 scFv	QVQLVESGGGLVQPGGSLRLSCAASGFTFSDYVINWVRQAPGKGLEWVSGISWSGVNTHYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARLGATANNIRYKFMDVWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GGGSGGSDIVLTQSPATLSLSPGERATLSCRASQFIGSRYLAWYQQKPGQAPRLLIYGASNRATGVPARFSGSGSGT DFTLTISSLEPEDFATYYCQQYYDYPQTFGQGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLKESGPALVKPTQT LTLTCTFSGFSLSNRGGGVGWIRQPPGKALEWLAWIDWDDDKSYSTSLKTRLTISKDTSKNQVVLTMTNMDPVD TATYYCARMHLPLVFDSWGQGTLVTVSS
SEQ ID NO:172	DNA Heavy MDR08168 hIgG1 LALA (w/o K) MOR06475 scFv	CAGGTGCAATTGGTCGAGTCTGGCGGAGGACTGGTGCAGCCTGGTGGCAGCCTGAGACTGAGCTGCGCCGC CAGCGGCTTCACCTTCAGCGACTACGTGATCAACTGGGTGCGACAGGCCCCTGGAAAGGGCCTGGAATGGGT GTCCGGCATCTCTTGGTCTGGCGTGAACACCCACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCCG GGACAACAGCAAGAACACCCTGTACCTGCAGATGAACAGCCTGAGAGCCGAGGACACCGCCGTGTACTACTG TGCCAGACTGGGCGCCACCGCCAACAACATCCGGTACAAGTTCATGGACGTGTGGGGCCAGGGCACACTGGT GACCGTCAGCTCAGCTAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGG CGGCACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCCTGGAACAGCGG AGCCCTGACCTCCGGCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGTCCAGCGTG

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		GTGACAGTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGCAACACC AAGGTGGACAAGAGAGTGGAGCCCAAGAGCTGCGACAAGACCCACACCTGCCCCCCCTGCCCAGCCCCAGA GGCAGCGGGCGGACCCTCCGTGTTCCTGTTCCCCCCCAAGCCCAAGGACACCCTGATGATCAGCAGGACCCCC GAGGTGACCTGCGTGGTGGTGGACGTGAGCCACGAGGACCCAGAGGTGAAGTTCAACTGGTACGTGGACGG CGTGGAGGTGCACAACGCCAAGACCAAGCCCAGAGAGGAGCAGTACAACAGCACCTACAGGGTGGTGTCCG TGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAATACAAGTGCAAGGTCTCCAACAAGGCCCTGC CAGCCCCCATCGAAAAGACCATCAGCAAGGCCAAGGGCCAGCCACGGGAGCCCCAGGTGTACACCCTGCCCC CCTCCCGGGAGGAGATGACCAAGAACCAGGTGTCCCTGACCTGTCTGGTGAAGGGCTTCTACCCCAGCGACA TCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCGAGAACAACTACAAGACCACCCCCCCAGTGCTGGACAGC GACGGCAGCTTCTTCCTGTACAGCAAGCTGACCGTGGACAAGTCCAGGTGGCAGCAGGGCAACGTGTTCAGC TGCAGCGTGATGCACGAAGCGCTGCACAACCACTACACCCAGAAGAGCCTGAGCCTGTCCCCCGGCGGCGGC TCCGGCGGAAGCGATATCGTGCTGACACAGAGCCCTGCCACCCTGTCTCTGAGCCCTGGCGAGAGAGCCACC CTGAGCTGCCGGGCCAGCCAGTTCATCGGCTCCCGCTACCTGGCCTGGTATCAGCAGAAGCCCGGACAGGCT CCCAGACTGCTGATCTACGGCGCCAGCAACAGAGCTACCGGCGTGCCCGCCAGATTTTCTGGCAGCGGCAGC GGCACCGACTTCACCCTGACCATCAGCAGCCTGGAACCCGAGGACTTCGCCACCTACTACTGCCAGCAGTACT ACGACTACCCCCAGACCTTCGGCCAGGGCACCAAGGTGGAGATCAAGGGCGGAGGCGGATCCGGGGGTGG CGGAAGTGGAGGCGGAGGAAGCGGAGGGGGCGGAAGCCAGGTGCAATTGAAAGAGTCCGGCCCTGCCCTG GTGAAGCCTACCCAGACCCTGACCCTGACATGCACCTTCAGCGGCTTCAGCCTGAGCAACAGAGGCGGCGGA GTGGGCTGGATCAGACAGCCTCCCGGCAAGGCCCTGGAATGGCTGGCCTGGATCGACTGGGACGACGACAA GAGCTACAGCACCAGCCTGAAAACCCGGCTGACCATCTCCAAGGACACCAGCAAGAACCAGGTGGTGCTCAC CATGACCAACATGGACCCCGTGGACACCGCCACCTATTATTGCGCCCGGATGCATCTGCCCCTGGTGTTCGAT AGCTGGGGCCAGGGAACCCTGGTGACAGTGTCCAGC
SEQ ID ND:173	Heavy MDR08168 hIgG1 LALA MDR06475 scFv (DP to DA)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSDYVINWVRQAPGKGLEWVSGISWSGVNTHYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARLGATANNIRYKFMDVWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GKGGSGGSDIVLTQSPATLSLSPGERATLSCRASQFIGSRYLAWYQQKPGQAPRLLIYGASNRATGVPARFSGSGSG TDFTLTISSLEPEDFATYYCQQYYDYPQTFGQGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLKESGPALVKPTQ TLTLTCTFSGFSLSNRGGGVGWIRQPPGKALEWLAWIDWDDDKSYSTSLKTRLTISKDTSKNQVVLTMTNMDAV DTATYYCARMHLPLVFDSWGQGTLVTVSS
SEQ ID ND:174	DNA Heavy MOR08168 hIgG1 LALA MDR06475 scFv (DP to DA)	CAGGTGCAATTGGTCGAGTCTGGCGGAGGACTGGTGCAGCCTGGTGGCAGCCTGAGACTGAGCTGCGCCGC CAGCGGCTTCACCTTCAGCGACTACGTGATCAACTGGGTGCGACAGGCCCCTGGAAAGGGCCTGGAATGGGT GTCCGGCATCTCTTGGTCTGGCGTGAACACCCACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCCG GGACAACAGCAAGAACACCCTGTACCTGCAGATGAACAGCCTGAGAGCCGAGGACACCGCCGTGTACTACTG TGCCAGACTGGGCGCCACCGCCAACAACATCCGGTACAAGTTCATGGACGTGTGGGGCCAGGGCACACTGGT GACCGTCAGCTCAGCTAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGG CGGCACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCCTGGAACAGCGG AGCCCTGACCTCCGGCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGTCCAGCGTG GTGACAGTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGCAACACC AAGGTGGACAAGAGAGTGGAGCCCAAGAGCTGCGACAAGACCCACACCTGCCCCCCCTGCCCAGCCCCAGA GGCAGCGGGCGGACCCTCCGTGTTCCTGTTCCCCCCCAAGCCCAAGGACACCCTGATGATCAGCAGGACCCCC GAGGTGACCTGCGTGGTGGTGGACGTGAGCCACGAGGACCCAGAGGTGAAGTTCAACTGGTACGTGGACGG CGTGGAGGTGCACAACGCCAAGACCAAGCCCAGAGAGGAGCAGTACAACAGCACCTACAGGGTGGTGTCCG TGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAATACAAGTGCAAGGTCTCCAACAAGGCCCTGC CAGCCCCCATCGAAAAGACCATCAGCAAGGCCAAGGGCCAGCCACGGGAGCCCCAGGTGTACACCCTGCCCC CCTCCCGGGAGGAGATGACCAAGAACCAGGTGTCCCTGACCTGTCTGGTGAAGGGCTTCTACCCCAGCGACA TCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCGAGAACAACTACAAGACCACCCCCCCAGTGCTGGACAGC GACGGCAGCTTCTTCCTGTACAGCAAGCTGACCGTGGACAAGTCCAGGTGGCAGCAGGGCAACGTGTTCAGC TGCAGCGTGATGCACGAAGCGCTGCACAACCACTACACCCAGAAGAGCCTGAGCCTGTCCCCCGGCAAGGGC GGCTCCGGCGGAAGCGATATCGTGCTGACACAGAGCCCTGCCACCCTGTCTCTGAGCCCTGGCGAGAGAGCC ACCCTGAGCTGCCGGGCCAGCCAGTTCATCGGCTCCCGCTACCTGGCCTGGTATCAGCAGAAGCCCGGACAG GCTCCCAGACTGCTGATCTACGGCGCCAGCAACAGAGCTACCGGCGTGCCCGCCAGATTTTCTGGCAGCGGC AGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGGAACCCGAGGACTTCGCCACCTACTACTGCCAGCAGT ACTACGACTACCCCCAGACCTTCGGCCAGGGCACCAAGGTGGAGATCAAGGGCGGAGGCGGATCCGGGGGT GGCGGAAGTGGAGGCGGAGGAAGCGGAGGGGGCGGAAGCCAGGTGCAATTGAAAGAGTCCGGCCCTGCC CTGGTGAAGCCTACCCAGACCCTGACCCTGACATGCACCTTCAGCGGCTTCAGCCTGAGCAACAGAGGCGGC GGAGTGGGCTGGATCAGACAGCCTCCCGGCAAGGCCCTGGAATGGCTGGCCTGGATCGACTGGGACGACGA CAAGAGCTACAGCACCAGCCTGAAAACCCGGCTGACCATCTCCAAGGACACCAGCAAGAACCAGGTGGTGCT

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		CACCATGACCAACATGGACGCCGTGGACACCGCCACCTATTATTGCGCCCGGATGCATCTGCCCCTGGTGTTC GATAGCTGGGGCCAGGGAACCCTGGTGACAGTGTCCAGC
SEQ ID NO:175	Heavy MOR08168 hIgG1 LALA MOR06475 scFv (DP to TA)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSDYVINWVRQAPGKGLEWVSGISWSGVNTHYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARLGATANNIRYKFMDVWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GKGGSGGSDIVLTQSPATLSLSPGERATLSCRASQFIGSRYLAWYQQKPGQAPRLLIYGASNRATGVPARFSGSGSG TDFTLTISSLEPEDFATYYCQQYYDYPQTFGQGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLKESGPALVKPTQ TLTLTCTFSGFSLSNRGGGVGWIRQPPGKALEWLAWIDWDDDKSYSTSLKTRLTISKDTSKNQVVLTMTNMTAVD TATYYCARMHLPLVFDSWGQGTLVTVSS
SEQ ID NO:176	DNA Heavy MOR08168 hIgG1 LALA MOR06475 scFv (DP to TA)	CAGGTGCAATTGGTCGAGTCTGGCGGAGGACTGGTGCAGCCTGGTGGCAGCCTGAGACTGAGCTGCGCCGC CAGCGGCTTCACCTTCAGCGACTACGTGATCAACTGGGTGCGACAGGCCCCTGGAAAGGGCCTGGAATGGGT GTCCGGCATCTCTTGGTCTGGCGTGAACACCCACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCCG GGACAACAGCAAGAACACCCTGTACCTGCAGATGAACAGCCTGAGAGCCGAGGACACCGCCGTGTACTACTG TGCCAGACTGGGCGCCACCGCCAACAACATCCGGTACAAGTTCATGGACGTGTGGGGCCAGGGCACACTGGT GACCGTCAGCTCAGCTAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGG CGGCACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCCTGGAACAGCGG AGCCCTGACCTCCGGCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGTCCAGCGTG GTGACAGTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGCAACACC AAGGTGGACAAGAGAGTGGAGCCCAAGAGCTGCGACAAGACCCACACCTGCCCCCCCTGCCCAGCCCCAGA GGCAGCGGGCGGACCCTCCGTGTTCCTGTTCCCCCCCAAGCCCAAGGACACCCTGATGATCAGCAGGACCCCC GAGGTGACCTGCGTGGTGGTGGACGTGAGCCACGAGGACCCAGAGGTGAAGTTCAACTGGTACGTGGACGG CGTGGAGGTGCACAACGCCAAGACCAAGCCCAGAGAGGAGCAGTACAACAGCACCTACAGGGTGGTGTCCG TGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAATACAAGTGCAAGGTCTCCAACAAGGCCCTGC CAGCCCCCATCGAAAAGACCATCAGCAAGGCCAAGGGCCAGCCACGGGAGCCCCAGGTGTACACCCTGCCCC CCTCCCGGGAGGAGATGACCAAGAACCAGGTGTCCCTGACCTGTCTGGTGAAGGGCTTCTACCCCAGCGACA TCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCGAGAACAACTACAAGACCACCCCCCCAGTGCTGGACAGC GACGGCAGCTTCTTCCTGTACAGCAAGCTGACCGTGGACAAGTCCAGGTGGCAGCAGGGCAACGTGTTCAGC TGCAGCGTGATGCACGAAGCGCTGCACAACCACTACACCCAGAAGAGCCTGAGCCTGTCCCCCGGCAAGGGC GGCTCCGGCGGAAGCGATATCGTGCTGACACAGAGCCCTGCCACCCTGTCTCTGAGCCCTGGCGAGAGAGCC ACCCTGAGCTGCCGGGCCAGCCAGTTCATCGGCTCCCGCTACCTGGCCTGGTATCAGCAGAAGCCCGGACAG GCTCCCAGACTGCTGATCTACGGCGCCAGCAACAGAGCTACCGGCGTGCCCGCCAGATTTTCTGGCAGCGGC AGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGGAACCCGAGGACTTCGCCACCTACTACTGCCAGCAGT ACTACGACTACCCCCAGACCTTCGGCCAGGGCACCAAGGTGGAGATCAAGGGCGGAGGCGGATCCGGGGGT GGCGGAAGTGGAGGCGGAGGAAGCGGAGGGGGCGGAAGCCAGGTGCAATTGAAAGAGTCCGGCCCTGCC CTGGTGAAGCCTACCCAGACCCTGACCCTGACATGCACCTTCAGCGGCTTCAGCCTGAGCAACAGAGGCGGC GGAGTGGGCTGGATCAGACAGCCTCCCGGCAAGGCCCTGGAATGGCTGGCCTGGATCGACTGGGACGACGA CAAGAGCTACAGCACCAGCCTGAAAACCCGGCTGACCATCTCCAAGGACACCAGCAAGAACCAGGTGGTGCT CACCATGACCAACATGACCGCCGTGGACACCGCCACCTATTATTGCGCCCGGATGCATCTGCCCCTGGTGTTC GATAGCTGGGGCCAGGGAACCCTGGTGACAGTGTCCAGC
SEQ ID NO:177	Light MOR06475 scFv MOR08168 lambda	DIVLTQSPATLSLSPGERATLSCRASQFIGSRYLAWYQQKPGQAPRLLIYGASNRATGVPARFSGSGSGTDFTLTISSL EPEDFATYYCQQYYDYPQTFGQGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLKESGPALVKPTQTLTLTCTFS GFSLSNRGGGVGWIRQPPGKALEWLAWIDWDDDKSYSTSLKTRLTISKDTSKNQVVLTMTNMDPVDTATYYCAR MHLPLVFDSWGQGTLVTVSSGGSGGSDIELTQPPSVSVAPGQTARISCSGDSLRNKVYWYQQKPGQAPVLVIYKN NRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYDGQKSLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQA NKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVE KTVAPTECS
SEQ ID NO:178	DNA Light MOR06475 scFv MOR08168 lambda	GATATCGTGCTGACACAGAGCCCTGCCACCCTGTCTCTGAGCCCTGGCGAGAGAGCCACCCTGAGCTGCCGG GCCAGCCAGTTCATCGGCTCCCGCTACCTGGCCTGGTATCAGCAGAAGCCCGGACAGGCTCCCAGACTGCTG ATCTACGGCGCCAGCAACAGAGCTACCGGCGTGCCCGCCAGATTTTCTGGCAGCGGCAGCGGCACCGACTTC ACCCTGACCATCAGCAGCCTGGAACCCGAGGACTTCGCCACCTACTACTGCCAGCAGTACTACGACTACCCCC AGACCTTCGGCCAGGGCACCAAGGTGGAGATCAAGGGCGGAGGCGGATCCGGGGGTGGCGGAAGTGGAG GCGGAGGAAGCGGAGGGGGCGGAAGCCAGGTGCAATTGAAAGAGTCCGGCCCTGCCCTGGTGAAGCCTAC CCAGACCCTGACCCTGACATGCACCTTCAGCGGCTTCAGCCTGAGCAACAGAGGCGGCGGAGTGGGCTGGAT CAGACAGCCTCCCGGCAAGGCCCTGGAATGGCTGGCCTGGATCGACTGGGACGACGACAAGAGCTACAGCA CCAGCCTGAAAACCCGGCTGACCATCTCCAAGGACACCAGCAAGAACCAGGTGGTGCTCACCATGACCAACA

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		TGGACCCCGTGGACACCGCCACCTATTATTGCGCCCGGATGCATCTGCCCCTGGTGTTCGATAGCTGGGGCCA GGGAACCCTGGTGACAGTGTCCAGCGGCGGCTCCGGCGGAAGCGACATCGAGCTGACCCAGCCCCCTTCTGT GTCTGTGGCGCCCGGGCAGACCGCCAGAATCAGCTGCAGCGGCGACAGCCTGCGGAACAAGGTGTACTGGT ATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTACAAGAACAACCGGCCCAGCGGCATCCCTGAGC GGTTCAGCGGCAGCAACAGCGGCAATACCGCCACCCTGACCATCAGCGGCACCCAGGCCGAAGATGAGGCC GACTACTACTGCCAGAGCTACGACGGCCAGAAAAGCCTGGTGTTCGGCGGAGGCACCAAGCTTACCGTGCTG GGCCAGCCCAAAGCCGCCCCTAGCGTGACCCTGTTCCCCCCCAGCAGCGAGGAACTGCAGGCCAACAAGGCC ACCCTGGTCTGCCTGATCAGCGACTTCTACCCTGGCGCCGTGACCGTGGCCTGGAAGGCCGACAGCAGCCCC GTGAAGGCCGGCGTGGAGACAACCACCCCCAGCAAGCAGAGCAACAACAAGTACGCCGCCAGCAGCTACCT GAGCCTGACCCCCGAGCAGTGGAAGAGCCACAGAAGCTACAGCTGCCAGGTCACCCACGAGGGCAGCACCG TGGAGAAAACCGTGGCCCCCACCGAGTGCAGC
SEQ ID NO:179	VH MDR08168	QVQLVESGGGLVQPGGSLRLSCAASGFTFSDYVINWVRQAPGKGLEWVSGISWSGVNTHYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARLGATANNIRYKFMDVWGQGTLVTVSS
SEQ ID ND:180	DNA VH MDR08168	Caggtgcaattggtcgagtctggcggaggactggtgcagcctggtggcagcctgagactgagctgcgccgccagcggcttcaccttcagcgact acgtgatcaactgggtgcgacaggccccttggaaagggcctggaatgggtgtccggcatctcttggtctggcgtgaacacccactacgccgacag cgtgaagggccggttcaccatcagccgggacaacagcaagaacaccctgtacctgcagatgaacagcctgagagccgaggacaccgccgtgt actactgtgccagactgggcgccaccgccaacaacatccggtacaagttcatggacgtgtggggccagggcacactggtgaccgtcagctca
SEQ ID ND:181	Heavy MDR08168 hIgG1 LALA	QVQLVESGGGLVQPGGSLRLSCAASGFTFSDYVINWVRQAPGKGLEWVSGISWSGVNTHYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARLGATANNIRYKFMDVWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK
SEQ ID ND:182	DNA Heavy MDR08168 hIgG1 LALA	CAGGTGCAATTGGTCGAGTCTGGCGGAGGACTGGTGCAGCCTGGTGGCAGCCTGAGACTGAGCTGCGCCGC CAGCGGCTTCACCTTCAGCGACTACGTGATCAACTGGGTGCGACAGGCCCCTGGAAAGGGCCTGGAATGGGT GTCCGGCATCTCTTGGTCTGGCGTGAACACCCACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCCG GGACAACAGCAAGAACACCCTGTACCTGCAGATGAACAGCCTGAGAGCCGAGGACACCGCCGTGTACTACTG TGCCAGACTGGGCGCCACCGCCAACAACATCCGGTACAAGTTCATGGACGTGTGGGGCCAGGGCACACTGGT GACCGTCAGCTCAGCTAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGG CGGCACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCCTGGAACAGCGG AGCCCTGACCTCCGGCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGTCCAGCGTG GTGACAGTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGCAACACC AAGGTGGACAAGAGAGTGGAGCCCAAGAGCTGCGACAAGACCCACACCTGCCCCCCCTGCCCAGCCCCAGA GGCAGCGGGCGGACCCTCCGTGTTCCTGTTCCCCCCCAAGCCCAAGGACACCCTGATGATCAGCAGGACCCCC GAGGTGACCTGCGTGGTGGTGGACGTGAGCCACGAGGACCCAGAGGTGAAGTTCAACTGGTACGTGGACGG CGTGGAGGTGCACAACGCCAAGACCAAGCCCAGAGAGGAGCAGTACAACAGCACCTACAGGGTGGTGTCCG TGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAATACAAGTGCAAGGTCTCCAACAAGGCCCTGC CAGCCCCCATCGAAAAGACCATCAGCAAGGCCAAGGGCCAGCCACGGGAGCCCCAGGTGTACACCCTGCCCC CCTCCCGGGAGGAGATGACCAAGAACCAGGTGTCCCTGACCTGTCTGGTGAAGGGCTTCTACCCCAGCGACA TCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCGAGAACAACTACAAGACCACCCCCCCAGTGCTGGACAGC GACGGCAGCTTCTTCCTGTACAGCAAGCTGACCGTGGACAAGTCCAGGTGGCAGCAGGGCAACGTGTTCAGC TGCAGCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGAGCCTGAGCCTGTCCCCCGGCAAG
SEQ ID ND:183	VL MOR06475	DIVLTQSPATLSLSPGERATLSCRASQFIGSRYLAWYQQKPGQAPRLLIYGASNRATGVPARFSGSGSGTDFTLTISSL EPEDFATYYCQQYYDYPQTFGQGTKVEIK
SEQ ID NO:184	DNA VL MOR06475	Gatatcgtgctgacccagagcccggcgaccctgagcctgtctccgggcgaacgtgcgaccctgagctgcagagcgagccagtttattggttctc gttatctggcttggtaccagcagaaaccaggtcaagcaccgcgtctattaatttatggtgcttctaatcgtgcaactggggtcccggcgcgttttag cggctctggatccggcacggattttaccctgaccattagcagcctggaacctgaagactttgcgacttattattgccagcagtattatgattatcct cagacctttggccagggtacgaaagttgaaattaaa
SEQ ID NO:185	Light MDR06475 kappa	DIVLTQSPATLSLSPGERATLSCRASQFIGSRYLAWYQQKPGQAPRLLIYGASNRATGVPARFSGSGSGTDFTLTISSL EPEDFATYYCQQYYDYPQTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNAL QSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
SEQ ID ND:186	DNA Light MDR06475	GATATCGTGCTGACCCAGAGCCCGGCGACCCTGAGCCTGTCTCCGGGCGAACGTGCGACCCTGAGCTGCAGA GCGAGCCAGTTTATTGGTTCTCGTTATCTGGCTTGGTACCAGCAGAAACCAGGTCAAGCACCGCGTCTATTAA TTTATGGTGCTTCTAATCGTGCAACTGGGGTCCCGGCGCGTTTTAGCGGCTCTGGATCCGGCACGGATTTTAC

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	kappa	CCTGACCATTAGCAGCCTGGAACCTGAAGACTTTGCGACTTATTATTGCCAGCAGTATTATGATTATCCTCAGA CCTTTGGCCAGGGTACGAAAGTTGAAATTAAACGTACGGTGGCCGCTCCCAGCGTGTTCATCTTCCCCCCCAG CGACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGGGAGGCCA AGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTCACCGAGCAGGACAG CAAGGACTCCACCTACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCATAAGGTGTA CGCCTGCGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCAAGAGCTTCAACAGGGGCGAGTGC
SEQ ID NO:187	Heavy MOR0647S hIgG1LALA MOR08168 scFv (VH-3-VL)	QVQLKESGPALVKPTQTLTLTCTFSGFSLSNRGGGVGWIRQPPGKALEWLAWIDWDDDKSYSTSLKTRLTISKDTS KNQVVLTMTNMDPVDTATYYCARMHLPLVFDSWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHT CPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGSG GSQVQLVESGGGLVQPGGSLRLSCAASGFTFSDYVINWVRQAPGKGLEWVSGISWSGVNTHYADSVKGRFTISR DNSKNTLYLQMNSLRAEDTAVYYCARLGATANNIRYKFMDVWGQGTLVTVSSGGGGSGGGGSGGGGSDIELTQ PPSVSVAPGQTARISCSGDSLRNKVYWYQQKPGQAPVLVIYKNNRPSGIPERFSGSNSGNTATLTISGTQAEDEAD YYCQSYDGQKSLVFGGGTKLTVL
SEQ ID NO:188	DNA Heavy MOR0647S hIgG1LALA MOR08168 scFv (VH-3-VL)	CAGGTGCAATTGAAAGAAAGCGGCCCGGCCCTGGTGAAACCGACCCAAACCCTGACCCTGACCTGTACCTTTT CCGGATTTAGCCTGTCTAATCGTGGTGGTGGTGTGGGTTGGATTCGCCAGCCGCCTGGGAAAGCCCTCGAGT GGCTGGCTTGGATCGATTGGGATGATGATAAGTCTTATAGCACCAGCCTGAAAACGCGTCTGACCATTAGCA AAGATACTTCGAAAAATCAGGTGGTGCTGACTATGACCAACATGGACCCGGTGGATACGGCCACCTATTATTG CGCGCGTATGCATCTTCCTCTTGTTTTTGATTCTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCAGCTAGCA CCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCT GCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGCGTGC ACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGTCCAGCGTGGTGACAGTGCCCAGCAGCA GCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTG GAGCCCAAGAGCTGCGACAAGACCCACACCTGCCCCCCCTGCCCAGCCCCAGAGGCAGCGGGCGGACCCTCC GTGTTCCTGTTCCCCCCCAAGCCCAAGGACACCCTGATGATCAGCAGGACCCCCGAGGTGACCTGCGTGGTG GTGGACGTGAGCCACGAGGACCCAGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAACGC CAAGACCAAGCCCAGAGAGGAGCAGTACAACAGCACCTACAGGGTGGTGTCCGTGCTGACCGTGCTGCACCA GGACTGGCTGAACGGCAAGGAATACAAGTGCAAGGTCTCCAACAAGGCCCTGCCAGCCCCCATCGAAAAGAC CATCAGCAAGGCCAAGGGCCAGCCACGGGAGCCCCAGGTGTACACCCTGCCCCCCTCCCGGGAGGAGATGA CCAAGAACCAGGTGTCCCTGACCTGTCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGA GCAACGGCCAGCCCGAGAACAACTACAAGACCACCCCCCCAGTGCTGGACAGCGACGGCAGCTTCTTCCTGT ACAGCAAGCTGACCGTGGACAAGTCCAGGTGGCAGCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACGAA GCGCTGCACAACCACTACACCCAGAAGAGCCTGAGCCTGTCCCCCGGCAAGGGCGGCTCCGGCGGAAGCCA GGTTCAATTGGTTGAAAGCGGTGGTGGTCTGGTTCAGCCTGGTGGTAGCCTGCGTCTGAGCTGTGCAGCAAG CGGTTTTACCTTTAGCGATTATGTGATTAATTGGGTTCGTCAGGCACCGGGTAAAGGTCTGGAATGGGTTAGC GGTATTAGCTGGTCAGGTGTTAATACCCATTATGCAGATAGCGTGAAAGGTCGTTTTACCATTAGCCGTGATA ATAGCAAAAATACCCTGTATCTGCAGATGAATAGCCTGCGTGCAGAAGATACCGCAGTTTATTATTGTGCACG TCTGGGTGCAACCGCAAATAATATTCGCTATAAATTTATGGATGTGTGGGGTCAGGGTACACTAGTTACCGTT AGCAGTGGTGGTGGTGGTAGCGGTGGTGGCGGATCTGGTGGCGGTGGCAGTGATATCGAACTGACCCAGCC TCCGAGCGTTAGCGTTGCACCGGGTCAGACCGCACGTATTAGCTGTAGCGGTGATAGTCTGCGTAATAAAGTT TATTGGTATCAGCAGAAACCGGGTCAGGCTCCGGTTCTGGTTATTTATAAAAATAATCGTCCGAGCGGTATTC CGGAACGTTTTAGCGGTAGCAATAGCGGTAATACCGCAACCCTGACCATTAGCGGCACCCAGGCAGAAGATG AAGCCGATTATTATTGTCAGAGCTATGATGGTCAGAAAAGCCTGGTTTTTGGTGGTGGCACCAAGCTTACCGT TCTG
SEQ ID NO:189	Heavy MOR06475 hIgG1 LALA MOR08168 scFv (VH-4-VL)	QVQLKESGPALVKPTQTLTLTCTFSGFSLSNRGGGVGWIRQPPGKALEWLAWIDWDDDKSYSTSLKTRLTISKDTS KNQVVLTMTNMDPVDTATYYCARMHLPLVFDSWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHT CPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGSG GSQVQLVESGGGLVQPGGSLRLSCAASGFTFSDYVINWVRQAPGKGLEWVSGISWSGVNTHYADSVKGRFTISR DNSKNTLYLQMNSLRAEDTAVYYCARLGATANNIRYKFMDVWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGS DIELTQPPSVSVAPGQTARISCSGDSLRNKVYWYQQKPGQAPVLVIYKNNRPSGIPERFSGSNSGNTATLTISGTQA EDEADYYCQSYDGQKSLVFGGGTKLTVL
SEQ ID NO:190	DNA Heavy MOR06475	CAGGTGCAATTGAAAGAAAGCGGCCCGGCCCTGGTGAAACCGACCCAAACCCTGACCCTGACCTGTACCTTTT CCGGATTTAGCCTGTCTAATCGTGGTGGTGGTGTGGGTTGGATTCGCCAGCCGCCTGGGAAAGCCCTCGAGT

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	hIgG1 LALA MOR08168 scFv (VH-4-VL)	GGCTGGCTTGGATCGATTGGGATGATGATAAGTCTTATAGCACCAGCCTGAAAACGCGTCTGACCATTAGCA AAGATACTTCGAAAAATCAGGTGGTGCTGACTATGACCAACATGGACCCGGTGGATACGGCCACCTATTATTG CGCGCGTATGCATCTTCCTCTTGTTTTTGATTCTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCAGCTAGCA CCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCT GCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGCGTGC ACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGTCCAGCGTGGTGACAGTGCCCAGCAGCA GCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTG GAGCCCAAGAGCTGCGACAAGACCCACACCTGCCCCCCCTGCCCAGCCCCAGAGGCAGCGGGCGGACCCTCC GTGTTCCTGTTCCCCCCAAGCCCAAGGACACCCTGATGATCAGCAGGACCCCCGAGGTGACCTGCGTGGTG GTGGACGTGAGCCACGAGGACCCAGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAACGC CAAGACCAAGCCCAGAGAGGAGCAGTACAACAGCACCTACAGGGTGGTGTCCGTGCTGACCGTGCTGCACCA GGACTGGCTGAACGGCAAGGAATACAAGTGCAAGGTCTCCAACAAGGCCCTGCCAGCCCCCATCGAAAAGAC CATCAGCAAGGCCAAGGGCCAGCCACGGGAGCCCCAGGTGTACACCCTGCCCCCCTCCCGGGAGGAGATGA CCAAGAACCAGGTGTCCCTGACCTGTCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGA GCAACGGCCAGCCCGAGAACAACTACAAGACCACCCCCCCAGTGCTGGACAGCGACGGCAGCTTCTTCCTGT ACAGCAAGCTGACCGTGGACAAGTCCAGGTGGCAGCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACGAA GCGCTGCACAACCACTACACCCAGAAGAGCCTGAGCCTGTCCCCCGGCAAGGGCGGCTCCGGCGGAAGCCA GGTTCAATTGGTTGAAAGCGGTGGTGGTCTGGTTCAGCCTGGTGGTAGCCTGCGTCTGAGCTGTGCAGCAAG CGGTTTTACCTTTAGCGATTATGTGATTAATTGGGTTCGTCAGGCACCGGGTAAAGGTCTGGAATGGGTTAGC GGTATTAGCTGGTCAGGTGTTAATACCCATTATGCAGATAGCGTGAAAGGTCGTTTTACCATTAGCCGTGATA ATAGCAAAAATACCCTGTATCTGCAGATGAATAGCCTGCGTGCAGAAGATACCGCAGTTTATTATTGTGCACG TCTGGGTGCAACCGCAAATAATATTCGCTATAAATTTATGGATGTGTGGGGTCAGGGTACACTAGTTACCGTT AGCAGTGGTGGTGGTGGTAGCGGTGGTGGCGGATCTGGTGGCGGTGGTTCAGGTGGTGGTGGCAGTGATA TCGAACTGACCCAGCCTCCGAGCGTTAGCGTTGCACCGGGTCAGACCGCACGTATTAGCTGTAGCGGTGATA GTCTGCGTAATAAAGTTTATTGGTATCAGCAGAAACCGGGTCAGGCTCCGGTTCTGGTTATTTATAAAAATAA TCGTCCGAGCGGTATTCCGGAACGTTTTAGCGGTAGCAATAGCGGTAATACCGCAACCCTGACCATTAGCGGC ACCCAGGCAGAAGATGAAGCCGATTATTATTGTCAGAGCTATGATGGTCAGAAAAGCCTGGTTTTTGGTGGT GGCACCAAGCTTACCGTTCTG
SEQ ID NO:191	VL MDR08168wt	DIELTQPPSVSVAPGQTARISCSGDSLRNKVYWYQQKPGQAPVLVIYKNNRPSGIPERFSGSNSGNTATLTISGTQA EDEADYYCQSYDGQKSLVFGGGTKLTVL
SEQ ID NO:192	DNA VL MOR08168 wt	GACATCGAGCTGACTCAGCCCCCTAGCGTGTCAGTGGCTCCTGGCCAGACCGCTAGAATTAGCTGTAGCGGC GATAGCCTGCGTAACAAGGTCTACTGGTATCAGCAGAAGCCCGGCCAGGCCCCTGTGCTGGTCATCTATAAG AACAATAGGCCTAGCGGCATCCCCGAGCGGTTTAGCGGCTCTAATAGCGGCAACACCGCTACCCTGACTATTA GCGGCACTCAGGCCGAGGACGAGGCCGACTACTACTGTCAGTCCTACGACGGCCAGAAGTCACTGGTCTTTG GCGGCGGAACTAAGCTGACCGTGCTG
SEQ ID NO:193	Light lambda MDR08168 wt	DIELTQPPSVSVAPGQTARISCSGDSLRNKVYWYQQKPGQAPVLVIYKNNRPSGIPERFSGSNSGNTATLTISGTQA EDEADYYCQSYDGQKSLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSP VKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
SEQ ID NO:194	DNA Light lambda MOR08168 wt	GACATCGAGCTGACTCAGCCCCCTAGCGTGTCAGTGGCTCCTGGCCAGACCGCTAGAATTAGCTGTAGCGGC GATAGCCTGCGTAACAAGGTCTACTGGTATCAGCAGAAGCCCGGCCAGGCCCCTGTGCTGGTCATCTATAAG AACAATAGGCCTAGCGGCATCCCCGAGCGGTTTAGCGGCTCTAATAGCGGCAACACCGCTACCCTGACTATTA GCGGCACTCAGGCCGAGGACGAGGCCGACTACTACTGTCAGTCCTACGACGGCCAGAAGTCACTGGTCTTTG GCGGCGGAACTAAGCTGACCGTGCTGGGACAGCCTAAGGCTGCCCCCAGCGTGACCCTGTTCCCCCCCAGCA GCGAGGAGCTGCAGGCCAACAAGGCCACCCTGGTGTGCCTGATCAGCGACTTCTACCCAGGCGCCGTGACCG TGGCCTGGAAGGCCGACAGCAGCCCCGTGAAGGCCGGCGTGGAGACCACCACCCCCAGCAAGCAGAGCAAC AACAAGTACGCCGCCAGCAGCTACCTGAGCCTGACCCCCGAGCAGTGGAAGAGCCACAGGTCCTACAGCTGC CAGGTGACCCACGAGGGCAGCACCGTGGAAAAGACCGTGGCCCCAACCGAGTGCAGC
SEQ ID NO:195	Heavy MOR08168IgG 1LALA_6475sc Fv wt	QVQLVESGGGLVQPGGSLRLSCAASGFTFSDYVINWVRQAPGKGLEWVSGISWSGVNTHYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARLGATANNIRYKFMDVWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GKGGSGGSDIVLTQSPATLSLSPGERATLSCRASQFIGSRYLAWYQQKPGQAPRLLIYGASNRATGVPARFSGSGSG TDFTLTISSLEPEDFATYYCQQYYDYPQTFGQGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLKESGPALVKPTQ TLTLTCTFSGFSLSNRGGGVGWIRQPPGKALEWLAWIDWDDDKSYSTSLKTRLTISKDTSKNQVVLTMTNMDPV

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		DTATYYCARMHLPLVFDSWGQGTLVTVSS
SEQ ID NO:196	DNA Heavy MOR08168IgG 1LALA_6475sc Fv wt	CAGGTGCAGCTGGTGGAATCAGGCGGAGGACTGGTCCAGCCTGGCGGATCACTTAGACTGAGCTGTGCCGC TAGTGGCTTCACCTTTAGCGACTATGTGATTAACTGGGTCCGACAGGCCCCTGGCAAGGGACTGGAATGGGT GTCAGGCATTAGTTGGAGCGGCGTGAACACTCACTACGCCGATAGCGTGAAGGGCCGGTTCACTATTAGCCG GGATAACTCTAAGAACACCCTGTACCTGCAGATGAATAGCCTGAGAGCCGAGGACACCGCCGTCTACTACTG CGCTAGACTGGGCGCTACCGCTAACAACATCCGCTATAAGTTCATGGACGTGTGGGGCCAGGGCACCCTGGT CACAGTGTCTTCAGCTAGCACTAAGGGCCCCTCAGTGTTCCCCCTGGCCCCTAGCTCTAAGTCTACTAGCGGTG GCACCGCCGCTCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAGCCCGTGACCGTGTCTTGGAATAGCGGCG CTCTGACTAGCGGAGTGCACACCTTCCCCGCCGTGCTGCAGTCTAGCGGCCTGTATAGCCTGTCTAGCGTCGT GACCGTGCCTAGCTCTAGCCTGGGCACTCAGACCTATATCTGTAACGTGAACCACAAGCCTAGTAACACTAAG GTGGACAAGCGGGTGGAACCTAAGTCTTGCGATAAGACTCACACCTGTCCCCCCTGCCCTGCCCCAGAAGCTG CTGGCGGACCTAGCGTGTTCCTGTTCCCACCTAAGCCTAAAGACACCCTGATGATTAGTAGGACCCCCGAAGT GACCTGCGTGGTGGTGGACGTCAGCCACGAGGACCCTGAAGTGAAGTTCAATTGGTATGTGGACGGCGTGG AAGTGCACAACGCTAAGACTAAGCCTAGAGAGGAACAGTATAACTCCACCTATAGGGTGGTGTCAGTGCTGA CCGTGCTGCACCAGGACTGGCTGAACGGCAAAGAGTATAAGTGTAAAGTCTCTAACAAGGCCCTGCCTGCCC CTATCGAAAAGACTATCTCTAAGGCTAAGGGCCAGCCTAGAGAACCCCAGGTCTACACCCTGCCCCCTAGTAG AGAAGAGATGACTAAGAATCAGGTGTCCCTGACCTGTCTGGTCAAGGGCTTCTACCCTAGCGATATCGCCGTG GAGTGGGAGTCTAACGGCCAGCCCGAGAACAACTATAAGACTACCCCCCCTGTGCTGGATAGCGACGGCTCT TTCTTCCTGTACTCTAAACTGACCGTGGACAAGTCTAGGTGGCAGCAGGGCAACGTGTTCAGCTGTAGCGTGA TGCACGAGGCCCTGCACAATCACTACACTCAGAAGTCACTGAGCCTGAGTCCCGGCAAGGGCGGCTCAGGCG GTAGCGATATCGTGCTGACTCAGTCACCCGCTACCCTGAGTCTGAGCCCTGGCGAGCGGGCTACACTGAGCT GTAGAGCTAGTCAGTTTATCGGCTCACGCTACCTGGCCTGGTATCAGCAGAAGCCCGGCCAGGCCCCTAGACT GCTGATCTACGGCGCTAGTAATAGAGCTACCGGCGTGCCCGCTAGGTTTAGCGGCTCAGGATCAGGCACCGA CTTTACCCTGACTATTAGTAGCCTGGAACCCGAGGACTTCGCTACCTACTACTGTCAGCAGTACTACGACTACC CTCAGACCTTCGGCCAGGGAACTAAGGTCGAGATTAAGGGCGGTGGCGGTAGCGGCGGAGGCGGATCAGG TGGTGGTGGTAGTGGCGGCGGAGGTAGTCAGGTCCAGCTGAAAGAGTCAGGCCCTGCCCTGGTCAAGCCTA CTCAGACCCTGACCCTGACCTGCACTTTTAGCGGCTTTAGCCTGAGTAATAGAGGCGGCGGAGTGGGCTGGA TTAGACAGCCTCCAGGCAAAGCCCTGGAGTGGCTGGCCTGGATCGACTGGGACGACGATAAGTCCTACTCCA CTAGCCTGAAAACTAGGCTGACAATCAGCAAGGACACTAGTAAAAACCAGGTGGTGCTGACTATGACTAATA TGGACCCCGTGGACACCGCTACCTATTATTGCGCTAGAATGCACCTCCCACTGGTGTTCGATAGCTGGGGTCA GGGAACTCTGGTCACAGTCAGTAGC
SEQ ID NO:197	VL MOR08168 DI	SYELTQPPSVSVAPGQTARISCSGDSLRNKVYWYQQKPGQAPVLVIYKNNRPSGIPERFSGSNSGNTATLTISGTQA EDEADYYCQSYDGQKSLVFGGGTKLTVL
SEQ ID NO:198	DNA VL MOR08168 DI	TCTTACGAGCTGACCCAGCCCCCTTCCGTGTCTGTGGCTCCTGGCCAGACCGCCAGAATCTCTTGCTCCGGCGA CTCCCTGCGGAACAAGGTGTACTGGTATCAGCAGAAGCCCGGCCAGGCCCCTGTGCTGGTCATCTACAAGAA CAACCGGCCCTCCGGCATCCCCGAGAGATTCTCTGGCTCCAACTCCGGCAACACCGCCACCCTGACAATCTCT GGCACACAGGCCGAGGACGAGGCCGACTACTACTGCCAGTCCTACGACGGCCAGAAATCACTGGTGTTCGGC GGAGGCACCAAGCTGACAGTGCTG
SEQ ID NO:199	Light lambda MOR08168 DI	SYELTQPPSVSVAPGQTARISCSGDSLRNKVYWYQQKPGQAPVLVIYKNNRPSGIPERFSGSNSGNTATLTISGTQA EDEADYYCQSYDGQKSLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSP VKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
SEQ ID NO:200	DNA Light lambda MOR08168 DI	TCTTACGAGCTGACCCAGCCCCCTTCCGTGTCTGTGGCTCCTGGCCAGACCGCCAGAATCTCTTGCTCCGGCGA CTCCCTGCGGAACAAGGTGTACTGGTATCAGCAGAAGCCCGGCCAGGCCCCTGTGCTGGTCATCTACAAGAA CAACCGGCCCTCCGGCATCCCCGAGAGATTCTCTGGCTCCAACTCCGGCAACACCGCCACCCTGACAATCTCT GGCACACAGGCCGAGGACGAGGCCGACTACTACTGCCAGTCCTACGACGGCCAGAAATCACTGGTGTTCGGC GGAGGCACCAAGCTGACAGTGCTGGGACAGCCTAAGGCTGCCCCCAGCGTGACCCTGTTCCCCCCCAGCAGC GAGGAGCTGCAGGCCAACAAGGCCACCCTGGTGTGCCTGATCAGCGACTTCTACCCAGGCGCCGTGACCGTG GCCTGGAAGGCCGACAGCAGCCCCGTGAAGGCCGGCGTGGAGACCACCACCCCCAGCAAGCAGAGCAACAA CAAGTACGCCGCCAGCAGCTACCTGAGCCTGACCCCCGAGCAGTGGAAGAGCCACAGGTCCTACAGCTGCCA GGTGACCCACGAGGGCAGCACCGTGGAAAAGACCGTGGCCCCAACCGAGTGCAGC
SEQ ID NO:201	Heavy MOR08168IgG 1LALA_6475sc Fv DI	QVQLVESGGGLVQPGGSLRLSCAASGFTFSDYVINWVRQAPGKGLEWVSGISWSGVNTHYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARLGATANNIRYKFMDVWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP

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		GKGGSGGSDIVLTQSPATLSLSPGERATLSCRASQFIGSRYLAWYQQKPGQAPRLLIYGASNRATGVPARFSGSGSG TDFTLTISSLEPEDFATYYCQQYYDYPQTFGQGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLKESGPALVKPTQ TLTLTCTFSGFSLSNRGGGVGWIRQPPGKALEWLAWIDWDDDKSYSTSLKTRLTISKDTSKNQVVLTMTNMDPV DTATYYCARMHLPLVFDSWGQGTLVTVSS
SEQ ID ND:202	DNA Heavy MOR08168IgG 1LALA_6475sc Fv DI	CAGGTGCAGCTGGTGGAATCAGGCGGAGGACTGGTCCAGCCTGGCGGATCACTTAGACTGAGCTGTGCCGC TAGTGGCTTCACCTTTAGCGACTATGTGATTAACTGGGTCCGACAGGCCCCTGGCAAGGGACTGGAATGGGT GTCAGGCATTAGTTGGAGCGGCGTGAACACTCACTACGCCGATAGCGTGAAGGGCCGGTTCACTATTAGCCG GGATAACTCTAAGAACACCCTGTACCTGCAGATGAATAGCCTGAGAGCCGAGGACACCGCCGTCTACTACTG CGCTAGACTGGGCGCTACCGCTAACAACATCCGCTATAAGTTCATGGACGTGTGGGGCCAGGGCACCCTGGT CACAGTGTCTTCAGCTAGCACTAAGGGCCCCTCAGTGTTCCCCCTGGCCCCTAGCTCTAAGTCTACTAGCGGTG GCACCGCCGCTCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAGCCCGTGACCGTGTCTTGGAATAGCGGCG CTCTGACTAGCGGAGTGCACACCTTCCCCGCCGTGCTGCAGTCTAGCGGCCTGTATAGCCTGTCTAGCGTCGT GACCGTGCCTAGCTCTAGCCTGGGCACTCAGACCTATATCTGTAACGTGAACCACAAGCCTAGTAACACTAAG GTGGACAAGCGGGTGGAACCTAAGTCTTGCGATAAGACTCACACCTGTCCCCCCTGCCCTGCCCCAGAAGCTG CTGGCGGACCTAGCGTGTTCCTGTTCCCACCTAAGCCTAAAGACACCCTGATGATTAGTAGGACCCCCGAAGT GACCTGCGTGGTGGTGGACGTCAGCCACGAGGACCCTGAAGTGAAGTTCAATTGGTATGTGGACGGCGTGG AAGTGCACAACGCTAAGACTAAGCCTAGAGAGGAACAGTATAACTCCACCTATAGGGTGGTGTCAGTGCTGA CCGTGCTGCACCAGGACTGGCTGAACGGCAAAGAGTATAAGTGTAAAGTCTCTAACAAGGCCCTGCCTGCCC CTATCGAAAAGACTATCTCTAAGGCTAAGGGCCAGCCTAGAGAACCCCAGGTCTACACCCTGCCCCCTAGTAG AGAAGAGATGACTAAGAATCAGGTGTCCCTGACCTGTCTGGTCAAGGGCTTCTACCCTAGCGATATCGCCGTG GAGTGGGAGTCTAACGGCCAGCCCGAGAACAACTATAAGACTACCCCCCCTGTGCTGGATAGCGACGGCTCT TTCTTCCTGTACTCTAAACTGACCGTGGACAAGTCTAGGTGGCAGCAGGGCAACGTGTTCAGCTGTAGCGTGA TGCACGAGGCCCTGCACAATCACTACACTCAGAAGTCACTGAGCCTGAGTCCCGGCAAGGGCGGCTCAGGCG GTAGCGATATCGTGCTGACTCAGTCACCCGCTACCCTGAGTCTGAGCCCTGGCGAGCGGGCTACACTGAGCT GTAGAGCTAGTCAGTTTATCGGCTCACGCTACCTGGCCTGGTATCAGCAGAAGCCCGGCCAGGCCCCTAGACT GCTGATCTACGGCGCTAGTAATAGAGCTACCGGCGTGCCCGCTAGGTTTAGCGGCTCAGGATCAGGCACCGA CTTTACCCTGACTATTAGTAGCCTGGAACCCGAGGACTTCGCTACCTACTACTGTCAGCAGTACTACGACTACC CTCAGACCTTCGGCCAGGGAACTAAGGTCGAGATTAAGGGCGGTGGCGGTAGCGGCGGAGGCGGATCAGG TGGTGGTGGTAGTGGCGGCGGAGGTAGTCAGGTCCAGCTGAAAGAGTCAGGCCCTGCCCTGGTCAAGCCTA CTCAGACCCTGACCCTGACCTGCACTTTTAGCGGCTTTAGCCTGAGTAATAGAGGCGGCGGAGTGGGCTGGA TTAGACAGCCTCCAGGCAAAGCCCTGGAGTGGCTGGCCTGGATCGACTGGGACGACGATAAGTCCTACTCCA CTAGCCTGAAAACTAGGCTGACAATCAGCAAGGACACTAGTAAAAACCAGGTGGTGCTGACTATGACTAATA TGGACCCCGTGGACACCGCTACCTATTATTGCGCTAGAATGCACCTCCCACTGGTGTTCGATAGCTGGGGTCA GGGAACTCTGGTCACAGTCAGTAGC
SEQ ID NO:203	VL MOR08168 GL	SYELTQPLSVSVALGQTARITCSGDSLRNKVYWYQQKPGQAPVLVIYKNNRPSGIPERFSGSNSGNTATLTISRAQA GDEADYYCQSYDGQKSLVFGGGTKLTVL
SEQ ID NO:204	DNA VL MOR08168 GL	AGCTACGAGCTGACTCAGCCCCTGAGCGTGTCAGTGGCTCTGGGCCAGACCGCTAGAATCACCTGTAGCGGC GATAGCCTGAGAAACAAGGTCTACTGGTATCAGCAGAAGCCCGGCCAGGCCCCTGTGCTGGTCATCTATAAG AACAATAGGCCTAGCGGCATCCCCGAGCGGTTTAGCGGCTCTAATAGCGGCAACACCGCTACCCTGACTATTA GTAGGGCTCAGGCCGGCGACGAGGCCGACTACTACTGTCAGTCCTACGACGGCCAGAAGTCACTGGTCTTTG GCGGCGGAACTAAGCTGACCGTGCTG
SEQ ID NO:205	Light lambda MDR08168 GL	SYELTQPLSVSVALGQTARITCSGDSLRNKVYWYQQKPGQAPVLVIYKNNRPSGIPERFSGSNSGNTATLTISRAQA GDEADYYCQSYDGQKSLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSP VKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEG5TVEKTVAPTECS
SEQ ID NO:206	DNA Light lambda MOR08168 GL	AGCTACGAGCTGACTCAGCCCCTGAGCGTGTCAGTGGCTCTGGGCCAGACCGCTAGAATCACCTGTAGCGGC GATAGCCTGAGAAACAAGGTCTACTGGTATCAGCAGAAGCCCGGCCAGGCCCCTGTGCTGGTCATCTATAAG AACAATAGGCCTAGCGGCATCCCCGAGCGGTTTAGCGGCTCTAATAGCGGCAACACCGCTACCCTGACTATTA GTAGGGCTCAGGCCGGCGACGAGGCCGACTACTACTGTCAGTCCTACGACGGCCAGAAGTCACTGGTCTTTG GCGGCGGAACTAAGCTGACCGTGCTGGGACAGCCTAAGGCTGCCCCCAGCGTGACCCTGTTCCCCCCCAGCA GCGAGGAGCTGCAGGCCAACAAGGCCACCCTGGTGTGCCTGATCAGCGACTTCTACCCAGGCGCCGTGACCG TGGCCTGGAAGGCCGACAGCAGCCCCGTGAAGGCCGGCGTGGAGACCACCACCCCCAGCAAGCAGAGCAAC AACAAGTACGCCGCCAGCAGCTACCTGAGCCTGACCCCCGAGCAGTGGAAGAGCCACAGGTCCTACAGCTGC CAGGTGACCCACGAGGGCAGCACCGTGGAAAAGACCGTGGCCCCAACCGAGTGCAGC
SEQ ID NO:207	Heavy MOR08168IgG 1LALA_6475sc	EVQLLESGGGLVQPGGSLRLSCAASGFTF5DYVINWVRQAPGKGLEWVSGISWSGVNTHYADSVKGRFTI5RDN5 KNTLYLQMNSLRAEDTAVYYCARLGATANNIRYKFMDVWGQGTLVTVSSASTKGPSVFPLAP5SKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS5VVTVPSSSLGTQTYICNVNHKP5NTKVDKRVEPKSC

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	Fv GL	DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK GGSGGSDIVLTQSPATLSLSPGERATLSCRASQFIGSRYLAWYQQKPGQAPRLLIYGASNRATGVPARFSGSGSGTD FTLTISSLEPEDFATYYCQQYYDYPQTFGQGTKVEIKGGGGSGGGGSGGGGSGGGGSGGGGSQVQLKESGPALVKPTQTL TLTCTFSGFSLSNRGGGVGWIRQPPGKALEWLAWIDWDDDKSYSTSLKTRLTISKDTSKNQVVLTMTNMDPVDT ATYYCARMHLPLVFDSWGQGTLVTVSS
SEQ ID ND:208	DNA Heavy MDR08168IgG 1LALA_6475sc Fv GL	GAGGTGCAGCTGCTGGAATCAGGCGGAGGACTGGTGCAGCCTGGCGGATCACTGAGACTGAGCTGTGCCGC TAGTGGCTTCACCTTTAGCGACTATGTGATTAACTGGGTCCGACAGGCCCCTGGCAAGGGACTGGAATGGGT GTCAGGCATTAGTTGGAGCGGCGTGAACACTCACTACGCCGATAGCGTGAAGGGCCGGTTCACTATTAGCCG GGATAACTCTAAGAACACCCTGTACCTGCAGATGAATAGCCTGAGAGCCGAGGACACCGCCGTCTACTACTG CGCTAGACTGGGCGCTACCGCTAACAACATCCGCTATAAGTTCATGGACGTGTGGGGCCAGGGCACCCTGGT CACAGTGTCTTCAGCTAGCACTAAGGGCCCCTCAGTGTTCCCCCTGGCCCCTAGCTCTAAGTCTACTAGCGGTG GCACCGCCGCTCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAGCCCGTGACCGTGTCTTGGAATAGCGGCG CTCTGACTAGCGGAGTGCACACCTTCCCCGCCGTGCTGCAGTCTAGCGGCCTGTATAGCCTGTCTAGCGTCGT GACCGTGCCTAGCTCTAGCCTGGGCACTCAGACCTATATCTGTAACGTGAACCACAAGCCTAGTAACACTAAG GTGGACAAGCGGGTGGAACCTAAGTCTTGCGATAAGACTCACACCTGTCCCCCCTGCCCTGCCCCAGAAGCTG CTGGCGGACCTAGCGTGTTCCTGTTCCCACCTAAGCCTAAAGACACCCTGATGATTAGTAGGACCCCCGAAGT GACCTGCGTGGTGGTGGACGTCAGCCACGAGGACCCTGAAGTGAAGTTCAATTGGTATGTGGACGGCGTGG AAGTGCACAACGCTAAGACTAAGCCTAGAGAGGAACAGTATAACTCCACCTATAGGGTGGTGTCAGTGCTGA CCGTGCTGCACCAGGACTGGCTGAACGGCAAAGAGTATAAGTGTAAAGTCTCTAACAAGGCCCTGCCTGCCC CTATCGAAAAGACTATCTCTAAGGCTAAGGGCCAGCCTAGAGAACCCCAGGTCTACACCCTGCCCCCTAGTAG AGAAGAGATGACTAAGAATCAGGTGTCCCTGACCTGTCTGGTCAAGGGCTTCTACCCTAGCGATATCGCCGTG GAGTGGGAGTCTAACGGCCAGCCCGAGAACAACTATAAGACTACCCCCCCTGTGCTGGATAGCGACGGCTCT TTCTTCCTGTACTCTAAACTGACCGTGGACAAGTCTAGGTGGCAGCAGGGCAACGTGTTCAGCTGTAGCGTGA TGCACGAGGCCCTGCACAATCACTACACTCAGAAGTCACTGAGCCTGAGTCCCGGCAAGGGCGGCTCAGGCG GTAGCGATATCGTGCTGACTCAGTCACCCGCTACCCTGAGTCTGAGCCCTGGCGAGCGGGCTACACTGAGCT GTAGAGCTAGTCAGTTTATCGGCTCACGCTACCTGGCCTGGTATCAGCAGAAGCCCGGCCAGGCCCCTAGACT GCTGATCTACGGCGCTAGTAATAGAGCTACCGGCGTGCCCGCTAGGTTTAGCGGCTCAGGATCAGGCACCGA CTTTACCCTGACTATTAGTAGCCTGGAACCCGAGGACTTCGCTACCTACTACTGTCAGCAGTACTACGACTACC CTCAGACCTTCGGCCAGGGAACTAAGGTCGAGATTAAGGGCGGTGGCGGTAGCGGCGGAGGCGGATCAGG TGGTGGTGGTAGTGGCGGCGGAGGTAGTCAGGTCCAGCTGAAAGAGTCAGGCCCTGCCCTGGTCAAGCCTA CTCAGACCCTGACCCTGACCTGCACTTTTAGCGGCTTTAGCCTGAGTAATAGAGGCGGCGGAGTGGGCTGGA TTAGACAGCCTCCAGGCAAAGCCCTGGAGTGGCTGGCCTGGATCGACTGGGACGACGATAAGTCCTACTCCA CTAGCCTGAAAACTAGGCTGACAATCAGCAAGGACACTAGTAAAAACCAGGTGGTGCTGACTATGACTAATA TGGACCCCGTGGACACCGCTACCTATTATTGCGCTAGAATGCACCTCCCACTGGTGTTCGATAGCTGGGGTCA GGGAACTCTGGTCACAGTCAGTAGC

Other antibodies of the invention include those where the amino acids or nucleic acids encoding the amino acids have been mutated, yet have at least 60%, 70%, 80%, 90%, 95% or 98% identity to the sequences described in Table 1. In some embodiments, it include mutant amino acid sequences wherein no more than 1, 2, 3, 4 or 5 amino acids have been mutated in the variable regions when compared with the variable regions depicted in the sequence described in Table 1, while retaining substantially the same therapeutic activity.

Since each of these antibodies can bind to LRP6, the VH, VL, full length light chain, and full length heavy chain sequences (amino acid sequences and the nucleotide sequences encoding the amino acid sequences) can be "mixed and matched" to create other LRP6 antibodies of the invention. Such "mixed and matched" LRP6 antibodies can be tested

using the binding assays known in the art (*e.g.*, ELISAs, and other assays described in the Example section). When these chains are mixed and matched, a VH sequence from a particular VH/VL pairing should be replaced with a structurally similar VH sequence. Likewise a full length heavy chain sequence from a particular full length heavy chain / full length light chain pairing should be replaced with a structurally similar full length heavy chain sequence. Likewise, a VL sequence from a particular VH/VL pairing should be replaced with a structurally similar VL sequence. Likewise a full length light chain sequence from a particular full length heavy chain / full length light chain pairing should be replaced with a structurally similar full length light chain sequence. Accordingly, in one aspect, the invention provides an isolated monoclonal antibody or fragment thereof having: a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 34, 36, 44, 60, and 62; and a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 13, 33, 35, 43, 59 and 61; a heavy chain selected from the group consisting of SEQ ID NOs: 82, 106, 108, 128, 130 and 138; and a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 81, and 90, 105, 107, 127, 129, and 137; wherein the antibody specifically binds to LRP6 (*e.g.*, human and/or cynomologus LRP6).

In another aspect, the present invention provides LRP6 antibodies that bind to the β propeller 1 domain of LRP6 that comprise the heavy chain and light chain CDR1s, CDR2s and CDR3s as described in Table 1, or combinations thereof. The amino acid sequences of the VH CDR1s of the antibodies are shown in SEQ ID NOs: 1, 21, and 47. The amino acid sequences of the VH CDR2s of the antibodies and are shown in SEQ ID NOs: 2, 22, and 48. The amino acid sequences of the VH CDR3s of the antibodies are shown in SEQ ID NOs: 3, 23, and 49. The amino acid sequences of the VL CDR1s of the antibodies are shown in SEQ ID NOs: 4, 24, and 50. The amino acid sequences of the VL CDR2s of the antibodies are shown in SEQ ID NOs: 5, 25, and 51. The amino acid sequences of the VL CDR3s of the antibodies are shown in SEQ ID NOs: 6, 26, and 52. The CDR regions are delineated using the Kabat system (Kabat *et al.*, (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242; Chothia *et al.*, (1987) J. Mol. Biol. 196: 901-917; Chothia *et al.*, (1989) Nature 342: 877-883; and Al-Lazikani *et al.*, (1997) J. Mol. Biol. 273, 927-948).

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In another aspect, the present invention provides LRP6 antibodies that bind to the β propeller 3 domain of LRP6 that comprise the heavy chain and light chain CDR1s, CDR2s and CDR3s as described in Table 1, or combinations thereof. The amino acid sequences of the VH CDR1s of the antibodies are shown in SEQ ID NOs: 69, 93, and 115. The amino acid sequences of the VH CDR2s of the antibodies and are shown in SEQ ID NOs: 70, 94, and 116. The amino acid sequences of the VH CDR3s of the antibodies are shown in SEQ ID NOs: 71, 95, and 117. The amino acid sequences of the VL CDR1s of the antibodies are shown in SEQ ID NOs: 72, 96, and 118. The amino acid sequences of the VL CDR2s of the antibodies are shown in SEQ ID NOs: 73, 97, and 119. The amino acid sequences of the VL CDR3s of the antibodies are shown in SEQ ID NOs: 74, 98, and 120. The CDR regions are delineated using the Kabat system (Kabat *et al.*, (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242; Chothia *et al.*, (1987) J. Mol. Biol. 196: 901-917; Chothia *et al.*, (1989) Nature 342: 877-883; and Al-Lazikani *et al.*, (1997) J. Mol. Biol. 273, 927-948).

Given that each of these antibodies can bind to LRP6 and that antigen-binding specificity is provided primarily by the CDR1, 2 and 3 regions, the VH CDR1, 2 and 3 sequences and VL CDR1, 2 and 3 sequences can be "mixed and matched" (*i.e.*, CDRs from different antibodies can be mixed and match, although each antibody must contain a VH CDR1, 2 and 3 and a VL CDR1, 2 and 3 to create other LRP6 binding molecules of the invention. Such "mixed and matched" LRP6 antibodies can be tested using the binding assays known in the art and those described in the Examples (*e.g.*, ELISAs). When VH CDR sequences are mixed and matched, the CDR1, CDR2 and/or CDR3 sequence from a particular VH sequence should be replaced with a structurally similar CDR sequence(s). Likewise, when VL CDR sequences are mixed and matched, the CDR1, CDR2 and/or CDR3 sequence from a particular VL sequence should be replaced with a structurally similar CDR sequence(s). It will be readily apparent to the ordinarily skilled artisan that novel VH and VL sequences can be created by substituting one or more VH and/or VL CDR region sequences with structurally similar sequences from the CDR sequences shown herein for monoclonal antibodies of the present invention.

Accordingly, the present invention provides an isolated LRP6 β-propeller 1 monoclonal antibody or fragment thereof comprising a heavy chain variable region CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 21, and

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47; a heavy chain variable region CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 22, and 48; a heavy chain variable region CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 23, and 49; a light chain variable region CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 24, and 50; a light chain variable region CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 25, and 51; and a light chain variable region CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 26, and 52; wherein the antibody binds LRP6.

Accordingly, the present invention provides an isolated LRP6 β-propeller 3 monoclonal antibody or fragment thereof comprising a heavy chain variable region CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 69, 93, and 115; a heavy chain variable region CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 70, 94, and 116,; a heavy chain variable region CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 71, 95, and 117; a light chain variable region CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 72, 96, and 118; a light chain variable region CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 73, 97, and 119; and a light chain variable region CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 74, 98, and 120; wherein the antibody binds LRP6.

In a specific embodiment, an antibody that binds to LRP6 comprises a heavy chain variable region CDR1 of SEQ ID NO: 1; a heavy chain variable region CDR2 of SEQ ID NO: 2; a heavy chain variable region CDR3 of SEQ ID NO: 3; a light chain variable region CDR1 of SEQ ID NO: 4; a light chain variable region CDR2 of SEQ ID NO: 5; and a light chain variable region CDR3 of SEQ ID NO: 6.

In a specific embodiment, an antibody that binds to LRP6 comprises a heavy chain variable region CDR1 of SEQ ID NO: 21; a heavy chain variable region CDR2 of SEQ ID NO: 22; a heavy chain variable region CDR3 of SEQ ID NO: 23; a light chain variable region CDR1 of SEQ ID NO: 24; a light chain variable region CDR2 of SEQ ID NO: 25; and a light chain variable region CDR3 of SEQ ID NO: 26.

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In a specific embodiment, an antibody that binds to LRP6 comprises a heavy chain variable region CDR1 of SEQ ID NO: 47; a heavy chain variable region CDR2 of SEQ ID NO: 48; a heavy chain variable region CDR3 of SEQ ID NO: 49; a light chain variable region CDR1 of SEQ ID NO: 50; a light chain variable region CDR2 of SEQ ID NO: 51; and a light chain variable region CDR3 of SEQ ID NO: 52.

In a specific embodiment, an antibody that binds to LRP6 comprises a heavy chain variable region CDR1 of SEQ ID NO: 69; a heavy chain variable region CDR2 of SEQ ID NO: 70; a heavy chain variable region CDR3 of SEQ ID NO: 71; a light chain variable region CDR1 of SEQ ID NO: 72; a light chain variable region CDR2 of SEQ ID NO: 73; and a light chain variable region CDR3 of SEQ ID NO: 74.

In a specific embodiment, an antibody that binds to LRP6 comprises a heavy chain variable region CDR1 of SEQ ID NO: 93; a heavy chain variable region CDR2 of SEQ ID NO: 94; a heavy chain variable region CDR3 of SEQ ID NO: 95; a light chain variable region CDR1 of SEQ ID NO: 96; a light chain variable region CDR2 of SEQ ID NO: 97; and a light chain variable region CDR3 of SEQ ID NO: 98.

In a specific embodiment, an antibody that binds to LRP6 comprises a heavy chain variable region CDR1 of SEQ ID NO: 115; a heavy chain variable region CDR2 of SEQ ID NO: 116; a heavy chain variable region CDR3 of SEQ ID NO: 117; a light chain variable region CDR1 of SEQ ID NO: 118; a light chain variable region CDR2 of SEQ ID NO: 119; and a light chain variable region CDR3 of SEQ ID NO: 120.

In a specific embodiment, an antibody that binds to LRP6 comprises a VH of SEQ ID NO: 14 and VL of SEQ ID NO: 13. In a specific embodiment, an antibody that binds to LRP6 comprises a VH of SEQ ID NO: 34 and VL of SEQ ID NO: 33. In a specific embodiment, an antibody that binds to LRP6 comprises a VH of SEQ ID NO: 35 and VL of SEQ ID NO: 36. In a specific embodiment, an antibody that binds to LRP6 comprises a VH of SEQ ID NO; 43 and VL of SEQ ID NO: 44. In a specific embodiment, an antibody that binds to LRP6 comprises aVH of SEQ ID NO: 60 and VL of SEQ ID NO: 59. In a specific embodiment, an antibody that binds to LRP6 comprises a VH of SEQ ID NO; 62 and VL of SEQ ID NO: 61. In a specific embodiment, an antibody that binds to LRP6 comprises a SEQ ID NO: 82 and VL of SEQ ID NO: 81. In a specific embodiment, an antibody that binds to LRP6 comprises a VH of SEQ ID NO; 90 and VL of SEQ ID NO: 89. In a specific embodiment, an antibody that binds to LRP6 comprises a VH of

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SEQ ID NO: 106 and VL of SEQ ID NO: 105. In a specific embodiment, an antibody that binds to LRP6 comprises a VH of SEQ ID NO: 108 and VL of SEQ ID NO: 107. In a specific embodiment, an antibody that binds to LRP6 comprises aVH of SEQ ID NO: 128 and VL of SEQ ID NO: 127. In a specific embodiment, an antibody that binds to LRP6 comprises a VH of SEQ ID NO: 130 and VL of SEQ ID NO: 129. In a specific embodiment, an antibody that binds to LRP6 comprises a VH of SEQ ID NO: 138 and VL of SEQ ID NO: 137.

In one embodiment, the LRP6 antibodies are antagonist antibodies. In one embodiment, the LRP6 antibodies are agonist antibodies. In certain embodiments, an antibody that binds to LRP6 is an antibody that is described in Table 1.

As used herein, a human antibody comprises heavy or light chain variable regions or full length heavy or light chains that are "the product of" or "derived from" a particular germline sequence if the variable regions or full length chains of the antibody are obtained from a system that uses human germline immunoglobulin genes. Such systems include immunizing a transgenic mouse carrying human immunoglobulin genes with the antigen of interest or screening a human immunoglobulin gene library displayed on phage with the antigen of interest. A human antibody that is "the product of" or "derived from" a human germline immunoglobulin sequence can be identified as such by comparing the amino acid sequence of the human antibody to the amino acid sequences of human germline immunoglobulins and selecting the human germline immunoglobulin sequence that is closest in sequence (*i.e.*, greatest % identity) to the sequence of the human antibody. A human antibody that is "the product of" or "derived from" a particular human germline immunoglobulin sequence may contain amino acid differences as compared to the germline sequence, due to, for example, naturally occurring somatic mutations or intentional introduction of site-directed mutations. However, in the VH or VL framework regions, a selected human antibody typically is at least 90% identical in amino acids sequence to an amino acid sequence encoded by a human germline immunoglobulin gene and contains amino acid residues that identify the human antibody as being human when compared to the germline immunoglobulin amino acid sequences of other species (*e.g.*, murine germline sequences). In certain cases, a human antibody may be at least 60%, 70%, 80%, 90%, or at least 95%, or even at least 96%, 97%, 98%, or 99% identical in amino acid sequence to the amino acid sequence encoded by the germline immunoglobulin gene. Typically, a recombinant human antibody will display no more

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than 10 amino acid differences from the amino acid sequence encoded by the human germline immunoglobulin gene in the VH or VL framework regions. In certain cases, the human antibody may display no more than 5, or even no more than 4, 3, 2, or 1 amino acid difference from the amino acid sequence encoded by the germline immunoglobulin gene.

The antibodies disclosed herein can be derivatives of single chain antibodies, diabodies, domain antibodies, nanobodies, and unibodies. A "single-chain antibody" (scFv) consists of a single polypeptide chain comprising a VL domain linked to a V-domain wherein VL domain and VH domain are paired to form a monovalent molecule. Single chain antibody can be prepared according to method known in the art (see, for example, Bird *et al.*, (1988) Science 242:423-426 and Huston *et al.*, (1988) Proc. Natl. Acad. Sci. USA 85:5879-5883). A "disbud" consists of two chains, each chain comprising a heavy chain variable region connected to a light chain variable region on the same polypeptide chain connected by a short peptide linker, wherein the two regions on the same chain do not pair with each other but with complementary domains on the other chain to form a bispecific molecule. Methods of preparing diabodies are known in the art (See, e.g., Holliger *et al.*, (1993) Proc. Natl. Acad. Sci. USA 90:6444-6448, and Poljak *et al.*, (1994) Structure 2:1121-1123). Domain antibodies (dAbs) are small functional binding units of antibodies, corresponding to the variable regions of either the heavy or light chains of antibodies. Domain antibodies are well expressed in bacterial, yeast, and mammalian cell systems. Further details of domain antibodies and methods of production thereof are known in the art (see, for example, U.S. Pat. Nos. 6,291,158; 6,582,915; 6,593,081; 6,172,197; 6,696,245; European Patents 0368684 & 0616640; WO05/035572, WO04/101790, WO04/081026, WO04/058821, WO04/003019 and WO03/002609. Nanobodies are derived from the heavy chains of an antibody. A nanobody typically comprises a single variable domain and two constant domains (CH2 and CH3) and retains antigen-binding capacity of the original antibody. Nanobodies can be prepared by methods known in the art (See e.g., U.S. Pat. No. 6,765,087, U.S. Pat. No. 6,838,254, WO 06/079372). Unibodies consist of one light chain and one heavy chain of a IgG4 antibody. Unibodies may be made by the removal of the hinge region of IgG4 antibodies. Further details of unibodies and methods of preparing them may be found in WO2007/059782.

In addition to Wnt ligands LRP6 Propeller 1 antibodies are expected to inhibit the interaction with other Propeller 1 binding ligands (e.g. Sclerostin, Dkk1). Similarly,

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Propeller 3 antibodies are expected to inhibit the interaction with other propeller 3 binding ligands (e.g. Dkk1). Furthermore, propeller 1 and 3 binding antibodies may be expected to affect the activity of other Wnt signaling modulators e.g. R-spondins

Homologous antibodies

In yet another embodiment, the present invention provides an antibody or fragment thereof comprising amino acid sequences that are homologous to the sequences described in Table 1, and the antibody binds to a LRP6 protein (*e.g.*, human and/or cynomologus LRP6), and retains the desired functional properties of those antibodies described in Table 1.

For example, the invention provides an isolated monoclonal antibody (or a functional fragment thereof) comprising a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an amino acid sequence that is at least 80%, at least 90%, or at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 34, 36, 44, 60, and 62; the light chain variable region comprises an amino acid sequence that is at least 80%, at least 90%, at least 95% , or at least 98% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 13, 33, 37, 43, 59, and 61; the antibody binds to β-propeller 1 of LRP6 (*e.g.*, human and/or cynomologus LRP6), and inhibits the signaling activity of β-propeller 1 dependent Wnt proteins, which can be measured in Wnt reporter gene assay or other measure of Wnt directed signaling (e.g., LRP6 phosphorylation, β-catenin stabilization and nuclear translocation, cellular proliferation/ survival) as described herein. In a specific example, such antibodies have an EC_{50} value in a Wnt1 assay of less than 10 nM when using conditioned medium or using transfected cells.

For example, the invention provides an isolated monoclonal antibody (or a functional fragment thereof) comprising a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an amino acid sequence that is at least 80%, at least 90%, at least 95%, or at least 98% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 82, 89, 106, 108, 128, 130, and 138; the light chain variable region comprises an amino acid sequence that is at least 80%, at least 90%, at least 95%, or at least 98% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 81, 90,105, 107,127, 129, and 137; the antibody binds to β-propeller 3 of LRP6 (*e.g.*, human and/or cynomologus LRP6),

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and inhibits the signaling activity of β-propeller 3 dependent Wnt proteins, which can be measured in Wnt reporter gene assay or other measure of Wnt directed signaling (e.g., LRP6 phosphorylation, β-catenin stabilization and nuclear translocation, cellular proliferation/ survival) as described herein. In a specific example, such antibodies have an EC_{50} value in a Wnt3a assay of less than 10 nM when using conditioned medium or using transfected cells.

Further for Propeller 1 antibodies, variable heavy chain parental nucleotide sequences are shown in SEQ ID NOs: 16, 38, and 64. Variable light chain parental nucleotide sequences are shown in SEQ ID NOs: 15, 37, and 63. Full length heavy chain sequences optimized for expression in a mammalian cell are shown in SEQ ID NOs: 20, 42, and 68. Full length light chain sequences optimized for expression in a mammalian cell are shown in SEQ ID NOs: 19, 41, and 67. Other antibodies of the invention include amino acids or nucleic acids that have been mutated, yet have at least 60%, 70%, 80%, 90%, 95% or 98% identity identity to the sequences described above. In some embodiments, it include mutant amino acid sequences wherein no more than 1, 2, 3, 4 or 5 amino acids have been mutated by amino acid deletion, insertion or substitution in the variable regions when compared with the variable regions depicted in the sequence described above.

Further for Propeller 3 antibodies, variable heavy chain parental nucleotide sequences are shown in SEQ ID NO: 84, 110, and 132. Variable light chain parental nucleotide sequences are shown in SEQ ID NO: 83, 109, and 131. Full length heavy chain sequences optimized for expression in a mammalian cell are shown in SEQ ID NO: 88, 91, 114, 136, and 140. Full length light chain nucleotide sequences optimized for expression in a mammalian cell are shown in SEQ ID NO: 87, 92, 113, 135, and 139. Other antibodies of the invention include amino acids or nucleic acids that have been mutated, yet have at least 60%, 70%, 80%, 90%, 95% or 98% identity identity to the sequences described above. In some embodiments, it include mutant amino acid sequences wherein no more than 1, 2, 3, 4 or 5 amino acids have been mutated by amino acid deletion, insertion or substitution in the variable regions when compared with the variable regions depicted in the sequence described above.

In other embodiments, the VH and/or VL amino acid sequences may be 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98% or 99% identical to the sequences set forth in Table 1.

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In other embodiments, the VH and/or VL amino acid sequences may be identical except an amino acid substitution in no more than 1, 2, 3, 4 or 5 amino acid position.

An antibody having VH and VL regions having high (*i. e.*, 80% or greater) identity to the VH and VL regions of those Propeller 1 antibodies described in Table 1 can be obtained by mutagenesis (*e.g.*, site-directed or PCR-mediated mutagenesis) of nucleic acid molecules encoding SEQ ID NOs: 14, 34, 60, 13, 33, and 59 respectively, followed by testing of the encoded altered antibody for retained function using the functional assays described herein.

An antibody having VH and VL regions having high (*i. e.*, 80% or greater) identity to the VH and VL regions of those Propeller 3 antibodies described in Table 1 can be obtained by mutagenesis (*e.g.*, site-directed or PCR-mediated mutagenesis) of nucleic acid molecules encoding SEQ ID NOs: 82, 106, 128, 81, 105, and 127 respectively, followed by testing of the encoded altered antibody for retained function using the functional assays described herein.

In other embodiments, the variable regions of heavy chain and/or light chain nucleotide sequences may be 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98% or 99% identical to the sequences set forth above

As used herein, "percent identity" between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % identity equals number of identical positions/total number of positions x 100), taking into account the number of gaps, and the length of each gap, which needs to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm, as described in the non-limiting examples below.

Additionally or alternatively, the protein sequences of the present invention can further be used as a "query sequence" to perform a search against public databases to, for example, identifies related sequences. For example, such searches can be performed using the BLAST program (version 2.0) of Altschul *et al.* (1990) J.Mol. Biol. 215:403-10.

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Antibodies with Conservative Modifications

In certain embodiments, an antibody of the invention has a heavy chain variable region comprising CDR1, CDR2, and CDR3 sequences and a light chain variable region comprising CDR1, CDR2, and CDR3 sequences, wherein one or more of these CDR sequences have specified amino acid sequences based on the antibodies described herein or conservative modifications thereof, and wherein the antibodies retain the desired functional properties of the LRP6 antibodies of the invention.

Accordingly, the invention provides an isolated Propeller 1 monoclonal antibody, or a functional fragment thereof, consisting of a heavy chain variable region comprising CDR1, CDR2, and CDR3 sequences and a light chain variable region comprising CDR1, CDR2, and CDR3 sequences, wherein: the heavy chain variable region CDR1 amino acid sequences are selected from the group consisting of SEQ ID NOs: 1, 21, and, 47, and conservative modifications thereof; the heavy chain variable region CDR2 amino acid sequences are selected from the group consisting of SEQ ID NOs: 2, 22, and 48, , and conservative modifications thereof; the heavy chain variable region CDR3 amino acid sequences are selected from the group consisting of SEQ ID NOs: 3, 23, and 49, and conservative modifications thereof; the light chain variable regions CDR1 amino acid sequences are selected from the group consisting of SEQ ID NOs: 4, 24, 50, and conservative modifications thereof; the light chain variable regions CDR2 amino acid sequences are selected from the group consisting of SEQ ID NOs: 5, 25, and 51, and conservative modifications thereof; the light chain variable regions of CDR3 amino acid sequences are selected from the group consisting of SEQ ID NOs: 6, 26, and 52, and conservative modifications thereof; the antibody or fragment thereof specifically binds to LRP6, and inhibits LRP6 activity by inhibiting a Wnt signaling pathway, which can be measured in Wnt reporter gene assay or other measure of Wnt directed signaling (e.g., LRP6 phosphorylation, β-catenin stabilization and nuclear translocation, cellular proliferation/ survival) as described herein.

Accordingly, the invention provides an isolated Propeller 3 monoclonal antibody, or a fragment thereof, consisting of a heavy chain variable region comprising CDR1, CDR2, and CDR3 sequences and a light chain variable region comprising CDR1, CDR2, and CDR3 sequences, wherein: the heavy chain variable region CDR1 amino acid sequences are selected from the group consisting of SEQ ID NOs: 69, 93, and 115, and conservative

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modifications thereof; the heavy chain variable region CDR2 amino acid sequences are selected from the group consisting of SEQ ID NOs: 70, 94, and 116, and conservative modifications thereof; the heavy chain variable region CDR3 amino acid sequences are selected from the group consisting of SEQ ID NOs: 71, 95, and 117, and conservative modifications thereof; the light chain variable regions CDR1 amino acid sequences are selected from the group consisting of SEQ ID NOs:72, 96, and 118, and conservative modifications thereof; the light chain variable regions CDR2 amino acid sequences are selected from the group consisting of SEQ ID NOs: 73, 97, and 119, and conservative modifications thereof; the light chain variable regions of CDR3 amino acid sequences are selected from the group consisting of SEQ ID NOs: 74, 98, and 120, and conservative modifications thereof; the antibody or fragment thereof specifically binds to LRP6, and inhibits activities of Propeller 3-dependent Wnt proteins, which can be measured in Wnt reporter gene assay or other measure of Wnt directed signaling (e.g., LRP6 phosphorylation, β-catenin stabilization and nuclear translocation, cellular proliferation/ survival) as described herein.

Antibodies That Bind to the Same Epitope

The present invention provides antibodies that bind to the same epitope as do the LRP6 antibodies described in Table 1. Additional antibodies can therefore be identified based on their ability to cross-compete (*e.g.*, to competitively inhibit the binding of, in a statistically significant manner) with other antibodies of the invention in LRP6 binding assays. The ability of a test antibody to inhibit the binding of antibodies of the present invention to a LRP6 protein (*e.g.*, human and/or cynomologus LRP6) demonstrates that the test antibody can compete with that antibody for binding to LRP6; such an antibody may, according to non-limiting theory, bind to the same or a related (*e.g.*, a structurally similar or spatially proximal) epitope on the LRP6 protein as the antibody with which it competes. In an embodiment, the antibody that binds to the same epitope on LRP6 as the antibodies of the present invention is a human monoclonal antibody. Such human monoclonal antibodies can be prepared and isolated as described herein.

Engineered and Modified Antibodies

An antibody of the invention further can be prepared using an antibody having one or more of the VH and/or VL sequences shown herein as starting material to engineer a modified antibody, which modified antibody may have altered properties from the

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starting antibody. An antibody can be engineered by modifying one or more residues within one or both variable regions (*i. e.*, VH and/or VL), for example within one or more CDR regions and/or within one or more framework regions. Additionally or alternatively, an antibody can be engineered by modifying residues within the constant region(s), for example to alter the effector function(s) of the antibody.

One type of variable region engineering that can be performed is CDR grafting. Antibodies interact with target antigens predominantly through amino acid residues that are located in the six heavy and light chain complementarity determining regions (CDRs). For this reason, the amino acid sequences within CDRs are more diverse between individual antibodies than sequences outside of CDRs. Because CDR sequences are responsible for most antibody-antigen interactions, it is possible to express recombinant antibodies that mimic the properties of specific naturally occurring antibodies by constructing expression vectors that include CDR sequences from the specific naturally occurring antibody grafted onto framework sequences from a different antibody with different properties (see, *e.g.*, Riechmann *et al.*, (1998) Nature 332:323-327; Jones *et al.*, (1986) Nature 321:522-525; Queen *et al.*, (1989) Proc. Natl. Acad., U.S.A. 86:10029-10033; U.S. Patent No. 5,225,539 to Winter, and U.S. Patent Nos. 5,530,101; 5,585,089; 5,693,762 and 6,180,370 to Queen *et al.*)

Accordingly, another embodiment of the invention pertains to an isolated Propeller 1 monoclonal antibody, or fragment thereof, comprising a heavy chain variable region comprising CDR1 sequences having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 21, and 47; CDR2 sequences having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 22, and 48; CDR3 sequences having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 23, and 49, respectively; and a light chain variable region having CDR1 sequences having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 24, and 50; CDR2 sequences having an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 25, and 51; and CDR3 sequences consisting of an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 26, and 52, respectively. Thus, such antibodies contain the VH and VL CDR sequences of monoclonal antibodies, yet may contain different framework sequences from these antibodies.

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Accordingly, another embodiment of the invention pertains to an isolated Propeller 3 monoclonal antibody, or fragment thereof, comprising a heavy chain variable region comprising CDR1 sequences having an amino acid sequence selected from the group consisting of SEQ ID NOs: 69, 93, and 115; CDR2 sequences having an amino acid sequence selected from the group consisting of SEQ ID NOs: 70, 76, 100, and 116; CDR3 sequences having an amino acid sequence selected from the group consisting of SEQ ID NOs: 71, 95, and 117, respectively; and a light chain variable region having CDR1 sequences having an amino acid sequence selected from the group consisting of SEQ ID NOs: 72, 96, and 118; CDR2 sequences having an amino acid sequence selected from the group consisting of SEQ ID NOs: 73, 97, and 119; and CDR3 sequences consisting of an amino acid sequence selected from the group consisting of SEQ ID NOs: 74, 98, and 120, respectively. Thus, such antibodies contain the VH and VL CDR sequences of monoclonal antibodies, yet may contain different framework sequences from these antibodies.

Such framework sequences can be obtained from public DNA databases or published references that include germline antibody gene sequences. For example, germline DNA sequences for human heavy and light chain variable region genes can be found in the "Vase" human germline sequence database (available on the Internet at www.mrc-cpe.cam.ac.uk/vbase), as well as in Kabat *et al.*, (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242; Chothia *et al.*, (1987) J. Mol. Biol. 196:901-917; Chothia *et al.*, (1989) Nature 342:877-883; and Al-Lazikani *et al.*, (1997) J. Mol. Biol. 273:927-948; Tomlinson *et al.*, (1992) J. fol. Biol. 227:776-798; and Cox *et al.*, (1994) Eur. J Immunol. 24:827-836; the contents of each of which are expressly incorporated herein by reference.

An example of framework sequences for use in the antibodies of the invention are those that are structurally similar to the framework sequences used by selected antibodies of the invention, *e.g.*, consensus sequences and/or framework sequences used by monoclonal antibodies of the invention. The VH CDR1, 2 and 3 sequences, and the VL CDR1, 2 and 3 sequences, can be grafted onto framework regions that have the identical sequence as that found in the germline immunoglobulin gene from which the framework sequence derive, or the CDR sequences can be grafted onto framework regions that contain one or more mutations as compared to the germline sequences. For example, it has been found

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that in certain instances it is beneficial to mutate residues within the framework regions to maintain or enhance the antigen binding ability of the antibody (see *e.g.*, U.S. Patent Nos. 5,530,101; 5,585,089; 5,693,762 and 6,180,370 to Queen *et al*).

Another type of variable region modification is to mutate amino acid residues within the VH and/or VL CDR1, CDR2 and/or CDR3 regions to thereby improve one or more binding properties (*e.g.*, affinity) of the antibody of interest, known as "affinity maturation." Site-directed mutagenesis or PCR-mediated mutagenesis can be performed to introduce the mutation(s) and the effect on antibody binding, or other functional property of interest, can be evaluated in *in vitro* or *in vivo* assays as described herein and provided in the Examples. Conservative modifications (as discussed above) can be introduced. The mutations may be amino acid substitutions, additions or deletions. Moreover, typically no more than one, two, three, four or five residues within a CDR region are altered.

Accordingly, in another embodiment, the invention provides isolated Propeller 1 monoclonal antibodies, or fragment thereof, consisting of a heavy chain variable region having: a VH CDR1 region consisting of an amino acid sequence selected from the group having SEQ ID NOs: 1, 21, and 47or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 1, 21, and 47; a VH CDR2 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 22, and 48, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 2, 22, and 48; a VH CDR3 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 23, and 49, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 3, 23, and 49; a VL CDR1 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 24, and 50, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 4, 24, and 50; a VL CDR2 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 25, and 51, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 5, 25, and 51; and a VL CDR3 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 26, and 52, or

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an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 6, 26, and 52.

Accordingly, in another embodiment, the invention provides isolated Propeller 3 monoclonal antibodies, or fragment thereof, consisting of a heavy chain variable region having: a VH CDR1 region consisting of an amino acid sequence selected from the group having SEQ ID NOs: 69, 93, and 115 or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 69, 93, and 115; a VH CDR2 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 70, 94, and 116, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 70, 94, and 116; a VH CDR3 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 71, 95, and 117, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 71, 95, and 117; a VL CDR1 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 72, 96, and 118, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 72, 96, and 118; a VL CDR2 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 73, 97, and 119, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 73, 97, and 119; and a VL CDR3 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 74, 98, and 120, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 74, 98, and 120.

Grafting Antibody Fragments Into Alternative Frameworks or Scaffolds

A wide variety of antibody/ immunoglobulin frameworks or scaffolds can be employed so long as the resulting polypeptide includes at least one binding region which specifically binds to LRP6. Such frameworks or scaffolds include the 5 main idiotypes of human immunoglobulins, or fragments thereof, and include immunoglobulins of other animal species, preferably having humanized aspects. Novel frameworks, scaffolds and fragments continue to be discovered and developed by those skilled in the art.

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In one aspect, the invention pertains to generating non-immunoglobulin based antibodies using non- immunoglobulin scaffolds onto which CDRs of the invention can be grafted. Known or future non-immunoglobulin frameworks and scaffolds may be employed, as long as they comprise a binding region specific for the target LRP6 protein (*e.g.*, human and/or cynomologus LRP6). Known non-immunoglobulin frameworks or scaffolds include, but are not limited to, fibronectin (Compound Therapeutics, Inc., Waltham, MA), ankyrin (Molecular Partners AG, Zurich, Switzerland), domain antibodies (Domantis, Ltd., Cambridge, MA, and Ablynx nv, Zwijnaarde, Belgium), lipocalin (Pieris Proteolab AG, Freising, Germany), small modular immuno-pharmaceuticals (Trubion Pharmaceuticals Inc., Seattle, WA), maxybodies (Avidia, Inc., Mountain View, CA), Protein A (Affibody AG, Sweden), and affilin (gamma-crystallin or ubiquitin) (Scil Proteins GmbH, Halle, Germany).

The fibronectin scaffolds are based on fibronectin type III domain (*e.g.*, the tenth module of the fibronectin type III (^{10} Fn3 domain)). The fibronectin type III domain has 7 or 8 beta strands which are distributed between two beta sheets, which themselves pack against each other to form the core of the protein, and further containing loops (analogous to CDRs) which connect the beta strands to each other and are solvent exposed. There are at least three such loops at each edge of the beta sheet sandwich, where the edge is the boundary of the protein perpendicular to the direction of the beta strands (see US 6,818,418). These fibronectin-based scaffolds are not an immunoglobulin, although the overall fold is closely related to that of the smallest functional antibody fragment, the variable region of the heavy chain, which comprises the entire antigen recognition unit in camel and llama IgG. Because of this structure, the non-immunoglobulin antibody mimics antigen binding properties that are similar in nature and affinity to those of antibodies. These scaffolds can be used in a loop randomization and shuffling strategy *in vitro* that is similar to the process of affinity maturation of antibodies *in vivo*. These fibronectin-based molecules can be used as scaffolds where the loop regions of the molecule can be replaced with CDRs of the invention using standard cloning techniques.

The ankyrin technology is based on using proteins with ankyrin derived repeat modules as scaffolds for bearing variable regions which can be used for binding to different targets. The ankyrin repeat module is a 33 amino acid polypeptide consisting of two anti-parallel α-helices and a β-turn. Binding of the variable regions is mostly optimized by using ribosome display.

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Avimers are derived from natural A-domain containing protein such as LRP6. These domains are used by nature for protein-protein interactions and in human over 250 proteins are structurally based on A-domains. Avimers consist of a number of different "A-domain" monomers (2-10) linked via amino acid linkers. Avimers can be created that can bind to the target antigen using the methodology described in, for example, U.S. Patent Application Publication Nos. 20040175756; 20050053973; 20050048512; and 20060008844.

Affibody affinity ligands are small, simple proteins composed of a three-helix bundle based on the scaffold of one of the IgG-binding domains of Protein A. Protein A is a surface protein from the bacterium Staphylococcus aureus. This scaffold domain consists of 58 amino acids, 13 of which are randomized to generate affibody libraries with a large number of ligand variants (See *e.g.*, US 5,831,012). Affibody molecules mimic antibodies, they have a molecular weight of 6 kDa, compared to the molecular weight of antibodies, which is 150 kDa. In spite of its small size, the binding site of affibody molecules is similar to that of an antibody.

Anticalins are products developed by the company Pieris ProteoLab AG. They are derived from lipocalins, a widespread group of small and robust proteins that are usually involved in the physiological transport or storage of chemically sensitive or insoluble compounds. Several natural lipocalins occur in human tissues or body liquids. The protein architecture is reminiscent of immunoglobulins, with hypervariable loops on top of a rigid framework. However, in contrast with antibodies or their recombinant fragments, lipocalins are composed of a single polypeptide chain with 160 to 180 amino acid residues, being just marginally bigger than a single immunoglobulin domain. The set of four loops, which makes up the binding pocket, shows pronounced structural plasticity and tolerates a variety of side chains. The binding site can thus be reshaped in a proprietary process in order to recognize prescribed target molecules of different shape with high affinity and specificity. One protein of lipocalin family, the bilin-binding protein (BBP) of Pieris Brassicae has been used to develop anticalins by mutagenizing the set of four loops. One example of a patent application describing anticalins is in PCT Publication No. WO 199916873.

Affilin molecules are small non-immunoglobulin proteins which are designed for specific affinities towards proteins and small molecules. New affilin molecules can be very

quickly selected from two libraries, each of which is based on a different human derived scaffold protein. Affilin molecules do not show any structural homology to immunoglobulin proteins. Currently, two affilin scaffolds are employed, one of which is gamma crystalline, a human structural eye lens protein and the other is "ubiquitin" superfamily proteins. Both human scaffolds are very small, show high temperature stability and are almost resistant to pH changes and denaturing agents. This high stability is mainly due to the expanded beta sheet structure of the proteins. Examples of gamma crystalline derived proteins are described in WO200104144 and examples of "ubiquitin-like" proteins are described in WO2004106368.

Protein epitope mimetics (PEM) are medium-sized, cyclic, peptide-like molecules (MW 1-2kDa) mimicking beta-hairpin secondary structures of proteins, the major secondary structure involved in protein-protein interactions.

In some embodiments, the Fabs are converted to silent IgG1 format by changing the Fc region. For example, antibodies MOR08168, MOR08545, MOR06706, MOR06475, MOR08193, and MOR08473 in Table 1 can be converted to IgG1 format by adding the amino acid sequence:

CDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF
NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA
LPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWES
NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK (SEQ ID NO: 209).

and substituting the light chain with: CS if the light chain is lambda, or C if the light chain is kappa. As used herein, a "silent IgG1" is an IgG1 Fc sequence in which the amino acid sequence has been altered to decrease Fc-mediated effector functions (for example ADCC and/or CDC). Such an antibody will typically have decreased binding to Fc receptors . In some other embodiments, the Fabs are converted to IgG2 format. For example, antibodies MOR08168, MOR08545, MOR06706, MOR06475, MOR08193, and MOR08473 in Table 1 can be converted to IgG2 format by substituting the constant sequence with the constant sequence for the heavy chain of IgG2:

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
VLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCP

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APPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVH NAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKT KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT TPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 210).

Human or humanized antibodies

The present invention provides fully human antibodies that specifically bind to a LRP6 protein (*e.g.*, human and/or cynomologus LRP6). Compared to the chimeric or humanized antibodies, the human LRP6 antibodies of the invention have further decreased antigenicity when administered to human subjects.

The human LRP6 antibodies can be generated using methods that are known in the art. For example, the humaneering technology used to converting non-human antibodies into engineered human antibodies. U.S. Patent Publication No. 20050008625 describes an *in vivo* method for replacing a nonhuman antibody variable region with a human variable region in an antibody while maintaining the same or providing better binding characteristics relative to that of the nonhuman antibody. The method relies on epitope guided replacement of variable regions of a non-human reference antibody with a fully human antibody. The resulting human antibody is generally unrelated structurally to the reference nonhuman antibody, but binds to the same epitope on the same antigen as the reference antibody. Briefly, the serial epitope-guided complementarity replacement approach is enabled by setting up a competition in cells between a "competitor" and a library of diverse hybrids of the reference antibody ("test antibodies") for binding to limiting amounts of antigen in the presence of a reporter system which responds to the binding of test antibody to antigen. The competitor can be the reference antibody or derivative thereof such as a single-chain Fv fragment. The competitor can also be a natural or artificial ligand of the antigen which binds to the same epitope as the reference antibody. The only requirements of the competitor are that it binds to the same epitope as the reference antibody, and that it competes with the reference antibody for antigen binding. The test antibodies have one antigen-binding V-region in common from the nonhuman reference antibody, and the other V-region selected at random from a diverse source such as a repertoire library of human antibodies. The common V-region from the reference antibody serves as a guide, positioning the test antibodies on the same epitope

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on the antigen, and in the same orientation, so that selection is biased toward the highest antigen-binding fidelity to the reference antibody.

Many types of reporter system can be used to detect desired interactions between test antibodies and antigen. For example, complementing reporter fragments may be linked to antigen and test antibody, respectively, so that reporter activation by fragment complementation only occurs when the test antibody binds to the antigen. When the test antibody- and antigen-reporter fragment fusions are co-expressed with a competitor, reporter activation becomes dependent on the ability of the test antibody to compete with the competitor, which is proportional to the affinity of the test antibody for the antigen. Other reporter systems that can be used include the reactivator of an auto-inhibited reporter reactivation system (RAIR) as disclosed in U.S. Patent Application Ser. No. 10/208,730 (Publication No. 20030198971), or competitive activation system disclosed in U.S. Patent Application Ser. No. 10/076,845 (Publication No. 20030157579).

With the serial epitope-guided complementarity replacement system, selection is made to identify cells expresses a single test antibody along with the competitor, antigen, and reporter components. In these cells, each test antibody competes one-on-one with the competitor for binding to a limiting amount of antigen. Activity of the reporter is proportional to the amount of antigen bound to the test antibody, which in turn is proportional to the affinity of the test antibody for the antigen and the stability of the test antibody. Test antibodies are initially selected on the basis of their activity relative to that of the reference antibody when expressed as the test antibody. The result of the first round of selection is a set of "hybrid" antibodies, each of which is comprised of the same non-human V-region from the reference antibody and a human V-region from the library, and each of which binds to the same epitope on the antigen as the reference antibody. One of more of the hybrid antibodies selected in the first round will have an affinity for the antigen comparable to or higher than that of the reference antibody.

In the second V-region replacement step, the human V-regions selected in the first step are used as guide for the selection of human replacements for the remaining non-human reference antibody V-region with a diverse library of cognate human V-regions. The hybrid antibodies selected in the first round may also be used as competitors for the second round of selection. The result of the second round of selection is a set of fully human antibodies which differ structurally from the reference antibody, but which

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compete with the reference antibody for binding to the same antigen. Some of the selected human antibodies bind to the same epitope on the same antigen as the reference antibody. Among these selected human antibodies, one or more binds to the same epitope with an affinity which is comparable to or higher than that of the reference antibody.

Using one of the mouse or chimeric LRP6 antibodies described above as the reference antibody, this method can be readily employed to generate human antibodies that bind to human LRP6 with the same binding specificity and the same or better binding affinity. In addition, such human LRP6 antibodies can also be commercially obtained from companies which customarily produce human antibodies, *e.g.*, KaloBios, Inc. (Mountain View, CA).

Camelid antibodies

Antibody proteins obtained from members of the camel and dromedary (Camelus bactrianus and Calelus dromaderius) family including new world members such as llama species (Lama paccos, Lama glama and Lama vicugna) have been characterized with respect to size, structural complexity and antigenicity for human subjects. Certain IgG antibodies from this family of mammals as found in nature lack light chains, and are thus structurally distinct from the typical four chain quaternary structure having two heavy and two light chains, for antibodies from other animals. See PCT/EP93/02214 (WO 94/04678 published 3 March 1994).

A region of the camelid antibody which is the small single variable domain identified as VHH can be obtained by genetic engineering to yield a small protein having high affinity for a target, resulting in a low molecular weight antibody-derived protein known as a "camelid nanobody". See U.S. patent number 5,759,808 issued June 2, 1998; see also Stijlemans *et al.*, (2004) J Biol Chem 279:1256-1261; Dumoulin *et al.*, (2003) Nature 424:783-788; Pleschberger *et al.* (2003) Bioconjugate Chem 14:440-448; Cortez-Retamozo *et al.*(2002) Int J Cancer 89:456-62; and Lauwereys *et al.* (1998) EMBO J 17:3512-3520. Engineered libraries of camelid antibodies and antibody fragments are commercially available, for example, from Ablynx, Ghent, Belgium. As with other antibodies of non-human origin, an amino acid sequence of a camelid antibody can be altered recombinantly to obtain a sequence that more closely resembles a human sequence, *i.e.*, the nanobody can be "humanized". Thus the natural low antigenicity of camelid antibodies to humans can be further decreased.

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The camelid nanobody has a molecular weight approximately one-tenth that of a human IgG molecule, and the protein has a physical diameter of only a few nanometers. One consequence of the small size is the ability of camelid nanobodies to bind to antigenic sites that are functionally invisible to larger antibody proteins, *i.e.*, camelid nanobodies are useful as reagents detect antigens that are otherwise cryptic using classical immunological techniques, and as possible therapeutic agents. Thus yet another consequence of small size is that a camelid nanobody can inhibit as a result of binding to a specific site in a groove or narrow cleft of a target protein, and hence can serve in a capacity that more closely resembles the function of a classical low molecular weight drug than that of a classical antibody.

The low molecular weight and compact size further result in camelid nanobodies being extremely thermostable, stable to extreme pH and to proteolytic digestion, and poorly antigenic. Another consequence is that camelid nanobodies readily move from the circulatory system into tissues, and even cross the blood-brain barrier and can treat disorders that affect nervous tissue. Nanobodies can further facilitated drug transport across the blood brain barrier. See U.S. patent application 20040161738 published August 19, 2004. These features combined with the low antigenicity to humans indicate great therapeutic potential. Further, these molecules can be fully expressed in prokaryotic cells such as E. coli and are expressed as fusion proteins with bacteriophage and are functional.

Accordingly, a feature of the present invention is a camelid antibody or nanobody having high affinity for LRP6. In certain embodiments herein, the camelid antibody or nanobody is naturally produced in the camelid animal, *i.e.*, is produced by the camelid following immunization with LRP6 or a peptide fragment thereof, using techniques described herein for other antibodies. Alternatively, the LRP6 camelid nanobody is engineered, *i.e.*, produced by selection for example from a library of phage displaying appropriately mutagenized camelid nanobody proteins using panning procedures with LRP6 as a target as described in the examples herein. Engineered nanobodies can further be customized by genetic engineering to have a half life in a recipient subject of from 45 minutes to two weeks. In a specific embodiment, the camelid antibody or nanobody is obtained by grafting the CDRs sequences of the heavy or light chain of the human antibodies of the invention into nanobody or single domain antibody framework sequences, as described for example in PCT/EP93/02214.

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Multivalent Antibodies

The present invention features multivalent antibodies (e.g., biparatopic, bispecific antibodies) comprising at least two receptor binding domains for two different binding sites on one or more target(s) receptors. Clinical benefits may be provided by the binding of two or more binding specificities within one antibody (Morrison *et al.*, (1997) Nature Biotech. 15:159-163; Alt *et al.* (1999) FEBS Letters 454: 90-94; Zuo *et al.*, (2000) Protein Engineering 13:361-367; Lu *et al.*, (2004) JBC 279:2856-2865; Lu *et al.*, (2005) JBC 280:19665-19672; Marvin *et al.*, (2005) Acta Pharmacologica Sinica 26:649-658; Marvin *et al.*, (2006) Curr Opin Drug Disc Develop 9:184-193; Shen *et al.*, (2007) J Immun Methods 218:65-74; Wu *et al.*, (2007) Nat Biotechnol. 11:1290-1297; Dimasi *et al.*, (2009) J. Mol Biol. 393:672-692; and Michaelson *et al.*, (2009) mAbs 1:128-141.

The present invention is based on the discovery that the multivalent antibodies (e.g., a single LRP6 biparatopic or bispecific antibody) have the ability to inhibit both propeller 1 (e.g. Wnt1 and propeller 3 (e.g. Wnt3) ligand-mediated signaling Furthermore, and unexpectedly, the multivalent antibodies (e.g., a single LRP6 biparatopic or bispecific antibody) display no significant potentiation of a Wnt signal. The multivalent antibodies bind to distinct LRP6 β-propeller regions. Propeller 1 antibodies bind to the β-propeller 1 domain and block propeller1-dependent Wnts such as Wnt1, Wnt2, Wnt6, Wnt7A, Wnt7B, Wnt9, Wnt10A, Wnt10B and inhibit a Wnt 1 signal transduction pathway. Propeller 3 antibodies bind to the β-propeller 3 domain and block propeller3-dependent Wnts such as Wnt3a and Wnt3 and inhibit a Wnt3 signal transduction pathway. LRP6 antibodies differentiate propeller 1 and propeller 3 ligands into two separate classes and bind to distinct epitopes of the LRP6 target receptor. Conversion of fragments of the LRP6 antibodies (e.g., Fabs) to full length IgG antibody results in an antibody that potentiates (enhances) a Wnt signal in the presence of another protein such as a Wnt 1 or Wnt 3 ligand.

Multivalent antibodies provide advantages over traditional antibodies for example, expanding the repertoire of targets, having new binding specificities, increased potency, and no signal potentiation. A single LRP6 multivalent antibody can bind to multiple propeller regions on a single LRP6 target receptor on the same cell, and inhibit Wnt signaling. In one embodiment, the multivalent antibody binds to any combination of a β-propeller regions selected from the group consisting of propeller 1, propeller 2, propeller

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3, and propeller 4. In one embodiment, the multivalent antibody binds to propeller 1 and propeller 3 domains of LRP6. Thus, a single LRP6 multivalent antibody has increased potency of action by binding to multiple β-propeller regions and inhibiting Wnt signaling mediated by each domain. For example, a single LRP6 multivalent antibody inhibits both propeller 1 and propeller 3 mediated Wnt signaling by binding to both propeller 1 and propeller 3 domains, respectively. The increased potency of action may be due to increased avidity or better binding of the LRP6 multivalent antibody.

In one embodiment, multivalent antibodies are produced by linking an scFv to an IgG antibody. The VH and VL domains used to make an scFv may be derived from the same or from different antibodies. The scFv comprises at least one, two, three, four, five, or six CDRs.

The Fc region of the IgG antibody and the scFv fragment may be linked together in many different orientations. In one embodiment, the scFv is linked to the C-terminus of the Fc region. In other embodiments, the scFv is linked to the N-terminus of the Fc region. In other embodiments, scFvs are are linked to both the N-terminus and C-terminus of the Fc region. In another embodiment, the scFv can be linked to a light chain of an antibody. The multivalent antibodies of the invention can bind multiple binding sites of a target receptor concurrently. The receptor binding domains of multivalent antibodies of the invention may bind at least 1, 2, 3, 4, 5, 6, 7, 8or more binding sites. Each receptor binding domain can be specific for the same binding site. The multivalent antibodiesof the invention comprise one or more receptor binding domains that are specific for distinct epitopes on the same target receptor, e.g., β-propeller 1 domain or β-propeller 3 domain of LRP6. Alternatively, the multivalent antibodies of the invention comprise one or more receptor binding domains that are specific for epitopes on different target receptors, e.g., LRP6 and a receptor that is not LRP6 such as Erb, cmet, IGFR1, Smoothened, and Notch receptors.

Each receptor binding domain within the multivalent antibodies of the invention can also have different (i.e. a higher or lower) affinity for the antigen compared to the traditional antibodies.

In one embodiment, the multivalent antibodies of the invention are biparatopic antibody comprising at least one receptor binding domain for a first eptope on LRP6 target receptor

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and a second receptor binding domain for a second epitope on the same LRP6 target receptor.

The multivalent antibody of the invention comprises at least one CDR of an antibody, at least two CDRs of a given antibody, or at least three CDRs of a given antibody, at least four CDRs of a given antibody, at least five CDRs of a given antibody, or at least six CDRs of a given antibody. The multivalent antibody of the invention comprises at least one VH domain of an antibody, at least one VL domain of a given antibody, or at least one VH domain and one VL domain of an antibody. ScFv molecules can be constructed in a VH-linker-VL orientation or VL-linker-VH orientation.

The stability of scFv molecules of the invention or fusion proteins comprising them can be evaluated in reference to the biophysical properties (e.g., thermal stability) of a conventional control scFv molecule or a full length antibody. In one embodiment, the multivalent antibodies of the invention have a thermal stability that is greater than about 0.1, about 0.25, about 0.5, about 0.75, about 1, about 1.25, about 1.5, about 1.75, about 2, about 2.5, about about 3, about 3.5, about 4, about 4.5, about 5, about 5.5, about 6, about 6.5, about 7, about 7.5, about 8, about 8.5, about 9, about 9.5, about 10 degrees, about 11 degrees, about 12 degrees, about 13 degrees, about 14 degrees, or about 15 degrees Celsius than a control binding molecule (e.g. a conventional scFv molecule).

The scFv molecules comprise an scFv linker with an optimized length and/or amino acid composition. Preferred scFv linkers of the invention improve the thermal stability of a multivalent antibody of the invention by at least about 2°C or 3°C as compared to a conventional antibody. In one embodiment, a multivalent antibody of the invention has a 1°C improved thermal stability as compared to a conventional antibody. In another embodiment, a multivalent antibody of the invention has a 2°C improved thermal stability as compared to a conventional antibody. In another embodiment, a multivalent antibody of the invention has a 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15°C improved thermal stability as compared to a conventional antibody. Comparisons can be made, for example, between the scFv molecules of the invention and scFv molecules made using prior art methods or between scFv molecules and Fab fragments of an antibody from which the scFv VH and VL were derived. Thermal stability can be measured using methods known in the art. For example, in one embodiment, Tm can be measured. Methods for measuring Tm and other

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methods of determining protein stability are described in more detail below.

In one embodiment, the scFv linker consists of the amino acid sequence $(Gly_4Ser)_3$ or comprises a $(Gly_4Ser)_4$ sequence. Other exemplary linkers comprise or consist of $((Gly_4Ser)_5$ and $(Gly_4Ser)_6$ sequences. scFv linkers of the invention can be of varying lengths. In one embodiment, an scFv linker of the invention is from about 5 to about 50 amino acids in length. In another embodiment, an scFv linker of the invention is from about 10 to about 40 amino acids in length. In another embodiment, an scFv linker of the invention is from about 15 to about 30 amino acids in length. In another embodiment, an scFv linker of the invention is from about 15 to about 20 amino acids in length. Variation in linker length may retain or enhance activity, giving rise to superior efficacy in activity studies. scFv linkers can be introduced into polypeptide sequences using techniques known in the art. For example, PCR mutagenesis can be used. Modifications can be confirmed by DNA sequence analysis. Plasmid DNA can be used to transform host cells for stable production of the polypeptides produced.

In one embodiment, a scFv molecule of the invention comprises an scFv linker having the amino acid sequence of $(Gly_4Ser)_3$ or $(Gly_4Ser)_4$ interposed between a VH domain and a VL domain, wherein the VH and VL domains are linked by a disulfide bond.

The scFv molecules of the invention can further comprise at least one disulfide bond which links an amino acid in the VL domain with an amino acid in the VH domain. Cysteine residues are necessary to provide disulfide bonds. Disulfide bonds can be included in an scFv molecule of the invention, e.g., to connect FR4 of VL and FR2 of VH or to connect FR2 of VL and FR4 of VH. Exemplary positions for disulfide bonding include: 43, 44, 45, 46, 47, 103, 104, 105, and 106 of VH and 42, 43, 44, 45, 46, 98, 99, 100, and 101 of VL, Kabat numbering. Modifications of the genes which encode the VH and VL domains may be accomplished using techniques known in the art, for example, site-directed mutagenesis.

Mutations in scFv alter the stability of the scFv and improve the overall stability of the multivalent antibody comprising the mutated scFv compared to a multivalent antibody without the mutated in the scFv. Mutations to the scFv can be generated as shown in the Examples. Stability of the mutated scFv is compared against the unmutated scFv using

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measurements such as Tm, temperature denaturation and temperature aggregation as described in the Examples. The binding capacity of the mutant scFvs can be determined using assays such as ELISA.

In one embodiment, a multivalent antibody of the invention comprises at least one mutation in an scFv such that the mutated scFv confers improved stability to the multivalent antibody. In another embodiment, a multivalent antibody of the invention comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 mutations in an scFv such that the mutated scFv confers improved stability to the multivalent antibody. In another embodiment, a multivalent antibody of the invention comprises a comination of mutations in an scFv such that the mutated scFv confers improved stability to the multivalent antibody.

Multivalent antibodies, such as biparatopic antibodies of the invention are disclosed herein. These biparatopic antibodies bind to one or more epitopes of LRP6. ScFvs are linked to an Fc region, for example at the hinge region, using linkers such as GlySer linkers. In one embodiment, the invention pertains to an antibody or antigen binding fragment that binds to the β-propeller 1 domain of LRP6 linked to an scFv that binds to the β-propeller 3 domain of LRP6 using a $(GlyGlySer)_2$ linker lined to the CH3 region of the Fc. In one embodiment, a full length IgG antibody that binds to the LPR6 β-propeller 1 domain is used to attach a scFv fragment of an antibody that binds to the LRP6 β-propeller 3 domain.

Multivalent antibodies, such as biparatopic antibodies of the invention can be constructed using any combination of heavy and light chain sequences shown in Table 2.

Table 2: Biparatopic Constructs of the Invention

Construct	Heavy Chain SEQ ID NO:	Light Chain SEQ ID NO:
BiPa Propeller 1 IgG/Propeller 3 scFv attached to Fc	166, 171, 173, 175, 195, 201, and 207	170, 193, 199, and 205
Alternative BiPa Propeller 1 IgG/Propeller 3 scFv	177	181

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attached to light chain		
Reverse BiPa Propeller 3 IgG/Propeller 1 scFv attached to Fc	187, and 189	185

Accordingly, the invention pertains to biparatopic antibodies constructed using a Propeller 1 IgG antibody and a Propeller 3 scFv. In one embodiment, the biparatopic antibody is constructed using any heavy chains sequence selected from the group consisting of SEQ ID NOs: 166, 171, 173, 175, 195, 201, and 207; and any light chain sequence selected from the group consisting of SEQ ID NOs: 170, 193, 199, and 205. In one embodiment, the biparatopic antibody comprises heavy and light chain sequences selected from the group consisting of SEQ ID NOs: 166/170, 171/170, 173/170, 175/170, 201/199, 207/205, and 195/193.

In one embodiment, the biparatopic antibody comprises heavy chain SEQ ID NO: 166 and light chain SEQ ID NO: 170. In one embodiment, the biparatopic antibody comprises heavy chain SEQ ID NO: 171 and light chain SEQ ID NO: 170. In one embodiment, the biparatopic antibody comprises heavy chain SEQ ID NO: 173 and light chain SEQ ID NO: 170. In one embodiment, the biparatopic antibody comprises heavy chain SEQ ID NO: 175 and light chain SEQ ID NO: 170. In one embodiment, the biparatopic antibody comprises heavy chain SEQ ID NO: 201 and light chain SEQ ID NO: 199. In one embodiment, the biparatopic antibody comprises heavy chain SEQ ID NO: 207 and light chain SEQ ID NO: 205. In one embodiment, the biparatopic antibody comprises heavy chain SEQ ID NO: 195 and light chain SEQ ID NO: 193.

In another embodiment, the biparatopic antibody is an "alternative biparatopic antibody" whereby the scFv is attached to the light chain of IgG. In one embodiment, the biparatopic antibody comprises heavy chain SEQ ID NO: 177 and light chain SEQ ID NO: 181.

In another embodiment, a full length IgG antibody that binds to the LPR6 β-propeller 3 domain is used to attach a scFv fragment of an antibody that binds to the LRP6 β-propeller 1 domain, referred to as "reverse biparatopic". In one embodiment, reverse biparatopic antibodies of the invention are constructed using a Propeller 3 IgG antibody

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and a Propeller 1 scFv. In one embodiment, a reverse biparatopic antibody is constructed using any heavy chains sequence selected from the group consisting of SEQ ID NOs: 187 and 189; and a light chain sequence SEQ ID NO: 185. In one embodiment, the reverse biparatopic antibody comprises heavy SEQ ID NO: 187 and light chain SEQ ID NO: 185. In one embodiment, the reverse biparatopic antibody comprises heavy chain SEQ ID NO: 189 and light chain SEQ ID NO: 185.

The invention also pertains to biparatopic antibodies having a heavy chain variable region comprising a CDR1 sequences having an amino acid sequence selected from the group consisting of 1, 21, and 47, CDR2 sequences having an amino acid sequence selected from the group consisting of 2, 22, and 48, CDR3 sequences having an amino acid sequence selected from the group consisting of 3, 23, and 49, respectively; a light chain a light chain variable region comprising a CDR1 sequences having an amino acid sequence selected from the group consisting of 4, 24, and 50, CDR2 sequences having an amino acid sequence selected from the group consisting of 5, 25, and, 51, CDR3 sequences having an amino acid sequence selected from the group consisting of 6, 26, and 52; combined with a heavy chain variable region comprising a CDR1 sequences having an amino acid sequence selected from the group consisting of 69, 93, and 115, CDR2 sequences having an amino acid sequence selected from the group consisting of 70, 94, and 116, CDR3 sequences having an amino acid sequence selected from the group consisting of 71, 95, and 117, respectively; a light chain a light chain variable region comprising a CDR1 sequences having an amino acid sequence selected from the group consisting of 72, 96, and 118, CDR2 sequences having an amino acid sequence selected from the group consisting of 73, 97, and 119, CDR3 sequences having an amino acid sequence selected from the group consisting of 74, 98 and 120; the antibody binds to LRP6 (e.g., human and/or cynomologous LRP6) and inhibits LRP6 biological activity which can be measured in a Wnt reporter gene assay or any other measure of Wnt directed signaling (e.g., LRP6 phosphorylation, β-catenin stabilization and nuclear translocation, cellular proliferation/ survival) as described herein.

Antibodies that can be employed in the multivalent antibodies of the invention are human, murine, chimeric and humanized monoclonal antibodies.

The multivalent antibodies of the present invention can be prepared by conjugating the constituent receptor binding domains, using methods known in the art. For example, each

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receptor binding domain of the multivalent antibody can be generated separately and then conjugated to one another. When the receptor binding domains are proteins or peptides, a variety of coupling or cross-linking agents can be used for covalent conjugation. Examples of cross-linking agents include protein A, carbodiimide, N-succinimidyl-S-acetyl-thioacetate (SATA), 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB), o-phenylenedimaleimide (oPDM), N-succinimidyl-3-(2-pyridyldithio)propionate (SPDP), and sulfosuccinimidyl 4-(N-maleimidomethyl) cyclohaxane-l-carboxylate (sulfo-SMCC) (see *e.g.*, Karpovsky *et al.*, (1984) J. Exp. Med. 160:1686; Liu *et al.* (1985) Proc. Natl. Acad. Sci. USA 82:8648). Other methods include those described in Paulus (1985) Behring Ins. Mitt. No. 78:118-132; Brennan *et al.*, (1985) Science 229:81-83), and Glennie *et al.*, (1987) J. Immunol. 139: 2367-2375). Conjugating agents are SATA and sulfo-SMCC, both available from Pierce Chemical Co. (Rockford, IL).

When the receptor binding domains are antibodies, they can be conjugated by sulfhydryl bonding of the C-terminus hinge regions of the two heavy chains. In a particularly embodiment, the hinge region is modified to contain an odd number of sulfhydryl residues, for example one, prior to conjugation.

Alternatively, the receptor binding domains can be encoded in the same vector and expressed and assembled in the same host cell. This method is particularly useful where the multivalent antibody is a mAb x mAb, mAb x Fab, Fab x $F(ab')_2$ or ligand x Fab fusion protein. Methods for preparing multivalent antibodies are described for example in U.S. Patent Number 5,260,203; U.S. Patent Number 5,455,030; U.S. Patent Number 4,881,175; U.S. Patent Number 5,132,405; U.S. Patent Number 5,091,513; U.S. Patent Number 5,476,786; U.S. Patent Number 5,013,653; U.S. Patent Number 5,258,498; and U.S. Patent Number 5,482,858.

Binding of the multivalent antibodies to their targets can be confirmed by, for example, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (REA), FACS analysis, bioassay (*e.g.*, growth inhibition), or Western Blot assay. Each of these assays generally detects the presence of protein-antibody complexes of particular interest by employing a labeled reagent (*e.g.*, an antibody) specific for the complex of interest.

In another aspect, the present invention provides multivalent antibodies comprising at least two different receptor binding domains of the antibodies of the invention binding to LRP6. The receptor binding domains can be linked together via protein fusion or

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covalent or non covalent linkage. Tetravalent antibodies can be obtained for example by cross-linking the antibodies of the invention with an antibody that binds to the constant regions of the antibodies of the invention, for example the Fc or hinge region.

Multivalent Antibody Orientation

The invention pertains to multivalent antibodies that have multiple receptor binding domains ("RBD"), which include for example, antibody variable regions, antibody fragments (e.g., Fabs), scFvs, single chain diabodies, or IgG antibodies. Examples of RBDs are components of a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; a $F(ab)_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment consisting of the VH and CH1 domains; a Fv fragment consisting of the VL and VH domains of a single arm of an antibody; a dAb fragment (Ward *et al.*, (1989) Nature 341:544-546), which consists of a VH domain; and an isolated complementarity determining region (CDR). RBDs also are also components of single domain antibodies, maxibodies, unibodies, minibodies, diabodies, triabodies, tetrabodies, v-NAR and bis-scFv (see, *e.g.*, Hollinger and Hudson, (2005) Nature Biotechnology 23: 1126-1136.

The multivalent antibodies of the invention are generated in any orientation using at least one receptor binding domain (e.g., an scFv, a single chain diabody, an antibody variable region) as long as the resulting multivalent antibodies retain functional activity (e.g., inhibiting Wnt signaling). It should be understood that any number of receptor binding domains can be added to the C-terminus and /or N-terminus of the Fc as long as the resulting multivalent antibodies retain functional activity (e.g., inhibiting Wnt signaling). In an embodiment, one, two, three, or more receptor binding domains are linked to the C-terminus of the Fc region. In other embodiments one, two, three, or more receptor binding domains are linked to the N-terminus of the Fc region. In other embodiments, one, two, three, or more receptor binding domains are linked to both the N-terminus and C-terminus of the Fc region. For example, multivalent antibodies of the invention can comprise more than one receptor binding domain of the same type linked to the C-terminus and/or N-terminus of an Fc region, e.g., scFv-scFv-Fc –IgG. Alternatively, the multivalent antibodies of the invention can comprise more than one receptor binding domain of a different type linked to the C-terminus and/or N-terminus of the Fc region, e.g., scFv-diabody-Fc-IgG. In another embodiment, one, two, three or more receptor binding

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domains (e.g., scFv) are linked to the C-terminus of an IgG. In another embodiment, one, two, three or more receptor binding domains (e.g., scFv) are linked to the N-terminus of an IgG. In another embodiment, one, two, three or more receptor binding domains (e.g., scFv) are linked to the N-terminus and C-terminus of an IgG.

In other embodiments, the multivalent antibodies of the invention are generated using more than one receptor binding domain of a different type linked to the C-terminus, e.g., scFv-diabody-Fc-IgG; diabody-scFv-Fc-IgG; scFv-scFv-diabody-Fc-IgG; scFv- diabody-scFv-Fc-IgG; diabody- scFv-scFv-Fc-IgG; antibody variable region-scFv-diabody-Fc-IgG; and the like. Multivalent antibodies with any number of permutations of receptor binding domains can be generated. These multivalent antibodies can be tested for functionality using the methods and assays described within.

In other embodiments, the multivalent antibodies of the invention are generated using more than one receptor binding domain of a different type linked to the N-terminus, e.g., IgG-Fc-scFv-diabody; IgG-Fc-diabody-scFv; IgG-Fc-scFv-scFv-diabody; IgG-Fc- scFv-diabody-scFv; IgG-Fc-diabody-scFv-scFv; IgG-Fc-antibody variable region-scFv-diabody; and the like.

In yet other embodiments, multivalent antibodies of the invention are generated using a single receptor binding domain (e.g., an scFv, a single chain diabody, an antibody variable region) linked to the C-terminus and N-terminus of the Fc region. In another embodiment, multiple receptor binding domains are linked to the N-terminus of the Fc region, for example, at least 1, 2, 3, 4, 5, 6, 7, 8 or more receptor binding domains linked to the C-terminus and N-terminus of the Fc region. For example, the multivalent antibodies of the invention can comprise one or more scFvs linked to the C-terminus and N-terminus of the Fc region, e.g., scFv-Fc-scFv-scFv; -scFv-scFv-Fc-scFv-scFv, and the like. In other embodiments, the multivalent antibodies of the invention are generated using more than one receptor binding domain of a different type linked to the N-terminus, e.g., scFv-Fc-scFv-diabody; scFv-Fc-diabody-scFv; scFv-Fc-scFv-scFv-diabody; scFv-Fc- scFv- diabody-scFv; scFv-Fc-diabody-scFv-scFv; scFv-Fc-antibody variable region-scFv-diabody; and the like Multivalent antibodies with any number of permutations of receptor binding domains can be generated. These multivalent antibodies can be tested for functionality using the methods and assays described within.

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Linker Length

It is known that linker length can greatly affect how the variable regions of an scFv fold and interact. In fact, if a short linker is employed (e.g., between 5-10 amino acids; between 5-20 amino acids) intrachain folding is prevented and interchain folding is required to bring the two variable regions together to form a functional epitope binding site. For examples of linker orientation and size see, e.g., Hollinger et al. 1993 Proc Natl Acad. Sci. U.S.A. 90:6444-6448, U.S. Patent Application Publication Nos. 2005/0100543, 2005/0175606, 2007/0014794, and PCT publication Nos. WO2006/020258 and WO2007/024715, is incorporated herein by reference.

It is also understood that the receptor binding domains may be separated by linker regions of various lengths. The receptor binding domains can be separated from each other, a Ckappa/lambda, CH1, Hinge, CH2, CH3, or the entire Fc region by a linker sequence. Such linker sequence may comprise a random assortment of amino acids, or a restricted set of amino acids. Such linker sequence may be flexible or rigid.

The multivalent antibodies of the invention comprise a linker sequence of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, or more amino acid residues between one or more of its receptor binding domains, Ckappa/lambda domains, CH1 domains, Hinge region, CH2 domains, CH3 domains, or Fc regions. The linker sequence may be comprised of any naturally occurring amino acid. In some embodiments, the amino acids glycine and serine comprise the amino acids within the linker sequence. In another embodiment, the linker region orientation comprises sets of glycine repeats $(Gly_4Ser)_n$, where n is a positive integer equal to or greater than 1.

In one embodiment, the linkers include, but are not limited to, $(Gly_4\ Ser)_4$ or $(Gly_4\ Ser)_3$. In another embodiment, the linkers Glu and Lys residues can be interspersed within the Gly-Ser linkers for better solubility. In another embodiment, the linkers include multiple repeats of (Gly_2Ser), (GlySer) or (Gly_3Ser). In anther embodiment, the linkers include combinations and multiples of $(Gly_3Ser)+(Gly_4Ser)+(GlySer)$. In another embodiment, Ser can be replaced with Ala e.g., (Gly_4Ala) or (Gly_3Ala). In yet another embodiment, the linker comprises the motif $(GluAlaAlaAlaLys)_n$, where n is a positive integer equal to or greater than 1.

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Hinge Region

The multivalent antibodies of the invention may comprise all or at least a portion of an antibody Hinge region. The Hinge region or portion thereof may be connected directly to an receptor binding domain, a CH1, a Ckappa/lambda, a CH2, or a CH3. In one embodiment, the Hinge region, or portion thereof may be connected through a variable length linker region to a receptor binding domain, a CH1, a Ckappa/lambda, a CH2, or a CH3.

The multivalent antibodies of the invention can comprise 1, 2, 3, 4, 5, 6, or more Hinge regions or portions thereof. The Hinge regions or portions thereof can either be identical or be different. In one embodiment, the multivalent antibodies of the invention comprise a Hinge region or portion thereof from a human IgG1 molecule. In further embodiments, the Hinge region or portion thereof may be engineered to remove a naturally occurring cysteine residue, introduce a non-naturally occurring cysteine residue, or substitute a naturally occurring residue for a non-naturally occurring cysteine residue. In some embodiments, the multivalent antibodies of the invention contain at least one Hinge region or portion thereof that comprises the following amino acids sequence comprising: EPKSCDKTHTCPPCP (SEQ ID NO: 211) or EPKSC (SEQ ID NO: 212). In some embodiments, at least one Hinge region or portion thereof is engineered to substitute at least one naturally occurring cysteine residue with another amino acid residue. In some embodiments, at least one naturally occurring cysteine residue is substituted with serine.

Non-naturally occurring cysteine residues useful for site-specific conjugation can be engineered into the multivalent antibodies of the invention. Such approaches, compositions and methods are exemplified in U.S. Provisional Patent Application Ser. No. 61/022,073 filed Jan. 18, 2008, entitled "Cysteine Engineered Antibodies for Site-Specific Conjugation" and U.S. Patent Application Publication No. 20070092940, filed Sep. 22, 2005, each of which are hereby incorporated by reference in its entirety for all purposes.

Methods of Evaluating Protein Stability

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To assess the stability of multivalent antibodies, the stability of the least stable domain of a multidomain protein is predicted using the methods of the invention and those described below.

Such methods allow for the determination of multiple thermal unfolding transitions where the least stable domain either unfolds first or limits the overall stability threshold of a multidomain unit that unfolds cooperatively (i.e. a multidomain protein which exhibits a single unfolding transition). The least stable domain can be identified in a number of additional ways. Mutagenesis can be performed to probe which domain limits the overall stability. Additionally, protease resistance of a multidomain protein can be performed under conditions where the least stable domain is known to be intrinsically unfolded via DSC or other spectroscopic methods (Fontana, *et al.*, (1997) Fold. Des., 2: R17-26; Dimasi *et al.* (2009) J. Mol. Biol. 393: 672-692). Once the least stable domain is identified, the sequence encoding this domain (or a portion thereof) may be employed as a test sequence in the methods of the invention.

a) Thermal Stability

The thermal stability of the compositions of the invention may be analyzed using a number of non-limiting biophysical or biochemical techniques known in the art. In certain embodiments, thermal stability is evaluated by analytical spectroscopy.

An exemplary analytical spectroscopy method is Differential Scanning Calorimetry (DSC). DSC employs a calorimeter which is sensitive to the heat absorbances that accompany the unfolding of most proteins or protein domains (see, e.g. Sanchez-Ruiz, et al., Biochemistry, 27: 1648-52, 1988). To determine the thermal stability of a protein, a sample of the protein is inserted into the calorimeter and the temperature is raised until the Fab or scFv unfolds. The temperature at which the protein unfolds is indicative of overall protein stability.

Another exemplary analytical spectroscopy method is Circular Dichroism (CD) spectroscopy. CD spectrometry measures the optical activity of a composition as a function of increasing temperature. Circular dichroism (CD) spectroscopy measures differences in the absorption of left-handed polarized light versus right-handed polarized light which arise due to structural asymmetry. A disordered or unfolded structure results

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in a CD spectrum very different from that of an ordered or folded structure. The CD spectrum reflects the sensitivity of the proteins to the denaturing effects of increasing temperature and is therefore indicative of a protein's thermal stability (see van Mierlo and Steemsma, J. Biotechnol., 79(3):281-98, 2000).

Another exemplary analytical spectroscopy method for measuring thermal stability is Fluorescence Emission Spectroscopy (see van Mierlo and Steemsma, supra). Yet another exemplary analytical spectroscopy method for measuring thermal stability is Nuclear Magnetic Resonance (NMR) spectroscopy (see, e.g. van Mierlo and Steemsma, supra).

The thermal stability of a composition of the invention can be measured biochemically. An exemplary biochemical method for assessing thermal stability is a thermal challenge assay. In a "thermal challenge assay", a composition of the invention is subjected to a range of elevated temperatures for a set period of time. For example, in one embodiment, test scFv molecules or molecules comprising scFv molecules are subject to a range of increasing temperatures, e.g., for 1-1.5 hours. The activity of the protein is then assayed by a relevant biochemical assay. For example, if the protein is a binding protein (e.g. an scFv or scFv-containing polypeptide of the invention) the binding activity of the binding protein may be determined by a functional or quantitative ELISA.

Such an assay may be done in a high-throughput format and those disclosed in the Examles using E. coli and high throughput screening. A library of scFv variants may be created using methods known in the art. scFv expression may be induced an scFvs may be subjected to thermal challenge. The challenged test samples may be assayed for binding and those scFvs which are stable may be scaled up and further characterized.

Thermal stability is evaluated by measuring the melting temperature (Tm) of a composition of the invention using any of the above techniques (e.g. analytical spectroscopy techniques). The melting temperature is the temperature at the midpoint of a thermal transition curve wherein 50% of molecules of a composition are in a folded state (See e.g., Dimasi *et al.* (2009) J. Mol Biol. 393: 672-692). In one embodiment, Tm values for a scFv are about 40°C, 41°C, 42°C, 43°C, 44°C, 45°C, 46°C, 47°C, 48°C, 49°C, 50°C, 51°C, 52°C, 53°C, 54°C, 55°C, 56°C, 57°C, 58°C, 59°C, 60°C, 61°C, 62°C, 63°C, 64°C, 65°C, 66°C, 67°C, 68°C, 69°C, 70°C, 71°C, 72°C, 73°C, 74°C, 75°C, 76°C, 77°C,

78°C, 79°C, 80°C, 81°C, 82°C, 83°C, 84°C, 85°C, 86°C, 87°C, 88°C, 89°C, 90°C, 91°C, 92°C, 93°C, 94°C, 95°C, 96°C, 97°C, 98°C, 99°C, 100°C. In one embodiment, Tm values for an IgG is about 40°C, 41°C, 42°C, 43°C, 44°C, 45°C, 46°C, 47°C, 48°C, 49°C, 50°C, 51°C, 52°C, 53°C, 54°C, 55°C, 56°C, 57°C, 58°C, 59°C, 60°C, 61°C, 62°C, 63°C, 64°C, 65°C, 66°C, 67°C, 68°C, 69°C, 70°C, 71°C, 72°C, 73°C, 74°C, 75°C, 76°C, 77°C, 78°C, 79°C, 80°C, 81°C, 82°C, 83°C, 84°C, 85°C, 86°C, 87°C, 88°C, 89°C, 90°C, 91°C, 92°C, 93°C, 94°C, 95°C, 96°C, 97°C, 98°C, 99°C, 100°C. In one embodiment, Tm values for an multivalent antibody is about 40°C, 41°C, 42°C, 43°C, 44°C, 45°C, 46°C, 47°C, 48°C, 49°C, 50°C, 51°C, 52°C, 53°C, 54°C, 55°C, 56°C, 57°C, 58°C, 59°C, 60°C, 61°C, 62°C, 63°C, 64°C, 65°C, 66°C, 67°C, 68°C, 69°C, 70°C, 71°C, 72°C, 73°C, 74°C, 75°C, 76°C, 77°C, 78°C, 79°C, 80°C, 81°C, 82°C, 83°C, 84°C, 85°C, 86°C, 87°C, 88°C, 89°C, 90°C, 91°C, 92°C, 93°C, 94°C, 95°C, 96°C, 97°C, 98°C, 99°C, 100°C.

Thermal stability is also evaluated by measuring the specific heat or heat capacity (Cp) of a composition of the invention using an analytical calorimetric technique (e.g. DSC). The specific heat of a composition is the energy (e.g. in kcal/mol) required to raise by 1°C, the temperature of 1 mol of water. As large Cp is a hallmark of a denatured or inactive protein composition. The change in heat capacity (ΔCp) of a composition is measured by determining the specific heat of a composition before and after its thermal transition. Thermal stability may also be evaluated by measuring or determining other parameters of thermodynamic stability including Gibbs free energy of unfolding (ΔG), enthalpy of unfolding (ΔH), or entropy of unfolding (ΔS).

One or more of the above biochemical assays (e.g. a thermal challenge assay) is used to determine the temperature (i.e. the T_C value) at which 50% of the composition retains its activity (e.g. binding activity).

In addition, mutations to the scFv alter the thermal stability of the scFv compared with the unmutated scFv. When the mutated scFv is incorporated into a multivalent antibody, the mutated scFv confers thermal stability to the overall multivalent antibody. In one embodiment, the scFv comprises a single mutation that confers thermal stability to the scFv. In another embodiment, the scFv comprises multiple mutations that confer thermal

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stability to the scFv. In one embodiment, the multiple mutations in the scFv have an additive effect on thermal stability of the scFv.

b) % Aggregation

The stability of a composition of the invention can be determined by measuring its propensity to aggregate. Aggregation can be measured by a number of non-limiting biochemical or biophysical techniques. For example, the aggregation of a composition of the invention may be evaluated using chromatography, e.g. Size-Exclusion Chromatograpy (SEC). SEC separates molecules on the basis of size. A column is filled with semi-solid beads of a polymeric gel that will admit ions and small molecules into their interior but not large ones. When a protein composition is applied to the top of the column, the compact folded proteins (ie. non-aggregated proteins) are distributed through a larger volume of solvent than is available to the large protein aggregates. Consequently, the large aggregates move more rapidly through the column, and in this way the mixture can be separated or fractionated into its components. Each fraction can be separately quantified (e.g. by light scattering) as it elutes from the gel. Accordingly, the % aggregation of a composition of the invention can be determined by comparing the concentration of a fraction with the total concentration of protein applied to the gel. Stable compositions elute from the column as essentially a single fraction and appear as essentially a single peak in the elution profile or chromatogram.

c) Binding Affinity

The stability of a composition of the invention can be assessed by determining its target binding affinity. A wide variety of methods for determining binding affinity are known in the art. An exemplary method for determining binding affinity employs surface plasmon resonance. Surface plasmon resonance is an optical phenomenon that allows for the analysis of real-time biospecific interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIAcore system (Pharmacia Biosensor AB, Uppsala, Sweden and Piscataway, N.J.). For further descriptions, see Jonsson, U., et al. (1993) Ann. Biol. Clin. 51:19-26; Jonsson, U., i (1991) Biotechniques 11:620-627; Johnsson, B., *et al.* (1995) J. Mol. Recognit. 8:125-131; and Johnnson, B., *et al.* (1991) Anal. Biochem. 198:268-277.

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Antibodies with Extended Half Life

The present invention provides for antibodies and multivalent antibodies that specifically bind to LRP6 protein which have an extended half-life *in vivo*. Many factors may affect a protein's half life *in vivo*. For examples, kidney filtration, metabolism in the liver, degradation by proteolytic enzymes (proteases), and immunogenic responses (*e.g.*, protein neutralization by antibodies and uptake by macrophages and dentritic cells). A variety of strategies can be used to extend the half life of the antibodies of the present invention. For example, by chemical linkage to polyethyleneglycol (PEG), reCODE PEG, antibody scaffold, polysialic acid (PSA), hydroxyethyl starch (HES), albumin-binding ligands, and carbohydrate shields; by genetic fusion to proteins binding to serum proteins, such as albumin, IgG, FcRn, and transferring; by coupling (genetically or chemically) to other binding moieties that bind to serum proteins, such as nanobodies, Fabs, DARPins, avimers, affibodies, and anticalins; by genetic fusion to rPEG, albumin, domain of albumin, albumin-binding proteins, and Fc; or by incorporation into nancarriers, slow release formulations, or medical devices.

To prolong the serum circulation of antibodies *in vivo*, inert polymer molecules such as high molecular weight PEG can be attached to the antibodies with or without a multifunctional linker either through site-specific conjugation of the PEG to the N- or C-terminus of the antibodies or via epsilon-amino groups present on lysine residues. To pegylate, a antibody typically is reacted with polyethylene glycol (PEG), such as a reactive ester or aldehyde derivative of PEG, under conditions in which one or more PEG groups become attached to the antibody or antibody fragment. The pegylation can be carried out by an acylation reaction or an alkylation reaction with a reactive PEG molecule (or an analogous reactive water-soluble polymer). As used herein, the term "polyethylene glycol" is intended to encompass any of the forms of PEG that have been used to derivatize other proteins, such as mono (C1-C10) alkoxy- or aryloxy-polyethylene glycol or polyethylene glycol-maleimide. In certain embodiments, the antibody to be pegylated is an aglycosylated antibody. Linear or branched polymer derivatization that results in minimal loss of biological activity will be used. The degree of conjugation can be closely monitored by SDS-PAGE and mass spectrometry to ensure proper conjugation of PEG molecules to the antibody. Unreacted PEG can be separated from antibody-PEG conjugates by size-exclusion or by ion-exchange chromatography. PEG-derivatized antibodies can be tested for binding activity as well as for *in vivo* efficacy using methods

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well-known to those of skill in the art, for example, by immunoassays described herein. Methods for pegylating proteins are known in the art and can be applied to the antibodies of the invention. See for example, EP 0 154 316 by Nishimura *et al.* and EP 0 401 384 by Ishikawa *et al.*

Other modified pegylation technologies include reconstituting chemically orthogonal directed engineering technology (ReCODE PEG), which incorporates chemically specified side chains into biosynthetic proteins via a reconstituted system that includes tRNA synthetase and tRNA. This technology enables incorporation of more than 30 new amino acids into biosynthetic proteins in E.coli, yeast, and mammalian cells. The tRNA incorporates a nonnative amino acid any place an amber codon is positioned, converting the amber from a stop codon to one that signals incorporation of the chemically specified amino acid.

Recombinant pegylation technology (rPEG) can also be used for serum halflife extension. This technology involves genetically fusing a 300-600 amino acid unstructured protein tail to an existing pharmaceutical protein. Because the apparent molecular weight of such an unstructured protein chain is about 15-fold larger than its actual molecular weight, the serum halflife of the protein is greatly increased. In contrast to traditional PEGylation, which requires chemical conjugation and repurification, the manufacturing process is greatly simplified and the product is homogeneous.

Polysialytion is another technology, which uses the natural polymer polysialic acid (PSA) to prolong the active life and improve the stability of therapeutic peptides and proteins, such as antibodies of the invention. PSA is a polymer of sialic acid (a sugar). When used for protein and therapeutic peptide drug delivery, polysialic acid provides a protective microenvironment on conjugation. This increases the active life of the therapeutic protein in the circulation and prevents it from being recognized by the immune system. The PSA polymer is naturally found in the human body. It was adopted by certain bacteria which evolved over millions of years to coat their walls with it. These naturally polysialylated bacteria were then able, by virtue of molecular mimicry, to foil the body's defence system. PSA, nature's ultimate stealth technology, can be easily produced from such bacteria in large quantities and with predetermined physical characteristics. Bacterial PSA is completely non-immunogenic, even when coupled to proteins, as it is chemically identical to PSA in the human body.

Another technology include the use of hydroxyethyl starch ("HES") derivatives linked to antibodies. HES is a modified natural polymer derived from waxy maize starch and can be metabolized by the body's enzymes. HES solutions are usually administered to substitute deficient blood volume and to improve the rheological properties of the blood. Hesylation of an antibody enables the prolongation of the circulation half-life by increasing the stability of the molecule, as well as by reducing renal clearance, resulting in an increased biological activity. By varying different parameters, such as the molecular weight of HES, a wide range of HES antibodies conjugates can be customized.

Antibodies having an increased half-life *in vivo* can also be generated introducing one or more amino acid modifications (*i.e.*, substitutions, insertions or deletions) into an IgG constant domain, or FcRn binding fragment thereof (preferably a Fc or hinge Fc domain fragment). See, *e.g.*, International Publication No. WO 98/23289; International Publication No. WO 97/34631; and U.S. Patent No. 6,277,375.

Further, antibodies can be conjugated to albumin in order to make the antibodies more stable *in vivo* or have a longer half life *in vivo*. The techniques are well-known in the art, see, *e.g.*, International Publication Nos. WO 93/15199, WO 93/15200, and WO 01/77137; and European Patent No. EP 413,622.

Antibody Conjugates

The present invention provides antibodies and multivalent antibodies thereof that specifically bind to a LRP6 protein recombinantly fused or chemically conjugated (including both covalent and non-covalent conjugations) to a heterologous protein or polypeptide (or fragment thereof, preferably to a polypeptide of at least 10, at least 20, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90 or at least 100 amino acids) to generate fusion proteins. In particular, the invention provides fusion proteins comprising an antigen-binding fragment of antibodies described herein (*e.g.*, a Fab fragment, Fd fragment, Fv fragment, F(ab)2 fragment, a VH domain, a VH CDR, a VL domain or a VL CDR) and a heterologous protein, polypeptide, or peptide. Methods for fusing or conjugating proteins, polypeptides, or peptides to an antibody or an antibody fragment are known in the art. See, *e.g.*, U.S. Patent Nos. 5,336,603, 5,622,929, 5,359,046, 5,349,053, 5,447,851, and 5,112,946; European Patent Nos. EP 307,434 and EP 367,166; International Publication Nos. WO 96/04388 and WO 91/06570; Ashkenazi *et al.*, (1991) Proc. Natl. Acad. Sci. USA 88:10535-10539; Zheng *et al.*, (1995) J.

Immunol. 154:5590-5600; and Vil *et al.*, (1992) Proc. Natl. Acad. Sci. USA 89:11337-11341.

Additional fusion proteins may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to alter the activities of antibodies of the invention (*e.g.*, multivalent, biparatopic or bispecific antibodies or fragments thereof with higher affinities and lower dissociation rates). See, generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458; Patten *et al.*, (1997) Curr. Opinion Biotechnol. 8:724-33; Harayama, (1998) Trends Biotechnol. 16(2):76-82; Hansson *et al.*, (1999) J. Mol. Biol. 287:265-76; and Lorenzo and Blasco, (1998) Biotechniques 24(2):308- 313 (each of these patents and publications are hereby incorporated by reference in its entirety). Antibodies or fragments thereof, or the encoded antibodies or fragments thereof, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. A polynucleotide encoding a multivalent antibody or fragment thereof that specifically binds to a LRP6 protein may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

Moreover, the antibodies or fragments thereof can be fused to marker sequences, such as a peptide to facilitate purification. In one embodiment, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz *et al.*, (1989) Proc. Natl. Acad. Sci. USA 86:821-824, for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the hemagglutinin ("HA") tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson *et al.*, (1984) Cell 37:767), and the "flag" tag.

In other embodiments, antibodies of the present invention or fragments thereof conjugated to a diagnostic or detectable agent. Such antibodies can be useful for monitoring or prognosing the onset, development, progression and/or severity of a disease or disorder as part of a clinical testing procedure, such as determining the efficacy of a particular therapy. Such diagnosis and detection can accomplished by coupling the

antibodies to detectable substances including, but not limited to, various enzymes, such as, but not limited to, horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; prosthetic groups, such as, but not limited to, streptavidinlbiotin and avidin/biotin; fluorescent materials, such as, but not limited to, umbelliferone, fluorescein, fluorescein isothiocynate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; luminescent materials, such as, but not limited to, luminol; bioluminescent materials, such as but not limited to, luciferase, luciferin, and aequorin; radioactive materials, such as, but not limited to, iodine (^{131}I, ^{125}I, ^{123}I, and ^{121}I,), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{115}In, ^{113}In, ^{112}In, and ^{111}In,), technetium (^{99}Tc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, 47Sc, ^{186}Re, ^{188}Re, ^{142} Pr, ^{105}Rh, ^{97}Ru, ^{68}Ge, ^{57}Co, ^{65}Zn, ^{85}Sr, ^{32}P, ^{153}Gd, ^{169}Yb, ^{51}Cr, ^{54}Mn, ^{75}Se, ^{113}Sn, and ^{117}Tin; and positron emitting metals using various positron emission tomographies, and noradioactive paramagnetic metal ions.

The present invention further encompasses uses of antibodies or fragments thereof conjugated to a therapeutic moiety. The antibodies or fragment thereof may be conjugated to a therapeutic moiety such as a cytotoxin, *e.g.*, a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, *e.g.*, alpha-emitters. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells.

Further, antibodies or fragments thereof may be conjugated to a therapeutic moiety or drug moiety that modifies a given biological response. Therapeutic moieties or drug moieties are not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein, peptide, or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, cholera toxin, or diphtheria toxin; a protein such as tumor necrosis factor, α-interferon, β-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, an anti-angiogenic agent; or, a biological response modifier such as, for example, a lymphokine.

In one embodiment, the antibody, or a fragment thereof, conjugated to a therapeutic moiety, such as a cytotoxin, a drug (e.g., an immunosuppressant) or a radiotoxin. Such conjugates are referred to herein as "immunoconjugates". Immunoconjugates that include one or more cytotoxins are referred to as "immunotoxins." A cytotoxin or cytotoxic agent

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includes any agent that is detrimental to (e.g., kills) cells. Examples include taxon, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, t. colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1 -dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents also include, for example, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), ablating agents (e.g., mechlorethamine, thioepa chloraxnbucil, meiphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin, anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

Other examples of therapeutic cytotoxins that can be conjugated to a antibody of the invention include duocarmycins, calicheamicins, maytansines and auristatins, and derivatives thereof. An example of a calicheamicin antibody conjugate is commercially available (MylotargTm; Wyeth-Ayerst).

Cytoxins can be conjugated to antibodies of the invention using linker technology available in the art. Examples of linker types that have been used to conjugate a cytotoxin to an antibody include, but are not limited to, hydrazones, thioethers, esters, disulfides and peptide-containing linkers. A linker can be chosen that is, for example, susceptible to cleavage by low pH within the lysosomal compartment or susceptible to cleavage by proteases, such as proteases preferentially expressed in tumor tissue such as cathepsins (e.g., cathepsins B, C, D).

For further discussion of types of cytotoxins, linkers and methods for conjugating therapeutic agents to antibodies, see also Saito *et al.,* (2003) Adv. Drug Deliv. Rev. 55:199-215; Trail *et al.,* (2003) Cancer Immunol. Immunother. 52:328-337; Payne, (2003) Cancer Cell 3:207-212; Allen, (2002) Nat. Rev. Cancer 2:750-763; Pastan and Kreitman, (2002) Curr. Opin. Investig. Drugs 3:1089-1091; Senter and Springer, (2001) Adv. Drug Deliv. Rev. 53:247-264.

Antibodies of the present invention also can be conjugated to a radioactive isotope to generate cytotoxic radiopharmaceuticals, also referred to as radioimmunoconjugates.

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Examples of radioactive isotopes that can be conjugated to antibodies for use diagnostically or therapeutically include, but are not limited to, iodine^{131}, indium^{111}, yttrium^{90}, and lutetium^{177}. Method for preparing radioimmunconjugates are established in the art. Examples of radioimmunoconjugates are commercially available, including Zevalin^{TM} (DEC Pharmaceuticals) and Bexxar^{TM} (Corixa Pharmaceuticals), and similar methods can be used to prepare radioimmunoconjugates using the antibodies of the invention. In certain embodiments, the macrocyclic chelator is 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA) which can be attached to the antibody via a linker molecule. Such linker molecules are commonly known in the art and described in Denardo *et al.*, (1998) Clin Cancer Res. 4(10):2483-90; Peterson *et al.*, (1999) Bioconjug. Chem. 10(4):553-7; and Zimmerman *et al.*, (1999) Nucl. Med. Biol. 26(8):943-50, each incorporated by reference in their entireties.

Techniques for conjugating therapeutic moieties to antibodies are well known, see, *e.g.*, Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld *et al.* (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom *et al.*, "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson *et al.* (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies 84: Biological And Clinical Applications, Pinchera *et al.* (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin *et al.* (eds.), pp. 303-16 (Academic Press 1985), and Thorpe *et al.*, (1982) Immunol. Rev. 62:119-58.

Antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

Methods of Producing Antibodies

(i) Nucleic Acids Encoding the Antibodies

The invention provides substantially purified nucleic acid molecules which encode multiple epitope binding proteins, e.g., antibodies and antigen binding fragments thereof

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comprising segments or domains of the LRP6 antibody chains described above. Some of the nucleic acids of the invention comprise the nucleotide sequence encoding the propeller 1 antibody heavy chain variable region shown in SEQ ID NO: 14, 19, 34, and 60, and/or the nucleotide sequence encoding the light chain variable region shown in SEQ ID NO:13, 20, 33, and 59. In a specific embodiment, the nucleic acid molecules are those identified in Table 1. Some other nucleic acid molecules of the invention comprise nucleotide sequences that are substantially identical (*e.g.*, at least 65, 80%, 95%, or 99%) to the nucleotide sequences of those identified in Table 1. Some of the nucleic acids of the invention comprise the nucleotide sequence encoding the heavy chain variable region shown in SEQ ID NO: 82, 106, and 128, and/or the nucleotide sequence encoding the light chain variable region shown in SEQ ID NO: 81, 105, and 127. In a specific embodiment, the nucleic acid molecules are those identified in Table 1. Some other nucleic acid molecules of the invention comprise nucleotide sequences that are substantially identical (*e.g.*, at least 65, 80%, 95%, or 99%) to the nucleotide sequences of those identified in Table 1. When expressed from appropriate expression vectors, polypeptides encoded by these polynucleotides are capable of exhibiting LRP6 antigen binding capacity.

Also provided in the invention are polynucleotides which encode at least one CDR region and usually all three CDR regions from the heavy or light chain of the LRP6 antibody set forth above. Some other polynucleotides encode all or substantially all of the variable region sequence of the heavy chain and/or the light chain of the LRP6 antibody set forth above. Because of the degeneracy of the code, a variety of nucleic acid sequences will encode each of the immunoglobulin amino acid sequences.

The nucleic acid molecules of the invention can encode both a variable region and a constant region of the antibody. Some of nucleic acid sequences of the invention comprise nucleotides encoding a mature heavy chain variable region sequence that is substantially identical (*e.g.*, at least 80%, 90%, or 99%) to the mature heavy chain variable region sequence set forth in SEQ ID NO: 14, 19, 34, and 60. Some other nucleic acid sequences comprising nucleotide encoding a mature light chain variable region sequence that is substantially identical (e.g., at least 80%, 90%, or 99%) to the mature light chain variable region sequence set forth in SEQ ID NO: 13, 20, 33, and 59.

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The nucleic acid molecules of the invention can encode both a variable region and a constant region of the antibody. Some of nucleic acid sequences of the invention comprise nucleotides encoding a mature heavy chain variable region sequence that is substantially identical (*e.g.*, at least 80%, 90%, or 99%) to the mature heavy chain variable region sequence set forth in SEQ ID NO: 82, 106, and 128. Some other nucleic acid sequences comprising nucleotide encoding a mature light chain variable region sequence that is substantially identical (e.g., at least 80%, 90%, or 99%) to the mature light chain variable region sequence set forth in SEQ ID NO: 81, 105, and 129.

The polynucleotide sequences can be produced by de novo solid-phase DNA synthesis or by PCR mutagenesis of an existing sequence (*e.g.*, sequences as described in the Examples below) encoding an LRP6 antibody or its binding fragment. Direct chemical synthesis of nucleic acids can be accomplished by methods known in the art, such as the phosphotriester method of Narang *et al.*, (1979) Meth. Enzymol. 68:90; the phosphodiester method of Brown *et al.*, (1979) Meth. Enzymol. 68:109; the diethylphosphoramidite method of Beaucage *et al.*, (1981) Tetra. Lett., 22:1859; and the solid support method of U.S. Patent No. 4,458,066. Introducing mutations to a polynucleotide sequence by PCR can be performed as described in, *e.g.*, PCR Technology: Principles and Applications for DNA Amplification, H.A. Erlich (Ed.), Freeman Press, NY, NY, 1992; PCR Protocols: A Guide to Methods and Applications, Innis *et al.* (Ed.), Academic Press, San Diego, CA, 1990; Mattila *et al.*, (1991) Nucleic Acids Res. 19:967; and Eckert *et al.*, (1991) PCR Methods and Applications 1:17.

Also provided in the invention are expression vectors and host cells for producing the antibodies described above. Various expression vectors can be employed to express the polynucleotides encoding the antibody fragments thereof. Both viral-based and nonviral expression vectors can be used to produce the antibodies in a mammalian host cell. Nonviral vectors and systems include plasmids, episomal vectors, typically with an expression cassette for expressing a protein or RNA, and human artificial chromosomes (see, *e.g.*, Harrington *et al.*, (1997) Nat Genet 15:345). For example, nonviral vectors useful for expression of the antibody polynucleotides and polypeptides in mammalian (*e.g.*, human) cells include pThioHis A, B & C, pcDNA3.1/His, pEBVHis A, B & C, (Invitrogen, San Diego, CA), MPSV vectors, and numerous other vectors known in the art for expressing other proteins. Useful viral vectors include vectors based on retroviruses, adenoviruses, adenoassociated viruses, herpes viruses, vectors based on SV40, papilloma

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virus, HBP Epstein Barr virus, vaccinia virus vectors and Semliki Forest virus (SFV). See, Brent *et al.*, (1995) supra; Smith, Annu. Rev. Microbiol. 49:807; and Rosenfeld *et al.*, (1992) Cell 68:143.

The choice of expression vector depends on the intended host cells in which the vector is to be expressed. Typically, the expression vectors contain a promoter and other regulatory sequences (*e.g.*, enhancers) that are operably linked to the polynucleotides encoding a antibody or fragment thereof. In some embodiments, an inducible promoter is employed to prevent expression of inserted sequences except under inducing conditions. Inducible promoters include, *e.g.*, arabinose, lacZ, metallothionein promoter or a heat shock promoter. Cultures of transformed organisms can be expanded under noninducing conditions without biasing the population for coding sequences whose expression products are better tolerated by the host cells. In addition to promoters, other regulatory elements may also be required or desired for efficient expression of the antibody or fragment thereof. These elements typically include an ATG initiation codon and adjacent ribosome binding site or other sequences. In addition, the efficiency of expression may be enhanced by the inclusion of enhancers appropriate to the cell system in use (see, *e.g.*, Scharf *et al.*, (1994) Results Probl. Cell Differ. 20:125; and Bittner *et al.*, (1987) Meth. Enzymol., 153:516). For example, the SV40 enhancer or CMV enhancer may be used to increase expression in mammalian host cells.

The expression vectors may also provide a secretion signal sequence position to form a fusion protein with polypeptides encoded by inserted LRP6 antibody sequences. More often, the inserted LRP6 antibody sequences are linked to a signal sequences before inclusion in the vector. Vectors to be used to receive sequences encoding LRP6 antibody light and heavy chain variable domains sometimes also encode constant regions or parts thereof. Such vectors allow expression of the variable regions as fusion proteins with the constant regions thereby leading to production of intact antibodies or fragments thereof. Typically, such constant regions are human.

The host cells for harboring and expressing the antibodies can be either prokaryotic or eukaryotic. E. coli is one prokaryotic host useful for cloning and expressing the polynucleotides of the present invention. Other microbial hosts suitable for use include bacilli, such as Bacillus subtilis, and other enterobacteriaceae, such as Salmonella, Serratia, and various Pseudomonas species. In these prokaryotic hosts, one can also make

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expression vectors, which typically contain expression control sequences compatible with the host cell (*e.g.*, an origin of replication). In addition, any number of a variety of well-known promoters will be present, such as the lactose promoter system, a tryptophan (trp) promoter system, a beta-lactamase promoter system, or a promoter system from phage lambda. The promoters typically control expression, optionally with an operator sequence, and have ribosome binding site sequences and the like, for initiating and completing transcription and translation. Other microbes, such as yeast, can also be employed to express LRP6 antibodies of the invention. Insect cells in combination with baculovirus vectors can also be used.

In some preferred embodiments, mammalian host cells are used to express and produce the antibodies of the present invention. For example, they can be either a hybridoma cell line expressing endogenous immunoglobulin genes (*e.g.*, the 1D6.C9 myeloma hybridoma clone as described in the Examples) or a mammalian cell line harboring an exogenous expression vector (*e.g.*, the SP2/0 myeloma cells exemplified below). These include any normal mortal or normal or abnormal immortal animal or human cell. For example, a number of suitable host cell lines capable of secreting intact immunoglobulins have been developed including the CHO cell lines, various Cos cell lines, HeLa cells, myeloma cell lines, transformed B-cells and hybridomas. The use of mammalian tissue cell culture to express polypeptides is discussed generally in, *e.g.*, Winnacker, FROM GENES TO CLONES, VCH Publishers, N.Y., N.Y., 1987. Expression vectors for mammalian host cells can include expression control sequences, such as an origin of replication, a promoter, and an enhancer (see, *e.g.*, Queen *et al.*, (1986) Immunol. Rev. 89:49-68), and necessary processing information sites, such as ribosome binding sites, RNA splice sites, polyadenylation sites, and transcriptional terminator sequences. These expression vectors usually contain promoters derived from mammalian genes or from mammalian viruses. Suitable promoters may be constitutive, cell type-specific, stage-specific, and/or modulatable or regulatable. Useful promoters include, but are not limited to, the metallothionein promoter, the constitutive adenovirus major late promoter, the dexamethasone-inducible MMTV promoter, the SV40 promoter, the MRP polIII promoter, the constitutive MPSV promoter, the tetracycline-inducible CMV promoter (such as the human immediate-early CMV promoter), the constitutive CMV promoter, and promoter-enhancer combinations known in the art.

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Methods for introducing expression vectors containing the polynucleotide sequences of interest vary depending on the type of cellular host. For example, calcium chloride transfection is commonly utilized for prokaryotic cells, whereas calcium phosphate treatment or electroporation may be used for other cellular hosts. (See generally Sambrook, *et al.*, supra). Other methods include, *e.g.*, electroporation, calcium phosphate treatment, liposome-mediated transformation, injection and microinjection, ballistic methods, virosomes, immunoliposomes, polycation:nucleic acid conjugates, naked DNA, artificial virions, fusion to the herpes virus structural protein VP22 (Elliot and O'Hare, (1997) Cell 88:223), agent-enhanced uptake of DNA, and ex vivo transduction. For long-term, high-yield production of recombinant proteins, stable expression will often be desired. For example, cell lines which stably express antibody domains or binding fragments can be prepared using expression vectors of the invention which contain viral origins of replication or endogenous expression elements and a selectable marker gene. Following the introduction of the vector, cells may be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The purpose of the selectable marker is to confer resistance to selection, and its presence allows growth of cells which successfully express the introduced sequences in selective media. Resistant, stably transfected cells can be proliferated using tissue culture techniques appropriate to the cell type.

(ii) Generation of Antibodies

Monoclonal antibodies be produced using the methods disclosed in the Examples. These antibodies or fragments thereof can be used to generate multivalent antibodies, (e.g., bispecific/biparatopic) as disclosed in the Examples section. For example, a biparatopic LRP6 antibody can be generated by linking scFvs, e.g., an scFv that binds to the β-propeller 3 domain of LRP6, to a full length IgG monoclonal antibody.

Alternatively, monoclonal antibodies can be produced by a variety of techniques, including conventional monoclonal antibody methodology *e.g.*, the standard somatic cell hybridization technique of Kohler and Milstein, (1975) Nature 256: 495. Many techniques for producing monoclonal antibody can be employed *e.g.*, viral or oncogenic transformation of B lymphocytes.

An animal system for preparing hybridomas is the murine system. Hybridoma production in the mouse is a well established procedure. Immunization protocols and techniques for

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isolation of immunized splenocytes for fusion are known in the art. Fusion partners (*e.g.*, murine myeloma cells) and fusion procedures are also known.

Chimeric or humanized antibodies of the present invention can be prepared based on the sequence of a murine monoclonal antibody prepared as described above. DNA encoding the heavy and light chain immunoglobulins can be obtained from the murine hybridoma of interest and engineered to contain non-murine (*e.g.*,. human) immunoglobulin sequences using standard molecular biology techniques. For example, to create a chimeric antibody, the murine variable regions can be linked to human constant regions using methods known in the art (see *e.g.*, U.S. Patent No. 4,816,567 to Cabilly *et al.*). To create a humanized antibody, the murine CDR regions can be inserted into a human framework using methods known in the art. See *e.g.*, U.S. Patent No. 5225539 to Winter, and U.S. Patent Nos. 5530101; 5585089; 5693762 and 6180370 to Queen *et al.*

In a certain embodiment, the antibodies of the invention are human monoclonal antibodies. Such human monoclonal antibodies directed against LRP6 can be generated using transgenic or transchromosomic mice carrying parts of the human immune system rather than the mouse system. These transgenic and transchromosomic mice include mice referred to herein as HuMAb mice and KM mice, respectively, and are collectively referred to herein as "human Ig mice."

The HuMAb mouse® (Medarex, Inc.) contains human immunoglobulin gene miniloci that encode un-rearranged human heavy (μ and γ) and κ light chain immunoglobulin sequences, together with targeted mutations that inactivate the endogenous μ and κ chain loci (see *e.g.*, Lonberg, *et al.*, (1994) Nature 368(6474): 856-859). Accordingly, the mice exhibit decreased expression of mouse IgM or κ, and in response to immunization, the introduced human heavy and light chain transgenes undergo class switching and somatic mutation to generate high affinity human IgGκ monoclonal (Lonberg *et al.*, (1994) supra; reviewed in Lonberg, (1994) Handbook of Experimental Pharmacology 113:49-101; Lonberg and Huszar, (1995) Intern. Rev. Immunol.13: 65-93, and Harding and Lonberg, (1995) Ann. N. Y. Acad. Sci. 764:536-546). The preparation and use of HuMAb mice, and the genomic modifications carried by such mice, is further described in Taylor *et al.*, (1992) Nucleic Acids Research 20:6287-6295; Chen *et al.*, (1993) International Immunology 5: 647-656; Tuaillon *et al.*, (1993) Proc. Natl. Acad. Sci. USA 94:3720-3724; Choi *et al.*, (1993) Nature Genetics 4:117-123; Chen *et al.*, (1993) EMBO J.

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12:821-830; Tuaillon *et al.*, (1994) J. Immunol. 152:2912-2920; Taylor *et al.*, (1994) International Immunology 579-591; and Fishwild *et al.*, (1996) Nature Biotechnology 14: 845-851, the contents of all of which are hereby specifically incorporated by reference in their entirety. See further, U.S. Patent Nos. 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,789,650; 5,877,397; 5,661,016; 5,814,318; 5,874,299; and 5,770,429; all to Lonberg and Kay; U.S. Patent No. 5,545,807 to Surani *et al.*; PCT Publication Nos. WO 92103918, WO 93/12227, WO 94/25585, WO 97113852, WO 98/24884 and WO 99/45962, all to Lonberg and Kay; and PCT Publication No. WO 01/14424 to Korman *et al.*

In another embodiment, human antibodies of the invention can be raised using a mouse that carries human immunoglobulin sequences on transgenes and transchomosomes such as a mouse that carries a human heavy chain transgene and a human light chain transchromosome. Such mice, referred to herein as "KM mice", are described in detail in PCT Publication WO 02/43478 to Ishida *et al.*

Still further, alternative transgenic animal systems expressing human immunoglobulin genes are available in the art and can be used to raise LRP6 antibodies of the invention. For example, an alternative transgenic system referred to as the Xenomouse (Abgenix, Inc.) can be used. Such mice are described in, *e.g.*, U.S. Patent Nos. 5,939,598; 6,075,181; 6,114,598; 6, 150,584 and 6,162,963 to Kucherlapati *et al.*

Moreover, alternative transchromosomic animal systems expressing human immunoglobulin genes are available in the art and can be used to raise LRP6 antibodies of the invention. For example, mice carrying both a human heavy chain transchromosome and a human light chain tranchromosome, referred to as "TC mice" can be used; such mice are described in Tomizuka *et al.*, (2000) Proc. Natl. Acad. Sci. USA 97:722-727. Furthermore, cows carrying human heavy and light chain transchromosomes have been described in the art (Kuroiwa *et al.*, (2002) Nature Biotechnology 20:889-894) and can be used to raise LRP6 antibodies of the invention.

Human monoclonal antibodies of the invention can also be prepared using phage display methods for screening libraries of human immunoglobulin genes. Such phage display methods for isolating human antibodies are established in the art or described in the examples below. See for example: U.S. Patent Nos. 5,223,409; 5,403,484; and 5,571,698 to Ladner *et al.*; U.S. Patent Nos. 5,427,908 and 5,580,717 to Dower *et al.*; U.S. Patent

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Nos. 5,969,108 and 6,172,197 to McCafferty *et al.*; and U.S. Patent Nos. 5,885,793; 6,521,404; 6,544,731; 6,555,313; 6,582,915 and 6,593,081 to Griffiths *et al.*

Human monoclonal antibodies of the invention can also be prepared using SCID mice into which human immune cells have been reconstituted such that a human antibody response can be generated upon immunization. Such mice are described in, for example, U.S. Patent Nos. 5,476,996 and 5,698,767 to Wilson *et al.*

(iii) Framework or Fc engineering

Engineered antibodies of the invention include those in which modifications have been made to framework residues within VH and/or VL, *e.g.* to improve the properties of the antibody. Typically such framework modifications are made to decrease the immunogenicity of the antibody. For example, one approach is to "backmutate" one or more framework residues to the corresponding germline sequence. More specifically, an antibody that has undergone somatic mutation may contain framework residues that differ from the germline sequence from which the antibody is derived. Such residues can be identified by comparing the antibody framework sequences to the germline sequences from which the antibody is derived. To return the framework region sequences to their germline configuration, the somatic mutations can be "backmutated" to the germline sequence by, for example, site-directed mutagenesis. Such "backmutated" antibodies are also intended to be encompassed by the invention.

Another type of framework modification involves mutating one or more residues within the framework region, or even within one or more CDR regions, to remove T cell - epitopes to thereby decrease the potential immunogenicity of the antibody. This approach is also referred to as "deimmunization" and is described in further detail in U.S. Patent Publication No. 20030153043 by Carr *et al.*

In addition or alternative to modifications made within the framework or CDR regions, antibodies of the invention may be engineered to include modifications within the Fc region, typically to alter one or more functional properties of the antibody, such as serum half-life, complement fixation, Fc receptor binding, and/or antigen-dependent cellular cytotoxicity. Furthermore, an antibody of the invention may be chemically modified (*e.g.*, one or more chemical moieties can be attached to the antibody) or be modified to alter its glycosylation, again to alter one or more functional properties of the antibody. Each of

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these embodiments is described in further detail below. The numbering of residues in the Fc region is that Kabat (*Supra*).

The Hinge region of CH1 can be modified such that the number of cysteine residues in the Hinge region is altered, *e.g.*, increased or decreased. This approach is described further in U.S. Patent No. 5,677,425 by Bodmer *et al.* The number of cysteine residues in the Hinge region of CH1 is altered to, for example, facilitate assembly of the light and heavy chains or to increase or decrease the stability of the antibody.

The Fc-hinge region of a multivalent antibody can be modified to increase its biological half-life. Various approaches are possible. For example, one or more of the following mutations can be introduced: T252L, T254S, T256F, as described in U.S. Patent No. 6,277,375 to Ward. Alternatively, to increase the biological half life, the antibody can be altered within the CH1 or CL region to contain a salvage receptor binding epitope taken from two loops of a CH2 domain of an Fc region of an IgG, as described in U.S. Patent Nos. 5,869,046 and 6,121,022 by Presta *et al.* The Fc-hinge region of the multivalent antibody can be modified to decrease its biological half-life, for example to control dose, toxicity, and clearance therefore allowing for better clinical management through control of dose.

The Fc region can be altered by replacing at least one amino acid residue with a different amino acid residue to alter the effector functions of the antibody. For example, one or more amino acids can be replaced with a different amino acid residue such that the antibody has an altered affinity for an effector ligand but retains the antigen-binding ability of the parent antibody. The effector ligand to which affinity is altered can be, for example, an Fc receptor or the C1 component of complement. This approach is described in further detail in U.S. Patent Nos. 5,624,821 and 5,648,260, both by Winter *et al.*

One or more amino acids can be replaced with a different amino acid residue such that the antibody has altered C1q binding and/or decreased or abolished complement dependent cytotoxicity (CDC). This approach is described in further detail in U.S. Patent Nos. 6,194,551 by Idusogie *et al.*

One or more amino acid residues can be altered to alter the ability of the m antibody to fix complement. This approach is described further in PCT Publication WO 94/29351 by Bodmer *et al.*

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The Fc region can be modified to increase the ability of the antibody to mediate antibody dependent cellular cytotoxicity (ADCC) and/or to increase the affinity of the multivalent antibody for an Fcγ receptor by modifying one or more amino acids. This approach is described further in PCT Publication WO 00/42072 by Presta. Moreover, the binding sites on human IgG1 for FcγRI, FcγRII, FcγRIII and FcRn have been mapped and variants with improved binding have been described (see Shields *et al.*, (2001) J. Biol. Chen. 276:6591-6604).

The glycosylation of an antibody can be modified. For example, an aglycoslated antibody can be made (*i.e.*, the antibody lacks glycosylation). Glycosylation can be altered to, for example, increase the affinity of the antibody for antigen. Such carbohydrate modifications can be accomplished by, for example, altering one or more sites of glycosylation within the antibody sequence. For example, one or more amino acid substitutions can be made that result in elimination of one or more variable region framework glycosylation sites to thereby eliminate glycosylation at that site. Such aglycosylation may increase the affinity of the antibody for antigen. Such an approach is described in further detail in U.S. Patent Nos. 5,714,350 and 6,350,861 by Co *et al.*

Additionally or alternatively, antibody can be made that has an altered type of glycosylation, such as a hypofucosylated antibody having reduced amounts of fucosyl residues or an antibody having increased bisecting GlcNac structures. Such altered glycosylation patterns have been demonstrated to increase the ADCC ability of antibodies. Such carbohydrate modifications can be accomplished by, for example, expressing the antibody in a host cell with altered glycosylation machinery. Cells with altered glycosylation machinery have been described in the art and can be used as host cells in which to express recombinant antibodies of the invention to thereby produce an antibody with altered glycosylation. For example, EP 1,176,195 by Hang *et al.* describes a cell line with a functionally disrupted FUT8 gene, which encodes a fucosyl transferase, such that antibodies expressed in such a cell line exhibit hypofucosylation. PCT Publication WO 03/035835 by Presta describes a variant CHO cell line, Lecl3 cells, with reduced ability to attach fucose to Asn(297)-linked carbohydrates, also resulting in hypofucosylation of antibodies expressed in that host cell (see also Shields *et al.*, (2002) J. Biol. Chem. 277:26733-26740). PCT Publication WO 99/54342 by Umana *et al.* describes cell lines engineered to express glycoprotein-modifying glycosyl transferases (*e.g.*, beta(1,4)-N acetylglucosaminyltransferase III (GnTIII)) such that antibodies

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expressed in the engineered cell lines exhibit increased bisecting GlcNac structures which results in increased ADCC activity of the antibodies (see also Umana *et al.*, (1999) Nat. Biotech. 17:176-180).

The antibody can be modified to increase its biological half-life. Various approaches are possible. For example, one or more of the following mutations can be introduced: T252L, T254S, T256F, as described in U.S. Patent No. 6,277,375 to Ward. Alternatively, to increase the biological half life, the antibody can be altered within the CH1 or CL region to contain a salvage receptor binding epitope taken from two loops of a CH2 domain of an Fc region of an IgG, as described in U.S. Patent Nos. 5,869,046 and 6,121,022 by Presta *et al.*

(iv) Methods of Engineering Altered Antibodies

As discussed above, antibodies having VH and VL sequences or full length heavy and light chain sequences shown herein can be used to create new antibodies by modifying full length heavy chain and/or light chain sequences, VH and/or VL sequences, or the constant region(s) attached thereto. Thus, in another aspect of the invention, the structural features of a antibody of the invention are used to create structurally related antibody that retain at least one functional property of the antibodies of the invention, such as binding to human LRP6 and also inhibiting one or more functional properties of LRP6 (*e.g.*, Wnt signaling activity).

For example, one or more CDR regions of the antibodies of the present invention, or mutations thereof, can be combined recombinantly with known framework regions and/or other CDRs to create additional, recombinantly-engineered, antibodies of the invention, as discussed above. Other types of modifications include those described in the previous section. The starting material for the engineering method is one or more of the VH and/or VL sequences provided herein, or one or more CDR regions thereof. To create the engineered antibody, it is not necessary to actually prepare (*i.e.*, express as a protein) a antibody having one or more of the VH and/or VL sequences provided herein, or one or more CDR regions thereof. Rather, the information contained in the sequence(s) is used as the starting material to create a "second generation" sequence(s) derived from the original sequence(s) and then the "second generation" sequence(s) is prepared and expressed as a protein.

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Accordingly, in another embodiment, the invention provides a method for preparing a propeller 1 LRP6 antibody consisting of: a heavy chain variable region antibody sequence having a CDR1 sequence selected from the group consisting of SEQ ID NOs: 1, 21, and 47, a CDR2 sequence selected from the group consisting of SEQ ID NOs: 2, 22, and 48, and/or a CDR3 sequence selected from the group consisting of SEQ ID NOs: 3, 23, and 49; and a light chain variable region antibody sequence having a CDR1 sequence selected from the group consisting of SEQ ID NOs: 4, 24, and 50, a CDR2 sequence selected from the group consisting of SEQ ID NOs: 5, 25 and, 51, and/or a CDR3 sequence selected from the group consisting of SEQ ID NOs: 6, 26, and 52; altering at least one amino acid residue within the heavy chain variable region antibody sequence and/or the light chain variable region antibody sequence to create at least one altered antibody sequence; and expressing the altered antibody sequence as a protein.

Accordingly, in another embodiment, the invention provides a method for preparing a propeller 3 LRP6 antibody consisting of: a heavy chain variable region antibody sequence having a CDR1 sequence selected from the group consisting of SEQ ID NOs: 69, 93, and 115, a CDR2 sequence selected from the group consisting of SEQ ID NOs: 70, 94, and 116, and/or a CDR3 sequence selected from the group consisting of SEQ ID NOs: 71, 95, and 117; and a light chain variable region antibody sequence having a CDR1 sequence selected from the group consisting of SEQ ID NOs: 91, 107, and 118, a CDR2 sequence selected from the group consisting of SEQ ID NOs: 73, 97, and 121, and/or a CDR3 sequence selected from the group consisting of SEQ ID NOs: 74, 98, and 120; altering at least one amino acid residue within the heavy chain variable region antibody sequence and/or the light chain variable region antibody sequence to create at least one altered antibody sequence; and expressing the altered antibody sequence as a protein.

Accordingly, in another embodiment, the invention provides a method for preparing a multispecific (e.g., a biparatopic) LRP6 antibody consisting of: a heavy chain variable region antibody sequence having a CDR1 sequence selected from the group consisting of SEQ ID NOs: 1, 21, 47, 69, 93, and 115, a CDR2 sequence selected from the group consisting of SEQ ID NOs: 2, 22, 48, 70, 94, and 116, and/or a CDR3 sequence selected from the group consisting of SEQ ID NOs: 3, 23, 49, 71, 95, and 117; and a light chain variable region antibody sequence having a CDR1 sequence selected from the group consisting of SEQ ID NOs: 4, 24, 50, 72, 96, and 118, a CDR2 sequence selected from the group consisting of SEQ ID NOs: 5, 25, 51, 73, 97, and 119, and/or a CDR3 sequence

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selected from the group consisting of SEQ ID NOs: 6, 26, 52, 74, 98, and 120; altering at least one amino acid residue within the heavy chain variable region antibody sequence and/or the light chain variable region antibody sequence to create at least one altered antibody sequence; and expressing the altered antibody sequence as a protein.The altered antibody sequence can also be prepared by screening antibody libraries having fixed CDR3 sequences or minimal essential binding determinants as described in US20050255552 and diversity on CDR1 and CDR2 sequences. The screening can be performed according to any screening technology appropriate for screening antibodies from antibody libraries, such as phage display technology.

Standard molecular biology techniques can be used to prepare and express the altered antibody sequence. The antibody encoded by the altered antibody sequence(s) is one that retains one, some or all of the functional properties of the antibodies described herein, which functional properties include, but are not limited to, specifically binding to human and/or cynomolgus LRP6; the antibody binds to LRP6 and inhibits LRP6 biological activity by inhibiting the canonical Wnt signaling activity in a Wnt gene assay.

The functional properties of the altered antibodies can be assessed using standard assays available in the art and/or described herein, such as those set forth in the Examples (*e.g.*, ELISAs).

In certain embodiments of the methods of engineering antibody of the invention, mutations can be introduced randomly or selectively along all or part of an antibody coding sequence and the resulting modified antibodies can be screened for binding activity and/or other functional properties as described herein. Mutational methods have been described in the art. For example, PCT Publication WO 02/092780 by Short describes methods for creating and screening antibody mutations using saturation mutagenesis, synthetic ligation assembly, or a combination thereof. Alternatively, PCT Publication WO 03/074679 by Lazar *et al.* describes methods of using computational screening methods to optimize physiochemical properties of antibodies.

Characterization of the Antibodies

The antibodies and multivalent antibodies of the invention can be characterized by various functional assays. For example, they can be characterized by their ability to inhibit biological activity by inhibiting canonical Wnt signaling in a Wnt gene assay as

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described herein, their affinity to a LRP6 protein (*e.g.*, human and/or cynomolgus LRP6), the epitope binning, their resistance to proteolysis, and their ability to block the Wnt pathway. In addition, the antibodies are characterized by ability to potentiate an agonistic effect after cross linking to Fab fragments

The multivalent antibodies (e.g., a single biparatopic or a bispecific antibody) has the ability to inhibit both propeller 1 (e.g., Wnt 1) and propeller 3 (e.g., Wnt 3) ligands. Furthermore and unexpectedly, the multivalent antibodies (e.g., a single biparatopic or a bispecific antibody) displays no significant potentiation of a Wnt signal. The multivalent antibodies bind to distinct LRP6 β-propeller regions. For example a biparatopic antibody comprises an receptor binding domain that binds to the β-propeller 1 domain of LRP6 and blocks Propeller1-dependent Wnts such as Wnt1, Wnt2, Wnt6, Wnt7A, Wnt7B, Wnt9, Wnt10A, Wnt10B to inhibit Wnt 1 signal transduction, and also has an epitope binding domain that binds to the β-propeller 3 domain of LRP6 to block Propeller3-dependent Wnts such as Wnt3a and Wnt3 to inhibit Wnt 3 signal transduction.

The multivalent antibodies provide advantages over traditional antibodies for example, by expanding the repertoire of targets, having new binding specificities, increased potency and no signal potency. A single LRP6 multivalent antibody can bind to multiple β-propeller regions on a single LRP6 target on the same cell and inhibit Wnt signaling. In one embodiment, the multivalent antibody binds to any combination of β-propeller regions selected from the group consisting of propeller 1, propeller 2, propeller 3, and propeller 4. In one embodiment, the multivalent antibody binds to propeller 1 and propeller 3 domains of LRP6. Thus, a single LRP6 multivalent antibody has increased potency of action by binding to multiple β-propeller regions and inhibiting Wnt signaling mediated by each region. For example, an LRP6 biparatopic antibody inhibits both propeller 1 and propeller 3 mediated Wnt signaling by binding to both β- propeller 1 and β-propeller 3 domains, respectively. The increased potency of action may be due to increased avidity or better binding of the biparatopic antibody compared to a monospecific antibody.

Various methods can be used to measure LRP6-mediated Wnt signaling. For example, the Wnt signaling pathway can be monitored by (i) measurement of abundance and localization of β-catenin; and (ii) measurement of phosphorylation of LRP6 or other

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downstream Wnt signaling proteins (e.g. DVL), and (iii) measurement of specific gene signatures or gene targets (e.g. c-myc, Cyclin-D, Axin2).

The ability of antibodies to bind to LRP6 can be detected by labelling the antibodies of interest directly, or the antibodies may be unlabelled and binding detected indirectly using various sandwich assay formats known in the art.

In some embodiments, antibodies of the invention block or compete with binding of a reference LRP6 antibody to a LRP6 polypeptide. These can be fully human antibodies described above. They can also be other mouse, chimeric or humanized t antibodies which bind to the same epitope as the reference antibody. The capacity to block or compete with the reference antibody binding indicates that the antibodies under test binds to the same or similar epitope as that defined by the reference antibody, or to an epitope which is sufficiently proximal to the epitope bound by the reference LRP6 antibody. Such antibodies are especially likely to share the advantageous properties identified for the reference antibody. The capacity to block or compete with the reference antibody may be determined by, *e.g.*, a competition binding assay. With a competition binding assay, the antibody under test is examined for ability to inhibit specific binding of the reference antibody to a common antigen, such as a LRP6 polypeptide. A test antibody competes with the reference antibody for specific binding to the antigen if an excess of the test antibody substantially inhibits binding of the reference antibody. Substantial inhibition means that the test antibody decreases specific binding of the reference antibody usually by at least 10%, 25%, 50%, 75%, or 90%.

There are a number of known competition binding assays that can be used to assess competition of a antibodies with the reference LRP6 antibody for binding to a LRP6 protein. These include, *e.g.*, solid phase direct or indirect radioimmunoassay (RIA), solid phase direct or indirect enzyme immunoassay (EIA), sandwich competition assay (see Stahli *et al.*, (1983) Methods in Enzymology 9:242-253); solid phase direct biotin-avidin EIA (see Kirkland *et al.*, (1986) J. Immunol. 137:3614-3619); solid phase direct labeled assay, solid phase direct labeled sandwich assay (see Harlow & Lane, supra); solid phase direct label RIA using I-125 label (see Morel *et al.*, (1988) Molec. Immunol. 25:7-15); solid phase direct biotin-avidin EIA (Cheung *et al.*, (1990) Virology 176:546-552); and direct labeled RIA (Moldenhauer *et al.*, (1990) Scand. J. Immunol. 32:77-82). Typically, such an assay involves the use of purified antigen bound to a solid surface or cells bearing

either of these, an unlabelled test antibody and a labelled reference antibody. Competitive inhibition is measured by determining the amount of label bound to the solid surface or cells in the presence of the test antibody. Usually the test antibody is present in excess. Antibodies, e.g., a bispecific or biparatopic LRP6 antibodies identified by competition assay (competing antibodies) include antibodies binding to the same epitope as the reference antibody and antibodies binding to an adjacent epitope sufficiently proximal to the epitope bound by the reference antibody for steric hindrance to occur.

To determine if the selected antibody binds to unique epitopes, each antibody can be biotinylated using commercially available reagents (*e.g.*, reagents from Pierce, Rockford, IL). Competition studies using unlabeled antibodies and biotinylated antibodies can be performed using a LRP6 polypeptide coated-ELISA plates. Biotinylated antibodies binding can be detected with a strep-avidin-alkaline phosphatase probe. To determine the isotype of purified antibodies, isotype ELISAs can be performed. For example, wells of microtiter plates can be coated with 1 μg/ml of anti-human IgG overnight at 4°C. After blocking with 1% BSA, the plates are reacted with 1 μg/ml or less of the antibody or purified isotype controls, at ambient temperature for one to two hours. The wells can then be reacted with either human IgGl or human IgM-specific alkaline phosphatase-conjugated probes. Plates are then developed and analyzed so that the isotype of the purified antibody can be determined.

To demonstrate binding of antibodies to live cells expressing a LRP6 polypeptide, flow cytometry can be used. Briefly, cell lines expressing LRP6 (grown under standard growth conditions) can be mixed with various concentrations of a t antibodies in PBS containing 0.1% BSA and 10% fetal calf serum, and incubated at 37°C for 1 hour. After washing, the cells are reacted with Fluorescein-labeled anti-human IgG antibody under the same conditions as the primary antibody staining. The samples can be analyzed by FACScan instrument using light and side scatter properties to gate on single cells. An alternative assay using fluorescence microscopy may be used (in addition to or instead of) the flow cytometry assay. Cells can be stained exactly as described above and examined by fluorescence microscopy. This method allows visualization of individual cells, but may have diminished sensitivity depending on the density of the antigen.

The antibodies can be further tested for reactivity with a LRP6 polypeptide or antigenic fragment by Western blotting. Briefly, purified LRP6 polypeptides or fusion proteins, or

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cell extracts from cells expressing LRP6 can be prepared and subjected to sodium dodecyl sulfate polyacrylamide gel electrophoresis. After electrophoresis, the separated antigens are transferred to nitrocellulose membranes, blocked with 10% fetal calf serum, and probed with the antibodies to be tested. Human IgG binding can be detected using anti-human IgG alkaline phosphatase and developed with BCIP/NBT substrate tablets (Sigma Chem. Co., St. Louis, MO). Other examples of functional assays are also described in the Example section below.

Binding Characteristics of Antibodies of the Invention

(i) Binding Specificities

The invention provides antibodies and multivalent antibodies comprising multiple receptor binding domains (e.g., scFvs, single chain diabodies, antibody variable regions) that have specificities for different binding sites on one or more target receptor(s).

In one embodiment, multivalent antibodies of the invention comprise receptor binding domains (e.g., scFvs) with identical binding specificities. In another embodiment, multivalent antibodies of the invention comprise scFvs with non-identical binding specificities.

(ii) Binding Affinity

The antibodies or multivalent antibodies of the invention may have a high binding affinity to one or more of its cognate antigens. For example, an epitope binding protein described herein may have an association rate constant or k_{on} rate (epitope binding protein (RBP)+antigen->RBP-Ag) of at least $2x10^5M^1s^{-1}$, at least $5x10^5M^1s^{-1}$, at least $10^6M^1s^{-1}$, at least $5x10^6M^1s^{-1}$, at least $10^7M^1s^{-1}$, at least $5x10^7M^1s^{-1}$, or at least $10^8M^1s^{-1}$.

In one embodiment, the antibodies or multivalent antibody may have a k_{off} rate (RBP-Ag->RBP+Ag) of less than $5x10^{-1}s^{-1}$, less than $10^{-1}s^{-1}$, less than $5x10^{-2}s^{-1}$, less than $10^{-2}s^{-1}$, less than $5x10^{-3}s^{-1}$, less than $10^{-3}s^{-1}$, less than $5x10^{-4}s^{-1}$, or less than $5x10^{-4}s^{-1}$. The antibodies or multivalent antibodies have a k_{off} of less than $5x10^{-5}s^{-1}$, less than $10^{-5}s^1$, less than $5x10^{-6}s^{-1}$, less than $10^{-6}s^{-1}$, less than $5x10^{-7}s^{-1}$, less than $5x10^{-7}s^{-1}$, less than $5x10^{-8}s^{-1}$, less than $10^{-8}s^{-1}$, less than $5x10^{-9}s^{-1}$, less than $10^{-9}s^{-1}$, or less than $10^{-9}s^{-1}$.

In another embodiment, the antibodies or multivalent antibody may have an affinity

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constant or K_a (k_{on}/k_{off}) of at least 10^2M^{-1}, at least $5x10^2M^{-1}$, at least 10^3M^{-1}, at least $5x10^3M^{-1}$, at least 10^4M^{-1}, at least $5x10^4M^{-1}$, at least 10^5M^{-1}, at least $5x10^5M^{-1}$, at least 10^6M^{-1}, at least $5x10^6M^{-1}$, at least 10^7M^{-1}, at least $5x10^7M^{-1}$, at least 10^8M^{-1}, at least $5x10^8M^{-1}$, at least 10^9M^{-1}, at least $5x10^9M^{-1}$, at least $10^{10}M^{-1}$, at least $5x10^{10}M^{-1}$, at least $10^{11}M^{-1}$, at least $5x10^{11}M^{-1}$, at least $10^{12}M^{-1}$, at least $5x10^{12}M^{-1}$, at least $10^{13}M^{-1}$, at least $5x10^{13}$ M^{-1}, at least $10^{14}M^{-1}$, at least $5x10^{14}M^{-1}$, at least $10^{15}M^{-1}$, or at least $5x10^{15}M^{-1}$.

In yet another embodiment, the antibody or multivalent antibody may have a dissociation constant or K_d (k_{off}/k_{on}) of less than $5x10^{-2}M$, less than $10^{-2}M$, less than $5x10^{-3}M$, less than $10^{-3}M$, less than $5x10^{-4}M$, less than $10^{-4}M$, less than $5x10^{-5}M$, less than $10^{-5}M$, less than $5x10^{-6}M$, less than $10^{-6}M$, less than $5x10^{-7}M$, less than $10^{-7}M$, less than $5x10^{-8}M$, less than $10^{-8}M$, less than $5x10^{-9}M$, less than $10^{-9}M$, less than $5x10^{-10}M$, less than $10^{-10}M$, less than $5x10^{-11}M$, less than $10^{-11}M$, less than $5x10^{-12}M$, less than $10^{-12}M$, less than $5x10^{-13}M$, less than $10^{-13}M$, less than $5x10^{-14}M$, less than $10^{-14}M$, less than $5x10^{-15}M$, or less than $10^{-15}M$.

The antibody or multivalent antibody used in accordance with a method described herein may have a dissociation constant (K_d) of less than 3000 pM, less than 2500 pM, less than 2000 pM, less than 1500 pM, less than 1000 pM, less than 750 pM, less than 500 pM, less than 250 pM, less than 200 pM, less than 150 pM, less than 100 pM, less than 75 pM, less than 10 pM, less than 1 pM as assessed using a method described herein or known to one of skill in the art (e.g., a BIAcore assay, ELISA, FACS, SET) (Biacore International AB, Uppsala, Sweden). The antibody or multivalent antibodies used in accordance with a method described herein may have a dissociation constant (K_d) of between 25 to 3400 pM, 25 to 3000 pM, 25 to 2500 pM, 25 to 2000 pM, 25 to 1500 pM, 25 to 1000 pM, 25 to 750 pM, 25 to 500 pM, 25 to 250 pM, 25 to 100 pM, 25 to 75 pM, 25 to 50 pM as assessed using a method described herein or known to one of skill in the art (e.g., a BIAcore assay, ELISA, FACS, SET). The antibody or multivalent antibodies used in accordance with a method described herein may have a dissociation constant (K_d) of 500 pM, 100 pM, 75 pM or 50 pM as assessed using a method described herein or known to one of skill in the art (e.g., a BIAcore assay, ELISA, FACS, SET).

(iii) Relative Binding Affinities of Multivalent Antibodies

It is to be understood that the invention provides proteins carrying multiple receptor

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binding domains that may retain functionality within the protein in a similar fashion or better to the functionalities exhibited in an isolated state (i.e. the receptor binding domain exhibits similar properties as part of the multivalent antibody as compared to the domain if expressed or isolated independently). For example, an isolated scFv specific for epitope Y exhibits a specific functional profile including binding affinity, agonistic or antagonistic functions. It is to be understood that the same scFv expressed as a recptor binding domain within a multivalent antibody of the invention would exhibit similar binding affinity or better and/or agonistic or antagonistic properties as compared to the isolated scFv.

In one embodiment, the multivalent antibodies of the invention comprise receptor binding domains (e.g., scFvs) with binding affinities lower than the same isolated (free from other components of the multivalent antibody) receptor binding domains (e.g., scFvs). In another embodiment, multivalent antibodies of the invention comprise receptor binding domains (e.g., scFvs), with binding affinities higher than the same isolated (free from other components of the multivalent antibody) receptor binding domains (e.g., scFvs). In another embodiment, multivalent antibodies of the invention comprise receptor binding domains (e.g., scFvs), with binding affinities essentially the same as the corresponding isolated (free from other components of the multivalent antibody) receptor binding domains (e.g., scFvs).

Binding affinities can be routinely assayed by many techniques known in the art, such as ELISA, BiaCore™, KinExA™, cell surface receptor binding, competitive inhibition of binding assays, SET. The binding affinities of the multivalent antibodies of the invention can be assayed by the techniques presented in the Examples.

An receptor binding domain (e.g., scFv) of a multivalent antibody exhibits a binding affinity less than 99%, less than 95%, less than 90%, less than 80%, less than 70%, less than 60%, less than 50%, less than 40%, less than 30%, less than 20%, or less than 10% to a specific epitope than an identical functional isolated receptor binding domain (e.g., scFv) as measured by any assay known in the art. In another embodiment, a receptor binding domain (e.g., scFv) of a multivalent antibody exhibits a binding affinity less than 99%, less than 95%, less than 90%, less than 80%, less than 70%, less than 60%, less than 50%, less than 40%, less than 30%, less than 20%, or less than 10% to a specific epitope

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than an identical functional isolated receptor binding domain (e.g., scFv) as measured by the techniques presented in any of the Examples.

A receptor binding domain (e.g., scFv) of a multivalent antibody exhibits a binding affinity more than 99%, more than 95%, more than 90%, more than 80%, more than 70%, more than 60%, more than 50%, more than 40%, more than 30%, more than 20%, or more than 10% to a specific epitope than an identical functional isolated receptor binding domain (e.g., scFv) as measured by any assay known in the art. In another embodiment, an receptor binding domain (e.g., scFv) of a multivalent antibody exhibits a binding affinity more than 99%, more than 95%, more than 90%, more than 80%, more than 70%, more than 60%, more than 50%, more than 40%, more than 30%, more than 20%, or more than 10% to a specific epitope than an identical functional isolated receptor binding domain (e.g., scFv) as measured by the techniques presented in any of the Examples.

(iv) Assays For Epitope Binding and Activity

The antibodies and multivalent antibodies of the invention may be assayed for specific (i.e., immunospecific) binding by any method known in the art. The immunoassays which can be used, include but are not limited to, competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays, to name but a few. Such assays are routine and known in the art (see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X-100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (e.g., EDTA, PMSF, aprotinin, sodium vanadate), adding the epitope binding protein of interest to the cell lysate, incubating for a period of time (e.g., 1-4 hours) at 4°C., adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 4°C., washing the beads

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in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the protein of interest to immunoprecipitate a particular antigen can be assessed by, e.g., western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the epitope binding protein to an antigen and decrease the background (e.g., pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.16.1.

Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (e.g., 8%-20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (e.g., PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (e.g., PBS-Tween 20), blocking the membrane with primary antibody diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody) conjugated to an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) or radioactive molecule (e.g., ^{32}P or ^{125}I) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.8.1.

ELISAs comprise preparing antigen, coating the well of a 96 well microtiter plate with the antigen, adding the epitope binding protein of interest conjugated to a detectable compound such as an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) to the well and incubating for a period of time, and detecting the presence of the antigen. In ELISAs the epitope binding protein of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the protein of interest) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the protein of interest may be coated to the well. In this case, a second antibody conjugated to a detectable compound may be

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added following the addition of the antigen of interest to the coated well. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 11.2.1.

The binding affinity and other binding properties of an antibody or multivalent antibody to an antigen may be determined by a variety of in vitro assay methods known in the art including for example, equilibrium methods (e.g., enzyme-linked immunoabsorbent assay (ELISA; or radioimmunoassay (RIA)), or kinetics (e.g., BIACORE™ analysis), and other methods such as indirect binding assays, competitive binding assays fluorescence resonance energy transfer (FRET), gel electrophoresis and chromatography (e.g., gel filtration), FACS. These and other methods may utilize a label on one or more of the components being examined and/or employ a variety of detection methods including but not limited to chromogenic, fluorescent, luminescent, or isotopic labels. A detailed description of binding affinities and kinetics can be found in Paul, W. E., ed., Fundamental Immunology, 4th Ed., Lippincott-Raven, Philadelphia (1999), which focuses on antibody-immunogen interactions. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen with the epitope binding protein of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the epitope binding protein bound to the labeled antigen. The affinity of the epitope binding protein of interest for a particular antigen and the binding off-rates can be determined from the data by scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, the antigen is incubated with epitope binding protein of interest conjugated to a labeled compound in the presence of increasing amounts of an unlabeled second antibody.

Prophylactic and Therapeutic Uses

The present invention also encompasses the use of antibodies or multivalent antibodies of the invention for the prevention, diagnosis, management, treatment or amelioration of one or more symptoms associated with diseases, disorders of diseases or disorders, including but not limited to cancer, inflammatory and autoimmune diseases either alone or in combination with other therapies. The invention also encompasses the use of antibodies of the invention conjugated or fused to a moiety (e.g., therapeutic agent or drug) for

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prevention, management, treatment or amelioration of one or more symptoms associated with diseases, disorders or infections, including but not limited to cancer, inflammatory and autoimmune diseases either alone or in combination with other therapies.

Many cell types express various common cell surface antigens and it is the specific combination of antigens that distinguish a defined subset of cells. Using the multivalent antibodies of the invention, it is possible to target specific subsets of cells without cross-reacting with other unrelated populations of cells. Further, it is possible that multivalent antibodies of the invention comprise one to several (two, three, four, five, six, seven, eight, nine, ten, etc.) receptor binding domains that bind cell surface antigens present on non-target cell populations, however, it is the combined avidity of the set of receptor binding domains, which confer an effective level of binding (i.e., a therapeutically effective level of binding) to the target cell population. In other words, several of the receptor binding domains are engaged to facilitate the targeting of a particular cell type, which would not be achieved by binding of an individual isolated domain (e.g., isolated from the multivalent antibody) or not achieved by one or more, but not all (i.e., a subset) of receptor binding domains (control peptides) exposed to the same cell, but not as part of a multivalent antibody. It is envisioned that the relative avidity contribution of each receptor binding domain may be tailored to only target the specific cell population of interest. Such affinity alterations may be performed by art-accepted techniques, such as affinity maturation, site-specific mutagenesis, and others known in art. It is also contemplated that the relative avidity contribution of each receptor binding domain may also be altered by changing the relative orientation of the receptor binding domains in the multivalent antibody.

Accordingly, provided herein in one embodiment are methods of using multivalent antibodies of the invention to identify, deplete, modulate (e.g., activate, inhibit) a cell population (e.g., *in vivo* in a mammal (e.g., a human) and/or *in vitro*). In some embodiments, the increase in avidity exhibited by the multivalent antibodies of the invention for a target cell population *in vitro* or when administered to a mammal (e.g., a human) is at least 2 fold, at least 3 fold, at least 4 fold, at least 5 fold, at least 6, fold, at least 7 fold, at least 8 fold, at least 9 fold, at least 10 fold, at least 15 fold, at least 20 fold, or at least 25 fold as compared to a "control epitope binding protein" which comprises one or more, but not all (i.e., a subset) of receptor binding domains isolated from the

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multivalent antibody. In some embodiments, the increase in avidity exhibited by the multivalent antibodys of the invention is at least 5%, at least 10%, at least 15%, at least 20%, at least 30%, fold, at least 40%, at least 50%, at least 75%, at least 85%, at least 90%, at least 95%, or at least 150% over the "control epitope binding protein".

In some embodiments, multivalent antibodys of the invention have an increase in avidity for a particular antigen compared to a control receptor binding protein, which comprises one or more, but not all (i.e., a subset) of receptor binding domains isolated from the multivalent antibody. In some embodiments, the increase in avidity exhibited by the multivalent antibodys of the invention is at least 2 fold, at least 3 fold, at least 4 fold, at least 5 fold, at least 6, fold, at least 7 fold, at least 8 fold, at least 9 fold, at least 10 fold, at least 15 fold, at least 20 fold, or at least 100 fold over or at least 1000 fold over the control receptor binding protein. In some embodiments, the increase in avidity exhibited by the multivalent antibodys of the invention is at least 5%, at least 10%, at least 15%, at least 20%, at least 30%, fold, at least 40%, at least 50%, at least 75%, at least 85%, at least 90%, at least 95%, 100% over the control receptor binding protein.

In other embodiments, multivalent antibodies of the invention comprising X number of receptor binding domains (where X is any positive integer from 2 through 6) exhibit an increase in avidity (in vitro or when administered to a mammal (e.g., a human) for a particular antigen compared to a control receptor binding protein (such as, but not limited to an antibody, , an scFv) wherein the control receptor binding protein comprises X-Y (where X and Y are any positive integer from 2 through 6and X is greater than Y) receptor binding domains, wherein at least one receptor binding domain in the control receptor binding domain protein is specific for the same epitope as the receptor binding domain present in the protein of the invention. In other words, the invention provides multivalent antibodies with increased avidity for a particular target as compared to control receptor binding proteins with greater or fewer receptor binding domains wherein at least one receptor binding domain is specific for a common antigen with the protein of the invention.

Such avidity changes in multivalent antibodies allow for the decrease of toxicity of such therapeutic proteins (for example, combinations of any antibodies listed in Table 1. It is understood that the proteins of the invention may exhibit a "tailor-fit" avidity and/or

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affinity to decrease toxicity in vivo. As such, the invention also provides multivalent antibodies of the invention that exhibit a lower toxicity in an animal, than a control receptor binding protein.

It is also appreciated that avidity changes may be evaluated by readily available in vitro methods such as functional assays (including but not limited to cytokine expression/release/binding, gene expression, morphology changes, chemotaxis, calcium flux, and the like, growth and signaling), binding measurements determined by BIAcore or KinExa measurements with control receptor binding domain proteins. In some embodiments, control receptor binding proteins may contain a subset of receptor binding domains from the proteins of the invention. In other embodiments, control receptor binding proteins may comprise at least one or more isolated receptor binding domains from the multivalent antibodies of the invention. For example, for a protein of the invention with 8 epitope binding domains, a control receptor binding protein may comprise 1, 2, 3, 4, 5, or 6receptor binding domains, with at least one receptorbinding domain having specificity for an antigen recognized by both the protein of the invention and the control protein.

In one embodiment, the multivalent antibodies of the invention are used to specifically identify, deplete, activate, inhibit, or target for neutralization cells which are defined by the expression of multiple cell surface antigens.

In a specific embodiment, the present invention provides methods of treating cancers associated with a Wnt signaling pathway that include, but are not limited to breast cancer, lung cancer, multiple myeloma, ovarian cancer, liver cancer, bladder cancer gastric cancer, prostate cancer, acute myeloid leukemia, chronic myeloid leukemia, osteosarcoma, squamous cell carcinoma, and melanoma.

Antibodies can also be used to treat or prevent other disorders associated with aberrant or defective Wnt signaling, including but are not limited to osteoporosis, osteoarthritis, polycystic kidney disease, diabetes, schizophrenia, vascular disease, cardiac disease, non-oncogenic proliferative diseases, fibrosis, and neurodegenerative diseases such as Alzheimer's disease. The Wnt signaling pathway plays a critical role in tissue repair and regeneration. Agents that sensitize cells to Wnt signaling can be used to promote tissue

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regeneration for many conditions such as bone diseases, mucositis, acute and chronic kidney injury, and others.

Suitable agents for combination treatment with LRP6 antibodies include standard of care agents known in the art that are able to modulate the activities of canonical Wnt signaling pathway (e.g., PI3 kinase agents).

Diagnostic Uses

In one aspect, the invention encompasses diagnostic assays for determining LRP6 protein and/or nucleic acid expression as well as LRP6 protein function, in the context of a biological sample (*e.g.*, blood, serum, cells, tissue) or from individual afflicted with cancer, or is at risk of developing cancer.

Diagnostic assays, such as competitive assays rely on the ability of a labelled analogue (the "tracer") to compete with the test sample analyte for a limited number of binding sites on a common binding partner. The binding partner generally is insolubilized before or after the competition and then the tracer and analyte bound to the binding partner are separated from the unbound tracer and analyte. This separation is accomplished by decanting (where the binding partner was preinsolubilized) or by centrifuging (where the binding partner was precipitated after the competitive reaction). The amount of test sample analyte is inversely proportional to the amount of bound tracer as measured by the amount of marker substance. Dose-response curves with known amounts of analyte are prepared and compared with the test results in order to quantitatively determine the amount of analyte present in the test sample. These assays are called ELISA systems when enzymes are used as the detectable markers. In an assay of this form, competitive binding between antibodies and LRP6 antibodies results in the bound LRP6 protein, being a measure of antibodies in the serum sample, most particularly, antibodies in the serum sample.

A significant advantage of the assay is that measurement is made of neutralising antibodies directly (*i.e.*, those which interfere with binding of LRP6 protein, specifically, epitopes). Such an assay, particularly in the form of an ELISA test has considerable applications in the clinical environment and in routine blood screening.

The invention also provides for prognostic (or predictive) assays for determining whether an individual is at risk of developing a disorder associated with LRP6. For example,

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mutations in a LRP6 gene can be assayed in a biological sample. Such assays can be used for prognostic or predictive purpose to thereby prophylactically treat an individual prior to the onset of a disorder characterized by or associated with LRP6 protein, nucleic acid expression or activity.

Another aspect of the invention provides methods for determining LRP6 nucleic acid expression or LRP6 protein activity in an individual to thereby select appropriate therapeutic or prophylactic agents for that individual (referred to herein as "pharmacogenomics"). Pharmacogenomics allows for the selection of agents (*e.g.*, drugs) for therapeutic or prophylactic treatment of an individual based on the genotype of the individual (*e.g.*, the genotype of the individual examined to determine the ability of the individual to respond to a particular agent.)

Yet another aspect of the invention pertains to monitoring the influence of agents (*e.g.*, drugs) on the expression or activity of LRP6 protein in clinical trials.

Pharmaceutical Compositions

To prepare pharmaceutical or sterile compositions including an antibody or multivalent antibodies of the invention mixed with a pharmaceutically acceptable carrier or excipient. The compositions can additionally contain one or more other therapeutic agents that are suitable for treating or preventing cancer (breast cancer, lung cancer, multiple myeloma, ovarian cancer, liver cancer, bladder cancer gastric cancer, prostate cancer, acute myeloid leukemia, chronic myeloid leukemia, osteosarcoma, squamous cell carcinoma, and melanoma).

Formulations of therapeutic and diagnostic agents can be prepared by mixing with physiologically acceptable carriers, excipients, or stabilizers in the form of, e.g., lyophilized powders, slurries, aqueous solutions, lotions, or suspensions (see, e.g., Hardman, et al. (2001) Goodman and Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, N.Y.; Gennaro (2000) Remington: The Science and Practice of Pharmacy, Lippincott, Williams, and Wilkins, New York, N.Y.; Avis, et al. (eds.) (1993) Pharmaceutical Dosage Forms: Parenteral Medications, Marcel Dekker, NY; Lieberman, et al. (eds.) (1990) Pharmaceutical Dosage Forms: Tablets, Marcel Dekker, NY; Lieberman, et al. (eds.) (1990) Pharmaceutical Dosage Forms: Disperse Systems, Marcel Dekker, NY; Weiner and Kotkoskie (2000) Excipient Toxicity and

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Safety, Marcel Dekker, Inc., New York, N.Y.).

Selecting an administration regimen for a therapeutic depends on several factors, including the serum or tissue turnover rate of the entity, the level of symptoms, the immunogenicity of the entity, and the accessibility of the target cells in the biological matrix. In certain embodiments, an administration regimen maximizes the amount of therapeutic delivered to the patient consistent with an acceptable level of side effects. Accordingly, the amount of biologic delivered depends in part on the particular entity and the severity of the condition being treated. Guidance in selecting appropriate doses of antibodies, cytokines, and small molecules are available (see, e.g., Wawrzynczak (1996) Antibody Therapy, Bios Scientific Pub. Ltd, Oxfordshire, UK; Kresina (ed.) (1991) Monoclonal Antibodies, Cytokines and Arthritis, Marcel Dekker, New York, N.Y.; Bach (ed.) (1993) Monoclonal Antibodies and Peptide Therapy in Autoimmune Diseases, Marcel Dekker, New York, N.Y.; Baert *et al.*, (2003) New Engl. J. Med. 348:601-608; Milgrom *et al.*, (1999) New Engl. J. Med. 341:1966-1973; Slamon *et al.*, (2001) New Engl. J. Med. 344:783-792; Beniaminovitz *et al.*, (2000) New Engl. J. Med. 342:613-619; Ghosh *et al.*, (2003) New Engl. J. Med. 348:24-32; Lipsky *et al.*, (2000) New Engl. J. Med. 343:1594-1602).

Determination of the appropriate dose is made by the clinician, e.g., using parameters or factors known or suspected in the art to affect treatment or predicted to affect treatment. Generally, the dose begins with an amount somewhat less than the optimum dose and it is increased by small increments thereafter until the desired or optimum effect is achieved relative to any negative side effects. Important diagnostic measures include those of symptoms of, e.g., the inflammation or level of inflammatory cytokines produced.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of the present invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient. The selected dosage level will depend upon a variety of pharmacokinetic factors including the activity of the particular compositions of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs,

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compounds and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors known in the medical arts.

Compositions comprising antibodies of the invention can be provided by continuous infusion, or by doses at intervals of, e.g., one day, one week, or 1-7 times per week. Doses may be provided intravenously, subcutaneously, topically, orally, nasally, rectally, intramuscular, intracerebrally, or by inhalation. A specific dose protocol is one involving the maximal dose or dose frequency that avoids significant undesirable side effects. A total weekly dose may be at least 0.05 μg/kg body weight, at least 0.2 μg/kg, at least 0.5 μg/kg, at least 1 μg/kg, at least 10 μg/kg, at least 100 μg/kg, at least 0.2 mg/kg, at least 1.0 mg/kg, at least 2.0 mg/kg, at least 10 mg/kg, at least 25 mg/kg, or at least 50 mg/kg (see, e.g., Yang *et al.*, (2003) New Engl. J. Med. 349:427-434; Herold *et al.*, (2002) New Engl. J. Med. 346:1692-1698; Liu *et al.*, (1999) J. Neurol. Neurosurg. Psych. 67:451-456; Portielji *et al.*, (20003) Cancer Immunol. Immunother. 52:133-144). The desired dose of multivalent antibody is about the same as for an antibody or polypeptide, on a moles/kg body weight basis. The desired plasma concentration of a multivalent antibody is about the same as for an antibody, on a moles/kg body weight basis. The dose may be at least 15 μg at least 20 μg, at least 25 μg, at least 30 μg, at least 35 μg, at least 40 μg, at least 45 μg, at least 50 μg, at least 55 μg, at least 60 μg, at least 65 μg, at least 70 μg, at least 75 μg, at least 80 μg, at least 85 μg, at least 90 μg, at least 95 μg, or at least 100 μg. The doses administered to a subject may number at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12, or more.

For antibodies of the invention, the dosage administered to a patient may be 0.0001 mg/kg to 100 mg/kg of the patient's body weight. The dosage may be between 0.0001 mg/kg and 20 mg/kg, 0.0001 mg/kg and 10 mg/kg, 0.0001 mg/kg and 5 mg/kg, 0.0001 and 2 mg/kg, 0.0001 and 1 mg/kg, 0.0001 mg/kg and 0.75 mg/kg, 0.0001 mg/kg and 0.5 mg/kg, 0.0001 mg/kg to 0.25 mg/kg, 0.0001 to 0.15 mg/kg, 0.0001 to 0.10 mg/kg, 0.001 to 0.5 mg/kg, 0.01 to 0.25 mg/kg or 0.01 to 0.10 mg/kg of the patient's body weight.

The dosage of the antibody of the invention may be calculated using the patient's weight in kilograms (kg) multiplied by the dose to be administered in mg/kg. The dosage of the

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antibodies of the invention may be 150 μg/kg or less, 125 μg/kg or less, 100 μg/kg or less, 95 μg/kg or less, 90 μg/kg or less, 85 μg/kg or less, 80 μg/kg or less, 75 μg/kg or less, 70 μg/kg or less, 65 μg/kg or less, 60 μg/kg or less, 55 μg/kg or less, 50 μg/kg or less, 45 μg/kg or less, 40 μg/kg or less, 35 μg/kg or less, 30 μg/kg or less, 25 μg/kg or less, 20 μg/kg or less, 15 μg/kg or less, 10 μg/kg or less, 5 μg/kg or less, 2.5 μg/kg or less, 2 μg/kg or less, 1.5 μg/kg or less, 1 μg/kg or less, 0.5 μg/kg or less, or 0.5 μg/kg or less of a patient's body weight.

Unit dose of theantibodies of the invention may be 0.1 mg to 20 mg, 0.1 mg to 15 mg, 0.1 mg to 12 mg, 0.1 mg to 10 mg, 0.1 mg to 8 mg, 0.1 mg to 7 mg, 0.1 mg to 5 mg, 0.1 to 2.5 mg, 0.25 mg to 20 mg, 0.25 to 15 mg, 0.25 to 12 mg, 0.25 to 10 mg, 0.25 to 8 mg, 0.25 mg to 7 m g, 0.25 mg to 5 mg, 0.5 mg to 2.5 mg, 1 mg to 20 mg, 1 mg to 15 mg, 1 mg to 12 mg, 1 mg to 10 mg, 1 mg to 8 mg, 1 mg to 7 mg, 1 mg to 5 mg, or 1 mg to 2.5 mg.

The dosage of the antibodiesof the invention may achieve a serum titer of at least 0.1 μg/ml, at least 0.5 μg/ml, at least 1 μg/ml, at least 2 μg/ml, at least 5 μg/ml, at least 6 μg/ml, at least 10 μg/ml, at least 15 μg/ml, at least 20 μg/ml, at least 25 μg/ml, at least 50 μg/ml, at least 100 μg/ml, at least 125 μg/ml, at least 150 μg/ml, at least 175 μg/ml, at least 200 μg/ml, at least 225 μg/ml, at least 250 μg/ml, at least 275 μg/ml, at least 300 μg/ml, at least 325 μg/ml, at least 350 μg/ml, at least 375 μg/ml, or at least 400 μg/ml in a subject. Alternatively, the dosage of the antibodies of the invention may achieve a serum titer of at least 0.1 μg/ml, at least 0.5 μg/ml, at least 1 μg/ml, at least, 2 μg/ml, at least 5 μg/ml, at least 6 μg/ml, at least 10 μg/ml, at least 15 μg/ml, at least 20 .mu.g/ml, at least 25 μg/ml, at least 50 μg/ml, at least 100 μg/ml, at least 125 μg/ml, at least 150 μg/ml, at least 175 μg/ml, at least 200 μg/ml, at least 225 μg/ml, at least 250 μg/ml, at least 275 μg/ml, at least 300 μg/ml, at least 325 μg/ml, at least 350 μg/ml, at least 375 μg/ml, or at least 400 μg/ml in the subject.

Doses of antibodies of the invention may be repeated and the administrations may be separated by at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or at least 6 months.

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An effective amount for a particular patient may vary depending on factors such as the condition being treated, the overall health of the patient, the method route and dose of administration and the severity of side affects (see, e.g., Maynard, et al. (1996) A Handbook of SOPs for Good Clinical Practice, Interpharm Press, Boca Raton, Fla.; Dent (2001) Good Laboratory and Good Clinical Practice, Urch Publ., London, UK).

The route of administration may be by, e.g., sutaneous application, injection or infusion by intravenous, intraperitoneal, intracerebral, intramuscular, intraocular, intraarterial, intracerebrospinal, intralesional, or by sustained release systems or an implant (see, e.g., Sidman *et al.*, (1983) Biopolymers 22:547-556; Langer *et al.*, (1981) J. Biomed. Mater. Res. 15:167-277; Langer, (1982) Chem. Tech. 12:98-105; Epstein *et al.*, (1985) Proc. Natl. Acad. Sci. USA 82:3688-3692; Hwang *et al.*, (1980) Proc. Natl. Acad. Sci. USA 77:4030-4034; U.S. Pat. Nos. 6,350,466 and 6,316,024). Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lidocaine to ease pain at the site of the injection. In addition, pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent. See, e.g., U.S. Pat. Nos. 6,019,968, 5,985,320, 5,985,309, 5,934,272, 5,874,064, 5,855,913, 5,290,540, and 4,880,078; and PCT Publication Nos. WO 92/19244, WO 97/32572, WO 97/44013, WO 98/31346, and WO 99/66903, each of which is incorporated herein by reference their entirety.

A composition of the present invention may also be administered via one or more routes of administration using one or more of a variety of methods known in the art. As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results. Selected routes of administration for antibodies of the invention include intravenous, intramuscular, intradermal, intraperitoneal, subcutaneous, spinal or other parenteral routes of administration, for example by injection or infusion. Parenteral administration may represent modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion. In one embodiment, the antibody of the invention is administered by infusion. In another embodiment, the antibody of the invention is administered

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subcutaneously.

If the antibodies of the invention are administered in a controlled release or sustained release system, a pump may be used to achieve controlled or sustained release (see Langer, supra; Sefton, (1987) CRC Crit. Ref Biomed. Eng. 14:20; Buchwald *et al.,* (1980) Surgery 88:507; Saudek *et al.,* (1989) N. Engl. J. Med. 321:574). Polymeric materials can be used to achieve controlled or sustained release of the therapies of the invention (see e.g., Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Fla. (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, 1983, J., Macromol. Sci. Rev. Macromol. Chem. 23:61; see also Levy et al., 1985, Science 228:190; During et al., 1989, Ann. Neurol. 25:351; Howard et al., 1989, J. Neurosurg. 7 1:105); U.S. Pat. No. 5,679,377; U.S. Pat. No. 5,916,597; U.S. Pat. No. 5,912,015; U.S. Pat. No. 5,989,463; U.S. Pat. No. 5,128,326; PCT Publication No. WO 99/15154; and PCT Publication No. WO 99/20253. Examples of polymers used in sustained release formulations include, but are not limited to, poly(2-hydroxy ethyl methacrylate), poly(methyl methacrylate), poly(acrylic acid), poly(ethylene-co-vinyl acetate), poly(methacrylic acid), polyglycolides (PLG), polyanhydrides, poly(N-vinyl pyrrolidone), poly(vinyl alcohol), polyacrylamide, poly(ethylene glycol), polylactides (PLA), poly(lactide-co-glycolides) (PLGA), and polyorthoesters. In one embodiment, the polymer used in a sustained release formulation is inert, free of leachable impurities, stable on storage, sterile, and biodegradable. A controlled or sustained release system can be placed in proximity of the prophylactic or therapeutic target, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138 (1984)).

Controlled release systems are discussed in the review by Langer ((1990), Science 249:1527-1533). Any technique known to one of skill in the art can be used to produce sustained release formulations comprising one or more antibodies of the invention. See, e.g., U.S. Pat. No. 4,526,938, PCT publication WO 91/05548, PCT publication WO 96/20698, Ning *et al.,* (1996) "Intratumoral Radioimmunotheraphy of a Human Colon Cancer Xenograft Using a Sustained-Release Gel," Radiotherapy & Oncology 39:179-189, Song *et al.,* (1995), "Antibody Mediated Lung Targeting of Long-Circulating Emulsions," PDA Journal of Pharmaceutical Science & Technology 50:372-397, Cleek *et*

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al., (1997), "Biodegradable Polymeric Carriers for a bFGF Antibody for Cardiovascular Application," Pro. Int'l. Symp. Control. Rel. Bioact. Mater. 24:853-854, and Lam *et al.*, (1997), "Microencapsulation of Recombinant Humanized Monoclonal Antibody for Local Delivery," Proc. Int'l. Symp. Control Rel. Bioact. Mater. 24:759-760, each of which is incorporated herein by reference in their entirety.

If the antibodies of the invention are administered topically, they can be formulated in the form of an ointment, cream, transdermal patch, lotion, gel, shampoo, spray, aerosol, solution, emulsion, or other form well-known to one of skill in the art. See, e.g., Remington's Pharmaceutical Sciences and Introduction to Pharmaceutical Dosage Forms, 19th ed., Mack Pub. Co., Easton, Pa. (1995). For non-sprayable topical dosage forms, viscous to semi-solid or solid forms comprising a carrier or one or more excipients compatible with topical application and having a dynamic viscosity, in some instances, greater than water are typically employed. Suitable formulations include, without limitation, solutions, suspensions, emulsions, creams, ointments, powders, liniments, salves, and the like, which are, if desired, sterilized or mixed with auxiliary agents (e.g., preservatives, stabilizers, wetting agents, buffers, or salts) for influencing various properties, such as, for example, osmotic pressure. Other suitable topical dosage forms include sprayable aerosol preparations wherein the active ingredient, in some instances, in combination with a solid or liquid inert carrier, is packaged in a mixture with a pressurized volatile (e.g., a gaseous propellant, such as freon) or in a squeeze bottle. Moisturizers or humectants can also be added to pharmaceutical compositions and dosage forms if desired. Examples of such additional ingredients are well-known in the art.

If the compositions comprising antibodies are administered intranasally, it can be formulated in an aerosol form, spray, mist or in the form of drops.

Methods for co-administration or treatment with a second therapeutic agent, e.g., a cytokine, steroid, chemotherapeutic agent, antibiotic, or radiation, are known in the art (see, e.g., Hardman *et al.*, (eds.) (2001) Goodman and Gilman's The Pharmacological Basis of Therapeutics, 10.sup.th ed., McGraw-Hill, New York, N.Y.; Poole and Peterson (eds.) (2001) Pharmacotherapeutics for Advanced Practice:A Practical Approach, Lippincott, Williams & Wilkins, Phila., Pa.; Chabner and Longo (eds.) (2001) Cancer Chemotherapy and Biotherapy, Lippincott, Williams & Wilkins, Phila., Pa.). An effective

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amount of therapeutic may decrease the symptoms by at least 10%; by at least 20%; at least about 30%; at least 40%, or at least 50%.

Additional therapies (e.g., prophylactic or therapeutic agents), which can be administered in combination with the antibodies of the invention may be administered less than 5 minutes apart, less than 30 minutes apart, 1 hour apart, at about 1 hour apart, at about 1 to about 2 hours apart, at about 2 hours to about 3 hours apart, at about 3 hours to about 4 hours apart, at about 4 hours to about 5 hours apart, at about 5 hours to about 6 hours apart, at about 6 hours to about 7 hours apart, at about 7 hours to about 8 hours apart, at about 8 hours to about 9 hours apart, at about 9 hours to about 10 hours apart, at about 10 hours to about 11 hours apart, at about 11 hours to about 12 hours apart, at about 12 hours to 18 hours apart, 18 hours to 24 hours apart, 24 hours to 36 hours apart, 36 hours to 48 hours apart, 48 hours to 52 hours apart, 52 hours to 60 hours apart, 60 hours to 72 hours apart, 72 hours to 84 hours apart, 84 hours to 96 hours apart, or 96 hours to 120 hours apart from the antibodies of the invention. The two or more therapies may be administered within one same patient visit.

The antibodies of the invention and the other therapies may be cyclically administered. Cycling therapy involves the administration of a first therapy (e.g., a first prophylactic or therapeutic agent) for a period of time, followed by the administration of a second therapy (e.g., a second prophylactic or therapeutic agent) for a period of time, optionally, followed by the administration of a third therapy (e.g., prophylactic or therapeutic agent) for a period of time and so forth, and repeating this sequential administration, i.e., the cycle in order to reduce the development of resistance to one of the therapies, to avoid or reduce the side effects of one of the therapies, and/or to improve the efficacy of the therapies.

In certain embodiments, the multivalent antibodies of the invention can be formulated to ensure proper distribution in vivo. For example, the blood-brain barrier (BBB) excludes many highly hydrophilic compounds. To ensure that the therapeutic compounds of the invention cross the BBB (if desired), they can be formulated, for example, in liposomes. For methods of manufacturing liposomes, see, e.g., U.S. Pat. Nos. 4,522,811; 5,374,548; and 5,399,331. The liposomes may comprise one or more moieties which are selectively transported into specific cells or organs, thus enhance targeted drug delivery (see, e.g., V.

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V. Ranade (1989) J. Clin. Pharmacol. 29:685). Exemplary targeting moieties include folate or biotin (see, e.g., U.S. Pat. No. 5,416,016 to Low et al); mannosides (Umezawa *et al.*, (1988) Biochem. Biophys. Res. Commun. 153:1038); antibodies (P. G. Bloeman et al. (1995) FEBS Lett. 357:140; M. Owais *et al.*, (1995) Antimicrob. Agents Chemother. 39:180); surfactant protein A receptor (Briscoe *et al.*, (1995) Am. J. Physiol. 1233:134); p 120 (Schreier *et al.*, (1994) J. Biol. Chem. 269:9090); see also Keinanen *et al.*, (1994) FEBS Lett. 346:123; Killion *et al.*, (1994) Immunomethods 4:273.

The invention provides protocols for the administration of pharmaceutical composition comprising antibodies of the invention alone or in combination with other therapies to a subject in need thereof. The therapies (e.g., prophylactic or therapeutic agents) of the combination therapies of the present invention can be administered concomitantly or sequentially to a subject. The therapy (e.g., prophylactic or therapeutic agents) of the combination therapies of the present invention can also be cyclically administered. Cycling therapy involves the administration of a first therapy (e.g., a first prophylactic or therapeutic agent) for a period of time, followed by the administration of a second therapy (e.g., a second prophylactic or therapeutic agent) for a period of time and repeating this sequential administration, i.e., the cycle, in order to reduce the development of resistance to one of the therapies (e.g., agents) to avoid or reduce the side effects of one of the therapies (e.g., agents), and/or to improve, the efficacy of the therapies.

The therapies (e.g., prophylactic or therapeutic agents) of the combination therapies of the invention can be administered to a subject concurrently. The term "concurrently" is not limited to the administration of therapies (e.g., prophylactic or therapeutic agents) at exactly the same time, but rather it is meant that a pharmaceutical composition comprising antibodies of the invention are administered to a subject in a sequence and within a time interval such that the antibodiesof the invention can act together with the other therapy(ies) to provide an increased benefit than if they were administered otherwise. For example, each therapy may be administered to a subject at the same time or sequentially in any order at different points in time; however, if not administered at the same time, they should be administered sufficiently close in time so as to provide the desired therapeutic or prophylactic effect. Each therapy can be administered to a subject separately, in any appropriate form and by any suitable route. In various embodiments, the therapies (e.g., prophylactic or therapeutic agents) are administered to a subject less

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than 15 minutes, less than 30 minutes, less than 1 hour apart, at about 1 hour apart, at about 1 hour to about 2 hours apart, at about 2 hours to about 3 hours apart, at about 3 hours to about 4 hours apart, at about 4 hours to about 5 hours apart, at about 5 hours to about 6 hours apart, at about 6 hours to about 7 hours apart, at about 7 hours to about 8 hours apart, at about 8 hours to about 9 hours apart, at about 9 hours to about 10 hours apart, at about 10 hours to about 11 hours apart, at about 11 hours to about 12 hours apart, 24 hours apart, 48 hours apart, 72 hours apart, or 1 week apart. In other embodiments, two or more therapies (e.g., prophylactic or therapeutic agents) are administered to a within the samepatient visit.

The prophylactic or therapeutic agents of the combination therapies can be administered to a subject in the same pharmaceutical composition. Alternatively, the prophylactic or therapeutic agents of the combination therapies can be administered concurrently to a subject in separate pharmaceutical compositions. The prophylactic or therapeutic agents may be administered to a subject by the same or different routes of administration.

The invention having been fully described, it is further illustrated by the following examples and claims, which are illustrative and are not meant to be further limiting.

Examples

Methods and Materials

1: Pannings, antibody identification and characterization

(a) Panning

(i) HuCAL GOLD® Pannings

For the selection of antibodies recognizing human LRP6 several panning strategies were applied. Therapeutic antibodies against human LRP6 protein were generated by selection of clones having high binding affinities, using as the source of antibody variant proteins a commercially available phage display library, the MorphoSys HuCAL GOLD® library.

The phagemid library is based on the HuCAL® concept (Knappik *et al.*, (2000) J Mol Biol 296:57-86) and employs the CysDisplay™ technology for displaying the Fab on the phage surface (WO01/05950 to Lohning).

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In detail, the HuCAL GOLD® library used in the current project is described in (Rothe *et al.*, (2007) J Mol Biol) Either phagemids produced with helper phage VCSM13 or produced with Hyperphage (Rondot *et al.*, (2001) Nat Biotechnol 19:75-78) were used for selection of anti-LRP6 antibodies.

(ii) Whole Cell Panning Against LRP6

For whole cell pannings, the cell line HEK293-hLRP6ΔC-eGFP was used expressing the amino terminal fragment (amino acid 1-1482) of LRP6 fused to eGFP. Specific HuCAL GOLD® antibody phagemids were eluted after incubation to the LRP6 expressing cell line followed by post-adsorption to HEK293-LRP5/6-shRNA cells. The resulting HuCAL phage-containing supernatant was titered on *E. coli* TG1 cells and rescued after infection of *E. coli* TG1 cells using helper phage. The polyclonal amplified phage output was titered again and used in consecutive selection steps.

(iii) Fc Capture Panning Against LRP6

For Fc capture pannings, blocked phage were incubated with the Fc-captured LRP6-Fc and unspecific phage were washed away using different concentrations of PBST, and PBS at different times.

The remaining phage were eluted, and used immediately for infection of *E. coli* TG1 bacteria. Amplification, phage production and output titer determination were conducted as described above in whole cell panning against LRP6.

(iv) Differential Whole Cell Panning Against LRP6

Differential whole cell pannings with antibody selection on HEK293-hLRP6ΔC-eGFP cells and selection on recombinant human LRP6-Fc were performed as described above for whole cell pannings and for Fc capture pannings.

During the selection process, unspecific phage were removed using different concentrations of PBS and PBST for different time periods.

Phage infection of *E. coli* TG1, amplification, phage production and output titer determination were conducted as described above in whole cell panning against LRP6.

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(v) Semi-Solution Panning Against LRP6

For semi-solution pannings, recombinant human LRP6-Fc and BSA were covalently linked to tosylactivated M-280-Dynabeads.

Pre-cleared phage were incubated with LRP6-coated beads on a rotator. Beads were then collected using a magnetic separator and washed with PBST and PBS. Bead-bound phage were eluted and immediately used for infection of *E. coli* TG1 bacteria. Phage infection, amplification, phage production and output titer determination were conducted as described above in whole cell panning against LRP6.

(b) Subcloning and Microexpression of Selected Fab Fragments

To facilitate rapid expression of soluble Fab, the Fab encoding inserts of the selected HuCAL GOLD® phage were subcloned into an expression vector pMORPH®X9_FH or pMORPH®X9_FS. After transformation of TG1-F single clone expression and preparation of periplasmic extracts containing HuCAL®-Fab fragments were performed as described previously (Rauchenberger *et al.*, (2003)).

2: Screening

(i) FACS Screening on HEK293-hLRP6ΔC-eGFP cells

Clones selected by the panning strategies whole cell panning, differential whole cell panning, and semi-solution panning were screened by flow cytometry on HEK293-hLRP6ΔC-eGFP cells and HEK293-LRP5/6-shRNA cells for counterscreening. Primary hits of Fc capture panning strategy as described above were also tested by flow cytometry.

Cells were harvested at 70 to 80 % confluency, resuspended in FACS buffer, and stained with bacterial cell lysates in 96 well U-bottom microtiter plates. Antibody binding was revealed with flurochrome-conjugated detection antibodies. Stained cells were washed twice and mean fluorescence intensity was measured and analyzed using a FACSArray instrument (BectonDickinson).

(ii) Fc-capture Screening on Recombinant Human LRP6-Fc

Clones selected in the Fc-capture panning were screened in an Fc-capture-ELISA setup.

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Maxisorp (Nunc, Rochester, NY, USA) 384 well plates were coated with goat anti-human IgG, Fc fragment specific antibody. After washing with PBST and blocking the wells, recombinant human LRP6-Fc was added. After washing the coated plates, cell lysates were added and bound Fab fragments were detected using AP-conjugated goat IgG anti-human IgG $F(ab')_2$ with the substrate AttoPhos. Fluorescence was read at 535 nm using a Tecan Plate Reader.

3: Expression and Purification of HuCAL®-Fab Antibodies in E. coli

Expression of Fab fragments encoded by pMORPH®X9_Fab_FH or pMORPH®X11_Fab_FH in TG-1 cells was induced by addition of IPTG. Cells were disrupted using lysozyme and Fab fragments isolated by Ni-NTA chromatography (Bio-Rad, Germany). Protein concentrations were determined by UV-spectrophotometry. Purity of Fab fragments was analyzed in denatured, reduced state using SDS-PAGE and in native state by HP-SEC.

4: Affinity Determination

(i) Surface Plasmon Resonance Measurements

For determination of K_D values, surface plasmon resonance technology was applied. Anti-human-Fc-capture CM5 chip (Biacore, Sweden) was used for capturing LRP6-Fc-Fusion followed by ligand (Fab) injection at different concentrations.

(ii) Solution Equilibrium Titration (SET) Method for K_D Determination Using Sector Imager 6000 (MSD)

For K_D determination by solution equilibrium titration (SET), monomer fractions of antibody protein were used (at least 90% monomer content, analyzed by analytical SEC; Superdex75 (Amersham Pharmacia) for Fab, or Tosoh G3000SWXL (Tosoh Bioscience) for IgG, respectively).

Affinity determination in solution was basically performed as described in the literature (Friguet *et al.*, (1985) J Immunol Methods 77:305-319). In order to improve the sensitivity and accuracy of the SET method, it was transferred from classical ELISA to ECL based technology (Haenel *et al.*, (2005) Anal Biochem. 339:182-184).

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The data was evaluated with XLfit (IDBS) software applying customized fitting models. For K_D determination of Fab molecules the fit model was used (according to Haenel et al *supra*), modified according to Abraham et al. (1996) Journal of Molecular Recognition 9:456-461.

$$y = B_{max} - \left(\frac{B_{max}}{2[Fab]_t} \left([Fab]_t + x + K_D - \sqrt{([Fab]_t + x + K_D)^2 - 4x[Fab]_t} \right) \right)$$

$[Fab]_t$: applied total Fab concentration

x: applied total soluble antigen concentration (binding sites)

B_{max}: maximal signal of Fab without antigen

K_D: affinity

5: Screening After Affinity Maturation

EC_{50} Determination on HEK293T/17 cells

EC_{50} values were determined on parental HEK293T/17 cells in FACS measurements. A typical antibody titration curve contained ten to twelve different antibody dilutions, and titrations started at concentrations of approx. 150 to 200 µg / mL (final concentration). Cells were harvested using Accutase, resuspended in FACS buffer, distributed to the wells of a 96-well plate, and stained with antibody dilutions. EC_{50} values were determined with the program GraphPad Prism using non-linear regression analysis.

6: Conversion to IgG

In order to express full length IgG, variable domain fragments of heavy (VH) and light chains (VL) were subcloned from Fab expression vectors into appropriate pMORPH®_hIg vectors for human IgG2, human IgG4, human IgG4_Pro, and human IgG1f LALA.

7: Transient Expression and Purification of Human IgG

Eukaryotic HKB11 cells were transfected with equal amounts of IgG heavy and light chain expression vector (pMORPH2) or expression vector DNA encoding for heavy and light chains of IgGs (pMORPH4). After sterile filtration, the solution was subjected to standard protein A affinity chromatography (MabSelect SURE, GE Healthcare). Protein

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concentrations were determined by UV-spectrophotometry. Purity of IgG was analyzed under denaturing, reducing and non-reducing conditions in SDS-PAGE or by using Agilent BioAnalyzer and in native state by HP-SEC.

8: Wnt Reporter Gene Assay

The ability of anti-LRP6 antibodies to inhibit Wnt signaling was tested in a Wnt1 and Wnt3a responsive luciferase reporter gene assay. Cells were either stimulated with Wnt3a conditioned medium or by co-transfection of Wnt 1, Wnt3a, or other Wnt expression plasmids.

(i) Wnt3a Reporter Gene Assay with Conditioned Medium

10^4 HEK293-STF cells/well were seeded into a 96 well tissue culture plate, and cells were incubated overnight at 37 °C/5 % CO_2 in 100 µL medium.

The following day, various anti-LRP6 antibody dilutions and DKK1 dilutions (positive control) were prepared either in pure or in diluted in Wnt3a-conditioned medium. 60 µL/well of the supernatant was removed from the 96 well tissue culture plate and replaced by 60 µL/well of the conditioned medium/antibody dilutions.

After Incubation for 16 to 24 h at 37 °C/5 % CO_2, 100 µL BrightGlo Luciferase reagent (Promega) were added and plates were incubated for 10 min. For luminescence readout (Tecan Plate Reader), the cell lysates were transferred into a 96 well microtiter plate (Costar, Cat # 3917).

A similar assay can also be performed using co-culture of Wnt3 or Wnt3a over-expressing cells (e.g. CHO-K1, TM3, L or HEK293 cells)

(ii) Wnt1/Wnt3a Reporter Gene Assay with Transiently Transfected Cells

$3x10^4$ HEK293T/17 cells/well were seeded into a 96 well tissue culture plate (Costar), and cells were incubated at 37 °C/5 % CO_2 in 100 µL medium as described in Table 3. After 12 to 16 h, cells were transfected with empty vector Wnt expression plasmid1 ng/well; pTA-Luc-10xSTF (Firefly luciferase construct)50 ng/well; or phRL-SV40 (Renilla luciferase construct) 0.5 ng/well.

A transfection premix (10 µL/well) was prepared containing the plasmids listed above and 0.2 µL FuGene6/well (Roche). The transfection premix was incubated 15 min at RT

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and then distributed into the wells. The plate was rocked at 400 rpm for 2 min at RT and then incubated for 4 h at 37 °C/5 % CO_2. In the meantime, antibodies were diluted in medium and added to the transfected cells (75 µL/well).

After 18 to 24 h, 75 µL/well DualGlo Luciferase reagent (Promega) were added and the plate was rocked for 10 min for cell lysis before readout of the Firefly luciferase activity. After luminescence readout, 75 µL/well DualGlo Stop&Glow reagent (Promega) were added and luminescence was measured again to determine Renilla luciferase activity.

For analysis, the ratio between Firefly luciferase activity and Renilla luciferase activity was calculated. For IC_{50}-determination of the anti-LRP6 antibodies, the relative luciferase values were analyzed using GraphPad Prism.

A similar assay can also be performed using co-culture of Wnt1 or other Wnt1 class ligand over-expressing cells (e.g. CHO-K1, TM3, L or HEK293 cells).

9: FACS Cross-Reactivity Studies

Cross-species reactivity to murine and cynomologus LRP6 was determined on cells by FACS analysis. FACS staining was performed essentially as described above. Human U266 cells (no expression of LRP6) were used as a negative control.

Cross-reactivity to murine LRP6 was tested on murine NIH-3T3 cells. Cross-reactivity to cynomologus LRP6 was tested on the cynomologus cell line Cynom-K1 and on transiently transfected HEK293T/17 cells:

For testing cynomologus cross-reactivity on the human cell line HEK293T/17, the cells were transiently transfected using Lipofectamine (Invitrogen) according to the manufacturer's instructions. Cells were either transfected with a mixture of the human LRP6 expression plasmid pCMV6_XL4_LRP6 and the chaperone-encoding plasmid pcDNA3.1-flag_MESD or with a mixture of pcDNA3.1-nV5-DEST_cynoLRP6 and pcDNA3.1-flag_MESD (overexpression of cynomologus LRP6). 50 µg of LRP6 expression plasmid and 20 µg of MESD expression plasmid were used per T175 flask. After 24 h, cells were detached and stained with the goat anti human LRP6 control antibody (R&D Systems) and with anti-LRP6 HuCAL antibodies. Mock-transfected HEK293T/17 cells were used for negative control stainings (low endogenous LRP6 expression).

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10: Binder Optimization

Generation of Affinity Maturation Libraries

To increase affinity and biological activity of selected antibody fragments, L-CDR3 and HCDR2 regions were optimized in parallel by cassette mutagenesis using trinucleotide directed mutagenesis, while the framework regions were kept constant.

The different affinity maturation libraries were generated by standard cloning procedures and transformation of the diversified clones into electro-competent *E. coli* TOP10F cells (Invitrogen). Sequencing of randomly picked clones showed a diversity of 100%. No parental binders were found among the picked clones. Finally phage of all libraries were prepared separately.

11: MMTV-Wnt1 xenografts

Tumours from MMTV-Wnt1 transgenic mice were passaged as tumour pieces in the mammary fat pad of FVB mice for 5 passages prior to implantation into the mammary fat pad of nude mice. Eleven days post-implant, when tumours reached a mean volume of approximately 110 mm^3, mice were randomized into 3 groups with 8 mice per group and dosed every three days (DeAlmeida *et al.* (2007); Cancer Res. 67:5371-9).

12: Inhibition in Biochemical Assays

HEK293 cells were grown in D-MEM supplemented with 10% fetal bovine serum at 37 °C with 5% CO_2. Cells were seeded into a 96 well tissue culture plate (Costar) at $3x10^4$/well and transfected with 0.1ng/well Wnt expression plasmid, 50 ng/well STF reporter, and 0.5 ng/ml phRL-SV40 (Promega) mixed with 0.2 µL/well FuGene6 (Roche). Four hours after transfection, antibodies were diluted in PBS and added to the transfected cells. After 18 hincubation, Firefly luciferase and Renilla luciferase activities were measured using DualGlo Luciferase reagent (Promega). Renilla luciferase was used to normalize transfection efficiency

All IgG formats tested have potent and complete inhibition of Wnt1 (2, 6, 7A, 7B, 9, 10A, 10B) generated canonical signal. All give rise to a bell shaped potentiation curve in the presence of a Wnt3/3A generated signal.

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13: FACS-based competition assay

For FACS-based competition assay, anti-LRP6 Fabs and the negative control Fab MOR03207 were biotinylated using the ECL protein biotinylation module (GE Healthcare) according to the manufacturer's instructions. The biotinylated Fabs were used for FACS staining on HEK293-hLRP6ΔC-eGFP cells at a constant Fab concentration (20 nM final concentration) and were competed with a 100-fold molar excess of unlabelled Fab. Cells were incubated with the Fab dilutions for 1 hour at 4 °C on a plate shaker. After washing the cells 1x with FACS buffer, they were incubated with PE-conjugated Streptavidin (Dianova) for 1 hour at 4°C on a plate shaker in the dark. Cells were washed twice with FACS buffer and fluorescence was measured using FACS Array (BD). Similarly, unbiotinylated anti-LRP6 Fabs were competed with a 100-fold molar excess of the LRP6-binding protein SOST and binding of the Fabs to the cells was monitored by PE-conjugated anti human IgG antibody (Dianova).

14: Immunoblotting assay

Total cell lysates were prepared in RIPA buffer (50 mM Tris-HCl, pH 7.4, 150 mM NaCl, 1% NP-40, 0.5% sodium deoxycholate, 0.1% SDS, 1 mM EDTA). Lysates were normalized for protein concentration, resolved by SDS-PAGE, transferred onto nitrocellulose membranes and probed with the indicated antibodies. pT1479 LRP6 antibody requires generation of membrane extracts to achieve satisfactory results. To generate membrane extracts, cells were lysed in hypotonic buffer (10mM Tris-HCl pH7.5, 10mM KCl) by performing four freeze-thaw cycles, and insoluble membrane fraction was solubilized using RIPA buffer. Protease inhibitor cocktail (Sigma) and 1x phosphatase inhibitor cocktail (Upstate) were added into the lysis buffers. Commercial antibodies used in the western blot assay include rabbit anti-LRP6, rabbit anti-pT1479 LRP6, and rabbit anti-pS1490 LRP6 antibodies (Cell Signaling Technology).

Example 1: Specific binding of anti-LRP6 antibodies to endogenous LRP6 by FACS

Detection of endogenous cell surface expression of LRP6 was examined on a number of tumor cells using the anti-LRP6 antibodies and FACS analysis. As shown in Fig. 1A, PA1 cells express both LRP5 and LRP6 mRNA, while U266 and Daudi cells do not express LRP6 mRNA. PA1 cells, but not U266 and Daudi cells, show significant staining with a Propeller 1 anti-LRP6 IgG. More importantly, U266 cells are not stained by anti-LRP6 antibody, although they express LRP6, demonstrating the specificity of anti-LRP6

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antibody. Furthermore, anti-LRP6 antibody staining of PA1 cells is significantly reduced upon depletion of endogenous LRP6 using LRP6 shRNA, further demonstrating the specificity of the LRP6 antibody.

In additional studies, knockdown of LRP6 by shRNA in PA1 cells further confirms specificity of Prop1 and Prop3 antibodies for LRP6 (See Fig. 1B). Knockdown was achieved by infecting cells with lentivirus encoding short hairpin RNA directed to LRP6, and selecting a stable pool of infected cells. The shRNA infection method used for the study is described in Wiederschain *et al.* in 2009 Cell Cycle 8: 498-504. Epub 2009 Feb 25.

Example 2: Differential inhibition of Wnt1 and Wnt3a reporter gene assays by Propeller 1 and Propeller 3 anti-LRP6 Fabs

Different anti-LRP6 Fabs were tested in *in vitro* Wnt reporter assays. Wnt1 or Wnt3A ligands were transiently expressed in HEK293T/17 STF cells (gene reporter assay) and treated with varying concentrations of anti-LRP6 Fab fragments. STF assays were conducted using the protocols described by Huang *et al.* (2009), Nature; 461:614-20. Epub 2009 Sep 16. As seen in Fig. 2A, Propeller 1 anti-LRP6 Fabs (MOR08168, MOR08545, MOR06706) specifically reduced Wnt1-dependent signaling without much effect on Wnt3A-dependent signaling. Conversely as shown in Fig. 2B, Propeller 3 anti-LRP6 Fabs (MOR06475, MOR08193, MOR08473) specifically reduced Wnt3A-dependent signaling without significant effects on Wnt1-dependent Wnt1-dependent signaling. The results demonstrate that Wnt1 and Wnt3A activities are blocked separately by different LRP6 Fab fragment (epitopes).

Example 3: Binding of anti-LRP6 antibodies to LRP6 of different species.

To show cross-reactivity, cells expressing endogenous LRP6 of human (HEK293T/17) and mouse origin (NIH 3T3), or transiently transfected HEK293/T17 cells expressing cynomolgus LRP6, were treated and subjected to flow cytometry as described above. Fig. 3 summarizes the results of the findings of the results and show that all anti-LRP6 antibodies bind to human, mouse, and cynomologus LRP6.

Example 4: Classification of Wnts based on their sensitivity to Propeller 1 and Propeller 3 anti-LRP6 antibodies.

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To evaluate Wnts based on their sensitivity Propeller 1 and Propeller 3 anti-LRP6 antibodies, various Wnt ligands were transiently expressed into HEK293T/17 STF cells (gene reporter assay) and treated with Propeller 1 or Propeller 3 anti-LRP6 antibodies. STF assays were conducted using the protocols described by Huang *et al.* (2009), Nature; 461:614-20. Epub 2009 Sep 16. The results are shown in Fig. 4 which depicts the activity inhibition of particular Wnts based on antibody binding/blocking to specific propeller regions of LRP6. Fig. 4 shows that signaling induced by Wnt1, Wnt2, Wnt6, Wnt7A, Wnt7B, Wnt9, Wnt10A, Wnt10B can be specifically inhibited by Propeller 1 anti-LRP6 Fabs, while signaling induced by Wnt3 and Wnt3A can be specifically inhibited by Propeller 3 anti-LRP6 Fabs.

Example 5: Conversion of LRP6 antibodies from Fab fragments to IgG potentiates Wnt signaling induced by the other class of Wnt.

In a rather unexpected observation, conversion of LRP6 antibodies from Fab fragments to IgG potentiates WNT signaling. Propeller 1 anti-LRP6 IgG inhibits Wnt1-dependent and potentiates Wnt3A-dependent signaling in a 293T/17 STF reporter assay. Similarly, Propeller 3 anti-LRP6 IgG inhibits Wnt3A-dependent and potentiates Wnt1-dependent signaling as shown in Fig. 5. This finding suggests that the Wnt signaling pathway may be modified or "fine tuned" using Propeller 1 and Propeller 3 antibodies. Similar effects were observed in STF reporter assays in other cellular backgrounds (e.g. MDA-MB231, MDA-MB435, PA-1, TM3 and 3t3 cells – data not shown)

Example 6: Propeller1 or Propeller 3 anti-LRP6 Fabs specifically inhibits Wnt1 or Wnt3A-induced LRP6 phosphorylation.

HEK293T/17 cells were transiently transfected with Wnt1 or Wnt3A expression plasmids and treated with Propeller 1or Propeller 3 anti-LRP6 Fabs. As seen in Fig. 6, Propeller 1 anti-LRP6 Fabs specifically inhibits Wnt1-induced phosphorylation of LRP6, for example, T1479 and S1490 sites and Propeller 3 antibodies do not. In contrast, Propeller 3 anti-LRP6 specifically inhibits Wnt3A-induced phosphorylation of LRP6 and Propeller 1 antibodies do not. These results support that antibodies bind to distinct propeller domainsof LRP6 and block specific Wnt ligands.

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Example 7: Inhibition of expression of Wnt target gene in a MMTV-Wnt1 tumor xenograft model using a Propeller 1 anti-LRP6 IgG.

The LRP6 antibodies were further characterized *in vivo* in an art recognized genetically engineered mouse model known as MMTV-Wnt1. Experiments were conducted to determine if the anti-LRP6 antibodies in the IgG format could inhibit Wnt signaling and tumor growth *in vivo*. Mammary tumors derived from MMTV-Wnt1 transgenic mice are Wnt1 dependent; turning off Wnt1 expression using a tetracyclin-regulated system (Gunther *et al.* (2003), supra) or blocking Wnt activity using Fz8CRDFc (DeAlmeida et al. (2007) Cancer Research 67:5371-5379) inhibits tumor growth *in vivo*. To measure the effect of anti-LRP6 antibodies on Wnt signaling in MMTV-Wnt1 tumors, mice implanted with MMTV-Wnt1 tumors were dosed i.v. with a single dose of 5 mg/kg Wnt1 class-specific antagonistic anti-LRP6 antibody. Serum concentrations of the antibody as well as the mRNA expression of β-catenin target gene Axin2 were analyzed over a period of two weeks. The terminal β-phase half-life of the LRP6 antibody was about 108 hours. Corresponding to the antibody injection, a significant decrease of Axin2 mRNA expression was observed in tumors, and Axin2 expression gradually recovered one week after the antibody injection when the antibody level in serum decreased. These results suggest that Wnt1class-specific anti-LRP6 antibody suppresses Wnt signaling in MMTV-Wnt1 xenografts and this suppression is correlated with the concentration of LRP6 antibody in serum. To test the effect of anti-LRP6 antibodies on tumor growth, mice were dosed with Propeller 1 -, Propeller 3-specific anti-LRP6 antibodies, or isotype matched control antibodies. Mice were dosed i.v. with an initial dose of 20 mg/kg, followed every third day with 10 mg/kg. In this experiment Propeller 1, but not Propeller 3-specific anti-LRP6 antibody caused tumor regression. Together, these results demonstrate that Propeller 1-specific anti-LRP6 antibody induces regression of MMTV-Wnt1 xenografts,

MMTV-Wnt1 tumor xenografts in nude mice were treated with MOR08168, a Propeller 1 anti-LRP6 IgG at different timepoints ranging from 1 hour to 14 days. Fig. 7 shows an inverse correlation with PK serum concentration of the antibody and mRNA expression of Wnt target gene Axin2. Axin2 gene expression levels in tumors are inhibited with MOR08168 treatment, and return as antibody is cleared from the serum.

In addition to Axin2, the effect of MOR08168 on the expression of additional genes was evaluated. Affymetrix Mouse430 2.0 Arrays were used to profile a time course

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experiment of MMTV-Wnt1 allograft Tumors plus or minus a single dose of MOR08168 (5 mg/kg). There were six time points in all (0, 1, 3, 8, 24, 336 hours) and there were three replicates per time point. Based on data demonstrating maximal inhibition of Axin upon treatment with antibody, 8 h was chosen as best representative time point to determine differentially expressed genes putatively responding to Wnt pathway inhibition. The R / Bioconductor framework was utilized and Limma package was employed to determine differentially expressed genes between the 0 hour time point and the 8 hour time point. An adjusted P-value of .05 was used as the threshold to determine the set of differentially expressed genes. Based on this cutoff there are 1270 probe sets called differentially expressed mapped to 972 gene(s). Fig. 8A is a table that shows genes that were upregulated >2-fold with an adjusted P-value of <0.01 and Fig. 8B is a table that shows genes that were downregulated >2-fold with an adjusted P-value of <0.01.

Example 8: Anti-tumor activities of Propeller 1 and Propeller 3 anti-LRP6 antibodies in MMTV-Wnt1 allograft model.

Anti-tumor activity of LRP6 Propeller 1 and 3 antibodies was evaluated in the MMTV-Wnt1 allograft model. MMTV-Wnt1 tumor fragments were implanted subcutaneously (s.c.) into female nude mice. 11 days after implantation, mice carrying MMTV-Wnt1 tumors (n=8, average 121 mm^3; range: 100-147 mm^3) were treated with vehicle IgG (10 mg/kg, intravenously (i.v.), every third day (q3d), LRP6-Propeller 1 Ab MOR08168 (10 mg/kg, i.v., q3d), or LRP6-Propeller 3 Ab MOR06475 (10 mg/kg, i.v., q3d), and tumors calipered every third day. LRP6-Propeller 1 MOR08168 Ab dose-dependently induced tumor regressions (-55%, $p<0.05$) (See Fig. 9).

Example 9: Anti-tumor activities of Propeller 1 and Propeller 3 anti-LRP6 antibodies in MMTV-Wnt3 allograft model.

Anti-tumor activity of LRP6 Propeller 1 and 3 antibodies was evaluated in the MMTV-Wnt3 allograft model. MMTV-Wnt3 tumor fragments were implanted subcutaneously (s.c.) into female nude mice. 15 days after implantation, mice carrying MMTV-Wnt3 tumors (n=6, average 209 mm^3; range: 113-337 mm^3) were treated with vehicle IgG (10mg/kg, intravenously (i.v.), twice a week (2qw), MOR08168 LRP6-Propeller 1 Ab (3 mg/kg, i.v., qw), or MOR06475 LRP6-Propeller 3 Ab (10 mg/kg, i.v., 2qw) and tumors calipered twice per week. MOR06475 LRP6-Propeller 3 Ab demonstrated antitumor activity (T/C=34%, $p<0.05$) (See Fig. 10).

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Example 10: Evaluation of ability of Propeller 1 and 3 anti-LRP6 antibodies to inhibit Wnt3A in vivo

The ability of LRP6-Propeller 1 and 3 antibodies to inhibit Wnt3 class Wnt signaling *in vivo* was tested in a co-implant system consisting of PA1-STF reporter cells co-implanted with Wnt3A secreting L cells. Female nude mice were implanted subcutaneously with 10x10e6 PA1-STF cells and 0.5x10e6 L-Wnt3A cells and randomized in groups of 5. 24 hours later, mice received a single intravenous dose of vehicle, MOR08168 LRP6-Propeller 1 Ab (10 mg/kg), or MOR06475 LRP6-Propeller 3 Ab (10 mg/kg) and were imaged by Xenogen 6 hours, 24 hours, 48 hours, 72 hours and 168 hours later. MOR06475 was able to inhibit Wnt3a induced signaling for at least 72 hours, whereas Mor08168 increased Wnt3A induced signaling (Fig. 11).

Example 11: Epitope mapping of LRP6 PD3/4 and its antibody complex by HDx MS

To identify antibody binding sites within YWTD-EGF region of Propeller 3, hydrogen-deuterium exchange (HDx) mass spectrometry (MS) was employed. LRP6 Propeller domains 3-4 (PD3/4) has 12 cysteines and 4 N-linked glycosylation sites. All 4 N-linked glycosylation sites are positioned in Propeller 3 domain (631-932). By HDx MS, close to 100% coverage (amount of protein it was possible to get structural information for) was mapped on the Propeller 4 domain, and about 70% coverage on Propeller 3 domain. Regions immediately surrounding the 4 glycosylated sites remain undetected (Fig. 12A). In the presence of Fab 06745, 2 weakly solvent protected peptides were found in Propeller 3 (Phe^{636}-Leu^{647}, Tyr^{844}-Glu^{856}; Fig. 11A). This suggests that the residues or a fraction of the residues responsible for the epitope are either on the protected peptides or spatially nearby. Based on the crystal structure of LRP6 PD34, the solvent protected regions correspond to the concave surface between blade 1 and 6 of Prop 3.

Mutations that disrupt the interaction of ScFv06475 with LRP6 PD34

To confirm that the rim of blade 1 and 6 is responsible for antibody mediated inhibition of Wnt3a signaling, a series of LRP6 surface mutations were constructed (R638A, W767A, Y706A/E708A, W850A/S851A, R852/R853A, and D874A/Y875A) that also approximately covered the region implicated by HDx in binding. To ensure that the mutant proteins are properly folded, differential static light scattering (DSLS) thermal-melt assay was performed. Temperature denaturation experiment showed that the

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aggregation temperature, T_{agg}, (the temperature at which 50% of the protein is denatured) of wild-type and mutant proteins was similar. Thus, the mutations had no effect on the folding or stability of the protein.

The binding capacity of mutant LRP6 to scFv MOR06475 was determined by ELISA. Mutation of residues (R638, W850/S851, and R852/R853) that are located on peptides that showed solvent protection in HDx MS experiments also showed dramatic decrease in antibody binding (See Fig. 12B). Mutation of residues (Y706/E708) that are located on peptides showing no solvent protection in HDx also showed no change in antibody binding capability (Fig. 11B). Thus the binding assay data are in good agreement with the binding interface as mapped by HDx MS suggesting the residues R638, W850, S851, R852, and R853 participate directly in the epitope.

Collectively, these results show that different Wnt proteins require different Propeller regions of LRP6 for signaling. The Wnt 1 class of Wnt proteins (Wnt1, 1, 2, 6, 7A, 7B, 9,10A, 10B) requires Propeller 1 of LRP6 for Wnt1 signaling, and they can be inhibited by Propeller 1 specific anti-LRP6 antibodies. The Wnt 3A class of Wnt proteins (Wnt3 and Wnt3a) requires Propeller 3 of LRP6 for Wnt3 signaling, and they can be inhibited by Propeller 3 specific anti-LRP6 antibodies (Fig. 13). Another unexpected finding was the Wnt-potentiating activity of the antibodies in the bivalent IgG format in the presence of Wnt ligands. All antibodies tested in IgG format enhanced either Wnt1 or Wnt3A signaling in the STF Luc reporter gene assay. Interestingly, most Fabs that inhibited Wnt1 and were inactive in the Wnt3A assay, still inhibited Wnt1 as an IgG, but potentiated Wnt3A signaling and vice versa. Most Fabs that inhibited Wnt3A potentiated Wnt1 activity as an IgG. The effect was independent of the IgG format, as several formats were tested (IgG1LALA, IgG2, IgG4, IgG4_Pro). These data shows that different Wnt proteins bind to different Propellers of LRP6 for signaling. Dimerization of LRP6 using bivalent LRP6 antibodies is not sufficient to stimulate Wnt signaling by itself, but can potentiate Wnt signaling initiated by the other class of Wnt proteins. These findings demonstrate that different canonical Wnt ligands use distinct binding sites on LRP6 and that all bivalent antibodies enhance Wnt activity in IgG format in the presence of the non-blocked Wnt Fab (single chain antibodies, unibodies). Monovalent structures of any kind as a final format circumvent the Wnt potentiation. Alternative ly, the construction of a bi-specific IgG or IgG-like molecule carrying both the Wnt1- and Wnt3A inhibitory activity

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circumvent potentiation. Thus, LRP6 antibody constructs can be deisgned to control and "fine-tune" the Wnt pathway

Example 12: Generating a Biparatopic LRP6 Antibody

This example describes the production and characterization of biparatopic anti-LRP6 IgG-scFv antibodies. Various anti-LRP6 scFv's containing different domain orientations (e.g. VH-VL or VL-VH) and different linker lengths (e.g. $(Gly_4Ser)_3$ or $(Gly_4Ser)_4$) were initially expressed, purified and characterized. Based on results of the scFv study, different biparatopic anti-LRP6 IgG-scFv's were prepared and further evaluated. The scFv may be placed at various positions within the IgG including the C-terminus of CH3 or CL and the N-terminus of VH or VL. Furthermore, various linkers may be used to connect the scFv to the IgG including Gly_4Ser and $(GlyGlySer)_2$.

(a) Materials and Methods

(i) Generation of anti-LRP6 scFv

Genes coding for all scFv-variants were synthesized by Geneart. DNA-fragments coding for scFv in both orientations (VH-VL and VL-VH, separated by two different linkers: $(Gly_4Ser)_3$ and $(Gly_4Ser)_4$, with N-terminal signal sequence and C-terminal 6xHis-tag) were directly cloned from Geneart vectors via NdeI/XbaI into vector pFAB15-FkpA, resulting constructs were called pFab15-MOR06475-VH-$(Gly_4Ser)_3$-VL, pFab15-MOR06475-VH-$(Gly_4Ser)_4$-VL, pFab15-MOR06475-VL-$(Gly_4Ser)_3$-VH, pFab15-MOR06475-VL-$(Gly_4Ser)_4$-VH, pFab15-MOR08168-VH-$(Gly_4Ser)_3$-VL, pFab15-MOR08168-VH-$(Gly_4Ser)_4$-VL, pFab15-MOR08168-VL-$(Gly_4Ser)_3$-VH, pFab15-MOR08168-VL-$(Gly_4Ser)_4$-VH, pFab15-MOR08545-VH-$(Gly_4Ser)_3$-VL, pFab15-MOR08545-VH-$(Gly_4Ser)_4$-VL, pFab15-MOR08545-VL-$(Gly_4Ser)_3$-VH and pFab15-MOR08545-VL-$(Gly_4Ser)_4$-VH.

(ii) Generation of biparatopic anti-LRP6 IgG-scFv

anti-LRP6_MOR08168 hIgG1LALA_6475scFv

Vector pRS5a MOR08168 hIgG1LALA containing codon-optimized VH-sequence (synthesized by Geneart) was used as source for generation of biparatopic construct. Initially, AfeI-site was introduced by QuickChange Site-Directed Mutagenesis (Stratagene) at 3'- end of sequence coding for hIgG1LALA (primer no. 1: 5'-agcgtgatgcacgaagcgctgcacaaccactac-3' (SEQ ID NO: 213) and primer no. 2: 5'-

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gtagtggttgtgcagcgcttcgtgcatcacgctg-3' (SEQ ID NO; 214)). Gene coding for MOR06475scFv (VL-VH-orientation, separated by $(Gly_4Ser)_4$-linker) was synthesized by Geneart. 5'-primer containing AfeI-site and sequence coding for $(GlyGlySer)_2$ -linker as well as 3'-primer containing AscI-site were used for amplification of entire MOR06475-scFv-gene (primer no. 3:
5'-tgatgcacgaagcgctgcacaaccactacacccagaagagcctgagcctgtccccggcaag ggcggctccggcggaagcgatatc-3' (SEQ ID NO: 215) and primer no. 4: 5'-gagcggccgcccggcgcgcc tcatcagctggacactgtcaccaggg-3' (SEQ ID NO: 216)). PCR-product was then cloned via AfeI/AscI into vector pRS5a MOR08168 hIgG1LALA resulting in the final construct pRS5a MOR08168 hIgG1LALA-6475sc-fv. Gene coding for codon-optimized VL of MOR08168 was synthesized by Geneart. 5'-primer containing AgeI-site and 3'-primer containing HindIII-site were used for amplification of entire MOR08168-VL-genes (primer no. 5: (5'-gcttccggacaccaccggt gacatcgagctgacccagcc-3'
SEQ ID NO: 217) and primer no. 6: 5'-cagcacggtaagctt ggtgcctccgccgaacaccag-3' (SEQ ID NO: 218)). PCR-product was then cloned via AgeI/HindIII into vector pRS5a-hlambda resulting in the final construct pRS5a MOR08168 hlambda.

<u>anti-LRP6_MOR08168 hIgG1LALA_6475scFv_without Lys (K)</u>
Vector pRS5a MOR08168 hIgG1LALA-6475scFv (SEQ ID NO:165) was used as template DNA for removal of C-terminal Lysin at CH3. Quick Change XL Site-Directed Mutagenesis Kit (Stratagene) was used in combination with following primers:
5'-ctgtcccccggcggcggctccggc-3' (SEQ ID NO: 219)
5'-gccggagccgccgccgggggacag-3'(SEQ ID NO: 220)
Site-Directed Mutagensis was done according to Stratagene protocol; resulting new construct was called pRS5a hIgG1LALA MOR08168opt 6475 scFv K.
Vector pRS5a MOR08168 hlambda (generation described for anti-LRP6_MOR08168 hIgG1LALA_6475scFv) containing codon-optimized VL-sequence (synthesized by Geneart) was used w/o any modifications for expression of LC.

<u>anti-LRP6_MOR08168 hIgG1LALA_6475scFv_AspPro to AspAla (DP_to_DA)</u>
Vector pRS5a MOR08168 hIgG1LALA-6475scFv (SEQ ID NO:165) was used as template DNA for substitution of DP to DA in VH of scFv. Quick Change XL Site-Directed Mutagenesis Kit (Stratagene) was used in combination with following primers:
5'-ccatgaccaacatggacgccgtggacaccgccacc-3' (SEQ ID NO: 221)

5'-ggtggcggtgtccacggcgtccatgttggtcatgg-3' (SEQ ID NO: 222)
Site-Directed Mutagensis was done according to Stratagene protocol; resulting new construct was called pRS5a hIgG1LALA MOR08168opt 6475 scFv DP to DA.
Vector pRS5a MOR08168 hlambda (generation described for anti-LRP6_MOR08168 hIgG1LALA_6475scFv) containing codon-optimized VL-sequence (synthesized by Geneart) was used w/o any modifications for expression of LC.

anti-LRP6_MOR08168 hIgG1LALA_6475scFv_AspPro to ThrAla (DP_to_TA)
Vector pRS5a MOR08168 hIgG1LALA-6475scFv (SEQ ID NO:165) was used as template DNA for substitution of DP to TA in VH of scFv. Quick Change XL Site-Directed Mutagenesis Kit (Stratagene) was used in combination with following primers:
5'-caccatgaccaacatgaccgccgtggacaccgccacc-3' (SEQ ID NO: 223)
5'-ggtggcggtgtccacggcggtcatgttggtcatggtg-3' (SEQ ID NO: 224)
Site-Directed Mutagensis was done according to Stratagene protocol; resulting new construct was called pRS5a hIgG1LALA MOR08168opt 6475 scFv DP to TA.
Vector pRS5a MOR08168 hlambda (generation described for anti-LRP6_MOR08168 hIgG1LALA_6475scFv) containing codon-optimized VL-sequence (synthesized by Geneart) was used w/o any modifications for expression of LC.

anti-LRP6_MOR08168hIgG1 LALA_6475scFv_at_ValLeu (VL)
Vector pRS5a MOR08168 hIgG1LALA containing codon-optimized VH-sequence (synthesized by Geneart) was used w/o any modifications for expression of HC.
Gene coding for codon-optimized MOR06475scFv and MOR08168-VL was synthesized by DNA2.0 and was cloned via AgeI/HindIII into vector pRS5a hlambda MOR08168.
Resulting vector was called pRS5a hlambda MOR08168 6475scFv at VL.

anti-LRP6_MOR06475hIgG1 LALA_8168scfv_(VH-3-VL), where 3 represents a $(Gly_4Ser)_3$ amino acid linker between the VH and VL chains.
MOR06475-VH was amplified from vector pM2 hIgG1LALA MOR06475 with following primers:
5'-gttcctggtcgcgatcctggaaggggtgcactgccaggtgcaattgaaagaaagcg-3' (SEQ ID NO: 225)
5'-cttggtggaggctgagctaac-3' (SEQ ID NO: 226)
PCR-roduct was cloned via NruI/BlpI into vector pRS5a hIgG1LALA MOR08168 6475scFv, resulting vector was called pRS5a hIgG1LALA MOR06475 6475scFv.

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MOR08168scFv was amplified from vector pRS5a MOR08168 scFv (VH-3-VL) with following primers:
5'-gcacgaagcgctgcacaaccactacacccagaagagcctgagcctgtcccccggcaagggcggctccggcggaagc caggttcaattggttgaaagc-3' (SEQ ID NO: 227)
5'-gggccctctagagcggccgcccggcgcgcctcatcacagaacggtaagcttggtgcc-3' (SEQ ID NO: 228)
PCR-product was cloned via AfeI/XbaI into vector pRS5a hIgG1LALA MOR06475 6475scFv, resulting final vector was called pRS5a hIgG1LALA MOR06475 8168scFv (VH-3-VL).
MOR06475-VL was amplified from vector pM2 hkappa MOR06475 with following primers:
5'-gacaccaccggtgatatcgtgctgacccagagc-3' (SEQ ID NO: 229)
5'-gcagccaccgtacgtttaatttcaac-3' (SEQ ID NO: 210)
PCR-product was cloned into vector pRS5a hkappa MOR06654 via AgeI/BsiWI, resulting vector was called pRS5a hkappa MOR06475.

anti-LRP6_MOR06475hIgG1 LALA_8168scfv_(VH-4-VL), where 4 represents a $(Gly_4Ser)_4$ amino acid linker between the VH and VL chains.
MOR06475-VH was amplified from vector pM2 hIgG1LALA MOR06475 with following primers:
5'-gttcctggtcgcgatcctggaaggggtgcactgccaggtgcaattgaaagaaagcg-3' (SEQ ID NO: 211)
5'-cttggtggaggctgagctaac-3' (SEQ ID NO: 212)
PCR-product was cloned via NruI/BlpI into vector pRS5a hIgG1LALA MOR08168 6475scFv, resulting vector was called pRS5a hIgG1LALA MOR06475 6475scFv.
MOR08168scFv was amplified from vector pRS5a MOR08168 scFv (VH-4-VL) with following primers:
5'-gcacgaagcgctgcacaaccactacacccagaagagcctgagcctgtcccccggcaagggcggctccggcggaagc caggttcaattggttgaaagc-3' (SEQ ID NO: 213)
5'-gggccctctagagcggccgcccggcgcgcctcatcacagaacggtaagcttggtgcc-3' (SEQ ID NO: 214)
MOR06475-VL was amplified from vector pM2 hkappa MOR06475 with following primers:
5'-gacaccaccggtgatatcgtgctgacccagagc-3' (SEQ ID NO: 215)
5'-gcagccaccgtacgtttaatttcaac-3' (SEQ ID NO: 216)
PCR-product was cloned into vector pRS5a hkappa MOR06654 via AgeI/BsiWI, resulting vector was called pRS5a hkappa MOR06475.

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(iii) Expression of anti-LRP6-scFv

Electrocompetent *E. coli* strain W3110 was transformed with plasmid-DNA. Pre-cultures (150 ml LB-medium containing 12.5 µg Tetracyline/ml and 0.4% Glucose, in 500 ml flask) were inoculated with a single colony and incubated over night at 37°C/230 rpm. Expression cultures (6x 500 ml SB-medium containing 12.5 µg Tetracycline/ml, in 2 l flask) were inoculated with pre-cultures to O.D600 of 0.1 and incubated at 25°C/230 rpm to O.D600 of ca. 0.6. Then IPTG (Roche) was added to an end concentration of 0.4 mM and cultures were incubated over night at 25°C/230 rpm. Cells were harvested by centrifugation (20 min at 4600 rpm, 4°C) and cell pellets were frozen at -20°C.

(iv) Purification of anti-LRP6-scFv

Pellets from 3 l expressions were suspended in 50 ml Lysis-Buffer (20 mM NaH2PO4, 20 mM Imidazole, 500 mM NaCl, pH 7.4; 1 tablet Complete without EDTA per 50 ml buffer, Roche # 11836170001, 10 mM $MgSO_4$ and Benzonase). Cell suspensions were treated by French Press (2x at 1000bar) and centrifuged for 30 min at 16000xg, 4°C. 1ml HisTrap HP column (GE Helthcare) was equilibrated with 10 ml Lysis-Buffer. Supernatants were filtrated through Stericup Filter (Millipore) and loaded into equilibrated column (1 ml/min). Column was washed with Lysis-Buffer (20 ml) and bound protein was eluted with 3 ml Elution-Buffer (as Lysis-Buffer but 250 mM Imidazole). Eluate was directly loaded on Superdex75-column (HiLoad 16/60, GE-Healthcare), equilibrated with 130 ml PBS (1 ml/min). Run was done with PBS at 1 ml/min, eluate was collected in 1.5 ml fractions and analyzed on 10% Bis-Tris-Gel (NuPage, Invitrogen). Adequate fractions were pooled, filtrated through 0.2 µm filter and stored at 4°C. All purified proteins were analyzed by LC-MS (with oxidized and reduced samples) and by SEC-MALS (aggregation analysis).

(v) Transient expression of biparatopic anti-LRP6 IgG-scFv

3.2 L HEK293-6E cells were cultivated in M11V3 Media : Lot# D07668B in a BioWave20 at Rocks 10 rpm, Angle 7°, Aeration 25 L/h, O_2 25%, CO_2 6% to a density of 2E6 viable cells/mL. The cells were transiently transfected with 1.8 L DNA:PEI-MIX (plasmid: pRS5a MOR08168 hIgG1 LALA-6475sc-Fv 5 mg + pRS5a MOR08168 hlambda 5 mg + 20 mg PEI). 6 hours after transfection 5 L Feeding media (Novartis) with Yeastolate: Lot# 09-021 was added to the culture. The cells were then further culivated at

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Rocks 24 rpm, Angle: 7°, Aeration 25 L/h, O_2 25%, CO_2 0-6%. Seven days after transfection, cells were removed by crossflow filtration using Fresenius filters 0.2 µm. Afterwards the cell free material was concentrated to 1.75 L with crossflow filtration using 10 kDa cut off filter from Fresenius. After the concentration the concentrate was sterile filtered through a stericup filter (0.22 µm). The sterile supernatant was stored at 4°C. All described biaparatopic anti-LRP6-scFv variants were expressed in a similar manner.

(vi) Purification of biparatopic anti-LRP6 IgG-scFv

The purification of the biparatopic IgG was performed on a ÄKTA 100 explorer Air chromatography system at 6°C in a cooling cabinet, using a freshly sanitised (0.2 M NaOH/ 30% isopropanol) XK16/20 column with 25 ml of self-packed MabSelect SuRe resin (all GE Healthcare). All flow rates were 3.5 ml/min, except for loading, at a pressure limit of 5 bar. The column was equilibrated with 3 CV of PBS (made from 10x, Gibco), then the concentrated and sterile filtrated fermentation supernatant (1.35 L) was loaded at 2.0 ml/min o/n. The column was washed with 8 CV of PBS. Then the IgG was eluted with a pH gradient, starting at 50 mM citrate, 70 mM NaCl, pH 4.5, going linearly down in 12 CV to 50 mM citrate, 70 mM NaCl, pH 2.5, followed by a 2 CV constant step of the same pH 2.5 buffer. The biparatopic IgG eluted during the gradient in a single symmetric peak around pH 3.8, and was collected into 4 ml fractions. The fractions were pooled into three pools, left slope, main peak and right slope. The pools were immediately titrated to pH 7.0, slowly and under stirring, using 2 M Tris, pH 9.0. The pools were sterile filtered (Millipore Steriflip, 0.22 µm), OD 280 nm was measured in a Lambda 35 Spectrometer (Perkin Elmer), and the protein concentration was calculated based on the sequence data. The pools were separately tested for aggregation (SEC-MALS) and purity (SDS-PAGE and MS), and based on the results, only the central pool (35 ml at 2.55 mg/ml protein) was further used. All described biaparatopic anti-LRP6-scFv variants were purified in a similar manner.

(vii) Cross-reactivity analysis by protein microarrays

The microarrays were custom-made high-density protein chips manufactured by Protagen AG (UNIchip® AV-VAR-EP) and contained 384 pre-defined and purified human proteins printed in quadruplicates on a nitrocellulose coated glass slide. The proteins are classified as extracellular or secretory proteins based on gene ontology and expressed as

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an N-terminal His-tag fusion protein using *Escherichia coli,* and purified using immobilized metal ion affinity chromatography (IMAC). The hybridization of the antibody was done using the TECAN Hybridization Station HS400Pro, programmed with a protocol developed by Protagen AG. The primary antibodies were tested at a final concentration of 5 µg/ml. The secondary labeled antibody, a Cy5-conjugated AffiniPure Goat anti-hsIgG F(ab')$_2$, fragment specific (Jackson Immunoresearch, code no. 109-175-097), was used at a final concentration of 7.5 µg/ml. Microarray image acquisition was done using a GenePix Professional 4200A fluorescence microarray scanner (Axon Instruments, CA) equipped with a red laser (635 nm). Image analysis was performed using the GenePix Pro v6.0 software. Data analysis was done using Protagen UNIchip® Data Analysis Tool v1.8. To determine unspecific cross-reactivity derived from binding of the secondary antibody directly to the printed antigens, the secondary antibody was also incubated on the UNIchip® without the use of the primary antibody. For the determination of the level of cross reactivity normalized to the corresponding antigen, the fluorescent signal intensity value at saturated concentration (20 fmol/spot) was set as 100%. All signal intensities for a given protein, which were more than 4 % of the antigen signal, were considered as positive hits, providing they were not also found in the respective control with only the secondary labeled antibody.

(viii) Conformational stability measured by Differential Scanning Calorimetry (DSC)

DSC was measured using a capillary cell microcalorimeter VP-DSC from Microcal, equipped with a deep-well plate auto-sampler. Data were analyzed with the software Origin 7.5. The samples (400 µl), were added to 2 ml deep-well plates from Nunc^{Tm}. The samples in PBS pH 7.0 were analyzed at 1 mg/ml. The reference sample contained 400 µl of the same buffer as the analyte, usually PBS. Heat change associated with thermal denaturation was measured between 20 °C and 100 °C, with a heating rate of 3.3 °C min^{-1}. The apparent melting temperature (Tm), corresponded to the thermal transition midpoint, where 50% of the analyte is unfolded.

(ix) Serum stability studies

Purified proteins were solved in 35 µl rat serum or mouse serum (Gene Tex) resulting in an end concentration of 0.3 mg/ml. Samples were incubated at 37°C in a plate incubator. 4 µl of each sample were taken at different time-points, 10 µl sample buffer (4x, NuPage,

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Invitrogen) and 26 µl water were added and samples were frozen at -20°C. 12 µl of each sample were loaded into 12% Bis-Tris-Gel (NuPage, Invitrogen), electrophoresis was done at 200V for 35min. Protein transfer was done to PVDF-membrane (Invitrogen) in Borate buffer (50 mM Borate, 50 mM Tris) at 30V for 1 h. Membranes were briefly washed in TBST (10 mM Tris-HCl, pH 7.5, 150 mM NaCl, 0.1% Tween80) and then incubated for 2 h at RT/shaker in TBST containing 5% milk powder. Membranes were briefly washed in TBST and then incubated for 1 h at RT/shaker in TBST containing POD-conjugated Goat-anti-human IgG, Fab fragment specific (Dianova), diluted 1:10.000 or anti-His POD (Roche) diluted 1:500. Membranes were washed three times for 5min at RT/shaker in TBST. Signal detection was done using BM Blue POD Substrate (Roche) or ECL/ECL Plus (GE-Healthcare).

(b) Results

(i) Expression, purification and characterisation of anti-LRP6-scFvs

All scFv's were successfully expressed in *E. coli* W3110 and purified by affinity chromatography followed by size exclusion chromatography. Expected size (MOR06475 $(Gly_4Ser)_3$ /$(Gly_4Ser)_4$: 26.74 and 27.06 kDa respectively, MOR08168 $(Gly_4Ser)_3$ /$(Gly_4Ser)_4$: 26.5 and 26.85 kDa respectively, MOR08545 $(Gly_4Ser)_3$ /$(Gly_4Ser)_4$: 25.99 and 26.31 kDa respectively was confirmed for all purified samples by LC-MS analysis done with reduced and oxidized samples and by SDS PAGE. Purities > 95% were obtained. Fig. 14 shows the results of SDS-PAGE analysis in which 1.5 µg of each purified protein were loaded into 10% Bis-Tris gel (NuPage, Invitrogen) M: Marker See Blue Plus2 (Invitrogen); (1): MOR06475-VH-$(Gly_4Ser)_4$-VL; (2) MOR06475-VL-$(Gly_4Ser)_4$-VH; (3) MOR08168-VH-$(Gly_4Ser)_4$-VL; (4) MOR08168-VL-$(Gly_4Ser)_4$-VH; (5) MOR08545-VH-$(Gly_4Ser)_4$-VL; (6) MOR08545-VL-$(Gly_4Ser)_4$-VH (7) MOR06475-VH-$(Gly_4Ser)_3$-VL; (8) MOR06475-VL-$(Gly_4Ser)_3$-VH (9) MOR08168-VH-$(Gly_4Ser)_3$-VL; (10) MOR08168-VL-$(Gly_4Ser)_3$-VH; (11) MOR08545-VH-$(Gly_4Ser)_3$-VL; (12) MOR08545-VL-$(Gly_4Ser)_3$-VH.

Thermal Stability was compared for all ScFv's by DSC. The melting temperature (Tm) was significantly higher for the MOR06475 variants. The highest Tm (64.7°C) was observed for MOR06475-VL-$(Gly_4Ser)_4$-VH therefore this molecule is believed to be potentially more stable then the other constructs produced.

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Activity of MOR06475, MOR08168 and MOR08545 scFv and Fab constructs, as well as several biparatopic formats was assessed in the HEK293 STF assay (Fig. 17 and 18). Collectively, the data show that Propeller 1 IgG (MOR08168) inhibits Propeller 1 ligands such as Wnt1, while potentiating Propeller 3 ligands such as Wnt3 in the STF assay. Propeller 3 scFv6475 inhibits Propeller 3 ligands such as Wnt3, while having no activity on Propeller 1 ligands such as Wnt1. Furthermore, MOR08168/6475 biparatopic antibodies have activity against both Propeller 1 and Propeller 3 ligands, and no potentiating activity at any concentrations applied in the HEK293 Wnt STF assay.

(ii) Expression, purification and characterisation of biparatopic anti-LRP6 IgG-scFv
A schematic representation of biparatopic anti-LRP6 Ig-scFv format produced in this study is presented in Fig. 15. Fig. 15A represents a scFv scFv attached to the C-terminus of an IgG; 15B scFv scFv attached to the N-terminus of an Fc; 15C represents an scFv scFv attached to the C-terminus of an Fc; and 15D represents an scFv scFv attached to the N- and C-terminus of an Fc.

The biparatopic antibody in the current experiment is the biparatopic full-IgG with scFv fused to the C-terminus of hIgG1 LALA CH3. In this particular study the scFv was separated by a $(GlyGlySer)_2$-linker from the full-IgG. The scFv consists of VL-VH orientation with a $(Gly_4Ser)_4$ linker.

Biparatopic anti-LRP6 IgG-scFv's were transiently expressed in HEK293-6E cells and purified by affinity chromatography with gradient elution from pH 4.5 to 2.5. The expected size of 197.4kDa was determined by LC-MS analysis and SDS-PAGE with a purity greater than 97% . Aggregation, determined by SEC MALS, was less than 5%. Fig. 16 is an SDS-Page analysis of purified biparatopic anti-LRP IgG-scfV. Samples were loaded into 12% Bis-Tris gel (NuPage, Invitrogen). Marker: Invitrogen Mark12; (1): Non-reduced; (2): Reduced

Biparatopic anti-LRP6 IgG scFv and parental anti-LRP6 IgG bound to human FcRn at pH 6.0 with a Kd of 0.021 and 0.023μM respectively, as determined by Biacore. Both formats demonstrated low level binding to human FcRn at pH 7.4, so this BpAb is expected to behave as a standard IgG *in vivo* (PK characteristics similar to IgG1) (See Fig. 19).

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Biparatopic anti-LRP6 IgG scFv was stable in both mouse and rat serum at 37°C, tested up to 336 hours (data not shown) and showed no binding >4% when evaluated on a custom Protagen Unichip containing 384 purified extracellualr or secreted proteins (data not shown).

(c) Discussion

Various anti-LRP6 scFv's were initially characterised to enable optimisation of the final biparatopic antibody. ScFv's in both orientations and with two different linker lengths were expressed in *E. coli*. Anti-LRP6 MOR06475, 8168 and 8545 were expressed as VH-VL and VL-VH scFv's with a $(Gly_4Ser)_3$ and $(Gly_4Ser)_4$ linker. All MOR06475 and MOR08168 variants were successfully expressed and purified with a low level (<5%) of aggregates. Correctly processed protein with expected sizes were obtained. Thermal stability data showed that the most stable scFv format was MOR06475-VL- $(Gly_4Ser)_4$ - VH with a Tm of 64.7°C. All tested MOR08168 scFv formats showed significantly reduced thermal stability with a Tm of 50-52°C.

Biparatopic anti-LRP6 IgG's with scFv at CH3 and VL as well as modified variants (without C-terminal Lys (K) at CH3, with substitutions AspPro (DP) to AspAla (DA) and AspPro (DP) to ThrAla (TA) in VH of scFv) were successfully expressed and purified with a low level (<5%) of aggregates from cell culture. The expected sizes of approximately 197-198 kDa were determined. Constructs anti-LRP6 MOR08168 hIgG1LALA 6475scFv and anti-LRP6 MOR08168hIgG1 LALA 6475scFv at VL as well as mutated constructs (deletion of C-terminal Lys (K) at CH3 and substitutions AspPro (DP) to AspAla (DA) and AspAla (DP) to ThrAla (TA)) consisted of a scFv with VL-VH orientation and were separated by a $(Gly_4Ser)_4$ linker. A $(GlyGlySer)_2$ linker was used to attach the scFv to the CH3 domain of hIgG1 LALA and to VL of hlambda respectively. As previously discussed, however, the scFv may also consist of VH-VL separated by alternative linkers, furthermore the scFv may also be attached using alternative linkers to other positions within the IgG including the C-terminus of CL and the N-terminus of VH. Constructs with MOR08168scFv consisted of a scFv with VH-VL orientation and were separated by a $(Gly_4Ser)_3$ and $(Gly_4Ser)_4$ linker. A $(GlyGlySer)_2$ linker was used to attach the scFv to the CH3 domain of hIgG1 LALA.

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The biparatopic anti-LRP6 MOR08168 hIgG1LALA 6475scFv was stable in serum (tested up to 336 hours). The biparatopic bound as expected to human FcRn at pH6.0, low level binding was seen at pH7.4. The parental antibody bound with similar kinetics.

Example 13: In vivo evaluation of biparatopic antibody anti-LRP6 MOR08168hIgG1LALA 6475 scfv

The ability of biparatopic antibody anti-LRP6 MOR08168hIgG1LALA 6475 scfv to inhibit Wnt3 class Wnt signaling *in vivo* was tested in a co-implant system consisting of PA1-STF reporter cells co-implanted with Wnt3A secreting L cells. Female nude mice were implanted subcutaneously with 10x10e6 PA1-STF cells and 0.5x10e6 L-Wnt3A cells and randomized in groups of 5. 24 hours later, mice received a single intravenous dose of vehicle, MOR08168 LRP6-Propeller 1 Ab (10 mg/kg), MOR06475 LRP6-Propeller 3 Ab (10 mg/kg), or the biparatopic antibody anti-LRP6 MOR08168hIgG1LALA 6475 scfv (1 mg/kg, 3 mg/kg, or 10 mg/kg) and were imaged by Xenogen 6 hours, 24 hours, 48 hours, 72 hours and 168 hours later. The biparatopic antibody anti-LRP6 MOR08168hIgG1LALA 6475 scfv showed a dose-related inhibition of Wnt3A induced signaling, with 1 mg/kg showing maximum inhibition at 24 hours, returning to baseline at 48 hours, and 3 mg/kg and 10 mg/kg showing sustained inhibition for at least 72 hours. The MOR06475 LRP6-Propeller 3 Ab dosed at 10 mg/kg was able to inhibit Wnt3a induced signaling for at least 72 hours, whereas MOR08168 LRP6-Propeller 1 Ab dosed at 10 mg/kg increased Wnt3a induced signaling (Fig. 20).

To measure the effect of the biparatopic antibody anti-LRP6 MOR08168hIgG1LALA 6475 scfv, relative to the MOR08168 LRP6-Propeller 1 Ab, on Wnt signaling in MMTV-Wnt1 tumors, mice implanted with MMTV-Wnt1 tumors were dosed i.v. with a single dose of 5 mg/kg of the biparatopic antibody anti-LRP6 MOR08168hIgG1LALA 6475 scfv or a single dose of 5 mg/kg of the MOR08168 LRP6-Propeller 1 antibody. Serum concentrations of the biparatopic antibody, and propeller 1 antibody, as well as the mRNA expression of β-catenin target gene Axin2, were analyzed over a period of two weeks. The terminal β-phase half-life of the biparatopic antibody was around 48 hours, whereas that of the LRP6 antibody was about 72 hours. A significant decrease of Axin2 mRNA expression was observed in tumors obtained from mice dosed with either the biparatopic antibody, or the propeller 1 antibody, and Axin2 expression gradually recovered with no significant differences observed between the biparatopic antibody anti-

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LRP6 MOR08168hIgG1LALA 6475 scfv and the MOR08168 LRP6-Propeller 1 antibody (Fig. 21).

Anti-tumor activity of the biparatopic antibody anti-LRP6 MOR08168hIgG1LALA 6475 scfv was evaluated in the MMTV-Wnt1 allograft model. MMTV-Wnt1 tumor fragments were implanted subcutaneously (s.c.) into female nude mice. 7 days after implantation, mice carrying MMTV-Wnt1 tumors (n=8, average 137 mm^3; range: 81-272 mm^3) were treated with vehicle IgG, MOR08168 LRP6-Propeller 1 Ab (3 mg/kg, i.v., qw), or biparatopic antibody anti-LRP6 MOR08168hIgG1LALA 6475 scfv (3 mg/kg, i.v., 2qw), and tumors calipered twice a week. Both MOR08168 LRP6-Propeller 1 Ab and biparatopic antibody anti-LRP6 MOR08168hIgG1LALA 6475 scfv antibody induced tumor regressions (-93%, $p<0.05$ and -91%, $p<0.05$ respectively) (See Fig. 22). The dose dependency of the biparatopic antibody anti-LRP6 MOR08168hIgG1LALA 6475 scfv was evaluated and is depicted in Fig. 23.

Inhibition of Wnt signaling in colorectal cancer cells by β-catenin siRNA or dominant-negative TCF-4 causes rapid cell cycle arrest and induces an intestinal differentiation program (van der Wetering *et al.* (2002), Cell, 111, 241-250; van der Wetering *et al.* (2003), EMBO Reports, 4, 609-615). To determine if inhibition of Wnt signaling by antagonistic LRP6 antibodies has similar consequences in murine MMTV-Wnt1 mammary tumors, secretory differentiation was examined by Oil Red O staining for lipid, a major component of milk. MMTV-Wnt1 tumor bearing mice were treated with either a single dose of PBS (control) or 5 mg/kg anti-LRP6 MOR08168hIgG1LALA 6475 scfv 24 h, 72 h or 5 days after treatment, sections of frozen murine tumor allografts were cut at 5 μm thickness. Slides were air-dried for 30-60 minutes at room temperature and then fixed in ice-cold 10% formalin for 5-10 minutes. Slides were immediately rinsed three times in dH_20. Oil Red O staining was performed using an Oil Red O staining kit (Poly Scientific R&D, Cat # k043). Slides were scanned with ScanScope CS/GL scanner (Aperio Technologies), and tissue sections analyzed with ImageScope v10.2.1.2315 software (Aperio Technologies), using the IHC color deconvolution algorithm with a positive-pixel count. Representative images of Oil Red O staining are shown in Fig 24A and quantification in Fig 24B. The graph represents mean±SEM values. n=4 in the 72 hour group, n=3 in 24 hour group, n=2 in the 5 Day group, and n=1 for PBS (control) and demonstrate an increase in Oil Red O staining during the time course of the experiment.

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Together, these results suggest that inhibition of Wnt signaling in mammary tumor cells may lead to cell cycle arrest and induction of a secretory differentiation program.

Anti-tumor activity of the biparatopic antibody anti-LRP6 MOR08168hIgG1LALA 6475 scfv was further evaluated in the MDA-MB-231 breast xenograft model. 5x10e6 MDA-MB-231 cells in 50% matrigel were implanted subcutaneously (s.c.) into female nude mice. 31 days after implantation, mice carrying MDA-MB-231 tumors (n=7, average 165 mm^3; range 99-238 mm^3) were treated with vehicle, or biparatopic antibody anti-LRP6 MOR08168hIgG1LALA 6475 scfv (3mg/kg, i.v., qw), and tumors calipered twice a week. The biparatopic antibody anti-LRP6 MOR08168hIgG1LALA 6475 scfv antibody dosed at 3 mg/kg weekly, significantly delayed tumor growth (T/C=23%, $p<0.05$) (See Fig. 25).

Example 14: In vivo evaluation of additional biparatopic antibodies in the MMTV-Wnt1 model

As described in Example 10, additional anti-LRP6 reverse biparatopic antibodies were generated consisting of the propeller 3 antibody MOR06475 and the propeller 1 MOR08168 scfv domains. The ability of these biparatopic antibodies (MOR06475hIgG1 LALA_8168scfv_(VH-3-VL) and MOR06475hIgG1 LALA_8168scfv_(VH-4-VL) to inhibit Wnt1 signaling *in vivo*, relative to MOR08168hIgG1LALA 6475 scfv, was determined in the MMTV-Wnt1 model. Mice implanted with MMTV-Wnt1 tumors were dosed i.v. with a single dose of 5 mg/kg of each of the antibodies described above. Serum concentrations of each antibody (MOR08168hIgG1LALA 6475 scfv, MOR06475hIgG1 LALA_8168scfv_(VH-3-VL), and MOR06475hIgG1 LALA_8168scfv_(VH-4-VL), as well as the mRNA expression of β-catenin target gene Axin2, were analyzed over a period of 5 days (timepoints evaluated were 0, 2, 7, 24, 72 and 120 h). Both of the reverse biparatopic antibodies showed a significant decrease in axin2 mRNA expression to the same maximal extent as MOR08168hIgG1LALA 6475 scfv. However, the duration of the decrease of axin2 mRNA expression was shorter than that observed with MOR08168hIgG1LALA 6475 scfv, with the signal returning to baseline at the 24 h timepoint for both of the reverse biparatopic molecules. This was consistent with decreased exposure of these molecules, with serum levels dropping to below 5 μg/ml at 24 h compared with 120 h for MOR08168hIgG1LALA 6475 scfv.

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Example 15: Binding affinity of a biparatopic antibody to recombinant LRP6 PD1/2 And PD 3/4

Binding affinities of anti-LRP6 MOR08168hIgG1LALA 6475 scfv, MOR08168, and MOR6475 to Propeller Domains 1-2 of LRP6 (PD1/2, amino acid residues 19 to 629 of Accession No. NP002327) and Propeller Domains 3-4 of LRP6 (PD3/4, amino acids 631-1246 of Accession No. NP002327) were evaluated via surface plasmon resonance (SPR) using a Biacore T-100 (GE Healthcare). For the affinity determinations, anti-human IgG Fcγ specific antibody (#109-005-098, Jackson Immunology) was diluted in 10 mM sodium acetate (pH 5.0) buffer, and then immobilized onto CM4 chip (GE Healthcare, BR-1005-34) for all 4-flow cells to a density of ~2000 RU using standard amine coupling chemistry. The carboxymethyl dextran surface was activated with a 7 min injection of a 1:1 ratio of 0.4 M EDC (1-Ethyl-3-[3-dimethylaminopropyl] carbodiimide hydrochloride) and 0.1 M NHS (*N*-hydroxysuccinimide). Excess reactive esters were then blocked with 1M ethanolamine. anti-LRP6 MOR08168hIgG1LALA 6475 scfv was prepared at 10 µg/ml in HBS-EP buffer (GE Healthcare), and captured onto a separate flow cell of the CM4 chip to a density of ~70 RU at flow rate 10 µl/min. PD1/2 and PD3/4 were prepared as two fold concentration series starting at 50 nM, and injected at 30 µl/min for 1 min. This allowed a 40 min dissociation phase over the anti-LRP6 MOR08168hIgG1LALA 6475 scfv-captured surface and the control surface without captured ligands. The surfaces were then regenerated two times with 10 mM glycine (pH 2.2). For the dual binding analysis of anti-LRP6 MOR08168hIgG1LALA 6475 scfv to PD1/2 and PD3/4, anti-LRP6 MOR08168hIgG1LALA 6475 scfv was captured onto the CM4 chip immobilized with anti-human IgG Fcγ specific antibody. PD3/4 at a saturating concentration of 100 nM was then flowed over the surface at a flow rate of 30 µl/min for 30 min. A saturating concentration of 100 nM PD1/2 was injected immediately after the PD3/4. The dissociation constant (K_D), association (k_{on}), and dissociation (k_{off}) rates were calculated from the baseline subtracted corrected binding curves using the BIAevaluation software (GE Healthcare).

Anti-LRP6 MOR08168hIgG1LALA 6475 scfv (biparatopic antibody) binding to PD1/2 and PD3/4 was compared with that of MOR08168 (propeller 1 antibody) and MOR6475(propeller 3 antibody). Fig. 26A shows affinities of the molecules for corresponding LRP6 receptor domains, PD1/2 and PD3/4. The determined K_D of anti-LRP6 MOR08168hIgG1LALA 6475 scfv for PD1/2 and PD3/4 was similar to that of

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MOR08168 to PD1/2 and MOR6475 to PD3/4, respectively. Fig. 26B shows the association and dissociation phases of anti-LRP6 MOR08168hIgG1LALA 6475 scfv binding to each of the proteins. The off-rate for binding of anti-LRP6 MOR08168hIgG1LALA 6475 scfv to PD1/2 is slower than that to PD3/4. Further studies demonstrated in which PD1/2 and PD3/4 were injected sequentually indicated that, as expected, anti-LRP6 MOR08168hIgG1LALA 6475 scfv was capable of binding to both propeller domain constructs (Fig. 26C).

Example 16: scFv Mutations to Improve Thermostability of scFv08168 and scFv06475

This Example describes mutatons made in the scFvs of propeller 1 and propeller 3 antibodies and the effect of individual and a combination of mutations to the stability of the scFv as determined by thermal stability. Improvments in the stability of the scFv can be translated to the overall stability of an antibody construct comprising the mutated scFv.

Material and methods

Constructs

For IgG based biparatopic molecules, scFv06475 was fused to the C-terminal of MOR08168 IgG1 via a GlyGlySer linker to make biparatopic antibody designated "901" in Fig. 27 (MOR08168IgG1LALA 6475 scfv), or scFv08168 was fused to the C-terminal of MOR06475 IgG1 via a GGS linker to make biparatopic antibody designated "902" in Fig. 27. . For detailed information, please refer to other parts of this patent application.

Rational design of the focused library for scFv06475 and scFv08168

Two approaches were used for selection of point mutations to stabilize scFv06475 and scFv08168: sequence consensus analysis and structure based mutation design using homology modeling in Molecular Operating Environment (MOE).

For sequence consensus analysis, the amino acid sequences of the VH and VL domains of scFv06475, and of the VH and VL domains of scFv08168 were BLASTed against the non-redundant protein sequence database of NCBI. After each BLAST run, the query sequence and the top 250 homologous sequences were aligned by the clustalW program. An in-house computer program was used to count the most common amino acid at every residue position among the aligned sequences. At each position where the amino acid in the query sequence differed from the most common amino acid in the aligned sequence

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pool, a mutation was designed to mutate the residue from its wild type amino acid to the most common amino acid.

A homology model of scFv06475 and a homology model of scFv08168 were built in MOE. The sequences were first read into the "sequence editor" module of MOE. Existing X-ray structures with homologous sequences were searched in the "antibody modeler" module of MOE. The X-ray structure 3L5X and 1W72 were identified by MOE as the suitable templates to build the homology models for scFv06475 and scFv08168, respectively. Homology models were then built by MOE, using the CHARMM27 force field to minimize the energy.

Models produced by MOE were then subject to five stages of energy minimization and MD simulation in NAMD. The whole models were energy minimized for 5000 steps in the first to the third stage, and with restraints of 30 kcal/mol/A^2 applied on different sets of atoms. In the first stage, the restraints were applied to all atoms but the side chain atoms in CDRs. In the second stage, the restraints were applied to all atoms but the residues in CDRs. In the third stage, the restraints were applied only to backbone atoms. The models were then simulated in vacuum for 100 ps at 50K in the fourth stage, with restraints of 30 kcal/mol/A^2 applied on the backbone atoms. In the last and the fifth stage, the models were energy minimized for 5000 steps with restraints of 30 kcal/mol/A^2 applied on the backbone atoms. The models after these five stages of minimization and MD simulation were taken as the homology models for structure based mutation design.

Mutant models were built upon the wild type homology models. The "mutate" command of the "psfgen" module of VMD was used to mutate residues to the designed amino acids (William Humphrey *et al.* (1996) J. Molecular Graphics, 14: 33-38. The mutated models were then energy minimized and simulated in six stages. 5000 steps of energy minimization were performed in the first to the fourth stage. Restraints of 30 kcal/mol/A^2 were applied on all atoms but the side chain of the mutated residue in the first stage. Restraints of the same strength were applied on all atoms but the mutated residue in the second stage. The restraints on the side chain atoms of the residues within 5Å to the mutated residue were removed in the third stage. The restraints on the backbone atoms of the residues within 5Å to the mutated residue were released as well in the fourth stage. With the same restraints as those in the fourth stage applied, the mutated models were simulated in vacuum for 100 ps at 50K. The last snapshots of the simulation trajectories

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were then energy minimized for 5000 steps again, with the same restraints as those in the fourth stage. These minimized models were taken as the homology models of the mutants.

Plate based-library construction, expression and purification in E. coli system

High throughput mutagenesis was performed using QuikChange XL site-directed mutagenesis kit (Stratagene). Primers were designed according to primer design software Mutaprimer and were ordered from IDT in a 96 well format with normalized concentrations. Mutant strand synthesis reaction volume was scaled down from 50 to 25 µl. The reactions were carried out in the 96 well PCR plate. After the cycling, 0.5 µl DpnI enzyme was added to each amplification reaction and incubated at 37°C for 2 h to digest the parental dsDNA. Transformation was done by adding 2 µl of DpnI digested mutagenesis reaction into 20 µl Acella chemical competent cells in 96 well PCR plate.

Three individual colonies were picked from each transformation plate for expression and purification. Expression was done in two 96-well deep-well plates using autoinduction media. Aliquots of bacterial culture were saved as glycerol stocks and sent for sequencing analysis. Bacterial pellet combined from the two plates for each individual colony was lysed and purified with MagneHis protein purification system from Promega. KingFisher instrument was set up for high-throughput purification. 1 M NaCl was added into the lysis and wash buffer to improve protein purity. Protein was eluted with 100 µl of 300 mM imidazole in PBS. Protein quantity was briefly checked with Coomasie plus (Thermo) in order to determine the optimal amount of protein for Differential Scanning Fluorimetry (DSF).

Screening of thermostable mutations by DSF and Differential Scanning Calorimetry (DSC)

Depending on the protein amount purified for each sample, usually 10 to 20 µl of elution was used for DSF analysis. Specifically, samples of 10-20 µl were mixed with Sypro Orange (Invitrogen) of a final dilution at 1:1000, in a total volume of 25 µl in PBS. The samples were run by BioRad CFX1000 (25°C for 2 min, then increment 0.5°C for 30 second, 25 to 95°C). Hits were defined as Tm over 2C above wild type scFv. scFv binding activity was determined by one-point ELISA.

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Protein production in mammalian cells

Mutations were introduced into mammalian construct pRS5a that has scFv06475 or scFv08168 with His tag. The constructs were transiently expressed in 50 ml of 293T suspension cells. Briefly, PEI was mixed with DNA 50 µg at 1:3 for optimal transfection efficiency. Cells at 1.4 e6 per ml were use for transfection. Transfected cells were collected after six days of incubation in CO_2 chamber 80 rpm shaking in filter paper flask of 250 ml. Supernatant was concentrated to around 1 ml for optimal protein recovery. Protein is purified manually by MagneHis kit according to the instructions from the manufacturer. Purified protein was dialyzed in PBS overnight with changing of buffers. Protein samples either before or after dialysis were used for DSF analysis.

Affinity measurement for scFvs

Binding EC_{50} of scFvs against LRP6 protein was measured by ELISA. Maxisorp plate was coated with LRP6-Fc (R&D Sysytems, catalog No: 1505-LR) at 3 µg/ml at 4°C overnight. The plate was blocked with 50 µl of 2% BSA for one hour, and washed five times with the wash solution. The samples were diluted with 1% BSA accordingly. The plate was incubated at RT for 1 h, and washed for 3 times. Detection was done by adding 50 µl pentaHis-HRP (Qiagen Mat. No. 1014992) at 1:2000 dilution in 1% BSA, incubated at RT for 1 h, and washed 3 times. 50 µl of substrate reagent A plus B (R&D systems) was added, then incubated for 5-20 min depending on the color. The reaction was stopped by adding 25 µl of the stop solution, followed by plate reading at 450 nm.

Kinetics experiments were performed using BioRad's Proteon XPR36 biosensor. All experiments were performed at room temperature using PBST (phosphate buffered saline with 0.05% Tween-20) as the running buffer. All of the six vertical channels on a GLM chip were activated for 5 min at a flow rate of 30 µl/min using freshly prepared mixture of EDC (400 mM) and sNHS (100 mM). Anti-His mouse IgG1 (R&D systems, catalog No: MAB050) was diluted to 20 µg/ml in 10 mM sodium acetate, PH 5.0 and coupled to the chip for 5 min along separate vertical channels at a flow rate of 30 µl/min. 1 M ethanolamine was then injected for 5 min at 30 µl/min to deactivate the un-reacted sNHS groups. 2 µg/ml MOR08168 scFv wild type or 2 µg/ml MOR08168 D1 mutant was then immobilized on different vertical channels for 15 sec at 100 µl/min followed by two 1 min injection of the running buffer at 30 µl/min in the horizontal direction. The sixth vertical channel was used as the channel reference and no ligand was immobilized on this

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channel. A dilution series of a 360 KD homodimer antigen LRP6-Fc (R&D systems, catalog No: 1505-LR) was prepared at final concentrations of 300, 100, 33, 11, and 3.7 nM and injected at 30 µl/min along each horizontal channel. Association was monitored for 5 min and dissociation was monitored for 20 min. Buffer was injected in the sixth channel to serve as a row reference for real time baseline drifting correction. Chip surface was regenerated by applying 0.85% phosphoric acid at 100 µl/min for 18 s in the horizontal direction followed by the same running condition in the vertical direction. Kinetics analysis on the Proteon was performed in Proteon Manager v.2.1.1. Each interaction spot data was subtracted by a channel reference followed by a row reference to correct the real time baseline drifting. The processed data were fit globally to a bivalent analyte model.

Results

The plate-based mutagenesis, expression and purification in E. coli allowed more efficient screening from focused libraries

In order to achieve high yield to facilitate downstream analysis, the effect of the leader sequence on expression was tested. It was shown that the leader with pelB yielded the highest amount of purified protein among the seven leaders tested, as shown in Fig. 28A. Several bacterial strains including BL21 (DE3), XL-1 Blue and W3110 were tested for expression with IPTG induction. The expression level of scFv06475 in BL21 (DE3) was higher than in XL-1 blue and slightly higher than in W3110, as shown in Fig. 28B. In order to facilitate mutagenesis cloning, transformation and expression, Acella (a derivative of BL21) was used for all the subsequent experiments as cloning and expression can be done in the same strain with high efficiency. The protein was purified from cell lysate by KingFisher using MagneHis kit. Estimated yield for scFv08168 was around 10 µg per sample of combined wells from deep well culturing plate, of which 2 µg was used for DSF thermostability analysis. The plate based HTP screening has shorted the time significantly to around one week from primers to hits with improved thermostability.

scFv thermostability improvement by single point mutation from focused libraries

A hit for improved thermostability was defined as improvement of Tm at least 1°C above wild type consistently. There were 9 hits from a total of 51 sequence confirmed variants

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for scFv06475 and 15 hits from a total of 83 sequence confirmed variants for scFv08168. Selected hits were shown in Fig. 28 for scFv06475 and Fig. 29 for scFv08168.

Two approaches were used for selection of point mutations to stabilize scFv06475 and scFv08168: sequence consensus analysis and structure based mutation design. Among the top 250 sequences homologous to the VH domain of scFv06475, VH: 34 position was commonly occupied by either Met (45%) or Val (48%) (all numbering system in the text is from Kabat system). Yet this position was a Gly residue in the wild type sequence of scFv06475. Two mutants, VH:G34M and VH:G34V, were designed to mutate the wild type amino acid to the more popular amino acids at this position. As listed in Fig. 28, the VH:G34V mutant consistently showed higher stability than the wild type scFv06475 when expressed and purified by two different protocols. The VH:G34M mutant did not express well in bacterial, likely due to wrong sequence caused by errors in the PCR procedure.

Based on the same sequence consensus analysis, mutations of VH:I34M, VH:G50S, VH:W52aG and VH:H58Y were designed to mutate residues in scFv08168 to the consensus amino acids in its top 250 homologous sequences. As shown in Fig. 30, these mutations improved the Tm of scFv08168 by 7.5°C, 3.0°C, 7.0°C, and 3.5°C, respectively.

In the structure based approach, a homology model of scFv06475 and a homology model of scFv08168 were first built with MOE then energy minimized with NAMD. These models were then visually inspected for potential mutations to enhance local interaction. Mutations on various residues of scFv06475 and scFv08168 were designed, based on five biophysical understandings of protein stability.

The first approach was to increase the size of side chains in the protein core to improve packing. A few hydrophobic residues with side chains facing the protein core were mutated to larger side chains so as to improve the packing around these residues. After screening, three mutations designed by this approach were found to improve the stability of scFv08168. As listed in Fig. 30, the VH:I34F, VL:V47L and VL:G64V mutations improved the melting temperature of the scFv08168 by 4.0°C, 2.5°C, and 2.0°C, respectively.

The second approach was to mutate hydrophobic residues to aromatic residues to form pi-pi stacking interaction. In the wild type scFv06475 homology model, as shown in Fig.

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33a, the side chain of the VH:I37 residue was in close vicinity to two aromatic residues of VH:W103 and VL:F98. The closest distance between any non-hydrogen side chain atom of VH:I37 and any non-hydrogen side chain atom of VH:W103 was 3.82A. The counterpart distance between VH:I37 and VL:F98 was 3.77Å. As shown in Fig. 33b, two perpendicular pi-pi stacking interaction were formed when an Phe residue was introduced to this local region through the VH:I37F mutation: one between VH:F37 and VH:W103, and the other between VH:F37 and VL:F98. Newly formed pi-pi stacking interaction must be stronger than the original hydrophobic interaction in this localized region, as the melting temperature of scFv6475 was improved by this mutation from 61 to 64.5°C (Fig. 28). The VH:M95F mutation also improved the stability of scFv06475 by forming pi-pi stacking interaction with VH:W50 and VH:F100 (Fig. 29). The Tm was improved from 61 to 64.5°C.

The third approach was to mutate non-charged residues to charged residues so as to form salt bridge. The VH:K43 residue of scFv6475 did not form a salt bridge with neighboring residues in the homology model. Since the VH:V85 side chain faced directly to VH:K43 in the homology model of scFv06475 (Fig. 33e), it was mutated to negative charged to form a salt bridge with VH:K43. As shown in Figure 33f, the distance between the mutated VH:E85 side chain non-hydrogen atoms and the VH:K43 side chain non-hydrogen atoms could be as short as 2.61Å, suggesting that a salt bridge could be established between the two residues. Improved stability of scFv6475 upon the VH:V85E mutation listed in Fig. 29 indeed supported the design rationale at this position.

The fourth approach was to mutate hydrophobic residues to polar residues to establish hydrogen bonds. As illustrated in Fig. 33c, the hydrophobic VH:V33 residue was close to a polar residue VH:N100a in the homology model of scFv08168. When a polar residue was inserted to this region through the VH:V33N mutation, an extra hydrogen bond could be formed between VH:N33 and VH:N100a. Homology modeling suggested that the distance between the ND2 atom of VH:N33 and one of the OD atoms of VH:N100a could be as short as 2.80Å, which was within the range of a hydrogen bond, as shown in Fig. 33d. As shown in Fig. 29, this VH:V33N mutation improved the stability of scFv08168 by 2.0°C. Likewise, the stability enhancement of the VL:D93N mutation on scFv06475 (see Fig. 29) could be attributed to the improved hydrogen bond geometry with VL:Q27 and VL:Q90.

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Based on the surprising observation in the homology model of scFv08168 that two polar residues of VL: T78 and VH S49 were both surrounded by purely hydrophobic side chains, the fifth approach was utilized to mutate the two polar residues in the otherwise hydrophobic environment to non-polar residues. Two polar residues of VL:T78 and VH:S49 were both surrounded by purely hydrophobic side chains. As listed in Fig. 29, the VL:T78V and VH:S49A mutations increased the melting temperature of scFv08168 by 2.5°C and 5.5°C, respectively.

One point ELISA was carried out to evaluate binding activity. Certain hits were eliminated due to reduced or loss of binding activity towards LRP6. For example, the mutation VH W052aG of scFv08168 improved Tm by 7°C but showed much reduced binding activity as compared to wild type scFv08168. Therefore it was not selected for further analysis.

The presence of 300 mM imidazole in the elution buffer sometimes caused an overall shift of Tm by DSF, as observed in scFv06475. But the effect did not affect the ranking of Tm. There was also difference in protein produced in E. coli vs. in mammalian cells for scFv06475, as shown in Fig. 28. On the contrary, the presence of imidazole has minimal effect on Tm of scFv8168, as shown in Fig. 30 and Fig. 31. In addition, the Tm value remained unchanged for protein produced from E. coli or from mammalian for scFv08168, as shown in Fig. 31. Whether there was shift in Tm or not, the Tm ranking remained the same.

To confirm the effect of thermostability in proteins produced in mammalian cells, these mutations were introduced into construct for mammalian expression vector and expressed in 293T suspension cells. They were purified by MagneHis beads. Tm was checked and hits were confirmed for improved thermostability in proteins expressed in mammalian cells as shown in Fig. 31 for scFv08168. The single point mutation with highest thermostability improvement for scFv08168 is VH: I34M with an improvement of 7.5°C.

Combination of mutations to further improve thermostability

To further improve thermostability single mutations that improved the thermostability of the scFv combined to make double mutations in scFv08168. As shown in Fig. 31, the additive effects were observed for most of the double mutants including D1, which

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showed a improvement of 12.5°C by combination of two mutations of VH: I34M and VH: S49A, whereas the single mutation leaded to 7.5 and 5.5°C increase in Tm, respectively.

Thermostable mutants characterized for binding and functional activity

Affinity analysis ELISA EC_{50} was carried out for both scFv08168 and scFv06475 wild type and variants. As shown in Fig. 32, for scFv08168, the hits showed mostly comparable EC_{50} as wild type scFv08168, with a few mutants appeared to be a little more active than wild type, including the double mutant D1. This was confirmed with Proteon affinity measurement and STF cell based assay activity (performed as described earlier in this application (Materials and Methods, section 8), as shown in Fig. 32. Affinity ranking by Octet of scFv08168 variants showed that they were comparable to wild type (data not shown), In Proteon kinetics analysis, KD of D1 was 2.55 nM, whereas KD of wild type was 3.82 nM (Fig.32).

For scFv06475, there were two mutations affecting the activity as detected by ELISA and Proteon kinetics analysis. Specifically, in ELISA, VH: G34V and VH: I37F showed EC_{50} to be 27 nM and 4.3 nM respectively as compared to wild type of 0.76 nM. In Proteon analysis, VH: G34V and VH: I39F showed significant drop in off rate (data not shown).

Improved thermostability of biparatopic molecules

For IgG based fusion molecules 902 and mutant version 902T, the first Tm peak shifted from 47°C to 62°C. This peak corresponded to scFv08168 unfolding. The second peak shifted from 72 °C to 76°C. This peak corresponded to Fab06475, as shown in Fig. 34.

Discussion

Rational design based on sequence analysis and homology modeling has yielded thermostable mutations for scFvs. In the current examples, the hit rate was around 18% for both scFv08168 and scFv06475. The most significant improvement was 7.5°C increase in Tm over wild type by a single point mutation VH: I34M in scFv08168. On the sequence perspective, this position was highly conserved to Met. Structurally, a larger hydrophobic side chain at this position could improve the packing around this residue. Another point mutation VH: S49A in scFv08168 variant raised Tm by 5°C. This mutation was picked by homology modeling. Though this position is more conserved to

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Ser than to Ala, structurally Ala may fit better due to the lack of polar side chain around this residue.

For structure based mutation design using homology modeling, a combination of mechanisms was utilized. In scFv06475 and scFv08168, positive hits were discovered by each of the five biophysical considerations: packing improvement, more Pi-Pi stacking, more hydrogen bonds, more salt bridges and removal of buried polar groups. It was by this combination of mechanisms that a total of 10 stabilizing mutations have been identified, as listed in Fig. 29 and 30.

Combination of mutations identified to improve thermal stability ("beneficial mutations") further improve thermostability if they were located in different areas. This was demonstrated in the case of scFv08168. When beneficial mutation VH: I34M and VH: S49A were combined, Tm was further increased to 62.5°C vs wild type at 49 °C. This was 13.5°C increase over wild type, where the individual mutation VH I34M and VH: S49A each raised Tm by 7.5°C and 5°C respectively. This was a clear indication for additive effect.

I34M was very close to CDR1-H of scFv08168, however the mutation did not affect the binding affinity as evidenced by a number of assays. CDR plays a role in overall scFv or full antibody stability. Significant improvement may be achieved through engineering of residues close to the CDR region using the methods disclosed, as long as the mutation does not affect binding affinity and specificity.

Most of stabilizing mutations have been located on VH. Out of the 15 stabilizing mutations listed in Fig. 29 and 30, 11 were mutations on the VH domain whereas only 4 were on the VL domain.

When incorporated into IgG or other formats (e.g. serum albumin fusions), the stabilized VH and VL led to a dramatic improvement in thermostability of the molecules. For IgG fusion, the lower Tm of 47°C corresponded to the Tm of scFv08168, whereas the higher peak at 72.5°C correspond to the Tm of CH2 and Fab06475. The incorporation of two mutations VH: I34M and VH: S49A has improved the Tm of scFv08168 from 47°C to 62°C, whereas the incorporation of VH: M95F in 6475 further improved the Tm of Fab from 72.5°C to 76°C. The improvement was not only shown on scFv itself, but also on the

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Fab due to the improved stability of VH and VL. This may provide a more general strategy for improving overall antibody stability.

Rational design coupled with HTP screening in E. coli system has offered very quick turnaround time and high hit rate. Tm measured with materials from E. coli correlated with that from mammalian, or ranking remained the same. This greatly simplied screening process to implemented as HTP in E. coli. Plate based mutagenesis, transformation, expression and purification has shorted the time to less than one week. Using the methods disclosed herein, a number of mutations can be made in scFvs or other antigen binding fragments and screened for thermal stability. These mutated scFvs or antigen binding fragments can then be used as components of larger antibody constructs such as biparatopic antibodies, to confer such stabilty to the larger antibody construct.

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Claims

1. An isolated multivalent antibody having at least two receptor binding domains for two different binding sites of an LRP6 target receptor, wherein the first receptor binding domain binds to a first binding site on the target receptor and the second receptor binding domain binds to a second binding site on the same LRP6 target receptor, wherein the first and second receptor binding domains are linked together such that the binding of the first and second receptor binding domains to the first and second binding sites of the LRP6 target receptor inhibits a canonical Wnt signal transduction pathway, and wherein the antibody or antigen binding fragment displays no significant potentiation of a Wnt signal.

2. The antibody of claim 1, wherein the antibody has an affinity for target receptor of approximately nanomolar affinity.

3. The antibody of claim 1, wherein the antibody has an affinity for target receptor of approximately 1 picomolar affinity.

4. The antibody of claim 1, wherein the first and second receptor binding domain is selected from the group consisting of an IgG antibody, an scFv fragment, a single chain diabody, an antibody mimetic, and an antibody variable domain.

5. The antibody of claim 1, wherein the antibody is selected from the group consisting of a multivalent antibody, a bivalent antibody, a bispecific antibody, and a biparatopic antibody.

6. The antibody of claim 1, wherein the first receptor binding domain is an IgG antibody and the second receptor binding domain is an scFv fragment, wherein the IgG antibody and scFv fragment are linked together by a linker with a spatial distribution that permits the IgG antibody and scFv fragment to bind to the first and second epitopes of LRP6, respectively.

7. The antibody of claim 6, wherein the linker is a Gly-Ser linker selected from the group consisting of $(Gly_4Ser)_4$, and $(Gly_4Ser)_3$.

8. The antibody of claim 1, wherein the first epitope of the LRP6 target receptor is

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a β-propeller 1 domain.

9. The antibody of claim 1, wherein the second epitope of the LRP6 target receptor is a β-propeller 3 domain.

10. The antibody of claim 1, wherein the antibody binds to the LPR6 β-propeller 1 domain and comprises a heavy chain CDR1 selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 21, and SEQ ID NO: 47; a CDR2 selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 22, and SEQ ID NO: 48; and a CDR3 selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 23, and SEQ ID NO: 49; and a light chain CDR1 selected from the group consisting of SEQ ID NO: 4, SEQ ID NO: 24, and SEQ ID NO: 50; a CDR2 selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 25, and SEQ ID NO: 51; and a CDR3 selected from the group consisting of SEQ ID NO: 6, SEQ ID NO: 26, and SEQ ID NO: 52.

11. The antibody of claim 1, wherein the antibody binds to the LPR6 β-propeller 3 domain and comprises a heavy chain CDR1 selected from the group consisting of SEQ ID NO: 69, SEQ ID NO: 93, and SEQ ID NO: 115; a CDR2 selected from the group consisting of SEQ ID NO: 70, SEQ ID NO: 94, and SEQ ID NO: 116; and a CDR3 selected from the group consisting of SEQ ID NO: 71, SEQ ID NO: 95, and SEQ ID NO: 117; and a light chain CDR1 selected from the group consisting of SEQ ID NO: 72, SEQ ID NO: 96, and SEQ ID NO: 118; a CDR2 selected from the group consisting of SEQ ID NO: 73, SEQ ID NO: 97, and SEQ ID NO: 119; and a CDR3 selected from the group consisting of SEQ ID NO: 74, SEQ ID NO: 98, and , SEQ ID NO: 120.

12. The antibody of claim 6, wherein the IgG heavy chain antibody is selected from the group consisting of SEQ ID NO: 18, 66, and 101 and the light chain is selected from the group consisting of SEQ ID NO: 17, 86, and 85.

13. The antibody of claim 6, wherein the scFv is selected from the group consisting of SEQ ID NO: 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, and 164.

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14. The antibody of claim 13, wherein the scFv fragment comprises at least one amino acid mutation that improves stability of the scFv compared with the unmutated scFv fragment, wherein the amino acid mutation is selected from Figures 29-32.

15. The antibody of claim 1, wherein the antibody has the functional activity of inhibiting a canonical Wnt signal transduction pathway selected from the group consisting of Wnt1 signal pathway and Wnt3 signal transduction pathway.

16. The antibody of claim 1, wherein the antibody has the functional activity of depleting a cell population, inhibiting or reducing proliferation of a cell population, inhibiting or reducing secretion of inflammatory mediators from a cell population, inhibiting or reducing secretion of cytoplasmic granules from a cell population, wherein the cell population is selected from the group consisting of tumor cells, T cells B cells, and Wnt dependent cells.

17. An isolated biparatopic antibody comprising an IgG antibody that binds to a β-propeller 1 domain on an LRP6 target receptor and a scFv that binds to a β-propeller 3 domain on the LRP6 target, wherein the IgG antibody and the scFv are linked by a linker such that the binding of the IgG antibody and the scFv to the β-propeller 1 domain and the β-propeller 3 domains, respectively inhibits a canonical Wnt signal transduction pathway, and wherein the biparatopic antibody displays no significant potentiation of a Wnt signal.

18. The antibody of claim 17, wherein the antibody has an affinity for target receptor of approximately nanomolar affinity.

19. The antibody of claim 17, wherein the antibody has an affinity for target receptor of approximately 1 picomolar affinity.

20. The antibody of claim 17, wherein the linker comprises a spatial distribution that permits binding of the IgG antibody and the scFv fragment to bind the β-propeller 1 domain of LRP6 and the β-propeller 3 domain of LRP6, respectively.

21. The antibody of claim 17, wherein the scFv is linked by a Ser-Gly linker to the Fc binding site of the IgG antibody, wherein the Ser-Gly linker is selected from the group consisting of $(Gly_4Ser)_4$, and $(Gly_4Ser)_3$.

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22. The antibody of claim 21, wherein the Fc binding site of the IgG antibody is a CH3 domain.

23. The antibody of claim 17, wherein the scFv is linked by a Ser-Gly linker to the light chain of the IgG antibody, wherein the Ser-Gly linker is selected from the group consisting of $(Gly_4Ser)_4$, and $(Gly_4Ser)_3$.

24. The antibody of claim 20, wherein the scFv comprises at least one amino acid mutation that improves stability of the scFv compared with the unmutated scFv fragment, wherein the amino acid mutation is selected from Figures 29-32.

25. The antibody of claim 17, comprising a heavy chain variable region CDR1 of SEQ ID NO: 1; a heavy chain variable region CDR2 of SEQ ID NO: 2; a heavy chain variable region CDR3 of SEQ ID NO: 3; a light chain variable region CDR1 of SEQ ID NO: 4; a light chain variable region CDR2 of SEQ ID NO: 5; and a light chain variable region CDR3 of SEQ ID NO: 6, wherein the antibody binds to a β-propeller 1 domain of LRP6; and a scFv heavy chain variable region CDR1 of SEQ ID NO: 69; a heavy chain variable region CDR2 of SEQ ID NO: 70; a heavy chain variable region CDR3 of SEQ ID NO: 71; a light chain variable region CDR1 of SEQ ID NO: 72; a light chain variable region CDR2 of SEQ ID NO: 73; and a light chain variable region CDR3 of SEQ ID NO: 74, wherein the scFv binds to a β-propeller 3 domain of LRP6.

26. The antibody of claim 25 further comprising a Lys deletion from position 454 of SEQ ID NO: 166.

27. The antibody of claim 25 further comprising a Pro to Ala mutation at position 677 of SEQ ID NO: 166.

28. The antibody of claim 25 further comprising an AspPro to ThrAla mutation at positions 676-677 of SEQ ID NO: 166.

29. The antibody of claim 17 comprising a heavy chain sequence selected from the group consisting of SEQ ID NOs: 166, 171, 173, 175, 195, 201 and 207 in combination with a light chain sequence selected from the group consisting of SEQ ID NOs: 170, 193, 199, and 205.

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30. The antibody of claim 17 comprising a combination of heavy and light chain sequences selected from the group consisting of SEQ ID NOs: 166/170, 171/170, 173/170, 175/170, 201/199, 207/205, ,and 195/193.

31. The antibody of claim 17, comprising heavy and light chain sequences with SEQ ID NOs: 166/170.

32. The antibody of claim 23, comprising a heavy chain sequence of SEQ ID NO; 177; and a light chain sequence comprising SEQ ID NO: 181.

33. The antibody of claim 17, wherein the antibody has the functional activity of inhibiting a canonical Wnt signal transduction pathway selected from the group consisting of Wnt1 signal pathway and Wnt3 signal transduction pathway.

34. The antibody of claim 17, wherein the antibody has the functional activity of depleting a cell population, inhibiting or reducing proliferation of a cell population, inhibiting or reducing secretion of inflammatory mediators from a cell population, inhibiting or reducing secretion of cytoplasmic granules from a cell population, wherein the cell population is selected from the group consisting of tumor cells, T cells B cells, and Wnt dependent cells.

35. An isolated biparatopic antibody comprising an IgG antibody that binds to a β-propeller 3 domain on an LRP6 target receptor and a scFv that binds to a β-propeller 1 domain on the LRP6 target, wherein the IgG antibody and the scFv are linked by a linker such that the binding of the IgG antibody and the scFv to the β-propeller 3 domain and the β-propeller 1 domains, respectively inhibits a canonical Wnt signal transduction pathway, and wherein the biparatopic antibody displays no significant potentiation of a Wnt signal.

36. The antibody of claim 35, wherein the antibody has an affinity for target receptor of approximately nanomolar affinity.

37. The antibody of claim 35, wherein the antibody has an affinity for target receptor of approximately 1 picomolar affinity.

38. The antibody of claim 35, wherein the linker comprises a spatial distribution that permits binding of the IgG antibody and the scFv to bind the β-propeller 3 domain of LRP6 and the β-propeller 1 domain of LRP6, respectively.

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39. The antibody of claim 35, wherein the scFv is linked by a Ser-Gly linker to the Fc binding site of the IgG antibody, wherein the Ser-Gly linker is selected from the group consisting of $(Gly_4Ser)_4$, and $(Gly_4Ser)_3$.

40. The antibody of claim 39, wherein the Fc binding site of the IgG antibody is a CH3 domain.

41. The antibody of claim 35, wherein the scFv comprises at least one amino acid mutation that improves stability of the scFv compared with the unmutated scFv fragment, wherein the amino acid mutation is selected from Figures 29-32.

42. The antibody of claim 35, comprising a heavy chain variable region CDR1 of SEQ ID NO: 69; a heavy chain variable region CDR2 of SEQ ID NO: 70; a heavy chain variable region CDR3 of SEQ ID NO: 71; a light chain variable region CDR1 of SEQ ID NO: 72; a light chain variable region CDR2 of SEQ ID NO: 73; and a light chain variable region CDR3 of SEQ ID NO: 74, wherein the antibody binds to a β-propeller 3 domain of LRP6; and an scFv with a heavy chain variable region CDR1 of SEQ ID NO: 1; a heavy chain variable region CDR2 of SEQ ID NO: 2; a heavy chain variable region CDR3 of SEQ ID NO: 3; a light chain variable region CDR1 of SEQ ID NO: 4; a light chain variable region CDR2 of SEQ ID NO: 5; and a light chain variable region CDR3 of SEQ ID NO: 6, wherein the scFv thereof binds to a β-propeller 1 domain of LRP6.

43. The antibody of claim 42, wherein scFv VH and VL are linked with a linker comprising 3 amino acids.

44. The antibody of claim 42, wherein scFv VH and VL are linked with a linker comprising 4 amino acids.

45. The antibody of claim 42, comprising a heavy chain sequence selected from the group consisting of SEQ ID NO:187, and 189; and a light chain sequence comprising SEQ ID NO: 185.

46. The antibody of claim 35, wherein the antibody has the functional activity of inhibiting a canonical Wnt signal transduction pathway selected from the group consisting of Wnt1 signal pathway and Wnt3 signal transduction pathway.

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47. The antibody of claim 35, wherein the antibody has the functional activity of depleting a cell population, inhibiting or reducing proliferation of a cell population, inhibiting or reducing secretion of inflammatory mediators from a cell population, inhibiting or reducing secretion of cytoplasmic granules from a cell population, wherein the cell population is selected from the group consisting of tumor cells, T cells B cells, and Wnt dependent cells.

48. A nucleic acid comprising a nucleotide sequence encoding a multivalent antibody of claims 1, 17, and 35.

49. A nucleic acid comprising a nucleotide sequence encoding a multivalent antibody comprising a heavy chain sequence selected from the group consisting of SEQ ID NOs: 166, 171, 173, 175, 195, 201, and 207; and light chain sequences selected from the group consisting of SEQ ID NOs: 170, 193, 199, and 205.

50. A nucleic acid comprising a nucleotide sequence encoding a multivalent antibody comprising a heavy chain sequence selected from the group consisting of SEQ ID NOs: 166, 171, 173, 175, 195, 201, and 207; and light chain sequences selected from the group consisting of SEQ ID NOs: 170, 193, 199, and 205 least, wherein the antibody has 98% sequence identity to SEQ ID NOs: 166, 171, 173, 175, 195, 201, and 207; and light chain sequences selected from the group consisting of SEQ ID NOs: 170, 193, 199, and 205.

51 A nucleic acid comprising a nucleotide sequence encoding a multivalent antibody comprising a SEQ ID NO: 166 and SEQ ID NO: 170.

52. A nucleic acid comprising a nucleotide sequence encoding a multivalent antibody comprising at least 98% sequence identity to a SEQ ID NO: 166 and SEQ ID NO: 170.

53. A nucleic acid comprising a nucleotide sequence encoding a multivalent antibody comprising a sequence selected from the group consisting of SEQ ID NOs: 177, and; and a light chain sequence of SEQ ID NO: 181.

54. A nucleic acid comprising a nucleotide sequence encoding a multivalent antibody comprising at least 98% sequence identity to SEQ ID NOs: 177; and a light chain sequence of SEQ ID NO: 181.

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