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(19) **United States**(12) **Patent Application Publication**
URANO et al.(10) **Pub. No.: US 2016/0317656 A1**(43) **Pub. Date: Nov. 3, 2016**(54) **COMBINATION OF ANTI-FGFR2 ANTIBODY
AND OTHER AGENT**(30) **Foreign Application Priority Data**

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KAMAI**, Tokyo (JP)(51) **Int. Cl.****A61K 39/395** (2006.01)**A61K 31/496** (2006.01)**A61K 31/47** (2006.01)**A61K 45/06** (2006.01)(73) Assignee: **Daiichi Sankyo Company, Limited**,
Chuo-ku, Tokyo (JP)(52) **U.S. Cl.**CPC **A61K 39/3955** (2013.01); **A61K 45/06**
(2013.01); **A61K 31/496** (2013.01); **A61K**
31/47 (2013.01)(21) Appl. No.: **15/027,489**(22) PCT Filed: **Oct. 7, 2014**(86) PCT No.: **PCT/JP2014/077276**

§ 371 (c)(1),

(2) Date: **Apr. 6, 2016**(57) **ABSTRACT**The present invention provides a combination of an antibody
binding to a fibroblast growth factor receptor, and another
agent.

FIG. 1

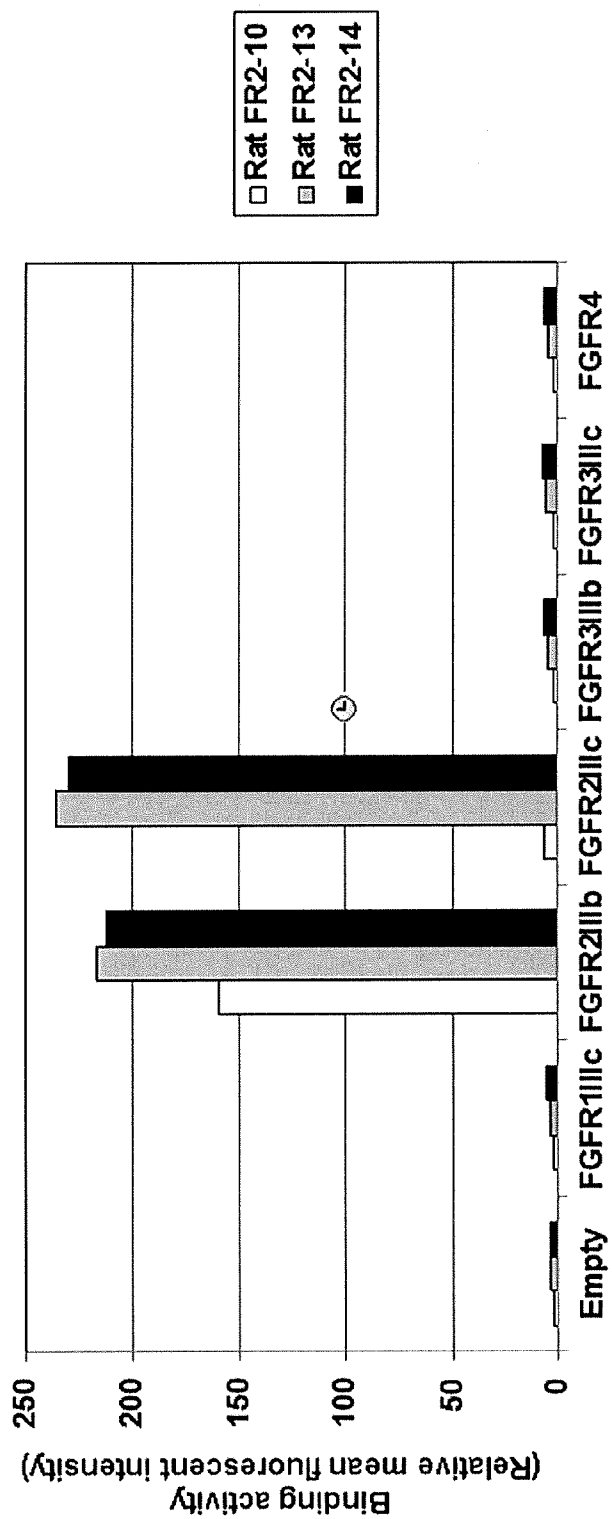


FIG. 2

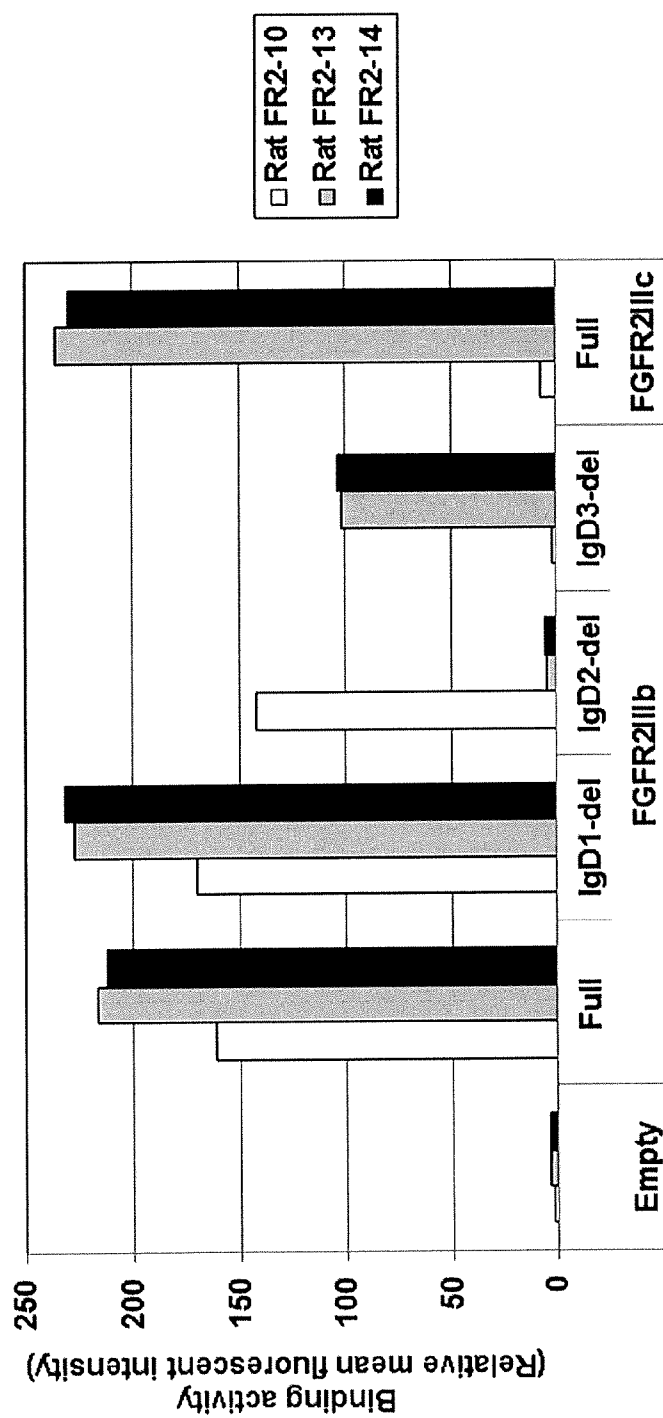


FIG. 3A

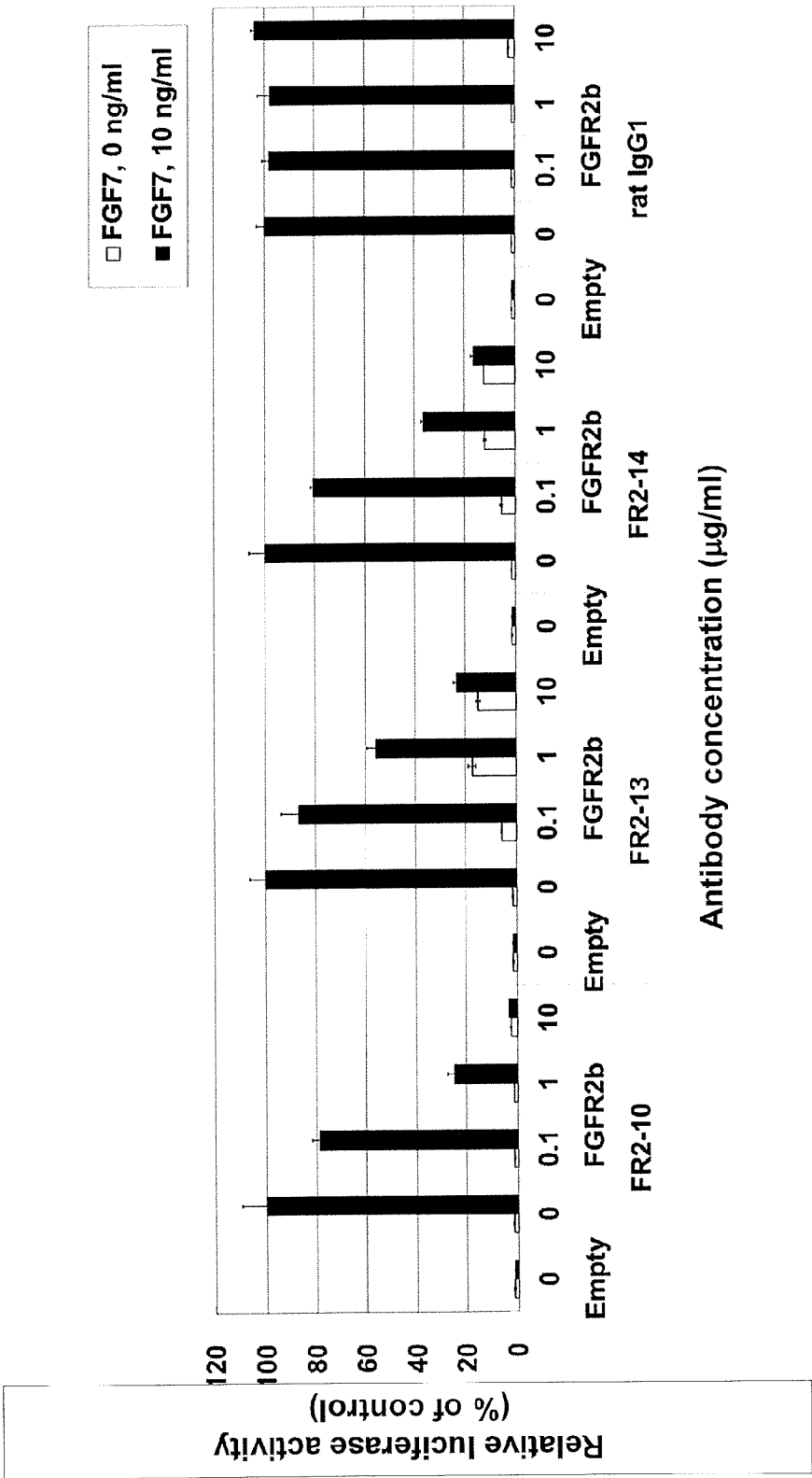


FIG. 3B

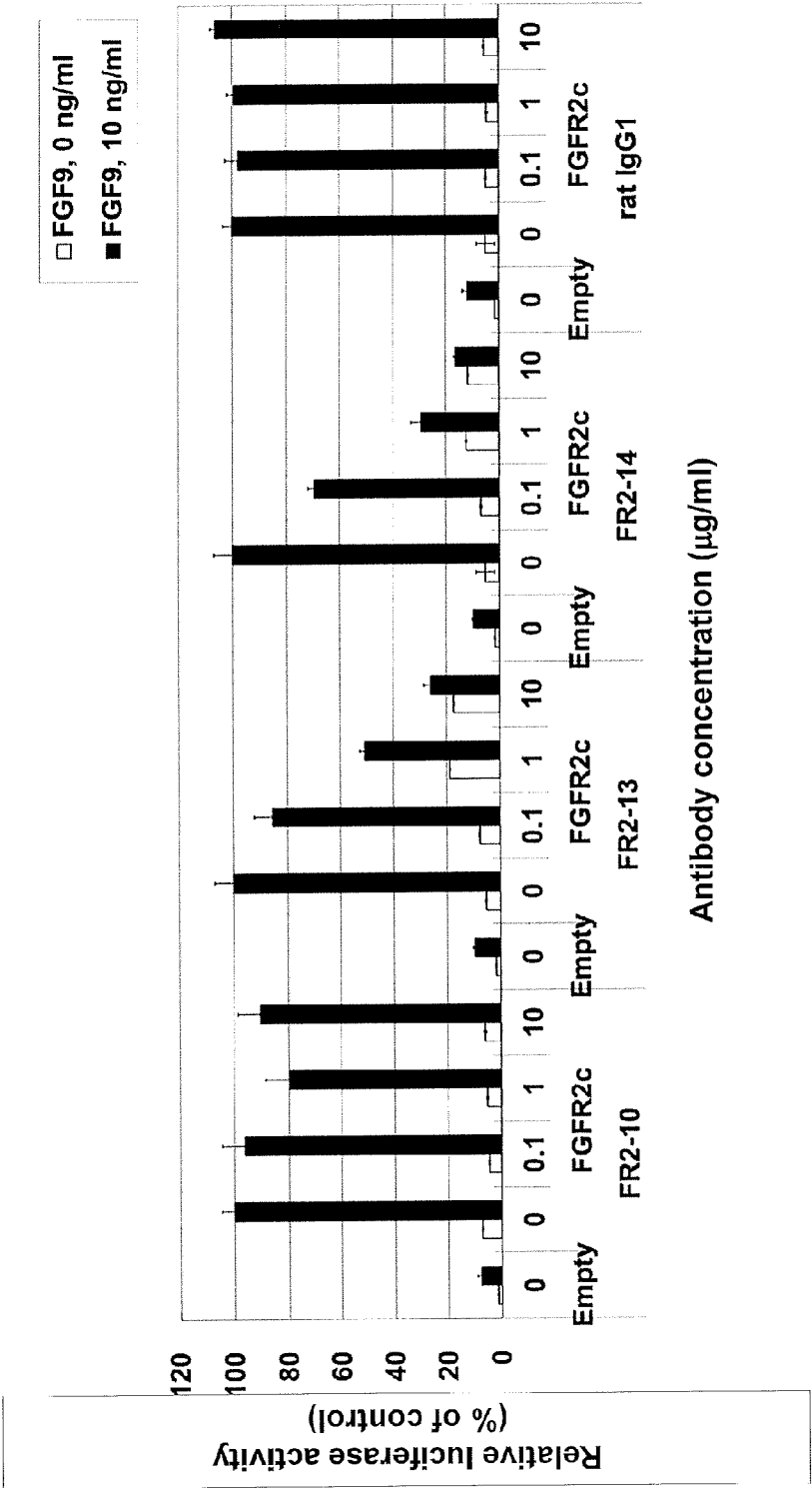


FIG. 4

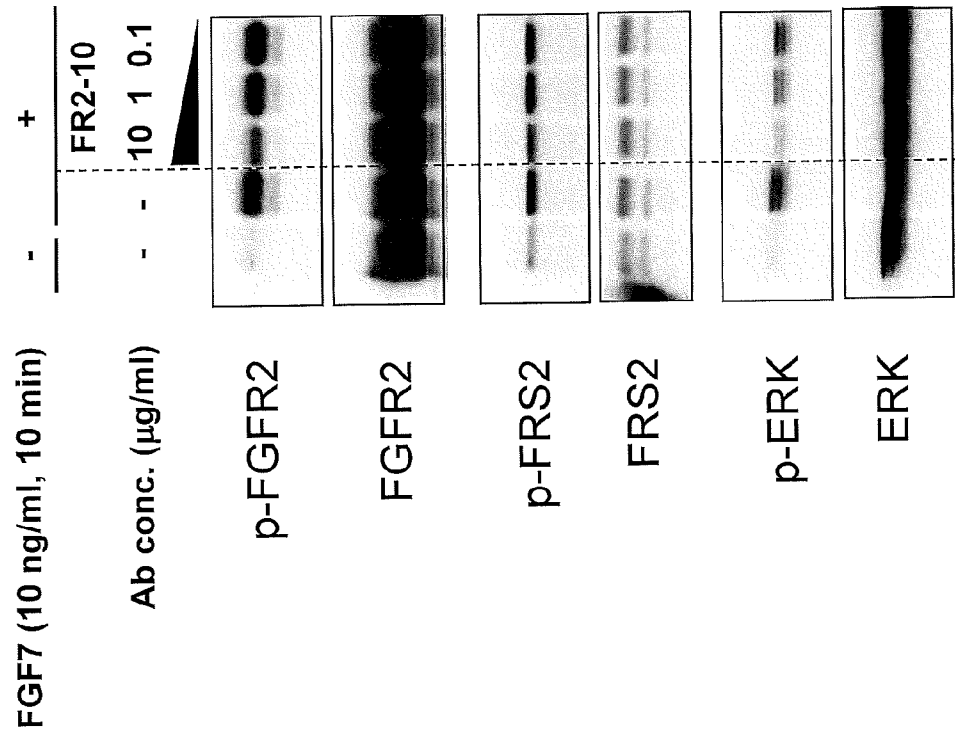


FIG. 5

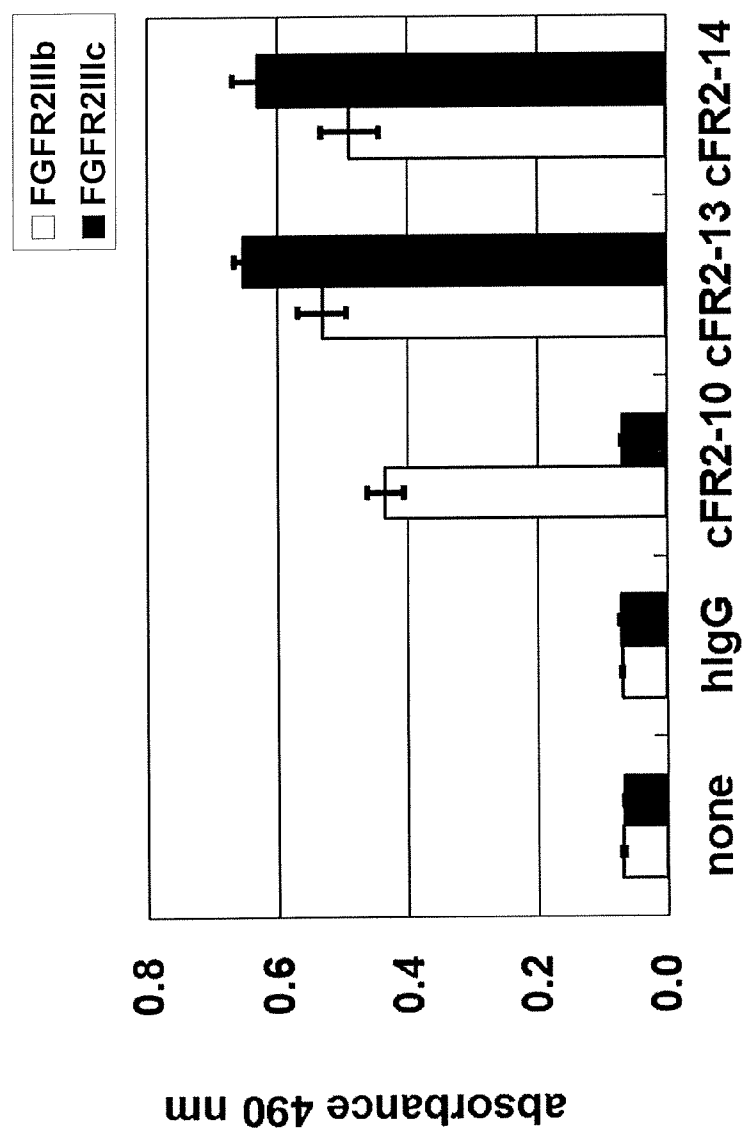


FIG. 6A

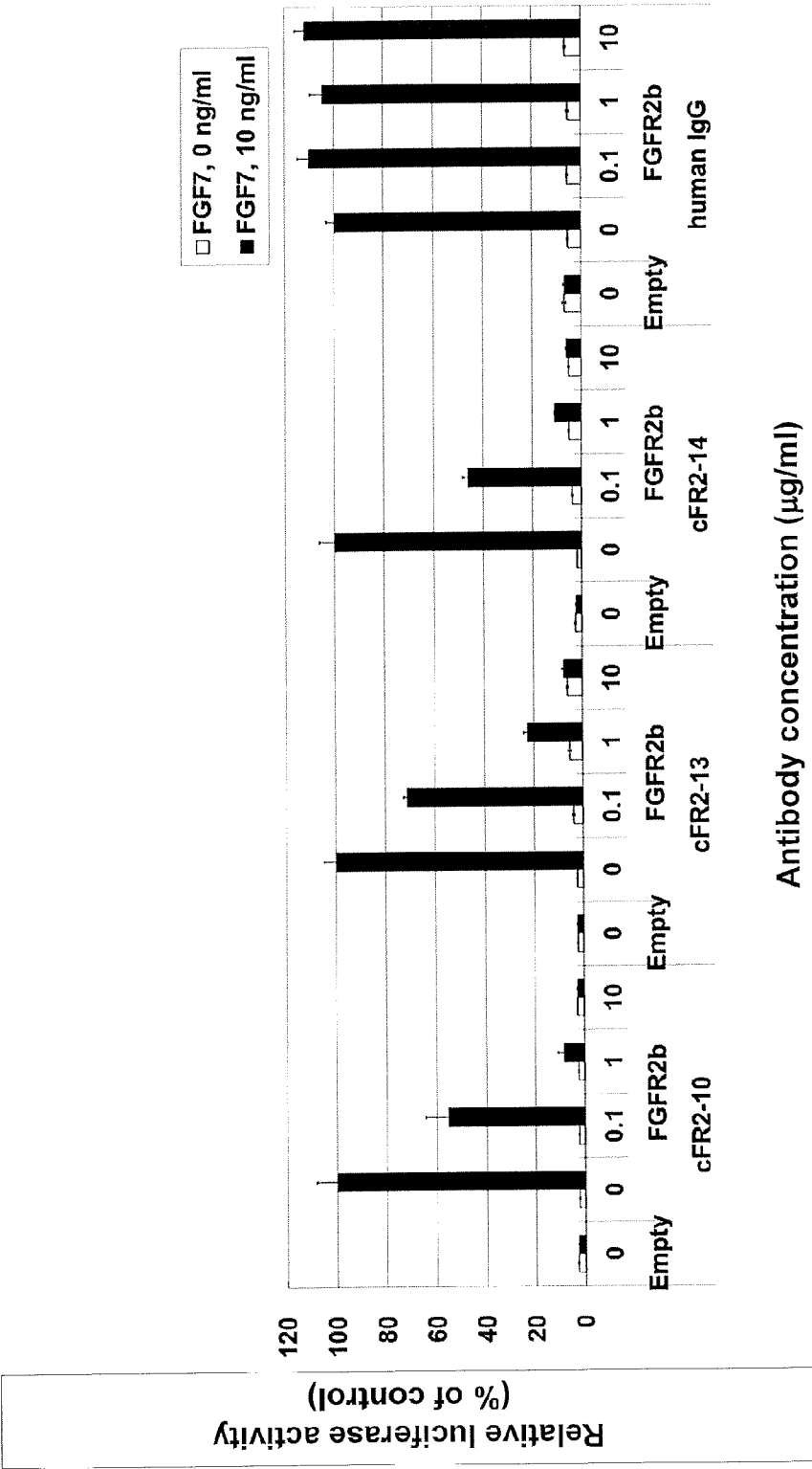


FIG. 6B

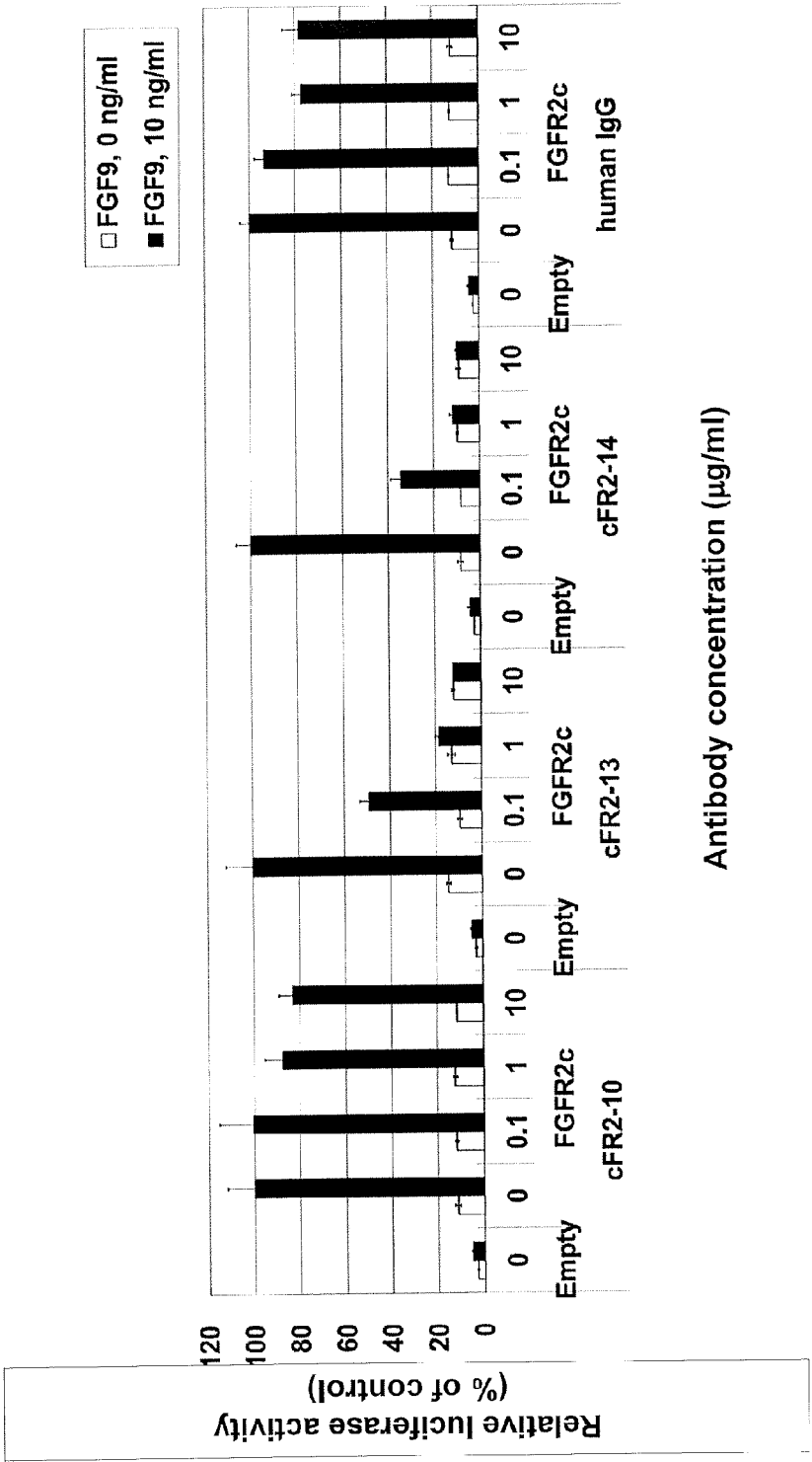


FIG. 7

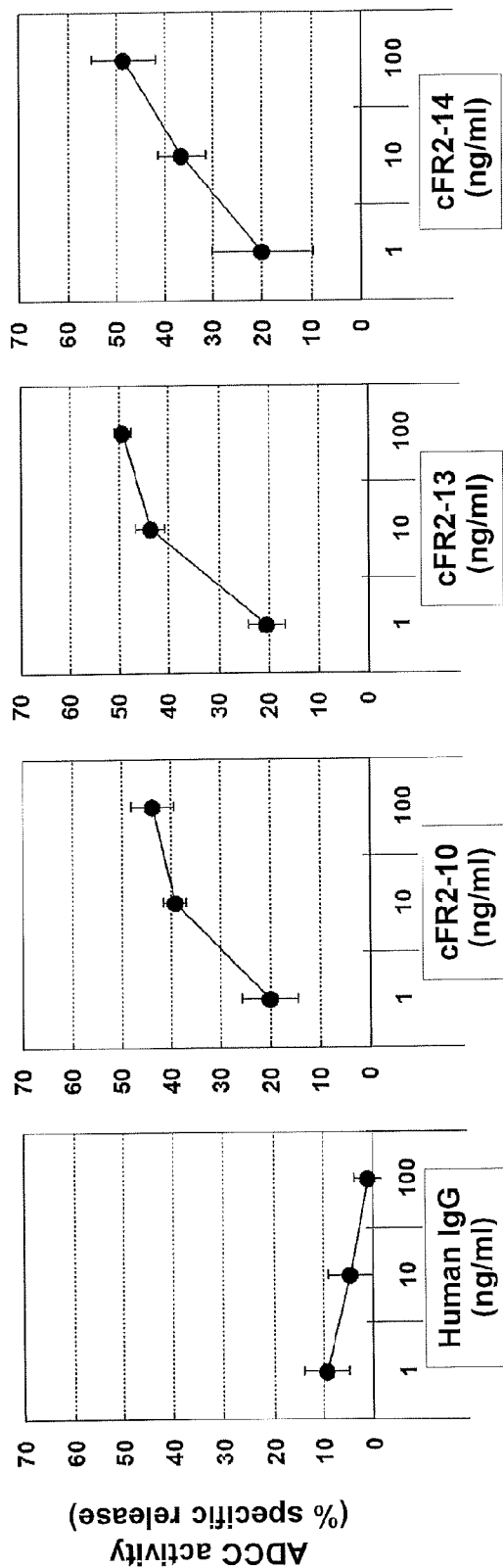


FIG. 8

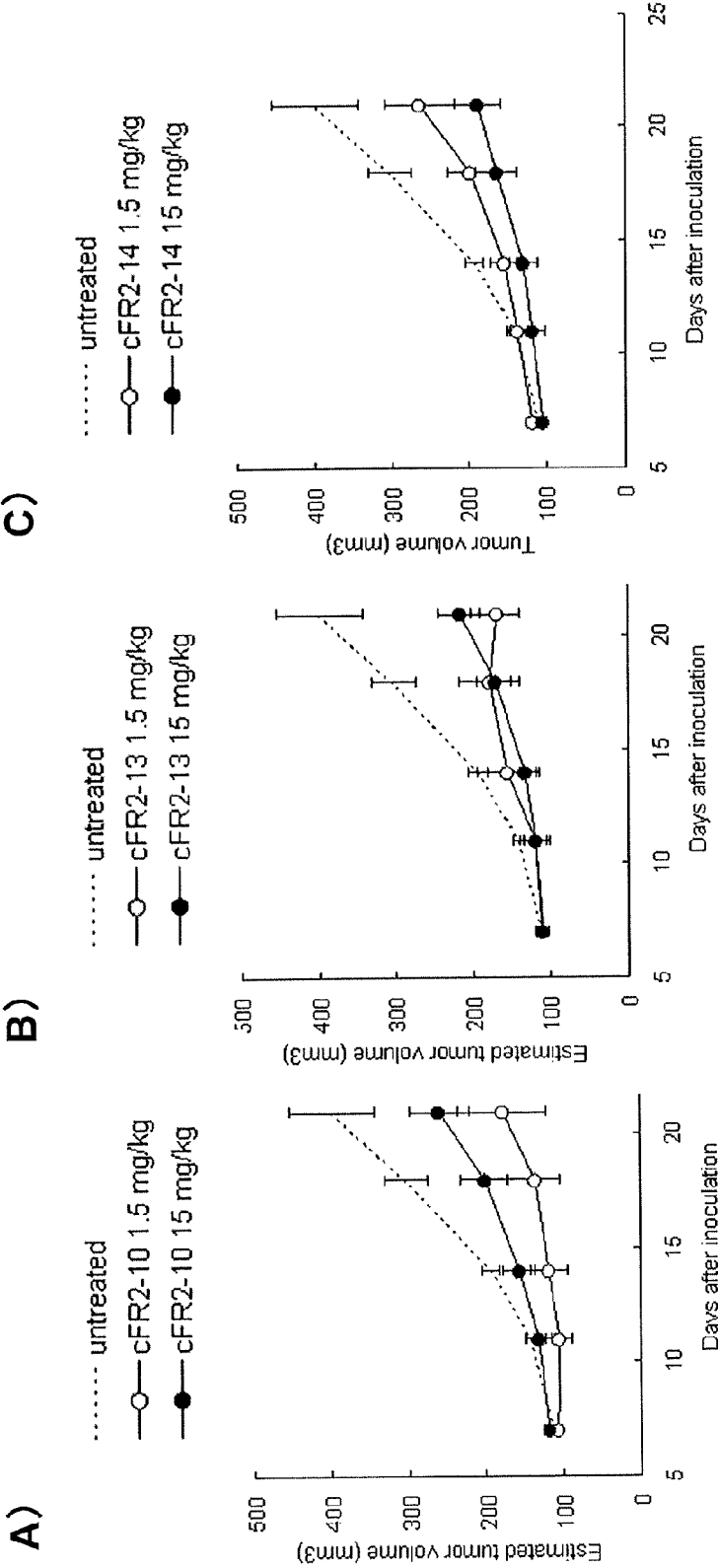


Figure 9

EVQLVESGGGLV
(SEQ ID NO: 1 of Sequence Listing)

Figure 10

DIQMTQSPSSLSA
(SEQ ID NO: 2 of Sequence Listing)

Figure 11

QVKLL
(SEQ ID NO: 3 of Sequence Listing)

Figure 12

DIQMTQSPASLSASLGE
(SEQ ID NO: 4 of Sequence Listing)

Figure 13

QVKLL
(SEQ ID NO: 5 of Sequence Listing)

Figure 14

DIQMTQSPASLSASLGE
(SEQ ID NO: 6 of Sequence Listing)

Figure 15

GAGTTACTTTTGAGAGCAGTTCCAGGAG
(SEQ ID NO: 7 of Sequence Listing)

Figure 16

GGTTCTCCCACTCAGTAATC
(SEQ ID NO: 8 of Sequence Listing)

Figure 17

CATATGATCAGTGTCTCTC
(SEQ ID NO: 9 of Sequence Listing)

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Figure 18

ATATGATCAGTGTCTCTCC

(SEQ ID NO: 10 of Sequence Listing)

Figure 19

gaggatgcagctgggtggagctctggggaggcctgggtgcagcctggaaggctctgaaactatcctgtgtagccctggall
cagattcaatgacttttggatgacctggatccgccaggctccagggaagggcctggagtggttgcatccattacttata
ciggatgataaaccttactatgcagcctctgtgaaggccgaatcactatctccagagataatgcgaagagcaccctatc
ctgcaaatgaacagctcagggtcaggacacggccacttattactgtlacaagagatgactacggaggatatagccctc
ctataatggatgcctgggtcaaggaacttcagtcactgtctcctca

Variable region (1-366)

(SEQ ID NO: 11 of Sequence Listing)

Figure 20

EVQLVESGGGLVQPGKSLKLSVASGFRFNDFWMTWIRQAPGKGLEWVASITYTGDNTYYAGSVKGRITISRDNAKSTLY
LQMNSLRSEDATYYCTRDDYGGYSPYYMDAWGQGTSTVSS

Variable region (1-122)

(SEQ ID NO: 12 of Sequence Listing)

Figure 21

caggtaagctgctgcagctcggggctgagctggtaaaacctgggtgcttcagtgaagtgtcccgcaagactcttggttt
taccttcagcactagctataatgagttggttgaagcaggctgctggaccgagttatgagtggaatggatggattatgctg
gagatgggtggtactaagtaatacagaagttcaaggccaaggccacactgacagtagacaaatctcttagcacagcatac
atggatctcagcagcctgacatctgaggacgctgcagctcattttgtgcaacggatggttatggggatgggttgctta
ctggggccaaggcactctggtcactgtctcttca

Variable region (1-354)

(SEQ ID NO: 13 of Sequence Listing)

Figure 22

QVKLLQSGAELVKPGASVKLSCKTSGFTFSTSYMSWLKQVPGPSIEWIGWIYAGDGGTKYNQKFKGKATLTVDKSSSTAY
MDLSSLTSEDAAVYFCATDGYGDWFAFWGQGTLYTVSS

Variable region (1-118)

(SEQ ID NO: 14 of Sequence Listing)

Figure 23

caggtaagctgctgcagctcggggctgagctggtaaaacctgggtgcttcagtgaagtgtcccgcaagactcttggttt
tacatlcagcactagttataatgagttggttgaagcaggctgctggaccgagttatgagtggaatggatggattatgctg
gagatgggtggtactaagtaatacagaagttcaaggccaaggccacactgacagtagacaaatctcttagcacagcatac
atggatctcagcagcctgacatctgaggacgctgcagctcattttgtgcaacggatggttatggggatgggttactta
ctggggccaaggcactctggtcactgtctcttca

Variable region (1-354)

SEQ ID NO: 15 of Sequence Listing

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Figure 24

QVKLLQSGAELVKPGASVKLSCKTSGFTFSTSYMSWLKQVPGPSTEWIGWIYAGDGGTKYNQKFKGKATLTVDKFSSTAY
MDLSSLTSEDAAVYFCATDGYGDWFTYWGQCTLVTYSS

Variable region (1-118)

(SEQ ID NO: 16 of Sequence Listing)

Figure 25

TTCATGAGGCACACGACTGAGGCACCTCC
(SEQ ID NO: 17 of Sequence Listing)

Figure 26

TCCAGTTGCTAACTGTTCCG
(SEQ ID NO: 18 of Sequence Listing)

Figure 27

CAGTGGTATCAACGCAGAG
(SEQ ID NO: 19 of Sequence Listing)

Figure 28

gacatccagatgacccagtc tccatcttccctgtctgcatttctgggagacagagtcactattacttgccgggcaagtca
agacattggaaattatttaagatgggtccagcagaaacccggggaatctccctaggcttatgatttatggcgcaaccaact
tggcaaatggggctcccatcaaggctcagtggcagtaggtctgggtcagattattctctgaccatcaacaacttggagct
gaagacatggctatttattactgtctgaagcataatgagtaiccatcaccgttcggctcaggacgaagttggaaataaa
acgggct

Variable region (1-327)

(SEQ ID NO: 20 of Sequence Listing)

Figure 29

DIQMTQSPSSLSAFLGDRVITTCRASQDIGNYLRFQKPKGKSPRLMIYGATNLANGVPSRFSGRSGSDYSLTINNLES
EDMAIYYCLKHNEYPTFGSGTKLEIKRA

Variable region (1-109)

(SEQ ID NO: 21 of Sequence Listing)

Figure 30

TACGTGCTGTCTTTGCTGTCCTGATCAG
(SEQ ID NO: 22 of Sequence Listing)

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Figure 31

gacatccagatgacacagctccagcttcccgtctgcatctctgggagaaactgtcaccatcgaaatgtcgagcaagtga
ggacatttacagtaatttagcgtggatcagcagaaaccagggaactctcctcagctcctgaltatgatgcaaatatct
tggcagatggggctcccatcacggttcagtggcagtggtcggcacacagtatctctaaagataaacagcctgcaatct
gaagatgtcgcaagtatttctgtcaacagtataacaattatcctccgttcaggttggagtgggaccaagctggaact
gaaacgggct

Variable region (1-330)

(SEQ ID NO: 23 of Sequence Listing)

Figure 32

DIQMTQSPASLSASLGETVTIECRASEDIYSNLAWYQQKPGNSPQLLIYDANILADGVPSRFSGSGSGTQYSLKINSLQS
EDVASYFCQQYNNYPPTFGVGTKLELKRA

Variable region (1-110)

(SEQ ID NO: 24 of Sequence Listing)

Figure 33

gacatccagatgacacagctccagcttcccgtctgcatctctgggagaaactgtcaccatcgaaatgtcgagcaagtga
ggacataacagtaatttagcgtggatcagcagaaaccagggaactctcctcagctcctgaltatgatgcaaatatcc
tggcagatggggctcccatcacggttcagtggcagtggtcggcacacagtatctctaaagataaacagcctgcaatct
gaagatgtcgcaagtatttctgtcaacagtataacaattatcctccgttcaggttggagtgggaccaagctggaact
gaaacgggct

Variable region (1-330)

(SEQ ID NO: 25 of Sequence Listing)

Figure 34

DIQMTQSPASLSASLGETVTIECRASEDIYSNLAWYQQKPGNSPQLLIYDANILADGVPSRFSGSGSGTQYSLKINSLQS
EDVASYFCQQYNNYPPTFGAGTKLELKRA

Variable region (1-110)

(SEQ ID NO: 26 of Sequence Listing)

Figure 35

gcctccggactctagagccaccATGGTGCTGCAGACCCAGGTGTTTCATCTCCCTGCTGCTGTGGATCTCCGGCGCGTACG
GCGATATCGTGATGATTAAACGTACGGTGGCGCGCCCTCCGTGTTTCATCTTCCCCCTCCGACGAGCAGCTGAAGTCC
GGCACCGCCTCCGTGGTGTGCTGCTGAATAACTTACCCAGAGAGGCCAAGGTGCAGTGAAGGTGGACAACGCCCT
GCAGTCCGGGAACCTCCAGGAGAGCCTGACCGAGCAGGACAGCAAGGACAGCACCTACAGCCTGAGCAGCACCCGTACCC
TGAGCAAAGCCGACTACGAGAAGCACAAGGTGTACGCTGCGAGGTGACCCACCAGGGCCTGAGCTCCCCCGTCACCAAG
AGCTTCAACAGGGGGGAGTGTAGggggccgctttaaacgggggaggcta

(SEQ ID NO: 27 of Sequence Listing)

Figure 36

TATACCGTCGACCTCTAGCTAGAGCTTGGC

(SEQ ID NO: 28 of Sequence Listing)

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Figure 37

GCTATGGCAGGGCCTGCCGCCCCGACGTTG
(SEQ ID NO: 29 of Sequence Listing)

Figure 38

gcctccggactctagagccaccATGAAACACCTGTGGTTCTTCTCCTGCTGGTGGCAGCTCCCAGATGGGTGCTGAGCC
AGGTGCAATTGTGCAGGCGGTAGCTCAGCCTCCACCAAGGGCCCAAGCGTCTTCCCCCTGGCACCCCTCCTCAAGAGCA
CCTCTGGCGGCACAGCCGCTGGGTGCTGGTCAAGGACTACTTCCCGAACCCTGACCGTGAGCTGGAACCTCAGGC
GCCCCGACCAGCGCGGTGCACACCTTCCCGCTGTCTGCACTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGT
GCCCCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCAGCAACACCAAGGTGGACAAGAGAG
TTGAGCCCAATCTTGTGACAAAATCACAATGCCACCCCTGCCAGCACCTGAACTCCTGGGGGACCCCTCAGTCTTC
CTCTTCCCCCAAAACCAAGGACCCCTCATGATCTCCCGGACCCCTGAGGTACATGCGTGGTGGTGAGCTGAGCCA
CGAAGACCCCTGAGGTCAAGTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCCCGGGAGGAGC
AGTACAACAGCAGCTACCGGTGGTCAAGCTCCTCACCCTCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGC
AAGGTCTCCAACAAAGCCCTCCAGCCCCATCGAGAAAACCATCTCAAAGCCAAAGGCCAGCCCCGGGAACCAAGGT
GTACACCCTGCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTGAGCTGACCTGCCTGGTCAAAGGCTTCTATCCCA
GCGACATCGCCGTGGAGTGGGAGAGCAATGGCCAGCCCGAGAACAACTACAAGACCACCCCTCCCGTCTGGACTCCGAC
GGCTCCTTCTCTCTACAGCAAGTCAACCGTGGACAAGAGCAGGTGGCAGCAGGGCAACGCTTCTCATGCTCCGTGAT
GCATGAGGCTCTGCACAACCACTACACCCAGAAGAGCCTCTCCTGTCTCCCGCAAAATGAgatatacgggcccgtttaaa
cgggggaggcta
(SEQ ID NO: 30 of Sequence Listing)

Figure 39

atggtgctgcagaccagggtgttcatctccttgcctgctggtggaatctccggcgctacggcgacatccagatgaccagtc
tccatcttcccgtctgcatcttctgggagacagagtcactatcttccgggcaagtcagacatggaaatatttaa
gatggttccagcagaaaccggggaatctcctaggcttatgatttatggtgcaaccaacttggcaaatgggttcccatca
agggtcagtgccagtaggtcgggtcagattatctctgaccatcaacaacttggagtcgaagacatggctattatta
ctgtctgaagcatalaagatattccattcagcttcggctcaggacgaagtggaaaiaaacgggctgtggccgccccct
ccgtgttcatcttcccccttccgacgagcagctgaagtcgggcacccgctccgtggtgtgctgtcgaiaaacttctac
cccagagaggccaaggtgcagtggaaggtggacaacgcccgcagtcgggaactcccaggagagcgtgaccgagcagga
cagcaaggacagcaccacagcctgagcagcaccctgacccagcagaagccgactacgagaagcacaaggtglacgct
ggcagggtgacccaccaggccctgagctccccgctaccaagagcttcaacaggggggagtggt
Signal sequence (1-60), Variable region (61-387), Constant region(389-702)
(SEQ ID NO: 31 of Sequence Listing)

Figure 40

MVLQTQVFI SLLLWISGAYGDIQMTQSPSSLSAFLGDRVITTCRASQDIGNYLRFQKPKSPRLMIYGATNLANGVPS
RFGSRSGSDYSLTINNLESEDMAIYYCLKHNEYFPFTFGSGTKLEIKRAVAAPSVFIFPPSDEQLKSGTASVVCLLNPFY
PREAKVQWKVDNALQSGNSQESVTEQDSKDSSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC
Signal sequence (1-20), Variable region (21-129), Constant region(130-234)
(SEQ ID NO: 32 of Sequence Listing)

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Figure 41

ATCTCCGGCGCGTACGGCGACATCCAGATGACCCAGTCTCCATCTTCC
(SEQ ID NO: 33 of Sequence Listing)

Figure 42

GGAGGGGGCGGCCACAGCCCGTTTTATTTCCAACCTTCGTCCCTG
(SEQ ID NO: 34 of Sequence Listing)

Figure 43

atgaaacacctgtgggttcttccctcgtcgtggcagctcccagatgggtgctgagcaggtgcagctggaggagctgg
gggaggccctggcagccctggaaggctctcigaacataccctgtgtagccctcaggatcagattcaatgacttttggatga
ccctggatccgccaggctccagggaagggcctggagtggttgcatccattacttatactggtgataaacacttactatgca
ggctctcgtgaagggccgaatcactatctccagagataatgcgaagagcaccctataccctgcaaatgaacagctcaggctc
tgaggacacggccacttattactgtacaagagatgactacggaggaatagccctactataatggatgcctggggcgaag
gaacttcagtcactgtcagctcagcctccaccaagggcccaagcgtcttcccttgccacccctcctccaagagcaccctt
ggcggcacagccgcccctggcctggcgaaggacttacttcccgaaaccgtgaccgtgagctgggaactcaggcggcct
gaccagcggcgtgcacaccttcccgctgctcctgcagctcctcaggactctactcctcagcagcgtggtgaccgtgccc
ccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaaacaccaaggtggacaagagagttag
cccaaatcttctgacaaaaactcacacatgcccaccttcccagcaccctgaactcctggggggaccctcagcttctcctt
ccccccaaaacccaaggacacctcatgatctcccgacccttgaggcacaatgctggtggaggacgtgagccacgaag
accttgaggctcaagtcaacttggtacgtggagggcgtggaggtgcataatgccaagacaaagcccgggaggagcagtac
aacagcagctaccgggtggtcagcgtctcaccgtctcgcaccaggactggctgaatggcaaggagtaacatgcaagg
ctccaaacaaagccctcccagccccaatcagaaaaacatactccaaagccaaaggccagcccccgggaaccacaggtgtaca
ccctgcccccaatccgggaggagatgaccaagaaccaggtcagcctgacctgcttggcgaaggcttctatcccagcgac
atcggcgtggagtgggagagcaatggccagcccagagaacaatacaagaccacccctcccgtgctggactccgacggctc
cttcttctctacagcaagctcaccgtggacaagagcaggtggcagcagggaacgtcttctcatgctccgtgatgcatg
aggctcgcacaaccactacaccagaagagccttctccctgctcctccggcaaa
Signal sequence (1-57), Variable region (58-423), Constant region(424-1413)
(SEQ ID NO: 35 of Sequence Listing)

Figure 44

MKHLWFFLLVAAPRWVLSEVQLVESGGGLVQPGKSLKSLSCVASGFRFNDFWMTWIRQAPGKGLEWVASITYTGDNTYYA
GSVKGRITISRDNASTLYLQMNLSRSEDATYYCTRDDYGGYSPYYMDAWGQGTSTVTVSSASTKGPSVFPLAPSSKSTS
GGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKVKDRVE
PKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVSCSYMHEALHNHYTQKSLSLSPGK
Signal sequence (1-19), Variable region (20-141), Constant region(142-471)
(SEQ ID NO: 36 of Sequence Listing)

Figure 45

CCAGATGGGTGCTGAGCGAGGTGCAGCTGGTGGAGTCTGGGGGAGGC
(SEQ ID NO: 37 of Sequence Listing)

Figure 46

CTTGGTGCAGGCTGAGCTGACAGTGAAGTTCCTTGACCCAGGC
(SEQ ID NO: 38 of Sequence Listing)

Figure 47

atggtgctgcagaccagggtgttcattccctgctgctgtggatctccggcgcgtacggcgacatccagatgacacagtc
tccagcttccctgctgcatctctgggagaaactgtcaccatcgaaatgtcgagcaagtgaggacatttacagtaatttag
cgtggatcagcagaaaccagggaactctccctcagctcctgattatgatgcaaatatcttggcagatggggccccatca
cggttcagtggcagtggtgttgccacacaglattctctaaagataaacagcctgcaatctgaagatgtcgcaagttattt
ctgtcaacagtatatacaattatctccgttcagtttggagttgggaccaagctggaactgaaacgggctgtggccgcc
cctccgtgttcatttccccccctccgacgagcagctgaagtcggcaccgcctccgtggtgtgcttgcctgctgaataacttc
taccagagaggccaaggtgcagtggaagtggaacaacgcccgcagtcgggaactcccaggagagcgtgaccgagca
ggacagcaaggacagcaccctacagcctgagcagcaccctgacctgagcaagccgactacgagaagcacaaggtgtacg
cctgagagtgaccaccaggccctgagctccccctcaccaagagcttcaacaggggggagtggt
Signal sequence (1-60), Variable region (61-390), Constant region (391-705)
(SEQ ID NO: 39 of Sequence Listing)

Figure 48

MVLQTQVFISLLIWISGAYGDIQMTQSPASLSASLGCTVTIECRASEDIYSNLAWYQQKPGNSPQLLIYDANILADGVPS
RFGSGSGTQYSLKINSLSQEDVASYFCQQYNNYPPFTFGVGTKLELKRAVAAPSVFI FPPSDEQLKSGTASVVCLLNNF
YPREAKVQWKVDNALQSGNSQESVTEQDSKDSYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
Signal sequence (1-20), Variable region (21-130), Constant region (131-235)
(SEQ ID NO: 40 of Sequence Listing)

Figure 49

ATCTCCGGCGCGTACGGCGACATCCAGATGACACAGTCTCCAGCTTCC
(SEQ ID NO: 41 of Sequence Listing)

Figure 50

GGAGGGGGCGGCCACAGCCCGTTTCAGTTCAGCTTGGTCCCAAC
(SEQ ID NO: 42 of Sequence Listing)

Figure 51

atgaaacaccigtggttcttctccctgcctgggtggcagctcccagatgggtgctlgagccagggttaagctgcctgcagctcgg
 ggcctgagctggtaaaacctgggtgcttcagtgaaagtgtccctgcaagacttctggttttaccttcagcactagctataatga
 gtgtgttgaagcaggctgctggaccgagatattgagtggaattggaaggatttattgctggagatgggtggtaactaagtataat
 cagaagttcaagggaaggccacacatgacagtagacaaatcttctagcacagcatataggatctcagcagcctgacatc
 tgaggacgctgcagctcatttttctgcaacggatgggttatggggattgggttgccttacitggggccaaggcacctcgttca
 ctgtcagctcagcctccaccaaggggccaagcgtcttccccctggcaccctcttccaagagcaccctcggcggcacagcc
 gccctgggctgcttggcaaggactacttccccgaaccctgaccgtgagctggaaactcaggcgcccctgaccagcggt
 gcacaccttccccctgtcttcagctcctcaggactctactccccctcagcagcgtgggtgaccgtgcccctcagcagcttgg
 gcaccagacctacatctgcaacgtgaatcacaagccagcaaacccaagggtggacaagagagttagccccaaatcttgt
 gacaaaactcacacatgcccacctgcccagcaccatgaactcctggggggaccctcagctctctcttccccccaaaacc
 caaggacacctcattgactcctcggacccttgaggtcacatgctgtgtgtggagctgagccacgaagacctgagggtca
 agttcaactggctacgtggacggcgtggaggtgcaataatgccaaagcaaaagccccgggaggagcagttacaacagcagctac
 cgggtgtgtcagctctcaccgtctcaccaggaatggctgaatggcaaggagtagaagtgcaaggcttccaacaaagc
 ctctccagcccccatcgagaaaacctctccaaagccaaaggccagccccgggaaccacagggtgtacacctgcccccat
 cccgggaggagatgaccaagaaccaggtcagcctgacctgcttgggtcaaaggcttctatcccagcgacatcgccgtggag
 tgggagagcaatggccagcccgagaacaactacaagaccacccctccgtgctggactccgacggctcctcttctctta
 cagcaagctcaccgtggacaagagcaggtggcagcagggaacgtctctcatgctccgtgattgcatgaggctctgcaca
 accactacaccagaagacctctctctgtctccccggcaaa

Signal sequence (1-57), Variable region (58-411), Constant region (412-1401)

(SEQ ID NO: 43 of Sequence Listing)

Figure 52

MKHLWFFLLVAAPRWVLSQVKLLQSGAELVKPGASVKLSCKTSGFTFSTSYMSWLKQVPGPSIEWIGWIYAGDGGTKYN
 QKFKGKATLTVDKSSSTAYMDLSSLTSEDAAVYFCATDGYGDWFAYWGQGLVTVSSASTKGPSVFPPLAPSSKSTSGGTA
 ALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSVTVTPSSSLGTQTYICNVNHKPSNTKVDKRVKPKSC
 DKHTHTCPPCPAPELGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
 RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
 WESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVMHLEAHNHYTQKSLSLSPGK

Signal sequence (1-19), Variable region (20-137), Constant region (138-467)

(SEQ ID NO: 44 of Sequence Listing)

Figure 53

CCAGATGGGTGCTGAGCCAGGTTAAGCTGCTGCAGTCTGGGGCTGAG

(SEQ ID NO: 45 of Sequence Listing)

Figure 54

CTTGGTGGAGGCTGAGCTGACAGTGACCAGAGTGCCTTGCCCCAG

(SEQ ID NO: 46 of Sequence Listing)

Figure 55

atgggtgctgcagacccaggtgttcattccctgcgtgttggaatccggcgcgacggcgacatccagatgacacagtc
tccagcttccctgtctgcattctctgggagaaactgtcaccatcgaatgtcgagcaagtgaggacatatacaglaatttag
cgtggatcagcagaaaccaggaactctctcagelccigtattatgatgcaaatatccaggagatgggtcccatca
cggttcagtgccagtggtctggcacacagtatctctaaagataaacagccgtcaatctgaagatgtcgcaagttatll
ctgtcaacagtalaacaattatctccgttcacgtttggagctgggaccaagctggaactgaaacgggctgtggccgccc
cctccgtgttcattctccccctccgacgagcagctgaagtcgggcaccgctccgtggtgtgctgctgaataacttc
taccacagagagccaaggtgcagtggaagtggaacaacgcccgtcagctccgggaaccccaggagagcgtgaccgagca
ggacagcaaggacagcacctacagcctgagcagcaccttgacctgagcaaacggactacgagaagcacaaggtgtacg
cctgcgaggtgaccaccaggccctgagctccccctcaccaagagcttcaacaggggggagtggt

Signal sequence (1-60), Variable region (61-390), Constant region (391-705)

(SEQ ID NO: 47 of Sequence Listing)

Figure 56

MVLQTQVFISLLWLISGAYGDIQMTQSPASLSASLGTVTIECRASEDIYSNLAWYQQKPGNSPQLLIYDANILADGVPS
RFSGSGSGTQYSLKINSLQSEDVASYFCQQYNNYPPFTFGAGTKLELKRAVAAPSVFIFFPSDEQLKSGTASVYVCLLNNF
YPREAKVQWKVDNALQSGNSQESVTEQDSKDSYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNREGC

Signal sequence (1-20), Variable region (21-130), Constant region (131-235)

(SEQ ID NO: 48 of Sequence Listing)

Figure 57

GGAGGGGGCGGCCACAGCCCGTTTCAGTTCAGCTTGGTCCCAGC

(SEQ ID NO: 49 of Sequence Listing)

Figure 58

algaaacaccctgtggttcttcttcttctgttggtggcagctcccagatgggtgctlgagccaggttaagctgctgcagctctgg
ggctgagctggtaaaacctgggtgcttcagtgaaagtgtcttgcgaagactcttggtttlacattcagcactagttatatga
gttggtlgaagcaggctgcttggaccgagtactagtggaatggatggatitattgctggagatgggtggtactaagtaaa
cagaagltcaagggaaggccacactgacagtagacaaaatttctagcacagcatacattggaatctcagcagccctgacatt
tgaggacgctgcagctctatttctgtgcaacggatgggttatggggatgggtttacttactcggggccaaggcactctggtca
ctgtcagctcagcccccacaaaggggcccaaggcttccccctggcaccctctcccaagagcaccctcggcgccacagcc
gccccctgggtgcttggltcaaggacttactccccgaaccctgaccgtgagctggaactcaggcgccctgaccagcgccgt
gcacaccttccccctgctcttgcagctctcaggacttctactccctcagcagcgtggtgaccgtgccctccagcagcttgg
gcaccagacctacatctgcaacgtlgaatcacaaagccagcaacaccaaggtggacaagagagttagcccaaatcttgt
gacaaaactcacacatgcccaccttcccagcaccatgaactctcggggggacctcagcttctcttccccccaaaacc
caaggacacctcattgacttcccggaaccttgggtacatgctgtggttgggtggacgtgagccaggaagaccttgggtca
agttaactggttactggtgacgggttggaggtgcataatgccaaagacaaagccccgggaggagcagtaaacagcacgtac
cgggtggtcagcgtctctcaccgtcttgcaccaggactggctlgaatggcaaggagtaaatgcaaggtctccaacaagc
cttcccagccccatcgagaaaaccttccaaagccaaaggccagccccgggaaccacaggtgtacaccttcccccat
ccccgggaggagatgaccaagaaccaggctagcctgacctgcttggltcaaaagcttctatcccagcgacatcgccgtggag
tgggagagcaatggccagcccgagaaacactacaagaccaccttcccgctgctggactccgacggctcttcttctctta
cagcaagctcaccgtggacaagagcaggttggcagcagggaacgtcttctcatgctccgigtatgcatgaggtcttgaca
accactacaccagaaagagccttctccctgtctcccggtcaaa

Signal sequence (1-57), Variable region (58-411), Constant region (412-1401)
(SEQ ID NO: 50 of Sequence Listing)

Figure 59

MKHLWFFLLVAAPRWVLSQVKLLQSGAELVKPGASVKLSCKTSGFTFSTSYMSWLKQVPGPSTEWIGWIYAGDGGTKYN
 QKFKGKATLTVDKFSSTAYMDLSSLTSEDAAYVFCATDGYGDWFTYWGGQGLTVTVSSASTKGPSVFLAPSSKSTSGGTA
 ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVPEKSC
 DKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
 RVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
 WESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

Signal sequence (1-19), Variable region (20-137), Constant region(138-467)
(SEQ ID NO: 51 of Sequence Listing)

Figure 60

DFWMT

(SEQ ID NO: 52 of Sequence Listing)

Figure 61

SITYTGDNTYYAGSVKG

(SEQ ID NO: 53 of Sequence Listing)

Figure 62

DDYGGYSPYYMDA

(SEQ ID NO: 54 of Sequence Listing)

Figure 63

TSYMS
(SEQ ID NO: 55 of Sequence Listing)

Figure 64

WIYAGDGGTKYNQKFKG
(SEQ ID NO: 56 of Sequence Listing)

Figure 65

DGYGDWFAY
(SEQ ID NO: 57 of Sequence Listing)

Figure 66

TSYMS
(SEQ ID NO: 58 of Sequence Listing)

Figure 67

WIYAGDGGTKYNQKFKG
(SEQ ID NO: 59 of Sequence Listing)

Figure 68

DGYGDWFTY
(SEQ ID NO: 60 of Sequence Listing)

Figure 69

RASQDIGNYLR
(SEQ ID NO: 61 of Sequence Listing)

Figure 70

GATNLAN
(SEQ ID NO: 62 of Sequence Listing)

Figure 71

LKHNEYPT
(SEQ ID NO: 63 of Sequence Listing)

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Figure 72

RASEDIYSNLA
(SEQ ID NO: 64 of Sequence Listing)

Figure 73

DANILAD
(SEQ ID NO: 65 of Sequence Listing)

Figure 74

QQYNNYPPFT
(SEQ ID NO: 66 of Sequence Listing)

Figure 75

RASEDIYSNLA
(SEQ ID NO: 67 of Sequence Listing)

Figure 76

DANILAD
(SEQ ID NO: 68 of Sequence Listing)

Figure 77

QQYNNYPPFT
(SEQ ID NO: 69 of Sequence Listing)

Figure 78

MVSWGRFICLVVVTMATLSLARPSFSLVEDTTLEPEEPPTKYQISQPEVYVAAPGESLEVRCCLKDAAVISWTKDGVHLG
PNNRTVLIGEYLQIKGATPRDSGLYACTASRTVDSETWYFMVNVTDAISSGDDDDTDGAEDFVSENSNNKRAPYWTNTE
KMEKRLHAVPAANTVKFRCPAGGNPMPIMRWLKNKEFKQEHRIGGYKVRNQHWSLIMESVVP SDKGNYTCVVENEYGS I
NHTYHLDVVERSHPRI LQAGLPANASTVVGDDVEFVCKVYSDAQPHIQWIKHVEKNGSKYGPDGLPYLKV LKHSGINSS
NAEVLALFNVTEADAGEYICKVSNYIGQANQSAWLT VLPKQQAPGREKEITASPDYLEIAIYCI GVFLIACMVVT VILCR
MKNTTKKPDFSSQPAVHKLTKRIPLRRQVT VSAESSSSMNSNTPLVRITTRLSSSTADTPMLAGVSEYELPEDPKWEFPRD
KLTLCGPLGEGCFQVVM AEAVGIDKDKPKEAVTVAVKMLKDDATEKDLSDLVSEMEMMKMIGKHKNI INLLGACTQDGP
LYVIVEYASKGNLREYLRARRPPGMEYSYDINRVPEEQMTFKDLVSCTYQLARGMEYLASQKCIHRDLAARNVLVTENNV
MKIADFG LARDINNIDYKKTTNGRLPVKWM APEALFDRVYTHQSDVWSFGVLMWEIFTLGGSPYPGIPVEELFKLLKEG
HRMDKPANCTNELYMMMRDCWHAVPSQRPTFKQLVEDLDRILTLTTNEEYLDLSQPLEQYSPSPDTRSSCSSGDDSVFS
PDPMPYEPCLPQYPHINGSVKT
(SEQ ID NO: 70 of Sequence Listing)

Figure 79

MVSWGRFICLVVVTMATLSLARPSFSLVEDTTLEPEEPPTKYQISQPEVYVAAPGESLEVRCLLKDAAVISWTKDGVHLG
 PNNRTVLIGEYLQIKGATPRDSGLYACTASRTVDSETWYFMVNVTDAISSGDEDDTDCAEDFVSENSNNKRAPYWTNTE
 KMEKRLHAVPAANTVKFRCPAGGNPMTNRWLKNGKEFKQEHRIGGYKVRNQHWSLIMESVVP SDKGNYTCVVENEYGS
 NHTYHLDVVERSHPRPILQAGLPANASTVVGDDVEFVCKVYSDAQPHIQWIKHVEKNGSKYGPDLPLYLKVLAAGVNTT
 DKEIEVLYIRNVT FEDAGEYTCLAGNSIGISFHSAWLTVLPAPGREKEITASPDYLEIAIYCIGVFLIACMVVTVILCRM
 KNTTKKPDFSSQPAVHKLTKRIPLRRQVTSAESSSSMNSNTPLVRITTRLSSSTADTPMLAGVSEYELPEDPKWEFPRDK
 LTLGKPLGEGCFQVYMAEAVGIDKDKPKAEAVTVAVKMLKDDATEKDLSDLVSEMEMMKMIGKHKNIIINLLGACTQDGPL
 YVIVFYASKGNLREYLRRRPPGMEYSYDINRVPEEQMTFKDLVSCITYQLARGMEYLASQKCIHRDLAARNVLVTENNVM
 KIADFLGARDINNIDYYKKTNGRLPVKWMAPALFDRVYTHQSDVWSFGVLMWEJFTLGGSPYPGIPVEELFKLLKEGH
 RMDKPANCTNELYMMMRDCWHA VPSQRPTFKQLVEDLDRI LTLTNEEYLDLSQPLEQYSPSPDTRSSCSDSDSVFSP
 DPMPEPCLPQYPHINGSVKT

(SEQ ID NO: 71 of Sequence Listing)

Figure 80

atgggtgcgcagaccagggtgttcacatccctgtcgtcgtggatcccgccgctacggcgacatccagatgaccagag
 cccagcagcctgagcgcagcgtggcgacagagtaccatcacctgtcggccagcaggacatctacagaaccitgg
 ccttggtatcagcagaagcccgcaagagccccagctgtgatctacgacccaacatcctggccgacggcgtgccagc
 agatcagcggcagcggciccgccaccgactacacctgacctcctcagcctgcagcccgaggacttcgccacctacta
 ctgccagcagtaacaactacccccallcacctcctcgccaggccaccaaggtggaaatcaagctacggtggccccc
 cctccgtgttcacatcccccctccgacgagcagctgaagtcggccaccgcccccggtgtgtcctgtgaataacttc
 taccacagagaggccaaggtgcagtggaaggtggacaacgccctgcagtcgggaactccagagagcgtgaccgagca
 ggacagcaaggacagcacctacagcctgagcagcaccctgacctgagcaagccgactacgagaagcacaaggtgtacg
 cctgcgaggtagccaccaggcctgagctccccgtcaccgaagagctcaacaggggggagtg

Signal sequence (1-60), Variable region (61-390), Constant region (391-705)

(SEQ ID NO: 72 of Sequence Listing)

Figure 81

MVLQTQVFISLLWISGAYGDIQMTQSPSSLSASVGDRTVITCRASEDIYSNLAWYQQKPKSPQLLYDANILADGVPS
 RFSGSGSGTDYTLTISSLQPEDFATYYCQQYNNYPPFTFGQGTKVEIKRTVAAPS VFI FPPSDEQLKSGTASVVCLLNFF
 YPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSLSSITLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Signal sequence (1-20), Variable region (21-130), Constant region (131-235)

(SEQ ID NO: 73 of Sequence Listing)

Figure 82

atgaaacaccgtgtggtctctccctgctgggtggcagctcccagatgggtgctgagccaggctgcagctggtgcagctcgtg
cgccgaagtgaagaacciggggttagcgtgaagggtgcttgcaggccagcggttcaccttcagcaccagctataatga
gctgggtccgccaggctccaggccaggac tggatggatgggtggatctatgcccggcgacggcgccaccaagtacaac
cagaaatcaagggcagagtgaacctgacctggacaagagcaccagcaccgctacatggaaatgagcagctgcggag
cgaggacaccgctgtactactgcccaccgacggctacggcgac tgggtcaca tactggggccagggcaccttggga
ccgtgagctcagctccaccaagggcccaagcgtctccccctggcaccctccccaagagcaccctcggcgccacagcc
gcccctgggtgctgctgggtcaaggactactccccgaaccctgacctgagctggaaatcaggcgccctgaccagcggt
gcacacctccccctgctcctgagctcctcaggactctactccctcagcagcgtggtgacctgcccctcagcagcttgg
gcaccagaccacatctgcaacgtgaatcacaagccagcaacaccaaggctggacaagagagttagaccctcttgt
gacaaaatcacacatgcccacctgcccagcactgaactcctgggggggacctcagctctcctctccccccaaaacc
caaggacacctcatgactccccggaccttgaggctacatgcgtggtgggtggacgtgagccacgaagacctgaggctca
agtcaactgggtacgtggacggctggaggtgcaataatgccaagacaaagccccgggaggagcaglacacagcagctac
cggtggtcagctcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgaaggcttccaacaaagc
ctccccagccccatcgagaaaacca tctccaaagccaaaggccagccccgggaaccacagggtgacacctgccccat
ccccgggaggagatgaccaagaaccaggctcagctgacctgcttggctcaaaggcttctatcccagcgacatcgccgtggag
tgggagagcaatggccagcccgagaacaactacaagaccacctccccgtgctggactccgacggctcctctctcctcta
cagcaagctcaccgtggacaagagcaggtggcagcagggaacgtctctcctatgctccgtgatgcatgaggctcgcaca
accactacaccagaagagctctccctgtctccccggcaaa

Signal sequence (1-57), Variable region (58-411), Constant region (412-1401)

(SEQ ID NO: 74 of Sequence Listing)

Figure 83

MKHLWFFLLLVAA PRWVLSQVQLVQSGAEVKKPGASVKVSCKASGFTFSTSYMSWVRQAPGQGLEWMGWIYAGDGGTKYN
QKFKGRVTLTVDKSTSTAYMELSSLRSEDTAVYYCATDGYGDWFTYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTA
ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSC
DKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQVMHEALHNHYTQKSLSLSPGK

Signal sequence (1-19), Variable region (20-137), Constant region (138-467)

(SEQ ID NO: 75 of Sequence Listing)

Figure 84

atgaaacacctgtggttcttccctcctgctgggtggcagctcccagatgggtgctgagccaggctgcagctgggtgcagctcgg
 cgccgaagtgaagaaacctggggctagcgtgaagggtgcttgcgaaggccagcggcttcaccttcagcaccagctata tga
 gctgggtccgccaggctccaggccagggtggaatggatgggtggatctatgccggcgacggcgccaccaagtlacaac
 cagaaa tcaagggcagagt gacctgacctggcagacaagagcaccagcaccgctacatggaaactgagcagcttcgggag
 cgaggacaccgcccgtgtactactgcgccaccgacggctacggcgactgggttcacalactggggccagggtcaccctgggtga
 ccgtgagctcagctccaccaagggtcccaagcgtcttccccctggcaccctccccaagagcaccctcggcggcacagcc
 gccc tgggtgctctgggtcaaggactacttccccgaaccggtgacctgagctggaactcaggcgccc taccagcggcgt
 gcacaccttccccgctgtctctgcagctctcaggactctactcccc cagcagcgtgggtgacctgccc tccagcagcttgg
 gcacccagacctacatctgcaacgtgaatcacaagccagcaacaccaagggtggacaagagagt gaggccaaatcttgt
 gacaaaactcacacalgccacacctggccagcacc tgaactcctgggggggacctcagctcttctcttccccccaaaacc
 caaggacacctcatgacttccccggacccctgaggtcacatgcgtgggtgggtgagctgagccacgaagacctgaggtca
 agt tcaactgggtacgtggcggcgtggagggtgcalaatgccaaagacaaagccccgggaggagcagtlacaacagcagctac
 cgggtgggtcagcgtcttaccgtcttgcaccaggtcggctgaatggcaaggagtacaagtgcaaggcttccaacaaagc
 cctcccagcccccatcgagaaaaccatctccaaagccaaaggccagccccgggaaccacagggtgtacaccttgcacctat
 cccgggaggagatgaccaagaaccagggtcagcttgacctggtcgtcaaaggcttctatcccagcgacatcgccgtggag
 tgggagagcaatggccagcccagagaacaactacaagaccacccctcccgtgtgactccgacggctccttcttctctca
 cagcaagctcaccgtggacaagagcaggtggcagcagggtgcaacgtcttctcatgtcctgtgaltgcatgaggtcttgcaca
 accactacacccagaagagccttctccctgtctccccggcaaa

Signal sequence (1-57), Variable region (58-411), Constant region(412-1401)

(SEQ ID NO: 76 of Sequence Listing)

Figure 85

MKHLWFFLLVLAAPRWVLSQVQLVQSGAEVKKPGASVKVSKASGFTFTSYMSWVRQAPGQGLEWMGW IYAGDGGTKYN
 QKFKGRVTLTADKSTSTAYMELSSLRSEDTAVYYCATDGYGDWFTYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTA
 ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSC
 DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
 RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYITLPPSRREEMTKNQVSLTCLVKGFYPSDIAVE
 WESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFPSCSVMEALHNHYTQKSLSLSPGK

Signal sequence (1-19), Variable region (20-137), Constant region(138-467)

(SEQ ID NO: 77 of Sequence Listing)

Figure 86

atgaaacacctgtggttcttcttcttgcgtgggtggcagctcccagatgggtgcttgagccaggtgcagctgggtgcagtciggtg
 cgcgaagtgaagaaacctggggctagcgtgaagggtgcttgcgaaggccagcggcttcaccttcagcaccagctatataga
 gctgggtccggcaggctccagggccagcaccgaatggatgggtggatctatgccggcgacggcgccaccaagtacaac
 cagaaatcaagggcagagtgacctgaccgtggacaagagcaccagcaccgctacatggaaatgagcagcctgcggag
 cgaggacaccgctgtactactgcgccaccgacggctacggcgactgggttcacatctggggccagggcacccctgggtga
 ccgtgagctcagcttcaccaaggcccaagcgtctccccctggcaccctctccaagagcaccctcggcgccacagcc
 gccctgggtgcttgcctgggtcaaggactacttccccgaacccgtgaccgtgagctggaaatcaggcgccctgaccagcggcgt
 gcaacacctccccctgcttgcagctcctcaggactctactccccagcagcgtgggtgaccgtgccctccagcagcttgg
 gcaaccagacctacatctgcaacgtgaatcacaaagccagcaacaccaaggtggacaagagagttagcccaaatcttgt
 gacaaaactcacacatgccaccctgcccagcaccctgaactctcgggggaccctcagctcttctcttccccccaaaacc
 caaggacacctcatgactctccggacccctgaggctacatgctgggtgggtggacgtgagccacgaagacctgaggctca
 agtcaactgggtacgtggacggcgtggaggtgcataatgccaaagacaagcccgaggagcagtagaacagcacgtac
 cgggtggctcagctctcaccgtctcgcaccaggactggctgaatggcaaggagtacaagtgcgaagctctcaacaaagc
 ctccccagccccatcgagaaaaccaatctccaaagccaaaggccagcccggaaccacaggtgtacacctgcccccat
 cccgggaggagatgaccaagaaccaggctcagcctgacctgacctgggtcaaaaggctctctatccccagcgacatcgccgtggag
 tgggagagcaatggccagcccgagaacaactacaagaccacccctcccgtgctggactccgacggctctctcttctctta
 cagcaagctcaccgtggacaagagcaggtggcagcagggaacgctctctcatgctccgtgatgcatgaggctctgcaca
 accactacacccagaagagccctctccctgcttcccggaacaa

Signal sequence (1-57), Variable region (58-411), Constant region (412-1401)

(SEQ ID NO: 78 of Sequence Listing)

Figure 87

MKHLWFFLLLVAAPRWVLQVQLVQSGAEVKKPGASVKVSKASGFTFSTSYMSWVRQAPGPSTEWMGWIYAGDGGTKYN
 QKPKGRVTLTVDKSTSTAYMELSSLRSEDTAVYYCATDGYGDWFTYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTA
 ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVPEKSC
 DKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
 RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
 WESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVVFSCSYMHEALHNHYTQKSLSLSPGK

Signal sequence (1-19), Variable region (20-137), Constant region (138-467)

(SEQ ID NO: 79 of Sequence Listing)

Figure 88

atgaaacacctgtgggtcttctctctgtctgggtggcagctcccagatgggtgctgagccaggtgcagctgggtgcagctcgg
 cgccgaagtgaaagaaacctggggctagcgtgaagggtgcttgcgaaggccagcggttcaccttcagcaccagctataatga
 gctgggtccgcccaggctccaggccccagcatcgaaaggatgggtggatctatgcccggcgacggcgccaccaagtiacaac
 cagaaatcaagggcagagtgaacctgacctgggacaagagcaccagcaccgccacatggaaatgagcagccctcgaggag
 cgaggacaccgcccgtgtactactgcgccaccgacggctacggcgactgggtcgccctacggggccaggggcaccctgggtga
 ccgtgagctcagcctccaccaaggggcccaagcgtcttccccctggcaccctccctccaagagcaccctcggcggcacagcc
 gcccctgggtcgccctgggtcaaggactacttccccgaaccctgacctgagctggaaatcaggcgccctgaccagcggcgt
 gcacaccttccccctgctctgcagctcctcaggactctacttccctcagcagcgtgggtgacctgcccctccagcagcttgg
 gcaccagagctacatctgcaacgtgaatcacaaagccagcaacaccaaggtggacaagagagttgagcccaaatcttgt
 gacaaaactcacacatgccaccctgccagcaccctgaactcctggggggaccctcagctcttctcttcccccaaaacc
 caaggacaccctcatgatctcccggacccctgaggctacatgcgtgggtggagctgagccacgaagaccctgaggctca
 agtcaactgggtacgtggacggcgtggaggctgcaataatggcaagacaagccccgggaggagcagtaaacagcagctac
 cgggtgggtcagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggcttccaacaaagc
 cctcccagcccccatcgagaaaaccatctccaaagccaaaggccagcccggaaccacaggtgtacacctgcccccat
 cccgggaggagatgaccaagaaccaggctcagcctgacctgacctgggtcaaaggcttctatcccagcgacatcgccgtggag
 tgggagagcaatggccagcccgagaacaactacaagaccacccctcccgtgctggactccgacggctccttcttctctta
 cagcaagctcaccgtggacaagagcaggctggcagcaggggcaacgtcttctcatgctccgtgatgcatgaggctcgcaca
 accactacaccagaagagcctctccctgtctcccggcaaa

Signal sequence (1-57), Variable region (58-411), Constant region(412-1401)
 (SEQ ID NO: 80 of Sequence Listing)

Figure 89

MKHLWFFLLLVAAPRWVLSQVQLVQSGAEVKKPGASVKVSCKASGFTFSTSYMSWVRQAPGPSIEWMGWIYAGDGGTKYN
 QKPKGRVTLTVDKSTSTAYMELSSLRSEDTAVYYCATDGYGDWFAFWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTA
 ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKREVEPKSC
 DKHTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQNSTY
 RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
 WESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

Signal sequence (1-19), Variable region (20-137), Constant region (138-467)
 (SEQ ID NO: 81 of Sequence Listing)

Figure 90

atgaaacacctgtgggtcttccctccigctgggtggcagctccagatgggtgcigagccaggtgcagciggigcagtcigg
 cccgaagtgaagaaacciggggttagcgtgaaggtgtccigcaaggccagcggcctcaccitcagcaccagctataiga
 gctgggtccgccaggctccagggccagcaccgaatggatgggtggatctatgccggcgacggcgccaccaagtacaac
 cagaaatcaaggcgagagtgaacctgacctgggacaagagcaccagcaccgctacatggaaatgagcagccigcggag
 cgaggacaccgctgtactactigcgcaccgagggctacggcgaciggttcacatctggggccagggcaccciggtga
 ccgtgagctcagcctccaccaagggcccaagcgtcttcccciggcacccctctccaagagcaccctggcgggcacagcc
 gcccigggctgcciggtcaaggactacttccccgaaccgctgacctgagctggaatcagggccctgaccagcggcgt
 gcacaccttccccgctgctcagctcctcaggactctactccctcagcagcgtggtagccgtgcccctcagcagcttgg
 gcacccagacctacatcigcaacgtgaatcacaagcccagcaacaccaaggtggacaagagattgagcccaaatctgt
 gacaaaactcacaatgcccacccctggccagcactgaactcctggggggacctcagctctctcttccccccaaaacc
 caaggacacctcatgatctcccgacccctgaggctacatgctgtgggtggagctgagccacgaagacctgaggtca
 agltcaactggtagctggagcggcgtggaggctgataatgccaaagacaaagccccgggaggagcagtaaacagcagctac
 cgggtggtagcgtctcaccgtctcaccaggtggttgatggcaaggagtaaatgcaaggtctccaacaaagc
 cctccagcccccatcgagaaaaccatctccaaagccaaaggccagccccgggaaccacaggtgtacacctgcccccat
 cccgggaggagatgaccaagaaccaggtcagcctgacctgcttggtcaaggcttctatcccagcgacatcgccgtggag
 tgggagagcaatggccagcccagagaacaactacaagaccacccctccccgtgctggactccgacggctcttcttctctta
 cagcaagctcaccgtggacaagagcaggtggcagcagggcaacgtcttctcatgctccgtgaltgaltgaggctctgcaca
 accactacaccacagaagagcctctctctcttcccgcaaaa

Signal sequence (1-57), Variable region (58-411), Constant region (412-1401)
 (SEQ ID NO: 82 of Sequence Listing)

Figure 91

MKHLWFFLLVAAPRWVLSQVQLVQSGAEVKKPGASVKVSCKASGFTFTSYMSWVRQAPGPSTEWMGWIYAGDGGTKYN
 QKFKGRVTLTVDKSTSTAYMELSSLRSEDTAVYYCATEGYGDWFTYWGQGLTVTVSSASTKGPSVFPPLAPSSKSTSGGTA
 ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVPEPKSC
 DKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
 RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
 WESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

Signal sequence (1-19), Variable region (20-137), Constant region (138-467)
 (SEQ ID NO: 83 of Sequence Listing)

Figure 92

atgaaacacctgiggttcttctccctgctgggtggcagctcccagatgggtgctgagccaggcgcagcgggtgcagctcgg
 cgccgaagtgaaagaacctggggctagcgtgaaggtgtcttgcaaggccagcggcttcaccttcagcaccagctataatga
 gctgggtccgccaggctccaggccccagcaccgaatggatgggttggaatcctatgccggcgacggcgccaccaagtacaac
 cagaaattcaaggcgagtgacctgacctgggacaagagcaccagcaccgctacatggaaatgagcagccctcgaggag
 cgaggacaccgctgtactactgcccaccgaagcctacggcgaciggttcacatactggggccagggcaccctgggtga
 ccgtgagctcagcctccaccaagggcccaagcgtctcccccggcaccctccccaagagcaccctcggcgccacagcc
 gcccgggtgcttggtaaggactactccccgaacccgtagcgtgagctggaactcaggcgccctgaccagcggcgt
 gcacaccttcccgcgtctctgcagctcctcaggacictactcccacagcagctgggtgacctgcccctccagcagcttgg
 gcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacaagagagtgagcccaaatcttgt
 gacaaaactcacacatgccaccctgcccagcaccigaactcctggggggaccctcagctctcccttccccccaaaacc
 caagacacccctcatgatctcccgacccttgaggtcacatgctgggtgggtggagctgagccacgaagacctgaggtca
 agtccaactggtagctggcggcgtggaggtgcataatgccaaagacaaagccccgggaggagcagtaaacagcagctac
 cgggtggctcagcgtctcaccgtctgcaccaggactggctgaatggcaaggagtacaagtgaaggcttccaacaaagc
 ctcccagcccccatcgagaaaaccaatcccaagccaaaggccagccccgggaaccacaggtgtacacctgccccca
 cccgggaggagatgaccaagaaccaggtcagcctgaactgcccggtaaaaggctctatcccagcgacatcgccgtggag
 tgggagagcaatggccagccccgagaacaactacaagaccacccctcccgctgctggactcagacggctccttcttctta
 cagcaagctcaccgtggaaagagcaggtggcagcagggaacgtcttctcatgctccgtgatgcatgaggctctgcaca
 accactacaccagaagagccttcccctgtctcccgcaaa

Signal sequence (1-57), Variable region (58-411), Constant region(412-1401)

(SEQ ID NO: 84 of Sequence Listing)

Figure 93

MKHLWFFLLVAAPRWVLSQVQLVQSGAEVKKPGASVKVSKASGFTFSTSYMSWVRQAPGPSTEWMGWIYAGDGGTKYN
 QKFKGRVTLTVDKSTSTAYMELSSLRSEDTAVYYCATDAYGDWFTYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTA
 ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVPEKSC
 DKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQNSTY
 RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
 WESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSTMHEALHNHYTQKSLSLSPGK

Signal sequence (1-19), Variable region (20-137), Constant region(138-467)

(SEQ ID NO: 85 of Sequence Listing)

Figure 94

atgaaacaccigtgttcttccctcctgctggcagctcccagatgggtgctgagccaggtgcagctgggtgagctcagg
cgccgaagtgagaaacctggggctagcgtgaaggctgcttgaagccagcggcttcaccttcagcaccagctataatga
gctgggtccgccaggtccagggccagcaccgaaatggatgggtggatctatgcccgcgacggcggcaccacgaatgacaac
cagaaattcaagggcagagtgaacctgaccgtggacaagagcaccagcaccgctacatggaacagagcagctggcgag
cgaggacaccgctgtactactgcccaccgacgagtagggcagctgggttcacatagggggccagggcaccctggga
ccgtgagctcagctccaccaagggcccaagcgtcttccccctggcaccctccccaagagcaccctcggcgccacagcc
gcccctgggtcgtcgtggaaggactacttccccgaaccctgaccgtgagctggaactcaggcgcccagaccagcggt
gcacaccttccccctgctcctgagctcctcaggactctactcccctcagcagcgtggtagcgtgcccctcagcagctgg
gcacccagacctacatcagcaagctgaatcacaagccagcaacaccaaggtggacaagagagtagagcccaaatcttgt
gacaaaacacacacatgcccacctgcccagcaccatgaactcctggggggaccctcagctcttctcttccccccaaacc
caaggacacctcctgctcctccggaccccagggctcacaagctgggtggagctgagccacgaagacctgaggtca
agttcaactggtagctggacggcgtggaggtgcaataatgccaagacaagccccgggagagcagtagacaacagcacgac
cgggtggctcagctcctcaccgtcctgacaccaggtggctgaaaggcaaggagtagaagtgcaaggtctccaacaaagc
ctcccagcccccatcgagaaaaccatctccaaagccaaagggcagcccggaaccacaggtgtacacctgcccccat
ccgggagagagatgaccaagaaccaggtcagcctgacctgcttgggtcaaaggctctatcccagcgacatcgccgtggag
tgggagagcaatggccagcccgagaacaactacaagaccaccccctcccgtgctggactccgacggctcctctctctctca
cagcaagctcaccgtggacaagagcaggtggcagcagggcaacgtctctcctatgctccgtgatgcatgaggctctgcaca
accactacaccagaagagccctcctctgtctcccgga

Signal sequence (1-57), Variable region (58-411), Constant region (412-1401)
(SEQ ID NO: 86 of Sequence Listing)

Figure 95

MKHLWFFLLLVAAPRWVLSQVQLVQSGAEVKKPGASVKVSKASGFTFSTSYMSWVRQAPGPSTEWMGWIYAGDGGTKYN
QKFKGRVTLTVDKSTSTAYMELSSLRSEDAVYYCATDEYGDWFTYWGQTLTVSSASTKGPSVFPLAPSSKSTSGGTA
ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSC
DKTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
RVYSVLTVQLHQLNGLKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVSCVMHEALHNYHTQKSLSPGK

Signal sequence (1-19), Variable region (20-137), Constant region (138-467)
(SEQ ID NO: 87 of Sequence Listing)

Figure 96

atgaaacaccctgtgggtcttccctcctgctgggtggcagctcccagatgggtgclgagccaggtgcagctgggtgcagctctgg
cgccgaagtgaagaacccctggggctagcgtgaagggtgcllgaaggccagcggttcaccctcagcaccagctatatga
gctgggtlccgcccaggctccaggccccagcaccgaatggatgggtggatctatgccggcgacggcgccaccaaglacaa
cagaaatcaagggcagagtgacctgaccgtggacaagagcaccagcaccgctacatggaaatgagcagcctgcggag
cgaggacaccgcccgtgtactactgcggccaccgacttclacggcgactgggttcacataclggggccagggcacccctggiga
ccgtgagctcagcctccaccaaggccccaaagcgtctccccctggcaccctccccaagagcacctctggcgccacagcc
gcccggggctgccgggtcaaggactacttccccgaaccctgaccgtgagctggaactcaggcgccctgaccagcgccgt
gcacaccttccccgtgtcttgcagtcctcaggactclactccccagcagcgtgggtgaccgtgcccctcagcagcctgg
gcaccagagctacatctgcaacgtgaatcacaaagccagcaacaccaaggtggacaagagagltgagcccaaatcttgt
gacaaaactcacacatgccaccctgccagcaccctgaactcctggggggacccctcagctcttctcttccccccaaaacc
caaggacacctcaatgctccccgacccctgaggtcacatgctgggtgggtgagcgtgagccacgaagacctgagggtca
agttcaactgggtacgtggcggcgtggaggtgcataatgccaaagacaaagccccgggagagcagtaaacagcagctac
cgggtgggtcagcgtctcaccgtcttgcaccaggactggctgaatggcaaggagtacaagtcaaggcttccaacaaagc
cttccagccccccatcgagaaaaccatctccaagccaaaggccagccccgggaaccacagggtgtacaccttcccccat
ccccgggagagatgaccaagaaccagggtcagcctgacctgctgggtcaaaggcttctatccagcgacatcgccgtggag
tgggagagcaatggccagcccgagaacaactacaagaccacccctcccggtcgtggactccgaaggcctcttctctta
cagcaagctcaccgtggacaagagcaggtggcagcagggcaacgtcttctcatgctccgtgatgcatgaggtctgcaca
accctacacccagaagagcctctccctgtctccccgcaaa

Signal sequence (1-57), Variable region (58-411), Constant region (412-1401)
(SEQ ID NO: 88 of Sequence Listing)

Figure 97

MKHLWFFLLLVAAPRWVLSQVQLVQSGAEVKKPGASVKVCKASGFTFSTSYMSWVRQAPGPSTEWMGWIYAGDGGTKYN
QKFKGRVTLTVDKSTSTAYMELSSLRSEDTAVYYCATDFYGDWFTYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTA
ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSC
DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVVFSCSVMEALHNHYTQKSLSLSPGK

Signal sequence (1-19), Variable region (20-137), Constant region (138-467)
(SEQ ID NO: 89 of Sequence Listing)

Figure 98

atgaaacaccctggtgtcttccctccctgctggtggcagctcccagatgggtgctgagccaggcgcagctggtgcagctcgg
 cgccgaagtgaagaaacctggggctagcgtgaaggtgtccctgcaaggccagcggcttcaccttcagcaccagctatatga
 gctgggtccgccaggcctcaggccccagcaccgaatggatgggtggatctatgcccggcgacggcgccaccaagtlacaac
 cagaaatcaagggcagagtgaacctgacctggacaagagcaccagcaccgctacatggaaatgagcagctcgggag
 cgaggacaccgctgtactactgcccaccgaccactacggcgactgggtcacatactggggccagggcaccttggtga
 ccgtgagctcagcctccaccaagggeccaagcgtcttccccctggcaccctcttccaagagcaccctcggcgccacagcc
 gcccctgggtgctcctggtcaaggactacttccccgaaccctgacctgagctggaactcaggcggcctgaccagcggcgt
 gcacaccttccccctgtctctgagctctcaggactctactcccctcagcagcgtggtgacctgcccctcagcagcttgg
 gcacccagacctacatctgcaactgaatcacaagcccagcaacaccaaggctggacaagagagttagcccaaatcttgt
 gacaaaactcacacatgccacacctgcccagcactgaactcctggggggacctcagctcttcttctccccccaaaacc
 caaggacacctctatgacttcccgacccccaggtcacatgctgggtgggtggacgtgagccacgaagacctgaggtca
 agtcaactgggtacgtggacggcgtggaggtgcataatgccaaagacaaagccccgggaggagcaglacaaacagcagctac
 cgggtgggtcagcgtctcaccgtctcaccaggactggctgaatggcaaggagtacaagtgaaggtctccaacaaagc
 cctcccagcccccatcgagaaaaccaacttccaaagccaaaggccagccccgggaaccacagggtgtacacctgccccat
 cccgggaggagatgaccaagaaccaggtcagcctgacctgcttgggtcaaaggctctctatcccagcgacatcgccgtggag
 .tgggagagcaatggccagccccgagaacaactacaagaccaccccctccgtgctggactccgacggctctcttctctta
 cagcaagctcaccgtggacaagagcagggtggcagcagggaacgtcttctcatgctccgtgaigcagaggtctgcaca
 accactacaccagaagagcctctccctgtcttccggcaaa

Signal sequence (1-57), Variable region (58-411), Constant region (412-1401)

(SEQ ID NO: 90 of Sequence Listing)

Figure 99

MKHLWFFLLLVAAAPRWVLSQVQLVQSGAEVKKPGASVKVSCASGFTFSTSYMSWVRQAPGPSTEWMGWIYAGDGGTKYN
 QKFKGRVTLTVDKSTSTAYMELSSLRSEDTAVYYCATDHYGDWFTYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTA
 ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSC
 DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
 RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
 WESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

Signal sequence (1-19), Variable region (20-137), Constant region (138-467)

(SEQ ID NO: 91 of Sequence Listing)

Figure 100

atgaaacaccitggttcttcccttgcctgggtggcagctcccagatgggtgctgagccaggtgcagctgggtgcagcttgg
 cgccgaagtgaagaaacctggggctagcgtgaagggtgccatgcaaggccagcggcttcacctcagcaccagctataatga
 gctgggtccgccaggctccagggccagcaccgaaatggatgggttggatctatgccggcgacggcgccaccaagtacaac
 cagaaatcaagggcagagtaccctgaccgtggacaagagcaccagcaccgctacaaggaaatgagcagcttgcggag
 cgaggacaccgctgtacttgcggccaccgacatctacggcgactgggtcacatctggggccagggcacccctgggtga
 ccgtgagctcagctccaccaaggcccaaggcttccccctggcaccctccccaagagcaccctggcgggcacagcc
 gcccctgggtgcctgggtcaggacttctccccgaaccctgaccgtgagctggaaatcaggcgcccctgaccagcggcgt
 gcacacctccccctgttcttgcagcttctcaggacttcttcccctcagcagcgtgggtgaccgtgcccctcagcagcttgg
 gcacccagacctacatctgcaacgtgaatcacaagccagcaaacaccaagggtggacaagagatgagcccaaatctgtt
 gacaaaactcaacatgccacccttgcgcagcaccctgaacttctggggggaccctcagcttcttcttccccccaaaacc
 caaggacacccctcatgacttccgggacccctgaggtcacaatgcgtgggtgggtggacgtgagccacgaagacccctgaggtca
 agtcaactgggtacgtggacggcgtggagggtgcataatgccaaagacaagccccgggaggagcagtaaacagcagctac
 cgggtggtcagcgttctcaccgttctgcaccaggactggctgaaatggcaaggagtacaatgcaaggcttccaacaaagc
 ctccccagccccctcgagaaaaccatctccaaagccaaaggccagccccgggaaccacaggtgtacacctgcccccat
 cccgggaggagatgaccaagaaccaggtcagcctgacctgcttgggtcaaaggcttctatcccagcgacatgcctgtggag
 tgggagagcaatggccagcccgagaacaactacaagaccacccctcccgctgctggactccgacggtctcttcttctcta
 cagcaagctcaccgtggacaagagcaggtggcagcaggggcaacgtcttctcagctcgtgatgcatgaggtctgcaca
 accactacaccagaaagagccttcccccttccccggcaaa

Signal sequence (1-57), Variable region (58-411), Constant region (412-1401)

(SEQ ID NO: 92 of Sequence Listing)

Figure 101

MKHLWFFLLVAAPRWVLSQVQLVQSGAEVKKPGASVKVSCASGFTFTSYMSWVRQAPGPSTEWGWIYAGDGGTKYN
 QKFKGRVTLTVDKSTSTAYMELSSLRSEDTAVYYCATDIYGDWFTYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTA
 ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKVDKRVKPKSC
 DKTHTCPPCPAPPELLGFPVFLFPPKPKDTLMI SRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQNSTY
 RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSRREMTKNQVSLTCLVKGFYPSDIAVE
 WESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVVFSCSYMHEALHNHYTQKSLSLSPGK

Signal sequence (1-19), Variable region (20-137), Constant region (138-467)

(SEQ ID NO: 93 of Sequence Listing)

Figure 102

atgaaacacctgltggttcttccctcctgctggtggcagctcccagatgggtgctgagccaggtgcagclggtgcagctctgg
cgccgaagtgaagaaacctggggctagcgtgaaggtgtccctgcaaggccagcggcttcaccttcagcaccagctataatga
gtgggtccgccaggctccagggcccagcaccgaatggatgggtggatctatgcccggcgacggcgccaccaagtacaac
cagaaatcaagggcagagtgacctgacctgggacaagagcaccagcaccgctacalggaaatgagcagcctgcggag
cgaggacaccgctgtactactgcgccaccgacaagtacggcgactgggttcacatactggggccagggcaccttgggtga
ccgtgagctcagctccaccaaggggcccaagcgtcttccccctggcaccctcttccaagagcaccctcggcgccacagcc
gcccgggtgcttgggtcaaggactacttccccgaaccctgacctgagctggaactcaggcgccctgaccagcggcgt
gcacaccttccccctgtcttgcagctctcaggactctactctctcagcagcgtggtgacctggccctccagcagcttgg
gcaccagacctacatctgcaacgtgaatcacaagcccagcaaacaccaaggtggacaagagagttagcccaaatcttgt
gacaaactcacacatgcccaccttcccagcaccctgaactcttggggggacctcagctctctcttccccccaaacc
caaggacacctctatgactctccggaccttgggtcacatgctgtgtgtggacgtgagccacgaagacctgaggtca
agtcaactgggtacgtggacggcgtggaggtgcataatgccaaagacaagccccgggaggagcaglacaaacagcagctac
cgggtgtgctagcgtctcaccgtcttgcaccaggactggctgaatggcaaggagtacaagtgaaggcttccaacaaagc
cttcccagccccatcgagaaaaccatctccaagccaaaggccagccccgggaaccacagggttacaccttgcacctat
cccgggaggagatgaccaagaaccaggtcagcctgacctgcttgggtcaaaggcttctatcccagcgacatcgccgtggag
tgggagagcaatggccagcccagagaacaactacaagaccaccccctccgtgctggactccgacggctcttcttctctta
cagcaagctcaccgtggacaagagcaggtggcagcagggcaacgtcttctcatgtccgtgatgcatgaggctctgcaca
accactacaccagaagagccttctccctgtctcccggcaaa

Signal sequence (1-57), Variable region (58-411), Constant region (412-1401)

(SEQ ID NO: 94 of Sequence Listing)

Figure 103

MKHLWFFLLLVAAPRWVLSQVQLVQSGAEVKKPGASVKVSKASGFTFSTSYMSWVRQAPGPSTEWGWIYAGDGGTKYN
QKFKGRVTLTVDKSTSTAYMELSSLRSEDTAVYYCATDKYGDWFTYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTA
ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSC
DKTHTCPPCPAPELLGGPSYFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVVFSCSVMEALHNHYTQKSLSLSPGK

Signal sequence (1-19), Variable region (20-137), Constant region (138-467)

(SEQ ID NO: 95 of Sequence Listing)

Figure 104

atgaaacacctgtggttcttccctcctgctggtggcagctcccagatgggtgctgagccaggtgcagctgggtgcagctcgg
 cgccgaagtgaagaaaccttggggctagcgtgaagggtgcttgcaggccagcggcttcaccttcagcaccagctatatga
 gctgggtccggcaggctccaggccccagcaccgaatggatgggttggaictatgccggcgacggcgccaccaagtacaac
 cagaaatcaagggcagagtgaacctgacctggacaagagcaccagcaccgctacalggaaatgagcagccttgcggag
 cgaggacaccgctgactacitggcccaccgacctgtacggcgactgggttcacatacctggggccaggggcaccctgggtga
 ccgtgagctcagcctccaccaaggggcccaagcgtcttccccctggcaccctccctccaagagcaccctcggcgccacagcc
 gcccctgggtgcttgggtcaaggactacttccccgaaccctgaccgtgagctggaaatcaggcgccctgaccagcggcgt
 gacaccttcccccgctgcttgcagctcctcaggactctacttccctcagcagcgtgggtgaccgtgcccctcagcagcttgg
 gcaaccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacaagagagttagagcccaaatcttgt
 gacaaaatcacacatgccaccctgccagcaccctgaactccttggggggaccctcagctcttcccttccccccaaaacc
 caaggacacctcatgacttccccgacccttgaggtcacaatggctgggtggacgtgagccacgaagacctgaggtca
 agtcaacttggtacgtggacggcgtggaggtgcataatgccaaagacaagccccgggaggagcagtacaacagcagctac
 cgggtgggtcagcgtccctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtcaaggtctccaacaaagc
 cctcccagcccccatcgagaaaacctatccaaagccaaaggccagccccgggaaccacagggtgacacctgcccccat
 cccgggaggagatgaccaagaaccaggctagcctgacctggctcgaaggcttctatcccagcgacatcgccgtggag
 tgggagagcaatggccagcccagagaacaactacaagaccaccttcccgctgtggactccgacggctccttcttccctta
 cagcaagctcaccgtggacaagagcaggtggcagcagggaacgtcttctcatgtccgtgatgcatgaggctctgcaca
 accactacaccagaagagccttccccctgtctccccggcaaa

Signal sequence (1-57), Variable region (58-411), Constant region(412-1401)
 (SEQ ID NO: 96 of Sequence Listing)

Figure 105

MKHLWFLLVLAAPRWVLSQVQLVQSGAEVKKPGASVKVSKASGFTFSTSYMSWVRQAPGPSTEWMGWIYAGDGGTKYN
 QKFKGRVTLTVDKSTSTAYMELSSLRSEDYAVYYCATDLYGDWFTYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTA
 ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSC
 DKHTHTCPPCPAPELGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
 RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
 WESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMEALHNHYTQKSLSLSPGK

Signal sequence (1-19), Variable region (20-137), Constant region(138-467)
 (SEQ ID NO: 97 of Sequence Listing)

Figure 106

atgaaacacctgtgggtcttctcctgtgtggcagctcccagatgggtgtgagccaggltgcagctgggtgcagctcgg
 cgccgaagtgaagaaacctggggctagcgtgaagggtgcttgcaggccagcggcttcacctcagcaccagctatatga
 gctgggtccgccaggtccaggccccagcaccgaatggatgggtggatctatgccggcgacggcgccaccaagtacaac
 cagaaatcaagggcagagtgaacctgaccgtggacaagagcaccagcaccgctacatggaaactgagcagcctgcggag
 cgaggacaccgcccgtgtactactgcgccaccgacatgtacggcgactggltcacatactggggccaggccacctgggtga
 ccgtgagctcagctccaccaaggccccaaagcgtcttccccctggcaccctccccaagagcaccctcggcgccacagcc
 gccctgggtgcctgggtcaaggactacttccccgaaccctgaccgtgagctggaaactcaggcgccctgaccagcgccgt
 gcacaccttccccgtgtcctgcagctcctcaggactctactcccacagcagctgggtgacctgcccaccagcagcttgg
 gcaccagacctacatctgcaactgaaatcacaagccagcaacaccaagggtggacaagagagltgagcccaaatcttgt
 gacaaaactcacacatgccaccctgccagcaccatgaactcctggggggaccctcagcttcccttccccccaaaacc
 caaggacacctctatgactccccggaccctgaggtcacatgcgtgggtgggtggacgtgagccacgaagacctgaggtca
 agttcaactgggtacgtggacggcgtggaggtgcataatgccaaagacaaagccccgggaggagcagtaaacagcagctac
 cgggtgggtcagcgtctcaccgtctgcaccaggactggctgaatggcaaggagtaacagtgcaaggtctccaacaaagc
 cctcccagcccccatcgagaaaaccaatcccaagccaaaggccagccccgggaaccacaggtgtacacctgcccccat
 cccgggaggagatgaccaagaaccaggtcagcctgacctgccctgggtcaaaagcttctatcccagcgacatcgccgtggag
 tgggagagcaatggccagcccgagaacaactacaagaccacccctcccgtgtggactccgacggctccttcttctctta
 cageaagctcaccgtggacaagagcaggtggcagcagggaacgtcttctcatgtccgtgaltgcatgaggctctgcaca
 accactacaccagaagagcctctcccgtctcccggcaaa

Signal sequence (1-57), Variable region (58-411), Constant region(412-1401)

(SEQ ID NO: 98 of Sequence Listing)

Figure 107

MKHLWFLLLVAAPRWVLSQVQLVQSGAEVKKPGASVKVSCKASGFTFSTSYMSWVRQAPGPSTEWGWIYAGDGGTKYN
 QKFKGRVTLTVDKSTSTAYMELSSLRSEDTAVYYCATDMYGDWFTYWGQGLTVTVSSASTKGPSVFPPLAPSSKSTSGGTA
 ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVKPKSC
 DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
 RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
 WESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVPSCSVMHEALHNHYTQKSLSLSPGK

Signal sequence (1-19), Variable region (20-137), Constant region(138-467)

(SEQ ID NO: 99 of Sequence Listing)

Figure 108

atgaaacacctgtggttcttccctcgtggtggcagcaccagatgggtgctgagccaggtgcagctgggtgcagcttgg
 cgccgaagtgaagaaacctggggctagcgtgaagggtgcttgcaggccagcggcttcaccttcagcaccagctataatga
 gctgggtccgcccaggctccaggccccagcaccgaatggatgggtggatctatgcccggcgacggcggcaccagttacaac
 cagaaatcaagggcagagtgaacctgacctgggacaagagcaccagcaccgctacatggaaactgagcagcttgcggag
 cgaggacaccgcccgtgactactgcccaccgaccagctacggcgactgggttcacatactggggccagggcacccctgggtga
 ccgtgagctcagctccaccaaggccccagcgtcttccccctggcaccctccctccaagagcacccttggcggcacagcc
 gcccctgggtgcccgtgcaaggactacttccccgaacccgtgacctgagctggaaactcaggcgccctgaccagcggcgt
 gcacaccttccccctgcttgcagctccaggactctactcccctcagcagcgtgggtgacctgcccctcagcagcttgg
 gcaccagaccttacttgcacagtgaaactcacaagcccagcaacaccaaggtggacaagagagttagccccaaatcttgi
 gacaaaacttcacacatgccaccctgccagcaccatgaactcctggggggacctcagcttcttcttccccccaaaacc
 caaggacaccttcatgacttcccgacccttgaggtcacaatgcgtgggtggagctgagccacgaagaacctgaggtca
 agtcaactggtacgtggcggcgtggaggtgcataatgccaaagacaagccccgggaggagcagttacaacagcagctac
 cgggtgggtcagcgtcctcaccgtcctgcaccaggactggc tgaatggcaaggagtacaagtgcaggcttccaacaagc
 cctcccagcccccatcgagaaaacctatccaaagccaaaggccagccccgggaaccacagggttacacctgcccccat
 cccgggaggagatgaccaagaaccaggtcagcctgacctgcttgggtcaaaggcttctatcccagcgacatcgccgtggag
 tgggagagcaatggccagcccagacaactacaagaccacccctcccggtgctggactccgacggctccttcttctctta
 cagcaagctcaccgtggacaagagcaggtggcagcagggaacgtcttctcatgctccgtgatgcatgaggtcttgcaca
 accactacaccagaagagccttccctgtctcccgcaaa

Signal sequence (1-57), Variable region (58-411), Constant region(412-1401)

(SEQ ID NO: 100 of Sequence Listing)

Figure 109

MKHLWFFLLLVAAPRWVLSQVQLVQSGAEVKKPGASVKVSKASGFTFSTSYMSWVRQAPGPSTEWMGWIYAGDGGTKYN
 QKFKGRVTLTVDKSTSTAYMELSSLRSEDTAVYYCATDQYGDWFTYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTA
 ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVPEPKSC
 DKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
 RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
 WESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVMEALHNHYTQKSLSLSPGK

Signal sequence (1-19), Variable region (20-137), Constant region(138-467)

(SEQ ID NO: 101 of Sequence Listing)

Figure 110

atgaaacacctgtggttcttccctcctgctgggtggcagctcccagatgggtgctgagccaggtgcagctgggtgcagctcgg
cgccgaagigaagaaacctggggctagcgtgaaggtgtcctgcaaggccagcggcttcaccttcagcaccagctatatga
gctgggtccgcccaggtccaggccccagcaccgaatggatgggtggatctatgcccggcgacggcgccaccaagtacaac
cagaaaatcaagggcagagtgacctgaccgtggacaagagcaccagcaccgctacatggaactgagcagcttcggag
cgaggacaccgctgtactactgcccaccgaccggtacggcgactgggttcacatactggggccagggcaccctgggtga
ccgtgagctcagcctccaccaagggcccaagcgtcttccccctggcaccctcctccaagagcaccctcggcgccacagcc
gcccctgggtgcttggtaaggactacttccccgaaccgctgaccgtgagctggaactcaggcgccctgaccagcggcgt
gcacaccttccccgctgtcctgacgtcctcaggactctactccctcagcagcgtgggtgaccgtgcccctccagcagcttgg
gcaccagacctacatctgcaacgtgaatcacaaagccagcaaacaccaaggtggacaagagagttgagccaaaatcttgt
gacaaaactcacacatgcccaccctgcccagcaccctgaactcctggggggaccctcagcttctcttccccccaaaacc
caaggacaccctcatgactcctggacccttgaggtcacatgctgggtgggtggacgtgagccacgaagaccctgaggtca
agttcaactgggtacgtggacggcgtggaggtgcataatgccaaagacaaagccccgggaggagcagtaaacagcagctac
cgggtgggtcagcgtcctcaccgtcctgaccaggttggctgaatggcaaggagtacaagtgcgaaggtctccaacaaagc
cttcccagcccccatcgagaaaaccatctccaaagccaaagccagccccgggaaccacaggtgtacacctgcccccat
ccggggaggagatgaccaagaaccaggtcagctgacctgcttgggtcaaaggcttctatcccagcgacatcgccgtggag
tgggagagcaatggccagcccgagaacaactacaagaccacccttccgtgctggactccgacggctccttcttctctta
cagcaagctcaccgtggacaagagcaggtggcagcagggaacgtcttctcaatgctccgtgaigcatgaggctctgcaca
accactacaccagaagagccttctccctgtcttcccggcaaa

Signal sequence (1-57), Variable region (58-411), Constant region(412-1401)

(SEQ ID NO: 102 of Sequence Listing)

Figure 111

MKHLWFFLLLVAAPRWVLSQVQLVQSGAEVKKPGASVKVSKASGFTFSTSYMSWVRQAPGPSTEWMGWIYAGDGGTKYN
QKFKGRVTLTVDKSTSTAYMELSSLRSEDTAVYYCATDRYGDWPTYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTA
ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKVDKRVPEPKSC
DKTHTCPPCPAPELIGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTTPVLDSDGSFFLYSLKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

Signal sequence (1-19), Variable region (20-137), Constant region(138-467)

(SEQ ID NO: 103 of Sequence Listing)

Figure 112

atgaaacacctgtgggtcttctccttcgttggtggcagctcccagatgggtgctgagccagggtgcagctgggtgcagctctgg
 cgccgaagtgaagaaaccttggggctagcgtgaagggtgctctgcaaggccagcggcttcaccttcagcaccagctatatga
 gctgggtccgccaggctccaggccccagcaccgaatggatgggtggatctatgccggcgacggcgccaccaagtacaac
 cagaaatcaaggcgagagtgaacctgaccgtggacaagagcaccagcaccgacctacatggaaclgagcagcctgcggag
 cgaggacaccgctgtactactgcgccaccgacgtgacggcgactgggttcacatctggggccagggcacctgggtga
 ccgtgagctcagcctccaccaaggggcccaagcgtcttccccctggcaccctctccaagagcaccctcggggccacagcc
 gccctgggtctgcttggltcaaggactacttccccgaaccctgaccgtgagctggaaclcaggcgccctgaccagcggcgt
 gcacaccttccccgctgctctgcagctcctcaggactctactcctcagcagcgtgggtgaccgtgcccctcagcagcttgg
 gcaaccagacctacatctgcaacgtgaaacacaagccagcaacaccaagggtggacaagagagttagagccaaatcttgt
 gacaaaactcacacatgccaccctgccagcaccatgaactcttggggggaccctcagctctctcttccccccaaaacc
 caaggacacctcctatctcctcgacccttgaggctacatgctgggtgggtggagctgagccacgaagacctgaggtca
 agltcaactggtagctggacggcgtggaggtgcataatgccaaagacaaagccccgggaggagcagtaaacagcagctac
 cgggtgggtcagcgtctcaccgtctcgcaccaggactggctgaatggcaaggagtacaagtgaaggtctccaacaaagc
 ctccccagccccatcgagaaaaccatctccaaagccaaaggccagccccgggaaccacaggtgtacaccttcccccat
 ccggggaggagatgaccaagaaccaggtcagcctgacctgcttgggtcaaaggtctctatccagcgacatcgccgtggag
 tgggagagcaatggccagcccgagaacaacacaaagaccaccttcccgctgcaggactccgacggctccttctctctta
 cagcaagctcaccgtggacaagagcaggtggcagcagggaacgtcttctcaigtctcgtgatgcatgaggctctgcaca
 accactacaccagaagacctctcctgtctccccggcaaa

Signal sequence (1-57), Variable region (58-411), Constant region(412-1401)
 (SEQ ID NO: 104 of Sequence Listing)

Figure 113

MKHLWFFLLLVAAPRWVLSQVQLVQSGAEVKKPGASVKVSCKASGFTFTSYMSWVRQAPGPSTEWMCWIYAGDGGTKYN
 QKFKGRVTLTVDKSTSTAYMELSSLRSEDYAVYYCATDVYGDWFTYWGQGLVTVSSASTKGPSVFPLAPSSKSTSGGTA
 ALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVPEKSC
 DKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQNSTY
 RVYSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
 WESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSVMSVHEALHNHYTQKSLSLSPGK

Signal sequence (1-19), Variable region (20-137), Constant region (138-467)
 (SEQ ID NO: 105 of Sequence Listing)

Figure 114

atgaaacacctgltggilcttccctectgcitggitggcagctcccagatgggtgctgagccagggtgcagctggltgcagcttgg
 cgccgaagtgaagaaacctggggctagcgtgaaggltgcttgaaggccagcggcttcaccttcagcaccagctatatga
 gctgggtccgccaggctccaggccccagcaccgaaatggatgggtggatctatgccggcgacggcgccaccaagtacaac
 cagaaattcaagggcagagtgacctgacctggacaagagcaccagcaccgctacatggaacagcagcctgcggag
 cgaggacaccgctgtactactgcccaccgactggtagggcgactggttcacalactggggccagggcacccgtgtga
 ccgtgagctcagcctccaccaaggccccagcgtcttccccctggcaccctccccaagagcaccctcggcgccacagcc
 gcccctgggtgcttggtaaggactacttccccgaaccctgaccgtgagctggaactcaggcgccctgaccagcgccgt
 gcacaccttccccctgttcttcagctccctcaggactctactccctcagcagcgtggtagccgtgcccctcagcagcttgg
 gcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggltggacaagagagttgagcccaaatctgt
 gacaaaactcacacatgccacccctgcccagcaccgaacacctgggggggacccctcagctcttctcttcccccaaaacc
 caaggacacccctcatgacttcccggacccctgaggctcactgctgggtggtagcgtgagccacgaagacccctgaggtca
 agttcaactggtagctggaaggctggaggtgcaataatgccaagacaaagccccgggaggagcagtaaacagcagctac
 cgggtggctcagcgtctcaccgtcttcaccaggactggctgaatggcaaggagtacaagtgcaaggcttccaacaaagc
 ctcccagccccctcagaaaaacatctccaaagccaaaggccagccccgggaaccacaggtgtacacctgcccccat
 cccgggaggagatgaccaagaaccaggtcagcctgacctgcttggtaaaaggctctatcccagcgacatcgccgtggag
 tgggagagcaatggccagcccagagaacaacataagaccacccctcccgtgctggactccgacggctcttcttctctta
 cagcaagctcaccgtggacaagagcaggtggcagcagggcaacgtcttctcatgctccgtgatgcatgaggctctgcaca
 accactacaccagaagagcctctccctgtcttcccggcaaa

Signal sequence (1-57), Variable region (58-411), Constant region(412-1401)

(SEQ ID NO: 106 of Sequence Listing)

Figure 115

MKHLWFFLLLVAAPRWVLSQVQLVQSGAEVKKPGASVKVSCKASGFTFSTSYMSWVRQAPGPSTEWGWIYAGDGGTKYN
 QKFKGRVTLTVDKSTSTAYMELSSLRSEDTAVYYCATDWYGDWFTYWGQGLVTVSSASTKGPSVFPLAPSSKSTSGGTA
 ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDRVEPKSC
 DKTHTCPPCPAPELLGGPSVFLEPPPKPDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
 RVVSYLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
 WESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQVMHEALHNHYTQKSLSLSPGK

Signal sequence (1-19), Variable region (20-137), Constant region(138-467)

(SEQ ID NO: 107 of Sequence Listing)

Figure 116

atgaaacaccatgggttcttccctctgtcgttggtggcagctcccagatgggtgctgagccaggtgcagctgggtgcagctctgg
cgccgaagtgaagaaaccctggggctagcgtgaaggtgtcttgcaggccagcggttcacctcagcaccagctatatga
gcctgggtccgcccaggctccaggccccagcaccgaatggatgggtggatcctatgccggcgacggcgccaccaagtacaac
cagaaattcaagggcagagtaccctgaccgtggacaagagcaccagcaccgctacatggaaatgagcagcctgcccag
cgaggacaccgctgtactactgcgccaccgactactacggcgactggttcacatactggggccagggcacccctgggtga
ccgtgagctcagctccaccaagggcccaagcgtcttccccctggcaccctccccaagagcacccttggcggcacagcc
ggcctgggtgcccgggtcaaggactacttccccgaaccctgaccgtgagctggaaatcaggcgccctgaccagcggtgt
gcacaccttccccgtgtcttgcagctccctcaggactctactccctcagcagcgtgggtgaccgtgcccctccagcagcttgg
gcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggctggacaagagagttagcccaaatcttgt
gacaaaactcacacatgcccccctgcccagcaccctgaactcctggggggacccctcagctcttctcttccccccaaaacc
caaggacacccctcatgactctcccgaccccttgaggtcacttgcgtgggtgggtggacgtgagccacgaagacctgaggtca
agttcaactggtagctggacggcgtggaggtgcataatgccaaagacaaagccccgggaggagcagtagaacagcacgtac
cgggtgttcagcgtctcaccgtcttgcaccaggactggctgaatggcaaggagtacaagtgaaggtctcccaaaaagc
ctccccagcccccatcgagaaaaccatctccaaagccaaagccagccccgggaaccacaggtgtacaccttggccccat
ccccgggaggagatgaccaagaaccaggctcagctgacctgcccgggtcgaaggtctctatccagcgacatcgccgtggag
tgaggagagcaatggccagcccgagaaacatacaagaccacccctcccgctgctggactccgacggctcttcttctctla
cagcaagctcaccgtggacaagagcaggtggcagcagggcaacgtcttctcatgctccgtgatgcatgaggtctgcaca
accactacaccagaagacctcttccctgtctccccggcaaa

Signal sequence (1-57), Variable region (58-411), Constant region (412-1401)

(SEQ ID NO: 108 of Sequence Listing)

Figure 117

MKHLWFFLLVAAPRWVLSQVQLVQSGAEVKKPGASVKVSCKASGFTFSTSYMSWVRQAPGPSTEWMGWIYAGDGGTKYN
QKFKGRVTLTVDKSTSTAYMELSSLRSEDAVYYCATDYCYGDWFTYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTA
ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVPEPKSC
DKHTHTCPPCPAPPELLGGPSVFLFPPPKPDTLMI SRTPEVTCVYVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVVFSCSYMHEALHNHYTQKSLSLSPGK

Signal sequence (1-19), Variable region (20-137), Constant region (138-467)

(SEQ ID NO: 109 of Sequence Listing)

Figure 118

GGCAGAGTGACCCTGACCGCCGACAAGAGCACCAGCACC

(SEQ ID NO: 110 of Sequence Listing)

Figure 119

GGTGCTGGTGCTCTTGTCCGCGGTCAGGGTCACTCTGCC

(SEQ ID NO: 111 of Sequence Listing)

Figure 120

CTGTTTCAAGGTCCGAGCAATAACAAACGTGCACCGTATTGG
(SEQ ID NO: 112 of Sequence Listing)

Figure 121

CGCAAGCTTGTGACTCAAACAACATCCAGATGATAGGTATG
(SEQ ID NO: 113 of Sequence Listing)

FIG. 122

	Name	KD (M)	Analyte (Antigen variant)
1	hFR2-14_H1/L1	1. 2E-08	I I I b
2	hFR2-14_H2/L1	8. 7E-09	I I I b
3	hFR2-14_H3/L1	7. 4E-09	I I I b
4	hFR2-14_H4/L1	5. 4E-09	I I I b
5	cFR2-14	6. 3E-08	I I I b
6	hFR2-14_H1/L1	3. 0E-09	I I I c
7	hFR2-14_H2/L1	6. 4E-09	I I I c
8	hFR2-14_H3/L1	3. 3E-09	I I I c
9	hFR2-14_H4/L1	2. 8E-09	I I I c

FIG. 123

	Name	KD (M)	Analyte (Antigen variant)
1	hFR2-14_H5/L1	9. 5E-10	III c
2	hFR2-14_H6/L1	1. 5E-09	III c
3	hFR2-14_H7/L1	1. 2E-09	III c
4	hFR2-14_H8/L1	1. 5E-09	III c
5	hFR2-14_H9/L1	5. 1E-10	III c
6	hFR2-14_H10/L1	6. 9E-10	III c
7	hFR2-14_H11/L1	2. 1E-09	III c
8	hFR2-14_H12/L1	7. 6E-10	III c
9	hFR2-14_H13/L1	6. 7E-10	III c
10	hFR2-14_H14/L1	2. 3E-09	III c
11	hFR2-14_H15/L1	3. 4E-09	III c
12	hFR2-14_H16/L1	9. 1E-10	III c
13	hFR2-14_H17/L1	1. 5E-09	III c
14	hFR2-14_H18/L1	1. 2E-09	III c
15	hFR2-14_H3/L1	6. 4E-09	III c

FIG. 124

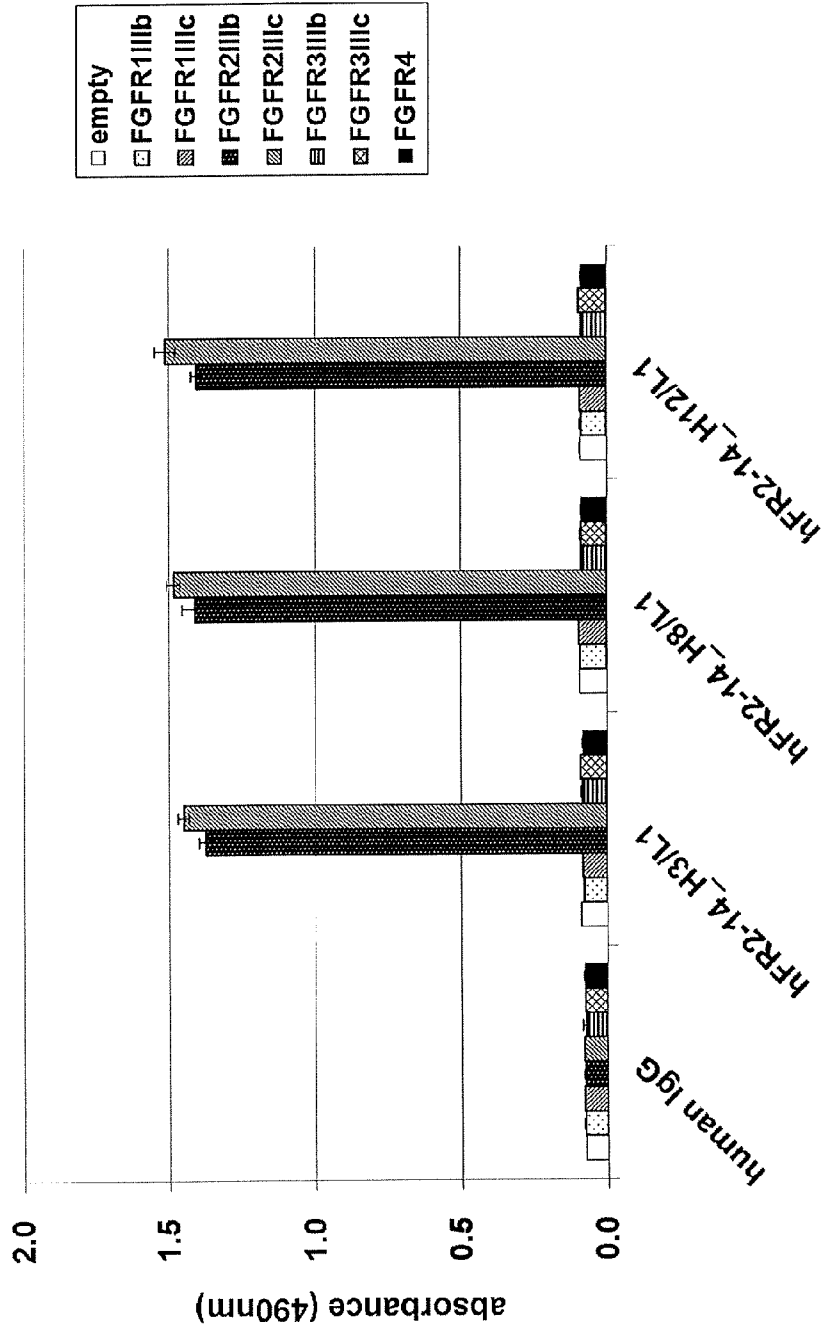


FIG. 125A

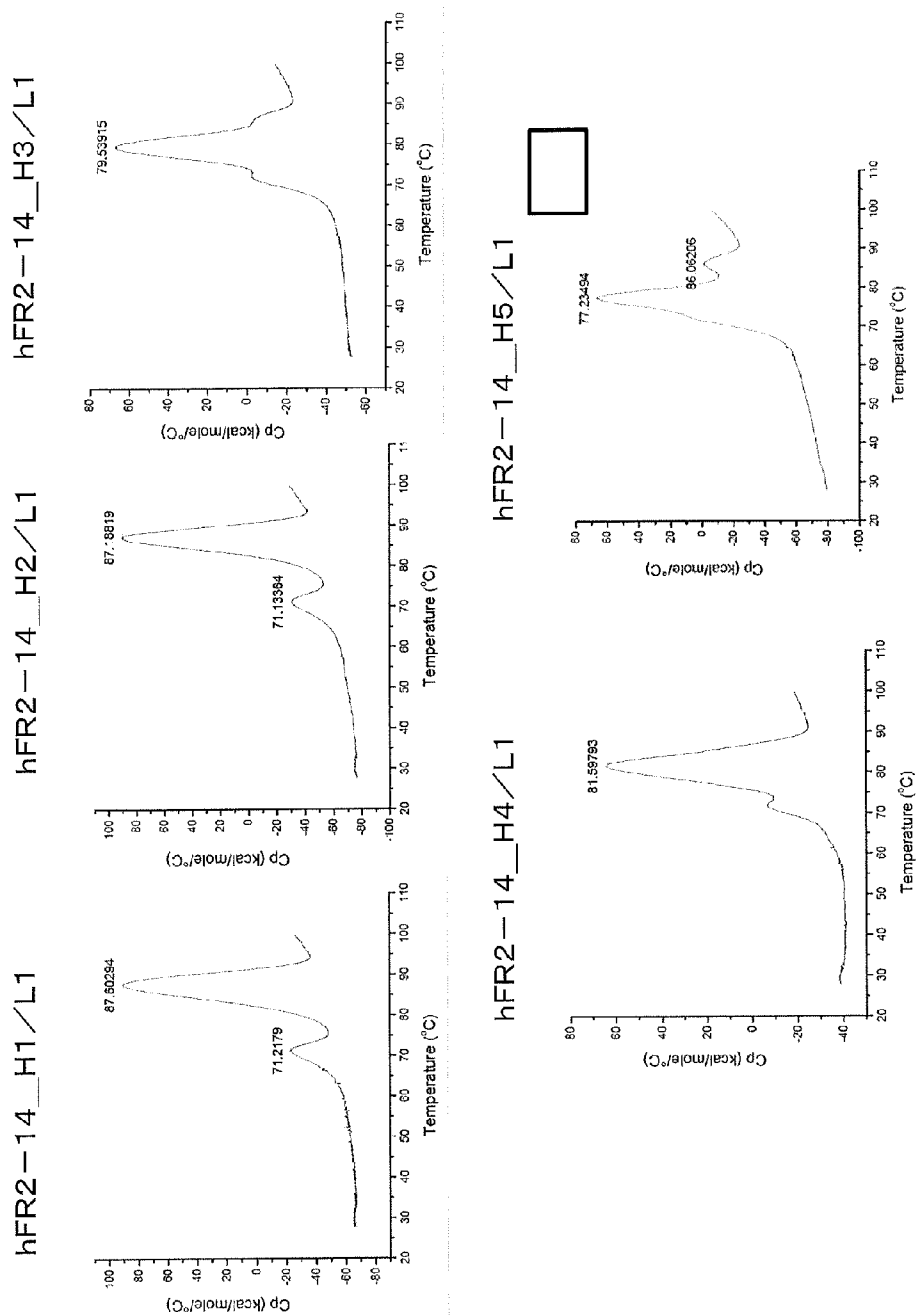


FIG. 125B

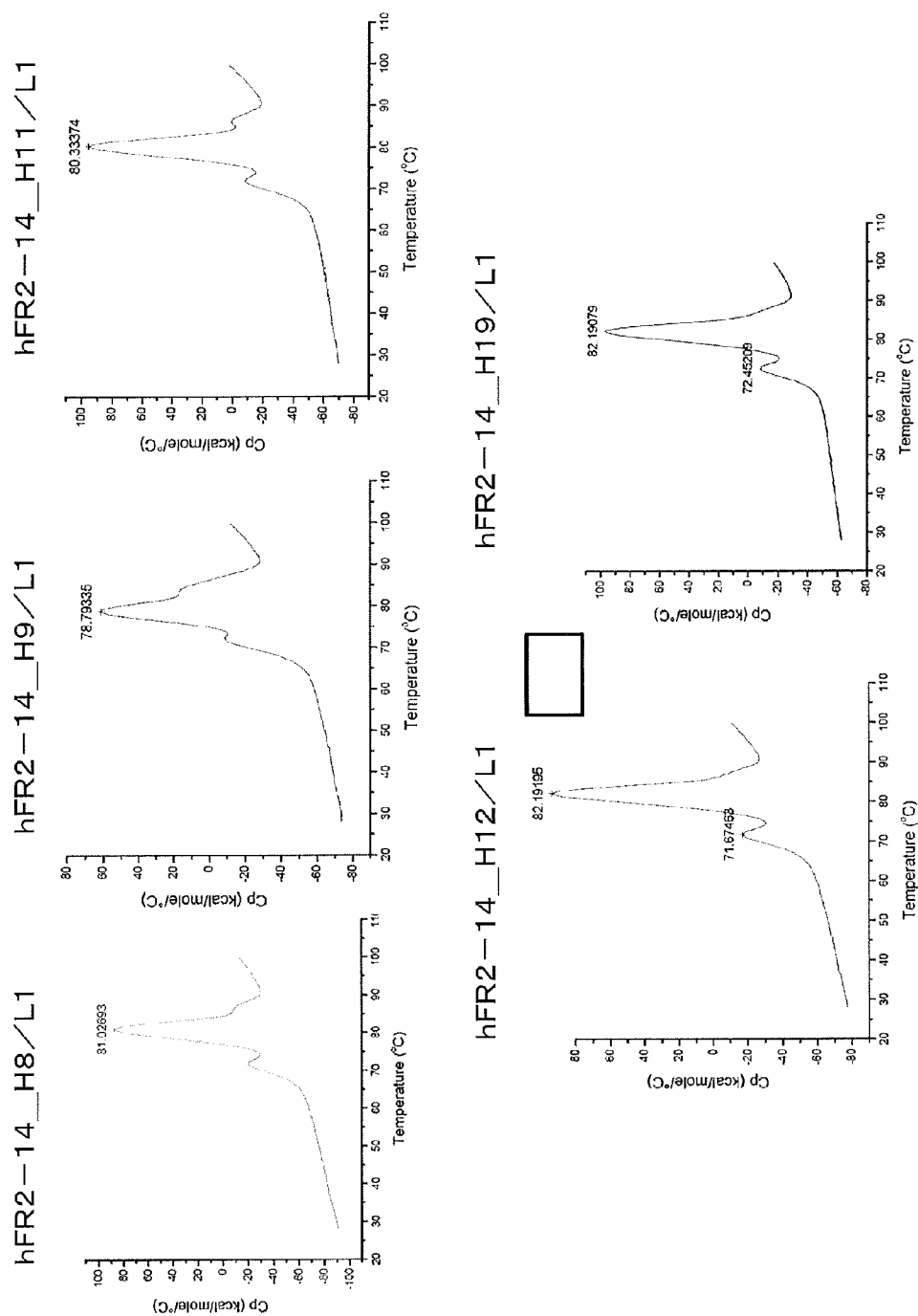


FIG. 125C

Name	T _m (°C)
hFR2-14_H1/L1	87.6
hFR2-14_H2/L1	87.2
hFR2-14_H3/L1	79.5
hFR2-14_H4/L1	81.6
hFR2-14_H5/L1	77.2
hFR2-14_H8/L1	81.0
hFR2-14_H9/L1	78.8
hFR2-14_H11/L1	80.3
hFR2-14_H12/L1	82.2
hFR2-14_H19/L1	82.2

FIG. 126

Experiment No.	Antibody name	Antibody-producing cell	KD (M)
1	hFR2-14_H1/L1	293F	3.4E-09
	hFR2-14_H1/L1 degraded analyte	293F	1.5E-07
	hFR2-14_H2/L1	293F	3.7E-09
	hFR2-14_H2/L1 degraded analyte	293F	4.0E-08
	hFR2-14_H3/L1	293F	1.2E-08
	hFR2-14_H3/L1 degraded analyte	293F	1.7E-07
	hFR2-14_H4/L1	293F	1.9E-09
	hFR2-14_H4/L1 degraded analyte	293F	8.3E-08
2	hFR2-14_H3/L1	293F	9.0E-09
	hFR2-14_H3/L1 degraded analyte	293F	1.1E-07
	hFR2-14_H5/L1	293F	1.5E-09
	hFR2-14_H5/L1 degraded analyte	293F	2.2E-09
	hFR2-14_H8/L1	293F	9.0E-10
	hFR2-14_H8/L1 degraded analyte	293F	1.6E-09
	hFR2-14_H9/L1	293F	1.9E-09
	hFR2-14_H9/L1 degraded analyte	293F	3.5E-08
3	hFR2-14_H11/L1	293F	1.4E-09
	hFR2-14_H11/L1 degraded analyte	293F	4.7E-09
	hFR2-14_H12/L1	293F	9.5E-10
	hFR2-14_H12/L1 degraded analyte	293F	1.3E-09
	hFR2-14_H12/L1	CHO	5.0E-09
	hFR2-14_H12/L1 degraded analyte	CHO	6.0E-09
	hFR2-14_H19/L1	CHO	5.5E-09
	hFR2-14_H19/L1 degraded analyte	CHO	4.7E-09

FIG. 127A

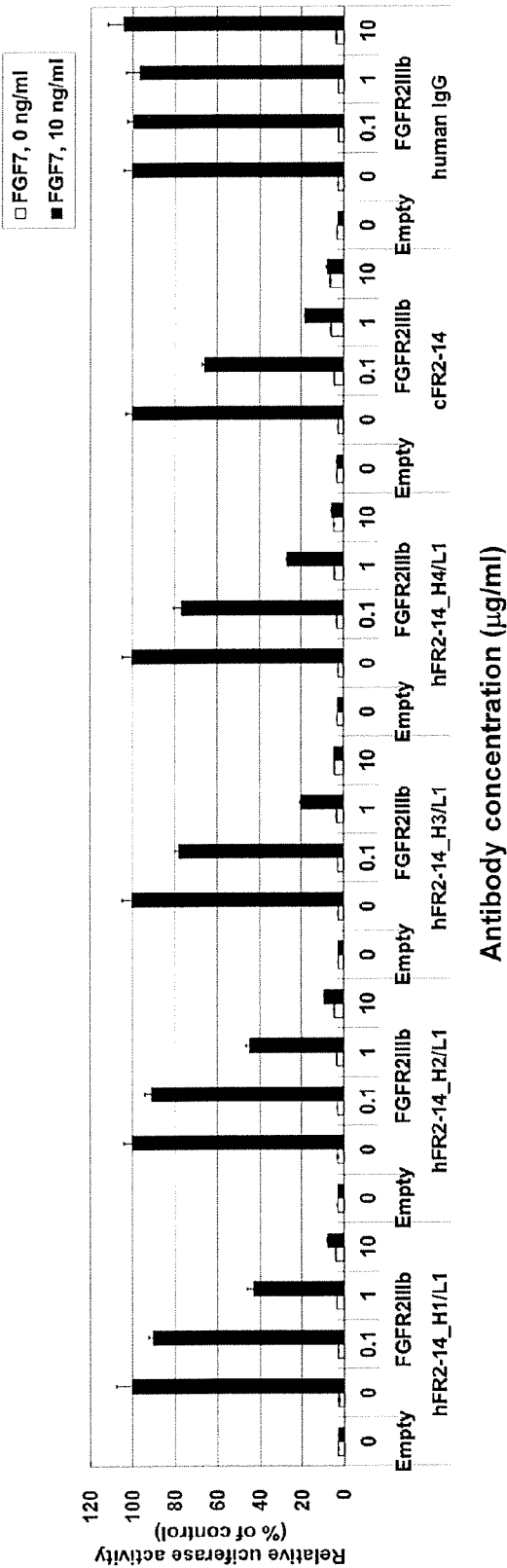


FIG. 127B

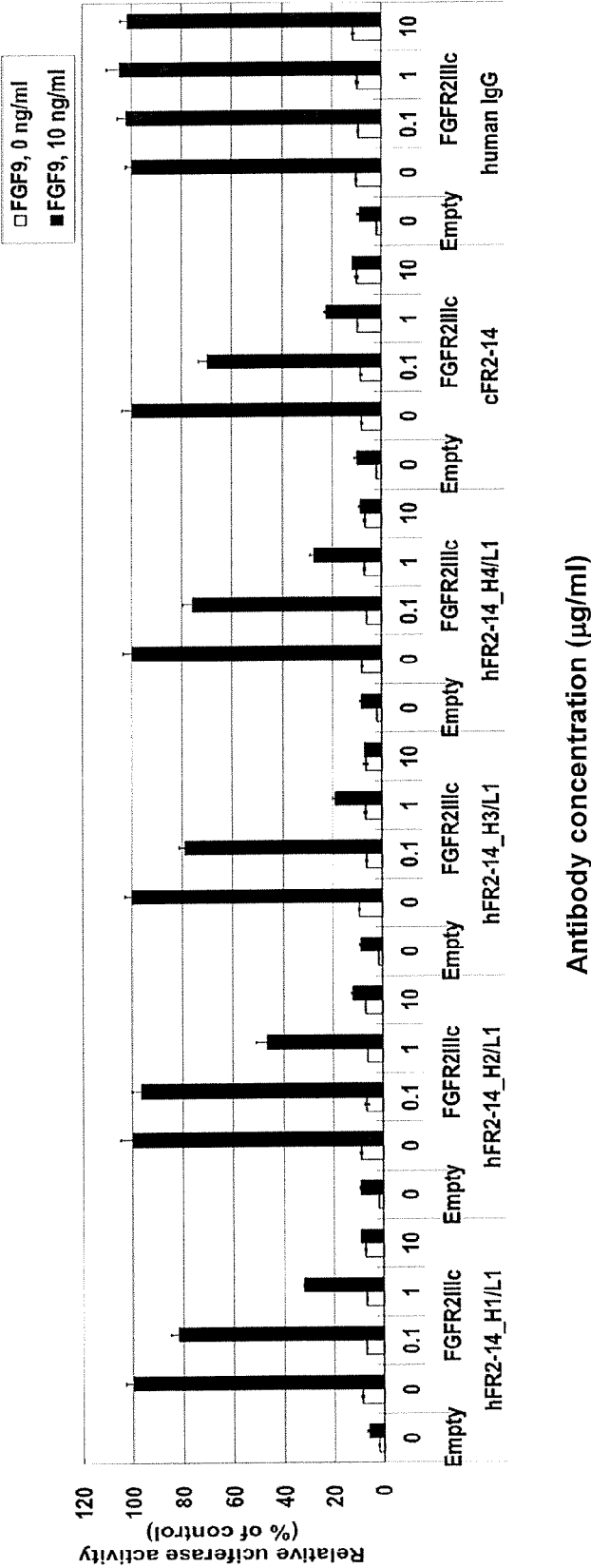


FIG. 128A

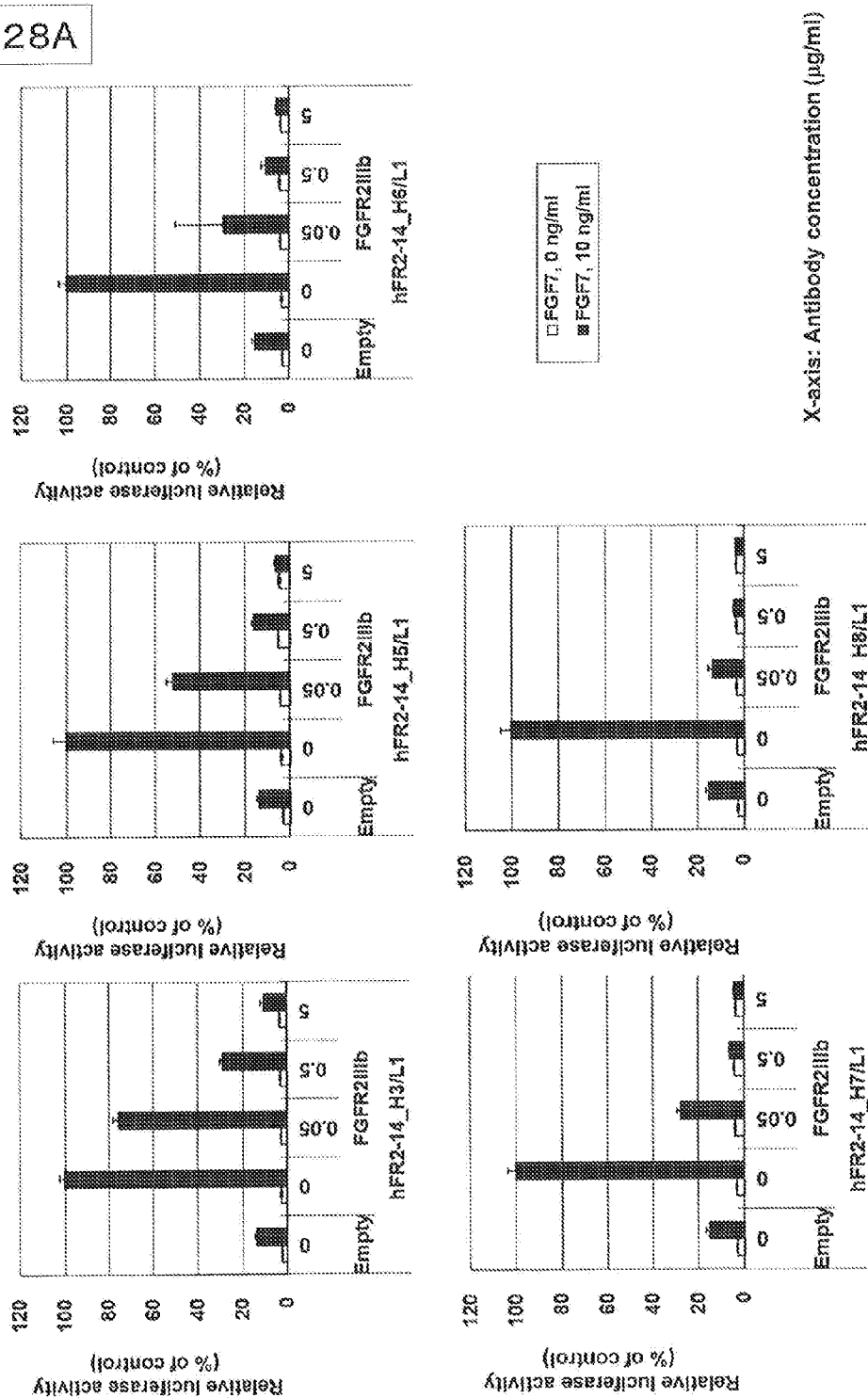
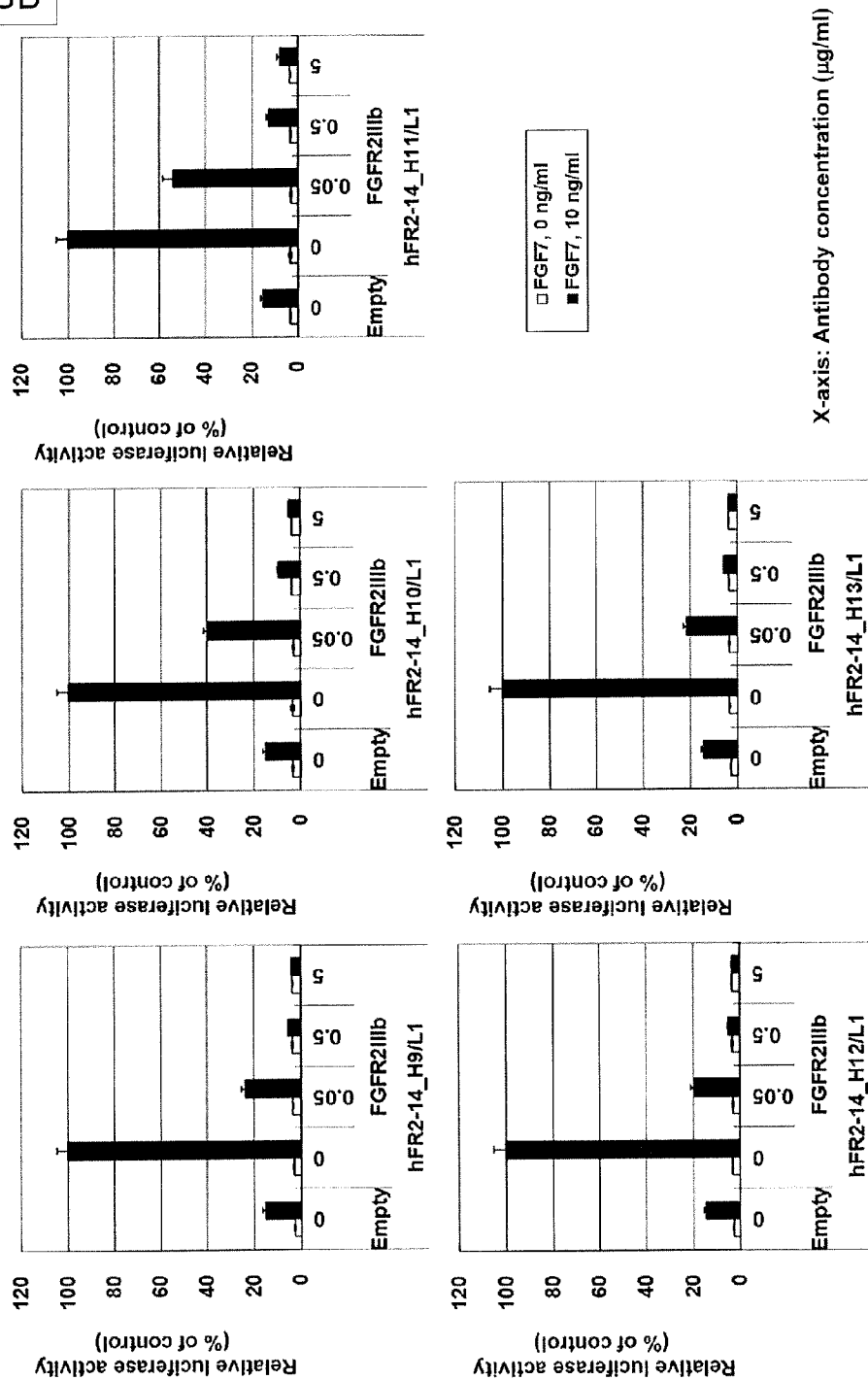


FIG. 128B



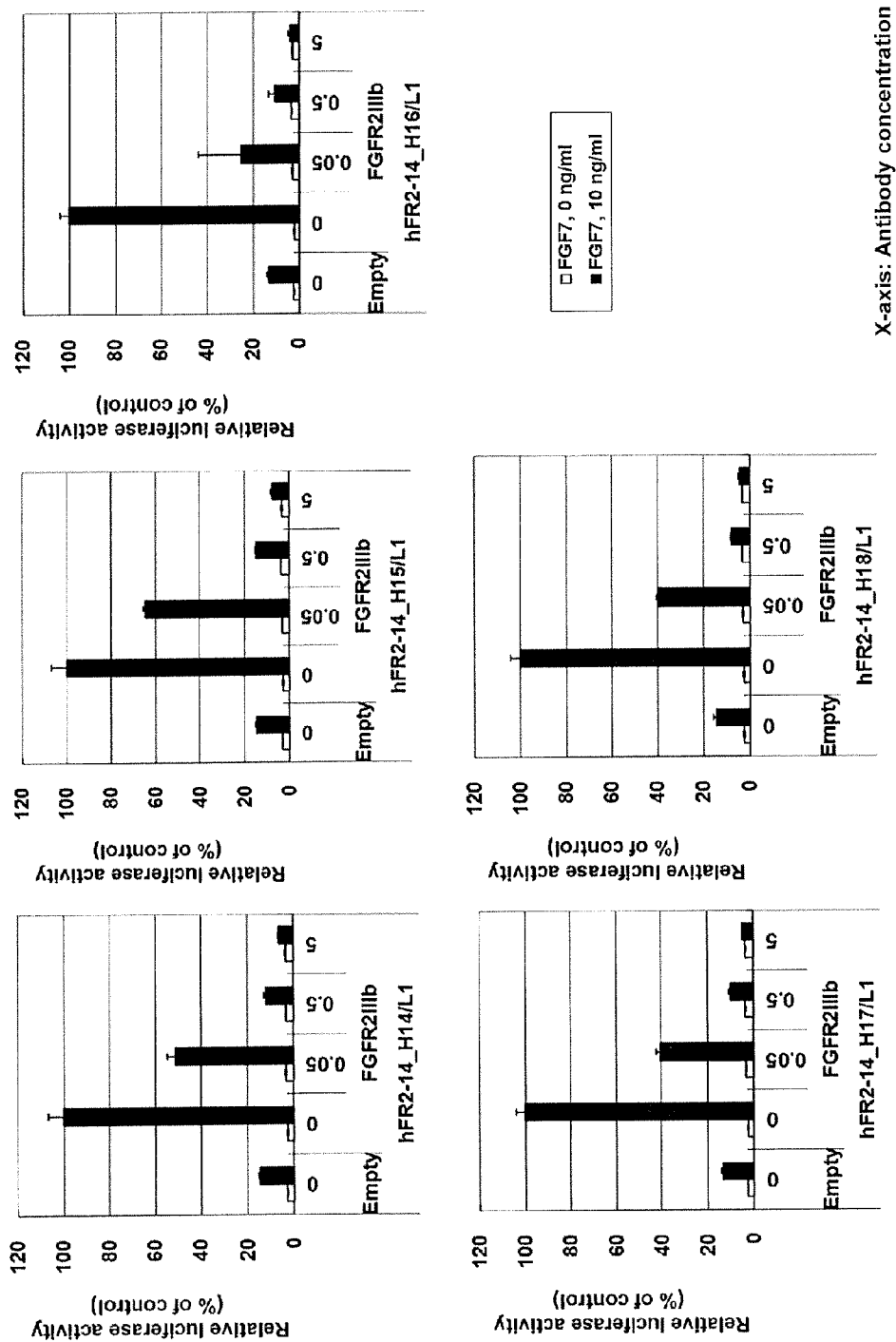


FIG. 129A

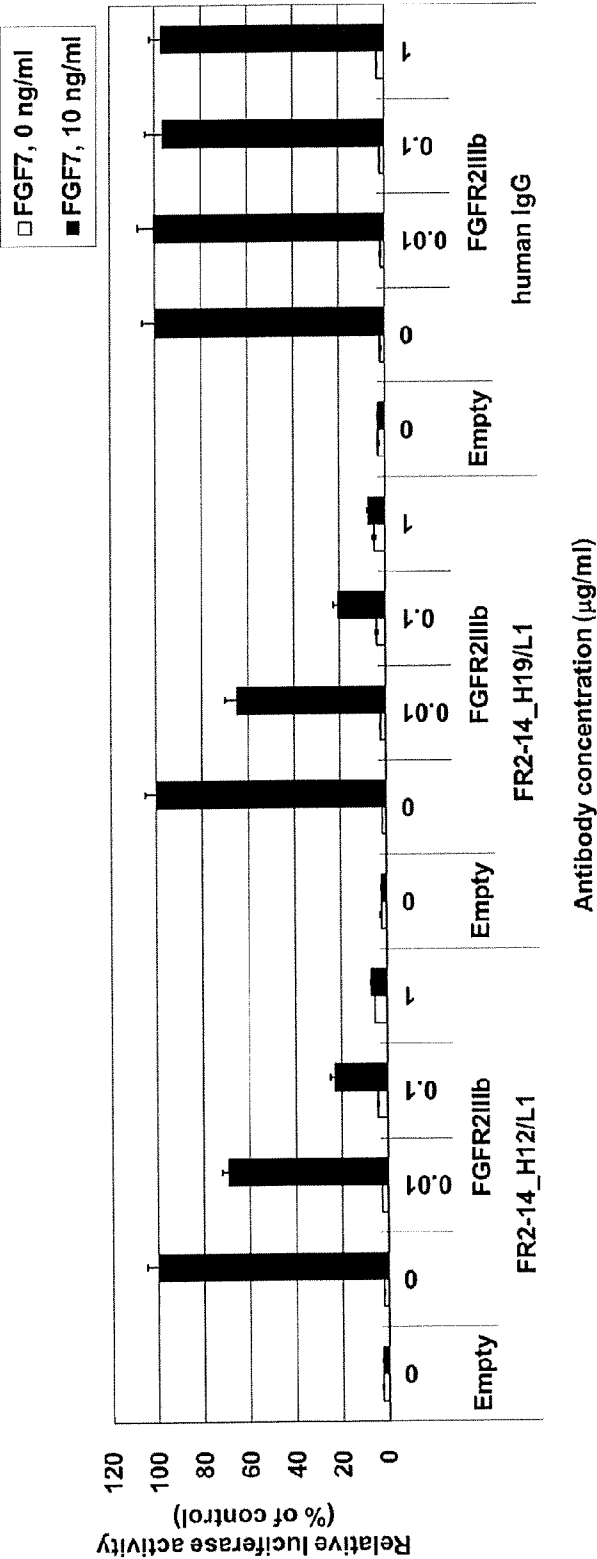


FIG. 129B

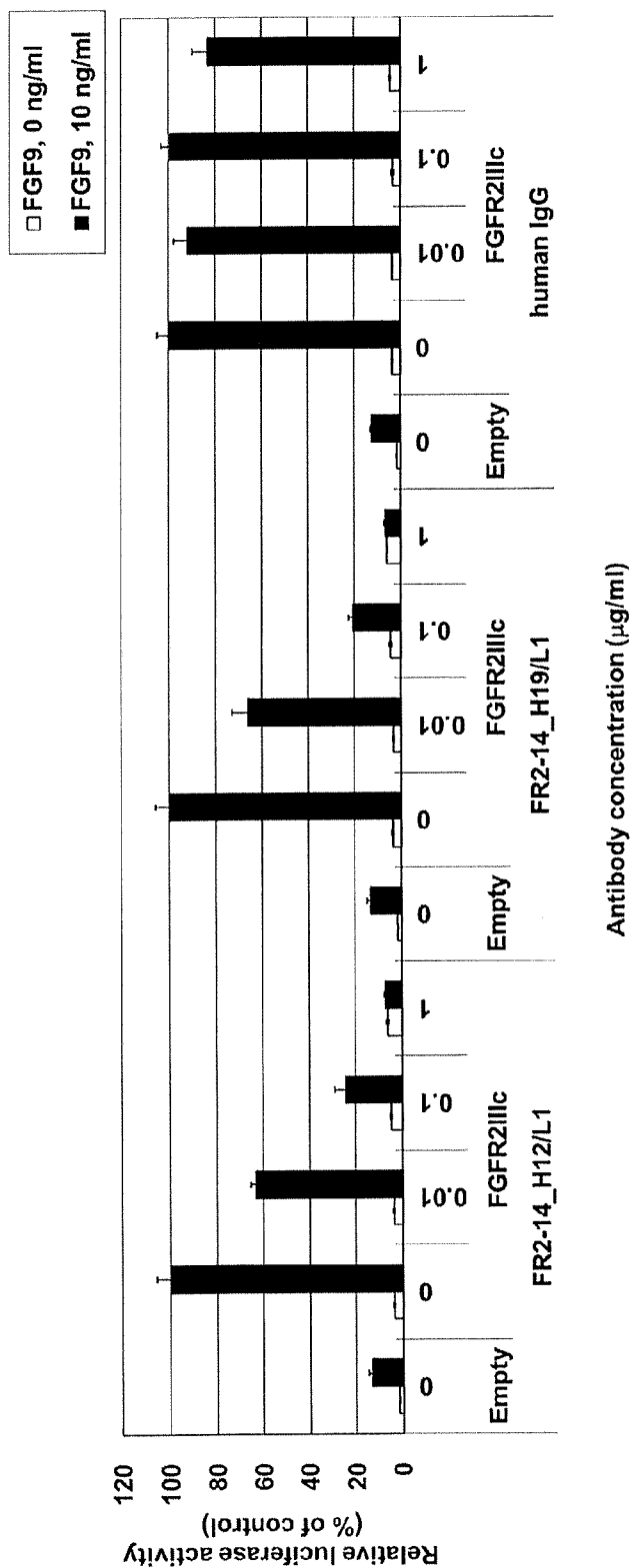


FIG. 130A

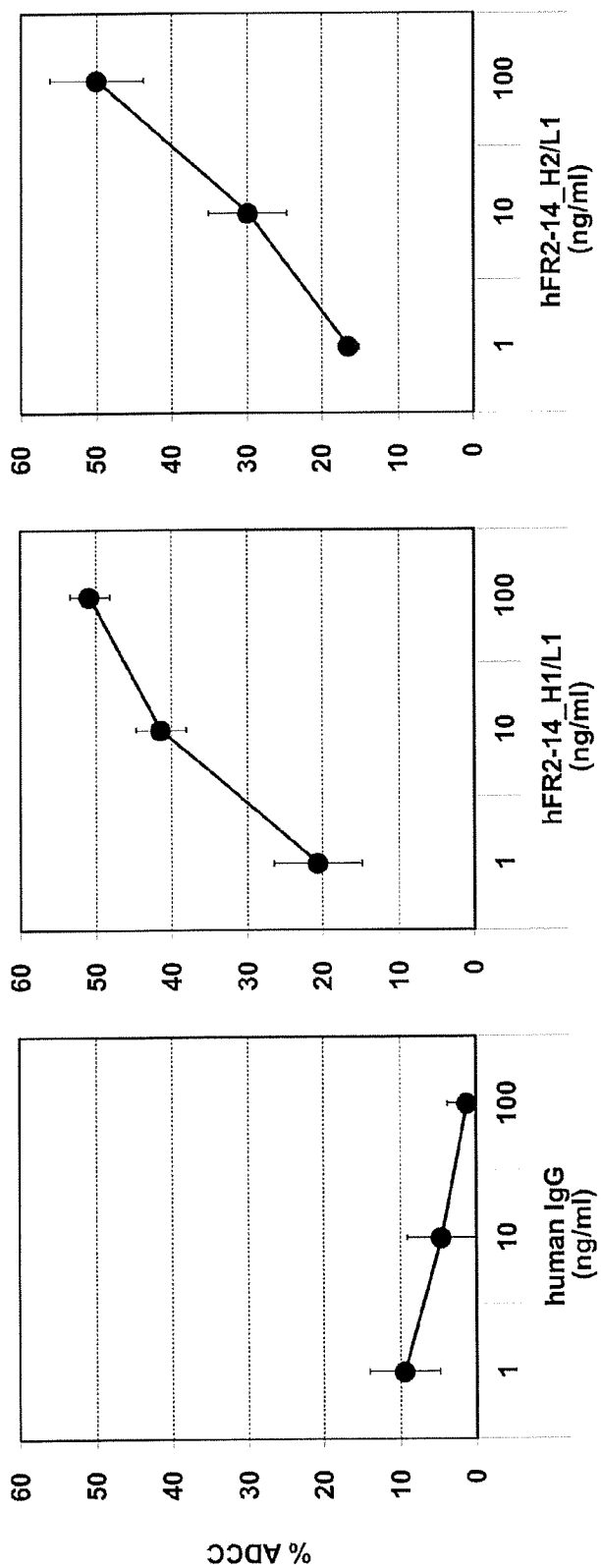


FIG. 130B

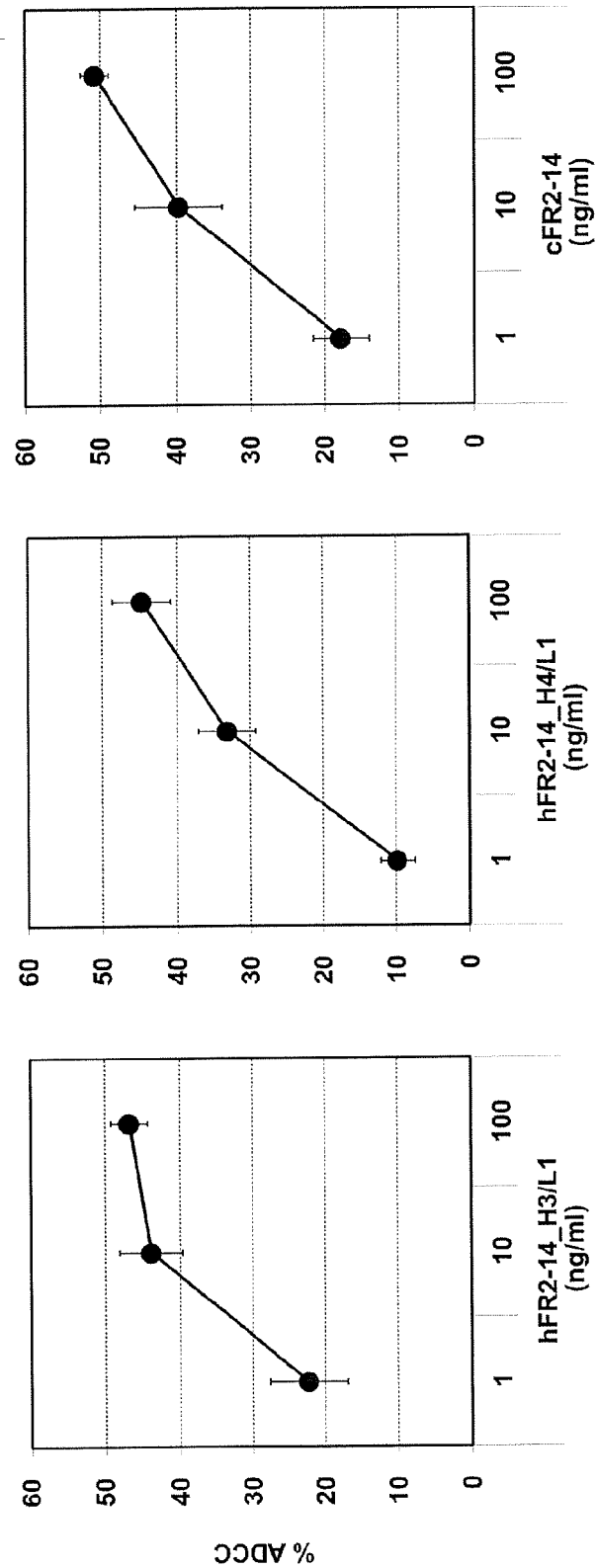


FIG. 131

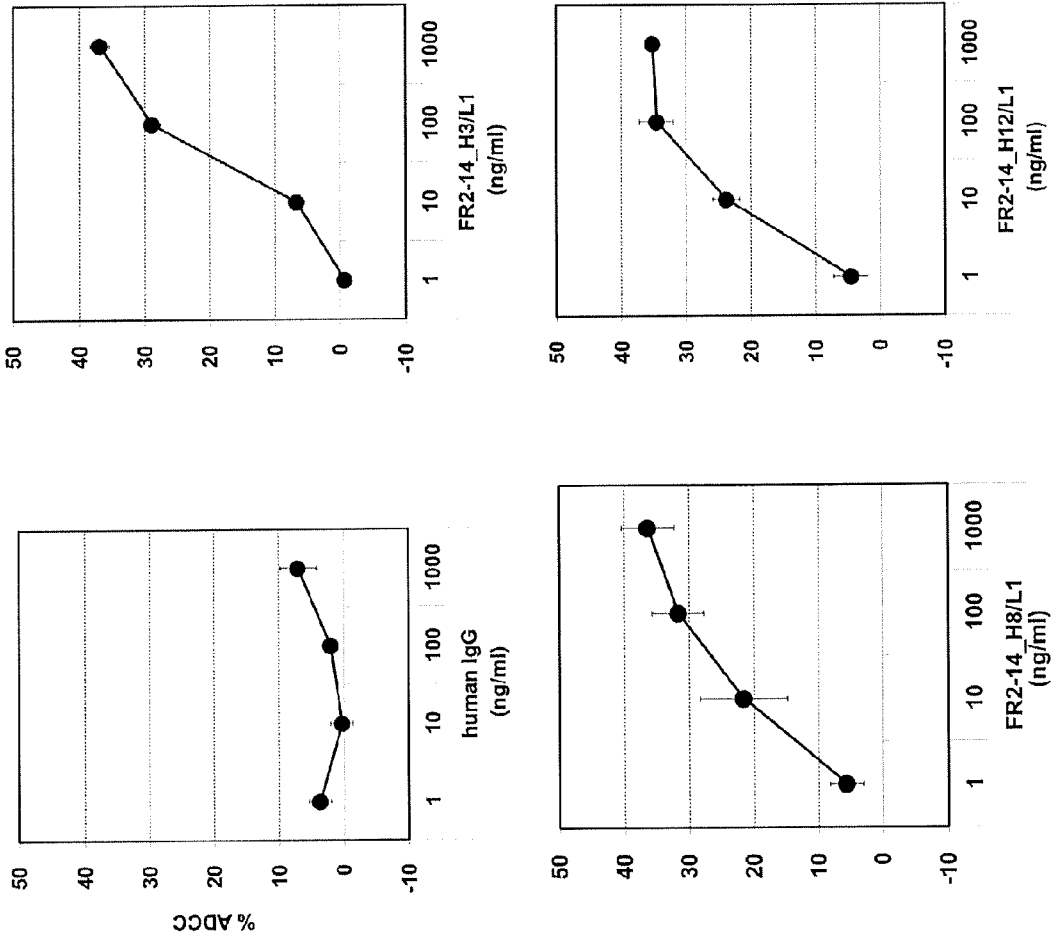


FIG. 132

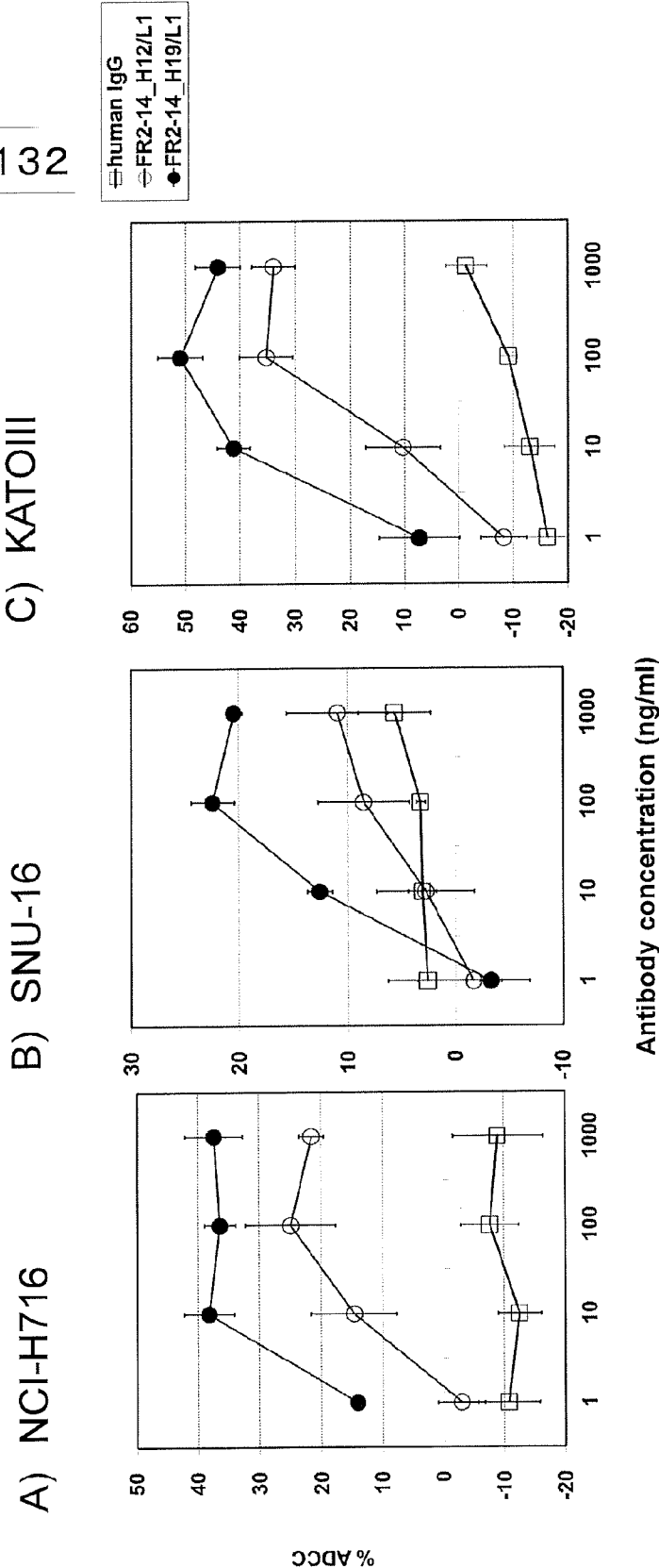
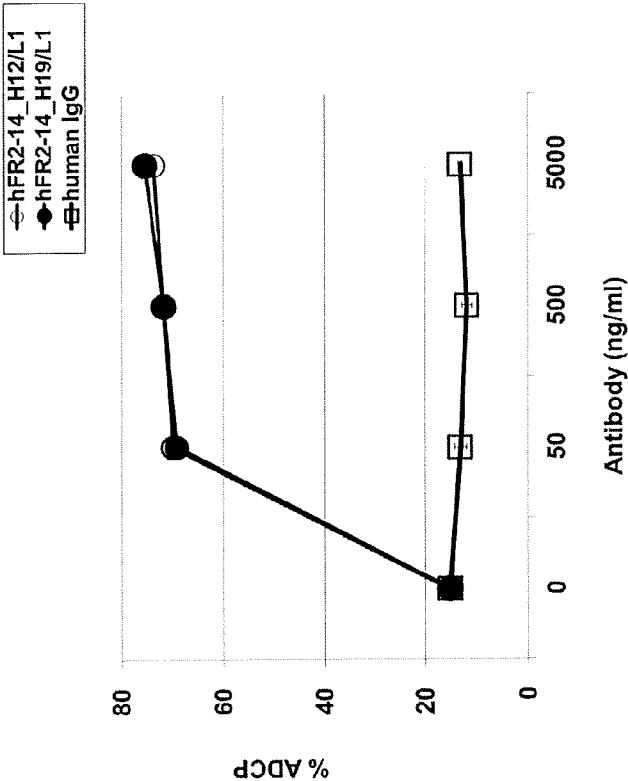


FIG. 133

B) KATOIII



A) NCI-H716

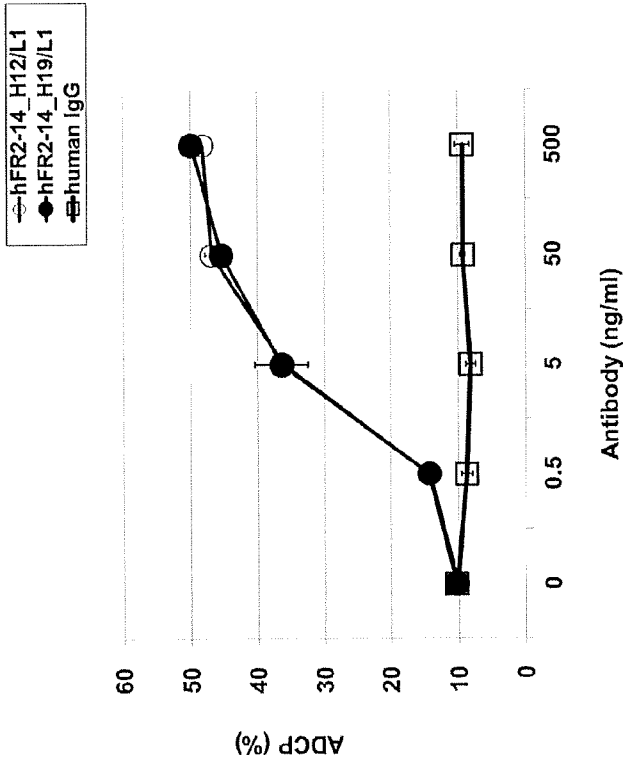


FIG. 134A

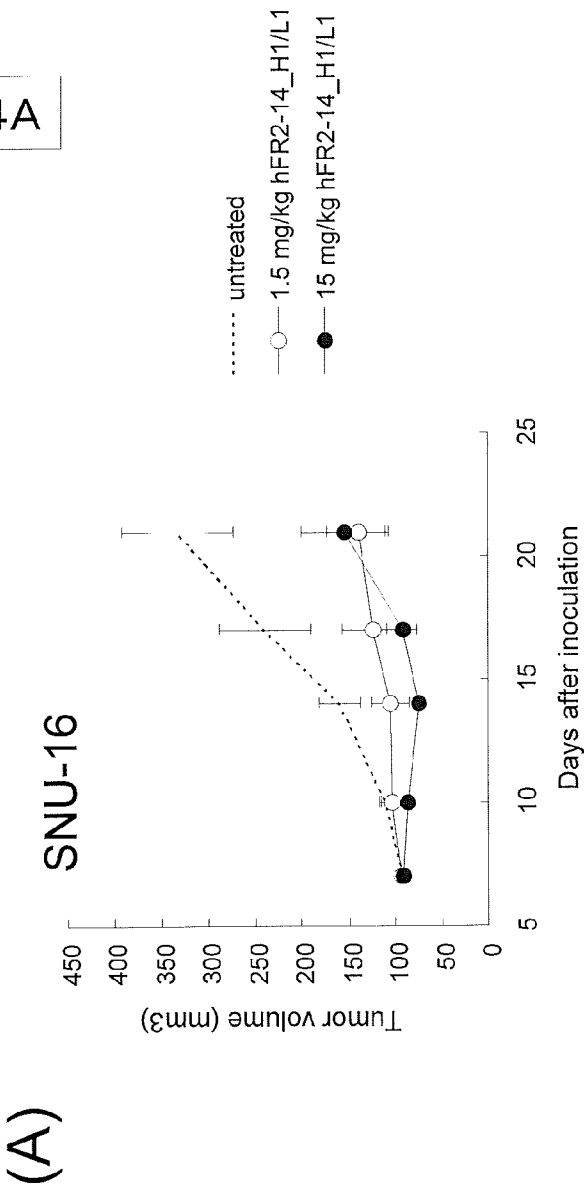


FIG. 134B

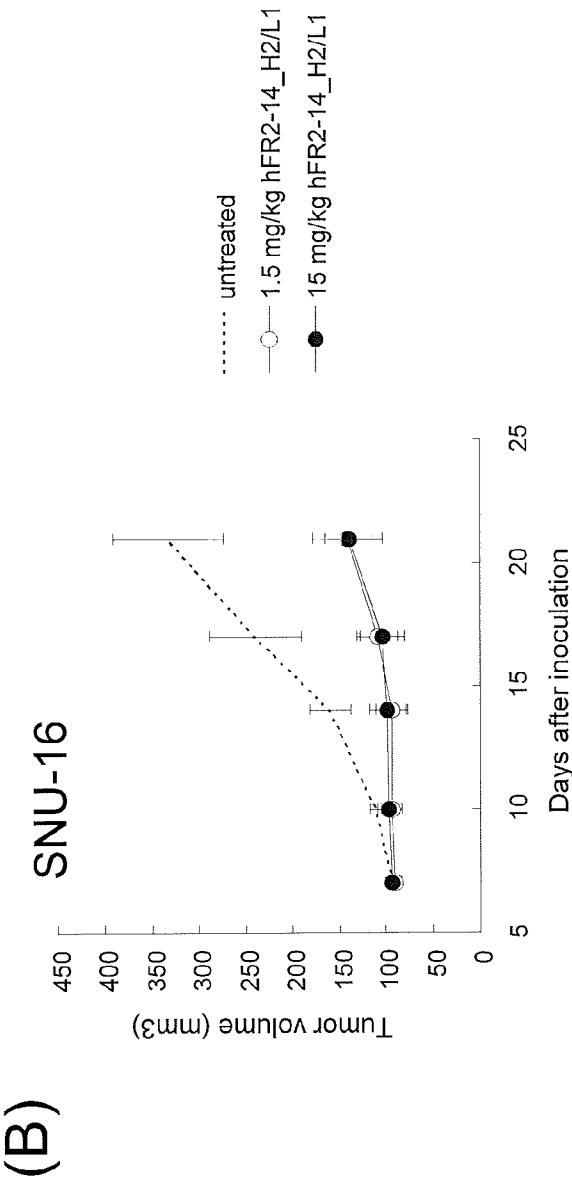


FIG. 134C

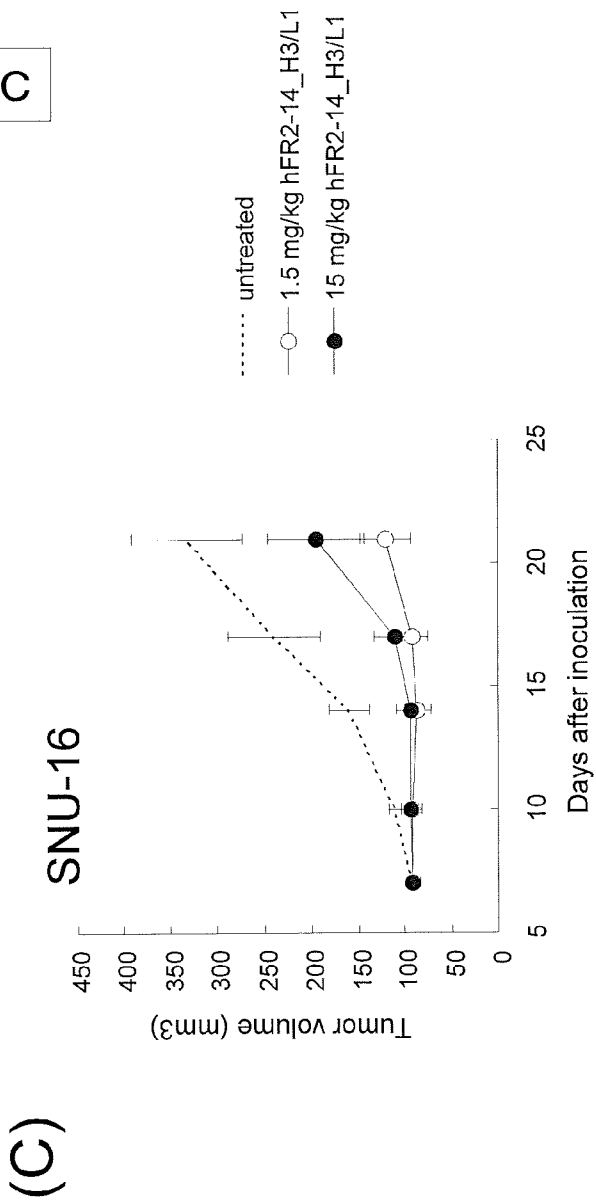


FIG. 134D

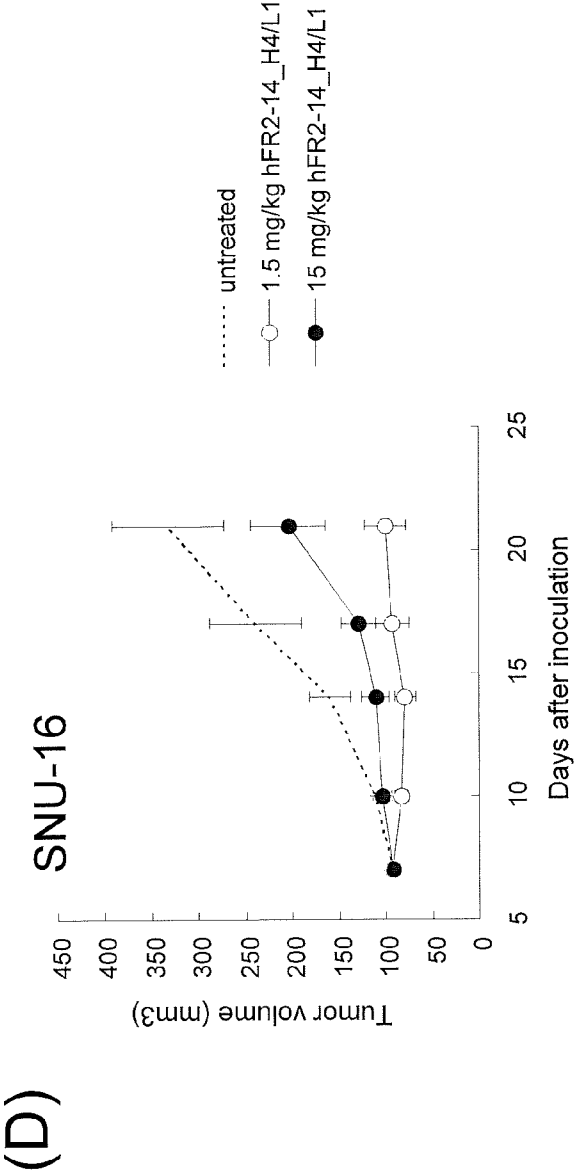


FIG. 135A

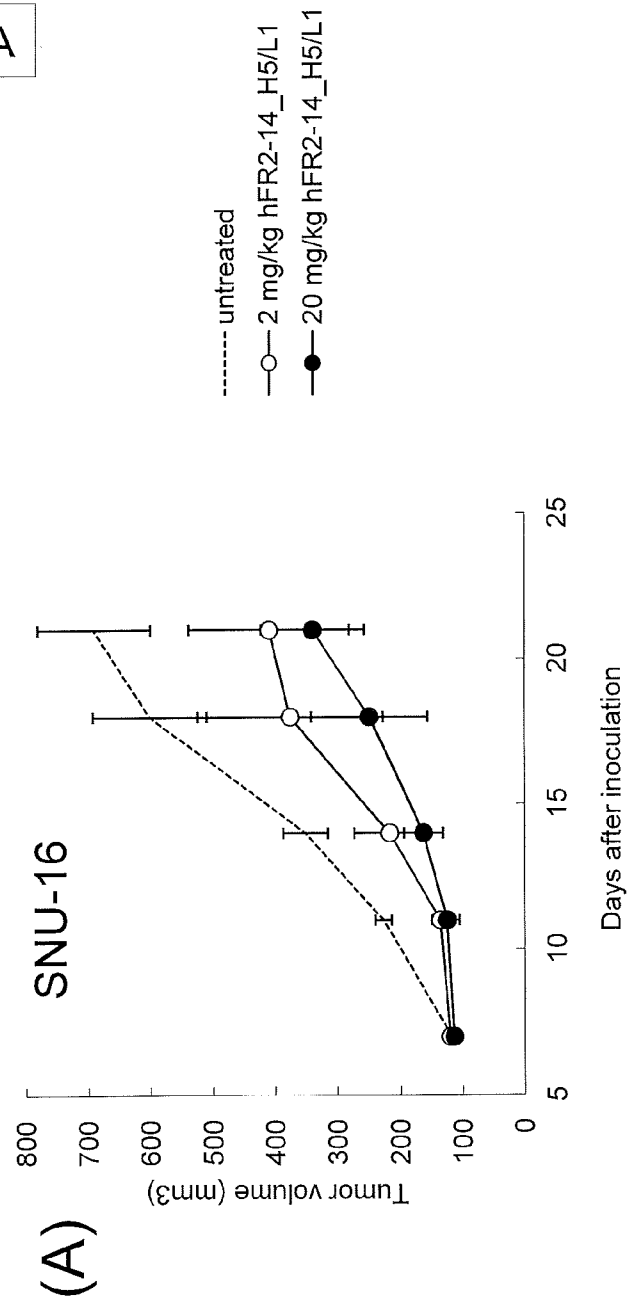


FIG. 135B

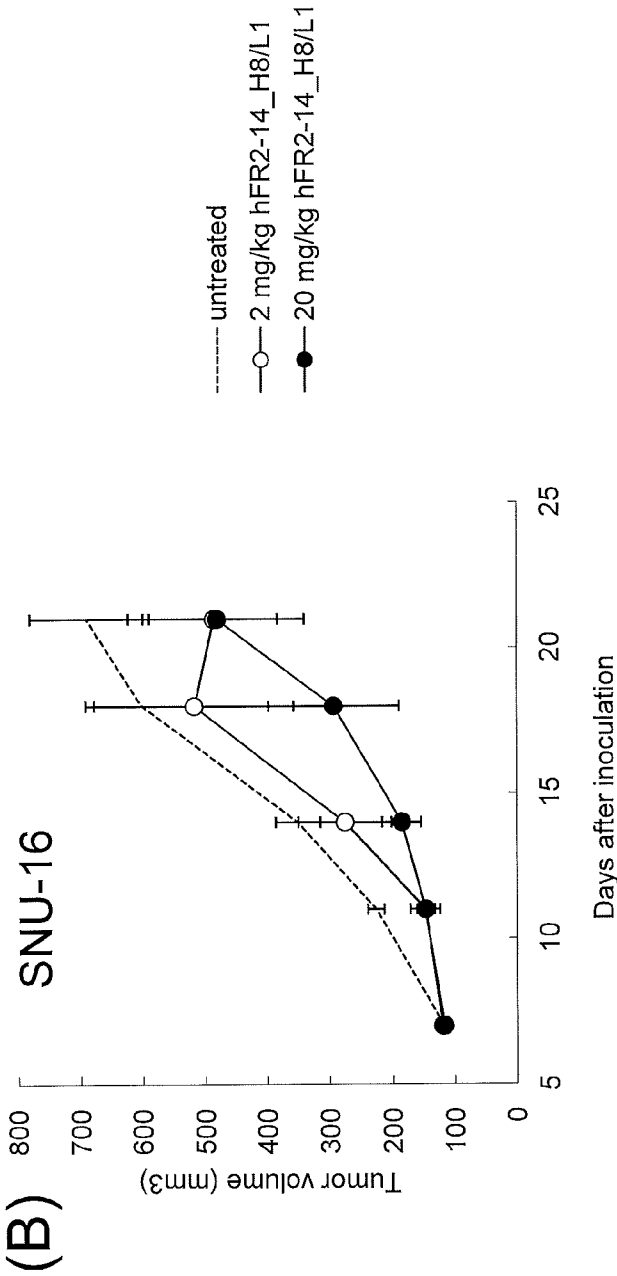


FIG. 135C

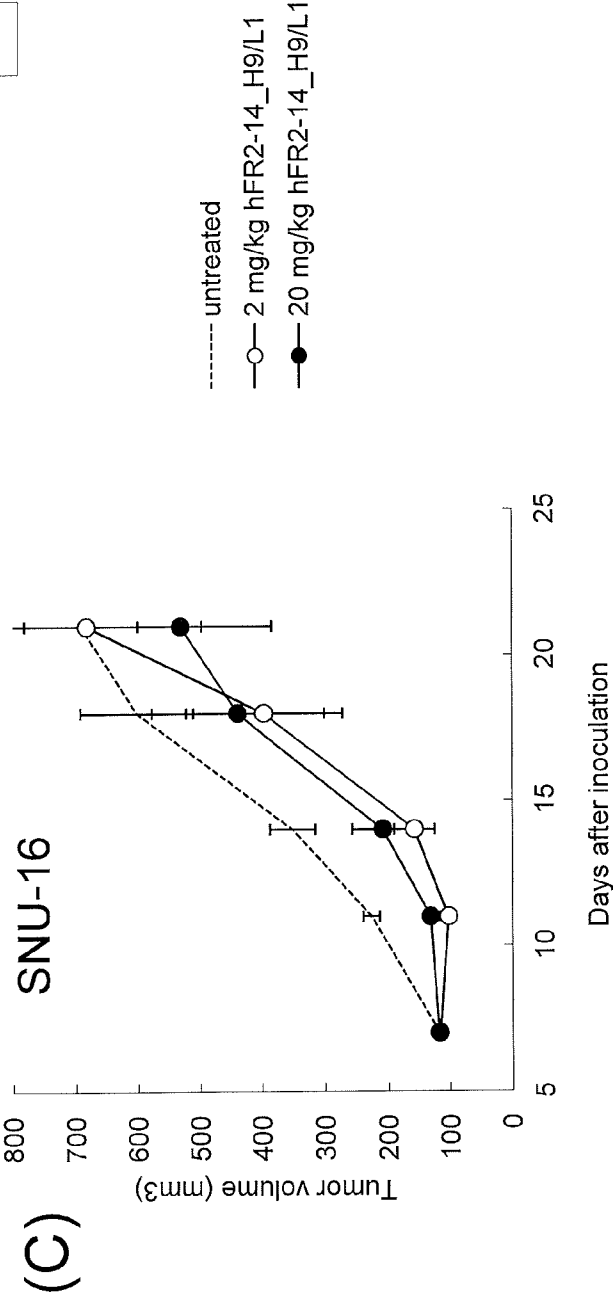


FIG. 135D

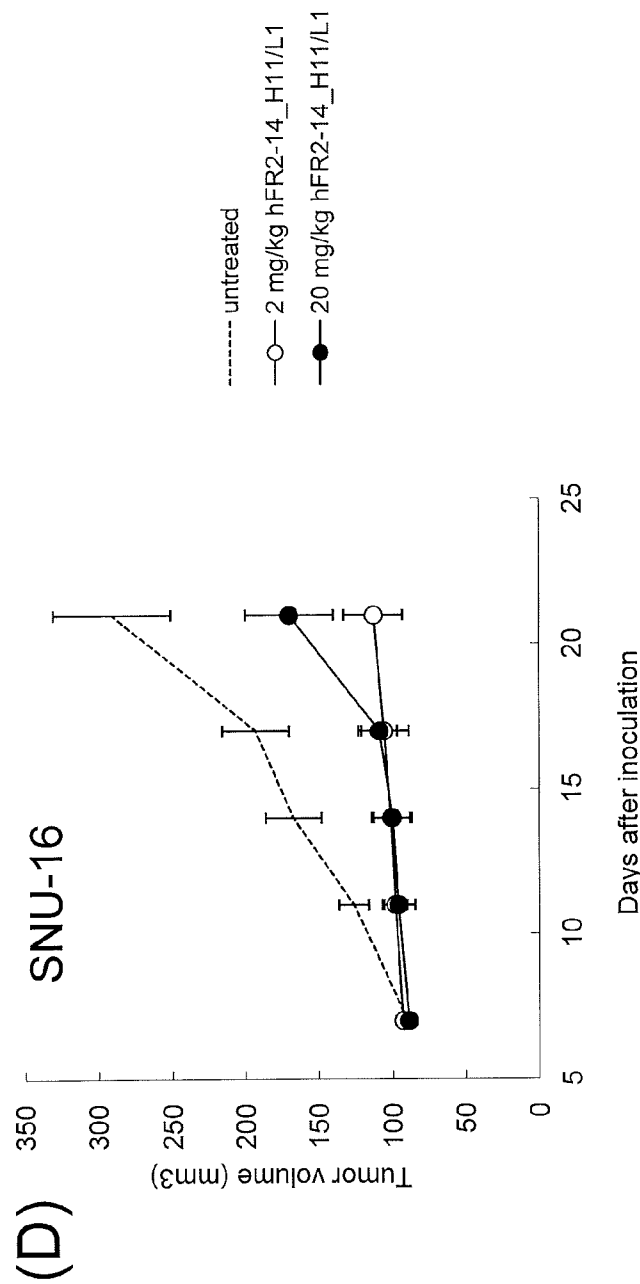


FIG. 135E

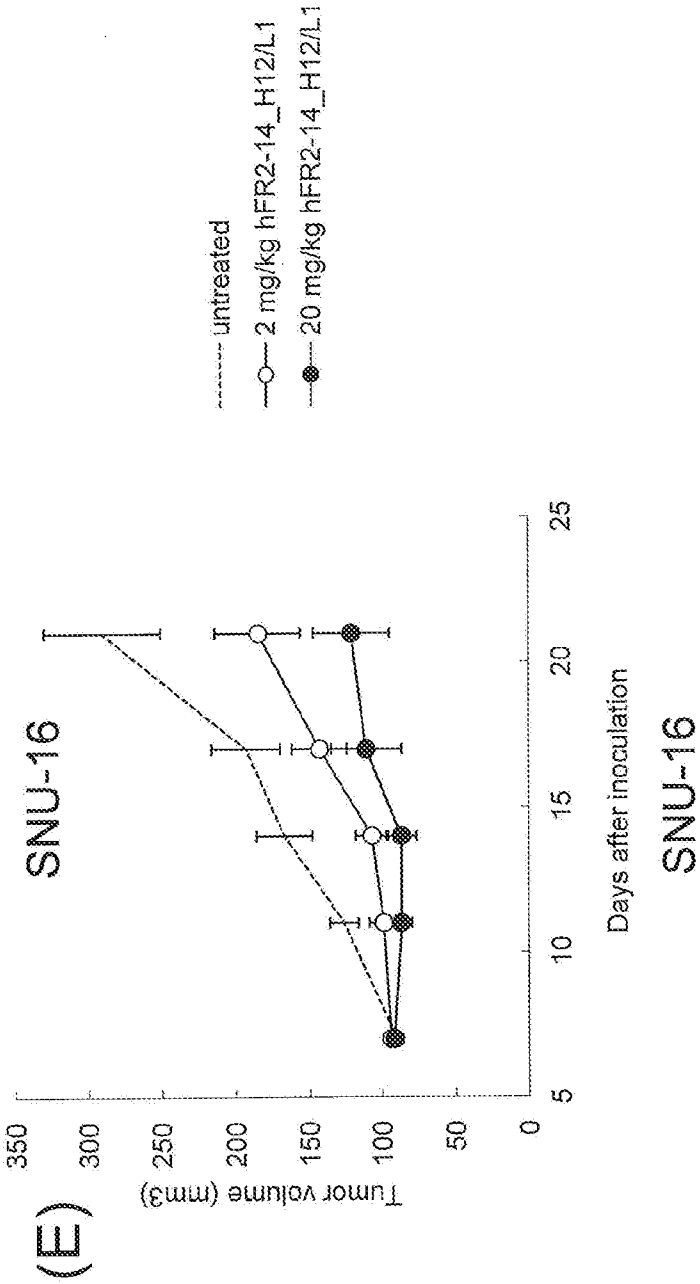


FIG. 135F

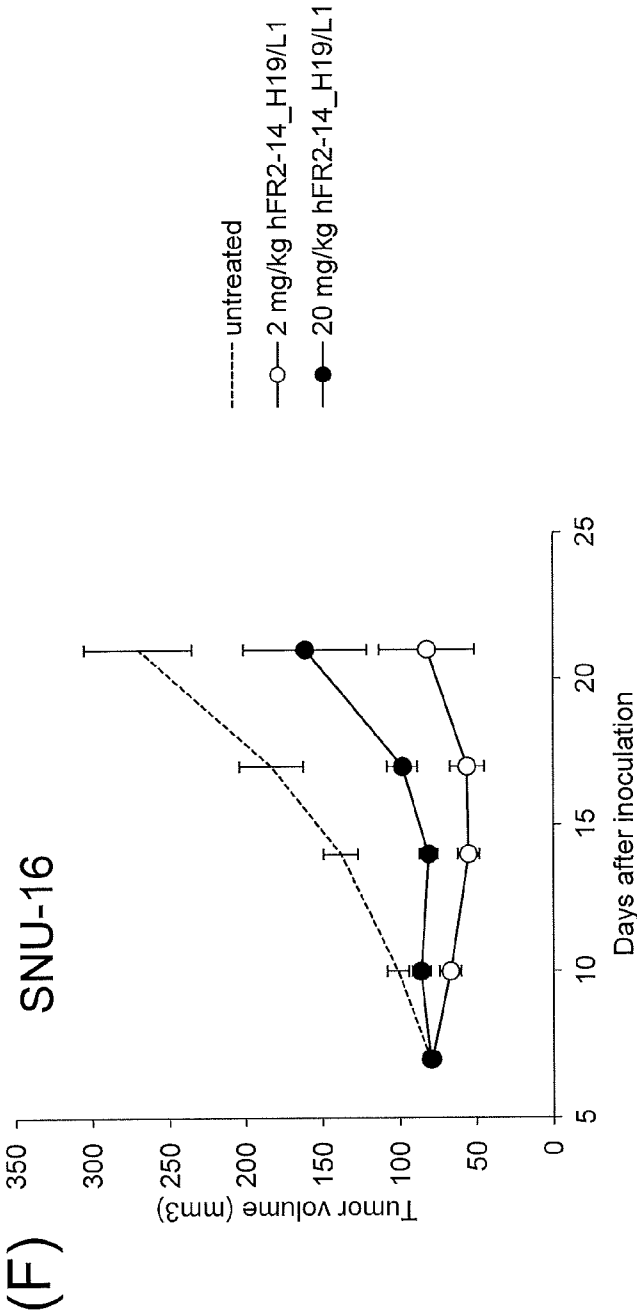
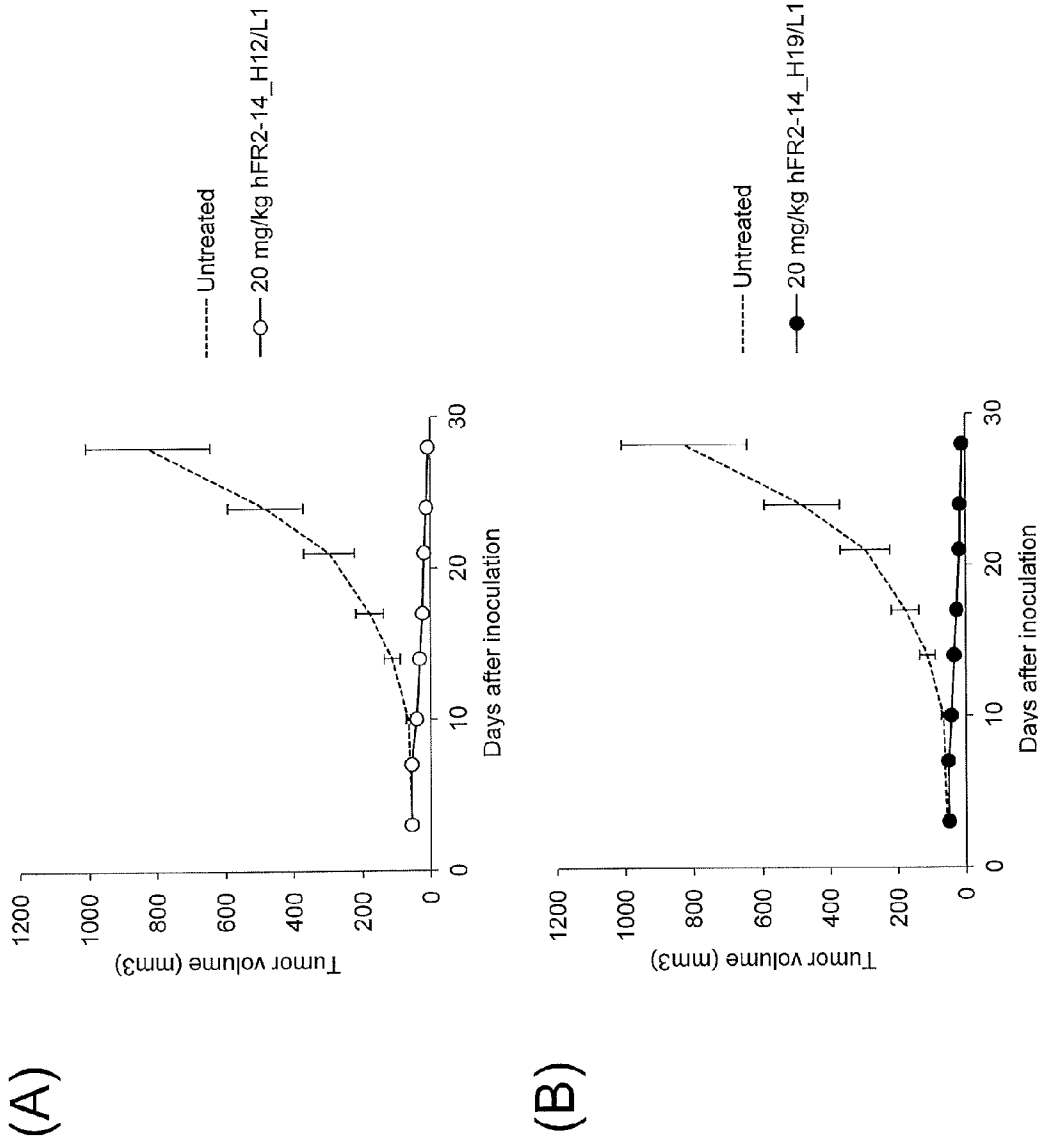
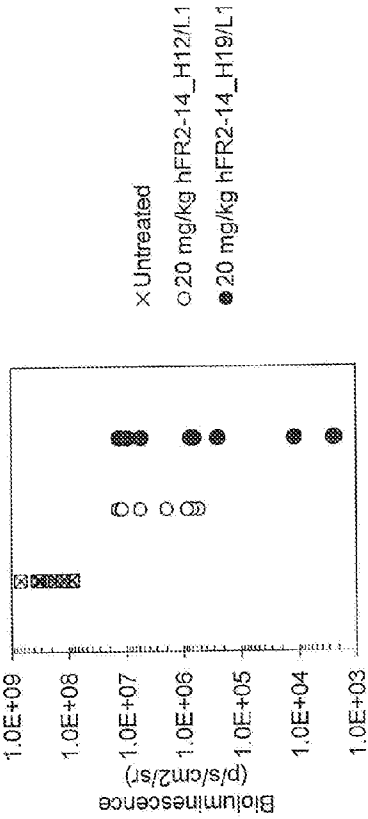


FIG. 136



(A)

FIG. 137



(B)

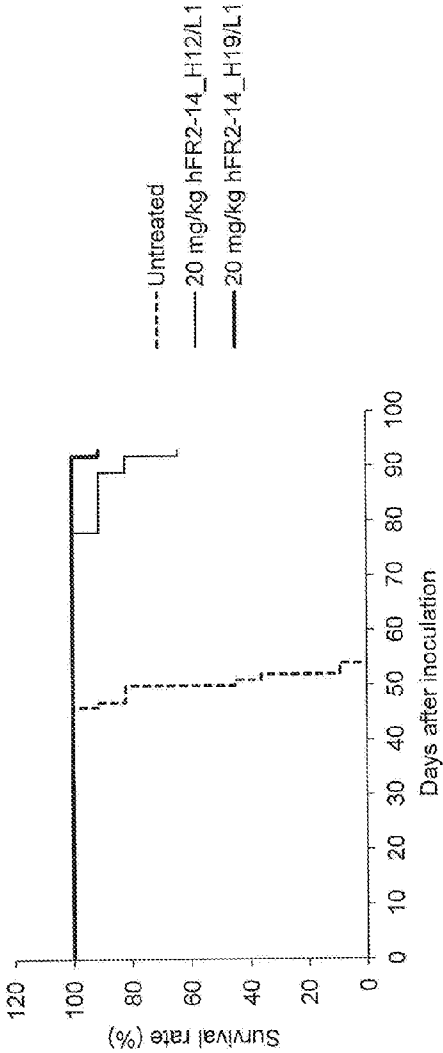


FIG. 138

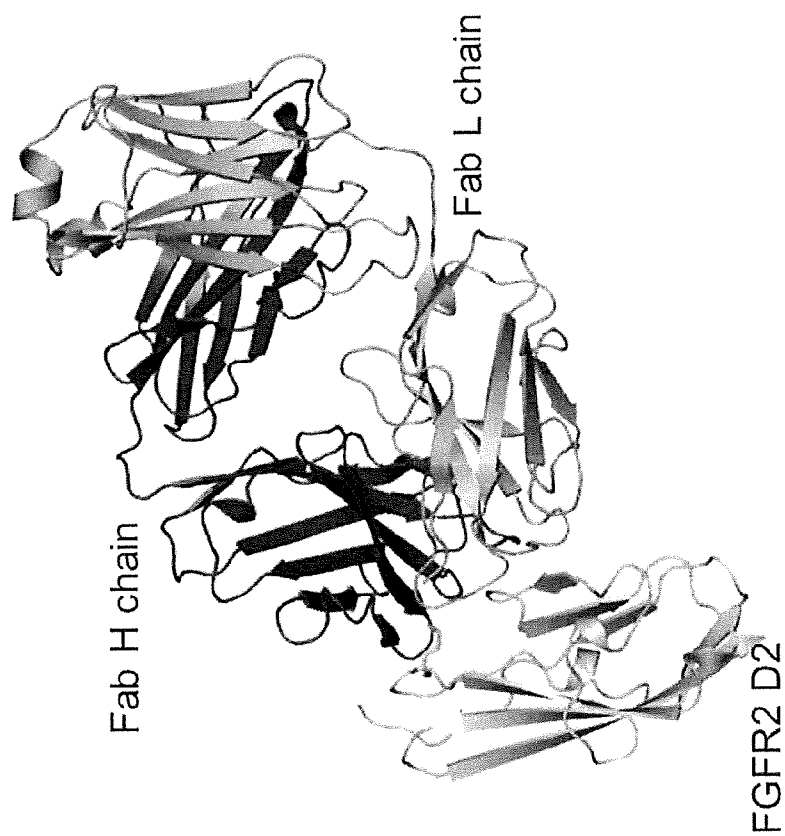


FIG. 139

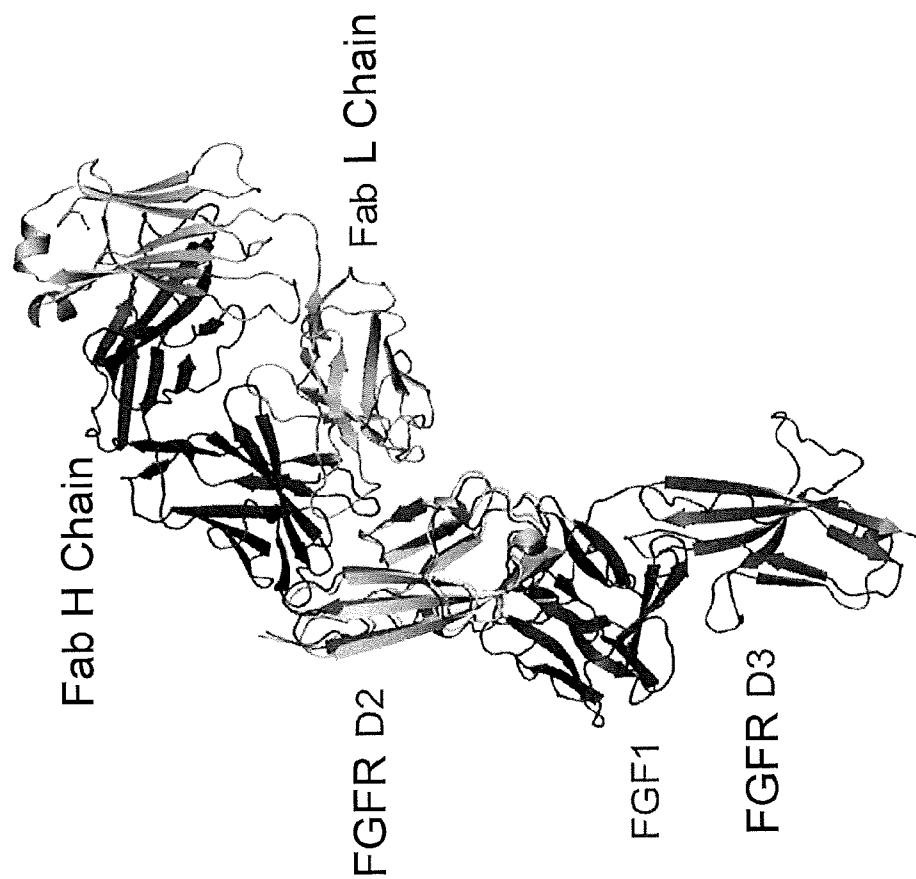


FIG. 140

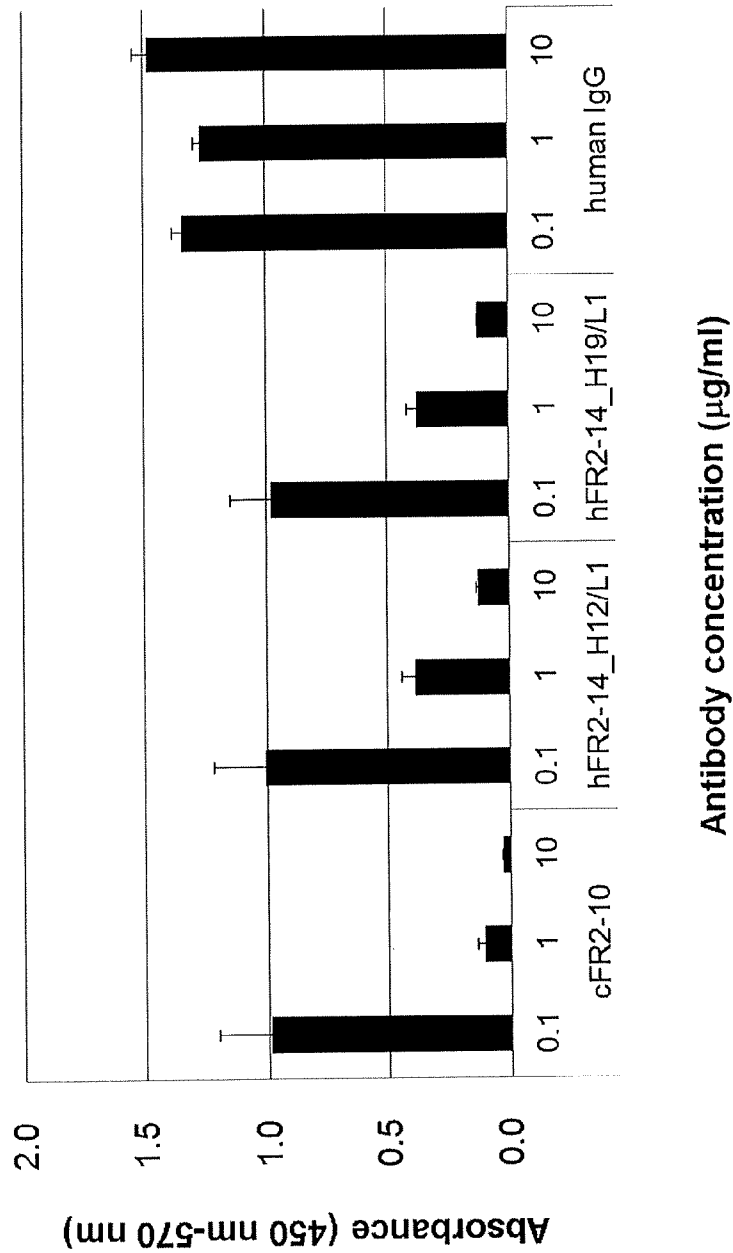


FIG. 141

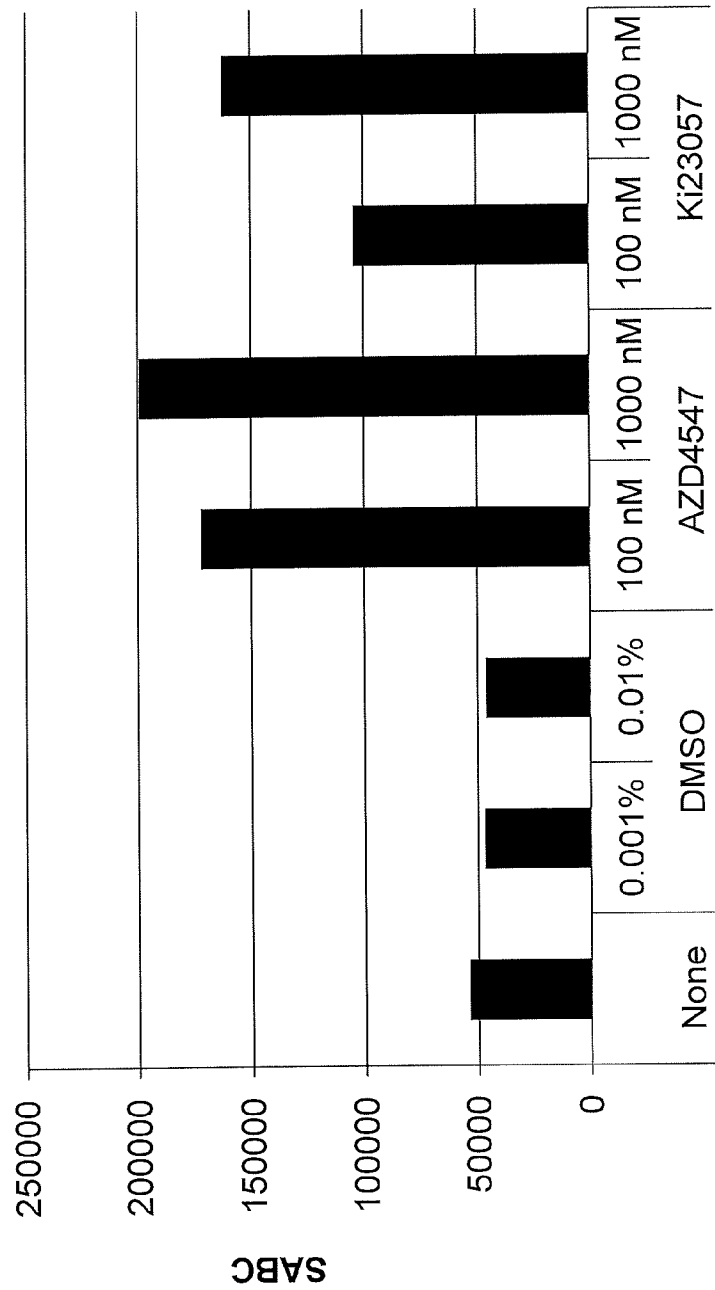


FIG. 142A

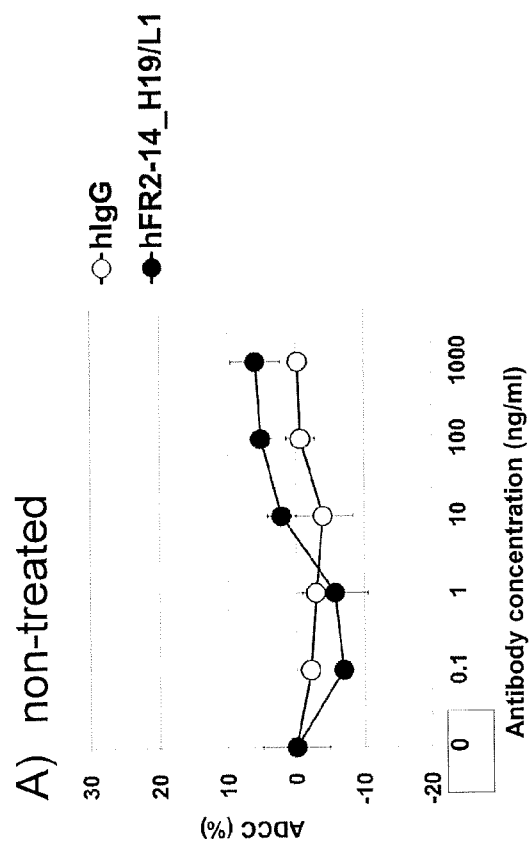


FIG. 142B

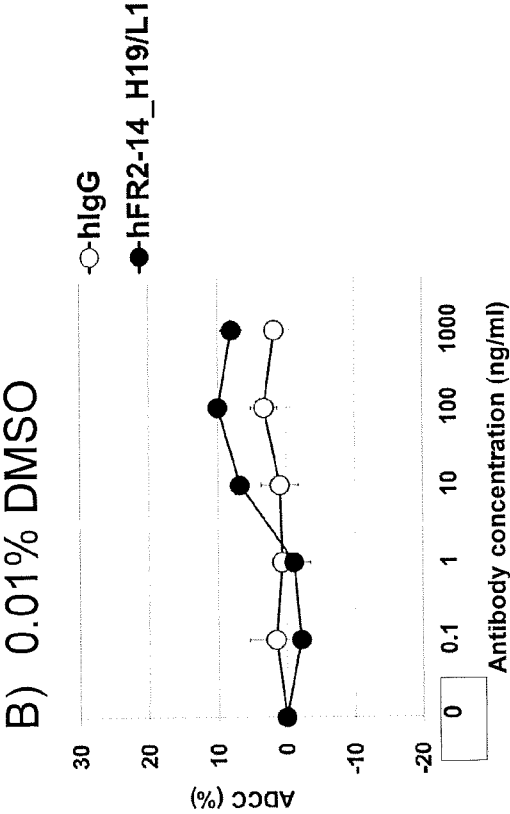


FIG. 142C

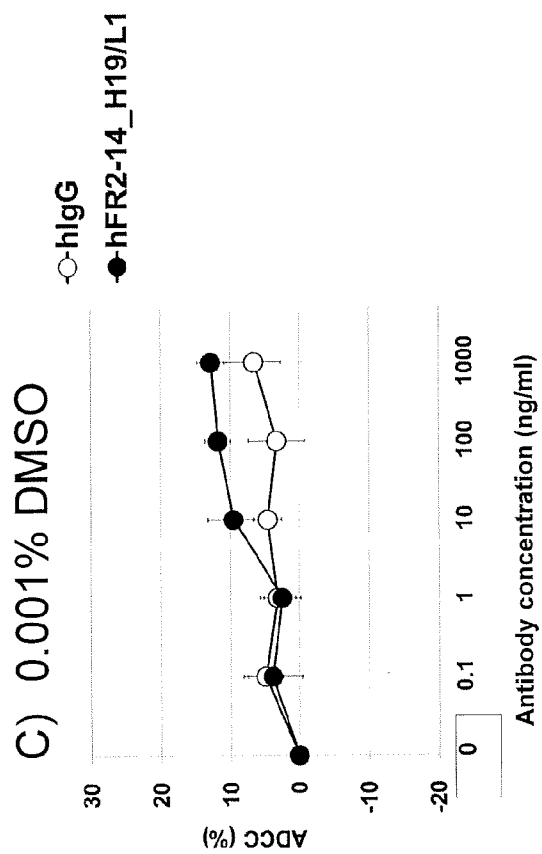


FIG. 142D

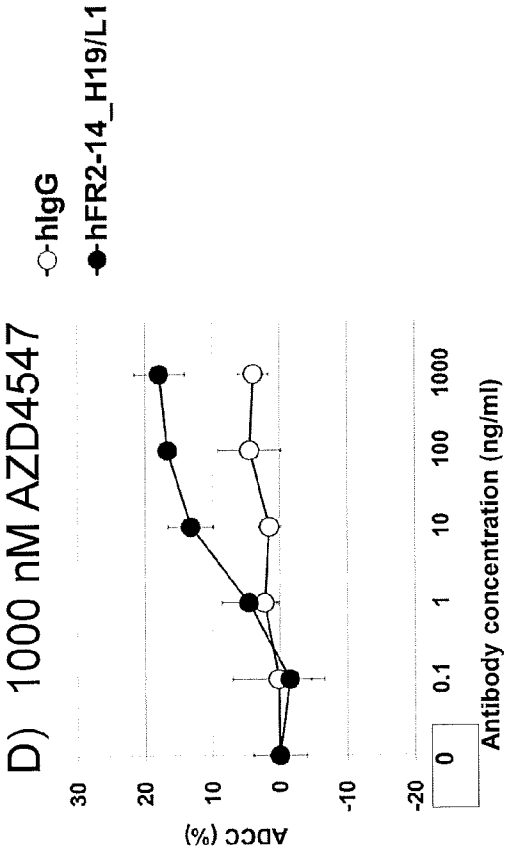


FIG. 142E

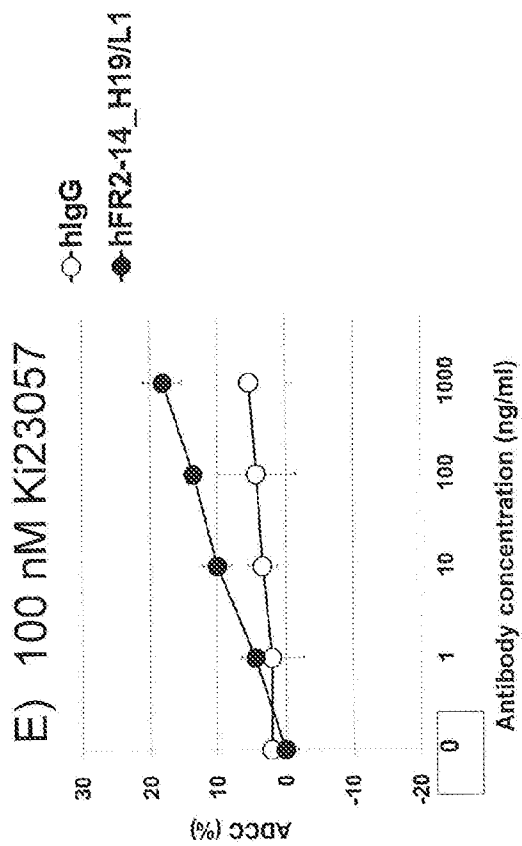


FIG. 143

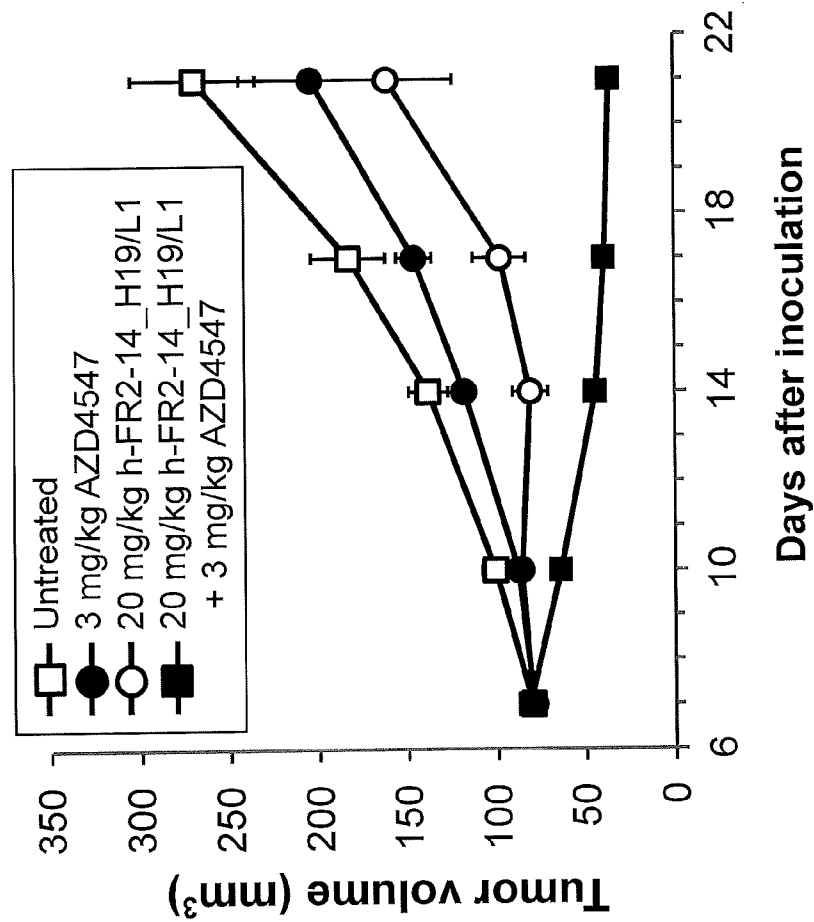


FIG. 144

Treatment	Number of CR per total number
Untreated	0 / 9
20 mg/kg h-FR2-14_H19/L1	0 / 9
3 mg/kg AZD4547	0 / 9
10 mg/kg AZD4547	0 / 9
30 mg/kg AZD4547	0 / 9
20 mg/kg h-FR2-14_H19/L1 + 3 mg/kg AZD4547	0 / 9
20 mg/kg h-FR2-14_H19/L1 + 10 mg/kg AZD4547	2 / 9
20 mg/kg h-FR2-14_H19/L1 + 30 mg/kg AZD4547	4 / 9

FIG. 145

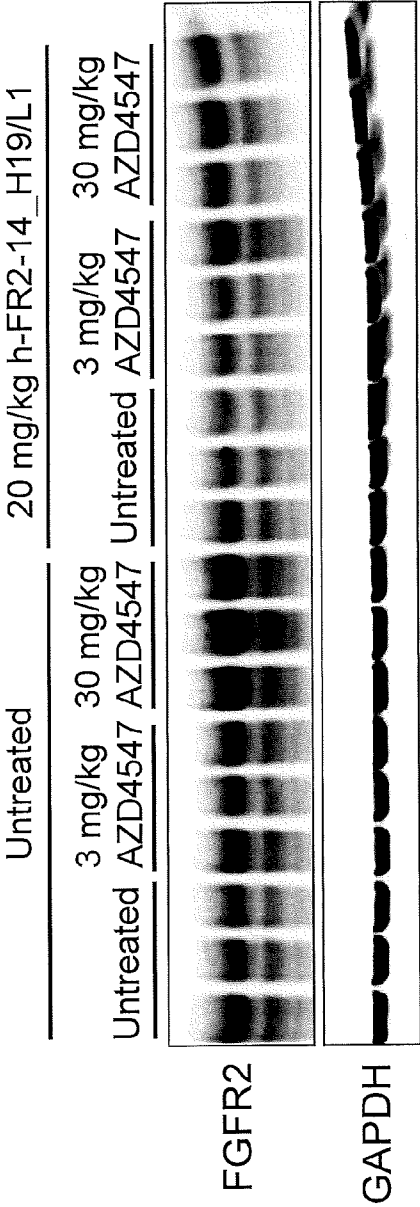
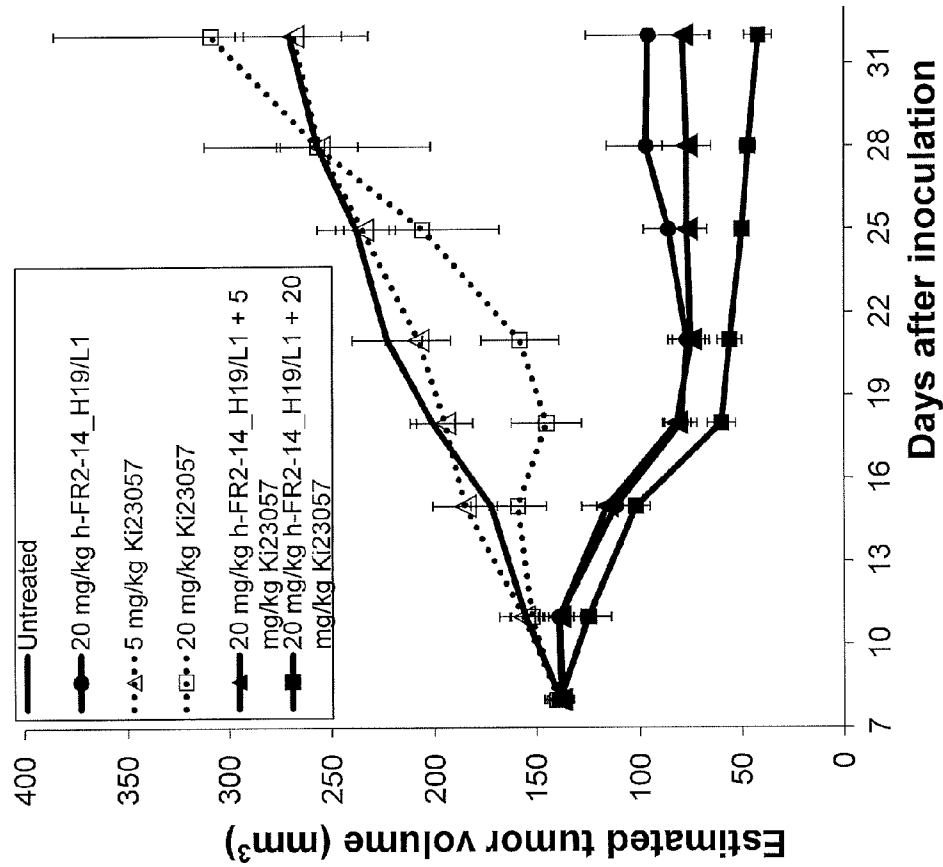


FIG. 146



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**COMBINATION OF ANTI-FGFR2 ANTIBODY
AND OTHER AGENT****TECHNICAL FIELD**

[0001] The present invention relates to a combination of a novel antibody, or a functional fragment thereof; or to a modified form of the antibody or the functional fragment, and another active ingredient; a pharmaceutical composition comprising the antibody or functional fragment thereof or the modified form of the antibody or the functional fragment, and another active ingredient, etc.

BACKGROUND ART

[0002] Fibroblast growth factors (FGFs) are known to play an important role in embryogenesis, tissue homeostasis, and metabolism via FGF receptor (FGFR) signals (Non Patent Literature 1). In humans, 22 FGFs (FGF1 to FGF14 and FGF16 to FGF23) and 4 FGF receptors (FGFR1 to FGFR4; hereinafter, collectively referred to as "FGFRs") having a tyrosine kinase domain are known. These FGFRs are each constituted by an extracellular region comprising a ligand binding site composed of 2 or 3 immunoglobulin-like domains (IgD1 to IgD3), a single-pass transmembrane region, and an intracellular region comprising the tyrosine kinase domain. FGFR1, FGFR2, and FGFR3 each have two splicing variants called IIIb and IIIc. These isoforms differ in the sequence of approximately 50 amino acids in the latter half of IgD3 and exhibit distinctive tissue distribution and ligand specificity. It is generally known that the IIIb isoform is expressed in epithelial cells, while the IIIc isoform is expressed in mesenchymal cells. Upon binding of FGFs to FGFRs, these FGFRs are dimerized and phosphorylated at their particular tyrosine residues. This phenomenon promotes the stimulation of important adaptor proteins such as FGFR substrate 2 α (FRS2 α) and induces the activation of many signaling pathways including MAPK and PI3K/Akt pathways. As a result, FGFs and their corresponding receptors control a wide range of cell functions including growth, differentiation, migration, and survival.

[0003] The abnormal activation of FGFRs is known to be involved in particular types of malignant tumor development in humans (Non Patent Literature 1 and 2). Particularly, findings such as the overexpression of FGFR2 and its ligand, receptor mutations or gene amplification, and isoform switching, have been made as to the association of FGFR2 signal abnormality with cancer. Specifically, a single nucleotide polymorphism (SNP) in intron 2 of the FGFR2 gene reportedly correlates with the risk of breast cancer progression caused by the high expression of FGFR2 (Non Patent Literature 3 and 4). Missense mutations that constitutively activate FGFR2 have been reported in endometrial cancer, ovarian cancer, breast cancer, lung cancer, and stomach cancer (Non Patent Literature 2, 3, and 5). Also, amplification or overexpression of the FGFR2 gene has been reported in stomach cancer and breast cancer (Non Patent Literature 2, 3, and 5). In addition, a class switch from FGFR2 IIIb to FGFR2 IIIc is also known to occur during the progression of prostate cancer or kidney cancer and correlates with poor prognosis (Non Patent Literature 6 and 7).

[0004] As mentioned above, the association of FGFR2 overexpression or mutations or switching from IIIb to IIIc, with many cancer types suggests the possibility of FGFR2 as an excellent therapeutic target for cancer. In fact, monoclo-

nal antibodies against FGFR2 have been obtained and are under evaluation for their antitumor effects in preclinical trials in order to reveal the role of FGFR2 in oncogenesis and determine the possibility of FGFR2 as a therapeutic target for cancer (Non Patent Literature 8 and 9). All of these antibodies have been shown to have a neutralizing effect that inhibits signaling derived from a ligand for FGFR2 IIIb. Unfortunately, there has been no report of a functional antibody having effector effects such as ADCC or a neutralizing effect on IIIc.

[0005] As for receptors responsible for cell growth or survival, there exists an antibody that directly blocks growth signals by acting on the extracellular region of the receptor or exhibits antitumor activity via ADCC, and a tyrosine kinase inhibitor (TKI) that acts on the intracellular tyrosine kinase of the receptor to block the signal transduction thereof and induce cell death. Approaches of potentiating anticancer effects have previously been practiced by the combined use of such drugs for the same receptor or the combined use of such drugs inhibiting different receptors.

[0006] The combined use of lapatinib (Her2 TKI) and Herceptin (anti-Her2 antibody) has been confirmed to be effective for the treatment of breast cancer. The possibility has been suggested that Her2 accumulates on cell surface by the action of lapatinib to thereby potentiate the effect of Her2 (Non Patent Literature 10). The dual inhibition of EGFR by afatinib, which inhibits the whole ErbB family, and an anti-EGFR monoclonal antibody cetuximab has been found to exhibit a strong anticancer effect (Non Patent Literature 11). Thus, the combined use of an antibody recognizing receptor tyrosine kinase with a low-molecular drug inhibiting the tyrosine kinase activity probably causes strong growth inhibition, leading to a useful method of treatment.

[0007] However, an anticancer effect enhanced by the combined use of an FGFR tyrosine kinase inhibitor and an anti-FGFR2 antibody has not so far been shown.

CITATION LIST**Non Patent Literature**

- [0008]** Non Patent Literature 1: Eswarakumar, V. P., et al., J. Cytokine Growth Factor Rev., April 2005, Vol. 16 (No. 2), p. 139-149, published online on Feb. 1, 2005, Review
- [0009]** Non Patent Literature 2: Turner, N. and Grose, R., Nat. Rev. Cancer, February 2010, Vol. 10 (No. 2), p. 116-129, Review
- [0010]** Non Patent Literature 3: Easton, D. F., et al., Nature, Jun. 28, 2007, Vol. 447 (No. 7148), p. 1087-1093
- [0011]** Non Patent Literature 4: Hunter D J, et al., Nat. Genet., July 2007, Vol. 39 (No. 7), p. 870-874, published online on May 27, 2007
- [0012]** Non Patent Literature 5: Katoh, Y. and Katoh, M., Int. J. Mol. Med., March 2009, Vol. 23 (No. 3), p. 307-311, Review
- [0013]** Non Patent Literature 6: Chaffer, C. L., et al., Differentiation, November 2007, Vol. 75 (No. 9), p. 831-842, published online on Aug. 14, 2007, Review
- [0014]** Non Patent Literature 7: Carstens, R. P., et al., Oncogene, Dec. 18, 1997, Vol. 15 (No. 25), p. 3059-3065
- [0015]** Non Patent Literature 8: Zhao, W. M., et al., Clin. Cancer Res., Dec. 1, 2010, Vol. 16 (No. 23), p. 5750-5758, published online on Jul. 29, 2010

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- [0016] Non Patent Literature 9: Bai, A., et al., Cancer Res., Oct. 1, 2010, Vol. 70 (No. 19), p. 7630-7639, published online on Aug. 13, 2010
- [0017] Non Patent Literature 10: Scaltriti, M. et al., Oncogene, February 2009, Vol. 28 (No. 6), p. 803-814, published online on Dec. 8, 2008
- [0018] Non Patent Literature 11: Regales, L., et al., J. Clin. Invest., October 2009, Vol. 119 (No. 10), p. 3000-3010, published online on Sep. 14, 2009

SUMMARY OF THE INVENTION

Technical Problem

[0019] An object of the present invention is to provide a combination of an anti-FGFR2 antibody with another agent, and a pharmaceutical composition, etc. comprising the antibody and another agent.

[0020] Another object of the present invention is to provide a combination of an anti-FGFR2 antibody with another agent for use in the treatment or prevention of cancer, and a pharmaceutical composition comprising the antibody and another agent for use in the treatment or prevention of cancer.

[0021] A further object of the present invention is to provide a method for treating or preventing cancer by administering the anti-FGFR2 antibody and another agent in combination or by administering the composition.

Solution to the Problem

[0022] The present inventors have conducted diligent studies to attain the objects and have developed a novel anti-FGFR2 antibody. The present inventors have completed the present invention by finding that the antibody has an anticancer effect and also finding that use of the antibody in combination with an FGFR kinase inhibitor produces an excellent antitumor effect.

[0023] The present invention relates to:

- (1) A combination of an antibody, or a functional fragment thereof, with another agent; or a pharmaceutical composition comprising the antibody, or functional fragment thereof, and another agent; wherein the antibody, or functional fragment thereof, has antibody dependent cellular cytotoxic activity and binds to a fibroblast growth factor receptor (FGFR);
- (2) The combination or the composition according to (1), wherein the fibroblast growth factor receptor (FGFR) is human FGFR;
- (3) The combination or the composition according to (1) or (2), wherein the fibroblast growth factor receptor (FGFR) is FGFR2;
- (4) The combination or the composition according to any one of (1) to (3), wherein the antibody, or functional fragment thereof, binds to human fibroblast growth factor receptor 2 (human FGFR2) IIb and/or human fibroblast growth factor receptor 2 (human FGFR2) IIc;
- (5) The combination or the composition according to any one of (1) to (4), wherein the antibody, or functional fragment thereof, binds to human fibroblast growth factor receptor 2 (human FGFR2) IIb and human fibroblast growth factor receptor 2 (human FGFR2) IIc;
- (6) The combination or the composition according to any one of (1) to (5), wherein the antibody, or functional

fragment thereof, binds to one or two or more immunoglobulin-like domains of the human fibroblast growth factor receptor 2;

(7) The combination or the composition according to any one of (1) to (6), wherein the antibody, or functional fragment thereof, binds to immunoglobulin-like domain 2 of the human fibroblast growth factor receptor 2;

(8) The combination or the composition according to any one of (1) to (4) and (6), wherein the antibody, or functional fragment thereof, binds to immunoglobulin-like domain 3 of the human fibroblast growth factor receptor 2;

(9) The combination or the composition according to any one of (1) to (8), wherein the antibody, or functional fragment thereof, has neutralizing activity against the human fibroblast growth factor receptor 2 (human FGFR2) IIb and/or the human fibroblast growth factor receptor 2 (human FGFR2) IIc;

(10) The combination or the composition according to any one of (1) to (9), wherein the antibody, or functional fragment thereof, has neutralizing activity against the human fibroblast growth factor receptor 2 (human FGFR2) IIb and the human fibroblast growth factor receptor 2 (human FGFR2) IIc;

(11) The combination or the composition according to any one of (1) to (10), wherein the antibody, or functional fragment thereof, has antitumor activity;

(12) The combination or the composition according to (11), wherein the antibody, or functional fragment thereof, exhibits antitumor activity in vivo;

(13) The combination or the composition according to any one of (1) to (4), (6), (8), (9), (11) and (12), wherein the antibody consists of a heavy chain comprising CDRH1 consisting of the amino acid sequence represented by SEQ ID NO: 52 (FIG. 60) of the Sequence Listing, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; CDRH2 consisting of the amino acid sequence represented by SEQ ID NO: 53 (FIG. 61) of the Sequence Listing, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; and CDRH3 consisting of the amino acid sequence represented by SEQ ID NO: 54 (FIG. 62) of the Sequence Listing, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; and a light chain comprising CDRL1 consisting of the amino acid sequence represented by SEQ ID NO: 61 (FIG. 69) of the Sequence Listing, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; CDRL2 consisting of the amino acid sequence represented by SEQ ID NO: 62 (FIG. 70) of the Sequence Listing, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; and CDRL3 consisting of the amino acid sequence represented by SEQ ID NO: 63 (FIG. 71) of the Sequence Listing, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; and binds to human FGFR2;

(14) The combination or the composition according to any one of (1) to (7) and (9) to (12), wherein the antibody consists of a heavy chain comprising CDRH1 consisting of the amino acid sequence represented by SEQ ID NO: 55 (FIG. 63) of the Sequence Listing, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; CDRH2 consisting

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of the amino acid sequence represented by SEQ ID NO: 56 (FIG. 64) of the Sequence Listing, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; and CDRH3 consisting of the amino acid sequence represented by SEQ ID NO: 57 (FIG. 65) of the Sequence Listing, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; and a light chain comprising CDRL1 consisting of the amino acid sequence represented by SEQ ID NO: 64 (FIG. 72) of the Sequence Listing, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; CDRL2 consisting of the amino acid sequence represented by SEQ ID NO: 65 (FIG. 73) of the Sequence Listing, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; and CDRL3 consisting of the amino acid sequence represented by SEQ ID NO: 66 (FIG. 74) of the Sequence Listing, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; and binds to human FGFR2;

(15) The combination or the composition according to any one of (1) to (7) and (9) to (12), wherein the antibody consists of a heavy chain comprising CDRH1 consisting of the amino acid sequence represented by SEQ ID NO: 58 (FIG. 66) of the Sequence Listing, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; CDRH2 consisting of the amino acid sequence represented by SEQ ID NO: 59 (FIG. 67) of the Sequence Listing, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; and CDRH3 consisting of the amino acid sequence represented by SEQ ID NO: 60 (FIG. 68) of the Sequence Listing, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; and a light chain comprising CDRL1 consisting of the amino acid sequence represented by SEQ ID NO: 67 (FIG. 75) of the Sequence Listing, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; CDRL2 consisting of the amino acid sequence represented by SEQ ID NO: 68 (FIG. 76) of the Sequence Listing, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; and CDRL3 consisting of the amino acid sequence represented by SEQ ID NO: 69 (FIG. 77) of the Sequence Listing, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; and binds to human FGFR2;

(16) The combination or the composition according to (15), wherein the CDRH3 consists of an amino acid sequence derived from the amino acid sequence represented by SEQ ID NO: 60 (FIG. 68) of the Sequence Listing by the substitution of one or two amino acids;

(17) The combination or the composition according to any one of (1) to (16), wherein the antibody is a monoclonal antibody;

(18) The combination or the composition according to any one of (1) to (17), wherein the antibody is a chimeric antibody;

(19) The combination or the composition according to any one of (1) to (17), wherein the antibody is a humanized antibody;

(20) The combination or the composition according to (19), wherein the antibody is selected from the following (i) to (xix):

(i) a humanized antibody (hFR2-14_H19/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73 (FIG. 81), and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 97 (FIG. 105);

(ii) a humanized antibody (hFR2-14_H12/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73 (FIG. 81), and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 97 (FIG. 105);

(iii) a humanized antibody (hFR2-14_H8/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73 (FIG. 81), and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 89 (FIG. 97);

(iv) a humanized antibody (hFR2-14_H11/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73 (FIG. 81), and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 95 (FIG. 103);

(v) a humanized antibody (hFR2-14_H5/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73 (FIG. 81), and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 83 (FIG. 91);

(vi) a humanized antibody (hFR2-14_H1/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73 (FIG. 81), and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 75 (FIG. 83);

(vii) a humanized antibody (hFR2-14_H2/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73 (FIG. 81), and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 77 (FIG. 85);

(viii) a humanized antibody (hFR2-14_H3/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73 (FIG. 81), and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 79 (FIG. 87);

(ix) a humanized antibody (hFR2-14_H4/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73 (FIG. 81), and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 81 (FIG. 89);

(x) a humanized antibody (hFR2-14_H6/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73 (FIG. 81), and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 85 (FIG. 93);

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(xi) a humanized antibody (hFR2-14_H7/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73 (FIG. 81), and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 87 (FIG. 95);

(xii) a humanized antibody (hFR2-14_H9/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73 (FIG. 81), and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 91 (FIG. 99);

(xiii) a humanized antibody (hFR2-14_H10/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73 (FIG. 81), and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 93 (FIG. 101);

(xiv) a humanized antibody (hFR2-14_H13/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73 (FIG. 81), and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 99 (FIG. 107);

(xv) a humanized antibody (hFR2-14_H14/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73 (FIG. 81), and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 101 (FIG. 109);

(xvi) a humanized antibody (hFR2-14_H15/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73 (FIG. 81), and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 103 (FIG. 111);

(xvii) a humanized antibody (hFR2-14_H16/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73 (FIG. 81), and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 105 (FIG. 113);

(xviii) a humanized antibody (hFR2-14_H17/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73 (FIG. 81), and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 107 (FIG. 115); and

(xix) a humanized antibody (hFR2-14_H18/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73 (FIG. 81), and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 109 (FIG. 117);

(21) The combination or the composition according to any one of (1) to (12), wherein the antibody comprises heavy and light chains comprising amino acid sequences having 95% or higher identity to the amino acid sequences of the heavy and light chains, respectively, of an antibody according to (20), and binds to human FGFR2;

(22) The combination or the composition according to any one of (1) to (12), wherein the antibody, or functional fragment thereof, binds to a site on an antigen recognized by an antibody according to any one of (13) to (16) and (20);

(23) The combination or the composition according to any one of (1) to (12), wherein the antibody, or functional fragment thereof, competes with an antibody according to any one of (13) to (16) and (20) for binding to human FGFR2;

(24) The combination or the composition according to any one of (1) to (12), wherein the antibody, or functional fragment thereof, binds to an epitope on human FGFR2, the epitope being constituted by tyrosine (Tyr) at residue 155, threonine (Thr) at residue 157, lysine (Lys) at residue 176, alanine (Ala) at residue 181, glycine (Gly) at residue 182, glycine (Gly) at residue 183, asparagine (Asn) at residue 184, proline (Pro) at residue 185, methionine (Met) at residue 186, threonine (Thr) at residue 188, glutamine (Gln) at residue 200, glutamic acid (Glu) at residue 201, glycine (Gly) at residue 205, glycine (Gly) at residue 206, lysine (Lys) at residue 208, valine (Val) at residue 209, arginine (Arg) at residue 210, asparagine (Asn) at residue 211, glutamine (Gln) at residue 212, histidine (His) at residue 213, tryptophan (Trp) at residue 214, and isoleucine (Ile) at residue 217 of the amino acid sequence represented by SEQ ID NO: 70 (FIG. 78);

(25) The combination or the composition according to any one of (1) to (12), wherein the antibody, or functional fragment thereof, has an interaction distance with each of tyrosine (Tyr) at residue 155, threonine (Thr) at residue 157, lysine (Lys) at residue 176, alanine (Ala) at residue 181, glycine (Gly) at residue 182, glycine (Gly) at residue 183, asparagine (Asn) at residue 184, proline (Pro) at residue 185, methionine (Met) at residue 186, threonine (Thr) at residue 188, glutamine (Gln) at residue 200, glutamic acid (Glu) at residue 201, glycine (Gly) at residue 205, glycine (Gly) at residue 206, lysine (Lys) at residue 208, valine (Val) at residue 209, arginine (Arg) at residue 210, asparagine (Asn) at residue 211, glutamine (Gln) at residue 212, histidine (His) at residue 213, tryptophan (Trp) at residue 214, and isoleucine (Ile) at residue 217 of the amino acid sequence represented by SEQ ID NO: 70 (FIG. 78);

(26) The combination or the composition according to (25), wherein the interaction distance is 6 angstroms or shorter;

(27) The combination or the composition according to (25) or (26), wherein the interaction distance is 4 angstroms or shorter;

(28) The combination or the composition according to any one of (1) to (12) and (21) to (27), wherein the antibody is a human antibody;

(29) The combination or the composition according to any one of (1) to (28), wherein the antibody, or functional fragment thereof, inhibits the binding of FGF to human FGFR2;

(30) The combination or the composition according to any one of (1) to (29), wherein the antibody, or functional fragment thereof, has antibody dependent cellular cytotoxic activity and/or antibody dependent cell phagocytosis activity;

(31) A combination of an antibody, or a functional fragment thereof, and another agent; or a pharmaceutical composition comprising the antibody, or functional fragment thereof, and another agent; wherein the antibody, or functional fragment thereof, is obtained by a method for producing an antibody or a functional fragment thereof, comprising the following steps (i) and (ii):

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(i) culturing a cell of the following (1) or (2):

[0024] (1) a recombinant cell comprising a recombinant vector having an insert of a nucleotide of any one of the following (i) to (iii), or comprising the nucleotide:

[0025] (i) a nucleotide comprising a nucleotide sequence encoding a partial or whole amino acid sequence of the heavy or light chain of an antibody according to any one of (1) to (30),

[0026] (ii) a nucleotide consisting of a nucleotide sequence comprising the nucleotide sequence encoding a partial or whole amino acid sequence of the heavy or light chain of an antibody according to any one of (1) to (30), and

[0027] (iii) a nucleotide consisting of the nucleotide sequence encoding a partial or whole amino acid sequence of the heavy or light chain of an antibody according to any one of (1) to (30); and

[0028] (2) a cell producing an antibody, or a functional fragment thereof, according to any one of (1) to (30); and (ii) recovering the antibody, or functional fragment thereof, according to any one of (1) to (30) from the cultures obtained in step (i);

(32) The combination or the composition according to any one of (1) to (31), wherein 1 to 5 amino acids are deleted from the amino terminus or carboxyl terminus of the heavy or light chain of the antibody;

(33) A combination of a modified form of an antibody, or a functional fragment thereof, according to any one of (1) to (32) with another agent; or a pharmaceutical composition comprising the modified form and another agent;

(34) The combination or the composition according to (33), wherein a sugar chain modification is regulated;

(35) The combination or the composition according to (34), wherein the antibody, or functional fragment thereof, is selected from antibodies (i) to (xix) of (20), or functional fragments thereof;

(36) The combination or the composition according to any one of (1) to (35), wherein the combination or the composition is used in the treatment or prevention of cancer;

(37) The combination or the composition according to (36), wherein the cancer is FGFR2-positive;

(38) The combination or the composition according to any one of (1) to (37), further being combined with another drug or further comprising another drug;

(39) The combination or the composition according to any one of (1) to (38), wherein the antibody, or functional fragment thereof, is conjugated with another compound;

(40) The combination or the composition according to any one of (1) to (39), wherein the other agent is an FGFR tyrosine kinase inhibitor;

(41) The combination or the composition according to (40), wherein the FGFR tyrosine kinase is an FGFR2 inhibitor;

(42) The combination or the composition according to (41), wherein the FGFR2 inhibitor is one or two or more selected from the group consisting of acylaminopyrazole, a quinolone or quinazoline derivative modified with a phenoxy group or a phenylthio group, BGJ398, LY2874455, brivanib, dovitinib, lenvatinib, masitinib, nintedanib, regorafenib, pazopanib, TSU68, ENMD-2076, and ponatinib;

(43) The combination or the composition according to (41) or (42), wherein the FGFR2 inhibitor is AZD4547;

(44) The combination or the composition according to (41) or (42), wherein the FGFR2 inhibitor is Ki23057;

(45) A pharmaceutical composition comprising an FGFR tyrosine kinase inhibitor for combined use with an antibody, or a functional fragment thereof, according to any one of (1) to (32) or a modified form according to (33) or (34);

(46) A pharmaceutical composition comprising an antibody, or a functional fragment thereof, according to any one of (1) to (32) or a modified form according to (33) or (34) for combined use with an FGFR tyrosine kinase inhibitor;

(47) A pharmaceutical composition comprising an FGFR tyrosine kinase inhibitor, wherein the pharmaceutical composition enhances the effect of an antibody, or a functional fragment, thereof according to any one of (1) to (32) or a modified form according to (33) or (34) by combined use with the antibody, the functional fragment, or the modified form;

(48) A pharmaceutical composition comprising an antibody, or a functional fragment thereof, according to any one of (1) to (32) or a modified form according to (33) or (34), wherein the pharmaceutical composition enhances the effect of an FGFR tyrosine kinase inhibitor by combined use with the FGFR tyrosine kinase inhibitor;

(49) A pharmaceutical composition in which an antibody, or a functional fragment thereof, according to any one of (1) to (32) or a modified form according to (33) or (34) is to be administered in combination with an FGFR tyrosine kinase inhibitor;

(50) The pharmaceutical composition according to (49), wherein the antibody, or functional fragment thereof, according to any one of (1) to (32) or the modified form according to (33) or (34) and the FGFR tyrosine kinase inhibitor are contained as active ingredients in separate preparations, which are to be administered concurrently or at different times; and

(51) The pharmaceutical composition according to (49), wherein the antibody, or functional fragment thereof, according to any one of (1) to (32) or the modified form according to (33) or (34) and the FGFR tyrosine kinase inhibitor are contained as active ingredients in a single preparation, etc.

Advantageous Effects of the Invention

[0029] Use of the combination of the antibody and the other agent provided by the present invention enables treatment or prevention of various cancers.

BRIEF DESCRIPTION OF THE DRAWINGS

[0030] FIG. 1 is a diagram showing the results of testing the binding activity of rat anti-FGFR2 antibodies (FR2-10, FR2-13, and FR2-14) against human FGFR2 by flow cytometry. The vertical axis represents a relative value of the average fluorescence intensity assayed by flow cytometry.

[0031] FIG. 2 is a diagram showing the results of testing for epitopes on human FGFR2 to which the rat anti-FGFR2 antibodies (FR2-10, FR2-13, and FR2-14) bind by flow cytometry. The vertical axis represents a relative value of the average fluorescence intensity assayed by flow cytometry.

[0032] FIG. 3A is a diagram showing the signal-neutralizing activity of the rat anti-FGFR2 antibodies (FR2-10, FR2-13, and FR2-14) against human FGFR2 IIIb by Elk1 trans-reporter assay.

[0033] FIG. 3B is a diagram showing the signal-neutralizing activity of the rat anti-FGFR2 antibodies (FR2-10, FR2-13, and FR2-14) against human FGFR2 IIIc by Elk1 trans-reporter assay.

[0034] FIG. 4 is a diagram showing the signal inhibitory effect of the rat anti-FGFR2 antibody FR2-10 on FGFR2 by Western blotting. This diagram illustrates that addition of the rat FR2-10 antibody inhibited FGFR2, FRS2, and ERK phosphorylation induced by the addition of FGF7 to a human stomach cancer cell line SNU-16.

[0035] FIG. 5 is a diagram showing the results of testing the binding activity of human chimeric anti-FGFR2 antibodies (cFR2-10, cFR2-13, and cFR2-14) against human FGFR2 by Cell-ELISA.

[0036] FIG. 6A is a diagram showing the signal-neutralizing activity of the human chimeric anti-FGFR2 antibodies (cFR2-10, cFR2-13, and cFR2-14) against human FGFR2 IIIb by Elk1 trans-reporter assay.

[0037] FIG. 6B is a diagram showing the signal-neutralizing activity of the human chimeric anti-FGFR2 antibodies (cFR2-10, cFR2-13, and cFR2-14) against human FGFR2 IIIc by Elk1 trans-reporter assay.

[0038] FIG. 7 is a diagram showing the ADCC activity of the human chimeric anti-FGFR2 antibodies (cFR2-10, cFR2-13, and cFR2-14). 293T-lacZ cells expressing human FGFR2 IIIb were used as target cells, and human PBMC was used as effector cells.

[0039] FIG. 8 is a diagram showing the in vivo antitumor activity of the human chimeric anti-FGFR2 antibodies (cFR2-10, cFR2-13, and cFR2-14) against human stomach cancer cell line SNU-16-transplanted nude mice. FIG. 8A) shows the results for the cFR2-10 antibody. FIG. 8B) shows the results for the cFR2-13 antibody. FIG. 8C) shows the results for the cFR2-14 antibody.

[0040] FIG. 9 shows the N-terminal amino acid sequence of a band corresponding to the heavy chain of the rat anti-FGFR2 antibody FR2-10 (SEQ ID NO: 1 of the Sequence Listing).

[0041] FIG. 10 shows the N-terminal amino acid sequence of a band corresponding to the light chain of the rat anti-FGFR2 antibody FR2-10 (SEQ ID NO: 2 of the Sequence Listing).

[0042] FIG. 11 shows the N-terminal amino acid sequence of a band corresponding to the heavy chain of the rat anti-FGFR2 antibody FR2-13 (SEQ ID NO: 3 of the Sequence Listing).

[0043] FIG. 12 shows the N-terminal amino acid sequence of a band corresponding to the light chain of the rat anti-FGFR2 antibody FR2-13 (SEQ ID NO: 4 of the Sequence Listing).

[0044] FIG. 13 shows the N-terminal amino acid sequence of a band corresponding to the heavy chain of the rat anti-FGFR2 antibody FR2-14 (SEQ ID NO: 5 of the Sequence Listing).

[0045] FIG. 14 shows the N-terminal amino acid sequence of a band corresponding to the light chain of the rat anti-FGFR2 antibody FR2-14 (SEQ ID NO: 6 of the Sequence Listing).

[0046] FIG. 15 shows a primer for gene amplification of a rat heavy chain (SEQ ID NO: 7 of the Sequence Listing).

[0047] FIG. 16 shows a sequencing primer for the heavy chain of FR2-10 (SEQ ID NO: 8 of the Sequence Listing).

[0048] FIG. 17 shows a sequencing primer for the heavy chain of FR2-13 (SEQ ID NO: 9 of the Sequence Listing).

[0049] FIG. 18 shows a sequencing primer for the heavy chain of FR2-14 (SEQ ID NO: 10 of the Sequence Listing).

[0050] FIG. 19 shows the nucleotide sequence of a cDNA encoding the heavy chain variable region of the rat anti-FGFR2 antibody FR2-10 (SEQ ID NO: 11 of the Sequence Listing).

[0051] FIG. 20 shows the amino acid sequence of the heavy chain variable region of the rat anti-FGFR2 antibody FR2-10 (SEQ ID NO: 12 of the Sequence Listing).

[0052] FIG. 21 shows the nucleotide sequence of a cDNA encoding the heavy chain variable region of the rat anti-FGFR2 antibody FR2-13 (SEQ ID NO: 13 of the Sequence Listing).

[0053] FIG. 22 shows the amino acid sequence of the heavy chain variable region of the rat anti-FGFR2 antibody FR2-13 (SEQ ID NO: 14 of the Sequence Listing).

[0054] FIG. 23 shows the nucleotide sequence of a cDNA encoding the heavy chain variable region of the rat anti-FGFR2 antibody FR2-14 (SEQ ID NO: 15 of the Sequence Listing).

[0055] FIG. 24 shows the amino acid sequence of the heavy chain variable region of the rat anti-FGFR2 antibody FR2-14 (SEQ ID NO: 16 of the Sequence Listing).

[0056] FIG. 25 shows a primer for gene amplification of a rat light chain (SEQ ID NO: 17 of the Sequence Listing).

[0057] FIG. 26 shows a sequencing primer for a rat light chain (SEQ ID NO: 18 of the Sequence Listing).

[0058] FIG. 27 shows a sequencing primer for the light chain of FR2-10 (SEQ ID NO: 19 of the Sequence Listing).

[0059] FIG. 28 shows the nucleotide sequence of a cDNA encoding the light chain variable region of the rat anti-FGFR2 antibody FR2-10 (SEQ ID NO: 20 of the Sequence Listing).

[0060] FIG. 29 shows the amino acid sequence of the light chain variable region of the rat anti-FGFR2 antibody FR2-10 (SEQ ID NO: 21 of the Sequence Listing).

[0061] FIG. 30 shows a primer for gene amplification of the rat FR2-13 or FR2-14 light chain (SEQ ID NO: 22 of the Sequence Listing).

[0062] FIG. 31 shows the nucleotide sequence of a cDNA encoding the light chain variable region of the rat anti-FGFR2 antibody FR2-13 (SEQ ID NO: 23 of the Sequence Listing).

[0063] FIG. 32 shows the amino acid sequence of the light chain variable region of the rat anti-FGFR2 antibody FR2-13 (SEQ ID NO: 24 of the Sequence Listing).

[0064] FIG. 33 shows the nucleotide sequence of a cDNA encoding the light chain variable region of the rat anti-FGFR2 antibody FR2-14 (SEQ ID NO: 25 of the Sequence Listing).

[0065] FIG. 34 shows the amino acid sequence of the light chain variable region of the rat anti-FGFR2 antibody FR2-14 (SEQ ID NO: 26 of the Sequence Listing).

[0066] FIG. 35 shows a DNA fragment comprising a DNA sequence encoding the amino acids of a human κ chain secretory signal sequence and a human κ chain constant region (SEQ ID NO: 27 of the Sequence Listing).

[0067] FIG. 36 shows a primer F for a light chain expression vector (SEQ ID NO: 28 of the Sequence Listing).

[0068] FIG. 37 shows a primer R for a light chain expression vector (SEQ ID NO: 29 of the Sequence Listing).

[0069] FIG. 38 shows a DNA fragment comprising a DNA sequence encoding the amino acids of a human heavy chain

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signal sequence and a human IgG1 constant region (SEQ ID NO: 30 of the Sequence Listing).

[0070] FIG. 39 shows the nucleotide sequence of the light chain of human chimeric FR2-10 (cFR2-10) (SEQ ID NO: 31 of the Sequence Listing). In this sequence, nucleotide positions 1 to 60 represent a signal sequence, which is usually not contained in the nucleotide sequences of most mature cFR2-10 light chains.

[0071] FIG. 40 shows the amino acid sequence of the light chain of human chimeric FR2-10 (cFR2-10) (SEQ ID NO: 32 of the Sequence Listing). In this sequence, amino acid positions 1 to 20 represent a signal sequence, which is usually not contained in the amino acid sequences of most mature cFR2-10 light chains.

[0072] FIG. 41 shows a primer set F for the light chain of human chimeric FR2-10 (SEQ ID NO: 33 of the Sequence Listing).

[0073] FIG. 42 shows a primer set R for the light chain of human chimeric FR2-10 (SEQ ID NO: 34 of the Sequence Listing).

[0074] FIG. 43 shows the nucleotide sequence of the heavy chain of human chimeric FR2-10 (cFR2-10) (SEQ ID NO: 35 of the Sequence Listing). In this sequence, nucleotide positions 1 to 57 represent a signal sequence, which is usually not contained in the nucleotide sequences of most mature cFR2-10 heavy chains.

[0075] FIG. 44 shows the amino acid sequence of the heavy chain of human chimeric FR2-10 (cFR2-10) (SEQ ID NO: 36 of the Sequence Listing). In this sequence, amino acid positions 1 to 19 represent a signal sequence, which is usually not included in the amino acid sequence of most mature cFR2-10 heavy chains.

[0076] FIG. 45 shows a primer set F for the heavy chain of human chimeric FR2-10 (SEQ ID NO: 37 of the Sequence Listing).

[0077] FIG. 46 shows a primer set R for the heavy chain of human chimeric FR2-10 (SEQ ID NO: 38 of the Sequence Listing).

[0078] FIG. 47 shows the nucleotide sequence of the light chain of human chimeric FR2-13 (cFR2-13) (SEQ ID NO: 39 of the Sequence Listing). In this sequence, nucleotide positions 1 to 60 represent a signal sequence, which is usually not contained in the nucleotide sequences of most mature cFR2-13 light chains.

[0079] FIG. 48 shows the amino acid sequence of the light chain of human chimeric FR2-13 (cFR2-13) (SEQ ID NO: 40 of the Sequence Listing). In this sequence, amino acid positions 1 to 20 represent a signal sequence, which is usually not contained in the amino acid sequences of most mature cFR2-13 light chains.

[0080] FIG. 49 shows a primer F for the light chain of human chimeric FR2-13 (SEQ ID NO: 41 of the Sequence Listing).

[0081] FIG. 50 shows a primer R for the light chain of human chimeric FR2-13 (SEQ ID NO: 42 of the Sequence Listing).

[0082] FIG. 51 shows the nucleotide sequence of the heavy chain of human chimeric FR2-13 (cFR2-13) (SEQ ID NO: 43 of the Sequence Listing). In this sequence, nucleotide positions 1 to 57 represent a signal sequence, which is usually not contained in the nucleotide sequences of most mature cFR2-13 heavy chains.

[0083] FIG. 52 shows the amino acid sequence of the heavy chain of human chimeric FR2-13 (cFR2-13) (SEQ ID

NO: 44 of the Sequence Listing). In this sequence, amino acid positions 1 to 19 represent a signal sequence, which is usually not contained in the amino acid sequences of most mature cFR2-13 heavy chains.

[0084] FIG. 53 shows a primer F for the heavy chain of human chimeric FR2-13 (SEQ ID NO: 45 of the Sequence Listing).

[0085] FIG. 54 shows a primer R for the heavy chain of human chimeric FR2-13 (SEQ ID NO: 46 of the Sequence Listing).

[0086] FIG. 55 shows the nucleotide sequence of the light chain of human chimeric FR2-14 (cFR2-14) (SEQ ID NO: 47 of the Sequence Listing). In this sequence, nucleotide positions 1 to 60 represent a signal sequence, which is usually not contained in the nucleotide sequences of most mature cFR2-14 light chains.

[0087] FIG. 56 shows the amino acid sequence of the light chain of human chimeric FR2-14 (cFR2-14) (SEQ ID NO: 48 of the Sequence Listing). In this sequence, amino acid positions 1 to 20 represent a signal sequence, which is usually not contained in the amino acid sequences of most mature cFR2-14 light chains.

[0088] FIG. 57 shows a primer for the light chain of human chimeric FR2-14 (SEQ ID NO: 49 of the Sequence Listing).

[0089] FIG. 58 shows the nucleotide sequence of the heavy chain of human chimeric FR2-14 (cFR2-14) (SEQ ID NO: 50 of the Sequence Listing). In this sequence, nucleotide positions 1 to 57 represent a signal sequence, which is usually not contained in the nucleotide sequences of most mature cFR2-14 heavy chains.

[0090] FIG. 59 shows the amino acid sequence of the heavy chain of human chimeric FR2-14 (cFR2-14) (SEQ ID NO: 51 of the Sequence Listing). In this sequence, amino acid positions 1 to 19 represent a signal sequence, which is usually not contained in the amino acid sequences of most mature cFR2-14 heavy chains.

[0091] FIG. 60 shows the amino acid sequence of the heavy chain CDR1 of the rat anti-FGFR2 antibody FR2-10 (SEQ ID NO: 52 of the Sequence Listing).

[0092] FIG. 61 shows the amino acid sequence of the heavy chain CDR2 of the rat anti-FGFR2 antibody FR2-10 (SEQ ID NO: 53 of the Sequence Listing).

[0093] FIG. 62 shows the amino acid sequence of the heavy chain CDR3 of the rat anti-FGFR2 antibody FR2-10 (SEQ ID NO: 54 of the Sequence Listing).

[0094] FIG. 63 shows the amino acid sequence of the heavy chain CDR1 of the rat anti-FGFR2 antibody FR2-13 (SEQ ID NO: 55 of the Sequence Listing).

[0095] FIG. 64 shows the amino acid sequence of the heavy chain CDR2 of the rat anti-FGFR2 antibody FR2-13 (SEQ ID NO: 56 of the Sequence Listing).

[0096] FIG. 65 shows the amino acid sequence of the heavy chain CDR3 of the rat anti-FGFR2 antibody FR2-13 (SEQ ID NO: 57 of the Sequence Listing).

[0097] FIG. 66 shows the amino acid sequence of the heavy chain CDR1 of the rat anti-FGFR2 antibody FR2-14 (SEQ ID NO: 58 of the Sequence Listing).

[0098] FIG. 67 shows the amino acid sequence of the heavy chain CDR2 of the rat anti-FGFR2 antibody FR2-14 (SEQ ID NO: 59 of the Sequence Listing).

[0099] FIG. 68 shows the amino acid sequence of the heavy chain CDR3 of the rat anti-FGFR2 antibody FR2-14 (SEQ ID NO: 60 of the Sequence Listing).

[0117] FIG. 86 shows the nucleotide sequence of hFR2-14_H3 (SEQ ID NO: 78 of the Sequence Listing). In this sequence, nucleotide positions 1 to 57 represent a signal

sequence, amino acid positions 1 to 19 represent a signal sequence, which is usually not included in the amino acid sequence of most mature hFR2-14_H9 heavy chains.

[0131] FIG. 100 shows the nucleotide sequence of hFR2-14_H10 (SEQ ID NO: 92 of the Sequence Listing). In this sequence, nucleotide positions 1 to 57 represent a signal sequence, which is usually not included in the nucleotide sequence of most mature hFR2-14_H10 heavy chains.

[0132] FIG. 101 shows the amino acid sequence of hFR2-14_H10 (SEQ ID NO: 93 of the Sequence Listing). In this sequence, amino acid positions 1 to 19 represent a signal sequence, which is usually not included in the amino acid sequence of most mature hFR2-14_H10 heavy chains.

[0133] FIG. 102 shows the nucleotide sequence of hFR2-14_H11 (SEQ ID NO: 94 of the Sequence Listing). In this sequence, nucleotide positions 1 to 57 represent a signal sequence, which is usually not included in the nucleotide sequence of most mature hFR2-14_H11 heavy chains.

[0134] FIG. 103 shows the amino acid sequence of hFR2-14_H11 (SEQ ID NO: 95 of the Sequence Listing). In this sequence, amino acid positions 1 to 19 represent a signal sequence, which is usually not included in the amino acid sequence of most mature hFR2-14_H11 heavy chains.

[0135] FIG. 104 shows the nucleotide sequence of hFR2-14_H12 or hFR2-14_H19 (SEQ ID NO: 96 of the Sequence Listing). In this sequence, nucleotide positions 1 to 57 represent a signal sequence, which is usually not included in the nucleotide sequence of most mature hFR2-14_H12 or hFR2-14_H19 heavy chains.

[0136] FIG. 105 shows the amino acid sequence of hFR2-14_H12 or hFR2-14_H19 (SEQ ID NO: 97 of the Sequence Listing). In this sequence, amino acid positions 1 to 19 represent a signal sequence, which is usually not included in the amino acid sequence of most mature hFR2-14_H12 or hFR2-14_H19 heavy chains.

[0137] FIG. 106 shows the nucleotide sequence of hFR2-14_H13 (SEQ ID NO: 98 of the Sequence Listing). In this sequence, nucleotide positions 1 to 57 represent a signal sequence, which is usually not included in the nucleotide sequence of most mature hFR2-14_H13 heavy chains.

[0138] FIG. 107 shows the amino acid sequence of hFR2-14_H13 (SEQ ID NO: 99 of the Sequence Listing). In this sequence, amino acid positions 1 to 19 represent a signal sequence, which is usually not included in the amino acid sequence of most mature hFR2-14_H13 heavy chains.

[0139] FIG. 108 shows the nucleotide sequence of hFR2-14_H14 (SEQ ID NO: 100 of the Sequence Listing). In this sequence, nucleotide positions 1 to 57 represent a signal sequence, which is usually not included in the nucleotide sequence of most mature hFR2-14_H14 heavy chains.

[0140] FIG. 109 shows the amino acid sequence of hFR2-14_H14 (SEQ ID NO: 101 of the Sequence Listing). In this sequence, amino acid positions 1 to 19 represent a signal sequence, which is usually not included in the amino acid sequence of most mature hFR2-14_H14 heavy chains.

[0141] FIG. 110 shows the nucleotide sequence of hFR2-14_H15 (SEQ ID NO: 102 of the Sequence Listing). In this sequence, nucleotide positions 1 to 57 represent a signal sequence, which is usually not included in the nucleotide sequence of most mature hFR2-14_H15 heavy chains.

[0142] FIG. 111 shows the amino acid sequence of hFR2-14_H15 (SEQ ID NO: 103 of the Sequence Listing). In this sequence, amino acid positions 1 to 19 represent a signal

sequence, which is usually not included in the amino acid sequence of most mature hFR2-14_H15 heavy chains.

[0143] FIG. 112 shows the nucleotide sequence of hFR2-14_H16 (SEQ ID NO: 104 of the Sequence Listing). In this sequence, nucleotide positions 1 to 57 represent a signal sequence, which is usually not included in the nucleotide sequence of most mature hFR2-14_H16 heavy chains.

[0144] FIG. 113 shows the amino acid sequence of hFR2-14_H16 (SEQ ID NO: 105 of the Sequence Listing). In this sequence, amino acid positions 1 to 19 represent a signal sequence, which is usually not included in the amino acid sequence of most mature hFR2-14_H16 heavy chains.

[0145] FIG. 114 shows the nucleotide sequence of hFR2-14_H17 (SEQ ID NO: 106 of the Sequence Listing). In this sequence, nucleotide positions 1 to 57 represent a signal sequence, which is usually not included in the nucleotide sequence of most mature hFR2-14_H17 heavy chains hFR2-14_H17.

[0146] FIG. 115 shows the amino acid sequence of hFR2-14_H17 (SEQ ID NO: 107 of the Sequence Listing). In this sequence, amino acid positions 1 to 19 represent a signal sequence, which is usually not included in the amino acid sequence of most mature hFR2-14_H17 heavy chains.

[0147] FIG. 116 shows the nucleotide sequence of hFR2-14_H18 (SEQ ID NO: 108 of the Sequence Listing). In this sequence, nucleotide positions 1 to 57 represent a signal sequence, which is usually not included in the nucleotide sequence of most mature hFR2-14_H18 heavy chains.

[0148] FIG. 117 shows the amino acid sequence of hFR2-14_H18 (SEQ ID NO: 109 of the Sequence Listing). In this sequence, amino acid positions 1 to 19 represent a signal sequence, which is usually not included in the amino acid sequence of most mature hFR2-14_H18 heavy chains.

[0149] FIG. 118 shows a primer VH3A-F for an hFR2-14_H2 type heavy chain (SEQ ID NO: 110 of the Sequence Listing).

[0150] FIG. 119 shows a primer VH3A-R for an hFR2-14_H2 type heavy chain (SEQ ID NO: 111 of the Sequence Listing).

[0151] FIG. 120 shows a primer D23fw for gene amplification of D2 (SEQ ID NO: 112 of the Sequence Listing).

[0152] FIG. 121 shows a primer D23ry for gene amplification of D2 (SEQ ID NO: 113 of the Sequence Listing).

[0153] FIG. 122 is a diagram showing the results of assaying the binding activity of 4 types of humanized anti-FGFR2 antibodies (hFR2-14_H1/L1 to hFR2-14_H4/L1) and the human chimeric anti-FGFR2 antibody (cFR2-14) against each human FGFR2 variant protein using Biacore. Each antibody was expressed in 293F cells and purified for use in the assay.

[0154] FIG. 123 is a diagram showing the results of assaying the binding activity of 15 types of humanized anti-FGFR2 antibodies (hFR2-14_H3/L1 and hFR2-14_H5/L1 to hFR2-14_H18/L1) against a human FGFR2 IIIc variant protein using Biacore. Each antibody was expressed in 293F cells, and its culture supernatant was used in the assay.

[0155] FIG. 124 is a diagram showing the results of testing the human FGFR2-selective binding activity of 3 types of humanized anti-FGFR2 antibodies (hFR2-14_H3/L1, hFR2-14_H8/L1, and hFR2-14_H12/L1) by Cell-ELISA.

[0156] FIG. 125A is a diagram showing the thermograms of 5 types of humanized anti-FGFR2 antibodies.

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[0157] FIG. 125B is a diagram showing the thermograms of 5 types of humanized anti-FGFR2 antibodies.

[0158] FIG. 125C is a diagram showing the Tm values of 10 types of humanized anti-FGFR2 antibodies.

[0159] FIG. 126 is a diagram showing the KD values of hFR2-14_H1/L1, hFR2-14_H2/L1, hFR2-14_H3/L1, hFR2-14_H4/L1, hFR2-14_H5/L1, hFR2-14_H8/L1, hFR2-14_H9/L1, hFR2-14_H11/L1, hFR2-14_H12/L1, and hFR2-14_H19/L1 antibody analytes for an antigen before and after degradation.

[0160] FIG. 127A is a diagram showing the signal-neutralizing activity of the humanized anti-FGFR2 antibodies (hFR2-14_H1/L1, hFR2-14_H2/L1, hFR2-14_H3/L1, and hFR2-14_H4/L1) and the human chimeric anti-FGFR2 antibody (cFR2-14) against human FGFR2 IIIb by Elk1 trans-reporter assay.

[0161] FIG. 127B is a diagram showing the signal-neutralizing activity of the humanized anti-FGFR2 antibodies (hFR2-14_H1/L1, hFR2-14_H2/L1, hFR2-14_H3/L1, and hFR2-14_H4/L1) and the human chimeric anti-FGFR2 antibody (cFR2-14) against human FGFR2 IIIc by Elk1 trans-reporter assay.

[0162] FIG. 128A is a diagram showing the signal-neutralizing activity of the humanized anti-FGFR2 antibodies (hFR2-14_H3/L1, hFR2-14_H5/L1, hFR2-14_H6/L1, hFR2-14_H7/L1, and hFR2-14_H8/L1) against human FGFR2 IIIb by Elk1 trans-reporter assay.

[0163] FIG. 128B is a diagram showing the signal-neutralizing activity of the humanized anti-FGFR2 antibodies (hFR2-14_H9/L1, hFR2-14_H10/L1, hFR2-14_H11/L1, hFR2-14_H12/L1, and hFR2-14_H13/L1) against human FGFR2 IIIb by Elk1 trans-reporter assay.

[0164] FIG. 128C is a diagram showing the signal-neutralizing activity of the humanized anti-FGFR2 antibodies (hFR2-14_H14/L1, hFR2-14_H15/L1, hFR2-14_H16/L1, hFR2-14_H17/L1, and hFR2-14_H18/L1) against human FGFR2 IIIb by Elk1 trans-reporter assay.

[0165] FIG. 129A is a diagram showing the signal-neutralizing activity of the humanized anti-FGFR2 antibodies (hFR2-14_H12/L1 and hFR2-14_H19/L1) against human FGFR2 IIIb by Elk1 trans-reporter assay.

[0166] FIG. 129B is a diagram showing the signal-neutralizing activity of the humanized anti-FGFR2 antibodies (hFR2-14_H12/L1 and hFR2-14_H19/L1) against human FGFR2 IIIc by Elk1 trans-reporter assay.

[0167] FIG. 130A is a diagram showing the ADCC activity of the humanized anti-FGFR2 antibodies (hFR2-14_H1/L1 and hFR2-14_H2/L1). 293T-lacZ cells expressing human FGFR2 IIIb were used as the target cells, and human PBMC were used as the effector cells.

[0168] FIG. 130B is a diagram showing the ADCC activity of the humanized anti-FGFR2 antibodies (hFR2-14_H3/L1 and hFR2-14_H4/L1) and the human chimeric anti-FGFR2 antibody (cFR2-14). 293T-lacZ cells expressing human FGFR2 IIIb were used as the target cells, and human PBMC were used as the effector cells.

[0169] FIG. 131 is a diagram showing the ADCC activity of the humanized anti-FGFR2 antibodies (hFR2-14_H3/L1, hFR2-14_H8/L1, and hFR2-14_H12/L1). NCI-H716 cells expressing human FGFR2 were used as the target cells, and human PBMC were used as the effector cells.

[0170] FIG. 132 is a diagram showing the ADCC activity of the humanized anti-FGFR2 antibodies (hFR2-14_H12/L1 and hFR2-14_H19/L1). NCI-H716 cells (FIG. 132A)),

SNU-16 cells (FIG. 132B)), or KATO III cells (FIG. 132C)) expressing human FGFR2 were used as the target cells, and human PBMC were used as the effector cells.

[0171] FIG. 133 is a diagram showing the ADCP activity of the humanized anti-FGFR2 antibodies (hFR2-14_H12/L1 and hFR2-14_H19/L1). NCI-H716 cells (FIG. 133A)) or KATO III cells (FIG. 133B)) expressing human FGFR2 were used as the target cells, and macrophage-like cells differentiated from human PBMC were used as the effector cells.

[0172] FIG. 134A is a diagram showing the in vivo antitumor activity of the humanized anti-FGFR2 antibody hFR2-14_H1/L1 against human stomach cancer cell line SNU-16-transplanted nude mice.

[0173] FIG. 134B is a diagram showing the in vivo antitumor activity of the humanized anti-FGFR2 antibody hFR2-14_H2/L1 against human stomach cancer cell line SNU-16-transplanted nude mice.

[0174] FIG. 134C is a diagram showing the in vivo antitumor activity of the humanized anti-FGFR2 antibody hFR2-14_H3/L1 against human stomach cancer cell line SNU-16-transplanted nude mice.

[0175] FIG. 134D is a diagram showing the in vivo antitumor activity of the humanized anti-FGFR2 antibody hFR2-14_H4/L1 against human stomach cancer cell line SNU-16-transplanted nude mice.

[0176] FIG. 135A is a diagram showing the in vivo antitumor activity of the humanized anti-FGFR2 antibody hFR2-14_H5/L1 against human stomach cancer cell line SNU-16-subcutaneously transplanted models.

[0177] FIG. 135B is a diagram showing the in vivo antitumor activity of the humanized anti-FGFR2 antibody hFR2-14_H8/L1 against human stomach cancer cell line SNU-16-subcutaneously transplanted models.

[0178] FIG. 135C is a diagram showing the in vivo antitumor activity of the humanized anti-FGFR2 antibody hFR2-14_H9/L1 against human stomach cancer cell line SNU-16-subcutaneously transplanted models.

[0179] FIG. 135D is a diagram showing the in vivo antitumor activity of the humanized anti-FGFR2 antibody hFR2-14_H11/L1 against human stomach cancer cell line SNU-16-subcutaneously transplanted models.

[0180] FIG. 135E is a diagram showing the in vivo antitumor activity of the humanized anti-FGFR2 antibody hFR2-14_H12/L1 against human stomach cancer cell line SNU-16-subcutaneously transplanted models.

[0181] FIG. 135F is a diagram showing the in vivo antitumor activity of the humanized anti-FGFR2 antibody hFR2-14_H19/L1 against human stomach cancer cell line SNU-16-subcutaneously transplanted models.

[0182] FIG. 136 is a diagram showing the in vivo antitumor activity of the humanized anti-FGFR2 antibodies (hFR2-14_H12/L1 and hFR2-14_H19/L1) against human colorectal cancer cell line NCI-H716 tumor block models. FIG. 136(A) shows the results for hFR2-14_H12/L1. FIG. 136(B) shows the results for hFR2-14_H19/L1.

[0183] FIG. 137 is a diagram showing the in vivo antitumor activity of the humanized anti-FGFR2 antibodies (hFR2-14_H12/L1 and hFR2-14_H19/L1) against human colorectal cancer cell line NCI-H716-luc-peritoneally disseminated models. FIG. 137(A) shows the results showing luciferase activity. FIG. 137(B) shows the results showing survival rates.

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[0184] FIG. 138 is a diagram showing a ribbon model of an FGFR2D2/H3L1Fab complex. FGFR2D2 is shown at the lower left. The H chain (dark gray) of H3L1Fab is shown from the center to the upper right. The L chain of H3L1Fab is shown at the right thereof.

[0185] FIG. 139 is a diagram showing the superposition of FGFR2/FGF1 and FGFR2D2/H3L1Fab. FGFRD3 (IgD3) is shown at the lower center. FGF1 (dark gray) is shown above FGFRD3. FGFRD2 is shown above FGF1. The H chain (dark gray) and L chain of H3L1Fab are each shown at the upper right of FGFRD2.

[0186] FIG. 140 is a diagram showing the extent of inhibition of the binding of the ligand FGF7 to its receptor FGFR2 by the cFR2-10, hFR2-14_H12/L1, and hFR2-14_H19/L1 antibodies.

[0187] FIG. 141 is a diagram showing that the number of the antigen FGFR2 on cell surface is elevated by the treatment of SNU-16 cells with AZD4547 or Ki23057 compared with no treatment (None) or DMSO treatment.

[0188] FIG. 142A is a diagram showing the ADCC activity of hFR2-14_H19/L1 when SNU-16 cells were not treated with a drug or DMSO.

[0189] FIG. 142B is a diagram showing the ADCC activity of hFR2-14_H19/L1 when SNU-16 cells were treated with 0.01% DMSO.

[0190] FIG. 142C is a diagram showing the ADCC activity of hFR2-14_H19/L1 when SNU-16 cells were treated with 0.001% DMSO.

[0191] FIG. 142D is a diagram showing the ADCC activity of hFR2-14_H19/L1 when SNU-16 cells were treated with 1000 nM AZD4547.

[0192] FIG. 142E is a diagram showing the ADCC activity of hFR2-14_H19/L1 when SNU-16 cells were treated with 100 nM Ki23057.

[0193] FIG. 143 is a diagram showing the in vivo antitumor effect of hFR2-14_H19/L1 administered alone, AZD4547 administered alone, or hFR2-14_H19/L1 and AZD4547 administered in combination on human stomach cancer cell line SNU-16-transplanted nude mice. An open square represents the results for an untreated control group. An open circle represents the results for 20 mg/kg hFR2-14_H19/L1. A filled circle represents the results for 3 mg/kg AZD4547. A filled square represents the results for 20 mg/kg hFR2-14_H19/L1+3 mg/kg AZD4547.

[0194] FIG. 144 is a table showing the number of complete response (CR) individuals per total number of human stomach cancer cell line SNU-16-transplanted nude mice in each group at 21 days after transplantation (final assay day).

[0195] FIG. 145 is a diagram showing the amount of the antigen FGFR2 in tumor detected by Western blotting on the day after the administration of hFR2-14_H19/L1 alone, the administration of AZD4547 alone, or the administration of hFR2-14_H19/L1 and AZD4547 in combination to human stomach cancer cell line SNU-16-transplanted nude mice. GAPDH was detected as a control.

[0196] FIG. 146 is a diagram showing the in vivo antitumor effect of hFR2-14_H19/L1 administered alone, Ki23057 administered alone, or hFR2-14_H19/L1 and Ki23057 administered in combination on human stomach cancer cell line SNU-16-transplanted nude mice. No symbol represents the results for an untreated control group. A filled circle represents the results for 20 mg/kg hFR2-14_H19/L1. An open triangle represents the results for 5 mg/kg Ki23057. An open square represents the results for 20 mg/kg Ki23057.

A filled triangle represents the results for 20 mg/kg hFR2-14_H19/L1+5 mg/kg Ki23057. A filled square represents the results for 20 mg/kg hFR2-14_H19/L1+20 mg/kg Ki23057.

DESCRIPTION OF THE EMBODIMENTS

1. Definitions

[0197] In the present invention, the term “gene” means a nucleotide comprising a nucleotide sequence encoding the amino acids of a protein, or its complementary strand. The “gene” is meant to include, for example, a polynucleotide, an oligonucleotide, DNA, mRNA, cDNA, and cRNA as the nucleotide comprising a nucleotide sequence encoding the amino acids of a protein, or its complementary strand. Such a gene can be a single-stranded, double-stranded, or triple or more stranded nucleotide. The “gene” is also meant to include an association of DNA and RNA strands, a mixture of ribonucleotides (RNAs) and deoxyribonucleotides (DNAs) on one nucleotide strand, and a double-stranded or triple or more stranded nucleotide comprising such a nucleotide strand. Examples of the “FGFR2 gene” of the present invention can include DNA, mRNA, cDNA, and cRNA comprising a nucleotide sequence encoding the amino acid sequence of the FGFR2 protein.

[0198] In the present invention, the term “nucleotide” has the same meaning as a “nucleic acid” and is also meant to include, for example, DNA, RNA, a probe, an oligonucleotide, a polynucleotide, and a primer. Such a nucleotide can be a single-stranded, double-stranded, or triple or more stranded nucleotide. The term “nucleotide” is also meant to include an association of DNA and RNA strands, a mixture of ribonucleotides (RNAs) and deoxyribonucleotides (DNAs) on one nucleotide strand, and an association of two strands or three or more strands comprising such a nucleotide strand.

[0199] In the present invention, the terms “polypeptide”, “peptide”, and “protein” have the same meaning.

[0200] In the present invention, the term “antigen” has the same meaning as “immunogen”.

[0201] In the present invention, the term “cell” also includes, for example, various cells derived from individual animals, subcultured cells, primary cultured cells, cell lines, recombinant cells, and microbial cells.

[0202] In the present invention, antibodies recognizing FGFR2, FGFR2 IIIb, FGFR2 IIIc, FGFR3, FGFRs, and the like are also referred to as an “anti-FGFR2 antibody”, an “anti-FGFR2 IIIb antibody”, an “anti-FGFR2 IIIc antibody”, an “anti-FGFR3 antibody”, and an “anti-FGFRs antibody”, respectively. These antibodies include chimeric antibodies, humanized antibodies, human antibodies, and the like.

[0203] In the present invention, the term “functional fragment of the antibody” means an antibody fragment that exerts at least a portion of functions exerted by the original antibody. Examples of the “functional fragment of the antibody” can include, but are not limited to, Fab, F(ab')₂, scFv, Fab', and single chain immunoglobulin. Such a functional fragment of the antibody may be obtained by treating a full-length molecule of the antibody protein with an enzyme such as papain or pepsin or may be a recombinant protein produced in an appropriate host cell using a recombinant gene.

[0204] In the present invention, the “site” to which an antibody binds, i.e., the “site” recognized by an antibody,

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means a partial peptide or partial conformation on an antigen bound or recognized by the antibody. In the present invention, such a site is also referred to as an epitope or an antibody binding site. Examples of the site on the FGFR2 protein bound or recognized by the anti-FGFR2 antibody of the present invention can include a partial peptide or partial conformation on the FGFR2 protein.

[0205] The heavy and light chains of an antibody molecule are known to each have three complementarity determining regions (CDRs). The complementarity determining regions are also called hypervariable domains. These regions are located in the variable regions of the antibody heavy and light chains. These sites have a particularly highly variable primary structure and are usually separated at three positions on the respective primary structures of heavy and light chain polypeptide strands. In the present invention, the complementarity determining regions of the antibody are referred to as CDRH1, CDRH2, and CDRH3 from the amino terminus of the heavy chain amino acid sequence for the complementarity determining regions of the heavy chain and as CDRL1, CDRL2, and CDRL3 from the amino terminus of the light chain amino acid sequence for the complementarity determining regions of the light chain. These sites are proximal to each other on the three-dimensional structure and determine specificity for the antigen to be bound.

[0206] In the present invention, the term “antibody mutant” means a polypeptide that has an amino acid sequence derived from the amino acid sequence of the original antibody by the substitution, deletion, addition, and/or insertion (hereinafter, collectively referred to as a “mutation”) of amino acid(s) and binds to the FGFR2 protein of the present invention. The number of mutated amino acids in such an antibody mutant is 1 to 2, 1 to 3, 1 to 4, 1 to 5, 1 to 6, 1 to 7, 1 to 8, 1 to 9, 1 to 10, 1 to 12, 1 to 15, 1 to 20, 1 to 25, 1 to 30, 1 to 40, or 1 to 50. Such an antibody mutant is also encompassed by the “antibody” of the present invention.

[0207] In the present invention, the term “several” in “1 to several” refers to 3 to 10.

[0208] Examples of activities or properties exerted by the antibody of the present invention can include biological activities or physicochemical properties and can specifically include various biological activities, binding activity against an antigen or an epitope, stability during production or storage, and thermal stability.

[0209] In the present invention, the phrase “hybridizing under stringent conditions” means hybridization under conditions involving hybridization at 65° C. in a solution containing 5×SSC, followed by washing at 65° C. for 20 minutes in an aqueous solution containing 2×SSC-0.1% SDS, at 65° C. for 20 minutes in an aqueous solution containing 0.5×SSC-0.1% SDS, and at 65° C. for 20 minutes in an aqueous solution containing 0.2×SSC-0.1% SDS, or hybridization under conditions equivalent thereto. SSC means an aqueous solution of 150 mM NaCl-15 mM sodium citrate, and n×SSC means SSC with an n-fold concentration.

[0210] In the present invention, the term “cytotoxicity” refers to some pathological change brought about to cells and means not only direct trauma but any structural or functional damage to cells, including DNA cleavage, formation of base dimers, chromosomal breakage, damage to mitotic apparatus, and reduction in the activities of various

enzymes. In the present invention, the term “cytotoxic activity” means activity that causes the cytotoxicity mentioned above.

[0211] In the present invention, the term “antibody dependent cellular cytotoxic activity”, also called “ADCC activity”, means the effect or activity of damaging target cells such as tumor cells by NK cells via antibodies.

[0212] In the present invention, the term “antibody dependent cell phagocytosis activity”, also called “ADCP activity”, means the effect or activity of englobing target cells such as tumor cells by monocyte or macrophage cells via antibodies. This activity is also referred to as “antibody dependent phagocytic activity”.

[0213] In the present invention, the term “complement dependent cytotoxic activity”, also called “CDC activity”, means the effect or activity of damaging target cells such as tumor cells by complement via antibodies.

[0214] In the present invention, the term “cancer” has the same meaning as “tumor”.

[0215] In the present invention, the term “immunohistochemistry (IHC)” means a histological (histochemical) approach of detecting an antigen in a tissue preparation. The immunohistochemistry is synonymous with an “immune antibody method” and has the same meaning as “immunostaining”.

[0216] In the present invention, the term “active ingredient” means an ingredient that is used in combination with the anti-FGFR2 antibody or contained with the anti-FGFR2 antibody in the pharmaceutical composition of the present invention and has the activity of treating or preventing a disease. According to a preferred aspect, the combination or the pharmaceutical composition is effective for the treatment or prevention of cancer. According to a more preferred aspect, the combination or the pharmaceutical composition exhibits a synergistic effect in the treatment or prevention of cancer.

[0217] In the present invention, the “synergistic effect” means that a plurality of active ingredients used in combination or contained in one pharmaceutical composition exhibit anticancer activity stronger than the sum of the respective anticancer activities exhibited by the active ingredients. For example, when active ingredients A and B exert anticancer activities a and b, respectively, and are used in combination or used in a state contained in one pharmaceutical composition, the combination or the pharmaceutical composition having anticancer activity larger than the sum of a and b can be regarded as exerting the synergistic effect. As another example, when active ingredients A and B exert anticancer activities a and zero (0; i.e., B exerts no anticancer activity at the concentration), respectively, and are used in combination or contained in one pharmaceutical composition, the combination or the pharmaceutical composition having anticancer activity larger than a can be regarded as exerting the synergistic effect. As a further example, when active ingredients A and B both exert zero anticancer activities (0; i.e., neither A nor B exerts anticancer activity at the concentration) and are used in combination or contained in one pharmaceutical composition, the combination or the pharmaceutical composition having anticancer activity larger than zero (0) can be regarded as exerting the synergistic effect.

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2. Antigenic Protein

[0218] (2-1) Properties

[0219] FGFRs are receptor proteins that bind to fibroblast growth factors (FGFs). In the present invention, FGFRs are derived from vertebrates, preferably mammals, more preferably humans. Human FGFs and FGFRs are classified into 22 FGFs (FGF1 to FGF14 and FGF16 to FGF23) and 4 FGFRs (FGFR1 to FGFR4) having a tyrosine kinase domain, respectively. These FGFRs are each composed of an extracellular region comprising a ligand binding site composed of 2 or 3 immunoglobulin-like domains (IgD1 to IgD3), a single-pass transmembrane region, and an intracellular region comprising the tyrosine kinase domain. Of these, FGFR1, FGFR2, and FGFR3 each have two splicing variants called IIIb and IIIc. These isoforms differ in a sequence of approximately 50 amino acids in the latter half of IgD3 and exhibit distinctive tissue distribution and ligand specificity. FGFRs have the following activities: (1) binding to FGFs; (2) this binding dimerizes the FGFRs; (3) this dimerization phosphorylates the FGFRs at their particular tyrosine residues; (4) this phosphorylation promotes the recruitment of adaptor proteins such as FGFR substrate 2 α (FRS2 α); and (5) this transduces signals generated by FGF stimulation to cells or tissues expressing the FGFRs or activates signal transduction.

[0220] The FGFR2 protein according to the present invention has the following properties:

[0221] (i) Binding to FGF.

[0222] The FGFR2 IIIb protein typically binds to one or two or more FGFs selected from the group consisting of FGF1, FGF3, FGF7 (KGF), FGF10, FGF22, and FGF23. The FGFR2 IIIb protein may bind to other FGFs and may not bind to mutated forms of the FGFs included in the above group.

[0223] The FGFR2 IIIc protein typically binds to one or two or more FGFs selected from the group consisting of FGF1, FGF2, FGF4, FGF6, FGF9, FGF17, FGF18, FGF21, and FGF23. The FGFR2 IIIc protein may bind to other FGFs and may not bind to mutated forms of the FGFs included in the above group.

[0224] (ii) Transducing Signals Generated by FGF Stimulation into FGFR2-Expressing Cells or Tissues

[0225] Examples of the transduction of signals generated by FGF stimulation can include, but are not particularly limited to, FGFR2 autophosphorylation, recruitment of FGFR substrates and promotion thereof, and activation of signaling pathways such as MAPK, PI3K, Akt, and extracellular signal-regulated kinase (ERK) pathways via these events. Examples of the FGFR substrates can include FGFR substrate 2 α (FRS2 α).

[0226] Testing methods for evaluating the activation of this signal transduction and the inhibition thereof are not particularly limited and can be arbitrarily selected from methods known in the art. Examples thereof can include evaluation systems for ERK signal transduction, and Elk1 luciferase reporter assay described later.

[0227] (iii) The FGFR2 IIIb protein according to the present invention comprises an amino acid sequence defined in any one of the following (a) to (d) (hereinafter, referred to as an "FGFR2 IIIb amino acid sequence"), consists of an amino acid sequence comprising the FGFR2 IIIb amino acid sequence, or consists of the FGFR2 IIIb amino acid sequence:

(a) the amino acid sequence represented by SEQ ID NO: 70 (FIG. 78) of the Sequence Listing;

(b) an amino acid sequence that exhibits 80% or higher, 82% or higher, 84% or higher, 86% or higher, 88% or higher, 90% or higher, 92% or higher, 94% or higher, 96% or higher, 98% or higher, or 99% or higher, sequence identity to the amino acid sequence represented by SEQ ID NO: 70 (FIG. 78) of the Sequence Listing and is carried by a polypeptide having FGF binding activity;

(c) an amino acid sequence that is derived from the amino acid sequence represented by SEQ ID NO: 70 (FIG. 78) of the Sequence Listing by the substitution, deletion, addition, or insertion of 1 to 50, 1 to 45, 1 to 40, 1 to 35, 1 to 30, 1 to 25, 1 to 20, 1 to 15, 1 to 10, 1 to 8, 1 to 6, 1 to 5, 1 to 4, 1 to 3, 1 or 2, or 1 amino acid(s) and is carried by a polypeptide having FGF binding activity; and

(d) an amino acid sequence that is encoded by the nucleotide sequence of a nucleotide hybridizing under stringent conditions to a nucleotide having a nucleotide sequence complementary to a nucleotide sequence encoding the amino acid sequence represented by SEQ ID NO: 70 (FIG. 78) of the Sequence Listing and is carried by a polypeptide having FGF binding activity.

[0228] The polypeptide defined in any one of (b) to (d) may have FGFR2 activities other than the FGF binding activity.

[0229] The FGFR2 IIIc protein according to the present invention comprises an amino acid sequence defined in any one of the following (a) to (d) (hereinafter, referred to as an "FGFR2 IIIc amino acid sequence"), consists of an amino acid sequence comprising the FGFR2 IIIc amino acid sequence, or consists of the FGFR2 IIIc amino acid sequence:

(a) an amino acid sequence represented by SEQ ID NO: 71 (FIG. 79) of the Sequence Listing;

(b) an amino acid sequence that exhibits 80% or higher, 82% or higher, 84% or higher, 86% or higher, 88% or higher, 90% or higher, 92% or higher, 94% or higher, 96% or higher, 98% or higher, or 99% or higher, sequence identity to the amino acid sequence represented by SEQ ID NO: 71 (FIG. 79) of the Sequence Listing and is carried by a polypeptide having FGF binding activity;

(c) an amino acid sequence that is derived from the amino acid sequence represented by SEQ ID NO: 71 (FIG. 79) of the Sequence Listing by the substitution, deletion, addition, or insertion of 1 to 50, 1 to 45, 1 to 40, 1 to 35, 1 to 30, 1 to 25, 1 to 20, 1 to 15, 1 to 10, 1 to 8, 1 to 6, 1 to 5, 1 to 4, 1 to 3, 1 or 2, or 1 amino acid(s) and is carried by a polypeptide having FGF binding activity; and

(d) an amino acid sequence that is encoded by the nucleotide sequence of a nucleotide hybridizing under stringent conditions to a nucleotide having a nucleotide sequence complementary to a nucleotide sequence encoding the amino acid sequence represented by SEQ ID NO: 71 (FIG. 79) of the Sequence Listing and is carried by a polypeptide having FGF binding activity.

[0230] The polypeptide defined in any one of (b) to (d) may have FGFR2 activities other than the FGF binding activity.

[0231] Examples of the amino acid sequences of human FGFR2 IIIb and human FGFR2 IIIc can include the amino acids (a) to (d) as well as the amino acids published under NP_075259 and NP_000132, respectively.

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[0232] (iv) The FGFR2 protein of the present invention can be obtained from FGFR2-expressing cells, tissues, or cancer tissues, cells derived from the tissues, cultures of the cells, and the like, of a vertebrate, preferably of a mammal, more preferably of a rodent such as a mouse or a rat and a human, even more preferably of a human, a rat, or a mouse.

[0233] Examples of the normal tissues highly expressing FGFR2 can include the brain, the large intestine, thyroid glands, the uterine, the gallbladder, and the skin. Gene amplification is found in some cancers highly expressing FGFR2, such as stomach cancer and breast cancer, while overexpression is found in some cancers highly expressing FGFR2, such as pancreatic cancer and ovarian cancer. Examples of the cultured cell lines highly expressing FGFR2 IIIb can include stomach cancer cell lines and breast cancer cell lines. Examples of the cultured cell lines highly expressing FGFR2 IIIb can include colorectal (cecal) cancer cell lines. Examples of cancer tissues expressing FGFR2 IIIc can include tissues with uterine cervix cancer and non-small cell lung cancer. Of these cancers, uterine cervix cancer highly expresses FGFR2 IIIc.

[0234] The FGFR2 protein of the present invention may be a native (non-recombinant) or recombinant protein. The FGFR2 protein is also meant to include fusion products with another peptide or protein such as a carrier or a tag. The FGFR2 protein is further meant to include forms provided with chemical modification including the addition of a polymer such as PEG and/or with biological modification including sugar chain modification. Moreover, the FGFR2 protein of the present invention is meant to include an FGFR2 protein fragment. An FGFR2 protein fragment possessing the properties defined above in (i) and/or (ii) is referred to as a functional fragment of the FGFR2 protein.

[0235] (2-2) Antigen Gene

[0236] The FGFR2 IIIb gene according to the present invention comprises a nucleotide sequence defined in any one of the following (a) to (c) (hereinafter, referred to as an “FGFR2 IIIb gene sequence”), consists of a nucleotide sequence comprising the FGFR2 IIIb gene sequence, or consists of the FGFR2 IIIb gene sequence:

(a) a nucleotide sequence encoding the amino acid sequence represented by SEQ ID NO: 70 (FIG. 78) of the Sequence Listing;

(b) a nucleotide sequence that hybridizes under stringent conditions to a nucleotide consisting of a nucleotide sequence complementary to the nucleotide sequence encoding the amino acid sequence represented by SEQ ID NO: 70 (FIG. 78) of the Sequence Listing and encodes the amino acid sequence of a polypeptide having FGF binding activity; and

(c) a nucleotide sequence that encodes an amino acid sequence derived from the amino acid sequence represented by SEQ ID NO: 70 (FIG. 78) of the Sequence Listing by the substitution, deletion, addition, or insertion of 1 to 50, 1 to 45, 1 to 40, 1 to 30, 1 to 25, 1 to 20, 1 to 15, 1 to 10, 1 to 8, 1 to 6, 1 to 5, 1 to 4, 1 to 3, 1 or 2, or 1 amino acid(s) and encodes the amino acid sequence of a polypeptide having FGF binding activity.

[0237] The polypeptide having the amino acid sequence encoded by the nucleotide sequence (b) or (c) may have FGFR2 activities other than the FGF binding activity.

[0238] The FGFR2 IIIc gene according to the present invention comprises a nucleotide sequence defined in any one of the following (a) to (c) (hereinafter, referred to as an

“FGFR2 IIIc gene sequence”), consists of a nucleotide sequence comprising the FGFR2 IIIc gene sequence, or consists of the FGFR2 IIIc gene sequence:

(a) a nucleotide sequence encoding the amino acid sequence represented by SEQ ID NO: 71 (FIG. 79) of the Sequence Listing;

(b) a nucleotide sequence that hybridizes under stringent conditions to a nucleotide consisting of a nucleotide sequence complementary to the nucleotide sequence encoding the amino acid sequence represented by SEQ ID NO: 71 (FIG. 79) of the Sequence Listing and encodes the amino acid sequence of a polypeptide having FGF binding activity; and

(c) a nucleotide sequence that encodes an amino acid sequence derived from the amino acid sequence represented by SEQ ID NO: 71 (FIG. 79) of the Sequence Listing by the substitution, deletion, addition, or insertion of 1 to 50, 1 to 45, 1 to 40, 1 to 30, 1 to 25, 1 to 20, 1 to 15, 1 to 10, 1 to 8, 1 to 6, 1 to 5, 1 to 4, 1 to 3, 1 or 2, or 1 amino acid(s) and encodes the amino acid sequence of a polypeptide having FGF binding activity.

[0239] The polypeptide having the amino acid sequence encoded by the nucleotide sequence (b) or (c) may have FGFR2 activities other than the FGF binding activity.

[0240] The expression and expression level of the FGFR2 gene may be assayed with either an FGFR2 gene transcript or the FGFR2 protein as an index. The former index can be determined by RT-PCR, Northern blot hybridization, or the like, while the latter index can be determined by, for example, immunoassay such as enzyme-linked immunosorbent assay (hereinafter, referred to as “ELISA”), Western blotting, or immunohistological staining.

[0241] In the present invention, the FGFR2 IIIb gene sequence and the FGFR2 IIIc gene sequence are collectively referred to as an FGFR2 gene sequence.

[0242] (2-3) Preparation of Antigenic Protein

[0243] The FGFR2 protein of the present invention can be prepared by purification or isolation from animal tissues (including body fluids), cells derived from the tissues, or cultures of the cells, gene recombination, in vitro translation, chemical synthesis, etc.

[0244] (2-3-1) Purification or Isolation of Non-Recombinant FGFR2

[0245] The non-recombinant FGFR2 protein can be purified or isolated from FGFR2-expressing cells, normal tissues, or cancer tissues, or cells derived therefrom. Examples of the FGFR2-expressing normal tissues, cancer tissues, or cancer cells can include those described in (iv) of paragraph (2-2), though the origin of the non-recombinant FGFR2 protein is not limited thereto.

[0246] The purification or isolation from such tissues, cells, cell cultures, or the like, can be performed by the combination of approaches well known by those skilled in the art, such as fractionation and chromatography. Such approaches include, but are not limited to, salting out, gel filtration, ion-exchange chromatography, affinity chromatography, hydrophobic chromatography, normal-phase or reverse-phase chromatography, and the like. A column for affinity chromatography can be prepared by packing the column with an affinity gel cross-linked with an anti-FGFR2 monoclonal antibody. A crude or partially purified fraction containing the FGFR2 protein is applied to this column. Subsequently, non-specifically adsorbed substances are removed with sterilized phosphate-buffered saline (PBS),

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and a buffer solution for elution can then be applied thereto to thereby selectively recover the FGFR2 protein. The solution containing the FGFR2 protein can be subjected to gel filtration or to buffer replacement and/or concentration using a concentrator such as Centriprep.

[0247] (2-3-2) Preparation of a Recombinant FGFR2 Protein

[0248] The FGFR2 protein of the present invention can also be prepared in a recombinant form. Specifically, host cells are transfected with a gene encoding the amino acid sequence of the FGFR2 protein or an FGFR2 protein fragment, and the FGFR2 protein can be recovered from cultures of the cells. For example, the FGFR2 gene or its fragment is inserted into an expression vector. Subsequently, prokaryotic or eukaryotic host cells are transfected with the resulting recombinant vector, and the obtained recombinant cells can be incubated to thereby express the FGFR2 protein. An expression pattern known in the art, such as secretion expression, intracellular expression of soluble forms, or expression in inclusion body forms can be used. Also, the FGFR2 protein can be expressed not only as a molecule having the same amino terminus (N terminus) and/or carboxy terminus (C terminus) as native ones, but also as a fusion protein with a secretory signal, an intracellular localization signal, a tag for affinity purification, or a partner peptide. The FGFR2 protein can be purified or isolated from such recombinant cell cultures by an appropriate combination of methods such as fractionation and chromatography described in (2-3-1) Purification or isolation of non-recombinant FGFR2 protein.

[0249] The FGFR2 gene or its fragment can be prepared by a method well known by those skilled in the art.

[0250] Examples thereof can include: polymerase chain reaction (hereinafter, referred to as "PCR"; Saiki, R. K., et al., Science (1988) 239, p. 487-489) with a cDNA library prepared from FGFR2-expressing cells, tissues, or the like as a template using one set of primers capable of specifically amplifying the sequence; reverse transcription PCR (hereinafter, referred to as "RT-PCR") with an mRNA fraction prepared from FGFR2-expressing cells, tissues, or the like as a template using a primer capable of reverse-transcribing the sequence and one set of primers capable of specifically amplifying the sequence; expression cloning using immunoassay; and cDNA cloning using the partial amino acid sequence of purified FGFR2 protein.

[0251] (2-3-3) In vitro Translation

[0252] The FGFR2 protein of the present invention can also be prepared by in vitro translation. Such a translation method is not particularly limited as long as the method employs a cell-free translation system involving enzymes necessary for transcription and translation, substrates, and energy substances. Examples thereof can include a method using Rapid Translation System (RTS) manufactured by Roche Diagnostics K.K.

[0253] (2-3-4) Chemical Synthesis

[0254] The FGFR2 protein of the present invention can also be prepared by chemical synthesis. Examples of the chemical synthesis method can include solid-phase peptide synthesis methods such as Fmoc and Boc synthesis methods.

3. Antibody

[0255] (3-1) Classification of the Antibody

[0256] The antibodies of the present invention may be either monoclonal or polyclonal antibodies. Examples of

monoclonal antibodies of the present invention can include non-human animal-derived antibodies (non-human animal antibodies), human-derived antibodies (human antibodies), chimeric antibodies, and humanized antibodies.

[0257] Examples of non-human animal antibodies can include antibodies derived from vertebrates such as mammals and birds. Examples of mammal-derived antibodies can include rodent-derived antibodies such as mouse antibodies and rat antibodies. Examples of bird-derived antibodies can include chicken antibodies. Examples of anti-human FGFR2 rat monoclonal antibodies can include FR2-10, FR2-13, and FR2-14.

[0258] Examples of chimeric antibodies can include, but are not limited to, antibodies comprising non-human animal antibody-derived variable regions bound with human antibody (human immunoglobulin) constant regions. Examples of chimeric antibodies comprising non-human animal antibody-derived variable regions bound with human antibody constant regions can include cFR2-10, cFR2-13, and cFR2-14 having heavy and light chain variable regions derived from the rat monoclonal antibody FR2-10, FR2-13, or FR2-14 mentioned above, and human heavy and light chain constant regions.

[0259] Examples of humanized antibodies can include, but are not limited to, a human antibody (human immunoglobulin variable regions) grafted with CDRs in the variable regions of a non-human animal antibody, a human antibody grafted with the CDRs as well as with partial sequences of framework regions of a non-human animal antibody, and an antibody having human antibody amino acid(s) substituted for one or two or more non-human animal antibody-derived amino acid(s) in any of these humanized antibodies. Examples of the CDRs in the variable regions of a non-human animal antibody can include CDRH1 to CDRH3 in the heavy chain variable region and CDRL1 to CDRL3 in the light chain variable region derived from FR2-10, FR2-13, or FR2-14 mentioned above.

[0260] The human antibody is not particularly limited as long as the antibody recognizes the antigen of the present invention. Examples thereof can include a human antibody binding to the same site, as in the case of an antibody having the CDRs of the antibodies of the present invention, and a human antibody binding to the same site on FGFR2 as in the case of FR2-10, FR2-13, or FR2-14 mentioned above.

[0261] The antibody according to the present invention may be comprised of portions derived from a plurality of different antibodies as long as the antibody has FGFR2 binding activity. Examples of such an antibody can include an antibody comprising heavy and/or light chains exchanged among a plurality of different antibodies, an antibody comprising full-length heavy and/or light chains exchanged thereamong, an antibody comprising variable or constant regions exchanged thereamong, and an antibody comprising all or some CDRs exchanged thereamong. The heavy and light chain variable regions of the chimeric antibody may be derived from different antibodies of the present invention. CDRH1 to CDRH3 and CDRL1 to CDRL3 in the heavy and light chain variable regions of the humanized antibody may be derived from two or more different antibodies of the present invention. CDRH1 to CDRH3 and CDRL1 to CDRL3 in the heavy and light chain variable regions of the human antibody may be a combination of CDRs carried by two or more different antibodies of the present invention. Such an antibody comprised of portions derived from a

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plurality of different antibodies may have one or two or more of the activities defined in paragraphs (3-3) to (3-6).

[0262] Examples of the isotype of the monoclonal antibody of the present invention can include, but are not particularly limited to, IgG such as IgG1, IgG2, IgG3, and IgG4, IgM, IgA such as IgA1 and IgA2, IgD, and IgE and can preferably include IgG and IgM. The isotype and subclass of the monoclonal antibody can be determined by, for example, an Ouchterlony test, ELISA, or radio immunoassay (hereinafter, referred to as "RIA"). A commercially available kit for identification (e.g., Mouse Typer Kit; Bio-Rad Laboratories, Inc., and RAT MONOCLONAL ANTIBODY ISOTYPING TEST KIT: AbD Serotec) may be used.

[0263] (3-2) Binding Specificity of the Antibody

[0264] The antibody of the present invention recognizes the FGFR2 protein. In other words, the antibody of the present invention binds to the FGFR2 protein. Such an antibody is referred to as an "anti-FGFR2 antibody". Preferably, the antibody of the present invention specifically recognizes the FGFR2 protein. In other words, preferably, the antibody of the present invention specifically binds to the FGFR2 protein. More preferably, the antibody of the present invention specifically binds to the FGFR2 IIIb protein and/or the FGFR2 IIIc protein. Even more preferably, the antibody of the present invention specifically binds to the immunoglobulin-like domain (hereinafter, referred to as "Ig-like domain") of the FGFR2 IIIb protein and/or the FGFR2 IIIc protein. Examples of such an Ig-like domain can include Ig-like domain 2 and Ig-like domain 3.

[0265] In the present invention, the "specific recognition", i.e., "specific binding", means binding which is not non-specific adsorption. Examples of criteria for determination of whether binding is specific or not can include a dissociation constant (hereinafter, referred to as "KD"). Preferably, the antibody of the present invention has a KD value of 1×10^{-5} or lower, 5×10^{-6} or lower, 2×10^{-6} or lower, or 1×10^{-6} or lower, more preferably 5×10^{-7} or lower, 2×10^{-7} or lower, or 1×10^{-7} or lower, even more preferably 5×10^{-8} or lower, 2×10^{-8} or lower, or 1×10^{-8} or lower, further more preferably 5×10^{-9} or lower, 2×10^{-9} or lower, or 1×10^{-9} or lower, most preferably 5×10^{-10} or lower, 2×10^{-10} or lower, or 1×10^{-10} or lower for the FGFR2 protein.

[0266] In the present invention, the binding of the antibody to the antigen can be assayed or determined by ELISA, RIA, surface plasmon resonance (hereinafter, referred to as "SPR") analysis, or the like. Examples of equipment used in the SPR analysis can include BIAcore™ (manufactured by GE Healthcare Bio-Sciences Corp.), ProteOn™ (manufactured by Bio-Rad Laboratories, Inc.), SPR-Nav™ (manufactured by BioNavis Oy Ltd.), Spreeta™ (manufactured by Texas Instruments Inc.), SPRi-Plex II™ (manufactured by Horiba, Ltd.), and Autolab SPR™ (manufactured by Metrohm Japan Ltd.). The binding of the antibody to the antigen expressed on cell surface can be assayed by flow cytometry, Cell-ELISA, or the like.

[0267] (3-3) Antitumor Activity of the Antibody

[0268] The antibody of the present invention has antitumor activity. Preferably, the antibody of the present invention has antitumor activity in vivo. In the present invention, the "antitumor activity" has the same meaning as "anti-cancer activity".

[0269] In the present invention, antitumor activity means the activity of inhibiting the growth, malignant transforma-

tion, invasion, or metastasis of tumor tissues and/or tumor cells, increase in tumor size or weight, etc.

[0270] The antitumor activity can be evaluated according to a standard method. The in vivo antitumor activity can be evaluated as an effect on human tumor, for example, by use of human cancer tissue- or cancer cell-transplanted non-human animal models (xenografts). Examples of the non-human animal used for the xenografts can include mice such as nude mice, and rats.

[0271] Alternatively, the antitumor activity may be evaluated as suppressive or inhibitory activity against the growth of cancer cells.

[0272] (3-4) Cytotoxic Activity of Antibody

[0273] The anti-FGFR2 antibody of the present invention may have antibody dependent cellular cytotoxic (ADCC) activity and/or complement dependent cytotoxic (CDC) activity and/or antibody dependent cell phagocytosis (ADCP) activity. Preferably, the antibody of the present invention has ADCC activity. More preferably, the antibody of the present invention has ADCC activity against FGFR2-expressing cells. The ADCC activity, the CDC activity, and the ADCP activity can be assayed by any method known in the art.

[0274] Cells expressing the antigen of interest (target cells) and effector cells capable of killing the target cells are used in the ADCC activity assay. The effector cells recognize the Fc regions of antibodies bound with the target cells via Fcγ receptors. The effector cells kill the target cells by signals transduced from the Fcγ receptors. In the case of assaying the ADCC activity of an antibody having a human-derived Fc region, human NK cells are used as the effector cells. The human NK cells can be prepared from human peripheral blood mononuclear cells (PBMCs) by any method known in the art. Alternatively, PBMCs may be used directly as the effector cells.

[0275] Cells expressing the antigen of interest (target cells) and effector cells (e.g., monocytes or macrophages) capable of englobing the target cells are used in the ADCP activity assay. These effector cells can be prepared by inducing, by any method known in the art, differentiation from monocyte fractions to macrophages, wherein said monocyte fractions have been separated from human peripheral blood mononuclear cells (PBMCs) by any method known in the art.

[0276] (3-5) Effect of the Antibody on Signal Transduction

[0277] The biological activities and properties of the anti-FGFR2 antibody of the present invention can also be evaluated through FGFR2-mediated FGF signals. Examples of FGFR2-mediated signal transduction by FGF stimulation can include, but are not particularly limited to, FGFR2 autophosphorylation, recruitment of FGFR substrates and promotion thereof, and activation of signaling pathways such as MAPK, PI3K, Akt, and extracellular signal-regulated kinase (ERK) pathways via these events. Examples of the FGFR substrates can include FGFR substrate 2α (FRS2α). Testing methods for evaluating the activation of this signal transduction and the inhibition thereof are not particularly limited and can be arbitrarily selected from methods known in the art. Examples thereof can include evaluation systems for ERK signal transduction, and Elk1 luciferase reporter assay described later.

[0278] Preferably, the antibody of the present invention also has neutralizing activity against FGFR2. More preferably, the antibody of the present invention has neutralizing

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activity against FGFR2 IIIB and/or FGFR2 IIIC. The neutralizing activity means the activity of inhibiting or suppressing the activation of FGFR2 by an FGFR2 ligand. For example, an antibody inhibiting FGF dependent FGFR2-mediated signals, signal transduction, or the like can be confirmed to have such neutralizing activity. An exemplary assay of the neutralizing activity is shown in 2)-3 of Example 2 and Example 11.

[0279] (3-6) Inhibition of Receptor-Ligand Binding by the Antibody

[0280] Preferably, the antibody of the present invention inhibits the binding of FGFR2 to its ligand. More preferably, the antibody of the present invention inhibits the binding of FGFR2 IIIB and/or FGFR2 IIIC to FGF. This inhibition of receptor-ligand binding may be any of competitive inhibition and noncompetitive inhibition. Examples of the ligands of FGFR2 IIIB and FGFR2 IIIC can include FGF1, FGF3, FGF7, FGF10, FGF22, and FGF23, and FGF1, FGF2, FGF4, FGF6, FGF9, FGF17, FGF18, FGF21, and FGF23, respectively.

[0281] (3-7) Monoclonal antibodies

[0282] The present invention provides a monoclonal antibody. The monoclonal antibody includes, for example, non-human animal-derived monoclonal antibodies such as rat, mouse, rabbit, chicken, and fish antibodies, chimeric antibodies, humanized antibodies, human antibodies, functional fragments thereof, and modified forms of these antibodies or functional fragments. Of them, examples of the rat monoclonal antibody can include the FR2-10, FR2-13, and FR2-14 antibodies.

[0283] FR2-10 is an anti-human FGFR2 rat monoclonal antibody obtained by the method described in Example 1. The nucleotide sequence of the heavy chain variable region of FR2-10 is defined in SEQ ID NO: 11 (FIG. 19) of the Sequence Listing, and its amino acid sequence is defined in SEQ ID NO: 12 (FIG. 20). The nucleotide sequence of the light chain variable region of FR2-10 is defined in SEQ ID NO: 20 (FIG. 28) of the Sequence Listing, and its amino acid sequence is defined in SEQ ID NO: 21 (FIG. 29). The amino acid sequence of CDRH1 of FR2-10 is defined in SEQ ID NO: 52 (FIG. 60). The amino acid sequence of CDRH2 thereof is defined in SEQ ID NO: 53 (FIG. 61). The amino acid sequence of CDRH3 thereof is defined in SEQ ID NO: 54 (FIG. 62). The amino acid sequence of CDRL1 thereof is defined in SEQ ID NO: 61 (FIG. 69). The amino acid sequence of CDRL2 thereof is defined in SEQ ID NO: 62 (FIG. 70). The amino acid sequence of CDRL3 thereof is defined in SEQ ID NO: 63 (FIG. 71).

[0284] FR2-13 is an anti-human FGFR2 rat monoclonal antibody obtained by the method described in Example 1. The nucleotide sequence of the heavy chain variable region of FR2-13 is defined in SEQ ID NO: 13 (FIG. 21) of the Sequence Listing, and its amino acid sequence is defined in SEQ ID NO: 14 (FIG. 22). The nucleotide sequence of the light chain variable region of FR2-13 is defined in SEQ ID NO: 23 (FIG. 31) of the Sequence Listing, and its amino acid sequence is defined in SEQ ID NO: 24 (FIG. 32). The amino acid sequence of CDRH1 of FR2-13 is defined in SEQ ID NO: 55 (FIG. 63). The amino acid sequence of CDRH2 thereof is defined in SEQ ID NO: 56 (FIG. 64). The amino acid sequence of CDRH3 thereof is defined in SEQ ID NO: 57 (FIG. 65). The amino acid sequence of CDRL1 thereof is defined in SEQ ID NO: 64 (FIG. 72). The amino acid sequence of CDRL2 thereof is defined in SEQ ID NO: 65

(FIG. 73). The amino acid sequence of CDRL3 thereof is defined in SEQ ID NO: 66 (FIG. 74).

[0285] FR2-14 is an anti-human FGFR2 rat monoclonal antibody obtained by the method described in Example 1. The nucleotide sequence of the heavy chain variable region of FR2-14 is defined in SEQ ID NO: 15 (FIG. 23) of the Sequence Listing, and its amino acid sequence is defined in SEQ ID NO: 16 (FIG. 24). The nucleotide sequence of the light chain variable region of FR2-14 is defined in SEQ ID NO: 25 (FIG. 33) of the Sequence Listing, and its amino acid sequence is defined in SEQ ID NO: 26 (FIG. 34). The amino acid sequence of CDRH1 of FR2-14 is defined in SEQ ID NO: 58 (FIG. 66). The amino acid sequence of CDRH2 thereof is defined in SEQ ID NO: 59 (FIG. 67). The amino acid sequence of CDRH3 thereof is defined in SEQ ID NO: 60 (FIG. 68). The amino acid sequence of CDRL1 thereof is defined in SEQ ID NO: 67 (FIG. 75). The amino acid sequence of CDRL2 thereof is defined in SEQ ID NO: 68 (FIG. 76). The amino acid sequence of CDRL3 thereof is defined in SEQ ID NO: 69 (FIG. 77).

[0286] The antibody mutant of the present invention preferably exhibits, for example, reduced sensitivity to protein degradation or oxidation, an improved biological activity, an improved ability to bind to the antigen, or physicochemical or functional properties imparted thereto. Examples of such an antibody mutant can include an antibody having an amino acid sequence derived from the amino acid sequence of the original antibody by conservative amino acid substitution. The conservative amino acid substitution is a substitution that occurs in an amino acid group related to amino acid side chains.

[0287] Preferred amino acid groups are as follows: an acidic group including aspartic acid and glutamic acid; a basic group including lysine, arginine, and histidine; a nonpolar group including alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, and tryptophan; and an uncharged polar family including glycine, asparagine, glutamine, cysteine, serine, threonine, and tyrosine. Other preferred amino acid groups are as follows: an aliphatic hydroxy group including serine and threonine; an amide-containing group including asparagine and glutamine; an aliphatic group including alanine, valine, leucine, and isoleucine; and an aromatic group including phenylalanine, tryptophan, and tyrosine. Such amino acid substitution in the antibody mutant is preferably performed without reducing the antigen binding activity of the original antibody.

[0288] Aspartic acid contained in a protein is easily converted to isoaspartic acid by isomerization when an amino acid linked thereto on the C terminal side has a small side chain. On the other hand, asparagine is easily converted to aspartic acid by deamidation and may be further converted to isoaspartic acid by isomerization. The progression of such isomerization or deamidation may influence the stability of the protein. Accordingly, aspartic acid or asparagine in the protein or, for example, an amino acid adjacent thereto, can be substituted by a different amino acid in order to circumvent such isomerization or deamidation. Preferably, an antibody mutant having such amino acid substitution maintains the antigen binding activity of the original antibody.

[0289] The present invention also encompasses, for example: an antibody mutant having an amino acid sequence derived from the amino acid sequence of FR2-10, FR2-13, or FR2-14 of the present invention by conservative amino

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acid substitution; and a mouse antibody, a rat antibody, a chimeric antibody, a humanized antibody, or a human antibody comprising a CDR having an amino acid sequence in which a conservative amino acid mutation occurs in the amino acid sequence of any of CDRH1 to CDRH3 and CDRL1 to CDRL3 derived from FR2-10, FR2-13, or FR2-14.

[0290] A mutant of the antibody of the present invention encompasses a human FGFR2-binding antibody mutant comprising CDRH1 to CDRH3 and CDRL1 to CDRL3 having amino acid sequences derived from the amino acid sequences of any one or two or more of CDRH1 to CDRH3 and CDRL1 to CDRL3 derived from FR2-10, FR2-13, or FR2-14 of the present invention by the substitution of 1 to several, preferably 1 to 3, more preferably 1 or 2, most preferably 1 amino acid(s) by different amino acid(s).

[0291] Preferred examples of a mutant of FR2-14 can include an antibody comprising CDRH3 having an amino acid sequence derived from the CDRH3 amino acid sequence by the substitution of amino acid(s) by different amino acid(s).

[0292] Preferred examples of a mutant of FR2-14 in which amino acid(s) of heavy chain CDRH3 is/are substituted can include: a mutant with the first amino acid aspartic acid (amino acid at position 118 of SEQ ID NO: 51 (FIG. 59)) substituted by glutamic acid; a mutant with the second amino acid glycine (amino acid at position 119 of SEQ ID NO: 51 (FIG. 59)) substituted by tyrosine, alanine, tryptophan, valine, arginine, asparagine, methionine, leucine, lysine, isoleucine, histidine, phenylalanine, or glutamic acid; and a mutant with the 8th amino acid threonine substituted by alanine.

[0293] The antibody mutant also includes an antibody having CDRH1 to CDRH3 and CDRL1 to CDRL3 derived from a plurality of antibodies. Examples of such a mutant can include an antibody mutant comprising CDRH3 derived from a certain antibody and CDRH1, CDRH2, and CDRL1 to CDRL3 derived from another antibody.

[0294] The “antibody” according to the present invention also encompasses these antibody mutants.

[0295] The constant regions of the antibody of the present invention are not particularly limited. Preferably, constant regions derived from a human antibody are used in the antibody of the present invention for the treatment or prevention of a disease in a human. Examples of the heavy chain constant region of the human antibody can include C γ 1, C γ 2, C γ 3, C γ 4, C μ , C δ , C α 1, C α 2, and C ϵ . Examples of the light chain constant region of the human antibody can include C κ and C λ .

[0296] (3-8) Chimeric Antibodies

[0297] An anti-FGFR2 chimeric antibody of the present invention or a functional fragment thereof has antitumor activity. Preferably, the anti-FGFR2 chimeric antibody of the present invention or the functional fragment thereof has antitumor activity in vivo. Also preferably, such a chimeric antibody, or a functional fragment thereof, specifically binds to the FGFR2 IIIb protein and/or the FGFR2 IIIc protein. More preferably, the chimeric antibody, or functional fragment thereof, binds to the Ig-like domains of these proteins. Preferably, such a chimeric antibody, or a functional fragment thereof, further has ADCC activity and/or ADCP activity. The chimeric antibody of the present invention, or the functional fragment thereof, also has neutralizing activity against FGFR2. Preferably, the chimeric antibody of the

present invention, or the functional fragment thereof, has neutralizing activity against FGFR2 IIIb and/or FGFR2 IIIc. More preferably, the chimeric antibody of the present invention, or the functional fragment thereof, has neutralizing activity against FGFR2 IIIb and FGFR2 IIIc. Preferably, the chimeric antibody of the present invention, or the functional fragment thereof, further inhibits the binding of FGFR2 to its ligand.

[0298] The nucleotide sequence and amino acid sequence of the light chain of cFR2-10 exemplified as the rat-human chimeric antibody of the present invention and the nucleotide sequence and amino acid sequence of the heavy chain thereof are shown in SEQ ID NOs: 31, 32, 35, and 36 (FIGS. 39, 40, 43, and 44), respectively, of the Sequence Listing. Likewise, the nucleotide sequence and amino acid sequence of the light chain of cFR2-13 and the nucleotide sequence and amino acid sequence of the heavy chain thereof are shown in SEQ ID NOs: 39, 40, 43, and 44 (FIGS. 47, 48, 51, and 52), respectively, of the Sequence Listing. The nucleotide sequence and amino acid sequence of the light chain of cFR2-14 and the nucleotide sequence and amino acid sequence of the heavy chain thereof are shown in SEQ ID NOs: 47, 48, 50, and 51 (FIGS. 55, 56, 58, and 59), respectively, of the Sequence Listing. Nucleotide positions 1 to 60 in the nucleotide sequences of the light chains and amino acid positions 1 to 20 in the amino acid sequences of the light chains represent a signal sequence, which is usually not contained in the nucleotide sequences and amino acid sequences of most of mature light chains, respectively. Likewise, nucleotide positions 1 to 57 in the nucleotide sequences of the heavy chains and amino acid positions 1 to 19 in the amino acid sequences of the heavy chains represent a signal sequence, which is usually not contained in the nucleotide sequences and amino acid sequences of most of mature heavy chains, respectively.

[0299] (3-9) Functional Fragment of Antibody

[0300] According to one aspect, the present invention provides a functional fragment of the anti-FGFR2 antibody of the present invention. The functional fragment of the antibody means a fragment that maintains at least a portion of the functions of the antibody. Examples of such functions of the antibody can generally include antigen binding activity, antigen activity-regulating activity, antibody dependent cellular cytotoxic (ADCC) activity, and antibody dependent cell phagocytosis (ADCP) activity. Examples of the functions of the anti-FGFR2 antibody of the present invention can include FGFR2 protein binding activity, ADCC activity, ADCP activity, neutralizing activity against FGFR2, in vivo antitumor activity, and the activity of inhibiting the binding of FGFR2 to its ligand.

[0301] The functional fragment of the antibody is not particularly limited as long as the fragment of the antibody maintains at least a portion of the activities of the antibody. Examples thereof can include, but are not limited to, Fab, F(ab')₂, Fv, single chain Fv (scFv) comprising heavy and light chain Fvs linked via an appropriate linker, diabodies, linear antibodies, multispecific antibodies formed from antibody fragments, and Fab', which is a monovalent fragment of antibody variable regions obtained by the treatment of F(ab')₂ under reducing conditions. The functional fragment of the antibody of the present invention is also meant to include a molecule comprising the fragment of the antibody of the present invention as well as other portions, such as scFv retaining a linker portion.

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[0302] A molecule that is derived from the antibody protein by the deletion of 1 to several or more amino acid(s) at its amino terminus and/or carboxy terminus and maintains at least a portion of the functions of the antibody is also encompassed in the meaning of the functional fragment of the antibody. For example, the heavy chain of an antibody produced by cultured mammalian cells is known to lack a lysine residue at the carboxy terminus (Journal of Chromatography A, 705: 129-134 (1995)). Also, the heavy chain of such an antibody is known to lack two amino acid residues (glycine and lysine) at the carboxy terminus and instead have an amidated proline residue at the carboxy terminus (Analytical Biochemistry, 360: 75-83 (2007)). The deletion and the modification in these heavy chain sequences, however, do not influence the ability of the antibody to bind to the antigen or its effector functions (complement activation, antibody dependent cytotoxic effects, etc.). Such a modified form of the functional fragment of the antibody is also encompassed by the antibody of the present invention or the functional fragment thereof, or a modified form (described later) of the antibody or functional fragment.

[0303] The antibody of the present invention, or the functional fragment thereof, may be a multispecific antibody having specificity for at least 2 types of different antigens. The multispecific antibody is not limited to a bispecific antibody, which binds to 2 types of different antigens, and an antibody having specificity for 3 or more types of different antigens is also encompassed in the meaning of the "multispecific antibody" of the present invention.

[0304] The multispecific antibody of the present invention may be a full-length antibody, or a functional fragment thereof (e.g., bispecific F(ab')₂ antibody). The bispecific antibody can also be prepared by linking the heavy and light chains (HL pairs) of two types of antibodies. Alternatively, the bispecific antibody may be obtained by fusing two or more types of monoclonal antibody-producing hybridomas to prepare bispecific antibody-producing fusion cells (Millstein et al., Nature (1983) 305, p. 537-539). The multispecific antibody can also be prepared in the same way as above.

[0305] According to one aspect, the antibody of the present invention is a single chain antibody (single chain Fv; hereinafter, referred to as "scFv"). The scFv is obtained by linking the heavy and light chain V regions of the antibody via a polypeptide linker (Pluckthun, The Pharmacology of Monoclonal Antibodies, 113, Rosenburg and Moore, ed., Springer Verlag, New York, p. 269-315 (1994); and Nature Biotechnology (2005), 23, p. 1126-1136). Also, bi-scFv comprising two scFvs linked via a polypeptide linker can be used as a bispecific antibody. Alternatively, multi-scFv comprising three or more scFvs may be used as a multispecific antibody.

[0306] The present invention includes a single chain immunoglobulin comprising full-length heavy and light chain sequences of the antibody linked via an appropriate linker (Lee, H-S, et al., Molecular Immunology (1999), 36, p. 61-71; and Shirmann, T. et al., mAbs (2010), 2 (1) p. 1-4). Such a single chain immunoglobulin can be dimerized to thereby maintain a structure and activities similar to those of the antibody, which is originally a tetramer. Also, the antibody of the present invention may be an antibody that has a single heavy chain variable region and has no light chain sequence. Such an antibody, called a single domain antibody (sdAb) or a nanobody, has been reported to main-

tain the ability to bind to an antigen (Muyldemans S. et al., Protein Eng. (1994), 7 (9), 1129-35; and Hamers-Casterman C. et al., Nature (1993), 363 (6428), 446-8). These antibodies are also encompassed in the meaning of the functional fragment of the antibody according to the present invention.

[0307] (3-10) Humanized Antibody and Human Antibody

[0308] According to one aspect, the present invention provides a humanized antibody or a functional fragment thereof.

[0309] The anti-FGFR2 humanized antibody of the present invention, or a functional fragment thereof, has antitumor activity. Preferably, the anti-FGFR2 humanized antibody of the present invention, or the functional fragment thereof, has antitumor activity in vivo. Also preferably, such a humanized antibody, or a functional fragment thereof, specifically binds to the FGFR2 IIIb protein and/or the FGFR2 IIIc protein. More preferably, the humanized antibody, or functional fragment thereof, binds to the Ig-like domains of these proteins. Preferably, such a humanized antibody, or a functional fragment thereof, further has ADCC activity and/or ADCP activity. The humanized antibody of the present invention, or the functional fragment thereof, also has neutralizing activity against FGFR2. Preferably, the humanized antibody of the present invention, or the functional fragment thereof, has neutralizing activity against FGFR2 IIIb and/or FGFR2 IIIc. More preferably, the humanized antibody of the present invention, or the functional fragment thereof, has neutralizing activity against FGFR2 IIIb and FGFR2 IIIc. Preferably, the humanized antibody of the present invention, or the functional fragment thereof, further inhibits the binding of FGFR2 to its ligand.

[0310] Preferred examples of the humanized antibody of the present invention can include humanized antibodies having the heavy chain CDRH1 to CDRH3 and light chain CDRL1 to CDRL3 of the rat FR2-10 antibody, the rat FR2-13 antibody, or the rat FR2-14 antibody as defined below in A to C.

[0311] (A. Humanized Antibody Having Heavy Chain CDRH1 to CDRH3 and Light Chain CDRL1 to CDRL3 of Rat FR2-10 Antibody)

[0312] Examples of the anti-FGFR2 humanized antibody of the present invention, or a functional fragment thereof, can include a humanized antibody that consists of a heavy chain having a variable region comprising CDRH1 consisting of the amino acid sequence represented by SEQ ID NO: 52 (FIG. 60) of the Sequence Listing, CDRH2 consisting of the amino acid sequence represented by SEQ ID NO: 53 (FIG. 61) of the Sequence Listing, and CDRH3 consisting of the amino acid sequence represented by SEQ ID NO: 54 (FIG. 62) of the Sequence Listing, and a light chain having a variable region comprising CDRL1 consisting of the amino acid sequence represented by SEQ ID NO: 61 (FIG. 69) of the Sequence Listing, CDRL2 consisting of the amino acid sequence represented by SEQ ID NO: 62 (FIG. 70) of the Sequence Listing, and CDRL3 consisting of the amino acid sequence represented by SEQ ID NO: 63 (FIG. 71) of the Sequence Listing, and that recognizes the FGFR2 protein of the present invention, and a fragment of the antibody that maintains the FGFR2 protein binding activity of the antibody, and mutants of the antibody or the fragment.

[0313] (B. Humanized Antibody Having Heavy Chain CDRH1 to CDRH3 and Light Chain CDRL1 to CDRL3 of Rat FR2-13 Antibody)

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[0314] Alternative examples of the anti-FGFR2 humanized antibody, or a functional fragment thereof, can include a humanized antibody that consists of a heavy chain having a variable region comprising CDRH1 consisting of the amino acid sequence represented by SEQ ID NO: 55 (FIG. 63) of the Sequence Listing, CDRH2 consisting of the amino acid sequence represented by SEQ ID NO: 56 (FIG. 64) of the Sequence Listing, and CDRH3 consisting of the amino acid sequence represented by SEQ ID NO: 57 (FIG. 65) of the Sequence Listing, and a light chain having a variable region comprising CDRL1 consisting of the amino acid sequence represented by SEQ ID NO: 64 (FIG. 72) of the Sequence Listing, CDRL2 consisting of the amino acid sequence represented by SEQ ID NO: 65 (FIG. 73) of the Sequence Listing, and CDRL3 consisting of the amino acid sequence represented by SEQ ID NO: 66 (FIG. 74) of the Sequence Listing, and that recognizes the FGFR2 protein of the present invention, and a fragment of the antibody that maintains the FGFR2 protein binding activity of the antibody, and mutants thereof.

[0315] (C. Humanized Antibody Having Heavy Chain CDRH1 to CDRH3 and Light Chain CDRL1 to CDRL3 of Rat FR2-14 Antibody)

[0316] Alternative examples of the anti-FGFR2 humanized antibody, or a functional fragment thereof, can include a humanized antibody that consists of a heavy chain having a variable region comprising CDRH1 consisting of the amino acid sequence represented by SEQ ID NO: 58 (FIG. 66) of the Sequence Listing, CDRH2 consisting of the amino acid sequence represented by SEQ ID NO: 59 (FIG. 67) of the Sequence Listing, and CDRH3 consisting of the amino acid sequence represented by SEQ ID NO: 60 (FIG. 68) of the Sequence Listing, and a light chain having a variable region comprising CDRL1 consisting of the amino acid sequence represented by SEQ ID NO: 67 (FIG. 75) of the Sequence Listing, CDRL2 consisting of the amino acid sequence represented by SEQ ID NO: 68 (FIG. 76) of the Sequence Listing, and CDRL3 consisting of the amino acid sequence represented by SEQ ID NO: 69 (FIG. 77) of the Sequence Listing, and that recognizes the FGFR2 protein of the present invention, and a fragment of the antibody that maintains the FGFR2 protein binding activity of the antibody, and mutants thereof.

[0317] The preferred humanized antibody of the present invention is not limited to those defined above in A to C. The humanized antibody is more preferably a humanized FR2-14 antibody or a mutant thereof. Examples thereof include, but are not limited to, hFR2-14_H1/L1 to hFR2-14_H19/L1. The more preferred humanized antibody of the present invention also includes, for example, an antibody comprising a heavy chain comprising the heavy chain variable region of any one of the humanized antibodies hFR2-14_H1/L1 to hFR2-14_H19/L1, and a light chain comprising the light chain variable region of any one of the humanized antibodies hFR2-14_H1/L1 to hFR2-14_H19/L1.

[0318] hFR2-14_H1/L1 is a humanized antibody obtained in Example 8. The nucleotide sequence of the light chain of this antibody comprises nucleotide positions 61 to 705 of SEQ ID NO: 72 (FIG. 80), and its amino acid sequence comprises amino acid positions 21 to 235 of SEQ ID NO: 73 (FIG. 81). The nucleotide sequence of the heavy chain of this antibody comprises nucleotide positions 58 to 1401 of SEQ ID NO: 74 (FIG. 82), and its amino acid sequence comprises amino acid positions 20 to 467 of SEQ ID NO: 75

(FIG. 83). The antibody was excellent in conformational stability because of its high T_m value and had a high binding activity against FGFR2, FGFR2 ligand dependent FGFR2 signal-neutralizing activity, ADCC activity, and in vivo antitumor activity (see the Examples).

[0319] hFR2-14_H2/L1 is a humanized antibody obtained in Example 8. The nucleotide sequence of the light chain of this antibody comprises nucleotide positions 61 to 705 of SEQ ID NO: 72 (FIG. 80), and its amino acid sequence comprises amino acid positions 21 to 235 of SEQ ID NO: 73 (FIG. 81). The nucleotide sequence of the heavy chain of this antibody comprises nucleotide positions 58 to 1401 of SEQ ID NO: 76 (FIG. 84), and its amino acid sequence comprises amino acid positions 20 to 467 of SEQ ID NO: 77 (FIG. 85). The antibody was excellent in conformational stability because of its high T_m value and had a high binding activity against FGFR2, FGFR2 ligand dependent FGFR2 signal-neutralizing activity, ADCC activity, and in vivo antitumor activity (see the Examples).

[0320] hFR2-14_H3/L1 is a humanized antibody obtained in Example 8. The nucleotide sequence of the light chain of this antibody comprises nucleotide positions 61 to 705 of SEQ ID NO: 72 (FIG. 80), and its amino acid sequence comprises amino acid positions 21 to 235 of SEQ ID NO: 73 (FIG. 81). The nucleotide sequence of the heavy chain of this antibody comprises nucleotide positions 58 to 1401 of SEQ ID NO: 78 (FIG. 86), and its amino acid sequence comprises amino acid positions 20 to 467 of SEQ ID NO: 79 (FIG. 87). The antibody was excellent in conformational stability because of its high T_m value and had a high binding activity against FGFR2, FGFR2 ligand dependent FGFR2 signal-neutralizing activity, ADCC activity, and in vivo antitumor activity (see the Examples).

[0321] hFR2-14_H4/L1 is a humanized antibody obtained in Example 8. The nucleotide sequence of the light chain of this antibody comprises nucleotide positions 61 to 705 of SEQ ID NO: 72 (FIG. 80), and its amino acid sequence comprises amino acid positions 21 to 235 of SEQ ID NO: 73 (FIG. 81). The nucleotide sequence of the heavy chain of this antibody comprises nucleotide positions 58 to 1401 of SEQ ID NO: 80 (FIG. 88), and its amino acid sequence comprises amino acid positions 20 to 467 of SEQ ID NO: 81 (FIG. 89). The antibody was excellent in conformational stability because of its high T_m value and had a high binding activity against FGFR2, FGFR2 ligand dependent FGFR2 signal-neutralizing activity, ADCC activity, and in vivo antitumor activity (see the Examples).

[0322] hFR2-14_H5/L1 is a humanized antibody obtained in Example 8. The nucleotide sequence of the light chain of this antibody comprises nucleotide positions 61 to 705 of SEQ ID NO: 72 (FIG. 80), and its amino acid sequence comprises amino acid positions 21 to 235 of SEQ ID NO: 73 (FIG. 81). The nucleotide sequence of the heavy chain of this antibody comprises nucleotide positions 58 to 1401 of SEQ ID NO: 82 (FIG. 90), and its amino acid sequence comprises amino acid positions 20 to 467 of SEQ ID NO: 83 (FIG. 91). The antibody was excellent in conformational stability because of its high T_m value, had a high binding activity against FGFR2, excellent thermal stability, FGFR2 ligand dependent FGFR2 signal-neutralizing activity, and in vivo antitumor activity, and maintained its high antigen binding activity even when exposed to severe conditions (see the Examples).

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[0323] hFR2-14_H6/L1 is a humanized antibody obtained in Example 8. The nucleotide sequence of the light chain of this antibody comprises nucleotide positions 61 to 705 of SEQ ID NO: 72 (FIG. 80), and its amino acid sequence comprises amino acid positions 21 to 235 of SEQ ID NO: 73 (FIG. 81). The nucleotide sequence of the heavy chain of this antibody comprises nucleotide positions 58 to 1401 of SEQ ID NO: 84 (FIG. 92), and its amino acid sequence comprises amino acid positions 20 to 467 of SEQ ID NO: 85 (FIG. 93). The antibody was excellent in conformational stability because of its high T_m value and had a high binding activity against FGFR2 and FGFR2 ligand dependent FGFR2 signal-neutralizing activity (see the Examples).

[0324] hFR2-14_H7/L1 is a humanized antibody obtained in Example 8. The nucleotide sequence of the light chain of this antibody comprises nucleotide positions 61 to 705 of SEQ ID NO: 72 (FIG. 80), and its amino acid sequence comprises amino acid positions 21 to 235 of SEQ ID NO: 73 (FIG. 81). The nucleotide sequence of the heavy chain of this antibody comprises nucleotide positions 58 to 1401 of SEQ ID NO: 86 (FIG. 94), and its amino acid sequence comprises amino acid positions 20 to 467 of SEQ ID NO: 87 (FIG. 95). The antibody was excellent in conformational stability because of its high T_m value and had a high binding activity against FGFR2 and FGFR2 ligand dependent FGFR2 signal-neutralizing activity (see the Examples).

[0325] hFR2-14_H8/L1 is a humanized antibody obtained in Example 8. The nucleotide sequence of the light chain of this antibody comprises nucleotide positions 61 to 705 of SEQ ID NO: 72 (FIG. 80), and its amino acid sequence comprises amino acid positions 21 to 235 of SEQ ID NO: 73 (FIG. 81). The nucleotide sequence of the heavy chain of this antibody comprises nucleotide positions 58 to 1401 of SEQ ID NO: 88 (FIG. 96), and its amino acid sequence comprises amino acid positions 20 to 467 of SEQ ID NO: 89 (FIG. 97). The antibody was excellent in conformational stability because of its high T_m value, had a high binding activity against FGFR2, excellent thermal stability, FGFR2 ligand dependent FGFR2 signal-neutralizing activity, ADCC activity, and in vivo antitumor activity, and maintained its high antigen binding activity even when exposed to severe conditions (see the Examples).

[0326] hFR2-14_H9/L1 is a humanized antibody obtained in Example 8. The nucleotide sequence of the light chain of this antibody comprises nucleotide positions 61 to 705 of SEQ ID NO: 72 (FIG. 80), and its amino acid sequence comprises amino acid positions 21 to 235 of SEQ ID NO: 73 (FIG. 81). The nucleotide sequence of the heavy chain of this antibody comprises nucleotide positions 58 to 1401 of SEQ ID NO: 90 (FIG. 98), and its amino acid sequence comprises amino acid positions 20 to 467 of SEQ ID NO: 91 (FIG. 99). The antibody was excellent in conformational stability because of its high T_m value and had a high binding activity against FGFR2, excellent thermal stability, FGFR2 ligand dependent FGFR2 signal-neutralizing activity, and in vivo antitumor activity (see the Examples).

[0327] hFR2-14_H10/L1 is a humanized antibody obtained in Example 8. The nucleotide sequence of the light chain of this antibody comprises nucleotide positions 61 to 705 of SEQ ID NO: 72 (FIG. 80), and its amino acid sequence comprises amino acid positions 21 to 235 of SEQ ID NO: 73 (FIG. 81). The nucleotide sequence of the heavy chain of this antibody comprises nucleotide positions 58 to 1401 of SEQ ID NO: 92 (FIG. 100), and its amino acid

sequence comprises amino acid positions 20 to 467 of SEQ ID NO: 93 (FIG. 101). The antibody was excellent in conformational stability because of its high T_m value and had a high binding activity against FGFR2 and FGFR2 ligand dependent FGFR2 signal-neutralizing activity (see the Examples).

[0328] hFR2-14_H11/L1 is a humanized antibody obtained in Example 8. The nucleotide sequence of the light chain of this antibody comprises nucleotide positions 61 to 705 of SEQ ID NO: 72 (FIG. 80), and its amino acid sequence comprises amino acid positions 21 to 235 of SEQ ID NO: 73 (FIG. 81). The nucleotide sequence of the heavy chain of this antibody comprises nucleotide positions 58 to 1401 of SEQ ID NO: 94 (FIG. 102), and its amino acid sequence comprises amino acid positions 20 to 467 of SEQ ID NO: 95 (FIG. 103). The antibody was excellent in conformational stability because of its high T_m value, had a high binding activity against FGFR2, excellent thermal stability, FGFR2 ligand dependent FGFR2 signal-neutralizing activity, ADCC activity, and in vivo antitumor activity, and maintained its high antigen binding activity even when exposed to severe conditions (see the Examples).

[0329] hFR2-14_H12/L1 is a humanized antibody obtained in Example 8. The nucleotide sequence of the light chain of this antibody comprises nucleotide positions 61 to 705 of SEQ ID NO: 72 (FIG. 80), and its amino acid sequence comprises amino acid positions 21 to 235 of SEQ ID NO: 73 (FIG. 81). The nucleotide sequence of the heavy chain of this antibody comprises nucleotide positions 58 to 1401 of SEQ ID NO: 96 (FIG. 104), and its amino acid sequence comprises amino acid positions 20 to 467 of SEQ ID NO: 97 (FIG. 105). The antibody was excellent in conformational stability because of its high T_m value, had a high binding activity against FGFR2, excellent thermal stability, FGFR2 ligand dependent FGFR2 signal-neutralizing activity, ADCC activity, ADCP activity, the activity of inhibiting the binding of an FGFR2 ligand to FGFR2, and in vivo antitumor activity, and maintained its high antigen binding activity even when exposed to severe conditions (see the Examples).

[0330] hFR2-14_H13/L1 is a humanized antibody obtained in Example 8. The nucleotide sequence of the light chain of this antibody comprises nucleotide positions 61 to 705 of SEQ ID NO: 72 (FIG. 80), and its amino acid sequence comprises amino acid positions 21 to 235 of SEQ ID NO: 73 (FIG. 81). The nucleotide sequence of the heavy chain of this antibody comprises nucleotide positions 58 to 1401 of SEQ ID NO: 98 (FIG. 106), and its amino acid sequence comprises amino acid positions 20 to 467 of SEQ ID NO: 99 (FIG. 107). The antibody was excellent in conformational stability because of its high T_m value and had a high binding activity against FGFR2 and FGFR2 ligand dependent FGFR2 signal-neutralizing activity (see the Examples).

[0331] hFR2-14_H14/L1 is a humanized antibody obtained in Example 8. The nucleotide sequence of the light chain of this antibody comprises nucleotide positions 61 to 705 of SEQ ID NO: 72 (FIG. 80), and its amino acid sequence comprises amino acid positions 21 to 235 of SEQ ID NO: 73 (FIG. 81). The nucleotide sequence of the heavy chain of this antibody comprises nucleotide positions 58 to 1401 of SEQ ID NO: 100 (FIG. 108), and its amino acid sequence comprises amino acid positions 20 to 467 of SEQ ID NO: 101 (FIG. 109). The antibody was excellent in

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conformational stability because of its high T_m value and had a high binding activity against FGFR2 and FGFR2 ligand dependent FGFR2 signal-neutralizing activity (see the Examples).

[0332] hFR2-14_H15/L1 is a humanized antibody obtained in Example 8. The nucleotide sequence of the light chain of this antibody comprises nucleotide positions 61 to 705 of SEQ ID NO: 72 (FIG. 80), and its amino acid sequence comprises amino acid positions 21 to 235 of SEQ ID NO: 73 (FIG. 81). The nucleotide sequence of the heavy chain of this antibody comprises nucleotide positions 58 to 1401 of SEQ ID NO: 102 (FIG. 110), and its amino acid sequence comprises amino acid positions 20 to 467 of SEQ ID NO: 103 (FIG. 111). The antibody was excellent in conformational stability because of its high T_m value and had a high binding activity against FGFR2 and FGFR2 ligand dependent FGFR2 signal-neutralizing activity (see the Examples).

[0333] hFR2-14_H16/L1 is a humanized antibody obtained in Example 8. The nucleotide sequence of the light chain of this antibody comprises nucleotide positions 61 to 705 of SEQ ID NO: 72 (FIG. 80), and its amino acid sequence comprises amino acid positions 21 to 235 of SEQ ID NO: 73 (FIG. 81). The nucleotide sequence of the heavy chain of this antibody comprises nucleotide positions 58 to 1401 of SEQ ID NO: 104 (FIG. 112), and its amino acid sequence comprises amino acid positions 20 to 467 of SEQ ID NO: 105 (FIG. 113). The antibody was excellent in conformational stability because of its high T_m value and had a high binding activity against FGFR2 and FGFR2 ligand dependent FGFR2 signal-neutralizing activity (see the Examples).

[0334] hFR2-14_H17/L1 is a humanized antibody obtained in Example 8. The nucleotide sequence of the light chain of this antibody comprises nucleotide positions 61 to 705 of SEQ ID NO: 72 (FIG. 80), and its amino acid sequence comprises amino acid positions 21 to 235 of SEQ ID NO: 73 (FIG. 81). The nucleotide sequence of the heavy chain of this antibody comprises nucleotide positions 58 to 1401 of SEQ ID NO: 106 (FIG. 114), and its amino acid sequence comprises amino acid positions 20 to 467 of SEQ ID NO: 107 (FIG. 115). The antibody was excellent in conformational stability because of its high T_m value and had a high binding activity against FGFR2 and FGFR2 ligand dependent FGFR2 signal-neutralizing activity (see the Examples).

[0335] hFR2-14_H18/L1 is a humanized antibody obtained in Example 8. The nucleotide sequence of the light chain of this antibody comprises nucleotide positions 61 to 705 of SEQ ID NO: 72 (FIG. 80), and its amino acid sequence comprises amino acid positions 21 to 235 of SEQ ID NO: 73 (FIG. 81). The nucleotide sequence of the heavy chain of this antibody comprises nucleotide positions 58 to 1401 of SEQ ID NO: 108 (FIG. 116), and its amino acid sequence comprises amino acid positions 20 to 467 of SEQ ID NO: 109 (FIG. 117). The antibody was excellent in conformational stability because of its high T_m value and had a high binding activity against FGFR2, FGFR2 ligand dependent FGFR2 signal-neutralizing activity, ADCC activity, and in vivo antitumor activity (see the Examples).

[0336] hFR2-14_H19/L1 is a humanized antibody with regulated sugar chain modification obtained in Example 9. The nucleotide sequence of the light chain of this antibody comprises nucleotide positions 61 to 705 of SEQ ID NO: 72

(FIG. 80), and its amino acid sequence comprises amino acid positions 21 to 235 of SEQ ID NO: 73 (FIG. 81). The nucleotide sequence of the heavy chain of this antibody comprises nucleotide positions 58 to 1401 of SEQ ID NO: 96 (FIG. 104), and its amino acid sequence comprises amino acid positions 20 to 467 of SEQ ID NO: 97 (FIG. 105). The antibody was excellent in conformational stability because of its high T_m value, had a high binding activity against FGFR2, excellent thermal stability, FGFR2 ligand dependent FGFR2 signal-neutralizing activity, ADCC activity, ADCC activity, the activity of inhibiting the binding of an FGFR2 ligand to FGFR2, and in vivo antitumor activity, and maintained its high antigen binding activity even when exposed to severe conditions (see the Examples).

[0337] These humanized FR2-14 antibodies were not found to cause weight loss or other significant toxic events, when administered to mice. The hFR2-14_H12/L1 antibody and the hFR2-14_H19/L1 antibody were administered at a single dose of approximately 150 mg/kg to each cynomolgus monkey and observed 14 days later. As a result, significant clinical findings, hematological change, weight loss, or other significant toxic events were not observed. Thus, the humanized antibody of the present invention possesses excellent safety as a pharmaceutical composition for treatment or prevention of a disease.

[0338] Among the more preferred humanized antibodies hFR2-14_H1/L1 to hFR2-14_H19/L1 of the present invention, the antibody is even more preferably hFR2-14_H5/L1, hFR2-14_H11/L1, hFR2-14_H8/L1, hFR2-14_H12/L1, or hFR2-14_H19/L1, further more preferably hFR2-14_H12/L1 or hFR2-14_H19/L1.

[0339] The present invention also encompasses an antibody that comprises a heavy or light chain comprising an amino acid sequence having 80% or higher, 82% or higher, 84% or higher, 86% or higher, 88% or higher, 90% or higher, 92% or higher, 94% or higher, 96% or higher, 98% or higher, or 99% or higher identity to the amino acid sequence of the heavy or light chain of any one of the rat FR2-10, FR2-13, and FR2-14 antibodies, the chimeric cFR2-10, cFR2-13, and cFR2-14 antibodies, and the humanized hFR2-14_H1/L1 to hFR2-14_H19/L1 antibodies of the present invention and binds to FGFR2, or a functional fragment thereof. Such sequence identity is preferably 94% or higher, more preferably 96% or higher, even more preferably 98% or higher, most preferably 99% or higher. Preferably, these antibodies have one or more of the activities defined in paragraphs (3-3) to (3-6).

[0340] The identity or homology between two types of amino acid sequences can be determined using the default parameter of Blast algorithm version 2.2.2 (Altschul, Stephen F., Thomas L. Madden, Alejandro A. Schaffer, Jinghui Zhang, Zheng Zhang, Webb Miller, and David J. Lipman (1997), "Gapped BLAST and PSI-BLAST: a new generation of protein database search programs", *Nucleic Acids Res.* 25: 3389-3402). The Blast algorithm is also available, for example, by Internet access at <http://blast.ncbi.nlm.nih.gov/>.

[0341] The present invention also encompasses an antibody that comprises a heavy or light chain comprising an amino acid sequence derived from the amino acid sequence of the heavy or light chain of any one of the rat FR2-10, FR2-13, and FR2-14 antibodies, the chimeric cFR2-10, cFR2-13, and cFR2-14 antibodies, and the humanized hFR2-14_H1/L1 to hFR2-14_H19/L1 antibodies of the present invention by the substitution, deletion, addition, or

insertion of 1 to 50, 1 to 45, 1 to 40, 1 to 35, 1 to 30, 1 to 25, 1 to 20, 1 to 15, 1 to 10, 1 to 8, 1 to 6, 1 to 5, 1 to 4, 1 to 3, 1 or 2, or 1 amino acid(s) and binds to the FGFR2 protein, or a functional fragment thereof. Such an amino acid mutation is preferably substitution. The number of mutated amino acids is preferably 1 to 5, more preferably 1 to 4, even more preferably 1 to 3, further more preferably 1 or 2, most preferably 1. Preferably, these antibodies have one or more of the activities defined in paragraphs (3-3) to (3-6).

[0342] The present invention also encompasses an antibody that comprises a heavy or light chain comprising an amino acid sequence encoded by the nucleotide sequence of a nucleotide hybridizing under stringent conditions to a nucleotide having a nucleotide sequence complementary to a nucleotide sequence encoding the amino acid sequence of the heavy or light chain of any one of the rat FR2-10, FR2-13FR, and FR2-14 antibodies, the chimeric cFR2-10, cFR2-13, and cFR2-14 antibodies, and the humanized hFR2-14_H1/L1 to hFR2-14_H19/L1 antibodies of the present invention and binds to the FGFR2 protein, or a functional fragment thereof. Preferably, these antibodies have one or more of the activities defined in paragraphs (3-3) to (3-6).

[0343] According to an alternative aspect, the present invention provides a human antibody or a functional fragment thereof. The human antibody of the present invention is not particularly limited as long as the antibody is derived from a human and binds to FGFR2. The human antibody of the present invention, or a functional fragment thereof, has antitumor activity, preferably in vivo antitumor activity. Also preferably, such a human antibody, or a functional fragment thereof, specifically binds to the FGFR2 IIIb protein and/or the FGFR2 IIIc protein. More preferably, the human antibody, or functional fragment thereof, binds to the Ig-like domains of these proteins. Preferably, such a human antibody, or a functional fragment thereof, further has ADCC activity and/or ADCP activity. The human antibody of the present invention, or the functional fragment thereof, also has neutralizing activity against FGFR2. Preferably, the human antibody of the present invention, or the functional fragment thereof, has neutralizing activity against FGFR2 IIIb and/or FGFR2 IIIc. More preferably, the human antibody of the present invention, or the functional fragment thereof, has neutralizing activity against FGFR2 IIIb and FGFR2 IIIc. Preferably, the human antibody of the present invention, or the functional fragment thereof, further inhibits the binding of FGFR2 to its ligand.

[0344] (3-11) Antibody Binding to the Epitope

[0345] An “antibody binding to the same site” as in the case of the antibody provided by the present invention is also included in the antibody of the present invention. The “antibody binding to the same site” as in the case of a certain antibody means another antibody that binds to a site on an antigen molecule recognized by the antibody. If a second antibody binds to a partial peptide or a partial three-dimensional structure on an antigen molecule bound by a first antibody, the first and second antibodies are determined as binding to the same site. Alternatively, the first and second antibodies are determined as binding to the same site by confirming that the second antibody competes with the first antibody for binding to the antigen, i.e., the second antibody interferes with the binding of the first antibody to the antigen, even if the peptide sequence or three-dimensional

structure of the specific binding site is not determined. When the first and second antibodies bind to the same site and the first antibody has an effect characteristic of one aspect of the antibody of the present invention, such as an antitumor activity, the second antibody also has an exceedingly high probability of having the same activity thereas. Thus, if a second anti-FGFR2 antibody binds to a site bound by a first anti-FGFR2 antibody, the first and second antibodies are determined as binding to the same site on the FGFR2 protein. Alternatively, the first and second anti-FGFR2 antibodies are determined as binding to the same site on the FGFR2 protein by confirming that the second anti-FGFR2 antibody competes with the first anti-FGFR2 antibody for binding to the FGFR2 protein.

[0346] The present invention also encompasses an antibody binding to a site on the FGFR2 protein recognized by the monoclonal antibody FR2-10, FR2-13, or FR2-14 of the present invention.

[0347] The antibody binding site can be determined by a method well known by those skilled in the art, such as immunoassay. For example, a series of peptides are prepared by appropriately sequentially cleaving the amino acid sequence of the antigen from its C terminus or N terminus, and the reactivity of the antibody thereto is studied to roughly determine a recognition site. Then, shorter peptides are synthesized, and the reactivity of the antibody to these peptides can be studied to thereby determine the binding site. The antigen fragment peptides can be prepared using a technique such as gene recombination or peptide synthesis.

[0348] When the antibody binds to or recognizes the partial conformation of the antigen, the binding site for the antibody can be determined by identifying amino acid residues on the antigen adjacent to the antibody using X-ray structural analysis. For example, the antibody or its fragment and the antigen or its fragment can be bound to each other and crystallized, followed by structural analysis to identify each amino acid residue on the antigen having an interaction distance with the antibody. The interaction distance is 8 angstroms or shorter, preferably 6 angstroms or shorter, more preferably 4 angstroms or shorter. One or more such amino acid residues having an interaction distance with the antibody can constitute a site (epitope) on the antigen to which the antibody binds. Two or more such amino acid residues may not be adjacent to each other on the primary sequence.

[0349] The Fab fragment of the rat, chimeric, or humanized FR2-14 antibody and the D2 fragment (peptide consisting of amino acid positions 128 to 249 of SEQ ID NO: 70 (FIG. 78)) of human FGFR2 IIIb are bound to each other and crystallized under conditions involving 1.1 to 2.1 M ammonium sulfate-0.15 M Tris-HCl buffer solution (pH 6.5 to 8.5) to obtain crystals in the tetragonal system with a space group of P41212 and unit cells of a=b=60.57 angstroms and c=331.2 angstroms. A molecular replacement method can be performed using the three-dimensional structure coordinates thereof to determine a phase (see Example 15).

[0350] The rat, chimeric, or humanized FR2-14 antibody recognizes partial conformation on human FGFR2 IIIb or human FGFR2 IIIc. The epitope for this antibody is constituted by tyrosine (Tyr) at residue 155, threonine (Thr) at residue 157, lysine (Lys) at residue 176, alanine (Ala) at residue 181, glycine (Gly) at residue 182, glycine (Gly) at residue 183, asparagine (Asn) at residue 184, proline (Pro)

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at residue 185, methionine (Met) at residue 186, threonine (Thr) at residue 188, glutamine (Gln) at residue 200, glutamic acid (Glu) at residue 201, glycine (Gly) at residue 205, glycine (Gly) at residue 206, lysine (Lys) at residue 208, valine (Val) at residue 209, arginine (Arg) at residue 210, asparagine (Asn) at residue 211, glutamine (Gln) at residue 212, histidine (His) at residue 213, tryptophan (Trp) at residue 214, and isoleucine (Ile) at residue 217 in the amino acid sequence (SEQ ID NO: 70; FIG. 78) of human FGFR2 IIIb or the amino acid sequence (SEQ ID NO: 71; FIG. 79) of human FGFR2 IIIc. In other words, this antibody has an interaction distance with each of tyrosine (Tyr) at residue 155, threonine (Thr) at residue 157, lysine (Lys) at residue 176, alanine (Ala) at residue 181, glycine (Gly) at residue 182, glycine (Gly) at residue 183, asparagine (Asn) at residue 184, proline (Pro) at residue 185, methionine (Met) at residue 186, threonine (Thr) at residue 188, glutamine (Gln) at residue 200, glutamic acid (Glu) at residue 201, glycine (Gly) at residue 205, glycine (Gly) at residue 206, lysine (Lys) at residue 208, valine (Val) at residue 209, arginine (Arg) at residue 210, asparagine (Asn) at residue 211, glutamine (Gln) at residue 212, histidine (His) at residue 213, tryptophan (Trp) at residue 214, and isoleucine (Ile) at residue 217 in the amino acid sequence (SEQ ID NO: 70; FIG. 78) of human FGFR2 IIIb or the amino acid sequence (SEQ ID NO: 71; FIG. 79) of human FGFR2 IIIc. The epitope site for this antibody is also found in the amino acid sequence of human FGFR2 IIIc. The antibody of the present invention, or the functional fragment thereof, or a modified form of the antibody, or functional fragment, also encompasses an antibody binding to this epitope or having an interaction distance with these amino acid residues, a functional fragment thereof, or a modified form of the antibody or functional fragment.

[0351] (3-12) Modified Form of the Antibody

[0352] The present invention provides a modified form of the antibody or functional fragment thereof. The modified form of the antibody of the present invention, or the functional fragment thereof, means an antibody of the present invention, or a functional fragment thereof, provided with chemical or biological modification. The chemically modified form includes, for example, a form having an amino acid skeleton conjugated with a chemical moiety, and a form having a chemically modified N-linked or O-linked carbohydrate chain. The biologically modified form includes, for example, a form that has undergone post-translational modification (e.g., N-linked or O-linked glycosylation, N-terminal or C-terminal processing, deamidation, isomerization of aspartic acid, or oxidation of methionine), and a form containing a methionine residue added to the N-terminus by expression using prokaryotic host cells. Such a modified form is also meant to include a form labeled to permit detection or isolation of the antibody or the antigen of the present invention, for example, an enzyme-labeled form, a fluorescently labeled form, or an affinity-labeled form. Such a modified form of the antibody of the present invention, or the functional fragment thereof, is useful for improvement of the stability or blood retention of the original antibody of the present invention, or the original functional fragment thereof, reduction in antigenicity, detection or isolation of the antibody or the antigen, etc.

[0353] Examples of the chemical moiety contained in the chemically modified form can include water-soluble poly-

mers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, and polyvinyl alcohol.

[0354] Examples of the biologically modified form can include a form modified by enzymatic treatment, cell treatment, or the like, a form fused with another peptide, such as a tag, added by gene recombination, and a form prepared from host cells expressing an endogenous or exogenous sugar chain-modifying enzyme.

[0355] The antibody dependent cellular cytotoxic activity of the antibody of the present invention, or the functional fragment thereof, may be enhanced by regulating the modification (glycosylation, defucosylation, etc.) of the sugar chain bound with the antibody or functional fragment. For example, methods described in WO99/54342, WO00/61739, and WO02/31140 are known as such a technique of regulating the sugar chain modification of the antibody, though this technique is not limited thereto. The modified form of the antibody of the present invention also includes an antibody that has undergone the sugar chain modification thus regulated.

[0356] Such a modification may be made at an arbitrary position or a desired position in the antibody or functional fragment thereof. Alternatively, the same or two or more different modifications may be made at one or two or more positions therein.

[0357] In the present invention, the “modified form of the antibody fragment” is also meant to include even a “fragment of the modified form of the antibody”.

[0358] In the present invention, the modified form of the antibody, or the modified form of the functional fragment thereof, is also simply referred to as an “antibody” or a “functional fragment of the antibody”.

[0359] hFR2-14_H19/L1 is a humanized antibody with regulated sugar chain modification obtained in Example 9. The nucleotide sequence of the light chain of this antibody comprises nucleotide positions 61 to 705 of SEQ ID NO: 72 (FIG. 80), and its amino acid sequence comprises amino acid positions 21 to 235 of SEQ ID NO: 73 (FIG. 81). The nucleotide sequence of the heavy chain of this antibody comprises nucleotide positions 58 to 1401 of SEQ ID NO: 96 (FIG. 104), and its amino acid sequence comprises amino acid positions 20 to 467 of SEQ ID NO: 97 (FIG. 105). Such a humanized antibody is also encompassed by the antibody of the present invention or the modified form of the antibody of the present invention.

[0360] In the present invention, the antibody, the functional fragment thereof, the modified form of the antibody, and the modified form of the functional fragment of the antibody also include their salts. The salt of the present invention is not particularly limited as long as the salt is formed by the antibody, the functional fragment, or the modified form of the present invention and is pharmacologically acceptable. Examples thereof include inorganic acid salts, organic acid salts, inorganic base salts, organic base salts, and acidic or basic amino acid salts. An inorganic acid salt or an organic acid salt is preferred. A hydrate of the salt is also included in the scope of the present invention. Preferred examples of the inorganic acid salts include hydrochloride, hydrobromide, sulfate, nitrate and phosphate. Hydrochloride, hydrobromide, sulfate, or phosphate is more preferred. Hydrobromide is most preferred. Preferred examples of the organic acid salts include acetate, succinate, fumarate, maleate, tartrate, citrate, lactate, stearate, benzo-

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ate, methanesulfonate, ethanesulfonate, p-toluenesulfonate, and benzenesulfonate. Fumarate or maleate is particularly preferred. Preferred examples of the inorganic base salts include: alkali metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as calcium salt and magnesium salt; and aluminum salt and ammonium salt. Preferred examples of the organic base salts include diethylamine salt, diethanolamine salt, meglumine salt, and N,N'-dibenzylethylenediamine salt. Preferred examples of the acidic amino acid salts include aspartate and glutamate. Preferred examples of the basic amino acid salts include arginine salt, lysine salt, and ornithine salt.

4. Methods for Producing the Antibody

[0361] (4-1) Method Using a Hybridoma

[0362] In order to prepare an anti-FGFR2 antibody of the present invention, anti-FGFR2 antibody-producing cells are isolated from the spleens of animals immunized with the FGFR2 protein or its soluble form according to the method of Kohler and Milstein (Kohler and Milstein, *Nature* (1975), 256, p. 495-497; and Kennet, R. ed., *Monoclonal Antibodies*, p. 365-367, Plenum Press, N.Y. (1980)). The cells are fused with myeloma cells to thereby establish hybridomas. Monoclonal antibodies can be obtained from cultures of these hybridomas.

[0363] (4-1-1) Preparation of the Antigen

[0364] The antigen for the preparation of the anti-FGFR2 antibody can be obtained according to, for example, the method for preparing a native or recombinant FGFR2 protein described in other paragraphs of the present specification. Examples of the antigen that may be thus prepared can include the FGFR2 protein and an FGFR2 protein fragment comprising a partial sequence with at least 6 consecutive amino acids of the FGFR2 protein, and their derivatives further comprising an arbitrary amino acid sequence or carrier added thereto (hereinafter, collectively referred to as an "FGFR2 antigen").

[0365] The recombinant FGFR2 antigen can be prepared by transfecting host cells with a gene comprising a nucleotide sequence encoding the amino acid sequence of the FGFR2 antigen, and recovering the antigen from cultures of the cells. Such a recombinant antigen may be a fusion protein with another protein such as an immunoglobulin Fc region. An FGFR2 antigen obtained in a cell-free in vitro translation system from a gene comprising a nucleotide sequence encoding the amino acid sequence of the FGFR2 antigen is also included in the recombinant FGFR2 antigen. The non-recombinant FGFR2 antigen can be purified or isolated from FGFR2-expressing normal tissues, cancer tissues, or cancer cells, cultures of the cancer cells, or the like described in (iv) of paragraph (2-2).

[0366] (4-1-2) Production of an Anti-FGFR2 Monoclonal Antibody

[0367] The monoclonal antibody is typically produced through the following steps:

- (a) preparing an antigen,
- (b) preparing antibody-producing cells,
- (c) preparing myeloma cells (hereinafter, referred to as "myelomas"),
- (d) fusing the antibody-producing cells with the myelomas,
- (e) screening for a hybridoma group producing the antibody of interest, and
- (f) obtaining single cell clones (cloning).

[0368] This production method further involves (g) culturing the hybridomas, raising hybridoma-transplanted animals, etc., and (h) assaying or determining the biological activity of the monoclonal antibody, etc., if necessary.

[0369] Hereinafter, the method for preparing the monoclonal antibody will be described in detail with reference to these steps. However, the method for preparing the antibody is not limited to those steps, and, for example, antibody-producing cells other than spleen cells and myelomas may be used.

[0370] (a) Purification of the Antigen

[0371] This step is performed according to the method for preparing the FGFR2 protein described above in (2-3).

[0372] (b) Preparing an Antibody-Producing Cell

[0373] The antigen obtained in step (a) is mixed with an adjuvant such as a complete or incomplete Freund's adjuvant or potassium aluminum sulfate, and laboratory animals are immunized with the resulting immunogen. Any laboratory animal used in a hybridoma preparation method known in the art can be used without limitations. Specifically, for example, mice, rats, goats, sheep, cattle, or horses can be used. From the viewpoint of readily available myeloma cells to be fused with isolated antibody-producing cells, etc., the animals to be immunized are preferably mice or rats.

[0374] The strain of mice or rats actually used is not particularly limited. In the case of mice, for example, A, AKR, BALB/c, BALB/cAnNCrj, BDP, BA, CE, C3H, 57BL, C57BL, C57L, DBA, FL, HTH, HT1, LP, NZB, NZW, RF, R III, SJL, SWR, WB, or 129 can be used. In the case of rats, for example, Wistar, Low, Lewis, Sprague-Dawley, ACI, BN, or Fischer can be used.

[0375] These mice and rats are available from laboratory animal breeders or distributors, for example, CLEA Japan, Inc. or Charles River Laboratories Japan Inc.

[0376] Of those mice and rats, a BALB/c mouse strain or Wistar and Low rat strains are particularly preferred as animals to be immunized in consideration of fusion compatibility with the myeloma cells described later.

[0377] Also, in consideration of the homology between human and mouse antigens, mice whose biological mechanism to remove autoantibodies has been reduced, i.e., autoimmune disease mice, are also preferably used.

[0378] In this context, these mice or rats are preferably 5 to 12 weeks old, more preferably 6 to 8 weeks old, at the time of immunization.

[0379] The animals can be immunized with the FGFR2 protein using, for example, the method of Weir, D. M., *Handbook of Experimental Immunology* Vol. I. II. III., Blackwell Scientific Publications, Oxford (1987), Kabat, E. A. and Mayer, M. M., *Experimental Immunochemistry*, Charles C Thomas Publisher Springfield, Ill. (1964).

[0380] Examples of methods for determining antibody titers can include, but are not limited to, immunoassay such as RIA and ELISA.

[0381] Antibody-producing cells derived from spleen cells or lymphocytes separated from the immunized animals, can be prepared according to a method known in the art, for example, Kohler et al., *Nature* (1975) 256, p. 495; Kohler et al., *Eur. J. Immunol.* (1977) 6, p. 511; Milstein et al., *Nature* (1977), 266, p. 550; Walsh, *Nature*, (1977) 266, p. 495.

[0382] In the case of spleen cells, a general method can be adopted, which involves chopping the spleens, filtering cells through a stainless mesh, and then floating the resulting cells

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in an Eagle's minimum essential medium (MEM) or the like, to separate antibody-producing cells.

[0383] (c) Preparation of the Myeloma

[0384] The myeloma cells used in cell fusion are not particularly limited and can be selected appropriately for use from cell lines known in the art. For example, a hypoxanthine-guanine phosphoribosyl transferase (HGPRT)-deficient line, i.e., mouse-derived X63-Ag8 (X63), NS1-ANS/1 (NS1), P3X63-Ag8.U1 (P3U1), X63-Ag8.653 (X63.653), SP2/0-Ag14 (SP2/0), MPC11-45.6TG1.7 (45.6TG), FO, S149/5XXO, or BU.1, rat-derived 210.RSY3.Ag.1.2.3 (Y3), or human-derived U266AR (SKO-007), GM1500-GTG-A12 (GM1500), UC729-6, LICR-LOW-HMy2 (HMy2), or 8226AR/NIP4-1 (NP41), whose screening procedures have already been established, is preferably used in consideration of convenience in the selection of hybridomas from fusion cells. These HGPRT-deficient lines are available from, for example, American Type Culture Collection (ATCC).

[0385] These cell lines are subcultured in an appropriate medium, for example, an 8-azaguanine medium [RPMI-1640 medium supplemented with glutamine, 2-mercaptoethanol, gentamicin, and fetal bovine serum (hereinafter, referred to as "FBS") and further supplemented with 8-azaguanine], an Iscove's modified Dulbecco's medium (hereinafter, referred to as "IMDM"), or a Dulbecco's modified Eagle medium (hereinafter, referred to as "DMEM") and subcultured in a normal medium [e.g., ASF104 medium (manufactured by Ajinomoto Co., Inc.) containing 10% FBS] 3 to 4 days before cell fusion to secure that the number of cells is equal to or greater than 2×10^7 cells on the day of cell fusion.

[0386] (D) Fusing the Antibody-Producing Cell with the Myeloma Cell

[0387] The antibody-producing cells can be fused with the myeloma cells under conditions that prevent cell viability from being excessively reduced, according to any method known in the art (e.g., Weir, D. M., Handbook of Experimental Immunology Vol. I. II. III., Blackwell Scientific Publications, Oxford (1987), Kabat, E. A. and Mayer, M. M., Experimental Immunochemistry, Charles C Thomas Publisher Springfield, Ill. (1964)). For example, a chemical method which involves mixing antibody-producing cells with myeloma cells in a high-concentration solution of a polymer such as polyethylene glycol, or a physical method using electric stimulation can be used.

[0388] (e) Screening for a Hybridoma Group Producing the Antibody of Interest

[0389] A method for selection from the hybridomas obtained by cell fusion is not particularly limited, and a hypoxanthine-aminopterin-thymidine (HAT) selection method (Kohler et al., Nature (1975) 256, p.495; Milstein et al., Nature (1977) 266, p.550) is typically used. This method is effective for obtaining hybridomas using an HGPRT-deficient myeloma cell line, which cannot survive in the presence of aminopterin. Specifically, unfused cells and hybridomas can be cultured in a HAT medium to thereby allow only hybridomas resistant to aminopterin to selectively live and grow.

[0390] (f) Obtaining a Single Cell Clone (Cloning)

[0391] The hybridomas can be cloned using any method known in the art, for example, a methylcellulose, soft agarose, or limiting dilution method (see e.g., Barbara, B. M. and Stanley, M. S.: Selected Methods in Cellular Immunol-

ogy, W.H. Freeman and Company, San Francisco (1980)). The limiting dilution method is preferred.

[0392] (g) Culturing the Hybridoma and Raising a Hybridoma-Transplanted Animal

[0393] The selected hybridomas can be cultured to thereby produce monoclonal antibodies. Preferably, the desired hybridomas are cloned and then subjected to antibody production.

[0394] A monoclonal antibody produced by such a hybridoma can be recovered from cultures of the hybridoma. Also, a recombinant antibody can be recovered from cultures of cells transfected with the monoclonal antibody gene. Alternatively, the hybridoma may be injected intraperitoneally to mice of the same strain (e.g., BALB/cAnNCrj described above) or Nu/Nu mice and allowed to grow. Then, the monoclonal antibody can be recovered from their ascites.

[0395] (h) Assaying or Determining the Biological Activity of the Monoclonal Antibody

[0396] Various biological tests can be selected and applied thereto according to the purpose.

[0397] (4-2) Cell Immunization Method

[0398] Cells expressing the native FGFR2 protein, cells expressing the recombinant FGFR2 protein or its fragment, or the like, can be used as immunogens to thereby prepare an anti-FGFR2 antibody by the hybridoma method described above.

[0399] Examples of cells expressing the native FGFR2 protein can include FGFR2-expressing cells, cell lines derived from FGFR2-expressing tissues or cancer, and cell lines derived from cancer tissues in which switching from FGFR2 IIIb to FGFR2 IIIc expression is seen. Cancer highly expressing FGFR2 includes: cancers found to have gene amplification, such as stomach cancer and breast cancer; and cancers found to have overexpression, such as pancreatic cancer and ovarian cancer. Examples of cultured cell lines highly expressing FGFR2 IIIb can include stomach cancer cell lines and breast cancer cell lines. Examples of cultured cell lines highly expressing FGFR2 IIIc can include colorectal (cecal) cancer cell lines. Examples of cancer tissues in which switching from FGFR2 IIIb to FGFR2 IIIc expression is seen can include tissues of prostate cancer, urinary bladder cancer, and breast cancer. Examples of cancer tissues expressing FGFR2 IIIc can include tissues of cervical cancer and non-small cell lung cancer. Of these cancers, cervical cancer highly expresses FGFR2 IIIc. Examples of normal tissues highly expressing FGFR2 can include the brain, the large intestine, thyroid glands, the uterus, the gallbladder, and skin.

[0400] These FGFR2-expressing cells are used in an amount of 1×10^5 to 1×10^9 cells, preferably 1×10^6 to 1×10^8 cells, more preferably 0.5 to 2×10^7 cells, even more preferably 1×10^7 cells, per immunization shot. The number of cells used for immunization can be changed according to the expression level of the FGFR2 protein. The immunogens are generally administered intraperitoneally and may be administered through an intradermal route or the like. The hybridomas can be prepared by the application of the method described in paragraph (4-1-2).

[0401] (4-3) Gene Recombination

[0402] In order to prepare the antibody of the present invention, a nucleotide (heavy chain nucleotide) comprising a nucleotide sequence encoding the amino acid sequence of its heavy chain and a nucleotide (light chain nucleotide) comprising a nucleotide sequence encoding the amino acid

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sequence of its light chain, or a vector having an insert of the heavy chain nucleotide and a vector having an insert of the light chain nucleotide are introduced into host cells, and then the cells are cultured, and the antibody can be recovered from the cultures. The heavy chain nucleotide and the light chain nucleotide may be inserted in one vector.

[0403] Prokaryotic or eukaryotic cells can be used as the host cells. In the case of using host eukaryotic cells, animal cells, plant cells, or eukaryotic microbes can be used.

[0404] Examples of animal cells can include mammal-derived cells, i.e., monkey-derived COS cells (Gluzman, Y. Cell (1981), 23, p. 175-182, ATCC CRL-1650), mouse fibroblast NIH3T3 (ATCC No. CRL-1658), a mouse NS0 cell line (ECACC), Chinese hamster ovary cells (CHO cells, ATCC CCL-61), dihydrofolate reductase-deficient lines thereof (CHO^{dhfr-}; Urlaub, G. and Chasin, L. A. Proc. Natl. Acad. Sci. U.S.A. (1980), 77, p. 4126-4220), CHOK1SV (Lonza Biologics), cells derived from birds such as chickens, and cells derived from insects.

[0405] Also, cells modified to regulate the sugar chain modification of proteins such as antibodies can be used as the hosts. For example, CHO cells modified such that sugar chains with fucose bound to N-acetylglucosamine at their reducing ends are reduced or removed among complex-type N-glycoside-linked sugar chains binding to the Fc region of the antibody, may be used in antibody expression to thereby prepare a defucosylated antibody (also referred to as a modified form of the antibody) (WO00/61739, WO02/31140, etc.).

[0406] Examples of eukaryotic microbes can include yeasts.

[0407] Examples of prokaryotic cells can include *E. coli* and *Bacillus subtilis*.

[0408] A signal peptide for the secretion of the antibody of the present invention (monoclonal antibody derived from each animal, rat antibody, mouse antibody, chimeric antibody, humanized antibody, human antibody, etc.) is not limited to the secretory signal of an antibody of the same species, the same type, and the same subtype as the antibody of the present invention or to the antibody of the present invention's own secretory signal. Any secretory signal of an antibody of different type or subtype therefrom or any secretory signal of a protein derived from a different eukaryotic species therefrom or a prokaryotic species can be selected and used.

[0409] (4-4) Methods for Designing and Preparing a Humanized Antibody

[0410] Examples of the humanized antibody can include, but are not limited to, a human-derived antibody having CDRs replaced with the CDRs of a non-human animal antibody (see Nature (1986), 321, p. 522-525), a human antibody grafted with the CDR sequences and with some amino acid residues of framework regions by CDR grafting (see WO90/07861 and U.S. Pat. No. 6,972,323), and an antibody having human antibody amino acid(s) replaced for one or two or more non-human animal antibody-derived amino acid(s) in any of these humanized antibodies.

[0411] (4-5) Methods for Preparing a Human Antibody

[0412] Further examples of the antibody of the present invention can include a human antibody. The anti-FGFR2 human antibody means an anti-FGFR2 antibody consisting of the amino acid sequence of a human-derived antibody. The anti-FGFR2 human antibody can be obtained by a method using human antibody-producing mice carrying

human genomic DNA fragments comprising human antibody heavy and light chain genes (see e.g., Tomizuka, K. et al., Nature Genetics (1997) 16, p.133-143; Kuroiwa, Y. et al., Nuc. Acids Res. (1998) 26, p.3447-3448; Yoshida, H. et al., Animal Cell Technology: Basic and Applied Aspects vol. 10, p.69-73 (Kitagawa, Y., Matuda, T. and Iijima, S. eds.), Kluwer Academic Publishers, 1999; Tomizuka, K. et al., Proc. Natl. Acad. Sci. USA (2000) 97, p.722-727).

[0413] Specifically, such human antibody-producing animals may be any of recombinant animals that are obtained by disrupting the endogenous immunoglobulin heavy and light chain gene loci of non-human mammals and instead introducing thereto human immunoglobulin heavy and light chain gene loci via yeast artificial chromosome (YAC) vectors or the like, and recombinant animals that are created by crossing these animals.

[0414] Alternatively, eukaryotic cells may be transfected with cDNAs encoding the heavy and light chains, respectively, of such a human antibody, preferably with vectors comprising the cDNAs, by a gene recombination technique. The transfected cells producing a recombinant human monoclonal antibody can be cultured. This antibody can be obtained from the culture supernatant.

[0415] In this context, for example, eukaryotic cells, preferably mammalian cells such as CHO cells, lymphocytes, or myelomas, can be used as the hosts.

[0416] Also, a method for obtaining a phage display-derived human antibody selected from a human antibody library (see e.g., Wormstone, I. M. et al, Investigative Ophthalmology & Visual Science. (2002) 43 (7), p.2301-2308; Carmen, S. et al., Briefings in Functional Genomics and Proteomics (2002), 1 (2), p.189-203; Siriwardena, D. et al., Ophthalmology (2002) 109 (3), p.427-431) is known.

[0417] For example, a phage display method (Nature Biotechnology (2005), 23, (9), p. 1105-1116) can be used, which involves allowing the variable regions of a human antibody to be expressed as a single chain antibody (scFv) on phage surface and selecting a phage binding to the antigen.

[0418] The phage selected on the basis of its ability to bind to the antigen can be subjected to gene analysis to thereby determine DNA sequences encoding the variable regions of the human antibody binding to the antigen.

[0419] If the DNA sequence of scFv binding to the antigen is determined, an expression vector having this sequence can be prepared and introduced to appropriate hosts to allow them to express the human antibody (WO92/01047, WO92/20791, WO93/06213, WO93/11236, WO93/19172, WO95/01438, WO95/15388, Annu. Rev. Immunol (1994) 12, p.433-455, Nature Biotechnology (2005) 23 (9), p.1105-1116).

[0420] (4-6) Method for Preparing Functional Fragment of Antibody

[0421] The method for preparing a single chain antibody is well known in the art (see e.g., U.S. Pat. Nos. 4,946,778, 5,260,203, 5,091,513, and 5,455,030). In this scFv, a heavy chain variable region and a light chain variable region are linked via a linker that prevents them from forming a conjugate, preferably a polypeptide linker (Huston, J. S. et al., Proc. Natl. Acad. Sci. U.S.A. (1988), 85, p. 5879-5883). The heavy chain variable region and the light chain variable region in scFv may be derived from the same antibody or may be derived from different antibodies.

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[0422] For example, an arbitrary single chain peptide consisting of 12 to 19 residues is used as the polypeptide linker that links these variable regions.

[0423] In order to obtain scFv-encoding DNA, each DNA portion encoding the whole or desired amino acid sequence of the sequences of DNA encoding the heavy chain or heavy chain variable region of the antibody and DNA encoding the light chain or light chain variable region thereof is used as a template and amplified by PCR using a primer pair flanking both ends of the template. Subsequently, DNA encoding the polypeptide linker moiety is further amplified in combination with a primer pair flanking both ends of the DNA so that the obtained fragment can be linked at its ends to the heavy and light chain DNAs, respectively.

[0424] The scFv-encoding DNA can be used to thereby prepare, according to a routine method, an expression vector containing the DNA and host cells transformed with the expression vector. In addition, the host cells can be cultured, and the scFv can be recovered from the cultures according to a routine method.

[0425] Also in order to obtain any other functional fragment of the antibody, a gene encoding the functional fragment is obtained according to the method described above and introduced into cells. The functional fragment of interest can be recovered from cultures of the cells.

[0426] The antibody of the present invention may be multimerized to thereby enhance its affinity for the antigen. In this case, antibodies of the same type may be multimerized, or a plurality of antibodies recognizing a plurality of epitopes, respectively, of the same antigen may be multimerized. Examples of methods for multimerizing these antibodies can include the binding of two scFvs to an IgG CH3 domain, the binding thereof to streptavidin, and the introduction of a helix-turn-helix motif.

[0427] The antibody of the present invention may be a mixture of plural types of anti-FGFR2 antibodies differing in amino acid sequence, i.e., a polyclonal antibody. Examples of the polyclonal antibody can include a mixture of plural types of antibodies differing in a portion or the whole of the CDRs. Such a polyclonal antibody can be recovered from cultures of mixed-cultured different antibody-producing cells (WO2004/061104). Alternatively, separately prepared antibodies may be mixed. Antiserum, which is one aspect of the polyclonal antibody, can be prepared by immunizing animals with the desired antigen and recovering serum from the animals according to a standard method.

[0428] Antibodies conjugated with various molecules such as polyethylene glycol (PEG) can also be used as modified forms of the antibody.

[0429] The antibody of the present invention may further be any conjugates formed by these antibodies with other drugs (immunoconjugates). Examples of such an antibody can include the antibody conjugated with a radioactive material or a compound having a pharmacological action (Nature Biotechnology (2005), 23, p. 1137-1146).

[0430] (4-7) Purification of the Antibody

[0431] The obtained antibody can be purified until homogeneous. Usual protein separation and purification methods can be used for the separation and purification of the antibody.

[0432] The antibody can be separated and purified by appropriately selected or combined approach(es), for example, chromatography columns, filters, ultrafiltration, salting out, dialysis, preparative polyacrylamide gel electro-

phoresis, and/or isoelectric focusing (Strategies for Protein Purification and Characterization: A Laboratory Course Manual, Daniel R. Marshak et al. eds., Cold Spring Harbor Laboratory Press (1996); Antibodies: A Laboratory Manual. Ed Harlow and David Lane, Cold Spring Harbor Laboratory (1988)) though the separation and purification method is not limited thereto.

[0433] Examples of chromatography include affinity chromatography, ion-exchange chromatography, hydrophobic chromatography, gel filtration, reverse-phase chromatography, and adsorption chromatography.

[0434] These chromatography approaches can be performed using liquid-phase chromatography such as HPLC or FPLC.

[0435] Examples of columns used in affinity chromatography can include protein A, protein G, and antigen columns.

[0436] Examples of the protein A columns include Protein A Ceramic HyperD (manufactured by Pall Corp.), POROS (manufactured by Applied Biosystems, Inc.), and Sepharose F. F. (manufactured by GE Healthcare Bio-Sciences Corp.).

[0437] Also, the antibody may be purified using its binding activity against the antigen using an antigen-immobilized carrier.

[0438] (4-8) Nucleotides Encoding the Antibody, a Recombinant Vector, and a Recombinant Cell

[0439] The present invention provides a nucleotide(s) encoding the antibody of the present invention or the functional fragment thereof, or the modified form of the antibody or functional fragment (hereinafter, this nucleotide is referred to as an "antibody gene"), a recombinant vector having an insert of the gene, a cell comprising the gene or the vector (hereinafter, this cell is referred to as an "antibody gene-transfected cell"), and a cell producing the antibody of the present invention or the functional fragment thereof, or the modified form of the antibody or functional fragment (hereinafter, this cell is referred to as an "antibody-producing cell").

[0440] Preferably, the antibody gene of the present invention comprises a nucleotide sequence defined in any one of the following (a) to (e) (hereinafter, referred to as an "antibody gene sequence"), consists of a nucleotide sequence comprising the antibody gene sequence, or consists of the antibody gene sequence:

(a) a combination of a nucleotide sequence encoding the heavy chain amino acid sequence of any one of the rat FR2-10, FR2-13, and FR2-14, chimeric cFR2-10, cFR2-13, and cFR2-14, and humanized hFR2-14_H1/L1 to hFR2-14_H19/L1 antibodies and a nucleotide sequence encoding the light chain amino acid sequence of any one thereof;

(b) a combination of a nucleotide sequence encoding the amino acid sequence of a heavy chain comprising CDRH1 to CDRH3 of any one of the rat FR2-10, FR2-13, and FR2-14, chimeric cFR2-10, cFR2-13, and cFR2-14, and humanized hFR2-14_H1/L1 to hFR2-14_H19/L1 antibodies and a nucleotide sequence encoding the amino acid sequence of a light chain comprising CDRL1 to CDRL3 of any one thereof;

(c) a combination of a nucleotide sequence encoding a heavy chain amino acid sequence comprising the amino acid sequence of the heavy chain variable region of any one of the rat FR2-10, FR2-13, and FR2-14, chimeric cFR2-10, cFR2-13, and cFR2-14, and humanized hFR2-14_H1/L1 to hFR2-14_H19/L1 antibodies and a nucleotide sequence

encoding a light chain amino acid sequence comprising the amino acid sequence of the light chain variable region of any one thereof;

(d) a nucleotide sequence that hybridizes under stringent conditions to a nucleotide consisting of a nucleotide sequence complementary to any one of the nucleotide sequences (a) to (c) and encodes the amino acid sequence of an antibody binding to FGFR2; and

(e) a nucleotide sequence that encodes an amino acid sequence derived from any one of the amino acid sequences (a) to (c) by the substitution, deletion, addition, or insertion of 1 to 50, 1 to 45, 1 to 40, 1 to 30, 1 to 25, 1 to 20, 1 to 15, 1 to 10, 1 to 8, 1 to 6, 1 to 5, 1 to 4, 1 to 3, 1 or 2, or 1 amino acid(s) and encodes the amino acid sequence of an antibody binding to FGFR2.

[0441] The antibody having the amino acid sequence encoded by the nucleotide sequence (d) or (e) may have one or two or more of the activities defined in paragraphs (3-3) to (3-6), in addition to FGFR2 binding activity.

[0442] However, the antibody gene of the present invention is not limited to those defined in (a) to (e).

[0443] The present invention provides, as described in paragraph (4-3), a method for producing the antibody of the present invention or the functional fragment thereof, or the modified form of the antibody or functional fragment, comprising the steps of: culturing the antibody gene-transfected cell of the present invention and recovering the antibody, the functional fragment, or the modified form from the cultures. The antibody or functional fragment thereof, or the modified form of the antibody or functional fragment obtained by this production method is also included in the present invention.

5. Pharmaceutical Compositions

[0444] The present invention provides a pharmaceutical composition comprising the anti-FGFR2 antibody or functional fragment thereof, or the modified form of the antibody or functional fragment.

[0445] The pharmaceutical composition of the present invention is useful in the treatment or prevention of various diseases that are initiated or exacerbated by abnormal or increased FGFR2 signals due to overexpression of FGFR2 or its ligand or FGFR2 mutations or gene amplification, or by isoform switching of FGFR2 (hereinafter, these diseases are referred to as "FGFR2-related diseases"), particularly, various cancers.

[0446] Examples of causes of the initiation or exacerbation of such cancers to be treated or prevented can include a single nucleotide polymorphism (SNP) in an intron of the FGFR2 gene, high expression of FGFR2, missense mutations that constitutively activate FGFR2, amplification or overexpression of the FGFR2 gene, and switching from FGFR2 IIb to FGFR2 IIc.

[0447] Examples of such cancer types can include breast cancer, endometrial cancer, ovarian cancer, lung cancer (e.g., non-small cell lung cancer), stomach cancer, prostate cancer, kidney cancer, liver cancer, pancreatic cancer, colorectal cancer, esophageal cancer, urinary bladder cancer, cervical cancer, blood cancer, lymphoma, and malignant melanoma. Preferred examples thereof can include these cancers expressing the FGFR2 protein.

[0448] In the present invention, the treatment or prevention of a disease includes, but is not limited to, the prevention of the onset of the disease, preferably the disease in an individual expressing the FGFR2 protein, the suppression or

inhibition of exacerbation or progression thereof, the alleviation of one or two or more symptoms exhibited by an individual affected with the disease, the suppression or remission of exacerbation or progression thereof, the treatment or prevention of a secondary disease, etc.

[0449] The pharmaceutical composition of the present invention can comprise a therapeutically or prophylactically effective amount of the anti-FGFR2 antibody, or the functional fragment of the antibody, and a pharmaceutically acceptable diluent, vehicle, solubilizer, emulsifier, preservative, and/or additive.

[0450] The "therapeutically or prophylactically effective amount" means an amount that exerts therapeutic or prophylactic effects on a particular disease by means of a particular dosage form and administration route and has the same meaning as a "pharmacologically effective amount".

[0451] The pharmaceutical composition of the present invention may comprise materials for changing, maintaining, or retaining pH, osmotic pressure, viscosity, transparency, color, tonicity, sterility, or the stability, solubility, sustained release, absorbability, permeability, dosage form, strength, properties, shape, etc., of the composition or the antibody comprised therein (hereinafter, referred to as "pharmaceutical materials"). The pharmaceutical materials are not particularly limited as long as the materials are pharmacologically acceptable. For example, no or low toxicity is a property preferably possessed by these pharmaceutical materials.

[0452] Examples of the pharmaceutical materials can include, but are not limited to, the following: amino acids such as glycine, alanine, glutamine, asparagine, histidine, arginine, and lysine; antimicrobial agents; antioxidants such as ascorbic acid, sodium sulfate, and sodium bisulfite; buffers such as phosphate, citrate, or borate buffers, sodium bicarbonate, and Tris-HCl solutions; fillers such as mannitol and glycine; chelating agents such as ethylenediaminetetraacetic acid (EDTA); complexing agents such as caffeine, polyvinylpyrrolidone, β -cyclodextrin, and hydroxypropyl- β -cyclodextrin; bulking agents such as glucose, mannose, and dextrin; other hydrocarbons such as monosaccharides, disaccharides, glucose, mannose, and dextrin; coloring agents; corrigents; diluents; emulsifiers; hydrophilic polymers such as polyvinylpyrrolidone; low-molecular-weight polypeptides; salt-forming counterions; antiseptics such as benzalkonium chloride, benzoic acid, salicylic acid, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid, and hydrogen peroxide; solvents such as glycerin, propylene glycol, and polyethylene glycol; sugar alcohols such as mannitol and sorbitol; suspending agents; surfactants such as PEG, sorbitan ester, polysorbates such as polysorbate 20 and polysorbate 80, triton, tromethamine, lecithin, and cholesterol; stability enhancers such as sucrose and sorbitol; elasticity enhancers such as sodium chloride, potassium chloride, mannitol, and sorbitol; transport agents; diluents; excipients; and/or pharmaceutical additives.

[0453] The amount of these pharmaceutical materials added is 0.001 to 1000 times, preferably 0.01 to 100 times, more preferably 0.1 to 10 times the weight of the anti-FGFR2 antibody or functional fragment thereof, or the modified form of the antibody or functional fragment.

[0454] An immunoliposome comprising the anti-FGFR2 antibody or functional fragment thereof, or the modified form of the antibody or functional fragment encapsulated in

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a liposome, or a modified antibody form comprising the antibody conjugated with a liposome (U.S. Pat. No. 6,214,388, etc.) is also included in the pharmaceutical composition of the present invention.

[0455] The excipients or vehicles are not particularly limited as long as they are liquid or solid materials usually used in injectable water, saline, artificial cerebrospinal fluids, and other preparations for oral or parenteral administration. Examples of saline can include neutral saline and serum albumin-containing saline.

[0456] Examples of buffers can include a Tris buffer adjusted to bring the final pH of the pharmaceutical composition to 7.0 to 8.5, an acetate buffer adjusted to bring the final pH thereof to 4.0 to 5.5, a citrate buffer adjusted to bring the final pH thereof to 5.0 to 8.0, and a histidine buffer adjusted to bring the final pH thereof to 5.0 to 8.0.

[0457] The pharmaceutical composition of the present invention is a solid, a liquid, a suspension, or the like. Another example of the pharmaceutical composition of the present invention can include freeze-dried preparations. The freeze-dried preparations can be formed using an excipient such as sucrose.

[0458] The administration route of the pharmaceutical composition of the present invention may be any of enteral administration, local administration, and parenteral administration. Examples thereof can include intravenous administration, intraarterial administration, intramuscular administration, intradermal administration, hypodermic administration, intraperitoneal administration, transdermal administration, intraosseous administration, intraarticular administration, and the like.

[0459] The composition of a pharmaceutical composition can be determined according to the administration method, the binding affinity of the antibody for the FGFR2 protein, etc. The anti-FGFR2 antibody of the present invention or the functional fragment thereof, or the modified form of the antibody or functional fragment having higher affinity (lower KD value) for the FGFR2 protein can exert its pharmaceutical efficacy at a lower dose.

[0460] The dose of the anti-FGFR2 antibody of the present invention is not limited as long as the dose is a pharmacologically effective amount. The dose can be appropriately determined according to the species of an individual, the type of disease, symptoms, sex, age, pre-existing conditions, the binding affinity of the antibody for the FGFR2 protein or its biological activity, and other factors. A dose of usually 0.01 to 1000 mg/kg, preferably 0.1 to 100 mg/kg, can be administered once every day to every 180 days or twice or three or more times a day.

[0461] Examples of the form of the pharmaceutical composition can include injections (including freeze-dried preparations and drops), suppositories, transnasal absorption preparations, transdermal absorption preparations, sublingual formulations, capsules, tablets, ointments, granules, aerosols, pills, powders, suspensions, emulsions, eye drops, and biological implant formulations.

[0462] The anti-FGFR2 antibody or functional fragment thereof, or the modified form of the antibody or the functional fragment (hereinafter, referred to as an “anti-FGFR2 antibody, etc.”) can be used in combination with another agent. The anti-FGFR2, etc. or the pharmaceutical composition comprising the anti-FGFR2 antibody, etc. as an active ingredient can be administered concurrently with or separately from the other agent, i.e., a pharmaceutical composition

comprising a compound other than the anti-FGFR2 antibody, etc. as an active ingredient. For example, the pharmaceutical composition comprising the anti-FGFR2 antibody, etc. as an active ingredient may be administered after administration of the other agent, or the other agent may be administered after administration of the pharmaceutical composition comprising the anti-FGFR2 antibody, etc. as an active ingredient. Alternatively, the pharmaceutical composition comprising the anti-FGFR2 antibody, etc. as an active ingredient and the other agent may be administered concurrently. In the present invention, the case where the anti-FGFR2 antibody, etc. and the other agent are both contained as active ingredients in a single pharmaceutical composition and the case where these active ingredients are separately contained in a plurality of pharmaceutical compositions are both included in the scope of the “pharmaceutical composition comprising the anti-FGFR2 antibody, etc. and the other agent”. In the present invention, the “pharmaceutical composition” has the same meaning as the “pharmaceutical composition in which the anti-FGFR2 antibody, etc. is to be administered in combination with an other agent”.

[0463] In the present invention, the phrase “administered in combination” used for the anti-FGFR2 antibody, etc. and the other agent means that the anti-FGFR2 antibody, etc. and the other agent are incorporated in the body of a recipient within a certain period. A single preparation containing the anti-FGFR2 antibody, etc. and the other agent may be administered, or the anti-FGFR2 antibody, etc. and the other agent may be separately formulated and administered as separate preparations. In the case of the separate preparations, the timings of administration thereof are not particularly limited, and the preparations may be administered concurrently or may be administered at different times or different days in a staggered manner. In the case where the anti-FGFR2 antibody, etc. and the other agent are separately administered at different times or different days, the order of administration thereof is not particularly limited. Since separate preparations are usually administered according to their respective administration methods, the frequency of administration thereof may be the same times or may be different times. Further, such separate preparations may be administered by the same administration method (administration route) or may be administered by different administration methods (administration routes). It is not necessary that the anti-FGFR2 antibody, etc. and the other agent exist in the body concurrently, and it is sufficient that the anti-FGFR2 antibody, etc. and the other agent are incorporated in the body within a certain period (e.g., for 1 month, preferably for 1 week, more preferably for several days, even more preferably for 1 day). Alternatively, when one of the active ingredients is administered, the other active ingredient may have already disappeared from the body.

[0464] Examples of the dosage form of the “pharmaceutical composition in which the anti-FGFR2 antibody, etc. is to be administered in combination with the other agent” can include 1) the administration of a single preparation containing the anti-FGFR2 antibody, etc. and the other agent, 2) the concurrent administration through the same administration route of two preparations obtained by separately formulating the anti-FGFR2 antibody, etc. and the other agent, 3) the administration in a staggered manner through the same administration route of two preparations obtained by separately formulating the anti-FGFR2 antibody, etc. and the

other agent, 4) the concurrent administration through different administration routes of two preparations obtained by separately formulating the anti-FGFR2 antibody, etc. and the other agent, and 5) the administration in a staggered manner through different administration routes of two preparations obtained by separately formulating the anti-FGFR2 antibody, etc. and the other agent. The dose, dosing interval, dosage form, preparation, etc., of the “pharmaceutical composition in which the anti-FGFR2 antibody, etc. is to be administered in combination with the other agent” abide by those of the pharmaceutical composition comprising the anti-FGFR2 antibody, etc., but are not limited thereto.

[0465] Such a pharmaceutical composition formulated in two different preparations may be in the form of a kit containing these preparations.

[0466] In the present invention, the “combination” of the anti-FGFR2 antibody, etc. and the other agent means that the anti-FGFR2 antibody, etc. and the other agent are “administered in combination”.

[0467] In the present invention, the “other agent” is not particularly limited as long as the agent is a tyrosine kinase inhibitor. The other agent is preferably an FGFR tyrosine kinase inhibitor (in the present invention, referred to as an “FGFR inhibitor”), more preferably an FGFR2 inhibitor having FGFR2 tyrosine kinase inhibitory activity (in the present invention, referred to as an “FGFR2 inhibitor”). Examples of the FGFR2 inhibitor can include acylaminopyrazole, a quinolone or quinazoline derivative modified with a phenoxy group or a phenylthio group, BGJ398, LY2874455, brivanib, dovitinib, lenvatinib, masitinib, nintedanib, regorafenib, pazopanib, TSU68, ENMD-2076, and ponatinib. Preferred examples of the acylaminopyrazole can include AZD4547 (N-(5-(3,5-dimethoxyphenethyl)-1H-pyrazol-3-yl)-4-((3S,5R)-3,5-dimethylpiperazin-1-yl)benzamide; International Publication No. WO2008/075068 A2). Preferred examples of the quinolone or quinazoline derivative modified with a phenoxy group or a phenylthio group can include Ki23057 (2-((2-((4-(4-(tert-butyl)phenyl)amino)phenoxy)-6-methoxyquinolin-7-yl)oxy)ethyl)amino)ethanol; International Publication No. WO2003/033472 A1). However, the “other agent” contained in the combination or the pharmaceutical composition of the present invention is not limited thereto.

[0468] An additional drug can be further used in the combination or the pharmaceutical composition of the present invention. Examples of the additional drug further used can include various anticancer agents such as chemotherapeutics and radiation therapy (radiation therapeutics).

[0469] The present invention provides a method for treating or preventing FGFR-related diseases such as cancer, use of the antibody of the present invention for preparing a pharmaceutical composition for treatment or prevention of the diseases, and use of the antibody of the present invention for treating or preventing the diseases. The present invention also encompasses a kit for treatment or prevention comprising the antibody of the present invention.

6. Selection of the Subject to be Treated

[0470] Examples of the antibody having human FGFR2 IIIb selectivity can include, but are not limited to, the rat FR2-10 antibody, the chimeric cFR2-10 antibody, and humanized FR2-10 antibodies. Test samples can be subjected to immunoassay using these antibodies to identify a sample expressing FGFR2 IIIb.

[0471] Examples of the antibody having selectivity for both human FGFR2 IIIb and human FGFR2 IIIc can include, but are not limited to, the rat FR2-13 antibody, the rat FR2-14 antibody, the chimeric cFR2-13 antibody, humanized FR2-13 antibodies, the chimeric cFR2-14 antibody, and the humanized FR2-14 antibodies.

[0472] Human FGFR2 IIIc in a test sample can be detected or assayed by: (i) detecting or assaying human FGFR2 IIIb and human FGFR2 IIIc in the test sample; (ii) detecting or assaying human FGFR2 IIIb in the sample; and (iii) comparing the results of detection or assay in step (i) with the results of detection or assay in step (ii) or subtracting the results of detection or assay in step (ii) from the results of detection or assay in step (i).

[0473] Human FGFR2 in a sample derived from the individual can be assayed. The individual can be determined to be positive when human FGFR2 is detected in the sample or when human FGFR2 is detected in a larger amount than that of human FGFR2 detected in a sample derived from a healthy individual. According to a preferred aspect, the individual in the identification method has cancer or is at risk thereof. According to one aspect, the drug combination or the pharmaceutical composition of the present invention can be administered to an individual determined to be positive by the identification method.

EXAMPLES

[0474] Hereinafter, the present invention will be described further specifically with reference to the Examples. However, the present invention is not intended to be limited to them.

[0475] Procedures related to gene manipulation in the Examples below were performed according to the methods described in “Molecular Cloning” (Sambrook, J., Fritsch, E. F. and Maniatis, T., Cold Spring Harbor Laboratory Press, 1989) or the methods described in other experimental manuals used by those skilled in the art, or using commercially available reagents or kits according to the instruction manuals, unless otherwise specified.

Example 1

Preparation of a Rat Anti-Human FGFR2 Antibody

[0476] 1)-1 Immunization

[0477] Eight-week-old female WKY/Izm rats (Japan SLC, Inc.) and 7-week-old female Crlj:WI rats (Charles River Laboratories Japan Inc.) were used. At day 0, a mixture of 50 µg of Recombinant Human FGFR2β (IIIb)/Fc Chimera (manufactured by R&D Systems, Inc.) and Freund's Complete Adjuvant (manufactured by Wako Pure Chemicals Industries, Ltd.) (volume ratio: 1:2) was administered to the tail base of each WKY/Izm rat. At day 21, 50 µg of Recombinant Human FGFR2β (IIIb)/Fc Chimera was administered to the tail base of each rat. At day 35, the lymph node or the spleen was collected from the rat and used in hybridoma preparation. At day 0, a mixture of 50 µg of FGFR2β (IIIb)/Fc Chimera and Freund's Complete Adjuvant (volume ratio: 1:1) was subcutaneously or intradermally administered to each Crlj:WI rat. At days 7, 14, and 21, a mixture of 50 µg of FGFR2β (IIIb)/Fc Chimera and Freund's Incomplete Adjuvant (volume ratio: 1:1) was subcutaneously or intradermally administered to the rat. At day 38, 50 µg of FGFR2β (IIIb)/Fc Chimera was administered

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into the tail vein of the rat. At day 42, the lymph node or the spleen was collected from the rat and used in hybridoma preparation.

[0478] 1)-2 Hybridoma Preparation

[0479] The lymph node cells or the spleen cells were electrically fused with mouse myeloma SP2/0-ag14 cells using HybriMune Hybridoma Production System (manufactured by Cyto Pulse Sciences, Inc.). The fused cells were diluted with ClonaCell-HY Selection Medium D (manufactured by StemCell Technologies Inc.) and cultured. Hybridoma colonies that appeared were recovered to prepare monoclonal hybridomas. Each hybridoma colony thus recovered was cultured, and the obtained hybridoma culture supernatant was used to screen for an anti-FGFR2 antibody-producing hybridoma.

[0480] 1)-3 Construction of an Expression Vector for Screening for Antigen-Binding Antibody

[0481] 1)-3-1 Construction of Human FGFR2 IIIb and FGFR2 IIIc Expression Vectors (pcDNA-DEST40-FGFR2 IIIb and pcDNA-DEST40-FGFR2 IIIc)

[0482] cDNAs encoding a human FGFR2 IIIb variant protein (isoform 2: NP_075259) and a human FGFR2 IIIc variant protein (isoform 1: NP_000132) were cloned into pcDNA-DEST40 vectors to construct vectors pcDNA-DEST40-FGFR2 IIIb and pcDNA-DEST40-FGFR2 IIIc for expression of each variant protein, respectively.

[0483] 1)-3-2 Construction of an Ig-Like Domain-Deficient FGFR2 IIIb Expression Vector

[0484] Vectors for expression of a mutant deficient in a region of amino acid positions 54 to 110 in the full-length amino acid sequence (1 to 822) of FGFR2 IIIb (hereinafter, referred to as an "IgD1-deletion mutant"), a mutant deficient in a region of amino acid positions 154 to 246 therein (hereinafter, referred to as an "IgD2-deletion mutant"), or a mutant deficient in a region of amino acid positions 263 to 358 therein (hereinafter, referred to as an "IgD3-deletion mutant") were constructed by PCR with pcDNA-DEST40-FGFR2 IIIb as a template.

[0485] 1)-4 Antibody Screening by Cell-ELISA

[0486] 1)-4-1 Preparation of an Antigen Gene-Expressing Cell for Cell-ELISA

[0487] HEK293 cells were adjusted to 7.5×10^5 cells/ml in a DMEM medium containing 10% FBS. pcDNA-DEST40-FGFR2 IIIb or a control pcDNA-DEST40 was transfected thereto using Lipofectamine 2000 (manufactured by Life Technologies Corp.). The resulting cells were dispensed in an amount of 50 μ l/well to a 96-well half area plate (manufactured by Corning Inc.) and cultured overnight at 37° C. under 5% CO₂ conditions in a DMEM medium containing 10% FBS. The obtained transfected cells were used in the attached state in Cell-ELISA.

[0488] 1)-4-2 Cell-ELISA

[0489] After removal of the culture supernatant from the expression vector-transfected HEK293 cells prepared in Example 1)-4-1, each hybridoma culture supernatant was added to the pcDNA-DEST40-FGFR2 IIIb- or pcDNA-DEST40-transfected HEK293 cells, and the plate was left standing at 4° C. for 1 hour. The cells in the wells were washed once with PBS containing 5% FBS. Then, Anti-Rat IgG-Peroxidase antibody produced in rabbit (manufactured by Sigma-Aldrich Corp.) diluted 500-fold with PBS containing 5% FBS was added thereto, and the plate was left standing at 4° C. for 1 hour. The cells in the wells were washed 5 times with PBS containing 5% FBS. Then, an

OPD chromogenic solution (OPD solution (o-phenylenediamine dihydrochloride (manufactured by Wako Pure Chemicals Industries, Ltd.) and H₂O₂ dissolved at concentrations of 0.4 mg/ml and 0.6% (v/v), respectively, in 0.05 M trisodium citrate and 0.1 M disodium hydrogen phosphate dodecahydrate, pH 4.5)) was added thereto at a concentration of 25 μ l/well. Color reaction was performed with occasional stirring and stopped by the addition of 1 M HCl at a concentration of 25 μ l/well. Then, the absorbance was measured at 490 nm using a plate reader (ENVISION; PerkinElmer, Inc.). In order to select a hybridoma producing an antibody specifically binding to FGFR2 expressed on cell membrane surface, hybridomas that yielded a culture supernatant exhibiting higher absorbance for the pcDNA-DEST40-FGFR2 IIIb expression vector-transfected HEK293 cells compared with the control pcDNA-DEST40-transfected HEK293 cells were selected as anti-FGFR2 antibody production-positive hybridomas.

[0490] 1)-5 Antibody Screening by Flow Cytometry

[0491] 1)-5-1 Preparation of an Antigen Gene-Expressing Cell for Flow Cytometry Analysis

[0492] HEK293T cells were inoculated at a density of 5×10^4 cells/cm² to a 225-cm² flask (manufactured by Sumitomo Bakelite Co., Ltd.) and cultured overnight at 37° C. under 5% CO₂ conditions in a DMEM medium containing 10% FBS. On the next day, the pcDNA-DEST40-FGFR2 IIIb IgD1-deletion mutant deficient in the N-terminal IgD1 domain or a control pcDNA-DEST40 was transfected to the HEK293T cells using Lipofectamine 2000, and the cells were further cultured overnight at 37° C. under 5% CO₂ conditions. On the next day, the expression vector-transfected HEK293T cells were treated with TrypLE Express (manufactured by Life Technologies Corp.), washed with DMEM containing 10% FBS, and then suspended in PBS containing 5% FBS. The obtained cell suspension was used in flow cytometry analysis.

[0493] 1)-5-2 Flow Cytometry Analysis

[0494] The FGFR2 IIIb binding specificity of the antibody produced by each hybridoma determined to be positive by Cell-ELISA in Example 1)-4 was further confirmed by flow cytometry. Each HEK293T cell suspension prepared in Example 1)-5-1 was centrifuged to remove a supernatant. Then, the pcDNA-DEST40-FGFR2 IIIb IgD1-deletion mutant-transfected HEK293T cells or the pcDNA-DEST40-transfected HEK293T cells were suspended by the addition of the hybridoma culture supernatant and left standing at 4° C. for 1 hour. The cells were washed twice with PBS containing 5% FBS, then suspended by the addition of Anti-Rat IgG FITC conjugate (manufactured by Sigma-Aldrich Corp.) diluted 320-fold with PBS containing 5% FBS, and left standing at 4° C. for 1 hour. The cells were washed 3 times with PBS containing 5% FBS and then resuspended in PBS containing 5% FBS and 2 μ g/ml 7-aminoactinomycin D (manufactured by Molecular Probes, Inc.), followed by detection using a flow cytometer (FC500; manufactured by Beckman Coulter Inc.). The data was analyzed using Flowjo (manufactured by Tree Star Inc.). After removal of 7-aminoactinomycin D-positive dead cells by gating, the FITC fluorescence intensity of live cells was plotted to a histogram. Hybridomas that yielded a sample exhibiting a shift to stronger fluorescence intensity in the histogram of the pcDNA-DEST40-FGFR2 IIIb IgD1-deletion mutant-transfected HEK293T cells compared with the fluorescence intensity histogram of the control pcDNA-

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DEST40-transfected HEK293T cells were obtained as anti-FGFR2 IIIb antibody-producing hybridomas.

[0495] 1)-6 Screening Based on the Signal-Neutralizing Effect

[0496] In order to evaluate the signal-neutralizing effect of the anti-FGFR2 antibody produced by each obtained hybridoma, an Elk1 luciferase reporter gene assay system for detecting ERK (extracellular signal-regulated kinase) activation induced by FGFR2 activation via ligand FGF7 stimulation was constructed by a method shown below and used in the evaluation of the obtained antibody for its effect.

[0497] 1)-6-1 Construction of a Vector for Reporter Assay

[0498] First, a pFR-Luc2CP vector was constructed. pFR-Luc (Stratagene #219005) was cleaved with HindIII, blunt-ended using T4 DNA polymerase, and then cleaved with BamHI to isolate a 140-bp fragment comprising five GAL4 binding elements and a TATA box. Next, pGL4.12[luc2CP] (Promega #E6661) was cleaved with EcoRI and BglII, dephosphorylated, and then ligated with the 140-bp fragment to prepare a pFR-Luc2CP vector.

[0499] 1)-6-2 Elk1 Luciferase Reporter Gene Assay

[0500] The Elk1 luciferase reporter gene assay was carried out using each hybridoma culture supernatant selected in Example 1)-5. A cell line 293 α , which was HEK293 cells stably transfected with integrin α v and integrin β 3 expression vectors, was transiently cotransfected with pcDNA-DEST40-FGFR2 IIIb or pcDNA-DEST40, pFA2-Elk1 (manufactured by Stratagene Corp.), pFR-Luc2CP, and pGL4.74[hRluc/TK] (manufactured by Promega Corp.) according to transfection procedures using Lipofectamine 2000 (manufactured by Invitrogen Corp.), inoculated to a white 96-well cell culture plate (manufactured by Corning Inc.), and cultured overnight at 37° C. under 5% CO₂ conditions. On the next day, the culture supernatant was removed, and the hybridoma culture supernatant diluted 5-fold with DMEM containing 5% FBS was added at a concentration of 50 μ l/well to the plate. After culture at 37° C. for 1 hour under 5% CO₂ conditions, a ligand human FGF7 (manufactured by R&D systems, Inc.) was added at a final concentration of 10 ng/ml to each well. After incubation for 6 hours, cell lysates were prepared and assayed for firefly luciferase activity (specific signal) and *Renilla* luciferase activity (signal for normalization) using Dual-luciferase reporter assay system (manufactured by Promega Corp.). The firefly/*Renilla* ratio was calculated to normalize data on each well. Hybridomas FR2-10, FR2-13, and FR2-14 were selected which produced anti-FGFR2 antibodies that reduced ligand FGF7 dependent reporter activation to a ligand-free level in the FGFR2-expressing HEK293 reporter cells.

[0501] 1)-7 Isotyping of the Antibody

[0502] The anti-FGFR2 antibody-producing hybridomas FR2-10, FR2-13, and FR2-14 were isotyped using Rat monoclonal isotyping test kit (manufactured by AbD Serotec). As a result, their isotypes were confirmed to be IgG2 α and κ chains for FR2-10 and IgG1 and κ chains for FR2-13 and FR2-14.

[0503] 1)-8 Preparation of Monoclonal Antibody

[0504] Each monoclonal antibody was purified from the ascites (hereinafter, referred to as an "antibody purification material") of a hybridoma-transplanted mouse.

[0505] The mouse ascites were prepared as follows: first, 7-to 8-week-old BALB/cAJcl-nu/nu (Japan SLC, Inc.) was treated with pristane (manufactured by Sigma-Aldrich

Corp.). Approximately 1 to 4 weeks later, each hybridoma washed with PBS was intraperitoneally transplanted in an amount of 1 to 2 $\times$ 10⁷ cells per mouse. One to 2 weeks later, ascites accumulated intraperitoneally were collected, sterilized through a 0.22- μ m filter, and used as an antibody purification material.

[0506] Each antibody was purified using Hitrap MabSelect SuRe (manufactured by GE Healthcare Bio-Sciences Corp.). The antibody purification material was applied to a column, which was then washed with PBS, followed by elution with 2 M arginine-HCl (pH 4.0). The eluted antibody solution was neutralized and then buffer-replaced with PBS. The concentration of the purified antibody was determined by the elution of the antibody bound with POROS G 20 μ m Column PEEK, 4.6 mm $\times$ 50 mm, 0.83 ml (manufactured by Applied Biosystems, Inc.) and the subsequent measurement of the absorbance (O.D. 280 nm) of the eluate. Specifically, the antibody sample diluted with PBS was applied to POROS G 20 μ m equilibrated with an equilibration buffer (30.6 mM sodium dihydrogen phosphate dodecahydrate, 19.5 mM monopotassium phosphate, and 0.15 M NaCl, pH 7.0). The column was washed with an equilibration buffer, followed by the elution of the antibody bound with the column using an eluent (0.1% (v/v) HCl and 0.15 M NaCl). The peak area of the absorbance (O.D. 280 nm) of the eluate was measured, and the concentration was calculated according to the following expression: Antibody sample concentration (mg/ml)=(Peak area of the antibody sample)/(Peak area of a standard (human IgG1)) $\times$ Concentration (mg/ml) of the standard $\times$ Dilution ratio of the sample. Also, the concentration of endotoxin contained in the obtained antibody was measured using Limulus ES-II Single Test Wako (Wako Pure Chemicals Industries, Ltd. 295-51030; containing control standard endotoxin) and Toxinometer (Wako Pure Chemicals Industries, Ltd. ET-301 or ET-5000) and confirmed to be 1 EU/mg or lower. The antibody was used in the subsequent experiments.

Example 2

In Vitro Evaluation of Rat Anti-Human FGFR2 Antibodies (FR2-10, FR2-13, and FR2-14)

[0507] 2)-1 Study on Selective Binding Activity of Obtained Rat Anti-FGFR2 Antibodies (FR2-10, FR2-13, and FR2-14) Against Human FGFR2

[0508] 2)-1-1 Construction of Human FGFR1 IIIc, Human FGFR3 IIIb, Human FGFR3 IIIc, and Human FGFR4 Expression Vectors

[0509] cDNAs encoding a human FGFR1 IIIc variant protein (isoform 1: NP_075598), a human FGFR3 IIIb variant protein (isoform 3: NP_001156685), a human FGFR3 IIIc variant protein (isoform 1: NP_000133), and a human FGFR4 protein (isoform 1: NP_002002) were cloned into pcDNA-DEST40 vectors to construct vectors pcDNA-DEST40-FGFR1 IIIc, pcDNA-DEST40-FGFR3 IIIb, pcDNA-DEST40-FGFR3 IIIc, and pcDNA-DEST40-FGFR4 for expression of each variant protein, respectively.

[0510] 2)-1-2 Flow Cytometry Analysis

[0511] Each human FGFR expression vector constructed in Examples 1)-3-1 and 2)-1-1 was transfected to HEK293T cells by the method shown in Example 1)-5-1. The cell suspension was centrifuged to remove the supernatant. Then, these various human FGFR expression vector-transfected HEK293T cells and the pcDNA-DEST40-transfected

HEK293T cells were separately suspended by the addition of the hybridoma culture supernatant containing the FR2-10, FR2-13, or FR2-14 antibody and left standing at 4° C. for 1 hour. The cells were washed twice with PBS containing 5% FBS, then suspended by the addition of Anti-Rat IgG FITC conjugate (manufactured by Sigma-Aldrich Corp.) diluted 320-fold with PBS containing 5% FBS, and left standing at 4° C. for 1 hour. The cells were washed 3 times with PBS containing 5% FBS and then resuspended in PBS containing 5% FBS and 2 µg/ml 7-aminoactinomycin D (manufactured by Molecular Probes, Inc.), followed by detection using a flow cytometer (FC500; manufactured by Beckman Coulter Inc.). The data was analyzed using Flowjo (manufactured by Tree Star Inc.). After removal of 7-aminoactinomycin D-positive dead cells by gating, the FITC fluorescence intensity of live cells was plotted to a histogram to calculate average fluorescence intensity (MFI). As seen from FIG. 1, the rat FR2-10 antibody was shown to selectively bind to human FGFR2 IIb, while the rat FR2-13 and FR2-14 antibodies were shown to selectively bind to both human FGFR2 IIb and FGFR2 IIc.

[0512] 2)-2 Identification of the Epitope for Obtained Rat Anti-FGFR2 Antibodies (FR2-10, FR2-13, and FR2-14)

[0513] Epitopes bound by the obtained rat anti-FGFR2 antibodies were identified using vectors for expression of mutants lacking any one of the three Ig-like domains present in the FGFR2 extracellular region. The FGFR2 IIb IgD1, IgD2, or IgD3-deletion mutant expression vector constructed in Example 1)-3-2 was transfected to HEK293T cells by the method shown in Example 1)-5-1. The cell suspension was centrifuged to remove a supernatant. Then, these various Ig-like domain-deficient FGFR2 IIb expression vector-transfected HEK293T cells and the pcDNA-DEST40-transfected HEK293T cells were separately suspended by the addition of the hybridoma culture supernatant containing the FR2-10, FR2-13, or FR2-14 antibody and left standing at 4° C. for 1 hour. The cells were washed twice with PBS containing 5% FBS, then suspended by the addition of Anti-Rat IgG FITC conjugate (manufactured by Sigma-Aldrich Corp.) diluted 320-fold with PBS containing 5% FBS, and left standing at 4° C. for 1 hour. The cells were washed 3 times with PBS containing 5% FBS and then resuspended in PBS containing 5% FBS and 2 µg/ml 7-aminoactinomycin D (manufactured by Molecular Probes, Inc.), followed by detection using a flow cytometer (FC500; manufactured by Beckman Coulter Inc.). The data was analyzed using Flowjo (manufactured by Tree Star Inc.). After removal of 7-aminoactinomycin D-positive dead cells by gating, the FITC fluorescence intensity of live cells was plotted to a histogram to calculate average fluorescence intensity (MFI). As seen from FIG. 2, the rat FR2-10 antibody was shown to bind to the Ig-like domain 3 of human FGFR2 IIb. By contrast, the rat FR2-13 and FR2-14 antibodies, which also exhibited binding activity against human FGFR2 IIc, were shown to bind to the common Ig-like domain 2 of human FGFR2 IIb and FGFR2 IIc.

[0514] 2)-3 Signal-Neutralizing Effects of Obtained Rat Anti-FGFR2 Antibodies (FR2-10, FR2-13, and FR2-14)

[0515] In order to evaluate the signal-neutralizing effects of the obtained antibodies by the Elk1 luciferase reporter gene assay, 293α cells were cotransfected with pcDNA-DEST40-FGFR2 IIb or pcDNA-DEST40-FGFR2 IIc constructed in Example 1)-3-1, pFA2-Elk1 (manufactured by Stratagene Corp.), pFR-Luc2CP, and pGL4.74[hRluc/TK]

(manufactured by Promega Corp.) by the method shown in Example 1)-6-2, and cultured overnight at 37° C. under 5% CO₂ conditions. On the next day, the culture supernatant was removed, and the cells were then preincubated for 1 hour with the rat FR2-10, FR2-13, or FR2-14 antibody diluted with DMEM containing 2% FBS. Subsequently, a ligand human FGF7 (manufactured by R&D systems, Inc.) or human FGF9 (manufactured by PeproTech Inc.) was added at a final concentration of 10 ng/ml to each well. After incubation for 6 hours, firefly luciferase activity (specific signal) and *Renilla* luciferase activity (signal for normalization) were assayed using Dual-Glo Luciferase Assay System (manufactured by Promega Corp.). The firefly/*Renilla* ratio was calculated to normalize data on each well. As shown in FIG. 3A, the rat FR2-10, FR2-13, and FR2-14 antibodies inhibited ligand FGF7 dependent reporter activation in the FGFR2 IIb-expressing cells. As shown in FIG. 3B, the rat FR2-13 and FR2-14 antibodies inhibited ligand FGF9 dependent reporter activity in the FGFR2 IIc-expressing cells. These results demonstrated that these antibodies have the effect of inhibiting the activation of FGFR2 by its ligand.

[0516] 2)-4 FGFR2 Signal Inhibitory Effect of an Obtained Rat Anti-FGFR2 Antibody (FR2-10) on a Human Cancer Cell Line

[0517] The FGFR2 signal inhibitory effect of the obtained antibody was tested using a stomach cancer cell line SNU-16 endogenously expressing FGFR2. SNU-16 cells (3×10⁶) suspended in an RPMI medium containing 0.1% bovine serum albumin were seeded onto a 12-well plate and incubated overnight. The rat FR2-10 antibody was added thereto, and the cells were incubated at 37° C. for 1 hour. Then, 10 ng/ml FGF7 (manufactured by R&D systems, Inc.) was added thereto, and the cells were further incubated for 10 minutes. Subsequently, the cells were lysed with an RIPA buffer (1% NP-40, 0.5% sodium deoxycholate, and 0.1% SDS in PBS) containing Complete Mini (manufactured by Roche Applied Science) and a phosphatase inhibitor (manufactured by Nacalai Tesque Inc.). The lysates were centrifuged to obtain the cell lysis solution, and the protein concentration was determined using BCA protein assay (manufactured by Pierce Biotechnology, Inc.). The lysates were resuspended in a DTT-containing buffer and denatured at 99° C. for 5 minutes. The protein (20 µg/lane) was separated by SDS-PAGE on a 5 to 20% gel. The protein was blotted onto a PVDF membrane (manufactured by Bio-Rad Laboratories, Inc.). The membrane was blocked with TBS-T (2 mM Tris, 50 mM NaCl, and 0.1% Tween-20 (pH 7.4)) containing 5% skimmed milk (MEGMILK SNOW BRAND Co., Ltd.) at room temperature for 1 hour. Then, antibodies against FGFR2, phosphorylated FGFR2 (p-FGFR2), FRS2, phosphorylated FRS2 (p-FRS2), ERK, or phosphorylated ERK (p-ERK) were added thereto, followed by incubation overnight at 4° C. After washing, the membrane was incubated with a horseradish peroxidase-conjugated anti-rabbit secondary antibody (Amersham Biosciences Corp.). Immunoreactive bands were visualized with X-ray films using ECL plus substrate (GE Healthcare Bio-Sciences Corp.). As shown in FIG. 4, the ligand FGF7 stimulation increased the phosphorylation of FGFR2, FRS2, and ERK, whereas the rat FR2-10 antibody inhibited the increase in the phosphorylation of these molecules in a concentration dependent manner.

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Example 3

Sequencing of the cDNAs Encoding Variable Regions of Rat Anti-Human FGFR2 Antibodies (FR2-10, FR2-13, and FR2-14)

[0518] 3)-1 Identification of the N-Terminal Amino Acid Sequences of Heavy and Light Chains of Rat FR2-10, FR2-13, and FR2-14 Antibodies

[0519] In order to identify the N-terminal amino acid sequences of the heavy and light chains of the rat FR2-10, FR2-13, and FR2-14 antibodies, the rat FR2-10, FR2-13, and FR2-14 antibodies purified in Example 1)-8 were each separated by SDS-PAGE. After the separation, each protein in the gel was transferred from the gel to Sequi-Blot PVDF membrane (Bio-Rad Laboratories, Inc.). The membrane was washed with a washing buffer (25 mM NaCl and 10 mM sodium borate buffer, pH 8.0), then stained by dipping in a staining solution (50% methanol, 20% acetic acid, and 0.05% Coomassie brilliant blue) for 5 minutes, and then decolorized with 90% methanol. Bands corresponding to the heavy chain (band with a smaller mobility) and light chain (band with a larger mobility) of each antibody visualized on the PVDF membrane were excised, and their respective N-terminal amino acid sequences were identified by the automatic Edman method (see Edman et al. (1967) Eur. J. Biochem. 1, 80) using Procise cLC protein sequencer Model 492cLC (Applied Biosystems, Inc.). As a result, the N-terminal amino acid sequence of the band corresponding to the heavy chain of FR2-10 was EVQLVESGGGLV (SEQ ID NO: 1 of the Sequence Listing; FIG. 9), and the N-terminal amino acid sequence of the band corresponding to the light chain thereof was DIQMTQSPSSLSA (SEQ ID NO: 2 of the Sequence Listing; FIG. 10).

[0520] The N-terminal amino acid sequence of the band corresponding to the heavy chain of FR2-13 was QVKLL (SEQ ID NO: 3 of the Sequence Listing; FIG. 11), and the N-terminal amino acid sequence of the band corresponding to the light chain thereof was DIQMTQSPASLSASLGE (SEQ ID NO: 4 of the Sequence Listing; FIG. 12).

[0521] The N-terminal amino acid sequence of the band corresponding to the heavy chain of FR2-14 was QVKLL (SEQ ID NO: 5 of the Sequence Listing; FIG. 13), and the N-terminal amino acid sequence of the band corresponding to the light chain thereof was DIQMTQSPASLSASLGE (SEQ ID NO: 6 of the Sequence Listing; FIG. 14).

[0522] 3)-2 Preparation of mRNA from FR2-10-, FR2-13-, and FR2-14-Producing Hybridomas

[0523] In order to amplify cDNAs encoding the variable regions of FR2-10, FR2-13, and FR2-14, mRNAs were prepared from each of the FR2-10-, FR2-13-, and FR2-14-producing hybridoma cells using mRNA Isolation kit (Roche Applied Science).

[0524] 3)-3 Synthesis of cDNA (5'-RACE-Ready cDNA)

[0525] cDNAs (5'-RACE-Ready cDNAs) were synthesized using 70 ng of each mRNA prepared in Example 3)-2, PrimeScript Reverse Transcriptase (Takara Bio Inc.), and SMART RACE cDNA Amplification Kit (Clontech Laboratories, Inc.).

[0526] 3)-4 5'-RACE PCR Amplification and Sequencing of the cDNAs Encoding FR2-10, FR2-13, and FR2-14 Heavy Chain Variable Regions

[0527] Since the isotype of the FR2-10 heavy chain was IgG2 α and the isotypes of the FR2-13 and FR2-14 heavy chains were IgG1 (Example 1)-7), the primers used for PCR

amplification of the variable region-encoding cDNA of each heavy chain gene were oligonucleotides having the nucleotide sequences of UPM (Universal Primer A Mix; attached to SMART RACE cDNA Amplification Kit) and 5'-GAGT-TACTTTTGAGAGCAGTTCCAGGAG-3' (RG1R1: SEQ ID NO: 7 of the Sequence Listing; FIG. 15). The UPM used was attached to SMART RACE cDNA Amplification Kit (Clontech Laboratories, Inc.), while RG1R1 was designed from the sequences of rat heavy chain (IgG2 α and IgG1) constant regions registered in the database.

[0528] cDNAs encoding the heavy chain variable regions of FR2-10, FR2-13, and FR2-14 were each amplified by 5'-RACE PCR using this primer set and the cDNAs (5'-RACE-Ready cDNAs) synthesized in Example 3)-3 as templates. This PCR was carried out on the Touchdown PCR program according to the manual of SMART RACE cDNA Amplification Kit (Clontech Laboratories, Inc.) using polymerase KOD-Plus-(Toyobo Co., Ltd.).

[0529] Each heavy chain variable region-encoding cDNA amplified by 5'-RACE PCR was purified using MinElute PCR Purification Kit (Qiagen N.V.) and then analyzed by sequencing.

[0530] The sequencing primer used was an oligonucleotide having the nucleotide sequence 5'-GAGT-TACTTTTGAGAGCAGTTCCAGGAG-3' (RG1R1: SEQ ID NO: 7 of the Sequence Listing; FIG. 15).

[0531] On the basis of the results of this sequencing analysis, a sequencing primer for a complementary strand of each cDNA was further designed as shown below and used in sequencing analysis.

[0532] Sequencing primer for FR2-10 5'-GGTTCTC-CCACTCAGTAATC-3' (10HF: SEQ ID NO: 8 of the Sequence Listing; FIG. 16)

[0533] Sequencing primer for FR2-13 5'-CATATGATCA-GTGTCTCTCTC-3' (13HF: SEQ ID NO: 9 of the Sequence Listing; FIG. 17)

[0534] Sequencing primer for FR2-14 5'-ATATGATCA-GTGTCTCTCTC-3' (14HF: SEQ ID NO: 10 of the Sequence Listing; FIG. 18)

[0535] The sequencing analysis was carried out using a gene sequence analyzer ("ABI PRISM 3700 DNA Analyzer; Applied Biosystems, Inc." or "Applied Biosystems 3730x1 Analyzer; Applied Biosystems, Inc."). GeneAmp 9700 (Applied Biosystems, Inc.) was used in sequencing reaction.

[0536] The determined nucleotide sequences of the cDNAs encoding the heavy chain variable regions of FR2-10, FR2-13, and FR2-14 and the amino acid sequences of these variable regions are shown in SEQ ID NOs: 11, 13, and 15 and SEQ ID NOs: 12, 14, and 16 (FIGS. 19, 21, and 23 and FIGS. 20, 22, and 24), respectively, of the Sequence Listing.

[0537] The amino acid sequences of the FR2-10, FR2-13, and FR2-14 heavy chain variable regions determined on the basis of their nucleotide sequences were consistent with the N-terminal amino acid sequences determined in Example 3)-1.

[0538] 3)-5 5'-RACE PCR Amplification and Sequencing of the cDNA Encoding FR2-10 Light Chain Variable Region

[0539] Since the isotype of the FR2-10 light chain was κ (Example 1)-7), the primers used for PCR amplification of the variable region-encoding cDNA of the light chain gene were oligonucleotides having the nucleotide sequences of UPM (Universal Primer A Mix; attached to SMART RACE cDNA Amplification Kit) and 5'-TTCATGAGGCACAC-

GACTGAGGCACCTCC-3' (RKR3: SEQ ID NO: 17 of the Sequence Listing; FIG. 25). The UPM used was attached to SMART RACE cDNA Amplification Kit (Clontech Laboratories, Inc.), while RKR3 was designed from the sequences of rat light chain constant regions registered in the database.

[0540] A cDNA encoding the light chain variable region of FR2-10 was amplified by 5'-RACE PCR using this primer set and the cDNA (5'-RACE-Ready cDNA) synthesized in Example 3)-3 as a template. This PCR was carried out on the Touchdown PCR program according to the manual of SMART RACE cDNA Amplification Kit (Clontech Laboratories, Inc.) using polymerase KOD-Plus-(Toyobo Co., Ltd.). The light chain variable region-encoding cDNA amplified by 5'-RACE PCR was purified using MinElute PCR Purification Kit (Qiagen N.V.) and then analyzed by sequencing.

[0541] The sequencing primer used was an oligonucleotide having the nucleotide sequence 5'-TCCAGTT-GCTAACTGTTCCG-3' (sqRK: SEQ ID NO: 18 of the Sequence Listing; FIG. 26) designed from the sequences of rat light chain constant regions registered in the database.

[0542] On the basis of the results of this sequencing analysis, a sequencing primer for a complementary strand of the cDNA was further designed as shown below and used in sequencing analysis.

[0543] Sequencing primer for FR2-10 5'-CAGTGGTAT-CAACGCAGAG-3' (10LF: SEQ ID NO: 19 of the Sequence Listing; FIG. 27)

[0544] Sequencing analysis and sequencing reaction were performed as mentioned above.

[0545] The determined nucleotide sequence of the cDNA encoding the light chain variable region of FR2-10 and the amino acid sequence of this variable region are shown in SEQ ID NO: 20 and SEQ ID NO: 21 (FIGS. 28 and 29), respectively, of the Sequence Listing.

[0546] The amino acid sequence of the FR2-10 light chain variable region determined on the basis of its nucleotide sequence was consistent with the N-terminal amino acid sequence determined in Example 3)-1.

[0547] 3)-6 5'-RACE PCR Amplification and Sequencing of the cDNAs Encoding FR2-13 and FR2-14 Light Chain Variable Regions

[0548] Since the isotypes of the FR2-13 and FR2-14 light chains were κ (Example 1)-7), the primers used for PCR amplification of the variable region-encoding cDNA of each light chain gene were oligonucleotides having the nucleotide sequences of UPM (Universal Primer A Mix; attached to SMART RACE cDNA Amplification Kit) and 5'-TACGT-GCTGTTCTTGCTGTCCTGATCAG-3' (RKR6: SEQ ID NO: 22 of the Sequence Listing; FIG. 30). The UPM used was attached to SMART RACE cDNA Amplification Kit (Clontech Laboratories, Inc.), while RKR6 was designed from the sequences of rat light chain constant regions registered in the database.

[0549] Variable region-encoding cDNAs of the light chain genes of FR2-13 and FR2-14 were each amplified by 5'-RACE PCR using this primer set and the cDNAs (5'-RACE-Ready cDNAs) synthesized in Example 3)-3 as templates. This PCR was carried out on the Touchdown PCR program according to the manual of SMART RACE cDNA Amplification Kit (Clontech Laboratories, Inc.) using polymerase KOD-Plus-(Toyobo Co., Ltd.).

[0550] Each light chain variable region-encoding cDNA amplified by 5'-RACE PCR was purified using MinElute PCR Purification Kit (Qiagen N.V.) and then cloned using Zero Blunt TOPO PCR Cloning Kit (Invitrogen Corp.). The cloned cDNAs encoding the light chain variable regions were analyzed by sequencing.

[0551] The sequencing primers used were an oligonucleotide having the nucleotide sequence 5'-TTCATGAGGCACAGCTGAGGCACCTCC-3' (RKR3: SEQ ID NO: 17 of the Sequence Listing; FIG. 25) designed from the sequences of rat light chain constant regions registered in the database, and NUP (Nested Universal Primer A: attached to SMART RACE cDNA Amplification Kit).

[0552] Sequencing analysis and sequencing reaction were performed as mentioned above.

[0553] The determined nucleotide sequences of the cDNAs encoding the light chain variable regions of FR2-13 and FR2-14 and the amino acid sequences of these variable regions are shown in SEQ ID NOs: 23 and 25 (FIGS. 31 and 33) and SEQ ID NOs: 24 and 26 (FIGS. 32 and 34), respectively, of the Sequence Listing.

[0554] The amino acid sequences of the FR2-13 and FR2-14 light chain variable regions determined on the basis of their nucleotide sequences were consistent with the N-terminal amino acid sequences determined in Example 3)-1.

Example 4

Preparation of Human Chimeric Anti-FGFR2 Antibodies (cFR2-10, cFR2-13, and cFR2-14)

[0555] 4)-1 Construction of a Chimeric and Humanized Light Chain Expression Vector pCMA-LK

[0556] A plasmid pcDNA3.3-TOPO/LacZ (Invitrogen Corp.) was digested with restriction enzymes XbaI and PmeI. The obtained fragment of approximately 5.4 kb was ligated with a DNA fragment comprising a DNA sequence (shown in SEQ ID NO: 27 (FIG. 35) of the Sequence Listing) encoding a human κ chain secretory signal and a human κ chain constant region using In-Fusion Advantage PCR cloning kit (Clontech Laboratories, Inc.) to prepare pcDNA3.3/LK.

[0557] PCR was performed with pcDNA3.3/LK as a template using a primer set shown below. The obtained fragment of approximately 3.8 kb was phosphorylated and then self-ligated to construct a chimeric and humanized light chain expression vector pCMA-LK having a signal sequence, a cloning site, and the nucleotide sequence encoding the human κ chain constant region, downstream of the CMV promoter.

Primer set

5'-tataccgtcgacacctagctagagcttgcc-3' (3.3-F1: SEQ

ID NO: 28 of the Sequence Listing; FIG. 36)

5'-gctatggcagggcctgccgcccccagcttg-3' (3.3-R1: SEQ

ID NO: 29 of the Sequence Listing; FIG. 37)

[0558] 4)-2 Construction of a Chimeric and Humanized IgG1 Type Heavy Chain Expression Vector pCMA-G1

[0559] pCMA-LK was digested with XbaI and PmeI. The obtained DNA fragment except for the DNA sequence encoding the κ chain secretory signal and the human κ chain

constant region was ligated with a DNA fragment comprising a DNA sequence (shown in SEQ ID NO: 30 (FIG. 38) of the Sequence Listing) encoding the amino acids of a human heavy chain signal sequence and a human IgG1 constant region using In-Fusion Advantage PCR cloning kit (Clontech Laboratories, Inc.) to construct a chimeric and humanized IgG1 type heavy chain expression vector pCMA-G1 having a signal sequence, a cloning site, and the nucleotide sequence encoding the human IgG1 heavy chain constant region, downstream of the CMV promoter.

[0560] 4)-3 Construction of a Human Chimeric FR2-10 Light Chain Expression Vector

[0561] A DNA fragment comprising a light chain variable region-encoding cDNA was amplified using the FR2-10 light chain variable region-encoding cDNA obtained in Example 3) as a template, KOD-Plus-(Toyobo Co., Ltd.), and a primer set shown below, and inserted to the restriction enzyme BsiWI-cleaved site of the general-purpose vector pCMA-LK for chimeric and humanized antibody light chain expression using In-Fusion Advantage PCR cloning kit (Clontech Laboratories, Inc.) to construct a human chimeric FR2-10 light chain expression vector. The obtained expression vector was designated as “pCMA-LK/cFR2-10”. The nucleotide sequence of the human chimeric FR2-10 light chain and the amino acid sequence of this light chain are shown in SEQ ID NOS: 31 and 32 (FIGS. 39 and 40), respectively, of the Sequence Listing.

[0562] Primer set for human chimeric FR2-10 light chain 5'-atctccgcgcggtacggcgacatccagatgacacagttccagttcc-3' (c10-LF: SEQ ID NO: 33 of the Sequence Listing; FIG. 41) 5'-ggagggggcgccacagcccggtttattccaactctgctcc-3' (c10-LR: SEQ ID NO: 34 of the Sequence Listing; FIG. 42)

[0563] 4)-4 Construction of a Human Chimeric FR2-10 Heavy Chain Expression Vector

[0564] A DNA fragment comprising a heavy chain variable region-encoding cDNA was amplified using the FR2-10 heavy chain variable region-encoding cDNA obtained in Example 3) as a template, KOD-Plus-(Toyobo Co., Ltd.), and a primer set shown below, and inserted to the restriction enzyme BspI-cleaved site of the chimeric and humanized IgG1 type heavy chain expression vector pCMA-G1 using In-Fusion Advantage PCR cloning kit (Clontech Laboratories, Inc.) to construct a human chimeric FR2-10 heavy chain expression vector. The obtained expression vector was designated as “pCMA-G1/cFR2-10”. The nucleotide sequence encoding the human chimeric FR2-10 heavy chain and the amino acid sequence of this heavy chain are shown in SEQ ID NOS: 35 and 36 (FIGS. 43 and 44), respectively, of the Sequence Listing.

[0565] Primer set for human chimeric FR2-10 heavy chain 5'-ccagatgggtgctgagcgaggtgcagctggtgagtgctggggagggc-3' (c10-HF: SEQ ID NO: 37 of the Sequence Listing; FIG. 45) 5'-cttggtgaggtgagctgacagtgactgaagttccttgacccaggc-3' (c10-HR: SEQ ID NO: 38 of the Sequence Listing; FIG. 46)

[0566] 4)-5 Construction of a Human Chimeric FR2-13 Light Chain Expression Vector

[0567] A DNA fragment comprising a light chain variable region-encoding cDNA was amplified using the FR2-13 light chain variable region-encoding cDNA obtained in Example 3) as a template, KOD-Plus-(Toyobo Co., Ltd.), and a primer set shown below, and inserted to the restriction enzyme BsiWI-cleaved site of the general-purpose vector pCMA-LK for chimeric and humanized antibody light chain expression using In-Fusion Advantage PCR cloning kit

(Clontech Laboratories, Inc.) to construct a human chimeric FR2-13 light chain expression vector. The obtained expression vector was designated as “pCMA-LK/cFR2-13”. The nucleotide sequence encoding the human chimeric FR2-13 light chain and the amino acid sequence of this light chain are shown in SEQ ID NOS: 39 and 40 (FIGS. 47 and 48), respectively, of the Sequence Listing.

[0568] Primer set for human chimeric FR2-13 light chain 5'-atctccgcgcggtacggcgacatccagatgacacagttccagttcc-3' (c13-LF: SEQ ID NO: 41 of the Sequence Listing; FIG. 49) 5'-ggagggggcgccacagcccggtttcagttccagcttggtcccaac-3' (c13-LR: SEQ ID NO: 42 of the Sequence Listing; FIG. 50)

[0569] 4)-6 Construction of a Human Chimeric FR2-13 Heavy Chain Expression Vector

[0570] A DNA fragment comprising a heavy chain variable region-encoding cDNA was amplified using the FR2-13 heavy chain variable region-encoding cDNA obtained in Example 3) as a template, KOD-Plus-(Toyobo Co., Ltd.), and a primer set shown below, and inserted to the restriction enzyme BspI-cleaved site of the chimeric and humanized IgG1 type heavy chain expression vector pCMA-G1 using In-Fusion Advantage PCR cloning kit (Clontech Laboratories, Inc.) to construct a human chimeric FR2-13 heavy chain expression vector. The obtained expression vector was designated as “pCMA-G1/cFR2-13”. The nucleotide sequence encoding the human chimeric FR2-13 heavy chain and the amino acid sequence of this heavy chain are shown in SEQ ID NOS: 43 and 44 (FIGS. 51 and 52), respectively, of the Sequence Listing.

[0571] Primer set for human chimeric FR2-13 heavy chain 5'-ccagatgggtgctgagccaggttaagctgctgagctggggctgag-3' (c13-HF: SEQ ID NO: 45 of the Sequence Listing; FIG. 53) 5'-cttggtgaggtgagctgagctgacagtgaccagagtgcttgcccccag-3' (c13-HR: SEQ ID NO: 46 of the Sequence Listing; FIG. 54)

[0572] 4)-7 Construction of a Human Chimeric FR2-14 Light Chain Expression Vector

[0573] A DNA fragment comprising a light chain variable region-encoding cDNA was amplified using the FR2-14 light chain variable region-encoding cDNA obtained in Example 3) as a template, KOD-Plus-(Toyobo Co., Ltd.), and a primer set shown below, and inserted to the restriction enzyme BsiWI-cleaved site of the general-purpose vector pCMA-LK for chimeric and humanized antibody light chain expression using In-Fusion Advantage PCR cloning kit (Clontech Laboratories, Inc.) to construct a human chimeric FR2-14 light chain expression vector. The obtained expression vector was designated as “pCMA-LK/cFR2-14”. The nucleotide sequence encoding the human chimeric FR2-14 light chain and the amino acid sequence of this light chain are shown in SEQ ID NOS: 47 and 48 (FIGS. 55 and 56), respectively, of the Sequence Listing.

[0574] Primer set for human chimeric FR2-14 light chain 5'-atctccgcgcggtacggcgacatccagatgacacagttccagttcc-3' (c13-LF: SEQ ID NO: 41 of the Sequence Listing; FIG. 49) 5'-ggagggggcgccacagcccggtttcagttccagcttggtcccaac-3' (c14-LR: SEQ ID NO: 49 of the Sequence Listing; FIG. 57)

[0575] 4)-8 Construction of a Human Chimeric FR2-14 Heavy Chain Expression Vector

[0576] A DNA fragment comprising a heavy chain variable region-encoding cDNA was amplified using the FR2-14 heavy chain variable region-encoding cDNA obtained in Example 3) as a template, KOD-Plus-(Toyobo Co., Ltd.), and a primer set shown below, and inserted to the restriction enzyme BspI-cleaved site of the chimeric and humanized

IgG1 type heavy chain expression vector pCMA-G1 using In-Fusion Advantage PCR cloning kit (Clontech Laboratories, Inc.) to construct a human chimeric FR2-14 heavy chain expression vector. The obtained expression vector was designated as "pCMA-G1/cFR2-14". The nucleotide sequence encoding the human chimeric FR2-14 heavy chain and the amino acid sequence of this heavy chain are shown in SEQ ID NOs: 50 and 51 (FIGS. 58 and 59), respectively, of the Sequence Listing.

[0577] Primer set for human chimeric FR2-14 heavy chain 5'-ccagatgggtgctgagccagggttaagctgctgcagctggggctgag-3' (c13-HF: SEQ ID NO: 45 of the Sequence Listing; FIG. 53) 5'-cttggtggaggtgagctgacagtgaccagagtgccctggcccccag-3' (c13-HR: SEQ ID NO: 46 of the Sequence Listing; FIG. 54)

[0578] 4)-9 Preparation of a Human Chimeric Anti-FGFR2 Antibody

[0579] 4)-9-1 Production of a Human Chimeric Anti-FGFR2 Antibody

[0580] FreeStyle 293F cells (Invitrogen Corp.) were sub-cultured and cultured according to the manual.

[0581] 1.2×10^9 FreeStyle 293F cells (Invitrogen Corp.) in the logarithmic growth phase were inoculated to a 3-L Fernbach Erlenmeyer Flask (Corning Inc.), adjusted to 1.0×10^6 cells/ml by dilution with FreeStyle 293 expression medium (Invitrogen Corp.), and then shake-cultured at 90 rpm at 37° C. for 1 hour in an 8% CO₂ incubator. 3.6 mg of polyethyleneimine (Polysciences #24765) was dissolved in 20 ml of Opti-Pro SFM medium (Invitrogen Corp.). Next, each H chain expression vector (0.4 mg) and each L chain expression vector (0.8 mg) prepared using PureLink HiPure Plasmid kit (Invitrogen Corp.) were suspended in 20 ml of Opti-Pro SFM medium (Invitrogen Corp.). 20 ml of the expression vector/Opti-Pro SFM mixed solution was added to 20 ml of the polyethyleneimine/Opti-Pro SFM mixed solution, and the mixture was gently stirred, left for 5 minutes, and then added to the FreeStyle 293F cells. The cells were shake-cultured at 90 rpm at 37° C. for 7 days in an 8% CO₂ incubator, and the obtained culture supernatant was filtered through Disposable Capsule Filter (ADVANTEC #CCS-045-EIH).

[0582] The human chimeric FR2-10 antibody obtained by the combination of pCMA-G1/cFR2-10 and pCMA-LK/cFR2-10 was designated as "cFR2-10". The human chimeric FR2-13 antibody obtained by the combination of pCMA-G1/cFR2-13 and pCMA-LK/cFR2-13 was designated as "cFR2-13". The human chimeric FR2-14 antibody obtained by the combination of pCMA-G1/cFR2-14 and pCMA-LK/cFR2-14 was designated as "cFR2-14".

[0583] 4)-9-2 Purification of a Human Chimeric Anti-FGFR2 Antibody

[0584] Each culture supernatant obtained in Example 4)-9-1 was purified by two steps using rProtein A affinity chromatography (at 4 to 6° C.) and ceramic hydroxyapatite (at room temperature). Buffer replacement steps after the rProtein A affinity chromatography purification and after the ceramic hydroxyapatite purification were carried out at room temperature. First, 1100 to 1200 ml of the culture supernatant was applied to MabSelect SuRe (manufactured by GE Healthcare Bio-Sciences Corp., HiTrap column; volume 1 mlx2 connected) equilibrated with PBS. After entry of the whole culture solution into the column, the column was washed with 15 to 30 ml of PBS. Next, antibody-containing fractions were collected by elution with a 2 M arginine hydrochloride solution (pH 4.0). The fractions were buffer-

replaced with 5 mM sodium phosphate, 50 mM MES, and 20 mM NaCl (pH 6.5) using a desalting column (manufactured by GE Healthcare Bio-Sciences Corp., HiTrap Desalting column; volume 5 mlx2 connected). The buffer-replaced antibody solution was further applied to a ceramic hydroxyapatite column (Bio-Rad Laboratories, Inc., Bio-Scale CHT2-1 Hydroxyapatite Column; volume 2 ml) equilibrated with a buffer of 5 mM NaPi, 50 mM MES, and 20 mM NaCl (pH 6.5). Antibody-containing fractions were collected by linear concentration gradient elution using sodium chloride. The fractions were buffer-replaced with CBS (10 mM citrate buffer solution and 140 mM sodium chloride, pH 6.0) using a desalting column (manufactured by GE Healthcare Bio-Sciences Corp., HiTrap Desalting column; volume 5 mlx2 connected). Finally, the fractions were concentrated and adjusted to an IgG concentration of 1.0 mg/ml or higher using Centrifugal UF Filter Device VIVASPIN 20 (molecular weight cutoff: 30K, Sartorius Japan K.K., at 4° C.), and used as a purified sample.

Example 5

In Vitro Activity of Human Chimeric Anti-FGFR2 Antibodies (cFR2-10, cFR2-13, and cFR2-14)

[0585] 5)-1 Antigen Binding Activity of Human Chimeric Anti-FGFR2 Antibodies (cFR2-10, cFR2-13, and cFR2-14)

[0586] 293 α cells (described in Example 1)-6) were adjusted to 5×10^5 cells/ml in a DMEM medium containing 10% FBS. pcDNA-DEST40-FGFR2 IIIb or pcDNA-DEST40-FGFR2 IIIc was transfected thereto using Lipofectamine 2000 (manufactured by Invitrogen Corp.). The resulting cells were dispensed in an amount of 100 μ l/well to a 96-well plate (manufactured by Corning Inc.) and cultured overnight at 37° C. under 5% CO₂ conditions in a DMEM medium containing 10% FBS. The obtained transfected cells were used in the attached state in Cell-ELISA. After removal of the culture supernatant, the cFR2-10, cFR2-13, or cFR2-14 antibody was added at a final concentration of 2 μ g/ml to the pcDNA-DEST40-FGFR2 IIIb- or pcDNA-DEST40-FGFR2 IIIc-transfected cells, and the plate was left standing at 4° C. for 1 hour. The cells in the wells were washed once with PBS containing 5% FBS. Then, Anti-Human IgG-Peroxidase antibody produced in goat (manufactured by Sigma-Aldrich Corp.) diluted 500-fold with PBS containing 5% FBS was added thereto, and the plate was left standing at 4° C. for 1 hour. The cells in the wells were washed 5 times with PBS containing 5% FBS. Then, an OPD chromogenic solution (OPD solution (o-phenylenediamine dihydrochloride (manufactured by Wako Pure Chemicals Industries, Ltd.) and H₂O₂ dissolved at concentrations of 0.4 mg/ml and 0.6% (v/v), respectively, in 0.05 M trisodium citrate and 0.1 M disodium hydrogen phosphate dodecahydrate, pH 4.5)) was added thereto at a concentration of 100 μ l/well. Color reaction was performed with occasional stirring and stopped by the addition of 1 M HCl at a concentration of 100 μ l/well. Then, the absorbance was measured at 490 nm using a plate reader (ARVO; PerkinElmer, Inc.). As shown in FIG. 5, the cFR2-10 antibody selectively bound to FGFR2 IIIb, while the cFR2-13 and cFR2-14 antibodies bound to both FGFR2 IIIb and FGFR2 IIIc.

[0587] 5)-2 Signal-Neutralizing Effects of Human Chimeric Anti-FGFR2 Antibodies (cFR2-10, cFR2-13, and cFR2-14)

[0588] In order to evaluate the signal-neutralizing effects of the obtained antibodies by the Elk1 luciferase reporter gene assay, 293 α cells were transfected with pcDNA-DEST40-FGFR2 IIIb or pcDNA-DEST40-FGFR2 IIIc constructed in Example 1)-3-1 by the method shown in Example 1)-6-2, and cultured overnight at 37° C. under 5% CO₂ conditions. On the next day, the culture supernatant was removed, and the cells were then preincubated for 1 hour with the cFR2-10, cFR2-13, or cFR2-14 antibody (final concentration: 0.05 to 5 μ g/ml) diluted with DMEM containing 2% FBS. Subsequently, a ligand human FGF7 (manufactured by R&D systems, Inc.) or human FGF9 (manufactured by PeproTech Inc.) was added at a final concentration of 10 ng/ml to each well. After incubation for 6 hours, cell lysates were prepared and assayed for firefly luciferase activity (specific signal) and *Renilla* luciferase activity (signal for normalization) using Dual-luciferase reporter assay system (manufactured by Promega Corp.). The firefly/*Renilla* ratio was calculated to normalize data on each well. As shown in FIG. 6A, cFR2-10, cFR2-13, and cFR2-14 inhibited ligand FGF7 dependent reporter activation in the FGFR2 IIIb-expressing cells. As shown in FIG. 6B, cFR2-13 and cFR2-14 inhibited ligand FGF9 dependent reporter activation in the FGFR2 IIIc-expressing cells. These results demonstrated that these antibodies have the effect of inhibiting the activation of FGFR2 by its ligand.

[0589] 5)-3 ADCC Activity of Human Chimeric Anti-FGFR2 Antibodies (cFR2-10, cFR2-13, and cFR2-14)

[0590] 5)-3-1 Preparation of Target Cells

[0591] 293FT cells (Invitrogen Corp.) were cotransfected with pLenti6/V5-GW/lacZ and ViraPower™ Packaging Mix (Invitrogen Corp.) according to the attached protocols to prepare a recombinant lentivirus expressing the β -galactosidase gene. 293T cells were infected by the obtained recombinant lentivirus according to the protocol of ViraPower Lentiviral Expression Systems (Invitrogen Corp.). Virus-infected cells were selected using 10 μ g/ml Blasticidin (Invitrogen Corp.) to obtain a line stably expressing β -galactosidase. These 293T cells stably expressing β -galactosidase were used as target cells in the assay of ADCC activity.

[0592] 5)-3-2 Preparation of Target Cells

[0593] The stably β -galactosidase-expressing 293T cells (hereinafter, referred to as 293T-lacZ) obtained in Example 5)-3-1 were inoculated to a 225-cm² flask in an amount of 1 $\times$ 10⁷ cells/ml in a DMEM medium containing 10% FBS. After overnight culture at 37° C., pcDNA-DEST40-FGFR2 IIIb was transfected to the cells using Lipofectamine 2000 (manufactured by Invitrogen Corp.), and the cells were cultured at 37° C. for 2 days under 5% CO₂ conditions in a DMEM medium containing 10% FBS and then dissociated and recovered from the flask using TrypLE Express (manufactured by Invitrogen Corp.). The cells were washed twice with phenol red-free RPMI1640 containing 5% FBS (hereinafter, referred to as a “medium for ADCC”). The number of live cells was counted by the trypan blue dye exclusion test. The cells were resuspended to 1 $\times$ 10⁵ cells/ml in a medium for ADCC and used as target cells.

[0594] 5)-3-3 Preparation of Effector Cells

[0595] Uncharacterized Cryopreserved PBMC (manufactured by Cellular Technology Ltd.) was suspended in a

phenol red-free RPMI1640 medium (manufactured by Invitrogen Corp.) containing 10% FBS, centrifuged, and then resuspended. The number of live cells was counted by the trypan blue dye exclusion test. After centrifugation, the medium was removed, and the cells were suspended and adjusted to a live cell density of 2.3 $\times$ 10⁶ cells/ml in a medium for ADCC and used as effector cells.

[0596] 5)-3-4 ADCC Assay

[0597] The 293T-lacZ cells prepared in Example 5)-3-2 were added at a concentration of 50 μ l/well to a 96-well U-bottomed microplate. The cFR2-10, cFR2-13, cFR2-14, or human control antibody (hIgG) diluted to 1 to 100 ng/ml (final concentration) with a medium for ADCC was added thereto at a concentration of 50 μ l/well, and the plate was left standing at 4° C. for 1 hour. The effector cells prepared in Example 5)-3-3 were further added thereto at a concentration of 75 μ l/well. The plate was centrifuged at 1200 rpm at room temperature for 5 minutes, followed by overnight culture at 37° C. under 5% CO₂ conditions. On the next day, 50 μ l of the supernatant in each well was recovered into a white plate (manufactured by Corning Inc.). A solution of β -Glo assay system (manufactured by Promega Corp.) was added thereto at a concentration of 50 μ l/well. The luminescence intensity was measured using a plate reader (ENVISION; manufactured by PerkinElmer, Inc.). The percentage of cells lysed by ADCC activity was calculated according to the following expression:

$$\text{Percentage of cells lysed (\%)} = (A-B)/(C-B) \times 100$$

[0598] A: Count of sample wells

[0599] B: Average of spontaneous release (wells supplemented with neither the antibody nor the effector cells) counts (n=3). The same operation as in the sample well was performed except that 50 μ l and 75 μ l of a medium for ADCC were added instead of the antibody and the effector cells, respectively.

[0600] C: Average of maximum release (wells containing target cells lysed in a surfactant) counts (n=3). 50 μ l and 75 μ l of a medium for ADCC were added instead of the antibody and the effector cells, respectively. For the assay, 175 μ l of the β -Glo assay system solution was added to each well containing the target cells and mixed therewith. A 100 μ l aliquot thereof was added to a white plate to carry out the assay.

[0601] As shown in FIG. 7, cFR2-10, cFR2-13, and cFR2-14 had ADCC activity against the FGFR2 IIIb-expressing cells.

Example 6

In Vivo Antitumor Activity of Human Chimeric Anti-FGFR2 Antibodies (cFR2-10, cFR2-13, and cFR2-14)

[0602] 5 $\times$ 10⁶ cells of a human stomach cancer line SNU-16 (purchased from ATCC) were suspended in 50% Matrigel (purchased from Nippon Becton Dickinson Company, Ltd.) and subcutaneously transplanted to the axillary region of each nude mouse (CAnN.Cg-Foxnltm/CrJ, purchased from Charles River Laboratories Japan Inc.). The mice were grouped according to their tumor volumes. Seven, 11, 14, and 18 days after transplantation, each human chimeric anti-FGFR2 antibody (cFR2-10, cFR2-13, or cFR2-14) was intraperitoneally administered at a dose of 1.5 or 15 mg/kg to the cancer-bearing mice (n=8). The major axis and minor

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axis of the transplanted tumor were measured twice a week using an electronic digital caliper (manufactured by Mitsutoyo Corp.). The tumor volume was calculated according to the following expression:

$$\text{Tumor volume (mm}^3\text{)} = \frac{1}{2} \times \text{Minor axis (mm)} \times \text{Minor axis (mm)} \times \text{Major axis (mm)}$$

[0603] The results for the cFR2-10 antibody are shown in FIG. 8-A. The percentage of tumor growth inhibition at 21 days after transplantation (final assay day) was 55% for the 1.5 mg/kg administration group and 35% for the 15 mg/kg administration group.

[0604] The results for the cFR2-13 antibody are shown in FIG. 8-B. The percentage of tumor growth inhibition at 21 days after transplantation (final assay day) was 57% for the 1.5 mg/kg administration group and 46% for the 15 mg/kg administration group.

[0605] The results for the cFR2-14 antibody are shown in FIG. 8-C. The percentage of tumor growth inhibition at 21 days after transplantation (final assay day) was 34% for the 1.5 mg/kg administration group and 53% for the 15 mg/kg administration group.

Example 7

Design of a Humanized Version (hFR2-14) of the Human Chimeric Anti-FGFR2 Antibody (cFR2-14)

[0606] 7)-1 Molecular Modeling of the FR2-14 Variable Region

[0607] The molecular modeling of the cFR2-14 variable regions was carried out by a method generally known as homology modeling (Methods in Enzymology, 203, 121-153, (1991)). The variable regions of FR2-14 determined above were compared with the primary sequences (three-dimensional structures derived from X-ray crystal structures are available) of human immunoglobulin variable regions registered in Protein Data Bank (Nuc. Acid Res. 28, 235-242 (2000)). As a result, 1ZAN was selected because it had the highest sequence homology to the light chain variable region of cFR2-14. Also, 1CT8 was selected because of its highest sequence homology to the heavy chain variable region of cFR2-14. The three-dimensional structures of framework regions were prepared as a "framework model" by combining the coordinates of 1ZAN and 1CT8 corresponding to the light and heavy chains of cFR2-14. The CDRs of cFR2-14 were assigned as clusters 11A, 7A, 10A, 10A, and 10A to CDRL1, CDRL2, CDRL3, CDRH1, and CDRH2, respectively, according to the classification of Thornton et al. (J. Mol. Biol., 263, 800-815, (1996)). Its CDRH3 was classified into k(6)-according to the H3 rule (FEBS letter, 399, 1-8 (1996)). Subsequently, the typical conformation of each CDR was incorporated into the framework model.

[0608] Finally, energy calculation for excluding disadvantageous interatomic contact was conducted in order to obtain possible molecular models of the cFR2-14 variable regions in terms of energy. These procedures were performed using a commercially available protein three-dimensional structure prediction program Prime and conformation search program MacroModel (Schrodinger, LLC).

[0609] 7)-2 Design of an Amino Acid Sequence of Humanized FR2-14

[0610] The humanized FR2-14 antibody was constructed by a method generally known as CDR grafting (Proc. Natl.

Acad. Sci. USA 86, 10029-10033 (1989)). An acceptor antibody was selected on the basis of the homology of amino acids in framework regions.

[0611] The sequences of the cFR2-14 framework regions were compared with the sequences of all human frameworks registered in the Kabat database (Nuc. Acid Res., 29, 205-206 (2001)) of antibody amino acid sequences. As a result, an FV/IL-2'CL antibody was selected as an acceptor due to its 72% sequence homology as to framework regions. The amino acid residues of the framework regions in FV/IL-2'CL were aligned with the amino acid residues of the cFR2-14 framework regions to identify the positions of amino acids that did not match there between. The positions of these residues were analyzed using the three-dimensional model of cFR2-14 constructed above. Then, the donor residues to be grafted onto the acceptor were selected according to the criteria provided by Queen et al. (Proc. Natl. Acad. Sci. USA 86, 10029-10033 (1989)).

[0612] Some donor residues thus selected were transferred to the acceptor antibody to construct the humanized FR2-14 sequence as described in the Examples below.

[0613] In addition, 1 to 3 amino acid residues in each CDR of cFR2-14 were substituted by different amino acid residues to construct a humanized FR2-14 sequence containing modified CDRs as described in the Examples below.

[0614] 7)-3 Humanization of the FR2-14 Light Chain

[0615] 7)-3-1 hFR2-14_L1 Type Light Chain:

[0616] A humanized FR2-14 light chain designed by the replacement of amino acid positions 29 (alanine), 35 (leucine), 37 (glutamic acid), 38 (threonine), 42 (glutamic acid), 62 (asparagine), 90 (glutamine), 92 (serine), 94 (lysine), 96 (asparagine), 100 (serine), 103 (valine), 105 (serine), 107 (phenylalanine), 121 (alanine), 125 (leucine), 127 (leucine), and 130 (alanine) in the cFR2-14 light chain shown in SEQ ID NO: 48 of the Sequence Listing with serine, valine, aspartic acid, arginine, threonine, lysine, aspartic acid, threonine, threonine, serine, proline, phenylalanine, threonine, tyrosine, glutamine, valine, isoleucine, and threonine, respectively, was designated as an "hFR2-14_L1 type light chain".

[0617] A nucleotide sequence encoding the hFR2-14_L1 type light chain is shown in SEQ ID NO: 72 of the Sequence Listing. Nucleotide positions 61 to 705 encode a mature light chain produced by the cleavage of the signal sequence. Also, the amino acid sequence of the hFR2-14_L1 type light chain is shown in SEQ ID NO: 73 of the Sequence Listing. Amino acid positions 21 to 235 represent a mature light chain produced by the cleavage of the signal sequence. The sequences of SEQ ID NOs: 72 and 73 are further defined in FIGS. 80 and 81, respectively.

[0618] 7)-4 Humanization of the FR2-14 Heavy Chain

[0619] 7)-4-1 hFR2-14_H1 Type Heavy Chain:

[0620] A humanized FR2-14 heavy chain designed by the replacement of amino acid positions 22 (lysine), 24 (leucine), 30 (leucine), 31 (valine), 39 (leucine), 43 (threonine), 56 (leucine), 57 (lysine), 59 (valine), 62 (proline), 63 (serine), 64 (threonine), 67 (isoleucine), 86 (lysine), 87 (alanine), 94 (phenylalanine), 95 (serine), 101 (aspartic acid), 106 (threonine), 110 (alanine) and 114 (phenylalanine) in the cFR2-14 heavy chain shown in SEQ ID NO: 51 of the Sequence Listing with glutamine, valine, valine, lysine, valine, alanine, valine, arginine, alanine, glutamine, glycine, leucine, methionine, arginine, valine, serine, threo-

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nine, glutamic acid, arginine, threonine and tyrosine, respectively, was designated as an “hFR2-14_H1 type heavy chain”.

[0621] A nucleotide sequence encoding the hFR2-14_H1 type heavy chain is shown in SEQ ID NO: 74 of the Sequence Listing. Nucleotide positions 58 to 1401 encode a mature heavy chain produced by the cleavage of the signal sequence. Also, the amino acid sequence of the hFR2-14_H1 type heavy chain is shown in SEQ ID NO: 75 of the Sequence Listing. Amino acid positions 20 to 467 represent a mature heavy chain produced by the cleavage of the signal sequence. The sequences of SEQ ID NOs: 74 and 75 are further defined in FIGS. 82 and 83, respectively.

[0622] 7)-4-2 hFR2-14_H2 Type Heavy Chain:

[0623] A humanized FR2-14 heavy chain designed by the replacement of amino acid positions 22 (lysine), 24 (leucine), 30 (leucine), 31 (valine), 39 (leucine), 43 (threonine), 56 (leucine), 57 (lysine), 59 (valine), 62 (proline), 63 (serine), 64 (threonine), 67 (isoleucine), 86 (lysine), 87 (alanine), 91 (valine), 94 (phenylalanine), 95 (serine), 101 (aspartic acid), 106 (threonine), 110 (alanine) and 114 (phenylalanine) in the cFR2-14 heavy chain shown in SEQ ID NO: 51 of the Sequence Listing with glutamine, valine, valine, lysine, valine, alanine, valine, arginine, alanine, isoleucine, methionine, arginine, valine, serine, threonine, glutamic acid, arginine, threonine and tyrosine, respectively, was designated as an “hFR2-14_H2 type heavy chain”.

[0624] A nucleotide sequence encoding the hFR2-14_H2 type heavy chain is shown in SEQ ID NO: 76 of the Sequence Listing. Nucleotide positions 58 to 1401 encode a mature heavy chain produced by the cleavage of the signal sequence. Also, the amino acid sequence of the hFR2-14_H2 type heavy chain is shown in SEQ ID NO: 77 of the Sequence Listing. Amino acid positions 20 to 467 represent a mature heavy chain produced by the cleavage of the signal sequence. The sequences of SEQ ID NOs: 76 and 77 are further defined in FIGS. 84 and 85, respectively.

[0625] 7)-4-3 hFR2-14_H3 Type Heavy Chain:

[0626] A humanized FR2-14 heavy chain designed by the replacement of amino acid positions 22 (lysine), 24 (leucine), 30 (leucine), 31 (valine), 39 (leucine), 43 (threonine), 56 (leucine), 57 (lysine), 59 (valine), 67 (isoleucine), 86 (lysine), 87 (alanine), 94 (phenylalanine), 95 (serine), 101 (aspartic acid), 106 (threonine), 110 (alanine) and 114 (phenylalanine) in the cFR2-14 heavy chain shown in SEQ ID NO: 51 of the Sequence Listing with glutamine, valine, valine, lysine, valine, alanine, valine, arginine, alanine, methionine, arginine, valine, serine, threonine, glutamic acid, arginine, threonine and tyrosine, respectively, was designated as an “hFR2-14_H3 type heavy chain”.

[0627] A nucleotide sequence encoding the hFR2-14_H3 type heavy chain is shown in SEQ ID NO: 78 of the Sequence Listing. Nucleotide positions 58 to 1401 encode a mature heavy chain produced by the cleavage of the signal sequence. Also, the amino acid sequence of the hFR2-14_H3 type heavy chain is shown in SEQ ID NO: 79 of the Sequence Listing. Amino acid positions 20 to 467 represent a mature heavy chain produced by the cleavage of the signal sequence. The sequences of SEQ ID NOs: 78 and 79 are further defined in FIGS. 86 and 87, respectively.

[0628] 7)-4-4 hFR2-14_H4 Type Heavy Chain:

[0629] A humanized FR2-14 heavy chain designed by the replacement of amino acid positions 22 (lysine), 24 (leu-

cine), 30 (leucine), 31 (valine), 39 (leucine), 43 (threonine), 56 (leucine), 57 (lysine), 59 (valine), 64 (threonine), 67 (isoleucine), 86 (lysine), 87 (alanine), 94 (phenylalanine), 95 (serine), 101 (aspartic acid), 106 (threonine), 110 (alanine), 114 (phenylalanine) and 125 (threonine) in the cFR2-14 heavy chain shown in SEQ ID NO: 51 of the Sequence Listing with glutamine, valine, valine, lysine, valine, alanine, valine, arginine, alanine, isoleucine, methionine, arginine, valine, serine, threonine, glutamic acid, arginine, threonine, tyrosine and alanine, respectively, was designated as an “hFR2-14_H4 type heavy chain”.

[0630] A nucleotide sequence encoding the hFR2-14_H4 type heavy chain is shown in SEQ ID NO: 80 of the Sequence Listing. Nucleotide positions 58 to 1401 encode a mature heavy chain produced by the cleavage of the signal sequence. Also, the amino acid sequence of the hFR2-14_H4 type heavy chain is shown in SEQ ID NO: 81 of the Sequence Listing. Amino acid positions 20 to 467 represent a mature heavy chain produced by the cleavage of the signal sequence. The sequences of SEQ ID NOs: 80 and 81 are further defined in FIGS. 88 and 89, respectively.

[0631] 7)-4-5 hFR2-14_H5 Type Heavy Chain:

[0632] A humanized FR2-14 heavy chain designed by the replacement of amino acid positions 22 (lysine), 24 (leucine), 30 (leucine), 31 (valine), 39 (leucine), 43 (threonine), 56 (leucine), 57 (lysine), 59 (valine), 67 (isoleucine), 86 (lysine), 87 (alanine), 94 (phenylalanine), 95 (serine), 101 (aspartic acid), 106 (threonine), 110 (alanine), 114 (phenylalanine) and 118 (aspartic acid) in the cFR2-14 heavy chain shown in SEQ ID NO: 51 of the Sequence Listing with glutamine, valine, valine, lysine, valine, alanine, valine, arginine, alanine, methionine, arginine, valine, serine, threonine, glutamic acid, arginine, threonine, tyrosine and glutamic acid, respectively, was designated as an “hFR2-14_H5 type heavy chain”.

[0633] A nucleotide sequence encoding the hFR2-14_H5 type heavy chain is shown in SEQ ID NO: 82 of the Sequence Listing. Nucleotide positions 58 to 1401 encode a mature heavy chain produced by the cleavage of the signal sequence. Also, the amino acid sequence of the hFR2-14_H5 type heavy chain is shown in SEQ ID NO: 83 of the Sequence Listing. Amino acid positions 20 to 467 represent a mature heavy chain produced by the cleavage of the signal sequence. The sequences of SEQ ID NOs: 82 and 83 are further defined in FIGS. 90 and 91, respectively.

[0634] 7)-4-6 hFR2-14_H6 Type Heavy Chain:

[0635] A humanized FR2-14 heavy chain designed by the replacement of amino acid positions 22 (lysine), 24 (leucine), 30 (leucine), 31 (valine), 39 (leucine), 43 (threonine), 56 (leucine), 57 (lysine), 59 (valine), 67 (isoleucine), 86 (lysine), 87 (alanine), 94 (phenylalanine), 95 (serine), 101 (aspartic acid), 106 (threonine), 110 (alanine), 114 (phenylalanine) and 119 (glycine) in the cFR2-14 heavy chain shown in SEQ ID NO: 51 of the Sequence Listing with glutamine, valine, valine, lysine, valine, alanine, valine, arginine, alanine, methionine, arginine, valine, serine, threonine, glutamic acid, arginine, threonine, tyrosine and alanine, respectively, was designated as an “hFR2-14_H6 type heavy chain”.

[0636] A nucleotide sequence encoding the hFR2-14_H6 type heavy chain is shown in SEQ ID NO: 84 of the Sequence Listing. Nucleotide positions 58 to 1401 encode a mature heavy chain produced by the cleavage of the signal sequence. Also, the amino acid sequence of the hFR2-14_H6

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type heavy chain is shown in SEQ ID NO: 85 of the Sequence Listing. Amino acid positions 20 to 467 represent a mature heavy chain produced by the cleavage of the signal sequence. The sequences of SEQ ID NOs: 84 and 85 are further defined in FIGS. 92 and 93, respectively.

[0637] 7)-4-7 hFR2-14_H7 Type Heavy Chain:

[0638] A humanized FR2-14 heavy chain designed by the replacement of amino acid positions 22 (lysine), 24 (leucine), 30 (leucine), 31 (valine), 39 (leucine), 43 (threonine), 56 (leucine), 57 (lysine), 59 (valine), 67 (isoleucine), 86 (lysine), 87 (alanine), 94 (phenylalanine), 95 (serine), 101 (aspartic acid), 106 (threonine), 110 (alanine), 114 (phenylalanine) and 119 (glycine) in the cFR2-14 heavy chain shown in SEQ ID NO: 51 of the Sequence Listing with glutamine, valine, valine, lysine, valine, alanine, valine, arginine, alanine, methionine, arginine, valine, serine, threonine, glutamic acid, arginine, threonine, tyrosine and glutamic acid, respectively, was designated as an “hFR2-14_H7 type heavy chain”.

[0639] A nucleotide sequence encoding the hFR2-14_H7 type heavy chain is shown in SEQ ID NO: 86 of the Sequence Listing. Nucleotide positions 58 to 1401 encode a mature heavy chain produced by the cleavage of the signal sequence. Also, the amino acid sequence of the hFR2-14_H7 type heavy chain is shown in SEQ ID NO: 87 of the Sequence Listing. Amino acid positions 20 to 467 represent a mature heavy chain produced by the cleavage of the signal sequence. The sequences of SEQ ID NOs: 86 and 87 are further defined in FIGS. 94 and 95, respectively.

[0640] 7)-4-8 hFR2-14_H8 Type Heavy Chain:

[0641] A humanized FR2-14 heavy chain designed by the replacement of amino acid positions 22 (lysine), 24 (leucine), 30 (leucine), 31 (valine), 39 (leucine), 43 (threonine), 56 (leucine), 57 (lysine), 59 (valine), 67 (isoleucine), 86 (lysine), 87 (alanine), 94 (phenylalanine), 95 (serine), 101 (aspartic acid), 106 (threonine), 110 (alanine), 114 (phenylalanine) and 119 (glycine) in the cFR2-14 heavy chain shown in SEQ ID NO: 51 of the Sequence Listing with glutamine, valine, valine, lysine, valine, alanine, valine, arginine, alanine, methionine, arginine, valine, serine, threonine, glutamic acid, arginine, threonine, tyrosine and phenylalanine, respectively, was designated as an “hFR2-14_H8 type heavy chain”.

[0642] A nucleotide sequence encoding the hFR2-14_H8 type heavy chain is shown in SEQ ID NO: 88 of the Sequence Listing. Nucleotide positions 58 to 1401 encode a mature heavy chain produced by the cleavage of the signal sequence. Also, the amino acid sequence of the hFR2-14_H8 type heavy chain is shown in SEQ ID NO: 89 of the Sequence Listing. Amino acid positions 20 to 467 represent a mature heavy chain produced by the cleavage of the signal sequence. The sequences of SEQ ID NOs: 88 and 89 are further defined in FIGS. 96 and 97, respectively.

[0643] 7)-4-9 hFR2-14_H9 Type Heavy Chain:

[0644] A humanized FR2-14 heavy chain designed by the replacement of amino acid positions 22 (lysine), 24 (leucine), 30 (leucine), 31 (valine), 39 (leucine), 43 (threonine), 56 (leucine), 57 (lysine), 59 (valine), 67 (isoleucine), 86 (lysine), 87 (alanine), 94 (phenylalanine), 95 (serine), 101 (aspartic acid), 106 (threonine), 110 (alanine), 114 (phenylalanine) and 119 (glycine) in the cFR2-14 heavy chain shown in SEQ ID NO: 51 of the Sequence Listing with glutamine, valine, valine, lysine, valine, alanine, valine, arginine, alanine, methionine, arginine, valine, serine, threo-

nine, glutamic acid, arginine, threonine, tyrosine and histidine, respectively, was designated as an “hFR2-14_H9 type heavy chain”.

[0645] A nucleotide sequence encoding the hFR2-14_H9 type heavy chain is shown in SEQ ID NO: 90 of the Sequence Listing. Nucleotide positions 58 to 1401 encode a mature heavy chain produced by the cleavage of the signal sequence. Also, the amino acid sequence of the hFR2-14_H9 type heavy chain is shown in SEQ ID NO: 91 of the Sequence Listing. Amino acid positions 20 to 467 represent a mature heavy chain produced by the cleavage of the signal sequence. The sequences of SEQ ID NOs: 90 and 91 are further defined in FIGS. 98 and 99, respectively.

[0646] 7)-4-10 hFR2-14_H10 Type Heavy Chain:

[0647] A humanized FR2-14 heavy chain designed by the replacement of amino acid positions 22 (lysine), 24 (leucine), 30 (leucine), 31 (valine), 39 (leucine), 43 (threonine), 56 (leucine), 57 (lysine), 59 (valine), 67 (isoleucine), 86 (lysine), 87 (alanine), 94 (phenylalanine), 95 (serine), 101 (aspartic acid), 106 (threonine), 110 (alanine), 114 (phenylalanine) and 119 (glycine) in the cFR2-14 heavy chain shown in SEQ ID NO: 51 of the Sequence Listing with glutamine, valine, valine, lysine, valine, alanine, valine, arginine, alanine, methionine, arginine, valine, serine, threonine, glutamic acid, arginine, threonine, tyrosine and isoleucine, respectively, was designated as an “hFR2-14_H10 type heavy chain”.

[0648] A nucleotide sequence encoding the hFR2-14_H10 type heavy chain is shown in SEQ ID NO: 92 of the Sequence Listing. Nucleotide positions 58 to 1401 encode a mature heavy chain produced by the cleavage of the signal sequence. Also, the amino acid sequence of the hFR2-14_H10 type heavy chain is shown in SEQ ID NO: 93 of the Sequence Listing. Amino acid positions 20 to 467 represent a mature heavy chain produced by the cleavage of the signal sequence. The sequences of SEQ ID NOs: 92 and 93 are further defined in FIGS. 100 and 101, respectively.

[0649] 7)-4-11 hFR2-14_H11 Type Heavy Chain:

[0650] A humanized FR2-14 heavy chain designed by the replacement of amino acid positions 22 (lysine), 24 (leucine), 30 (leucine), 31 (valine), 39 (leucine), 43 (threonine), 56 (leucine), 57 (lysine), 59 (valine), 67 (isoleucine), 86 (lysine), 87 (alanine), 94 (phenylalanine), 95 (serine), 101 (aspartic acid), 106 (threonine), 110 (alanine), 114 (phenylalanine) and 119 (glycine) in the cFR2-14 heavy chain shown in SEQ ID NO: 51 of the Sequence Listing with glutamine, valine, valine, lysine, valine, alanine, valine, arginine, alanine, methionine, arginine, valine, serine, threonine, glutamic acid, arginine, threonine, tyrosine and lysine, respectively, was designated as an “hFR2-14_H11 type heavy chain”.

[0651] A nucleotide sequence encoding the hFR2-14_H11 type heavy chain is shown in SEQ ID NO: 94 of the Sequence Listing. Nucleotide positions 58 to 1401 encode a mature heavy chain produced by the cleavage of the signal sequence. Also, the amino acid sequence of the hFR2-14_H11 type heavy chain is shown in SEQ ID NO: 95 of the Sequence Listing. Amino acid positions 20 to 467 represent a mature heavy chain produced by the cleavage of the signal sequence. The sequences of SEQ ID NOs: 94 and 95 are further defined in FIGS. 102 and 103, respectively.

[0652] 7)-4-12 hFR2-14_H12 Type Heavy Chain: A humanized FR2-14 heavy chain designed by the replacement of amino acid positions 22 (lysine), 24 (leucine), 30

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(leucine), 31 (valine), 39 (leucine), 43 (threonine), 56 (leucine), 57 (lysine), 59 (valine), 67 (isoleucine), 86 (lysine), 87 (alanine), 94 (phenylalanine), 95 (serine), 101 (aspartic acid), 106 (threonine), 110 (alanine), 114 (phenylalanine) and 119 (glycine) in the cFR2-14 heavy chain shown in SEQ ID NO: 51 of the Sequence Listing with glutamine, valine, valine, lysine, valine, alanine, valine, arginine, alanine, methionine, arginine, valine, serine, threonine, glutamic acid, arginine, threonine, tyrosine and leucine, respectively, was designated as an “hFR2-14_H12 type heavy chain”.

[0653] A nucleotide sequence encoding the hFR2-14_H12 type heavy chain is shown in SEQ ID NO: 96 of the Sequence Listing. Nucleotide positions 58 to 1401 encode a mature heavy chain produced by the cleavage of the signal sequence. Also, the amino acid sequence of the hFR2-14_H12 type heavy chain is shown in SEQ ID NO: 97 of the Sequence Listing. Amino acid positions 20 to 467 represent a mature heavy chain produced by the cleavage of the signal sequence. The sequences of SEQ ID NOs: 96 and 97 are further defined in FIGS. 104 and 105, respectively.

[0654] 7)-4-13 hFR2-14_H13 type heavy chain: A humanized FR2-14 heavy chain designed by the replacement of amino acid positions 22 (lysine), 24 (leucine), 30 (leucine), 31 (valine), 39 (leucine), 43 (threonine), 56 (leucine), 57 (lysine), 59 (valine), 67 (isoleucine), 86 (lysine), 87 (alanine), 94 (phenylalanine), 95 (serine), 101 (aspartic acid), 106 (threonine), 110 (alanine), 114 (phenylalanine) and 119 (glycine) in the cFR2-14 heavy chain shown in SEQ ID NO: 51 of the Sequence Listing with glutamine, valine, valine, lysine, valine, alanine, valine, arginine, alanine, methionine, arginine, valine, serine, threonine, glutamic acid, arginine, threonine, tyrosine and methionine, respectively, was designated as an “hFR2-14_H13 type heavy chain”.

[0655] A nucleotide sequence encoding the hFR2-14_H13 type heavy chain is shown in SEQ ID NO: 98 of the Sequence Listing. Nucleotide positions 58 to 1401 encode a mature heavy chain produced by the cleavage of the signal sequence. Also, the amino acid sequence of the hFR2-14_H13 type heavy chain is shown in SEQ ID NO: 99 of the Sequence Listing. Amino acid positions 20 to 467 represent a mature heavy chain produced by the cleavage of the signal sequence. The sequences of SEQ ID NOs: 98 and 99 are further defined in FIGS. 106 and 107, respectively.

[0656] 7)-4-14 hFR2-14_H14 type heavy chain: A humanized FR2-14 heavy chain designed by the replacement of amino acid positions 22 (lysine), 24 (leucine), 30 (leucine), 31 (valine), 39 (leucine), 43 (threonine), 56 (leucine), 57 (lysine), 59 (valine), 67 (isoleucine), 86 (lysine), 87 (alanine), 94 (phenylalanine), 95 (serine), 101 (aspartic acid), 106 (threonine), 110 (alanine), 114 (phenylalanine) and 119 (glycine) in the cFR2-14 heavy chain shown in SEQ ID NO: 51 of the Sequence Listing with glutamine, valine, valine, lysine, valine, alanine, valine, arginine, alanine, methionine, arginine, valine, serine, threonine, glutamic acid, arginine, threonine, tyrosine and glutamine, respectively, was designated as an “hFR2-14_H14 type heavy chain”.

[0657] A nucleotide sequence encoding the hFR2-14_H14 type heavy chain is shown in SEQ ID NO: 100 of the Sequence Listing. Nucleotide positions 58 to 1401 encode a mature heavy chain produced by the cleavage of the signal sequence. Also, the amino acid sequence of the hFR2-14_H14 type heavy chain is shown in SEQ ID NO: 101 of the Sequence Listing. Amino acid positions 20 to 467 represent a mature heavy chain produced by the cleavage of the signal

sequence. The sequences of SEQ ID NOs: 100 and 101 are further defined in FIGS. 108 and 109, respectively.

[0658] 7)-4-15 hFR2-14_H15 type heavy chain: A humanized FR2-14 heavy chain designed by the replacement of amino acid positions 22 (lysine), 24 (leucine), 30 (leucine), 31 (valine), 39 (leucine), 43 (threonine), 56 (leucine), 57 (lysine), 59 (valine), 67 (isoleucine), 86 (lysine), 87 (alanine), 94 (phenylalanine), 95 (serine), 101 (aspartic acid), 106 (threonine), 110 (alanine), 114 (phenylalanine) and 119 (glycine) in the cFR2-14 heavy chain shown in SEQ ID NO: 51 of the Sequence Listing with glutamine, valine, valine, lysine, valine, alanine, valine, arginine, alanine, methionine, arginine, valine, serine, threonine, glutamic acid, arginine, threonine, tyrosine and arginine, respectively, was designated as an “hFR2-14_H15 type heavy chain”.

[0659] A nucleotide sequence encoding the hFR2-14_H15 type heavy chain is shown in SEQ ID NO: 102 of the Sequence Listing. Nucleotide positions 58 to 1401 encode a mature heavy chain produced by the cleavage of the signal sequence. Also, the amino acid sequence of the hFR2-14_H15 type heavy chain is shown in SEQ ID NO: 103 of the Sequence Listing. Amino acid positions 20 to 467 represent a mature heavy chain produced by the cleavage of the signal sequence. The sequences of SEQ ID NOs: 102 and 103 are further defined in FIGS. 110 and 111, respectively.

[0660] 7)-4-16 hFR2-14_H16 type heavy chain: A humanized FR2-14 heavy chain designed by the replacement of amino acid positions 22 (lysine), 24 (leucine), 30 (leucine), 31 (valine), 39 (leucine), 43 (threonine), 56 (leucine), 57 (lysine), 59 (valine), 67 (isoleucine), 86 (lysine), 87 (alanine), 94 (phenylalanine), 95 (serine), 101 (aspartic acid), 106 (threonine), 110 (alanine), 114 (phenylalanine) and 119 (glycine) in the cFR2-14 heavy chain shown in SEQ ID NO: 51 of the Sequence Listing with glutamine, valine, valine, lysine, valine, alanine, valine, arginine, alanine, methionine, arginine, valine, serine, threonine, glutamic acid, arginine, threonine, tyrosine and valine, respectively, was designated as an “hFR2-14_H16 type heavy chain”.

[0661] A nucleotide sequence encoding the hFR2-14_H16 type heavy chain is shown in SEQ ID NO: 104 of the Sequence Listing. Nucleotide positions 58 to 1401 encode a mature heavy chain produced by the cleavage of the signal sequence. Also, the amino acid sequence of the hFR2-14_H16 type heavy chain is shown in SEQ ID NO: 105 of the Sequence Listing. Amino acid positions 20 to 467 represent a mature heavy chain produced by the cleavage of the signal sequence. The sequences of SEQ ID NOs: 104 and 105 are further defined in FIGS. 112 and 113, respectively.

[0662] 7)-4-17 hFR2-14_H17 type heavy chain: A humanized FR2-14 heavy chain designed by the replacement of amino acid positions 22 (lysine), 24 (leucine), 30 (leucine), 31 (valine), 39 (leucine), 43 (threonine), 56 (leucine), 57 (lysine), 59 (valine), 67 (isoleucine), 86 (lysine), 87 (alanine), 94 (phenylalanine), 95 (serine), 101 (aspartic acid), 106 (threonine), 110 (alanine), 114 (phenylalanine) and 119 (glycine) in the cFR2-14 heavy chain shown in SEQ ID NO: 51 of the Sequence Listing with glutamine, valine, valine, lysine, valine, alanine, valine, arginine, alanine, methionine, arginine, valine, serine, threonine, glutamic acid, arginine, threonine, tyrosine and tryptophan, respectively, was designated as an “hFR2-14_H17 type heavy chain”.

[0663] A nucleotide sequence encoding the hFR2-14_H17 type heavy chain is shown in SEQ ID NO: 106 of the Sequence Listing. Nucleotide positions 58 to 1401 encode a

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mature heavy chain produced by the cleavage of the signal sequence. Also, the amino acid sequence of the hFR2-14_H17 type heavy chain is shown in SEQ ID NO: 107 of the Sequence Listing. Amino acid positions 20 to 467 represent a mature heavy chain produced by the cleavage of the signal sequence. The sequences of SEQ ID NOs: 106 and 107 are further defined in FIGS. 114 and 115, respectively.

[0664] 7)-4-18 hFR2-14_H18 type heavy chain: A humanized FR2-14 heavy chain designed by the replacement of amino acid positions 22 (lysine), 24 (leucine), 30 (leucine), 31 (valine), 39 (leucine), 43 (threonine), 56 (leucine), 57 (lysine), 59 (valine), 67 (isoleucine), 86 (lysine), 87 (alanine), 94 (phenylalanine), 95 (serine), 101 (aspartic acid), 106 (threonine), 110 (alanine), 114 (phenylalanine) and 119 (glycine) in the cFR2-14 heavy chain shown in SEQ ID NO: 51 of the Sequence Listing with glutamine, valine, valine, lysine, valine, alanine, valine, arginine, alanine, methionine, arginine, valine, serine, threonine, glutamic acid, arginine, threonine, tyrosine and tyrosine, respectively, was designated as an “hFR2-14_H18 type heavy chain”.

[0665] A nucleotide sequence encoding the hFR2-14_H18 type heavy chain is shown in SEQ ID NO: 108 of the Sequence Listing. Nucleotide positions 58 to 1401 encode a mature heavy chain produced by the cleavage of the signal sequence. Also, the amino acid sequence of the hFR2-14_H18 type heavy chain is shown in SEQ ID NO: 109 of the Sequence Listing. Amino acid positions 20 to 467 represent a mature heavy chain produced by the cleavage of the signal sequence. The sequences of SEQ ID NOs: 108 and 109 are further defined in FIGS. 116 and 117, respectively.

Example 8

Production and Expression of Humanized Antibody (hFR2-14) of Rat Anti-Human FGFR2 Antibody FR2-14

[0666] 8)-1 Construction of a Light Chain Expression Vector for Humanized Antibody (hFR2-14) of Rat Anti-Human FGFR2 Antibody FR2-14

[0667] 8)-1-1 Construction of a hFR2-14_L1 Type Light Chain Expression Vector

[0668] A DNA comprising a gene encoding the hFR2-14_L1 type light chain variable region shown in amino acid positions 21 to 130 of SEQ ID NO: 73 was synthesized and cleaved with a restriction enzyme BsiWI. The resulting DNA fragment was inserted to the restriction enzyme BsiWI-cleaved site of the general-purpose vector (pCMA-LK) for chimeric and humanized antibody light chain expression to construct an hFR2-14_L1 type light chain expression vector. The obtained expression vector was designated as “pCMA-LK/hFR2-14_L1”.

[0669] 8)-2 Construction of a Heavy Chain Expression Vector for Humanized Antibody (hFR2-14) of Rat Anti-Human FGFR2 Antibody FR2-14

[0670] 8)-2-1 Construction of hFR2-14_H1, hFR2-14_H3, and hFR2-14_H4 Type Heavy Chain Expression Vectors

[0671] A DNA comprising a gene encoding each of the hFR2-14_H1, hFR2-14_H3, and hFR2-14_H4 type heavy chain variable regions shown in amino acid positions 20 to 137 of SEQ ID NO: 75, amino acid positions 20 to 137 of SEQ ID NO: 79, and amino acid positions 20 to 137 of SEQ ID NO: 81, respectively, of the Sequence Listing was synthesized and cleaved with a restriction enzyme BlnI. The resulting DNA fragment was inserted to the restriction enzyme BlnI-cleaved site of the general-purpose vector

(pCMA-G1) for humanized antibody heavy chain expression to construct hFR2-14_H1, hFR2-14_H3, and hFR2-14_H4 type heavy chain expression vectors. The obtained expression vectors were designated as “pCMA-G1/hFR2-14_H1”, “pCMA-G1/hFR2-14_H3”, and “pCMA-G1/hFR2-14_H4”, respectively.

[0672] 8)-2-2 Construction of a hFR2-14_H2 Type Heavy Chain Expression Vector

[0673] An hFR2-14_H2 type heavy chain expression vector was constructed using pCMA-G1/hFR2-14_H1 constructed in Example 8)-2-1 as a template, a primer set shown below, and QuikChange XL Site-Directed Mutagenesis Kit (Agilent Technologies, Inc.). The obtained expression vector was designated a “pCMA-G1/hFR2-14_H2”. The nucleotide sequence of the hFR2-14_H2 type heavy chain is shown in SEQ ID NO: 76 of the Sequence Listing, and its amino acid sequence is shown in SEQ ID NO: 77.

Primer Set 5'-ggcagagtgcacctgacgcgcgacaagagcaccagcacc-3' (VH3A-F: SEQ ID NO: 110 of the Sequence Listing) 5'-gggtcgtggtgctctgtgcggcggtcagggtcactctgcc-3' (VH3A-R: SEQ ID NO: 111 of the Sequence Listing)

[0674] 8)-2-3 Construction of a hFR2-14_H5 Type Heavy Chain Expression Vector

[0675] The hFR2-14_H3 type heavy chain expression vector pCMA-G1/hFR2-14_H3 prepared in Example 8)-2-1 was used as a template and mutated using a primer set described below and KOD-Plus-Mutagenesis Kit (Toyobo Co., Ltd.) to construct an hFR2-14_H5 type heavy chain expression vector. The obtained expression vector was designated as “pCMA-G1/hFR2-14_H5”.

Primer Set: 5'-GAGGGCTACGGCGACTGGTTTCACATAC-3' (H5-F) 5'-GGTGGCGCAGTAGTACACGGCGGT-3' (H-R, which is used as a common primer in the description below)

[0676] 8)-2-4 Construction of a hFR2-14_H6 Type Heavy Chain Expression Vector

[0677] The hFR2-14_H3 type heavy chain expression vector pCMA-G1/hFR2-14_H3 prepared in Example 8)-2-1 was used as a template and mutated using a primer set described below and KOD-Plus-Mutagenesis Kit (Toyobo Co., Ltd.) to construct an hFR2-14_H6 type heavy chain expression vector. The obtained expression vector was designated as “pCMA-G1/hFR2-14_H6”.

Primer set:

5'-GACGCCTACGGCGACTGGTTTCACATAC-3' (H6-F)

5'-GGTGGCGCAGTAGTACACGGCGGT-3' (H-R)

[0678] 8)-2-5 Construction of a hFR2-14_H7 Type Heavy Chain Expression Vector

[0679] The hFR2-14_H3 type heavy chain expression vector pCMA-G1/hFR2-14_H3 prepared in Example 8)-2-1 was used as a template and mutated using a primer set described below and KOD-Plus-Mutagenesis Kit (Toyobo Co., Ltd.) to construct an hFR2-14_H7 type heavy chain expression vector. The obtained expression vector was designated as “pCMA-G1/hFR2-14_H7”.

Primer set:

5'-GACGAGTACGGCGACTGGTTTCACATAC-3' (H7-F)

5'-GGTGGCGCAGTAGTACACGGCGGT-3' (H-R)

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[0680] 8)-2-6 Construction of a hFR2-14_H8 Type Heavy Chain Expression Vector

[0681] The hFR2-14_H3 type heavy chain expression vector pCMA-G1/hFR2-14_H3 prepared in Example 8)-2-1 was used as a template and mutated using a primer set described below and KOD-Plus-Mutagenesis Kit (Toyobo Co., Ltd.) to construct an hFR2-14_H8 type heavy chain expression vector. The obtained expression vector was designated as “pCMA-G1/hFR2-14_H8”.

Primer set:
5'-GACTTCTACGGCGACTGGTTCACATAC-3' (H8-F)
5'-GGTGGCGCAGTAGTACACGGCGGT-3' (H-R)

[0682] 8)-2-7 Construction of a hFR2-14_H9 Type Heavy Chain Expression Vector

[0683] The hFR2-14_H3 type heavy chain expression vector pCMA-G1/hFR2-14_H3 prepared in Example 8)-2-1 was used as a template and mutated using a primer set described below and KOD-Plus-Mutagenesis Kit (Toyobo Co., Ltd.) to construct an hFR2-14_H9 type heavy chain expression vector. The obtained expression vector was designated as “pCMA-G1/hFR2-14_H9”.

Primer set:
5'-GACCACTACGGCGACTGGTTCACATAC-3' (H9-F)
5'-GGTGGCGCAGTAGTACACGGCGGT-3' (H-R)

[0684] 8)-2-8 Construction of a hFR2-14_H10 Type Heavy Chain Expression Vector

[0685] The hFR2-14_H3 type heavy chain expression vector pCMA-G1/hFR2-14_H3 prepared in Example 8)-2-1 was used as a template and mutated using a primer set described below and KOD-Plus-Mutagenesis Kit (Toyobo Co., Ltd.) to construct an hFR2-14_H10 type heavy chain expression vector. The obtained expression vector was designated as “pCMA-G1/hFR2-14_H10”.

Primer set:
5'-GACATCTACGGCGACTGGTTCACATAC-3' (H10-F)
5'-GGTGGCGCAGTAGTACACGGCGGT-3' (H-R)

[0686] 8)-2-9 Construction of a hFR2-14_H11 Type Heavy Chain Expression Vector

[0687] The hFR2-14_H3 type heavy chain expression vector pCMA-G1/hFR2-14_H3 prepared in Example 8)-2-1 was used as a template and mutated using a primer set described below and KOD-Plus-Mutagenesis Kit (Toyobo Co., Ltd.) to construct an hFR2-14_H11 type heavy chain expression vector. The obtained expression vector was designated as “pCMA-G1/hFR2-14_H11”.

Primer set:
5'-GACAAGTACGGCGACTGGTTCACATAC-3' (H11-F)
5'-GGTGGCGCAGTAGTACACGGCGGT-3' (H-R)

[0688] 8)-2-10 Construction of a hFR2-14_H12 Type Heavy Chain Expression Vector

[0689] The hFR2-14_H3 type heavy chain expression vector pCMA-G1/hFR2-14_H3 prepared in Example 8)-2-1 was used as a template and mutated using a primer set

described below and KOD-Plus-Mutagenesis Kit (Toyobo Co., Ltd.) to construct an hFR2-14_H12 type heavy chain expression vector. The obtained expression vector was designated as “pCMA-G1/hFR2-14_H12”.

Primer set:
5'-GACCTGTACGGCGACTGGTTCACATAC-3' (H12-F)
5'-GGTGGCGCAGTAGTACACGGCGGT-3' (H-R)

[0690] 8)-2-11 Construction of a hFR2-14_H13 Type Heavy Chain Expression Vector

[0691] The hFR2-14_H3 type heavy chain expression vector pCMA-G1/hFR2-14_H3 prepared in Example 8)-2-1 was used as a template and mutated using a primer set described below and KOD-Plus-Mutagenesis Kit (Toyobo Co., Ltd.) to construct an hFR2-14_H13 type heavy chain expression vector. The obtained expression vector was designated as “pCMA-G1/hFR2-14_H13”.

Primer set:
5'-GACATGTACGGCGACTGGTTCACATAC-3' (H13-F)
5'-GGTGGCGCAGTAGTACACGGCGGT-3' (H-R)

[0692] 8)-2-12 Construction of a hFR2-14_H14 Type Heavy Chain Expression Vector

[0693] The hFR2-14_H3 type heavy chain expression vector pCMA-G1/hFR2-14_H3 prepared in Example 8)-2-1 was used as a template and mutated using a primer set described below and KOD-Plus-Mutagenesis Kit (Toyobo Co., Ltd.) to construct an hFR2-14_H14 type heavy chain expression vector. The obtained expression vector was designated as “pCMA-G1/hFR2-14_H14”.

Primer set:
5'-GACCAGTACGGCGACTGGTTCACATAC-3' (H14-F)
5'-GGTGGCGCAGTAGTACACGGCGGT-3' (H-R)

[0694] 8)-2-13 Construction of a hFR2-14_H15 Type Heavy Chain Expression Vector

[0695] The hFR2-14_H3 type heavy chain expression vector pCMA-G1/hFR2-14_H3 prepared in Example 8)-2-1 was used as a template and mutated using a primer set described below and KOD-Plus-Mutagenesis Kit (Toyobo Co., Ltd.) to construct an hFR2-14_H15 type heavy chain expression vector. The obtained expression vector was designated as “pCMA-G1/hFR2-14_H15”.

Primer set:
5'-GACCGGTACGGCGACTGGTTCACATAC-3' (H15-F)
5'-GGTGGCGCAGTAGTACACGGCGGT-3' (H-R)

[0696] 8)-2-14 Construction of a hFR2-14_H16 Type Heavy Chain Expression Vector

[0697] The hFR2-14_H3 type heavy chain expression vector pCMA-G1/hFR2-14_H3 prepared in Example 8)-2-1 was used as a template and mutated using a primer set described below and KOD-Plus-Mutagenesis Kit (Toyobo Co., Ltd.) to construct an hFR2-14_H16 type heavy chain expression vector. The obtained expression vector was designated as “pCMA-G1/hFR2-14_H16”.

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Primer set:
5'-GACGTGTACGGCGACTGGTTCACATAC-3' (H16-F)
5'-GGTGGCGCAGTAGTACACGGCGGT-3' (H-R)

[0698] 8)-2-15 Construction of a hFR2-14_H17 Type Heavy Chain Expression Vector

[0699] The hFR2-14_H3 type heavy chain expression vector pCMA-G1/hFR2-14_H3 prepared in Example 8)-2-1 was used as a template and mutated using a primer set described below and KOD-Plus-Mutagenesis Kit (Toyobo Co., Ltd.) to construct an hFR2-14_H17 type heavy chain expression vector. The obtained expression vector was designated as "pCMA-G1/hFR2-14_H17".

Primer set:
5'-GACTGGTACGGCGACTGGTTCACATAC-3' (H17-F)
5'-GGTGGCGCAGTAGTACACGGCGGT-3' (H-R)

[0700] 8)-2-16 Construction of hFR2-14_H18 Type Heavy Chain Expression Vector

[0701] The hFR2-14_H3 type heavy chain expression vector pCMA-G1/hFR2-14_H3 prepared in Example 8)-2-1 was used as a template and mutated using a primer set described below and KOD-Plus-Mutagenesis Kit (Toyobo Co., Ltd.) to construct an hFR2-14_H18 type heavy chain expression vector. The obtained expression vector was designated as "pCMA-G1/hFR2-14_H18".

Primer set:
5'-GACTACTACGGCGACTGGTTCACATAC-3' (H18-F)
5'-GGTGGCGCAGTAGTACACGGCGGT-3' (H-R)

[0702] 8)-3 Preparation of Humanized FR2-14 Antibodies (FreeStyle 293F Cell)

[0703] 8)-3-1 Production of Humanized FR2-14 Antibody
[0704] FreeStyle 293F cells (Invitrogen Corp.) were subcultured and cultured according to the manual.

[0705] 1.2×10^9 FreeStyle 293F cells (Invitrogen Corp.) in the logarithmic growth phase were inoculated to a 3-L Fernbach Erlenmeyer Flask (Corning Inc.), adjusted to 1.0×10^6 cells/mL by dilution with FreeStyle 293 expression medium (Invitrogen Corp.), and then shake-cultured at 90 rpm at 37° C. for 1 hour in an 8% CO₂ incubator. 3.6 mg of polyethyleneimine (Polysciences #24765) was dissolved in 20 ml of Opti-Pro SFM medium (Invitrogen Corp.). Next, each H chain expression vector (0.4 mg) and the L chain expression vector (0.8 mg) prepared using PureLink HiPure Plasmid kit (Invitrogen Corp.) were suspended in 20 ml of Opti-Pro SFM medium (Invitrogen Corp.). 20 ml of the expression vector/Opti-Pro SFM mixed solution was added to 20 ml of the polyethyleneimine/Opti-Pro SFM mixed solution, and the mixture was gently stirred, further left for 5 minutes, and then added to the FreeStyle 293F cells. The cells were shake-cultured at 90 rpm at 37° C. for 7 days in an 8% CO₂ incubator, and the obtained culture supernatant was filtered through Disposable Capsule Filter (ADVANTEC #CCS-045-EIH).

[0706] The humanized FR2-14 antibodies obtained by the combination of pCMA-G1/hFR2-14_H5, pCMA-G1/hFR2-14_H6, pCMA-G1/hFR2-14_H7, pCMA-G1/hFR2-14_H8, pCMA-G1/hFR2-14_H9, pCMA-G1/hFR2-14_H10, pCMA-G1/hFR2-14_H11, pCMA-G1/hFR2-14_H12,

pCMA-G1/hFR2-14_H13, pCMA-G1/hFR2-14_H14, pCMA-G1/hFR2-14_H15, pCMA-G1/hFR2-14_H16, pCMA-G1/hFR2-14_H17 and pCMA-G1/hFR2-14_H18 with pCMA-LK/hFR2-14_L1 were designated as "hFR2-14_H5/L1", "hFR2-14_H6/L1", "hFR2-14_H7/L1", "hFR2-14_H8/L1", "hFR2-14_H9/L1", "hFR2-14_H10/L1", "hFR2-14_H11/L1", "hFR2-14_H12/L1", "hFR2-14_H13/L1", "hFR2-14_H14/L1", "hFR2-14_H15/L1", "hFR2-14_H16/L1", "hFR2-14_H17/L1" and "hFR2-14_H18/L1, respectively.

[0707] 8)-3-2 Purification of the Humanized FR2-14 Antibodies

[0708] Each antibody was purified from the culture supernatant obtained in Example 8)-3-1 by two steps using rProtein A affinity chromatography (at 4 to 6° C.) and ceramic hydroxyapatite (at room temperature). Buffer replacement steps after the rProtein A affinity chromatography purification and after the ceramic hydroxyapatite purification were carried out at 4 to 6° C. First, the culture supernatant was applied to MabSelect SuRe (manufactured by GE Healthcare Bio-Sciences Corp., HiTrap column) equilibrated with PBS. After entry of the whole culture solution in the column, the column was washed with PBS in an amount at least twice the column volume. Next, antibody-containing fractions were collected by elution with a 2 M arginine hydrochloride solution (pH 4.0). The fractions were buffer-replaced with PBS by dialysis (Thermo Fisher Scientific Inc., Slide-A-Lyzer Dialysis Cassette) and then diluted 5-fold with a buffer of 5 mM sodium phosphate and 50 mM MES (pH 7.0). The resulting antibody solution was applied to a ceramic hydroxyapatite column (Bio-Rad Laboratories, Inc., Bio-Scale CHT Type-I Hydroxyapatite Column) equilibrated with a buffer of 5 mM NaPi, 50 mM MES, and 30 mM NaCl (pH 7.0). Antibody-containing fractions were collected by linear concentration gradient elution using sodium chloride. The fractions were buffer-replaced with HBSor (25 mM histidine and 5% sorbitol, pH 6.0) by dialysis (Thermo Fisher Scientific Inc., Slide-A-Lyzer Dialysis Cassette). Finally, the fractions were concentrated and adjusted to an IgG concentration of 25 mg/ml or higher using Centrifugal UF Filter Device VIVASPIN 20 (molecular weight cutoff: UF10K, Sartorius Japan K.K., at 4° C.), and used as a purified sample.

Example 9

Preparation of a Humanized FR2-14 Antibody with a Regulated Sugar Chain Modification

[0709] The humanized antibody comprising the heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 97 (FIG. 105), and the light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73 (FIG. 81) was defucosylated according to a method known in the art to regulate the sugar chain modification of the antibody protein. The obtained antibody was designated as hFR2-14_H19/L1. This modified form was subjected to mass spectrometry. As a result, the peak of a fucose-containing H chain was equal to or lower than the detection limit. In the present invention, the antibody with regulated sugar chain modification, such as hFR2-14_H19/L1, is also referred to as an "antibody" or a "modified form of the antibody".

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Example 10

Physical Property Evaluation of a Humanized
Anti-Human FGFR2 Antibody (hFR2-14)

[0710] 10)-1 Biacore Assay of the Antigen Binding Activity of a Humanized Anti-Human FGFR2 Antibody (hFR2-14)

[0711] The antibody was assayed for its dissociation constant for an antigen (rhFGFR2 alpha (IIIb) Fc chimera or rhFGFR2 alpha (IIIc) Fc chimera) using Biacore 3000 (GE Healthcare Bio-Sciences Corp.) by the capture method, which involves capturing the antibody as a ligand onto an immobilized anti-human IgG(Fab) antibody and assaying the antigen as an analyte. Approximately 5000 RU of the anti-human IgG(Fab) antibody (Human Fab capture kit, GE Healthcare Bio-Sciences Corp.) was covalently bound to a sensor chip CM5 (BIAcore, Inc.) by the amine coupling method. Similarly, this antibody was immobilized onto a reference cell. The running buffer used was HBS-EP+ (10 mM HEPES (pH 7.4), 0.15 M NaCl, 3 mM EDTA, and 0.05% Surfactant P20). A 1 µg/mL antibody solution of the purified antibody was added onto the anti-human IgG(Fab) antibody-immobilized chip, at a flow rate of 10 µL/min for 60 seconds or the culture supernatant containing the antibody was added for 60 seconds. Then, serial dilutions (0.3 to 500 nM) of the antigen were added thereto at a flow rate of 30 µL/min for 180 seconds. Subsequently, the dissociation phase was monitored for 300 seconds. 10 mM Gly-HCl (pH 2.1) was added twice thereto as a regenerating solution at a flow rate of 10 µL/min for 60 seconds. The data was analyzed using the Bivalent binding model of analytical software (BIAevaluation software, version 4.1) to calculate an association rate constant k_{on} , a dissociation rate constant k_{off} , and a dissociation constant (KD; $KD=k_{off}/k_{on}$).

[0712] 10)-1-1 Binding Activity Evaluation of 4 Types of Humanized Anti-FGFR2 Antibodies (hFR2-14_H1/L1 to hFR2-14_H4/L1) and a Human Chimeric Anti-FGFR2 Antibody (cFR2-14)

[0713] Four types of humanized anti-FGFR2 antibodies (hFR2-14_H1/L1 to hFR2-14_H4/L1) and the human chimeric anti-FGFR2 antibody (cFR2-14) were expressed and purified by the methods of Examples 8)-3 and 4)-9 and evaluated for their binding activity against each human FGFR2 variant protein by the method shown in Example 10)-1. The Biacore assay results are shown in FIG. 122.

[0714] 10)-1-2 Binding Activity Evaluation of 15 Types of Humanized Anti-FGFR2 Antibodies (hFR2-14_H3/L1 and hFR2-14_H5/L1 to hFR2-14_H18/L1)

[0715] Fifteen types of humanized anti-FGFR2 antibodies (hFR2-14_H3/L1 and hFR2-14_H5/L1 to hFR2-14_H18/L1) were expressed by the method of Example 8)-3, and the culture supernatant containing each antibody was used in the evaluation of binding activity against the FGFR2 IIIc protein by the method shown in Example 10)-1. The Biacore assay results are shown in FIG. 123.

[0716] 10)-2 Study on the Selective Binding Activity of Humanized Anti-Human FGFR2 Antibodies (hFR2-14_H3/L1, hFR2-14_H8/L1, and hFR2-14_H12/L1) Against Human FGFR2

[0717] 10)-2-1 Construction of a Human FGFR1 IIIb Expression Vector (pcDNA-DEST40-FGFR1 IIIb)

[0718] A cDNA encoding a human FGFR1 IIIb variant protein (a protein comprising the amino acid sequence of the FGFR1 IIIb domain (AAB19502) between an amino acid

sequence of positions 1 to 310 and an amino acid sequence of positions 359 to 820 of isoform 2 (NP_056934)) was cloned into a pcDNA-DEST40 vector to construct pcDNA-DEST40-FGFR1 IIIb.

[0719] 10)-2-2 Cell-ELISA

[0720] Various human FGFR expression vectors constructed in Examples 1)-3-1, 2)-1-1, and 10)-2-1 were separately transfected to 293α cells (described in Example 1)-6) using Lipofectamine 2000 (manufactured by Life Technologies Corp.). The resulting cells were dispensed in an amount of 100 µL/well to a 96-well plate (manufactured by Corning Inc.) and cultured overnight at 37° C. under 5% CO₂ conditions in a DMEM medium containing 10% FBS. After removal of the culture supernatant, a solution of hFR2-14_H3/L1, hFR2-14_H8/L1, or hFR2-14_H12/L1 diluted to 3 µg/mL with PBS containing 5% FBS was added at a concentration of 50 µL/well to the plate, and the plate was left standing at 4° C. for 1 hour. The cells in the wells were washed twice with PBS containing 5% FBS. Then, Anti-human IgG-Peroxidase conjugate antibody produced in goat (manufactured by Sigma-Aldrich Corp.) and diluted 2000-fold with PBS containing 5% FBS was added thereto, and the plate was left standing at 4° C. for 1 hour. The cells in the wells were washed 3 times with PBS containing 5% FBS. Then, an OPD chromogenic solution (OPD solution (o-phenylenediamine dihydrochloride (manufactured by Wako Pure Chemicals Industries, Ltd.) and H₂O₂ dissolved at concentrations of 0.4 mg/mL and 0.6% (v/v), respectively, in 0.05 M trisodium citrate and 0.1 M disodium hydrogen phosphate dodecahydrate, pH 4.5)) was added thereto at a concentration of 100 µL/well. Color reaction was performed with occasional stirring and stopped by the addition of 1 M HCl at a concentration of 100 µL/well. Then, the absorbance was measured at 490 nm using a plate reader (ARVO; PerkinElmer, Inc.). As seen from FIG. 124, the hFR2-14_H3/L1, hFR2-14_H8/L1, and hFR2-14_H12/L1 antibodies were shown to specifically bind to both human FGFR2 IIIb and FGFR2 IIIc.

[0721] 10)-3 Thermal Stability Assay of a Humanized Anti-Human FGFR2 Antibody (hFR2-14) Using Differential Scanning Calorimetry (DSC)

[0722] Thermal stability was assayed using differential scanning calorimetry (DSC). Each sample was dissolved at a concentration of 0.5 mg/mL in an HBSor buffer solution (prepared to contain 25 mM histidine (pH 6.0) and 5% sorbitol), and 400 µL of the sample solution was used in the DSC assay. The DSC assay conditions were set as follows: an initial temperature of 20° C.; a final temperature of 100° C.; a rate of temperature rise of 200° C./hour; a filtering time of 2 seconds; and a feedback mode of Low. The reference solution used was HBSor. VP-Capillary DSC Platform manufactured by GE Healthcare Bio-Sciences Corp. (USA) was used as a DSC assay apparatus in all experiments. Baseline correction was conducted by the subtraction of the baseline (scan curve obtained from the reference solution also charged into a sample cell) from a scan curve obtained from the sample solution. Next, concentration calibration was conducted using molar concentration calculated from the molecular weight of each sample. FIGS. 125A and 125B show the thermograms of various humanized FGFR2 antibodies. The thermal denaturation midpoint T_m is defined as the temperature at which the maximum peak in each thermogram exhibited a peak top. As shown in FIG. 125C, the hFR2-14_H1/L1 antibody had a T_m value of 87.6° C. The

hFR2-14_H2/L1 antibody had a T_m value of 87.2° C. The hFR2-14_H3/L1 antibody had a T_m value of 79.5° C. The hFR2-14_H4/L1 antibody had a T_m value of 81.6° C. The hFR2-14_H5/L1 antibody had a T_m value of 77.2° C. The hFR2-14_H8/L1 antibody had a T_m value of 81.0° C. The hFR2-14_H9/L1 antibody had a T_m value of 78.8° C. The hFR2-14_H11/L1 antibody had a T_m value of 80.3° C. The hFR2-14_H12/L1 antibody had a T_m value of 82.2° C. The hFR2-14_H19/L1 antibody had a T_m value of 82.2° C.

[0723] 10)-4 Binding Stability Test of a Humanized Anti-Human FGFR2 Antibody (hFR2-14) Using Biacore

[0724] The humanized anti-human FGFR2 antibody (hFR2-14) was evaluated for its antigen binding stability by a method described below.

[0725] Various humanized anti-FGFR2 antibodies (hFR2-14_H1/L1 to hFR2-14_H5/L1, hFR2-14_H8/L1, hFR2-14_H9/L1, hFR2-14_H11/L1, hFR2-14_H12/L1, and hFR2-14_H19/L1) and the human chimeric anti-FGFR2 antibody (cFR2-14) were expressed and purified by the methods of Examples 8)-3, 9), and 4)-9 and each dissolved at a concentration of 20 mg/mL in an HBSor buffer solution (prepared to contain 25 mM histidine (pH 6.0) and 5% sorbitol). The solutions were heated to 40° C. for 4 weeks to prepare degraded analytes. The analytes were assayed for their binding activity before and after degradation by the method shown in Example 10)-1 using Biacore. The Biacore assay results are shown in FIG. 126.

Example 11

Signal-Neutralizing Effect of a Humanized Anti-Human FGFR2 Antibody (hFR2-14)

[0726] 11)-1 Signal-Neutralizing Effects of Humanized Anti-FGFR2 Antibodies (hFR2-14_H1/L1, hFR2-14_H2/L1, hFR2-14_H3/L1, and hFR2-14_H4/L1) and Human Chimeric Anti-FGFR2 Antibody (cFR2-14)

[0727] In order to evaluate the signal-neutralizing effects of the humanized antibodies by the Elk1 luciferase reporter gene assay, 293α cells were cotransfected with pcDNA-DEST40-FGFR2 IIIb or pcDNA-DEST40-FGFR2 IIIC, pFA2-Elk1 (manufactured by Stratagene Corp.), pFR-Luc2CP, and pGL4.74[hRluc/TK] (manufactured by Promega Corp.) by the method shown in Example 1)-6-2, and cultured overnight at 37° C. under 5% CO₂ conditions. On the next day, the culture supernatant was removed, and the cells were then preincubated for 1 hour with the hFR2-14_H1/L1, hFR2-14_H2/L1, hFR2-14_H3/L1, hFR2-14_H4/L1, or cFR2-14 antibody diluted with DMEM containing 2% FBS. Subsequently, a ligand (human FGF7 or human FGF9, manufactured by PeproTech Inc.) was added at a final concentration of 10 ng/ml to each well. After incubation for 6 hours, firefly luciferase activity (specific signal) and *Renilla* luciferase activity (signal for normalization) were assayed using Dual-Glo Luciferase Assay System (manufactured by Promega Corp.). The firefly/*Renilla* ratio was calculated to normalize data on each well. As shown in FIG. 127A, hFR2-14_H1/L1, hFR2-14_H2/L1, hFR2-14_H3/L1, hFR2-14_H4/L1, and cFR2-14 inhibited ligand FGF7 dependent reporter activation in the FGFR2 IIIb-expressing cells. As shown in FIG. 127B, hFR2-14_H1/L1, hFR2-14_H2/L1, hFR2-14_H3/L1, hFR2-14_H4/L1, and cFR2-14 inhibited ligand FGF9 dependent reporter activity in the FGFR2 IIIC-expressing cells. These results demonstrated

that these antibodies have the effect of inhibiting the activation of FGFR2 by its ligand.

[0728] 11)-2 Signal-Neutralizing Effects of Humanized Anti-FGFR2 Antibodies (hFR2-14_H3/L1, hFR2-14_H5/L1, hFR2-14_H6/L1, hFR2-14_H7/L1, hFR2-14_H8/L1, hFR2-14_H9/L1, hFR2-14_H10/L1, hFR2-14_H11/L1, hFR2-14_H12/L1, hFR2-14_H13/L1, hFR2-14_H14/L1, hFR2-14_H15/L1, hFR2-14_H16/L1, hFR2-14_H17/L1, and hFR2-14_H18/L1)

[0729] In order to evaluate the signal-neutralizing effects of the humanized antibodies by the Elk1 luciferase reporter gene assay, 293α cells were cotransfected with pcDNA-DEST40-FGFR2 IIIb or pcDNA-DEST40-FGFR2 IIIC, pFA2-Elk1 (manufactured by Stratagene Corp.), pFR-Luc2CP, and pGL4.74[hRluc/TK] (manufactured by Promega Corp.) by the method shown in Example 1)-6-2, and cultured overnight at 37° C. under 5% CO₂ conditions. On the next day, the culture supernatant was removed, and the cells were then preincubated for 1 hour with the culture supernatant of the 293 FreeStyle cells (manufactured by Invitrogen Corp.) producing the antibodies hFR2-14_H3/L1, hFR2-14_H5/L1, hFR2-14_H6/L1, hFR2-14_H7/L1, hFR2-14_H8/L1, hFR2-14_H9/L1, hFR2-14_H10/L1, hFR2-14_H11/L1, hFR2-14_H12/L1, hFR2-14_H13/L1, hFR2-14_H14/L1, hFR2-14_H15/L1, hFR2-14_H16/L1, hFR2-14_H17/L1, and hFR2-14_H18/L1 (prepared in Example 8)-3-1) diluted with DMEM containing 2% FBS. Subsequently, a ligand (human FGF7, manufactured by R&D systems, Inc.) was added at a final concentration of 10 ng/ml to each well. After incubation for 6 hours, firefly luciferase activity (specific signal) and *Renilla* luciferase activity (signal for normalization) were assayed using Dual-Glo Luciferase Assay System (manufactured by Promega Corp.). The firefly/*Renilla* ratio was calculated to normalize data on each well. As shown in FIGS. 128A, 128B, and 128C, hFR2-14_H3/L1, hFR2-14_H5/L1, hFR2-14_H6/L1, hFR2-14_H7/L1, hFR2-14_H8/L1, hFR2-14_H9/L1, hFR2-14_H10/L1, hFR2-14_H11/L1, hFR2-14_H12/L1, hFR2-14_H13/L1, hFR2-14_H14/L1, hFR2-14_H15/L1, hFR2-14_H16/L1, hFR2-14_H17/L1, and hFR2-14_H18/L1 inhibited ligand FGF7 dependent reporter activation in the FGFR2 IIIb-expressing cells.

[0730] 11)-3 Signal-Neutralizing Effects of Humanized Anti-FGFR2 Antibodies (hFR2-14_H12/L1 and hFR2-14_H19/L1)

[0731] In order to evaluate the signal-neutralizing effects of the humanized antibodies by the Elk1 luciferase reporter gene assay, 293α cells were cotransfected with pcDNA-DEST40-FGFR2 IIIb or pcDNA-DEST40-FGFR2 IIIC, pFA2-Elk1 (manufactured by Stratagene Corp.), pFR-Luc2CP, and pGL4.74[hRluc/TK] (manufactured by Promega Corp.) by the method shown in Example 1)-6-2, and cultured overnight at 37° C. under 5% CO₂ conditions. On the next day, the culture supernatant was removed, and the cells were then preincubated for 1 hour with the hFR2-14_H12/L1 or hFR2-14_H19/L1 antibody (prepared in Examples 8) and 9)) diluted with DMEM containing 2% FBS. Subsequently, a ligand human FGF7 (manufactured by R&D systems, Inc.) or human FGF9 (manufactured by PeproTech Inc.) was added at a final concentration of 10 ng/ml to each well. After incubation for 6 hours, firefly luciferase activity (specific signal) and *Renilla* luciferase activity (signal for normalization) were assayed using Dual-Glo Luciferase Assay System (manufactured by Promega

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Corp.). The firefly/*Renilla* ratio was calculated to normalize data on each well. As shown in FIG. 129A, hFR2-14_H12/L1 and hFR2-14_H19/L1 inhibited ligand FGF7 dependent reporter activation in the FGFR2 IIIb-expressing cells. As shown in FIG. 129B, hFR2-14_H12/L1 and hFR2-14_H19/L1 inhibited ligand FGF9 dependent reporter activity in the FGFR2 IIIc-expressing cells. These results demonstrated that these antibodies have the effect of inhibiting the activation of FGFR2 by its ligand.

Example 12

ADCC Activity of a Humanized Anti-Human FGFR2 Antibody (hFR2-14)

[0732] 12)-1 ADCC Activity of Humanized Anti-FGFR2 Antibodies (hFR2-14_H1/L1, hFR2-14_H2/L1, hFR2-14_H3/L1, and hFR2-14_H4/L1) and Human Chimeric Anti-FGFR2 Antibody (cFR2-14) Against a FGFR2-Overexpressing Cell

[0733] The FGFR2 IIIb-expressing 293T-lacZ cells prepared by the method of Example 5)-3-2 were added at a concentration of 50 μ l/well to a 96-well U-bottomed microplate. hFR2-14_H1/L1, hFR2-14_H2/L1, hFR2-14_H3/L1, hFR2-14_H4/L1, cFR2-14, or human IgG diluted to 1 to 100 ng/ml (final concentration) with a medium for ADCC described in Example 5)-3-2 was added thereto at a concentration of 50 μ l/well, and the plate was left standing at 4° C. for 1 hour. The effector cells of Example 5)-3-3 were further added thereto at a concentration of 75 μ l/well. The plate was centrifuged at 1200 rpm at room temperature for 5 minutes, followed by overnight culture at 37° C. under 5% CO₂ conditions. On the next day, 50 μ l of the supernatant in each well was recovered into a white plate (manufactured by Corning Inc.). A solution of β -Glo assay system (manufactured by Promega Corp.) was added thereto at a concentration of 50 μ l/well. The luminescence intensity was measured using a plate reader (ENVISION; manufactured by PerkinElmer, Inc.). The percentage of cells lysed by ADCC activity was calculated according to the following expression:

$$\text{Percentage of cells lysed (\%)} = (A-B)/(C-B) \times 100$$

[0734] A: Count of sample well

[0735] B: Average of spontaneous release (wells supplemented with neither the antibody nor the effector cells) counts (n=3). The same operation as in the sample well was performed except that 50 μ l and 75 μ l of a medium for ADCC were added instead of the antibody and the effector cells, respectively.

[0736] C: Average of maximum release (wells containing target cells lysed in a surfactant) counts (n=3). 50 μ l and 75 μ l of a medium for ADCC were added instead of the antibody and the effector cells, respectively. For the assay, 175 μ l of the β -Glo assay system solution was added to each well containing the target cells and mixed therewith. A 100 μ l aliquot thereof was added to a white plate to carry out the assay.

[0737] As shown in FIGS. 130A and 130B, hFR2-14_H1/L1, hFR2-14_H2/L1, hFR2-14_H3/L1, hFR2-14_H4/L1, and cFR2-14 had ADCC activity against the FGFR2 IIIb-expressing cells.

[0738] 12)-2 ADCC Activity of Humanized Anti-FGFR2 Antibodies (hFR2-14_H3/L1, hFR2-14_H8/L1, and hFR2-14_H12/L1) Against a FGFR2-Expressing Cancer Cell Line

[0739] 12)-2-1 Preparation of Target Cells

[0740] KATO III, NCI-H716, or SNU16 cells were washed twice with a medium for ADCC and passed through a cell strainer (manufactured by Becton Dickinson and Company). Then, the number of live cells was counted by the trypan blue dye exclusion test. The cells were resuspended to 1×10^5 cells/ml and used as target cells.

[0741] 12)-2-2 Preparation of PBMC Cells

[0742] 25 ml of healthy human blood was gradually layered over 20 ml of Lymphosepar I (manufactured by Immuno-Biological Laboratories Co., Ltd.), followed by centrifugation at 1500 rpm at room temperature for 30 minutes. A cell layer located between plasma and Lymphosepar I (manufactured by Immuno-Biological Laboratories Co., Ltd.) was recovered using a dropper and suspended in 20 ml of a phenol red-free RPMI1640 medium (manufactured by Life Technologies Corp.) containing 10% FBS. The suspension was centrifuged at 1500 rpm for 5 minutes. After removal of the supernatant, the cells were washed twice by the addition of 20 ml of a medium for ADCC. The number of live cells was counted by the trypan blue dye exclusion test. After centrifugation, the medium was removed, and the cells were suspended in a medium for ADCC and used as effector cells.

[0743] 12)-2-3 Evaluation of ADCC Activity

[0744] The NCI-H716 cells prepared by the method of Example 12)-2-1 were added at a concentration of 50 μ l/well to a 96-well U-bottomed microplate. hFR2-14_H3/L1, hFR2-14_H8/L1, hFR2-14_H12/L1, or human IgG diluted to 1 to 1000 ng/ml (final concentration) with a medium for ADCC was added thereto at a concentration of 50 μ l/well, and the plate was left standing at 4° C. for 1 hour. The PBMC cells (13.4×10^6 cells/ml) of Example 12)-2-2 were further added thereto at a concentration of 75 μ l/well. The plate was centrifuged at 1200 rpm at room temperature for 5 minutes, followed by overnight culture at 37° C. under 5% CO₂ conditions. On the next day, 10 $\times$ Lysis Solution attached to CytoTox 96 Non-Radioactive Cytotoxicity Assay (manufactured by Promega Corp.) kit was added at a concentration of 17.5 μ l/well to the wells containing only the target cells and the medium and stirred, and the plate was then left standing at 37° C. for 45 minutes under 5% CO₂ conditions. After centrifugation at 200 g at room temperature for 4 minutes, 50 μ l of the supernatant in each well was recovered into a 96-well flat-bottomed microplate (manufactured by Corning Inc.). Substrate Mix was added thereto at a concentration of 50 μ l/well, and the plate was left standing at room temperature for 30 minutes while shielded from light. Stop Solution was further added thereto at a concentration of 50 μ l/well. The absorbance was measured at 490 nm using a plate reader (ARVO; manufactured by PerkinElmer, Inc.). The percentage of cells lysed by ADCC activity was calculated according to the following expression:

$$\text{Cytotoxicity (\%)} = (A-B-C)/(D-C) \times 100$$

[0745] A: Count of sample well

[0746] B: Average of spontaneous release (correction of culture solution-containing wells from effector cell-containing wells) counts from effector cells (n=3).

[0747] C: Average of spontaneous release (correction of culture solution-containing wells from target cell-containing wells) counts from target cells (n=3).

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[0748] D: Average of maximum release (correction of wells containing a culture solution lysed in a surfactant from wells containing target cells lysed in a surfactant) counts ($n=3$).

[0749] As shown in FIG. 131, hFR2-14_H3/L1, hFR2-14_H8/L1, and hFR2-14_H12/L1 had ADCC activity against the FGFR2-expressing cancer cell line NCI-H716 cells.

[0750] 12)-3 ADCC Activity of Humanized Anti-FGFR2 Antibodies (hFR2-14_H12/L1 and hFR2-14_H19/L1) Against a FGFR2-Expressing Cancer Cell Line

[0751] The KATO III, NCI-H716, or SNU16 cells prepared by the method of Example 12)-2-1 were added at a concentration of 50 μ l/well to a 96-well U-bottomed microplate. hFR2-14_H12/L1 or hFR2-14_H19/L1 (prepared in Examples 8) and 9)) or human IgG diluted to 1 to 1000 ng/ml (final concentration) with a medium for ADCC was added thereto at a concentration of 50 μ l/well, and the plate was left standing at 4° C. for 1 hour. The effector cells (20×10^6 cells/ml) of Example 12)-2-2 were further added thereto at a concentration of 75 μ l/well. The plate was centrifuged at 1200 rpm at room temperature for 5 minutes, followed by overnight culture at 37° C. under 5% CO₂ conditions. On the next day, 10 $\times$ Lysis Solution attached to CytoTox 96 Non-Radioactive Cytotoxicity Assay (manufactured by Promega Corp.) kit was added at a concentration of 17.5 μ l/well to the wells containing only the target cells and the medium and stirred, and the plate was then left standing at 37° C. for 45 minutes under 5% CO₂ conditions. After centrifugation at 200 g at room temperature for 4 minutes, 50 μ l of the supernatant in each well was recovered into a 96-well flat-bottomed microplate (manufactured by Corning Inc.). Substrate Mix was added thereto at a concentration of 50 μ l/well, and the plate was left standing at room temperature for 30 minutes while shielded from light. Stop Solution was further added thereto at a concentration of 50 μ l/well. The absorbance was measured at 490 nm using a plate reader (ARVO; manufactured by PerkinElmer, Inc.). The percentage of cells lysed by ADCC activity was calculated according to the calculation method shown in Example 12)-2-3.

[0752] As shown in FIGS. 132A, 132B, and 132C, hFR2-14_H12/L1 and hFR2-14_H19/L1 had ADCC activity against the FGFR2-expressing cancer cell lines NCI-H716, SNU-16, and KATO III, and this activity was shown to be higher in hFR2-14_H19/L1.

Example 13

ADCP Activity of a Humanized Anti-Human FGFR2 Antibody (hFR2-14)

[0753] 13)-1 ADCP Activity of Humanized Anti-FGFR2 Antibodies (hFR2-14_H12/L1 and hFR2-14_H19/L1) Against a FGFR2-Expressing Cancer Cell Line

[0754] 13)-1-1 Preparation of Target Cell

[0755] KATO III or NCI-H716 cells were recovered and washed 3 times with PBS. Then, the number of live cells was counted by the trypan blue dye exclusion test. 1×10^6 cells were separated, centrifuged, and then suspended in 200 μ l of Diluent C attached to PKH26 Red Fluorescent Cell Linker Kit for General Cell Membrane Labeling (manufactured by Sigma-Aldrich Corp.). 1 mM PKH26 Linker was diluted as a labeling solution to 10 μ M with Diluent C. Immediately thereafter, the cell suspension was mixed with an equal volume of the PKH26 Linker solution, and the mixture was

left standing at room temperature for 5 minutes. The cells were washed twice by the addition of 5 ml of an RPMI1640 medium (manufactured by Life Technologies Corp.) containing 10% FBS, then resuspended to 5×10^5 cells/ml, and used as target cells.

[0756] 13)-1-2 Preparation of PBMC Cells

[0757] 25 ml of healthy human blood was gradually layered over 20 ml of Lymphosepar I (manufactured by Immuno-Biological Laboratories Co., Ltd.), followed by centrifugation at 1500 rpm at room temperature for 30 minutes. A cell layer located between plasma and Lymphosepar I (manufactured by Immuno-Biological Laboratories Co., Ltd.) was recovered using a dropper and suspended in 20 ml of an RPMI1640 medium (manufactured by Life Technologies Corp.) containing 10% FBS. The suspension was centrifuged at 1500 rpm for 5 minutes. After removal of the supernatant, the cells were washed twice by the addition of 20 ml of an RPMI1640 medium (manufactured by Life Technologies Corp.) containing 10% FBS. The number of live cells was counted by the trypan blue dye exclusion test. The resulting cells were used as effector cells.

[0758] 13)-1-3 Preparation of Effector Cells

[0759] The PBMC cells prepared in Example 13)-1-2 was adjusted to 5×10^7 cells/ml with RoboSep buffer (manufactured by StemCell Technologies Inc.). 50 μ l of EasySep human Monocyte enrichment cocktail attached to Human monocyte Enrichment Kit Without CD16 Depletion (manufactured by StemCell Technologies Inc.) was added per ml of the PBMC cell suspension. After reaction at 4° C. for 10 minutes, 50 μ l of EasySep Magnetic Particles was added per ml of the PBMC cell suspension. After reaction at 4° C. for 5 minutes, RoboSep buffer (manufactured by StemCell Technologies Inc.) was added thereto up to 2.5 ml, and the reaction mixture was loaded to EasySep Magnet. After 2 minutes and 30 seconds, the supernatant was recovered and then centrifuged at 1200 rpm for 5 minutes to separate monocyte fractions. The fractions were washed once by the addition of an RPMI1640 medium (manufactured by Life Technologies Corp.) containing 10% FBS. Then, an RPMI1640 medium (manufactured by Life Technologies Corp.) containing 10% FBS, 10 ng/ml GM-CSF (manufactured by PeproTech Inc.), and 10 ng/ml M-CSF (manufactured by PeproTech Inc.) was added thereto, and the mixture was inoculated to a 225-cm² flask for suspension culture (manufactured by Sumitomo Bakelite Co., Ltd.). The cells were cultured at 37° C. for 14 days under 5% CO₂ conditions. During the culture period, the medium was replaced every 3 to 4 days with an RPMI1640 medium (manufactured by Life Technologies Corp.) containing 10% FBS, 10 ng/ml GM-CSF (manufactured by PeproTech Inc.), and 10 ng/ml M-CSF (manufactured by PeproTech Inc.). Fourteen days later, 0.05% trypsin-EDTA (manufactured by Life Technologies Corp.) was added to macrophages differentiated therefrom by induction. After reaction at 37° C. for 40 minutes, the cells were dissociated from the flask. The cells were washed twice by the addition of an RPMI1640 medium (manufactured by Life Technologies Corp.) containing 10% FBS, then resuspended to 5×10^5 cells/ml in an RPMI1640 medium (manufactured by Life Technologies Corp.) containing 10% FBS, 10 ng/ml M-CSF (manufactured by PeproTech Inc.), and 250 U/ml IFN- γ (manufactured by PeproTech Inc.), and used as effector cells.

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[0760] 13)-1-4 Evaluation of ADCP Activity

[0761] The target cells prepared by the method of Example 13)-1-1 were added at a concentration of 100 μ l/well to Ultra-Low Attachment 96-well U-bottomed microplate (manufactured by Corning Inc.). hFR2-14_H12/L1 or hFR2-14_H19/L1 (prepared in Examples 8) and 9)) or human IgG diluted to 0.5 to 500 ng/ml (final concentration) with an RPMI1640 medium (manufactured by Life Technologies Corp.) containing 10% FBS was added thereto at a concentration of 100 μ l/well, and the plate was left standing at 4° C. for 30 minutes. After centrifugation at 1200 rpm at room temperature for 5 minutes and removal of the supernatant, the cells were suspended in 100 μ l/well of an RPMI1640 medium (manufactured by Life Technologies Corp.) containing 10% FBS. The effector cells (5×10^5 cells/ml) prepared in Example 13)-1-3 were added thereto at a concentration of 100 μ l/well, and the plate was then left standing at 37° C. for 3 hours under 5% CO₂ conditions. After centrifugation at 1200 rpm at 4° C. for 5 minutes and removal of the supernatant, the cells were washed with 200 μ l/well of PBS containing 5% FBS. 45 μ l/well of PBS containing 5% FBS and 5 μ l/well of APC human CD11b (manufactured by Becton Dickinson and Company) were added to the cells, and the plate was left standing at 4° C. for 15 minutes. The cells were washed twice with 200 μ l/well of PBS containing 5% FBS. The cells were suspended in 200 μ l/well of PBS containing 1% paraformaldehyde, and the plate was left overnight at 4° C. On the next day, the cells were assayed by flow cytometry (FACS Canto II; manufactured by Becton Dickinson and Company). The data was analyzed using Flowjo (manufactured by Tree Star Inc.). After development on FSC (forward scatter)/SSC (side scatter), the number of PE-positive cells (A) and the number of cells positive for both APC and PE (B) were calculated. The cells positive for both APC and PE (B) mean that the macrophages englobed the target cells. The percentage of cells phagocytosed by ADCP activity was calculated according to the following expression:

$$\text{Percentage of cells phagocytosed (\%)} = B / (A + B) \times 100$$

[0762] As shown in FIGS. 133A and 133B, hFR2-14_H12/L1 and hFR2-14_H19/L1 had ADCP activity against the FGFR2-expressing cancer cell lines NCI-H716 and KATO III.

Example 14

In Vivo Antitumor Activity of a Humanized Anti-FGFR2 Antibody (hFR2-14)

[0763] 14)-1 In Vivo Antitumor Activity of Humanized Anti-FGFR2 Antibodies (hFR2-14_H1/L1, hFR2-14_H2/L1, hFR2-14_H3/L1, and hFR2-14_H4/L1) Against a Human Stomach Cancer Cell Line SNU-16-Subcutaneously Transplanted Model

[0764] 5×10^6 cells of a human stomach cancer line SNU-16 (purchased from ATCC) were suspended in 50% Matrigel (purchased from Nippon Becton Dickinson Company, Ltd.) and subcutaneously transplanted to the axillary region of each nude mouse (CAnN.Cg-Foxnl^{tm1}/CrJ, purchased from Charles River Laboratories Japan Inc.). The mice were grouped according to their tumor volumes. Seven, 10, 14, 17, and 21 days after transplantation, each humanized anti-FGFR2 antibody (hFR2-14_H1/L1, hFR2-14_H2/L1, hFR2-14_H3/L1, or hFR2-14_H4/L1) prepared in Example

8)-3 was intraperitoneally administered at a dose of 1.5 or 15 mg/kg to the cancer-bearing mice (n=8). The major axis and minor axis of the transplanted tumor were measured twice a week using an electronic digital caliper (manufactured by Mitsutoyo Corp.). The tumor volume was calculated according to the following expression:

$$\text{Tumor volume (mm}^3\text{)} = \frac{1}{2} \times \text{Minor axis (mm)} \times \text{Minor axis (mm)} \times \text{Major axis (mm)}$$

[0765] The results for the hFR2-14_H1/L1 antibody are shown in FIG. 134A. The percentage of tumor growth inhibition at 21 days after transplantation (final assay day) was 58% for the 1.5 mg/kg administration group and 53% for the 15 mg/kg administration group.

[0766] The results for the hFR2-14_H2/L1 antibody are shown in FIG. 134B. The percentage of tumor growth inhibition at 21 days after transplantation (final assay day) was 58% for the 1.5 mg/kg administration group and 58% for the 15 mg/kg administration group.

[0767] The results for the hFR2-14_H3/L1 antibody are shown in FIG. 134C. The percentage of tumor growth inhibition at 21 days after transplantation (final assay day) was 64% for the 1.5 mg/kg administration group and 41% for the 15 mg/kg administration group.

[0768] The results for the hFR2-14_H4/L1 antibody are shown in FIG. 134D. The percentage of tumor growth inhibition at 21 days after transplantation (final assay day) was 70% for the 1.5 mg/kg administration group and 39% for the 15 mg/kg administration group.

[0769] 14)-2 In Vivo Antitumor Activity of Humanized Anti-FGFR2 Antibodies (hFR2-14_H5/L1, hFR2-14_H8/L1, hFR2-14_H9/L1, hFR2-14_H11/L1, hFR2-14_H12/L1, and hFR2-14_H19/L1) Against a Human Stomach Cancer Cell Line SNU-16-Subcutaneously Transplanted Model

[0770] 5×10^6 cells of a human stomach cancer line SNU-16 (purchased from ATCC) were suspended in 50% Matrigel (purchased from Nippon Becton Dickinson Company, Ltd.) and subcutaneously transplanted to the axillary region of each nude mouse (CAnN.Cg-Foxnl^{tm1}/CrJ, purchased from Charles River Laboratories Japan Inc.). The mice were grouped according to their tumor volumes. Seven, 10 (or 11), 14, and 17 (or 18) days after transplantation, each humanized antibody (hFR2-14_H5/L1, hFR2-14_H8/L1, hFR2-14_H9/L1, hFR2-14_H11/L1, or hFR2-14_H12/L1) prepared in Example 8)-3 or the humanized antibody (hFR2-14_H19/L1) prepared in Example 9) was intraperitoneally administered at a dose of 2 or 20 mg/kg to the cancer-bearing mice (n=8 or 9). The major axis and minor axis of the transplanted tumor were measured twice a week using an electronic digital caliper (manufactured by Mitsutoyo Corp.). The tumor volume was calculated according to the following expression:

$$\text{Tumor volume (mm}^3\text{)} = \frac{1}{2} \times \text{Minor axis (mm)} \times \text{Minor axis (mm)} \times \text{Major axis (mm)}$$

[0771] The results for hFR2-14_H5/L1 are shown in FIG. 135A. The percentage of tumor growth inhibition at 21 days after transplantation (final assay day) was 41% for the 2 mg/kg administration group and 51% for the 20 mg/kg administration group.

[0772] The results for hFR2-14_H8/L1 are shown in FIG. 135B. The percentage of tumor growth inhibition at 21 days after transplantation (final assay day) was 30% for the 2 mg/kg administration group and 30% for the 20 mg/kg administration group.

[0773] The results for hFR2-14_H9/L1 are shown in FIG. 135C. The percentage of tumor growth inhibition at 21 days after transplantation (final assay day) was 1% for the 2 mg/kg administration group and 23% for the 20 mg/kg administration group.

[0774] The results for hFR2-14_H11/L1 are shown in FIG. 135D. The percentage of tumor growth inhibition at 21 days after transplantation (final assay day) was 61% for the 2 mg/kg administration group and 42% for the 20 mg/kg administration group.

[0775] The results for hFR2-14_H12/L1 are shown in FIG. 135E. The percentage of tumor growth inhibition at 21 days after transplantation (final assay day) was 36% for the 2 mg/kg administration group and 58% for the 20 mg/kg administration group.

[0776] The results for hFR2-14_H19/L1 are shown in FIG. 135F. The percentage of tumor growth inhibition at 21 days after transplantation (final assay day) was 70% for the 2 mg/kg administration group and 40% for the 20 mg/kg administration group.

[0777] 14)-3 In Vivo Antitumor Activity of Humanized Anti-FGFR2 Antibodies (hFR2-14_H12/L1 and hFR2-14_H19/L1) Against a Human Colorectal Cancer Cell Line NCI-H716 Block-Transplanted Model

[0778] A tumor block (5×5×5 mm³) of a human colorectal cancer line NCI-H716 (purchased from ATCC) was subcutaneously transplanted to the axillary region of each nude mouse (CAnN.Cg-Foxnl^{tm1}/CrJ, purchased from Charles River Laboratories Japan Inc.). On the transplantation day and 3, 7, 10, 14, 17, 21, and 24 days after transplantation, each humanized antibody (hFR2-14_H12/L1 or hFR2-14_H19/L1) prepared in Example 8) or 9) was intraperitoneally administered at a dose of 20 mg/kg to the cancer-bearing mice (n=11). The major axis and minor axis of the transplanted tumor were measured twice a week using an electronic digital caliper (manufactured by Mitsutoyo Corp.). The tumor volume was calculated according to the following expression:

$$\text{Tumor volume (mm}^3\text{)} = \frac{1}{2} \times \text{Minor axis (mm)} \times \text{Minor axis (mm)} \times \text{Major axis (mm)}$$

[0779] The results for hFR2-14_H12/L1 are shown in FIG. 136A. The percentage of tumor growth inhibition at 28 days after transplantation (final assay day) was 99%.

[0780] The results for hFR2-14_H19/L1 are shown in FIG. 136B. The percentage of tumor growth inhibition at 28 days after transplantation (final assay day) was 99%.

[0781] 14)-4 In Vivo Antitumor Activity of Humanized Anti-FGFR2 Antibodies (hFR2-14_H12/L1 and hFR2-14_H19/L1) Against a Human Colorectal Cancer Cell Line NCI-H716-Luc-Peritoneally Disseminated Model

[0782] 3×10⁶ cells of luciferase gene-expressing human colorectal cancer line NCI-H716-luc (NCI-H716 (purchased from ATCC) transfected with the luciferase gene) were suspended in saline (purchased from Otsuka Pharmaceutical Co., Ltd.) and intraperitoneally transplanted to each NOG mouse (NOD/Shi-SCID, IL-2R^γnull, purchased from Central Institute for Experimental Animals). One day after transplantation, the mice were grouped according to their weights. One, 5, 8, 12, 16, 19, and 26 days after transplantation, each humanized antibody (hFR2-14_H12/L1 or hFR2-14_H19/L1) prepared in Examples 8) and 9) was intraperitoneally administered at a dose of 20 mg/kg to the cancer-bearing mice (n=11). The date of death of a mouse was recorded, and the survival rate (%) was calculated.

Thirty-seven days after transplantation, VivoGlo Luciferin (purchased from Promega Corp.) was administered at a dose of 150 mg/kg to the tail veins of the cancer-bearing mice. Ten minutes after administration, the luciferase activity of the cancer-bearing mice was assayed using IVIS (manufactured by Caliper, A PerkinElmer Company). The luciferase activity (p/s/cm²/sr) was quantified using Living Image (manufactured by Caliper, A PerkinElmer Company).

[0783] FIG. 137(A) shows the tumor growth inhibitory effects of the humanized antibodies. The percentage of tumor growth inhibition relative to the non-administered group, with the luciferase activity as an index, at 37 days after transplantation was 98% for the hFR2-14_H12/L1-administered group and 98% for the hFR2-14_H19/L1-administered group.

[0784] FIG. 137(B) shows the life prolonging effects of the humanized antibodies. The survival rate at 93 days after transplantation was 0% for the non-administered group, whereas the survival rate was 64% for the hFR2-14_H12/L1 antibody-administered group and 91% for the hFR2-14_H19/L1 antibody-administered group.

Example 15

X-Ray Structural Analysis of a Complex of a Humanized Anti-FGFR2 Antibody (hFR2-14_H3/L1) and a FGFR2 Protein

[0785] 15)-1 Preparation of a FGFR2 Protein for Crystallization

[0786] 15)-1-1 Preparation of a FGFR2 Protein Expression Vector for Crystallization

[0787] In order to construct a vector for expression of a region consisting of an amino acid sequence of amino acid positions 148 to 249 in the common portion of human FGFR2 IIb and IIc (FIG. 78; SEQ ID NO: 70 and FIG. 79; SEQ ID NO: 71) (hereinafter, this region is referred to as "D2"), PCR reaction was performed using a primer set shown below and a vector plasmid comprising amino acid positions 126 to 313 of human FGFR2 (FIG. 78; SEQ ID NO: 70 and FIG. 79; SEQ ID NO: 71) as a template.

Primer set for gene amplification of D2:

D23fw:
5'-CTGTTTCAAGGTCGAGCAATAACAAACGTCACCGTATTGG-3'

(FIG. 120; SEQ ID NO: 112)
and

D23rv:
5'-CGCAAGCTTGTCTGACTCAAACAACATCCAGATGATAGGTATG-3'

(FIG. 121; SEQ ID NO: 113).

The obtained PCR product was inserted to pET24b(+) (manufactured by Merck KGaA (Novagen)) preliminarily containing nucleotide sequences encoding a His tag and an HRV3c protease cleavage site using In-Fusion HD Cloning Kit (manufactured by Takara Bio Inc.) (hereinafter, the resulting vector is referred to as "pET24b(+)-D2", and hereinafter and in the drawings, the recombinant protein expressed by "pET24b(+)-D2" is referred to as FGFR2D2).

[0788] 15)-1-2 Preparation of a FGFR2 Protein (FGFR2D2) for Crystallization

[0789] *E. coli* Origami 2 (DE3) (manufactured by Merck KGaA (Novagen)) was transformed with the expression

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plasmid pET24b(+)-D2 and precultured overnight at 200 rpm at 37° C. in 50 mL of Terrific medium (manufactured by ForMedium Ltd.) supplemented with 25 µg/ml kanamycin (manufactured by Wako Pure Chemicals Industries, Ltd.) and 12 µg/ml tetracycline (manufactured by Wako Pure Chemicals Industries, Ltd.). 50 mL of the precultured solution was added to 1 L of Terrific medium also supplemented with 25 µg/ml kanamycin and 12 µg/ml tetracycline, and cultured at 250 rpm at 37° C. for 1 hour. Then, the temperature was lowered to 16° C., and the expression of FGFR2D2 was induced by the addition of 1 mM IPTG, followed by culture for 26 hours. The bacterial cells were collected by centrifugation at 4500 rpm for 30 minutes, suspended in a binding buffer (50 mM Tris-HCl (pH 8.0), 400 mM NaCl, and 20 mM imidazole) containing Inhibitor Cocktail (manufactured by Roche Applied Science) dissolved therein, and then sonicated on ice. After centrifugation at 25000 rpm for 20 minutes, the supernatant was recovered and applied to HisTrap FF crude column (manufactured by GE Healthcare Bio-Sciences Corp.). The column was washed with the binding buffer, followed by gradient elution with an elution buffer (50 mM Tris-HCl (pH 8.0), 400 mM NaCl, and 500 mM imidazole) to collect fractions containing the protein of interest. The collected sample was diluted with a buffer (50 mM Tris-HCl (pH 7.5) and 0.1 mM EDTA) and then applied to HiTrap SP HP, followed by gradient elution with a buffer (50 mM Tris-HCl (pH 7.5), 1 M NaCl, and 0.1 mM EDTA) to collect fractions containing the protein of interest. The obtained sample was applied to a gel filtration column (HiLoad 16/600 Superdex 75 pg; manufactured by GE Healthcare Bio-Sciences Corp.) equilibrated with a buffer (25 mM HEPES (pH 7.5), 300 mM NaCl, and 0.1 mM EDTA) to collect fractions containing the protein of interest. The obtained FGFR2D2 was concentrated into 15 mg/mL using Amicon Ultra-4 (manufactured by Merck Millipore).

[0790] 15)-2 Preparation of a Fab Fragment of a Humanized Anti-FGFR2 Antibody (hFR2-14_H3/L1)

[0791] hFR2-14_H3/L1 was dialyzed against 20 mM phosphate and 10 mM EDTA (pH 7.0) and then concentrated into 24 mg/ml using Amicon Ultra-15 MWCO 10K (manufactured by Merck Millipore) to prepare 1.9 ml of a concentrate. 5.5 ml of cysteine (manufactured by Sigma-Aldrich Corp.) adjusted to 0.005 mM with 20 mM phosphate and 10 mM EDTA (pH 7.0), and 0.19 ml of papain (manufactured by Sigma-Aldrich Corp.) diluted 1/100 with 20 mM phosphate and 10 mM EDTA (pH 7.0) were added to the concentrate and reacted at 37° C. for 18 hours. After 18 hours, the reaction was stopped by the addition of 2.53 ml of N-ethylmaleimide (manufactured by Tokyo Chemical Industry Co., Ltd.) dissolved at a concentration of 120 mM in 20 mM phosphate and 10 mM EDTA (pH 7.0). The reaction solution was applied to MabSelect SuRe 5 ml (manufactured by GE Healthcare Bio-Sciences Corp.) equilibrated with PBS to recover 18 ml of a flow-through fraction corresponding to the Fab fragment. The fraction was concentrated using Amicon Ultra-15 MWCO 10K (manufactured by Merck Millipore) and applied to Superdex 200 16/60 (manufactured by GE Healthcare Bio-Sciences Corp.) equilibrated with 50 mM Tris-HCl and 20 mM NaCl (pH 7.5) to recover 18 ml of a fraction corresponding to the Fab fragment (hereinafter, the resulting fragment is referred to as an "H3L1Fab fragment").

[0792] 15)-3 Preparation of a H3L1Fab Fragment/FGFR2D2 Complex Sample

[0793] 0.5 mL of 15 mg/mL FGFR2D2 was mixed per mL of 12.5 mg/mL H3L1Fab fragment, and the mixture was left overnight at 4° C. and then applied to HisTrap FF crude equilibrated with a binding buffer (50 mM Tris-HCl (pH 8.0), 400 mM NaCl, and 20 mM imidazole). The column was washed with the binding buffer, followed by elution with an elution buffer (50 mM Tris-HCl (pH 8.0), 400 mM NaCl, and 500 mM imidazole). The eluted sample was applied to a gel filtration column (HiLoad 16/600 Superdex 200 pg; manufactured by GE Healthcare Bio-Sciences Corp.) equilibrated with a buffer (25 mM Tris-HCl (pH 7.5) and 50 mM NaCl) to recover 11 mL of a fraction corresponding to the complex.

[0794] 15)-4 Crystallization and Structural Analysis of the H3L1Fab Fragment/FGFR2D2 Complex

[0795] The obtained complex of H3L1Fab and FGFR2D2 was concentrated into 22 mg/mL and used in crystallization. The vapor diffusion method was used for the crystallization. To 0.5 to 0.7 µL of the protein solution, an equal amount of a precipitant solution (1.225 M ammonium sulfate and 0.15 M Tris-HCl, pH 8.5) was added, and the resulting solution was placed in a sealed container containing 0.45 mL of a precipitant solution such that these solutions had no contact with each other. The container was left standing at 20° C. Three days later, 0.2 mm×0.2 mm×0.2 mm single crystals were obtained.

[0796] The obtained crystals were dipped in a precipitant solution supplemented with 30% (v/v) ethylene glycol and subsequently frozen under nitrogen stream of -180° C. X-ray diffraction data was collected under nitrogen stream of 95 K using BL5A of Photon Factory, Institute of Materials Structure Science, High Energy Accelerator Research Organization. Diffraction intensity was digitized from the obtained diffraction image using software HKL2000 (manufactured by HKL Research Inc.) to determine crystal structure factors. The crystals were in the tetragonal system with a space group of P41212 and unit cells of a=b=60.57 angstroms and c=331.2 angstroms.

[0797] The molecular replacement method was performed using the obtained structure factors and the three-dimensional structure coordinates of FGFR2 (the portion concerned was extracted from PDB code: 3OJ2) and Fab (the antibody structure previously subjected to crystal structural analysis was utilized) to determine a phase. Software phaser (CCP4: Collaborative Computational Project No. 4) was used in calculation. The crystals each contained 1 complex in the asymmetric unit.

[0798] Structure refinement was performed using software refinac5 (CCP4), and model correction was performed using software coot. This operation was repetitively performed to obtain a final R factor of 21.8% and a free R factor of 25.8% with a resolution of 2.3 angstroms. The model is composed of 1 complex and contains amino acid residues 1 to 215 of the H3L1Fab L chain, amino acid residues 1 to 221 of the H3L1Fab H chain, amino acid residues 150 to 249 of FGFR2D2, 1 sulfate ion, and 285 water molecules. The C-terminal 1 residue of the H3L1Fab L chain, the C-terminal 4 residues of the H3L1Fab H chain, and N-terminal 20 residues comprising the His tag and protease cleavage site of FGFR2D2 were not included in the model because of their obscure electric density.

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[0799] The determined amino acid residues of FGFR2D2 within 4 angstroms from H3L1Fab are as follows: Tyr155, Thr157, Lys176, Ala181, Gly182, Gly183, Asn184, Pro185, Met186, Thr188, Gln200, Glu201, Gly205, Gly206, Lys208, Val209, Arg210, Asn211, Gln212, His213, Trp214, and Ile217. FIG. 138 shows a ribbon model of the whole complex. FIG. 139 shows a diagram showing the superposition of the D2 region in the FGFR2D2/H3L1Fab complex onto the corresponding region of an FGFR2/FGF1 complex structure (PDB code: 3OJ2).

Example 16

Inhibitory Activity of Ahumanized Anti-Human
FGFR2 Antibody (hFR2-14) Against
Ligand-Receptor Binding

[0800] The binding of the ligand FGF7 to the antigen (C-terminally His-tagged rhFGFR2 alpha (IIIb)) was detected by ELISA. rhFGFR2 alpha (IIIb) was diluted to 2 µg/ml with PBS and added at a concentration of 100 µl/well to 96 well Clear Polystyrene High Bind Stripwell Microplate (manufactured by Corning Inc.), and the plate was left overnight at 4° C. On the next day, the solution was removed using an aspirator, and the contents in the wells were washed 3 times with PBS containing 0.05% Tween-20 (manufactured by Bio-Rad Laboratories, Inc.). Then, PBS containing 1% BSA (manufactured by Sigma-Aldrich Corp.) was added thereto at a concentration of 200 µl/well, and the plate was left at room temperature for 1 hour. After removal of the solution, the contents in the wells were washed 3 times with PBS containing 0.05% Tween-20. FGF7 diluted to 9 ng/ml with PBS containing 1% BSA, heparin (manufactured by Sigma-Aldrich Corp.) diluted to 300 µg/ml, and the cFR2-10 (prepared in Example 4), hFR2-14_H12/L1 (prepared in Example 8), or hFR2-14_H19/L1 antibody (prepared in Example 9) diluted to 0.3 to 30 µg/ml were each added thereto at a concentration of 50 µl/well, and the plate was left at room temperature for 2 hours. After removal of the solution, the contents in the wells were washed 3 times with PBS containing 0.05% Tween-20. A biotinylated anti-FGF-7 antibody (Human KGF/FGF-7 DuoSet, manufactured by R&D Systems, Inc.) diluted 180-fold with PBS containing 1% BSA was added thereto at a concentration of 100 µl/well, and the plate was left at room temperature for 2 hours. After removal of the solution, the contents in the wells were washed 3 times with PBS containing 0.05% Tween-20. Streptavidin-HRP (Human KGF/FGF-7 DuoSet, manufactured by R&D Systems, Inc.) diluted 200-fold with PBS containing 1% BSA was added thereto at a concentration of 100 µl/well, and the plate was left at room temperature for 20 minutes while shielded from light. After removal of the solution, the contents in the wells were washed 3 times with PBS containing 0.05% Tween-20. A substrate solution containing Reagent A and Reagent B mixed in equal amounts (Substrate Reagent Pack, manufactured by R&D Systems, Inc.) was added thereto at a concentration of 100 µl/well, and the plate was left at room temperature for 20 minutes for color reaction while shielded from light. The reaction was stopped by the addition of Stop solution (manufactured by R&D Systems, Inc.) at a concentration of 50 µl/well. Then, the absorbance was measured at 450 nm and 570 nm using a plate reader. The measurement value at 570 nm was subtracted from the measurement value at 450 nm to determine a value. As shown in FIG. 140, the cFR2-10, hFR2-

14_H12/L1, and hFR2-14_H19/L1 antibodies all had the activity of inhibiting the binding of the ligand to the receptor.

Example 17

Measurement of the Expression Level of Antigen
FGFR2 in a FGFR2-Expressing Cancer Cell Line
Treated with a Low-Molecular Compound

[0801] 17)-1 Preparation of Cells

[0802] SNU-16 cells were washed twice with a medium for ADCC. The number of live cells was counted by the trypan blue dye exclusion test. The cells were resuspended to 1.25×10^5 cells/ml in a medium for ADCC and added at a concentration of 2 ml/well to a 6-well plate. AZD4547 or Ki23057 diluted to 100 to 1000 nM (final concentration) with a medium for ADCC or DMSO diluted to 0.001% to 0.01% (final concentration) with a medium for ADCC was added thereto at a concentration of 500 µl/well, and the plate was left standing at 37° C. for 6 hours under 5% CO₂ conditions. After 6 hours, a medium for ADCC was further added thereto at a concentration of 2.5 ml/well, followed by overnight culture at 37° C. under 5% CO₂ conditions. The cells were recovered and centrifuged at 1200 rpm for 5 minutes. After removal of the supernatant, the cells were suspended in 120 µl of ice-cold PBS containing 5% FBS.

[0803] 17)-2 Measurement of the Amount of Antigen

[0804] The amount of antigen expressed on the cell surface was measured using QIFIKIT (manufactured by Dako/Agilent Technologies Inc.). Specifically, a rat-mouse chimeric antibody in which the heavy and light chain variable regions of an anti-human FGFR2 rat monoclonal antibody were linked to the heavy and light chain constant regions, respectively, of mouse IgG1, or control mouse IgG1 (manufactured by R&D Systems, Inc.) was diluted to 100 µg/ml with ice-cold PBS containing 5% FBS and added at a concentration of 50 µl/well to a 96-well U-bottomed microplate. The SNU-16 cells prepared by the method of Example 17)-1 were added thereto at a concentration of 50 µl/well. The plate was left standing at 4° C. for 1 hour. Then, 100 µl of set-up beads or calibration beads attached to the kit was added to another well, and ice-cold PBS containing 5% FBS was added at a concentration of 150 µl/well to all wells, followed by centrifugation at 1200 rpm at 4° C. for 5 minutes. After removal of the supernatant, ice-cold PBS containing 5% FBS was added thereto at a concentration of 250 µl/well, followed by centrifugation at 1200 rpm at 4° C. for 5 minutes. After removal of the supernatant, an FITC-conjugated antibody (attached to the kit) diluted 50-fold with ice-cold PBS containing 5% FBS was added thereto at a concentration of 100 µl/well. The plate was left standing at 4° C. for 1 hour while shielded from light. Then, ice-cold PBS containing 5% FBS was added thereto at a concentration of 150 µl/well, followed by centrifugation at 1200 rpm at 4° C. for 5 minutes. After removal of the supernatant, ice-cold PBS containing 5% FBS was added thereto at a concentration of 250 µl/well, followed by centrifugation at 1200 rpm at 4° C. for 5 minutes. This operation was repeated twice. Then, the supernatant was removed, and the cells were suspended in 200 µl/well of ice-cold PBS containing 5% FBS and used as a sample for assay in detection using a flow cytometry (FC500; manufactured by Beckman Coulter Inc.). The data was analyzed using Flowjo (manufactured by Tree Star Inc.). Average fluorescence intensity

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was calculated from the fluorescence intensity of a negative peak of the set-up beads, and the fluorescence intensity of the calibration beads bound with the antibody in 5 different amounts. A calibration curve was prepared to calculate the SABC (the ability of the antibody to specifically bind to the antigen per cell) value of the test sample. The results shown in FIG. 141 demonstrated that the number of the antigen is increased in the SNU-16 cells treated with AZD4547 or Ki23057 compared with the untreated SNU-16 cells or the SNU-16 cells treated with DMSO.

Example 18

ADCC Activity of a Humanized Anti-FGFR2 Antibody (hFR2-14_H19/L1) Against a FGFR2-Expressing Cancer Cell Line Treated with a Low-Molecular Compound

[0805] 18)-1-1 Preparation of the Target Cell

[0806] SNU-16 cells were washed twice with a medium for ADCC. The number of live cells was counted by the trypan blue dye exclusion test. The cells were resuspended to 1.25×10^5 cells/ml in a medium for ADCC and dispensed in an amount of 5 ml each to 15-ml tubes. AZD4547 (containing 0.01% DMSO) diluted to 1000 nM (final concentration) with a medium for ADCC, Ki23057 (containing 0.001% DMSO) diluted to 100 nM with a medium for ADCC, DMSO diluted to 0.001% to 0.01% (final concentration) with a medium for ADCC, or a medium for ADCC was further added thereto at a concentration of 1.25 ml/tube and stirred. After addition at 50 μ l/well to a 96-well black plate (manufactured by Corning Inc.), the plate was left standing at 37° C. for 6 hours under 5% CO₂ conditions.

[0807] 18)-1-2 Preparation of PBMC Cells

[0808] 25 ml of healthy human blood was gradually layered over 20 ml of Lymphosepar I (manufactured by Immuno-Biological Laboratories Co., Ltd.), followed by centrifugation at 1500 rpm at room temperature for 30 minutes. A cell layer located between plasma and Lymphosepar I (manufactured by Immuno-Biological Laboratories Co., Ltd.) was recovered using a dropper and suspended in 20 ml of a phenol red-free RPMI1640 medium (manufactured by Life Technologies Corp.) containing 10% FBS. The suspension was centrifuged at 1500 rpm for 5 minutes. After removal of the supernatant, the cells were washed twice by the addition of 20 ml of a medium for ADCC. The number of live cells was counted by the trypan blue dye exclusion test. After centrifugation, the medium was removed, and the cells were suspended in a medium for ADCC and used as effector cells.

[0809] 18)-2 Evaluation of ADCC Activity

[0810] To the SNU-16 cells prepared by the method of Example 18)-1-1, hFR2-14_H19/L1 or human IgG diluted to 0 or 0.1 to 1000 ng/ml (final concentration) with a medium for ADCC was added at a concentration of 25 μ l/well, and the plate was left standing at 4° C. for 1 hour. The PBMC cells (12×10^6 cells/ml) of Example 18)-1-2 were further added thereto at a concentration of 25 μ l/well (15 μ l of a medium was added to a well for maximum release count assay). The plate was centrifuged at 1200 rpm at room temperature for 5 minutes, followed by overnight culture at 37° C. under 5% CO₂ conditions. On the next day, 10x Lysis Solution attached to CytoTox-ONE Homogeneous Membrane Integrity Assay (manufactured by Promega Corp.) kit was diluted 5-fold with a medium for ADCC and added at

a concentration of 10 μ l/well to the wells containing only the target cells and the medium and stirred. The plate was left standing for 5 minutes. Then, Substrate Mix dissolved in an assay buffer was added thereto at a concentration of 100 μ l/well. The plate was left standing for 10 minutes while shielded from light. Then, Stop Solution was added thereto at a concentration of 50 μ l/well and stirred. Then, an excitation wavelength of 560 nm and a fluorescence wavelength of 590 nm were measured using a plate reader (SPECTRAMAX M3; manufactured by Molecular Devices, LLC).

[0811] The percentage of cells lysed by ADCC activity was calculated according to the following expression:

$$\text{Cytotoxicity (\%)} = (A-B)/(C-D) \times 100$$

[0812] A: Count of sample well

[0813] B: Average of spontaneous release counts from wells containing only target cells and effector cells (n=3).

[0814] C: Average of maximum release (wells containing target cells lysed in a surfactant) counts (n=3).

[0815] D: Average of spontaneous release counts from wells containing only target cells (n=3).

[0816] The results shown in FIGS. 142A, 142B, 142C, 142D, and 142E demonstrated that the ADCC activity exhibited by hFR2-14_H19/L1 is increased by the treatment of the SNU-16 cells with AZD4547 or Ki23057 compared with no treatment or DMSO treatment.

Example 19

In Vivo Effect of the Combined Use of a Humanized Anti-FGFR2 Antibody (hFR2-14_H19/L1) and AZD4547 on a FGFR2-Expressing Cancer Cell Line

[0817] A human stomach cancer cell line SNU-16 (purchased from ATCC) was adjusted to 5×10^7 cells/mL with a 1:1 mixed solution of PBS and Matrigel (purchased from Nippon Becton Dickinson Company, Ltd.), and 0.1 mL of the cell suspension was subcutaneously transplanted to the axillary region of each nude mouse (CAnN.Cg-Foxnl^{nu}/CrJ, female, 5 to 6 weeks old, purchased from Charles River Laboratories Japan Inc.). The mice were grouped according to their tumor volumes (n=9). hFR2-14_H19/L1 was intraperitoneally administered at a dose of 20 mg/kg to the cancer-bearing mice, and AZD4547 was forcibly administered orally at a dose of 3 mg/kg, 10 mg/kg, or 30 mg/kg to the mice. Administration of hFR2-14_H19/L1 was carried out 7, 10, 14, and 17 days after transplantation, and administration of AZD4547 was carried out 7, 8, 9, 10, 13, 14, 15, 16, 17, and 20 days after transplantation. The major axis (mm) and minor axis (mm) of the tumor were measured over time using an electronic digital caliper (manufactured by Mitsutoyo Corp.). The tumor volume was calculated according to the following expression:

$$\text{Tumor volume (mm}^3\text{)} = \frac{1}{2} \times [\text{Major axis of the tumor}] \times [\text{Minor axis of the tumor}] \times [\text{Minor axis of the tumor}]$$

[0818] The antitumor effect was evaluated on the basis of the percentage of tumor growth inhibition (TGI %) at 21 days after transplantation (final assay day) according to the following expression:

$$\text{TGI (\%)} = (1-A/B) \times 100$$

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[0819] A: Average tumor volume of the compound administration group at the date of determination

[0820] B: Average tumor volume of the untreated control group at the date of determination

[0821] The results for hFR2-14_H19/L1 administered alone, AZD4547 (3 mg/kg) administered alone, and hFR2-14_H19/L1 and AZD4547 administered in combination are shown in FIG. 143. TGI at 21 days after transplantation (final assay day) was 40% for the group given hFR2-14_H19/L1 alone and 24% for the group given AZD4547 (3 mg/kg) alone, whereas TGI at 21 days after transplantation (final assay day) was 87% for the group given hFR2-14_H19/L1 and AZD4547 in combination, indicating that the antitumor effect is enhanced by the combined use.

[0822] FIG. 144 shows the number of complete response (CR) individuals whose tumor disappeared completely at 21 days after transplantation (final assay day). The number of CR individuals among 9 mice was 0 for hFR2-14_H19/L1 administered alone and AZD4547 administered alone. The number of CR individuals among 9 mice was 0 for the group given hFR2-14_H19/L1 and 3 mg/kg AZD4547 in combination. The number of CR individuals among 9 mice was 2 for the group given hFR2-14_H19/L1 and 10 mg/kg AZD4547 in combination. The number of CR individuals among 9 mice was 4 for the group given hFR2-14_H19/L1 and 30 mg/kg AZD4547 in combination. These results indicated that the combined use of hFR2-14_H19/L1 and AZD4547 increases the ratio of individuals whose tumor disappears completely in a manner dependent on the dose of AZD4547.

Example 20

Analysis of In Vivo Expression Level of the Antigen FGFR2 in a FGFR2-Expressing Cancer Cell Line after Administration of AZD4547

[0823] A human stomach cancer cell line SNU-16 (purchased from ATCC) was adjusted to 5×10^7 cells/mL with a 1:1 mixed solution of PBS and Matrigel (purchased from Nippon Becton Dickinson Company, Ltd.), and 0.1 mL of the cell suspension was subcutaneously transplanted to the axillary region of each nude mouse (CAnN.Cg-Foxnl^{tmu}/CrJCrJ, female, 5 to 6 weeks old, purchased from Charles River Laboratories Japan Inc.). The mice were grouped according to their tumor volumes (n=3). hFR2-14_H19/L1 was intraperitoneally administered at a dose of 20 mg/kg to the cancer-bearing mice, and AZD4547 was forcibly administered orally at a dose of 3 mg/kg or 30 mg/kg to the mice. On the day after administration, the tumor was recovered from each mouse and homogenized in T-PER (purchased from Thermo Fisher Scientific Inc.) containing a protease inhibitor and a phosphatase inhibitor. The extracted proteins were subjected to SDS electrophoresis and transferred to a PVDF membrane. Subsequently, the membrane was reacted with an anti-FGFR2 antibody (purchased from Abcam plc.) or an anti-GAPDH antibody (purchased from Cell Signaling Technology, Inc.) and subsequently reacted with a fluorescently labeled appropriate secondary antibody (purchased from LI-COR, Inc.). The FGFR2 protein or GAPDH on the blot was detected using Odyssey Imaging System (manufactured by LI-COR, Inc.).

[0824] The results are shown in FIG. 145. The results indicated that the expression level of the antigen FGFR2 in

the SNU16 tumor is increased by administration of AZD4547 as compared with the untreated control group.

Example 21

In Vivo Effect of the Combined Use of Ahumanized Anti-FGFR2 Antibody (hFR2-14_H19/L1) and Ki23057 on a FGFR2-Expressing Cancer Cell Line

[0825] A human stomach cancer cell line SNU-16 (purchased from ATCC) was adjusted to 5×10^7 cells/mL with a 1:1 mixed solution of PBS and Matrigel (purchased from Nippon Becton Dickinson Company, Ltd.), and 0.1 mL of the cell suspension was subcutaneously transplanted to the axillary region of each nude mouse (CAnN.Cg-Foxnl^{tmu}/CrJCrJ, female, 5 to 6 weeks old, purchased from Charles River Laboratories Japan Inc.). The mice were grouped according to their tumor volumes (n=5). hFR2-14_H19/L1 was intraperitoneally administered at a dose of 20 mg/kg to the cancer-bearing mice, and Ki23057 was forcibly administered orally at a dose of 5 mg/kg or 20 mg/kg to the mice. Administration of hFR2-14_H19/L1 was carried out 8, 11, 15, and 18 days after transplantation, and administration of Ki23057 was carried out 8, 9, 10, 11, 15, 16, 17, and 18 days after transplantation. The major axis (mm) and minor axis (mm) of the tumor were measured over time using an electronic digital caliper (manufactured by Mitsutoyo Corp.). The tumor volume was calculated according to the following expression:

$$\text{Tumor volume (mm}^3\text{)} = \frac{1}{2} \times [\text{Major axis of the tumor}] \times [\text{Minor axis of the tumor}] \times [\text{Minor axis of the tumor}]$$

[0826] The antitumor effect was evaluated on the basis of the percentage of tumor growth inhibition (TGI %) at 21 days after transplantation (3 days after final administration) and 32 days after transplantation (final assay day) according to the following expression:

$$\text{TGI (\%)} = (1 - A/B) \times 100$$

[0827] A: Average tumor volume of the compound administration group at the date of determination

[0828] B: Average tumor volume of the untreated control group at the date of determination

[0829] The results for hFR2-14_H19/L1 administered alone, Ki23057 administered alone, and hFR2-14_H19/L1 and Ki23057 administered in combination are shown in FIG. 146. TGI at 21 days after transplantation was 65% for the group given hFR2-14_H19/L1 alone, 7% for the group given Ki23057 (5 mg/kg) alone, and 29% for the group given Ki23057 (20 mg/kg) alone, whereas TGI at 21 days after transplantation was 66% for the group given hFR2-14_H19/L1 and Ki23057 (5 mg/kg) in combination and 75% for the group given hFR2-14_H19/L1 and Ki23057 (20 mg/kg) in combination. TGI at 32 days after transplantation (final assay day) was 65% for the group given hFR2-14_H19/L1 alone, 1% for the group given Ki23057 (5 mg/kg) alone, and -14% for the group given Ki23057 (20 mg/kg) alone, whereas TGI at 32 days after transplantation (final assay day) was 71% for the group given hFR2-14_H19/L1 and Ki23057 (5 mg/kg) in combination and 85% for the group given hFR2-14_H19/L1 and Ki23057 (20 mg/kg) in combination. The antitumor effect brought about by the combined use was sustained even after 14 days from the final administration.

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INDUSTRIAL APPLICABILITY

[0830] Use of the combination of the antibody with the other agent provided by the present invention enables treatment or prevention of various cancers.

Sequence Listing Free Text

[0831] SEQ ID NO: 1: N-terminal amino acid sequence of a band corresponding to the heavy chain of a rat anti-FGFR2 antibody FR2-10 (FIG. 9).

SEQ ID NO: 2: N-terminal amino acid sequence of a band corresponding to the light chain of a rat anti-FGFR2 antibody FR2-10 (FIG. 10).

SEQ ID NO: 3: N-terminal amino acid sequence of a band corresponding to the heavy chain of a rat anti-FGFR2 antibody FR2-13 (FIG. 11).

SEQ ID NO: 4: N-terminal amino acid sequence of a band corresponding to the light chain of a rat anti-FGFR2 antibody FR2-13 (FIG. 12).

SEQ ID NO: 5: N-terminal amino acid sequence of a band corresponding to the heavy chain of a rat anti-FGFR2 antibody FR2-14 (FIG. 13).

SEQ ID NO: 6: N-terminal amino acid sequence of a band corresponding to the light chain of a rat anti-FGFR2 antibody FR2-14 (FIG. 14).

SEQ ID NO: 7: Primer for gene amplification of a rat heavy chain (FIG. 15).

SEQ ID NO: 8: Sequencing primer for the heavy chain of FR2-10 (FIG. 16).

SEQ ID NO: 9: Sequencing primer for the heavy chain of FR2-13 (FIG. 17).

SEQ ID NO: 10: Sequencing primer for the heavy chain of FR2-14 (FIG. 18).

SEQ ID NO: 11: Nucleotide sequence of a cDNA encoding the heavy chain variable region of a rat anti-FGFR2 antibody FR2-10 (FIG. 19).

SEQ ID NO: 12: Amino acid sequence of the heavy chain variable region of the rat anti-FGFR2 antibody FR2-10 (FIG. 20).

SEQ ID NO: 13: Nucleotide sequence of a cDNA encoding the heavy chain variable region of a rat anti-FGFR2 antibody FR2-13 (FIG. 21).

SEQ ID NO: 14: Amino acid sequence of the heavy chain variable region of the rat anti-FGFR2 antibody FR2-13 (FIG. 22).

SEQ ID NO: 15: Nucleotide sequence of a cDNA encoding the heavy chain variable region of a rat anti-FGFR2 antibody FR2-14 (FIG. 23).

SEQ ID NO: 16: Amino acid sequence of the heavy chain variable region of the rat anti-FGFR2 antibody FR2-14 (FIG. 24).

SEQ ID NO: 17: Primer for gene amplification of a rat light chain (FIG. 25).

SEQ ID NO: 18: Sequencing primer for a rat light chain (FIG. 26).

SEQ ID NO: 19: Sequencing primer for the light chain of FR2-10 (FIG. 27).

SEQ ID NO: 20: Nucleotide sequence of a cDNA encoding the light chain variable region of a rat anti-FGFR2 antibody FR2-10 (FIG. 28).

SEQ ID NO: 21: Amino acid sequence of the light chain variable region of the rat anti-FGFR2 antibody FR2-10 (FIG. 29).

SEQ ID NO: 22: Primer for gene amplification of the rat FR2-13 or FR2-14 light chain (FIG. 30).

SEQ ID NO: 23: Nucleotide sequence of a cDNA encoding the light chain variable region of a rat anti-FGFR2 antibody FR2-13 (FIG. 31).

SEQ ID NO: 24: Amino acid sequence of the light chain variable region of the rat anti-FGFR2 antibody FR2-13 (FIG. 32).

SEQ ID NO: 25: Nucleotide sequence of a cDNA encoding the light chain variable region of a rat anti-FGFR2 antibody FR2-14 (FIG. 33).

SEQ ID NO: 26: Amino acid sequence of the light chain variable region of the rat anti-FGFR2 antibody FR2-14 (FIG. 34).

SEQ ID NO: 27: DNA fragment comprising a DNA sequence encoding the amino acids of a human 1 chain secretory signal sequence and a human 1 chain constant region (FIG. 35).

SEQ ID NO: 28: Primer F for a light chain expression vector (FIG. 36).

SEQ ID NO: 29: Primer R for a light chain expression vector (FIG. 37).

SEQ ID NO: 30: DNA fragment comprising a DNA sequence encoding the amino acids of a human heavy chain signal sequence and a human IgG1 constant region (FIG. 38).

SEQ ID NO: 31: Nucleotide sequence of the light chain of human chimeric FR2-10 (cFR2-10) (FIG. 39). In this sequence, nucleotide positions 1 to 60 represent a signal sequence, which is usually not contained in the nucleotide sequences of most mature cFR2-10 light chains.

SEQ ID NO: 32: Amino acid sequence of the light chain of human chimeric FR2-10 (cFR2-10) (FIG. 40). In this sequence, amino acid positions 1 to 20 represent a signal sequence, which is usually not contained in the amino acid sequences of most mature cFR2-10 light chains.

SEQ ID NO: 33: Primer set F for the light chain of human chimeric FR2-10 (FIG. 41).

SEQ ID NO: 34: Primer set R for the light chain of human chimeric FR2-10 (FIG. 42).

SEQ ID NO: 35: Nucleotide sequence of the heavy chain of human chimeric FR2-10 (cFR2-10) (FIG. 43). In this sequence, nucleotide positions 1 to 57 represent a signal sequence, which is usually not contained in the nucleotide sequences of most mature cFR2-10 heavy chains.

SEQ ID NO: 36: Amino acid sequence of the heavy chain of human chimeric FR2-10 (cFR2-10) (FIG. 44). In this sequence, amino acid positions 1 to 19 represent a signal sequence, which is usually not contained in the amino acid sequences of most mature cFR2-10 heavy chains.

SEQ ID NO: 37: Primer set F for the heavy chain of human chimeric FR2-10 (FIG. 45).

SEQ ID NO: 38: Primer set R for the heavy chain of human chimeric FR2-10 (FIG. 46).

SEQ ID NO: 39: Nucleotide sequence of the light chain of human chimeric FR2-13 (cFR2-13) (FIG. 47). In this sequence, nucleotide positions 1 to 60 represent a signal sequence, which is usually not contained in the nucleotide sequences of most mature cFR2-13 light chains.

SEQ ID NO: 40: Amino acid sequence of the light chain of human chimeric FR2-13 (cFR2-13) (FIG. 48). In this sequence, amino acid positions 1 to 20 represent a signal sequence, which is usually not contained in the amino acid sequences of most mature cFR2-13 light chains.

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SEQ ID NO: 41: Primer F for the light chain of human chimeric FR2-13 (FIG. 49).

SEQ ID NO: 42: Primer R for the light chain of human chimeric FR2-13 (FIG. 50).

SEQ ID NO: 43: Nucleotide sequence of the heavy chain of human chimeric FR2-13 (cFR2-13) (FIG. 51). In this sequence, nucleotide positions 1 to 57 represent a signal sequence, which is usually not contained in the nucleotide sequences of most mature cFR2-13 heavy chains.

SEQ ID NO: 44: Amino acid sequence of the heavy chain of human chimeric FR2-13 (cFR2-13) (FIG. 52). In this sequence, amino acid positions 1 to 19 represent a signal sequence, which is usually not contained in the amino acid sequences of most mature cFR2-13 heavy chains.

SEQ ID NO: 45: Primer F for the heavy chain of human chimeric FR2-13 (FIG. 53).

SEQ ID NO: 46: Primer R for the heavy chain of human chimeric FR2-13 (FIG. 54).

SEQ ID NO: 47: Nucleotide sequence of the light chain of human chimeric FR2-14 (cFR2-14) (FIG. 55). In this sequence, nucleotide positions 1 to 60 represent a signal sequence, which is usually not contained in the nucleotide sequences of most mature cFR2-14 light chains.

SEQ ID NO: 48: Amino acid sequence of the light chain of human chimeric FR2-14 (cFR2-14) (FIG. 56). In this sequence, amino acid positions 1 to 20 represent a signal sequence, which is usually not contained in the amino acid sequences of most mature cFR2-14 light chains.

SEQ ID NO: 49: Primer for the light chain of human chimeric FR2-14 (FIG. 57).

SEQ ID NO: 50: Nucleotide sequence of the heavy chain of human chimeric FR2-14 (cFR2-14) (FIG. 58). In this sequence, nucleotide positions 1 to 57 represent a signal sequence, which is usually not contained in the nucleotide sequences of most mature cFR2-14 heavy chains.

SEQ ID NO: 51: Amino acid sequence of the heavy chain of human chimeric FR2-14 (cFR2-14) (FIG. 59). In this sequence, amino acid positions 1 to 19 represent a signal sequence, which is usually not contained in the amino acid sequences of most mature cFR2-14 heavy chains.

SEQ ID NO: 52: Amino acid sequence of the heavy chain CDR1 of the rat anti-FGFR2 antibody FR2-10 (FIG. 60).

SEQ ID NO: 53: Amino acid sequence of the heavy chain CDR2 of the rat anti-FGFR2 antibody FR2-10 (FIG. 61).

SEQ ID NO: 54: Amino acid sequence of the heavy chain CDR3 of the rat anti-FGFR2 antibody FR2-10 (FIG. 62).

SEQ ID NO: 55: Amino acid sequence of the heavy chain CDR1 of the rat anti-FGFR2 antibody FR2-13 (FIG. 63).

SEQ ID NO: 56: Amino acid sequence of the heavy chain CDR2 of the rat anti-FGFR2 antibody FR2-13 (FIG. 64).

SEQ ID NO: 57: Amino acid sequence of the heavy chain CDR3 of the rat anti-FGFR2 antibody FR2-13 (FIG. 65).

SEQ ID NO: 58: Amino acid sequence of the heavy chain CDR1 of the rat anti-FGFR2 antibody FR2-14 (FIG. 66).

SEQ ID NO: 59: Amino acid sequence of the heavy chain CDR2 of the rat anti-FGFR2 antibody FR2-14 (FIG. 67).

SEQ ID NO: 60: Amino acid sequence of the heavy chain CDR3 of the rat anti-FGFR2 antibody FR2-14 (FIG. 68).

SEQ ID NO: 61: Amino acid sequence of the light chain CDR1 of the rat anti-FGFR2 antibody FR2-10 (FIG. 69).

SEQ ID NO: 62: Amino acid sequence of the light chain CDR2 of the rat anti-FGFR2 antibody FR2-10 (FIG. 70).

SEQ ID NO: 63: Amino acid sequence of the light chain CDR3 of the rat anti-FGFR2 antibody FR2-10 (FIG. 71).

SEQ ID NO: 64: Amino acid sequence of the light chain CDR1 of the rat anti-FGFR2 antibody FR2-13 (FIG. 72).

SEQ ID NO: 65: Amino acid sequence of the light chain CDR2 of the rat anti-FGFR2 antibody FR2-13 (FIG. 73).

SEQ ID NO: 66: Amino acid sequence of the light chain CDR3 of the rat anti-FGFR2 antibody FR2-13 (FIG. 74).

SEQ ID NO: 67: Amino acid sequence of the light chain CDR1 of the rat anti-FGFR2 antibody FR2-14 (FIG. 75).

SEQ ID NO: 68: Amino acid sequence of the light chain CDR2 of the rat anti-FGFR2 antibody FR2-14 (FIG. 76).

SEQ ID NO: 69: Amino acid sequence of the light chain CDR3 of the rat anti-FGFR2 antibody FR2-14 (FIG. 77).

SEQ ID NO: 70: Amino acid sequence of human FGFR2 IIIb (FIG. 78).

SEQ ID NO: 71: Amino acid sequence of human FGFR2 IIIc (FIG. 79).

SEQ ID NO: 72: Nucleotide sequence of a humanized FR2-14 light chain (hFR2-14_L1) (FIG. 80). In this sequence, nucleotide positions 1 to 60 represent a signal sequence, which is usually not contained in the nucleotide sequences of most mature hFR2-14_L1 light chains.

SEQ ID NO: 73: Amino acid sequence of the humanized FR2-14 light chain (hFR2-14_L1) (FIG. 81). In this sequence, amino acid positions 1 to 20 represent a signal sequence, which is usually not contained in the amino acid sequences of most mature hFR2-14_L1 light chains.

SEQ ID NO: 74: Nucleotide sequence of a humanized FR2-14 heavy chain (hFR2-14_H1) (FIG. 82). In this sequence, nucleotide positions 1 to 57 represent a signal sequence, which is usually not contained in the nucleotide sequences of most of mature hFR2-14_H1 heavy chains.

SEQ ID NO: 75: Amino acid sequence of the humanized FR2-14 heavy chain (hFR2-14_H1) (FIG. 83). In this sequence, amino acid positions 1 to 19 represent a signal sequence, which is usually not contained in the amino acid sequences of most mature hFR2-14_H1 heavy chains.

SEQ ID NO: 76: Nucleotide sequence of a humanized FR2-14 heavy chain (hFR2-14_H2) (FIG. 84). In this sequence, nucleotide positions 1 to 57 represent a signal sequence, which is usually not contained in the nucleotide sequences of most mature hFR2-14_H2 heavy chains.

SEQ ID NO: 77: Amino acid sequence of the humanized FR2-14 heavy chain (hFR2-14_H2) (FIG. 85). In this sequence, amino acid positions 1 to 19 represent a signal sequence, which is usually not contained in the amino acid sequences of most mature hFR2-14_H2 heavy chains.

SEQ ID NO: 78: Nucleotide sequence of a humanized FR2-14 heavy chain (hFR2-14_H3) (FIG. 86). In this sequence, nucleotide positions 1 to 57 represent a signal sequence, which is usually not contained in the nucleotide sequences of most mature hFR2-14_H3 heavy chains.

SEQ ID NO: 79: Amino acid sequence of the humanized FR2-14 heavy chain (hFR2-14_H3) (FIG. 87). In this sequence, amino acid positions 1 to 19 represent a signal sequence, which is usually not contained in the amino acid sequences of most mature hFR2-14_H3 heavy chains.

SEQ ID NO: 80: Nucleotide sequence of a humanized FR2-14 heavy chain (hFR2-14_H4) (FIG. 88). In this sequence, nucleotide positions 1 to 57 represent a signal sequence, which is usually not contained in the nucleotide sequences of most mature hFR2-14_H4 heavy chains.

SEQ ID NO: 81: Amino acid sequence of the humanized FR2-14 heavy chain (hFR2-14_H4) (FIG. 89). In this sequence, amino acid positions 1 to 19 represent a signal

sequence, nucleotide positions 1 to 57 represent a signal sequence, which is usually not contained in the nucleotide sequences of most mature hFR2-14_H11 heavy chains.

SEQ ID NO: 95: Amino acid sequence of the humanized FR2-14 heavy chain (hFR2-14_H11) (FIG. 103). In this sequence, amino acid positions 1 to 19 represent a signal sequence, which is usually not contained in the amino acid sequences of most mature hFR2-14_H11 heavy chains.

SEQ ID NO: 96: Nucleotide sequence of a humanized FR2-14 heavy chain (hFR2-14_H12 or hFR2-14_H19) (FIG. 104). In this sequence, nucleotide positions 1 to 57 represent a signal sequence, which is usually not contained in the nucleotide sequences of most mature hFR2-14_H12 or hFR2-14_H19 heavy chains.

SEQ ID NO: 97: Amino acid sequence of the humanized FR2-14 heavy chain (hFR2-14_H12 or hFR2-14_H19) (FIG. 105). In this sequence, amino acid positions 1 to 19 represent a signal sequence, which is usually not contained in the amino acid sequences of most mature hFR2-14_H12 or hFR2-14_H19 heavy chains.

SEQ ID NO: 98: Nucleotide sequence of a humanized FR2-14 heavy chain (hFR2-14_H13) (FIG. 106). In this sequence, nucleotide positions 1 to 57 represent a signal sequence, which is usually not contained in the nucleotide sequences of most mature hFR2-14_H13 heavy chains.

SEQ ID NO: 99: Amino acid sequence of the humanized FR2-14 heavy chain (hFR2-14_H13) (FIG. 107). In this sequence, amino acid positions 1 to 19 represent a signal sequence, which is usually not contained in the amino acid sequences of most mature hFR2-14_H13 heavy chains.

SEQ ID NO: 100: Nucleotide sequence of a humanized FR2-14 heavy chain (hFR2-14_H14) (FIG. 108). In this sequence, nucleotide positions 1 to 57 represent a signal sequence, which is usually not contained in the nucleotide sequences of most mature hFR2-14_H14 heavy chains.

SEQ ID NO: 101: Amino acid sequence of the humanized FR2-14 heavy chain (hFR2-14_H14) (FIG. 109). In this sequence, amino acid positions 1 to 19 represent a signal sequence, which is usually not contained in the amino acid sequences of most mature hFR2-14_H14 heavy chains.

SEQ ID NO: 102: Nucleotide sequence of a humanized FR2-14 heavy chain (hFR2-14_H15) (FIG. 110). In this sequence, nucleotide positions 1 to 57 represent a signal sequence, which is usually not contained in the nucleotide sequences of most mature hFR2-14_H15 heavy chains.

SEQ ID NO: 103: Amino acid sequence of the humanized FR2-14 heavy chain (hFR2-14_H15) (FIG. 111). In this sequence, amino acid positions 1 to 19 represent a signal sequence, which is usually not contained in the amino acid sequences of most mature hFR2-14_H15 heavy chains.

SEQ ID NO: 104: Nucleotide sequence of a humanized FR2-14 heavy chain (hFR2-14_H16) (FIG. 112). In this sequence, nucleotide positions 1 to 57 represent a signal sequence, which is usually not contained in the nucleotide sequences of most mature hFR2-14_H16 heavy chains.

SEQ ID NO: 105: Amino acid sequence of the humanized FR2-14 heavy chain (hFR2-14_H16) (FIG. 113). In this sequence, amino acid positions 1 to 19 represent a signal sequence, which is usually not contained in the amino acid sequences of most mature hFR2-14_H16 heavy chains.

SEQ ID NO: 106: Nucleotide sequence of a humanized FR2-14 heavy chain (hFR2-14_H17) (FIG. 114). In this sequence, nucleotide positions 1 to 57 represent a signal

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sequence, which is usually not contained in the nucleotide sequences of most mature hFR2-14_H17 heavy chains.

SEQ ID NO: 107: Amino acid sequence of the humanized FR2-14 heavy chain (hFR2-14_H17) (FIG. 115). In this sequence, amino acid positions 1 to 19 represent a signal sequence, which is usually not contained in the amino acid sequences of most mature hFR2-14_H17 heavy chains.

SEQ ID NO: 108: Nucleotide sequence of a humanized FR2-14 heavy chain (hFR2-14_H18) (FIG. 116). In this sequence, nucleotide positions 1 to 57 represent a signal sequence, which is usually not contained in the nucleotide sequences of most mature hFR2-14_H18 heavy chains.

SEQ ID NO: 109: Amino acid sequence of the humanized FR2-14 heavy chain (hFR2-14_H18) (FIG. 117). In this sequence, amino acid positions 1 to 19 represent a signal sequence, which is usually not contained in the amino acid sequences of most mature hFR2-14_H18 heavy chains.

SEQ ID NO: 110: Primer VH3A-F for an hFR2-14_H2 type heavy chain (FIG. 118).

SEQ ID NO: 111: Primer VH3A-R for an hFR2-14_H2 type heavy chain (FIG. 119).

SEQ ID NO: 112: Primer D23fw for gene amplification of D2 (FIG. 120).

SEQ ID NO: 113: Primer D23ry for gene amplification of D2 (FIG. 121).

SEQUENCE LISTING

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<211> LENGTH: 12

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<210> SEQ ID NO 2

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<210> SEQ ID NO 3

<211> LENGTH: 5

<212> TYPE: PRT

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<210> SEQ ID NO 4

<211> LENGTH: 17

<212> TYPE: PRT

<213> ORGANISM: Rattus norvegicus

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Glu

<210> SEQ ID NO 5

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<213> ORGANISM: Rattus norvegicus

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<211> LENGTH: 17
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Glu

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<212> TYPE: DNA
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<400> SEQUENCE: 11

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Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Arg	
1			5						10					15		
tct	ctg	aaa	cta	tcc	tgt	gta	gcc	tct	gga	ttc	aga	ttc	aat	gac	ttt	96
Ser	Leu	Lys	Leu	Ser	Cys	Val	Ala	Ser	Gly	Phe	Arg	Phe	Asn	Asp	Phe	
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tgg	atg	acc	tgg	atc	cgc	cag	gct	cca	ggg	aag	ggg	ctg	gag	tgg	gtt	144
Trp	Met	Thr	Trp	Ile	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
		35					40					45				
gca	tcc	att	act	tat	act	ggg	gat	aac	act	tac	tat	gca	ggc	tct	gtg	192
Ala	Ser	Ile	Thr	Tyr	Thr	Gly	Asp	Asn	Thr	Tyr	Tyr	Ala	Gly	Ser	Val	
		50				55						60				
aag	ggc	cga	atc	act	atc	tcc	aga	gat	aat	gcg	aag	agc	acc	cta	tac	240
Lys	Gly	Arg	Ile	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Ser	Thr	Leu	Tyr	
65					70					75				80		
ctg	caa	atg	aac	agt	ctg	agg	tct	gag	gac	acg	gcc	act	tat	tac	tgt	288
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Thr	Tyr	Tyr	Cys	
			85						90					95		
aca	aga	gat	gac	tac	gga	gga	tat	agc	ccc	tac	tat	atg	gat	gcc	tgg	336
Thr	Arg	Asp	Asp	Tyr	Gly	Gly	Tyr	Ser	Pro	Tyr	Tyr	Met	Asp	Ala	Trp	
			100					105						110		
ggg	caa	gga	act	tca	gtc	act	gtc	tcc	tca							366
Gly	Gln	Gly	Thr	Ser	Val	Thr	Val	Ser	Ser							
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Ser	Leu	Lys	Leu	Ser	Cys	Val	Ala	Ser	Gly	Phe	Arg	Phe	Asn	Asp	Phe
		20						25					30		
Trp	Met	Thr	Trp	Ile	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
		35					40					45			
Ala	Ser	Ile	Thr	Tyr	Thr	Gly	Asp	Asn	Thr	Tyr	Tyr	Ala	Gly	Ser	Val
		50				55						60			
Lys	Gly	Arg	Ile	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Ser	Thr	Leu	Tyr
65					70					75				80	
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Thr	Tyr	Tyr	Cys
			85						90					95	
Thr	Arg	Asp	Asp	Tyr	Gly	Gly	Tyr	Ser	Pro	Tyr	Tyr	Met	Asp	Ala	Trp
		100						105					110		
Gly	Gln	Gly	Thr	Ser	Val	Thr	Val	Ser	Ser						
		115					120								

<210> SEQ ID NO 13
 <211> LENGTH: 354
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Gln	Val	Lys	Leu	Leu	Gln	Ser	Gly	Ala	Glu	Leu	Val	Lys	Pro	Gly	Ala	
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tca	gtg	aag	ttg	tcc	tgc	aag	act	tct	ggt	ttt	acc	ttc	agc	act	agc	96
Ser	Val	Lys	Leu	Ser	Cys	Lys	Thr	Ser	Gly	Phe	Thr	Phe	Ser	Thr	Ser	
			20					25					30			
tat	atg	agt	tgg	ttg	aag	cag	gtg	cct	gga	ccg	agt	att	gag	tgg	att	144
Tyr	Met	Ser	Trp	Leu	Lys	Gln	Val	Pro	Gly	Pro	Ser	Ile	Glu	Trp	Ile	
		35					40					45				
gga	tgg	att	tat	gct	gga	gat	ggt	ggt	act	aag	tat	aat	cag	aag	ttc	192
Gly	Trp	Ile	Tyr	Ala	Gly	Asp	Gly	Gly	Thr	Lys	Tyr	Asn	Gln	Lys	Phe	
	50					55					60					
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Lys	Gly	Lys	Ala	Thr	Leu	Thr	Val	Asp	Lys	Ser	Ser	Ser	Thr	Ala	Tyr	
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atg	gat	ctc	agc	agc	ctg	aca	tct	gag	gac	gct	gca	gtc	tat	ttt	tgt	288
Met	Asp	Leu	Ser	Ser	Leu	Thr	Ser	Glu	Asp	Ala	Ala	Val	Tyr	Phe	Cys	
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gca	acg	gat	ggt	tat	ggg	gat	tgg	ttt	gct	tac	tgg	ggc	caa	ggc	act	336
Ala	Thr	Asp	Gly	Tyr	Gly	Asp	Trp	Phe	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	
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ctg	gtc	act	gtc	tct	tca											354
Leu	Val	Thr	Val	Ser	Ser											
			115													

<210> SEQ ID NO 14

<211> LENGTH: 118

<212> TYPE: PRT

<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 14

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Ser	Val	Lys	Leu	Ser	Cys	Lys	Thr	Ser	Gly	Phe	Thr	Phe	Ser	Thr	Ser	
			20					25					30			
Tyr	Met	Ser	Trp	Leu	Lys	Gln	Val	Pro	Gly	Pro	Ser	Ile	Glu	Trp	Ile	
		35					40					45				
Gly	Trp	Ile	Tyr	Ala	Gly	Asp	Gly	Gly	Thr	Lys	Tyr	Asn	Gln	Lys	Phe	
	50					55					60					
Lys	Gly	Lys	Ala	Thr	Leu	Thr	Val	Asp	Lys	Ser	Ser	Ser	Thr	Ala	Tyr	
	65				70					75				80		
Met	Asp	Leu	Ser	Ser	Leu	Thr	Ser	Glu	Asp	Ala	Ala	Val	Tyr	Phe	Cys	
			85					90						95		
Ala	Thr	Asp	Gly	Tyr	Gly	Asp	Trp	Phe	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	
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Leu	Val	Thr	Val	Ser	Ser											
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<212> TYPE: DNA

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<220> FEATURE:

<221> NAME/KEY: CDS

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Ser Val Lys Leu Ser Cys Lys Thr Ser Gly Phe Thr Phe Ser Thr Ser				
	20	25	30	
tat atg agt tgg ttg aag cag gtg cct gga ccg agt act gag tgg att				144
Tyr Met Ser Trp Leu Lys Gln Val Pro Gly Pro Ser Thr Glu Trp Ile				
	35	40	45	
gga tgg att tat gct gga gat ggt ggt act aag tat aat cag aag ttc				192
Gly Trp Ile Tyr Ala Gly Asp Gly Gly Thr Lys Tyr Asn Gln Lys Phe				
	50	55	60	
aag ggc aag gcc aca ctg aca gta gac aaa ttt tct agc aca gca tac				240
Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Phe Ser Ser Thr Ala Tyr				
	65	70	75	80
atg gat ctc agc agc ctg aca tct gag gac gct gca gtc tat ttc tgt				288
Met Asp Leu Ser Ser Leu Thr Ser Glu Asp Ala Ala Val Tyr Phe Cys				
	85	90	95	
gca acg gat ggt tat ggg gat tgg ttt act tac tgg ggc caa ggc act				336
Ala Thr Asp Gly Tyr Gly Asp Trp Phe Thr Tyr Trp Gly Gln Gly Thr				
	100	105	110	
ctg gtc act gtc tct tca				354
Leu Val Thr Val Ser Ser				
	115			

<210> SEQ ID NO 16
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<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 16

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Tyr Met Ser Trp Leu Lys Gln Val Pro Gly Pro Ser Thr Glu Trp Ile				
	35	40	45	
Gly Trp Ile Tyr Ala Gly Asp Gly Gly Thr Lys Tyr Asn Gln Lys Phe				
	50	55	60	
Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Phe Ser Ser Thr Ala Tyr				
	65	70	75	80
Met Asp Leu Ser Ser Leu Thr Ser Glu Asp Ala Ala Val Tyr Phe Cys				
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Ala Thr Asp Gly Tyr Gly Asp Trp Phe Thr Tyr Trp Gly Gln Gly Thr				
	100	105	110	
Leu Val Thr Val Ser Ser				
	115			

<210> SEQ ID NO 17
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

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<210> SEQ ID NO 18
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 18

tccagttgct aactgttccg 20

<210> SEQ ID NO 19
<211> LENGTH: 19
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

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cagtggtatc aacgcagag 19

<210> SEQ ID NO 20
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<212> TYPE: DNA
<213> ORGANISM: Rattus norvegicus
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<221> NAME/KEY: CDS
<222> LOCATION: (1)..(327)

<400> SEQUENCE: 20

gac atc cag atg acc cag tct cca tct tcc ctg tct gca ttt ctg gga 48
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Phe Leu Gly
1 5 10 15

gac aga gtc act att act tgc cgg gca agt caa gac att gga aat tat 96
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Gly Asn Tyr
20 25 30

tta aga tgg ttc cag cag aaa ccg ggg aaa tct cct agg ctt atg att 144
Leu Arg Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Arg Leu Met Ile
35 40 45

tat ggt gca acc aac ttg gca aat ggg gtc cca tca agg ttc agt ggc 192
Tyr Gly Ala Thr Asn Leu Ala Asn Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

agt agg tct ggg tca gat tat tct ctg acc atc aac aac ttg gag tct 240
Ser Arg Ser Gly Ser Asp Tyr Ser Leu Thr Ile Asn Asn Leu Glu Ser
65 70 75 80

gaa gac atg gct att tat tac tgt ctg aag cat aat gag tat cca ttc 288
Glu Asp Met Ala Ile Tyr Tyr Cys Leu Lys His Asn Glu Tyr Pro Phe
85 90 95

acg ttc ggc tca ggg acg aag ttg gaa ata aaa cgg gct 327
Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg Ala
100 105

<210> SEQ ID NO 21
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 21

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Phe Leu Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Gly Asn Tyr

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20										25					30				
Leu	Arg	Trp	Phe	Gln	Gln	Lys	Pro	Gly	Lys	Ser	Pro	Arg	Leu	Met	Ile				
35										40					45				
Tyr	Gly	Ala	Thr	Asn	Leu	Ala	Asn	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly				
50										55					60				
Ser	Arg	Ser	Gly	Ser	Asp	Tyr	Ser	Leu	Thr	Ile	Asn	Asn	Leu	Glu	Ser				
65										70					75				
Glu	Asp	Met	Ala	Ile	Tyr	Tyr	Cys	Leu	Lys	His	Asn	Glu	Tyr	Pro	Phe				
85										90					95				
Thr	Phe	Gly	Ser	Gly	Thr	Lys	Leu	Glu	Ile	Lys	Arg	Ala							
100										105									
<210> SEQ ID NO 22																			
<211> LENGTH: 28																			
<212> TYPE: DNA																			
<213> ORGANISM: Artificial Sequence																			
<220> FEATURE:																			
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer																			
<400> SEQUENCE: 22																			
tacgtgctgt ctttgctgtc ctgatacag															28				
<210> SEQ ID NO 23																			
<211> LENGTH: 330																			
<212> TYPE: DNA																			
<213> ORGANISM: Rattus norvegicus																			
<220> FEATURE:																			
<221> NAME/KEY: CDS																			
<222> LOCATION: (1)..(330)																			
<400> SEQUENCE: 23																			
gac	atc	cag	atg	aca	cag	tct	cca	gct	tcc	ctg	tct	gca	tct	ctg	gga				
Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ala	Ser	Leu	Ser	Ala	Ser	Leu	Gly				
1				5				10						15	48				
gaa	act	gtc	acc	atc	gaa	tgt	cga	gca	agt	gag	gac	att	tac	agt	aat				
Glu	Thr	Val	Thr	Ile	Glu	Cys	Arg	Ala	Ser	Glu	Asp	Ile	Tyr	Ser	Asn				
20										25					30				
tta	gcg	tgg	tat	cag	cag	aaa	cca	ggg	aac	tct	cct	cag	ctc	ctg	atc				
Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Asn	Ser	Pro	Gln	Leu	Leu	Ile				
35										40					45				
tat	gat	gca	aat	atc	ttg	gca	gat	ggg	gtc	cca	tca	cgg	ttc	agt	ggc				
Tyr	Asp	Ala	Asn	Ile	Leu	Ala	Asp	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly				
50										55					60				
agt	ggg	tct	ggc	aca	cag	tat	tct	cta	aag	ata	aac	agc	ctg	caa	tct				
Ser	Gly	Ser	Gly	Thr	Gln	Tyr	Ser	Leu	Lys	Ile	Asn	Ser	Leu	Gln	Ser				
65										70					75				
gaa	gat	gtc	gca	agt	tat	ttc	tgt	caa	cag	tat	aac	aat	tat	cct	ccg				
Glu	Asp	Val	Ala	Ser	Tyr	Phe	Cys	Gln	Gln	Tyr	Asn	Asn	Tyr	Pro	Pro				
85										90					95				
ttc	acg	ttt	gga	gtt	ggg	acc	aag	ctg	gaa	ctg	aaa	cgg	gct						
Phe	Thr	Phe	Gly	Val	Gly	Thr	Lys	Leu	Glu	Leu	Lys	Arg	Ala						
100										105					110				
<210> SEQ ID NO 24																			
<211> LENGTH: 110																			
<212> TYPE: PRT																			
<213> ORGANISM: Rattus norvegicus																			
<400> SEQUENCE: 24																			

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Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Leu Gly
1           5           10           15
Glu Thr Val Thr Ile Glu Cys Arg Ala Ser Glu Asp Ile Tyr Ser Asn
          20           25           30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Asn Ser Pro Gln Leu Leu Ile
          35           40           45
Tyr Asp Ala Asn Ile Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
          50           55           60
Ser Gly Ser Gly Thr Gln Tyr Ser Leu Lys Ile Asn Ser Leu Gln Ser
65           70           75           80
Glu Asp Val Ala Ser Tyr Phe Cys Gln Gln Tyr Asn Asn Tyr Pro Pro
          85           90           95
Phe Thr Phe Gly Val Gly Thr Lys Leu Glu Leu Lys Arg Ala
          100          105          110

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<210> SEQ ID NO 25
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Rattus norvegicus
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(330)

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<400> SEQUENCE: 25

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gac atc cag atg aca cag tct cca gct tcc ctg tct gca tct ctg gga      48
Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Leu Gly
1           5           10           15
gaa act gtc acc atc gaa tgt cga gca agt gag gac ata tac agt aat      96
Glu Thr Val Thr Ile Glu Cys Arg Ala Ser Glu Asp Ile Tyr Ser Asn
          20           25           30
tta gcg tgg tat cag cag aaa cca ggg aac tct cct cag ctc ctg atc     144
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Asn Ser Pro Gln Leu Leu Ile
          35           40           45
tat gat gca aat atc ctg gca gat ggg gtc cca tca cgg ttc agt ggc     192
Tyr Asp Ala Asn Ile Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
          50           55           60
agt ggg tct ggc aca cag tat tct cta aag ata aac agc ctg caa tct     240
Ser Gly Ser Gly Thr Gln Tyr Ser Leu Lys Ile Asn Ser Leu Gln Ser
65           70           75           80
gaa gat gtc gca agt tat ttc tgt caa cag tat aac aat tat cct ccg     288
Glu Asp Val Ala Ser Tyr Phe Cys Gln Gln Tyr Asn Asn Tyr Pro Pro
          85           90           95
ttc acg ttt gga gct ggg acc aag ctg gaa ctg aaa cgg gct           330
Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala
          100          105          110

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<210> SEQ ID NO 26
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

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<400> SEQUENCE: 26

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Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Leu Gly
1           5           10           15
Glu Thr Val Thr Ile Glu Cys Arg Ala Ser Glu Asp Ile Tyr Ser Asn
          20           25           30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Asn Ser Pro Gln Leu Leu Ile

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35	40	45
Tyr Asp Ala Asn Ile Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly		
50	55	60
Ser Gly Ser Gly Thr Gln Tyr Ser Leu Lys Ile Asn Ser Leu Gln Ser		
65	70	75 80
Glu Asp Val Ala Ser Tyr Phe Cys Gln Gln Tyr Asn Asn Tyr Pro Pro		
85	90	95
Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala		
100	105	110

<210> SEQ ID NO 27
<211> LENGTH: 449
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

```
gcctccggac tctagagcca ccatggtgct gcagaccag gtgttcatt cctgctgct 60
gtggatctcc ggcgctacg gcgatatcgt gatgattaaa cgtacggtgg ccgcccctc 120
cgtgttcatt tccccccct ccgacgagca gctgaagtcc ggccacgcct ccgtggtgtg 180
cctgctgaat aactcttacc ccagagaggg caaggtgcag tggaaggtgg acaacgcct 240
gcagtcgggg aactcccagg agagcgtgac cgagcaggac agcaaggaca gcacctacag 300
cctgagcagc accctgacct tgagcaaagc cgactacgag aagcacaagg tgtacgcctg 360
cgaggtgacc caccaggggc tgagctcccc cgtcaccaag agcttcaaca ggggggagtg 420
ttagggggcc gttaaaccgg gggaggcta 449
```

<210> SEQ ID NO 28
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 28

```
tataccgctg acctctagct agagcttggc 30
```

<210> SEQ ID NO 29
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 29

```
gctatggcag ggctgcccgc cccgacgttg 30
```

<210> SEQ ID NO 30
<211> LENGTH: 1132
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 30

```
gcctccggac tctagagcca ccatgaaaca cctgtggttc ttctctctgc tggtagcagc 60
tcccagatgg gtgctgagcc aggtgcaatt gtgcaggcgg ttagctcagc ctccaccaag 120
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ggcccaagcg ttttccccct ggcacctcc tccaagagca cctctggcgg cacagccgcc	180
ctgggctgcc tggtaagga ctacttcccc gaacctgtga cctgagctg gaactcaggc	240
gccctgacca gggcgctgca caccttcccc gctgtcctgc agtctcagg actctactcc	300
ctcagcagcg tggtagccgt gccctccagc agcttgggca cccagaccta catctgcaac	360
gtgaatcaca agcccagcaa caccaaggtg gacaagagag ttgagcccaa atcttgtgac	420
aaaactcaca catgcccacc ctgcccagca cctgaactcc tggggggacc ctcagtcttc	480
ctcttcccc caaaacccaa ggacacctc atgatctccc ggacctctga ggtcacatgc	540
gtggtggtgg acgtgagcca cgaagacct gaggtcaagt tcaactggta cgtggacggc	600
gtggaggtgc ataatgcaa gacaaagccc cgaggaggc agtacaacag cacgtaccgg	660
gtggtcagcg tcctcaccgt cctgcaccag gactggctga atggcaagga gtacaagtgc	720
aagggtctcca acaaagccct cccagccccc atcgagaaaa ccatctccaa agccaaaggc	780
cagccccggg aaccacaggt gtacacctg ccccatccc gggaggagat gaccaagaac	840
caggtcagcc tgacctgcct ggtcaaaggc ttctatccca gcgacatcgc cgtggagtgg	900
gagagcaatg gccagcccga gaacaactac aagaccaccc ctcccgtgct ggactccgac	960
ggctcttct tcctctacag caagctcacc gtggacaaga gcagggtggca gcagggcaac	1020
gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacca gaagagcctc	1080
tcctgtctc cgggcaaatg agatatcggg ccggtttaa cgggggaggc ta	1132

<210> SEQ ID NO 31
<211> LENGTH: 702
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(702)

<400> SEQUENCE: 31

atg gtg ctg cag acc cag gtg ttc atc tcc ctg ctg ctg tgg atc tcc	48
Met Val Leu Gln Thr Gln Val Phe Ile Ser Leu Leu Leu Trp Ile Ser	
1 5 10 15	
ggc gcg tac ggc gac atc cag atg acc cag tct cca tct tcc ctg tct	96
Gly Ala Tyr Gly Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser	
20 25 30	
gca ttt ctg gga gac aga gtc act att act tgc cgg gca agt caa gac	144
Ala Phe Leu Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp	
35 40 45	
att gga aat tat tta aga tgg ttc cag cag aaa ccg ggg aaa tct cct	192
Ile Gly Asn Tyr Leu Arg Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro	
50 55 60	
agg ctt atg att tat ggt gca acc aac ttg gca aat ggg gtc cca tca	240
Arg Leu Met Ile Tyr Gly Ala Thr Asn Leu Ala Asn Gly Val Pro Ser	
65 70 75 80	
agg ttc agt ggc agt agg tct ggg tca gat tat tct ctg acc atc aac	288
Arg Phe Ser Gly Ser Arg Ser Gly Ser Asp Tyr Ser Leu Thr Ile Asn	
85 90 95	
aac ttg gag tct gaa gac atg gct att tat tac tgt ctg aag cat aat	336
Asn Leu Glu Ser Glu Asp Met Ala Ile Tyr Tyr Cys Leu Lys His Asn	
100 105 110	

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gag tat cca ttc acg ttc ggc tca ggg acg aag ttg gaa ata aaa cgg	384
Glu Tyr Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg	
115 120 125	
gct gtg gcc gcc ccc tcc gtg ttc atc ttc ccc ccc tcc gac gag cag	432
Ala Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln	
130 135 140	
ctg aag tcc ggc acc gcc tcc gtg gtg tgc ctg ctg aat aac ttc tac	480
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr	
145 150 155 160	
ccc aga gag gcc aag gtg cag tgg aag gtg gac aac gcc ctg cag tcc	528
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser	
165 170 175	
ggg aac tcc cag gag agc gtg acc gag cag gac agc aag gac agc acc	576
Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr	
180 185 190	
tac agc ctg agc agc acc ctg acc ctg agc aaa gcc gac tac gag aag	624
Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys	
195 200 205	
cac aag gtg tac gcc tgc gag gtg acc cac cag ggc ctg agc tcc ccc	672
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro	
210 215 220	
gtc acc aag agc ttc aac agg ggg gag tgt	702
Val Thr Lys Ser Phe Asn Arg Gly Glu Cys	
225 230	

<210> SEQ ID NO 32

<211> LENGTH: 234

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 32

Met Val Leu Gln Thr Gln Val Phe Ile Ser Leu Leu Leu Trp Ile Ser	
1 5 10 15	
Gly Ala Tyr Gly Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser	
20 25 30	
Ala Phe Leu Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp	
35 40 45	
Ile Gly Asn Tyr Leu Arg Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro	
50 55 60	
Arg Leu Met Ile Tyr Gly Ala Thr Asn Leu Ala Asn Gly Val Pro Ser	
65 70 75 80	
Arg Phe Ser Gly Ser Arg Ser Gly Ser Asp Tyr Ser Leu Thr Ile Asn	
85 90 95	
Asn Leu Glu Ser Glu Asp Met Ala Ile Tyr Tyr Cys Leu Lys His Asn	
100 105 110	
Glu Tyr Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg	
115 120 125	
Ala Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln	
130 135 140	
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr	
145 150 155 160	
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser	
165 170 175	

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Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
180 185 190

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
195 200 205

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
210 215 220

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230

<210> SEQ ID NO 33
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 33

atctccggcg cgtacggcga catccagatg acccagtctc catcttcc 48

<210> SEQ ID NO 34
<211> LENGTH: 44
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 34

ggagggggcg gccacagccc gttttatttc caacttcgtc cctg 44

<210> SEQ ID NO 35
<211> LENGTH: 1413
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polynucleotide
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1) .. (1413)

<400> SEQUENCE: 35

atg aaa cac ctg tgg ttc ttc ctc ctg ctg gtg gca gct ccc aga tgg 48
Met Lys His Leu Trp Phe Phe Leu Leu Val Ala Ala Pro Arg Trp
1 5 10 15

gtg ctg agc gag gtg cag ctg gtg gag tct ggg gga ggc ctg gtg cag 96
Val Leu Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
20 25 30

cct gga agg tct ctg aaa cta tcc tgt gta gcc tct gga ttc aga ttc 144
Pro Gly Arg Ser Leu Lys Leu Ser Cys Val Ala Ser Gly Phe Arg Phe
35 40 45

aat gac ttt tgg atg acc tgg atc cgc cag gct cca ggg aag ggg ctg 192
Asn Asp Phe Trp Met Thr Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

gag tgg gtt gca tcc att act tat act ggt gat aac act tac tat gca 240
Glu Trp Val Ala Ser Ile Thr Tyr Thr Gly Asp Asn Thr Tyr Tyr Ala
65 70 75 80

ggc tct gtg aag ggc cga atc act atc tcc aga gat aat gcg aag agc 288
Gly Ser Val Lys Gly Arg Ile Thr Ile Ser Arg Asp Asn Ala Lys Ser
85 90 95

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acc	cta	tac	ctg	caa	atg	aac	agt	ctg	agg	tct	gag	gac	acg	gcc	act	336
Thr	Leu	Tyr	Leu	Gln	Met	Asn	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Thr	
			100				105			110						
tat	tac	tgt	aca	aga	gat	gac	tac	gga	gga	tat	agc	ccc	tac	tat	atg	384
Tyr	Tyr	Cys	Thr	Arg	Asp	Asp	Tyr	Gly	Gly	Tyr	Ser	Pro	Tyr	Tyr	Met	
			115				120			125						
gat	gcc	tgg	ggt	caa	gga	act	tca	gtc	act	gtc	agc	tca	gcc	tcc	acc	432
Asp	Ala	Trp	Gly	Gln	Gly	Thr	Ser	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	
			130				135			140						
aag	ggc	cca	agc	gtc	ttc	ccc	ctg	gca	ccc	tcc	tcc	aag	agc	acc	tct	480
Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	
			145	150			155			160						
ggc	ggc	aca	gcc	gcc	ctg	ggc	tgc	ctg	gtc	aag	gac	tac	ttc	ccc	gaa	528
Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	
			165			170			175							
ccc	gtg	acc	gtg	agc	tgg	aac	tca	ggc	gcc	ctg	acc	agc	ggc	gtg	cac	576
Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	
			180			185			190							
acc	ttc	ccc	gct	gtc	ctg	cag	tcc	tca	gga	ctc	tac	tcc	ctc	agc	agc	624
Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	
			195			200			205							
gtg	gtg	acc	gtg	ccc	tcc	agc	agc	ttg	ggc	acc	cag	acc	tac	atc	tgc	672
Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	
			210			215			220							
aac	gtg	aat	cac	aag	ccc	agc	aac	acc	aag	gtg	gac	aag	aga	gtt	gag	720
Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	
			225			230			235			240				
ccc	aaa	tct	tgt	gac	aaa	act	cac	aca	tgc	cca	ccc	tgc	cca	gca	cct	768
Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	
			245			250			255							
gaa	ctc	ctg	ggg	gga	ccc	tca	gtc	ttc	ctc	ttc	ccc	cca	aaa	ccc	aag	816
Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	
			260			265			270							
gac	acc	ctc	atg	atc	tcc	cgg	acc	cct	gag	gtc	aca	tgc	gtg	gtg	gtg	864
Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	
			275			280			285							
gac	gtg	agc	cac	gaa	gac	cct	gag	gtc	aag	ttc	aac	tgg	tac	gtg	gac	912
Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	
			290			295			300							
ggc	gtg	gag	gtg	cat	aat	gcc	aag	aca	aag	ccc	cgg	gag	gag	cag	tac	960
Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	
			305			310			315			320				
aac	agc	acg	tac	cgg	gtg	gtc	agc	gtc	ctc	acc	gtc	ctg	cac	cag	gac	1008
Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	
			325			330			335							
tgg	ctg	aat	ggc	aag	gag	tac	aag	tgc	aag	gtc	tcc	aac	aaa	gcc	ctc	1056
Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	
			340			345			350							
cca	gcc	ccc	atc	gag	aaa	acc	atc	tcc	aaa	gcc	aaa	ggc	cag	ccc	cgg	1104
Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	
			355			360			365							
gaa	cca	cag	gtg	tac	acc	ctg	ccc	cca	tcc	cgg	gag	gag	atg	acc	aag	1152
Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	
			370			375			380							
aac	cag	gtc	agc	ctg	acc	tgc	ctg	gtc	aaa	ggc	ttc	tat	ccc	agc	gac	1200
Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	
			385			390			395			400				

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atc gcc gtg gag tgg gag agc aat ggc cag ccc gag aac aac tac aag	1248
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys	
405 410 415	
acc acc cct ccc gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc	1296
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser	
420 425 430	
aag ctc acc gtg gac aag agc agg tgg cag cag ggc aac gtc ttc tca	1344
Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser	
435 440 445	
tgc tcc gtg atg cat gag gct ctg cac aac cac tac acc cag aag agc	1392
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser	
450 455 460	
ctc tcc ctg tct ccc ggc aaa	1413
Leu Ser Leu Ser Pro Gly Lys	
465 470	

<210> SEQ ID NO 36

<211> LENGTH: 471

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 36

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp	
1 5 10 15	
Val Leu Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln	
20 25 30	
Pro Gly Arg Ser Leu Lys Leu Ser Cys Val Ala Ser Gly Phe Arg Phe	
35 40 45	
Asn Asp Phe Trp Met Thr Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu	
50 55 60	
Glu Trp Val Ala Ser Ile Thr Tyr Thr Gly Asp Asn Thr Tyr Tyr Ala	
65 70 75 80	
Gly Ser Val Lys Gly Arg Ile Thr Ile Ser Arg Asp Asn Ala Lys Ser	
85 90 95	
Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ser Glu Asp Thr Ala Thr	
100 105 110	
Tyr Tyr Cys Thr Arg Asp Asp Tyr Gly Gly Tyr Ser Pro Tyr Tyr Met	
115 120 125	
Asp Ala Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Ser Thr	
130 135 140	
Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser	
145 150 155 160	
Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu	
165 170 175	
Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His	
180 185 190	
Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser	
195 200 205	
Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys	
210 215 220	
Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu	
225 230 235 240	

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Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	
				245					250					255		
Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	
			260					265					270			
Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	
	275						280					285				
Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	
	290					295					300					
Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	
305				310						315				320		
Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	
			325						330					335		
Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	
		340						345					350			
Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	
		355					360					365				
Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	
	370					375					380					
Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	
385				390						395					400	
Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	
			405						410					415		
Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	
		420						425					430			
Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	
		435					440					445				
Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	
	450					455					460					
Leu	Ser	Leu	Ser	Pro	Gly	Lys										
465					470											

<210> SEQ ID NO 37
<211> LENGTH: 47
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 37

ccagatgggt gctgagcgag gtgcagctgg tggagtctgg gggagggc

47

<210> SEQ ID NO 38
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 38

cttggtggag gctgagctga cagtgactga agttccttga ccccaggc

48

<210> SEQ ID NO 39
<211> LENGTH: 705
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(705)

<400> SEQUENCE: 39

atg gtg ctg cag acc cag gtg ttc atc tcc ctg ctg ctg tgg atc tcc 48
Met Val Leu Gln Thr Gln Val Phe Ile Ser Leu Leu Leu Trp Ile Ser
1 5 10 15

ggc gcg tac ggc gac atc cag atg aca cag tct cca gct tcc ctg tct 96
Gly Ala Tyr Gly Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser
20 25 30

gca tct ctg gga gaa act gtc acc atc gaa tgt cga gca agt gag gac 144
Ala Ser Leu Gly Glu Thr Val Thr Ile Glu Cys Arg Ala Ser Glu Asp
35 40 45

att tac agt aat tta gcg tgg tat cag cag aaa cca ggg aac tct cct 192
Ile Tyr Ser Asn Leu Ala Trp Tyr Gln Gln Lys Pro Gly Asn Ser Pro
50 55 60

cag ctc ctg atc tat gat gca aat atc ttg gca gat ggg gtc cca tca 240
Gln Leu Leu Ile Tyr Asp Ala Asn Ile Leu Ala Asp Gly Val Pro Ser
65 70 75 80

cgg ttc agt ggc agt ggg tct ggc aca cag tat tct cta aag ata aac 288
Arg Phe Ser Gly Ser Gly Ser Gly Thr Gln Tyr Ser Leu Lys Ile Asn
85 90 95

agc ctg caa tct gaa gat gtc gca agt tat ttc tgt caa cag tat aac 336
Ser Leu Gln Ser Glu Asp Val Ala Ser Tyr Phe Cys Gln Gln Tyr Asn
100 105 110

aat tat cct ccg ttc acg ttt gga gtt ggg acc aag ctg gaa ctg aaa 384
Asn Tyr Pro Pro Phe Thr Phe Gly Val Gly Thr Lys Leu Glu Leu Lys
115 120 125

cgg gct gtg gcc gcc ccc tcc gtg ttc atc ttc ccc ccc tcc gac gag 432
Arg Ala Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
130 135 140

cag ctg aag tcc ggc acc gcc tcc gtg gtg tgc ctg ctg aat aac ttc 480
Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
145 150 155 160

tac ccc aga gag gcc aag gtg cag tgg aag gtg gac aac gcc ctg cag 528
Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
165 170 175

tcc ggg aac tcc cag gag agc gtg acc gag cag gac agc aag gac agc 576
Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
180 185 190

acc tac agc ctg agc agc acc ctg acc ctg agc aaa gcc gac tac gag 624
Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
195 200 205

aag cac aag gtg tac gcc tgc gag gtg acc cac cag ggc ctg agc tcc 672
Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
210 215 220

ccc gtc acc aag agc ttc aac agg ggg gag tgt 705
Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> SEQ ID NO 40
<211> LENGTH: 235
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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polypeptide

<400> SEQUENCE: 40

Met Val Leu Gln Thr Gln Val Phe Ile Ser Leu Leu Leu Trp Ile Ser
1 5 10 15

Gly Ala Tyr Gly Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser
20 25 30

Ala Ser Leu Gly Glu Thr Val Thr Ile Glu Cys Arg Ala Ser Glu Asp
35 40 45

Ile Tyr Ser Asn Leu Ala Trp Tyr Gln Gln Lys Pro Gly Asn Ser Pro
50 55 60

Gln Leu Leu Ile Tyr Asp Ala Asn Ile Leu Ala Asp Gly Val Pro Ser
65 70 75 80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Gln Tyr Ser Leu Lys Ile Asn
85 90 95

Ser Leu Gln Ser Glu Asp Val Ala Ser Tyr Phe Cys Gln Gln Tyr Asn
100 105 110

Asn Tyr Pro Pro Phe Thr Phe Gly Val Gly Thr Lys Leu Glu Leu Lys
115 120 125

Arg Ala Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
130 135 140

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
145 150 155 160

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
165 170 175

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
180 185 190

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
195 200 205

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
210 215 220

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> SEQ ID NO 41
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 41

atctccggcg cgtacggcga catccagatg acacagtctc cagcttcc 48

<210> SEQ ID NO 42
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 42

ggagggggcg gccacagccc gtttcagttc cagcttggtc ccaac 45

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<210> SEQ ID NO 43
<211> LENGTH: 1401
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(1401)

<400> SEQUENCE: 43

atg aaa cac ctg tgg ttc ttc ctc ctg ctg gtg gca gct ccc aga tgg	48
Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp	
1 5 10 15	
gtg ctg agc cag gtt aag ctg ctg cag tct ggg gct gag ctg gta aaa	96
Val Leu Ser Gln Val Lys Leu Leu Gln Ser Gly Ala Glu Leu Val Lys	
20 25 30	
cct ggt gct tca gtg aag ttg tcc tgc aag act tct ggt ttt acc ttc	144
Pro Gly Ala Ser Val Lys Leu Ser Cys Lys Thr Ser Gly Phe Thr Phe	
35 40 45	
agc act agc tat atg agt tgg ttg aag cag gtg cct gga ccg agt att	192
Ser Thr Ser Tyr Met Ser Trp Leu Lys Gln Val Pro Gly Pro Ser Ile	
50 55 60	
gag tgg att gga tgg att tat gct gga gat ggt ggt act aag tat aat	240
Glu Trp Ile Gly Trp Ile Tyr Ala Gly Asp Gly Gly Thr Lys Tyr Asn	
65 70 75 80	
cag aag ttc aag ggc aag gcc aca ctg aca gta gac aaa tct tct agc	288
Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser	
85 90 95	
aca gca tac atg gat ctc agc agc ctg aca tct gag gac gct gca gtc	336
Thr Ala Tyr Met Asp Leu Ser Ser Leu Thr Ser Glu Asp Ala Ala Val	
100 105 110	
tat ttt tgt gca acg gat ggt tat ggg gat tgg ttt gct tac tgg ggc	384
Tyr Phe Cys Ala Thr Asp Gly Tyr Gly Asp Trp Phe Ala Tyr Trp Gly	
115 120 125	
caa ggc act ctg gtc act gtc agc tca gcc tcc acc aag ggc cca agc	432
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser	
130 135 140	
gtc ttc ccc ctg gca ccc tcc tcc aag agc acc tct ggc ggc aca gcc	480
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala	
145 150 155 160	
gcc ctg ggc tgc ctg gtc aag gac tac ttc ccc gaa ccc gtg acc gtg	528
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val	
165 170 175	
agc tgg aac tca ggc gcc ctg acc agc ggc gtg cac acc ttc ccc gct	576
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala	
180 185 190	
gtc ctg cag tcc tca gga ctc tac tcc ctc agc agc gtg gtg acc gtg	624
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val	
195 200 205	
ccc tcc agc agc ttg ggc acc cag acc tac atc tgc aac gtg aat cac	672
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His	
210 215 220	
aag ccc agc aac acc aag gtg gac aag aga gtt gag ccc aaa tct tgt	720
Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys	
225 230 235 240	
gac aaa act cac aca tgc cca ccc tgc cca gca cct gaa ctc ctg ggg	768
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly	
245 250 255	

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gga ccc tca gtc ttc ctc ttc ccc cca aaa ccc aag gac acc ctc atg	816
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met	
260 265 270	
atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac gtg agc cac	864
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His	
275 280 285	
gaa gac cct gag gtc aag ttc aac tgg tac gtg gac ggc gtg gag gtg	912
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val	
290 295 300	
cat aat gcc aag aca aag ccc cgg gag gag cag tac aac agc acg tac	960
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr	
305 310 315 320	
cgg gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg aat ggc	1008
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly	
325 330 335	
aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca gcc ccc atc	1056
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile	
340 345 350	
gag aaa acc atc tcc aaa gcc aaa ggc cag ccc cgg gaa cca cag gtg	1104
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val	
355 360 365	
tac acc ctg ccc cca tcc cgg gag gag atg acc aag aac cag gtc agc	1152
Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser	
370 375 380	
ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc gcc gtg gag	1200
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu	
385 390 395 400	
tgg gag agc aat ggc cag ccc gag aac aac tac aag acc acc cct ccc	1248
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro	
405 410 415	
gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc acc gtg	1296
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val	
420 425 430	
gac aag agc agg tgg cag cag ggc aac gtc ttc tca tgc tcc gtg atg	1344
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met	
435 440 445	
cat gag gct ctg cac aac cac tac acc cag aag agc ctc tcc ctg tct	1392
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser	
450 455 460	
ccc ggc aaa	1401
Pro Gly Lys	
465	

<210> SEQ ID NO 44

<211> LENGTH: 467

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 44

Met	Lys	His	Leu	Trp	Phe	Phe	Leu	Leu	Leu	Val	Ala	Ala	Pro	Arg	Trp
1			5						10					15	

Val	Leu	Ser	Gln	Val	Lys	Leu	Leu	Gln	Ser	Gly	Ala	Glu	Leu	Val	Lys
			20					25					30		

Pro	Gly	Ala	Ser	Val	Lys	Leu	Ser	Cys	Lys	Thr	Ser	Gly	Phe	Thr	Phe
		35					40					45			

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Ser	Thr	Ser	Tyr	Met	Ser	Trp	Leu	Lys	Gln	Val	Pro	Gly	Pro	Ser	Ile
50					55					60					
Glu	Trp	Ile	Gly	Trp	Ile	Tyr	Ala	Gly	Asp	Gly	Gly	Thr	Lys	Tyr	Asn
65					70					75					80
Gln	Lys	Phe	Lys	Gly	Lys	Ala	Thr	Leu	Thr	Val	Asp	Lys	Ser	Ser	Ser
				85						90				95	
Thr	Ala	Tyr	Met	Asp	Leu	Ser	Ser	Leu	Thr	Ser	Glu	Asp	Ala	Ala	Val
			100					105					110		
Tyr	Phe	Cys	Ala	Thr	Asp	Gly	Tyr	Gly	Asp	Trp	Phe	Ala	Tyr	Trp	Gly
		115					120					125			
Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser
						135						140			
Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala
145					150					155					160
Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val
				165					170					175	
Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala
		180						185					190		
Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val
		195					200					205			
Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His
		210				215					220				
Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys
225					230					235					240
Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly
				245					250					255	
Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met
			260					265					270		
Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His
		275					280					285			
Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val
		290				295					300				
His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr
305					310					315					320
Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly
				325				330						335	
Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile
			340					345					350		
Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val
		355					360					365			
Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser
		370				375					380				
Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu
385					390					395					400
Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro
			405					410						415	
Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val
			420					425					430		
Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met
		435					440					445			

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His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
450 455 460

Pro Gly Lys
465

<210> SEQ ID NO 45
<211> LENGTH: 47
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 45

ccagatgggt gctgagccag gttaagctgc tgcagtctgg ggctgag 47

<210> SEQ ID NO 46
<211> LENGTH: 46
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 46

cttggtggag gctgagctga cagtgaccag agtgccttgg ccccg 46

<210> SEQ ID NO 47
<211> LENGTH: 705
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polynucleotide
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(705)

<400> SEQUENCE: 47

atg gtg ctg cag acc cag gtg ttc atc tcc ctg ctg ctg tgg atc tcc 48
Met Val Leu Gln Thr Gln Val Phe Ile Ser Leu Leu Leu Trp Ile Ser
1 5 10 15

ggc gcg tac ggc gac atc cag atg aca cag tct cca gct tcc ctg tct 96
Gly Ala Tyr Gly Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser
20 25 30

gca tct ctg gga gaa act gtc acc atc gaa tgt cga gca agt gag gac 144
Ala Ser Leu Gly Glu Thr Val Thr Ile Glu Cys Arg Ala Ser Glu Asp
35 40 45

ata tac agt aat tta gcg tgg tat cag cag aaa cca ggg aac tct cct 192
Ile Tyr Ser Asn Leu Ala Trp Tyr Gln Gln Lys Pro Gly Asn Ser Pro
50 55 60

cag ctc ctg atc tat gat gca aat atc ctg gca gat ggg gtc cca tca 240
Gln Leu Leu Ile Tyr Asp Ala Asn Ile Leu Ala Asp Gly Val Pro Ser
65 70 75 80

cgg ttc agt ggc agt ggg tct ggc aca cag tat tct cta aag ata aac 288
Arg Phe Ser Gly Ser Gly Ser Gly Thr Gln Tyr Ser Leu Lys Ile Asn
85 90 95

agc ctg caa tct gaa gat gtc gca agt tat ttc tgt caa cag tat aac 336
Ser Leu Gln Ser Glu Asp Val Ala Ser Tyr Phe Cys Gln Gln Tyr Asn
100 105 110

aat tat cct ccg ttc acg ttt gga gct ggg acc aag ctg gaa ctg aaa 384
Asn Tyr Pro Pro Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys

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115	120	125	
cgg gct gtg gcc gcc ccc tcc gtg ttc atc ttc ccc ccc tcc gac gag			432
Arg Ala Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu			
130	135	140	
cag ctg aag tcc ggc acc gcc tcc gtg gtg tgc ctg ctg aat aac ttc			480
Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe			
145	150	155	160
tac ccc aga gag gcc aag gtg cag tgg aag gtg gac aac gcc ctg cag			528
Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln			
165	170	175	
tcc ggg aac tcc cag gag agc gtg acc gag cag gac agc aag gac agc			576
Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser			
180	185	190	
acc tac agc ctg agc agc acc ctg acc ctg agc aaa gcc gac tac gag			624
Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu			
195	200	205	
aag cac aag gtg tac gcc tgc gag gtg acc cac cag ggc ctg agc tcc			672
Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser			
210	215	220	
ccc gtc acc aag agc ttc aac agg ggg gag tgt			705
Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys			
225	230	235	

<210> SEQ ID NO 48

<211> LENGTH: 235

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 48

Met Val Leu Gln Thr Gln Val Phe Ile Ser Leu Leu Leu Trp Ile Ser			
1	5	10	15
Gly Ala Tyr Gly Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser			
20	25	30	
Ala Ser Leu Gly Glu Thr Val Thr Ile Glu Cys Arg Ala Ser Glu Asp			
35	40	45	
Ile Tyr Ser Asn Leu Ala Trp Tyr Gln Gln Lys Pro Gly Asn Ser Pro			
50	55	60	
Gln Leu Leu Ile Tyr Asp Ala Asn Ile Leu Ala Asp Gly Val Pro Ser			
65	70	75	80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Gln Tyr Ser Leu Lys Ile Asn			
85	90	95	
Ser Leu Gln Ser Glu Asp Val Ala Ser Tyr Phe Cys Gln Gln Tyr Asn			
100	105	110	
Asn Tyr Pro Pro Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys			
115	120	125	
Arg Ala Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu			
130	135	140	
Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe			
145	150	155	160
Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln			
165	170	175	
Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser			
180	185	190	

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Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
195 200 205

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
210 215 220

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> SEQ ID NO 49

<211> LENGTH: 45

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 49

ggagggggcg gccacagccc gtttcagttc cagcttggtc ccagc 45

<210> SEQ ID NO 50

<211> LENGTH: 1401

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<220> FEATURE:

<221> NAME/KEY: CDS

<222> LOCATION: (1)..(1401)

<400> SEQUENCE: 50

atg aaa cac ctg tgg ttc ttc ctc ctg ctg gtg gca gct ccc aga tgg 48
Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
1 5 10 15

gtg ctg agc cag gtt aag ctg ctg cag tct ggg gct gag ctg gta aaa 96
Val Leu Ser Gln Val Lys Leu Leu Ser Gly Ala Glu Leu Val Lys
20 25 30

cct ggt gct tca gtg aag ttg tcc tgc aag act tct ggt ttt aca ttc 144
Pro Gly Ala Ser Val Lys Leu Ser Cys Lys Thr Ser Gly Phe Thr Phe
35 40 45

agc act agt tat atg agt tgg ttg aag cag gtg cct gga ccg agt act 192
Ser Thr Ser Tyr Met Ser Trp Leu Lys Gln Val Pro Gly Pro Ser Thr
50 55 60

gag tgg att gga tgg att tat gct gga gat ggt ggt act aag tat aat 240
Glu Trp Ile Gly Trp Ile Tyr Ala Gly Asp Gly Gly Thr Lys Tyr Asn
65 70 75 80

cag aag ttc aag ggc aag gcc aca ctg aca gta gac aaa ttt tct agc 288
Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Phe Ser Ser
85 90 95

aca gca tac atg gat ctc agc agc ctg aca tct gag gac gct gca gtc 336
Thr Ala Tyr Met Asp Leu Ser Ser Leu Thr Ser Glu Asp Ala Ala Val
100 105 110

tat ttc tgt gca acg gat ggt tat ggg gat tgg ttt act tac tgg ggc 384
Tyr Phe Cys Ala Thr Asp Gly Tyr Gly Asp Trp Phe Thr Tyr Trp Gly
115 120 125

caa ggc act ctg gtc act gtc agc tca gcc tcc acc aag ggc cca agc 432
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
130 135 140

gtc ttc ccc ctg gca ccc tcc tcc aag agc acc tct ggc ggc aca gcc 480
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
145 150 155 160

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gcc ctg ggc tgc ctg gtc aag gac tac ttc ccc gaa ccc gtg acc gtg	528
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val	
165 170 175	
agc tgg aac tca ggc gcc ctg acc agc ggc gtg cac acc ttc ccc gct	576
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala	
180 185 190	
gtc ctg cag tcc tca gga ctc tac tcc ctc agc agc gtg gtg acc gtg	624
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val	
195 200 205	
ccc tcc agc agc ttg ggc acc cag acc tac atc tgc aac gtg aat cac	672
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His	
210 215 220	
aag ccc agc aac acc aag gtg gac aag aga gtt gag ccc aaa tct tgt	720
Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys	
225 230 235 240	
gac aaa act cac aca tgc cca ccc tgc cca gca cct gaa ctc ctg ggg	768
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly	
245 250 255	
gga ccc tca gtc ttc ctc ttc ccc cca aaa ccc aag gac acc ctc atg	816
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met	
260 265 270	
atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac gtg agc cac	864
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His	
275 280 285	
gaa gac cct gag gtc aag ttc aac tgg tac gtg gac ggc gtg gag gtg	912
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val	
290 295 300	
cat aat gcc aag aca aag ccc cgg gag gag cag tac aac agc acg tac	960
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr	
305 310 315 320	
cgg gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg aat ggc	1008
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly	
325 330 335	
aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca gcc ccc atc	1056
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile	
340 345 350	
gag aaa acc atc tcc aaa gcc aaa ggc cag ccc cgg gaa cca cag gtg	1104
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val	
355 360 365	
tac acc ctg ccc cca tcc cgg gag gag atg acc aag aac cag gtc agc	1152
Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser	
370 375 380	
ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc gcc gtg gag	1200
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu	
385 390 395 400	
tgg gag agc aat ggc cag ccc gag aac aac tac aag acc acc cct ccc	1248
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro	
405 410 415	
gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc acc gtg	1296
Val Leu Asp Ser Asp Gly Ser Phe Leu Tyr Ser Lys Leu Thr Val	
420 425 430	
gac aag agc agg tgg cag cag ggc aac gtc ttc tca tgc tcc gtg atg	1344
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met	
435 440 445	
cat gag gct ctg cac aac cac tac acc cag aag agc ctc tcc ctg tct	1392
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser	
450 455 460	

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ccc ggc aaa 1401
Pro Gly Lys
465

<210> SEQ ID NO 51
<211> LENGTH: 467
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polypeptide

<400> SEQUENCE: 51

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
1 5 10 15
Val Leu Ser Gln Val Lys Leu Leu Gln Ser Gly Ala Glu Leu Val Lys
20 25 30
Pro Gly Ala Ser Val Lys Leu Ser Cys Lys Thr Ser Gly Phe Thr Phe
35 40 45
Ser Thr Ser Tyr Met Ser Trp Leu Lys Gln Val Pro Gly Pro Ser Thr
50 55 60
Glu Trp Ile Gly Trp Ile Tyr Ala Gly Asp Gly Gly Thr Lys Tyr Asn
65 70 75 80
Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Phe Ser Ser
85 90 95
Thr Ala Tyr Met Asp Leu Ser Ser Leu Thr Ser Glu Asp Ala Ala Val
100 105 110
Tyr Phe Cys Ala Thr Asp Gly Tyr Gly Asp Trp Phe Thr Tyr Trp Gly
115 120 125
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
130 135 140
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
145 150 155 160
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
165 170 175
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
180 185 190
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
195 200 205
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
210 215 220
Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
225 230 235 240
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
245 250 255
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
260 265 270
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
275 280 285
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
290 295 300
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
305 310 315 320

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Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	
				325					330					335		
Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	
			340					345					350			
Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	
		355						360				365				
Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	
	370					375					380					
Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	
385					390					395					400	
Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	
			405					410						415		
Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	
		420						425					430			
Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	
	435					440						445				
His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	
	450				455						460					
Pro	Gly	Lys														
465																

<210> SEQ ID NO 52
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 52

Asp	Phe	Trp	Met	Thr
1				5

<210> SEQ ID NO 53
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 53

Ser	Ile	Thr	Tyr	Thr	Gly	Asp	Asn	Thr	Tyr	Tyr	Ala	Gly	Ser	Val	Lys
1				5					10					15	

Gly

<210> SEQ ID NO 54
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 54

Asp	Asp	Tyr	Gly	Gly	Tyr	Ser	Pro	Tyr	Tyr	Met	Asp	Ala
1			5						10			

<210> SEQ ID NO 55
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 55

Thr	Ser	Tyr	Met	Ser
1				5

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<210> SEQ ID NO 56
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 56

Trp Ile Tyr Ala Gly Asp Gly Gly Thr Lys Tyr Asn Gln Lys Phe Lys
1 5 10 15

Gly

<210> SEQ ID NO 57
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 57

Asp Gly Tyr Gly Asp Trp Phe Ala Tyr
1 5

<210> SEQ ID NO 58
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 58

Thr Ser Tyr Met Ser
1 5

<210> SEQ ID NO 59
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 59

Trp Ile Tyr Ala Gly Asp Gly Gly Thr Lys Tyr Asn Gln Lys Phe Lys
1 5 10 15

Gly

<210> SEQ ID NO 60
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 60

Asp Gly Tyr Gly Asp Trp Phe Thr Tyr
1 5

<210> SEQ ID NO 61
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 61

Arg Ala Ser Gln Asp Ile Gly Asn Tyr Leu Arg
1 5 10

<210> SEQ ID NO 62
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

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<400> SEQUENCE: 62

Gly Ala Thr Asn Leu Ala Asn
1 5

<210> SEQ ID NO 63

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 63

Leu Lys His Asn Glu Tyr Pro Phe Thr
1 5

<210> SEQ ID NO 64

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 64

Arg Ala Ser Glu Asp Ile Tyr Ser Asn Leu Ala
1 5 10

<210> SEQ ID NO 65

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 65

Asp Ala Asn Ile Leu Ala Asp
1 5

<210> SEQ ID NO 66

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 66

Gln Gln Tyr Asn Asn Tyr Pro Pro Phe Thr
1 5 10

<210> SEQ ID NO 67

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 67

Arg Ala Ser Glu Asp Ile Tyr Ser Asn Leu Ala
1 5 10

<210> SEQ ID NO 68

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 68

Asp Ala Asn Ile Leu Ala Asp
1 5

<210> SEQ ID NO 69

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Rattus norvegicus

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<400> SEQUENCE: 69

Gln Gln Tyr Asn Asn Tyr Pro Pro Phe Thr
1 5 10

<210> SEQ ID NO 70

<211> LENGTH: 822

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 70

Met Val Ser Trp Gly Arg Phe Ile Cys Leu Val Val Val Thr Met Ala
1 5 10 15

Thr Leu Ser Leu Ala Arg Pro Ser Phe Ser Leu Val Glu Asp Thr Thr
20 25 30

Leu Glu Pro Glu Glu Pro Pro Thr Lys Tyr Gln Ile Ser Gln Pro Glu
35 40 45

Val Tyr Val Ala Ala Pro Gly Glu Ser Leu Glu Val Arg Cys Leu Leu
50 55 60

Lys Asp Ala Ala Val Ile Ser Trp Thr Lys Asp Gly Val His Leu Gly
65 70 75 80

Pro Asn Asn Arg Thr Val Leu Ile Gly Glu Tyr Leu Gln Ile Lys Gly
85 90 95

Ala Thr Pro Arg Asp Ser Gly Leu Tyr Ala Cys Thr Ala Ser Arg Thr
100 105 110

Val Asp Ser Glu Thr Trp Tyr Phe Met Val Asn Val Thr Asp Ala Ile
115 120 125

Ser Ser Gly Asp Asp Glu Asp Asp Thr Asp Gly Ala Glu Asp Phe Val
130 135 140

Ser Glu Asn Ser Asn Asn Lys Arg Ala Pro Tyr Trp Thr Asn Thr Glu
145 150 155 160

Lys Met Glu Lys Arg Leu His Ala Val Pro Ala Ala Asn Thr Val Lys
165 170 175

Phe Arg Cys Pro Ala Gly Gly Asn Pro Met Pro Thr Met Arg Trp Leu
180 185 190

Lys Asn Gly Lys Glu Phe Lys Gln Glu His Arg Ile Gly Gly Tyr Lys
195 200 205

Val Arg Asn Gln His Trp Ser Leu Ile Met Glu Ser Val Val Pro Ser
210 215 220

Asp Lys Gly Asn Tyr Thr Cys Val Val Glu Asn Glu Tyr Gly Ser Ile
225 230 235 240

Asn His Thr Tyr His Leu Asp Val Val Glu Arg Ser Pro His Arg Pro
245 250 255

Ile Leu Gln Ala Gly Leu Pro Ala Asn Ala Ser Thr Val Val Gly Gly
260 265 270

Asp Val Glu Phe Val Cys Lys Val Tyr Ser Asp Ala Gln Pro His Ile
275 280 285

Gln Trp Ile Lys His Val Glu Lys Asn Gly Ser Lys Tyr Gly Pro Asp
290 295 300

Gly Leu Pro Tyr Leu Lys Val Leu Lys His Ser Gly Ile Asn Ser Ser
305 310 315 320

Asn Ala Glu Val Leu Ala Leu Phe Asn Val Thr Glu Ala Asp Ala Gly
325 330 335

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Glu	Tyr	Ile	Cys	Lys	Val	Ser	Asn	Tyr	Ile	Gly	Gln	Ala	Asn	Gln	Ser	
			340					345					350			
Ala	Trp	Leu	Thr	Val	Leu	Pro	Lys	Gln	Gln	Ala	Pro	Gly	Arg	Glu	Lys	
		355					360					365				
Glu	Ile	Thr	Ala	Ser	Pro	Asp	Tyr	Leu	Glu	Ile	Ala	Ile	Tyr	Cys	Ile	
	370					375					380					
Gly	Val	Phe	Leu	Ile	Ala	Cys	Met	Val	Val	Thr	Val	Ile	Leu	Cys	Arg	
385					390					395					400	
Met	Lys	Asn	Thr	Thr	Lys	Lys	Pro	Asp	Phe	Ser	Ser	Gln	Pro	Ala	Val	
			405						410					415		
His	Lys	Leu	Thr	Lys	Arg	Ile	Pro	Leu	Arg	Arg	Gln	Val	Thr	Val	Ser	
		420						425					430			
Ala	Glu	Ser	Ser	Ser	Ser	Met	Asn	Ser	Asn	Thr	Pro	Leu	Val	Arg	Ile	
		435					440					445				
Thr	Thr	Arg	Leu	Ser	Ser	Thr	Ala	Asp	Thr	Pro	Met	Leu	Ala	Gly	Val	
	450					455					460					
Ser	Glu	Tyr	Glu	Leu	Pro	Glu	Asp	Pro	Lys	Trp	Glu	Phe	Pro	Arg	Asp	
465					470					475					480	
Lys	Leu	Thr	Leu	Gly	Lys	Pro	Leu	Gly	Glu	Gly	Cys	Phe	Gly	Gln	Val	
			485					490						495		
Val	Met	Ala	Glu	Ala	Val	Gly	Ile	Asp	Lys	Asp	Lys	Pro	Lys	Glu	Ala	
		500						505					510			
Val	Thr	Val	Ala	Val	Lys	Met	Leu	Lys	Asp	Asp	Ala	Thr	Glu	Lys	Asp	
		515					520					525				
Leu	Ser	Asp	Leu	Val	Ser	Glu	Met	Glu	Met	Met	Lys	Met	Ile	Gly	Lys	
	530				535						540					
His	Lys	Asn	Ile	Ile	Asn	Leu	Leu	Gly	Ala	Cys	Thr	Gln	Asp	Gly	Pro	
545					550					555					560	
Leu	Tyr	Val	Ile	Val	Glu	Tyr	Ala	Ser	Lys	Gly	Asn	Leu	Arg	Glu	Tyr	
			565					570						575		
Leu	Arg	Ala	Arg	Arg	Pro	Pro	Gly	Met	Glu	Tyr	Ser	Tyr	Asp	Ile	Asn	
		580					585						590			
Arg	Val	Pro	Glu	Glu	Gln	Met	Thr	Phe	Lys	Asp	Leu	Val	Ser	Cys	Thr	
		595					600					605				
Tyr	Gln	Leu	Ala	Arg	Gly	Met	Glu	Tyr	Leu	Ala	Ser	Gln	Lys	Cys	Ile	
	610				615						620					
His	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Val	Leu	Val	Thr	Glu	Asn	Asn	Val	
625					630					635					640	
Met	Lys	Ile	Ala	Asp	Phe	Gly	Leu	Ala	Arg	Asp	Ile	Asn	Asn	Ile	Asp	
			645					650						655		
Tyr	Tyr	Lys	Lys	Thr	Thr	Asn	Gly	Arg	Leu	Pro	Val	Lys	Trp	Met	Ala	
		660					665						670			
Pro	Glu	Ala	Leu	Phe	Asp	Arg	Val	Tyr	Thr	His	Gln	Ser	Asp	Val	Trp	
		675					680					685				
Ser	Phe	Gly	Val	Leu	Met	Trp	Glu	Ile	Phe	Thr	Leu	Gly	Gly	Ser	Pro	
	690				695						700					
Tyr	Pro	Gly	Ile	Pro	Val	Glu	Glu	Leu	Phe	Lys	Leu	Leu	Lys	Glu	Gly	
705				710						715					720	
His	Arg	Met	Asp	Lys	Pro	Ala	Asn	Cys	Thr	Asn	Glu	Leu	Tyr	Met	Met	
				725					730					735		

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Met	Arg	Asp	Cys	Trp	His	Ala	Val	Pro	Ser	Gln	Arg	Pro	Thr	Phe	Lys
			740					745					750		
Gln	Leu	Val	Glu	Asp	Leu	Asp	Arg	Ile	Leu	Thr	Leu	Thr	Thr	Asn	Glu
		755					760					765			
Glu	Tyr	Leu	Asp	Leu	Ser	Gln	Pro	Leu	Glu	Gln	Tyr	Ser	Pro	Ser	Tyr
	770					775					780				
Pro	Asp	Thr	Arg	Ser	Ser	Cys	Ser	Ser	Gly	Asp	Asp	Ser	Val	Phe	Ser
785					790					795					800
Pro	Asp	Pro	Met	Pro	Tyr	Glu	Pro	Cys	Leu	Pro	Gln	Tyr	Pro	His	Ile
				805					810					815	
Asn	Gly	Ser	Val	Lys	Thr										
			820												

<210> SEQ ID NO 71

<211> LENGTH: 821

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 71

Met	Val	Ser	Trp	Gly	Arg	Phe	Ile	Cys	Leu	Val	Val	Val	Thr	Met	Ala
1				5					10					15	
Thr	Leu	Ser	Leu	Ala	Arg	Pro	Ser	Phe	Ser	Leu	Val	Glu	Asp	Thr	Thr
		20					25						30		
Leu	Glu	Pro	Glu	Glu	Pro	Pro	Thr	Lys	Tyr	Gln	Ile	Ser	Gln	Pro	Glu
		35					40					45			
Val	Tyr	Val	Ala	Ala	Pro	Gly	Glu	Ser	Leu	Glu	Val	Arg	Cys	Leu	Leu
	50					55					60				
Lys	Asp	Ala	Ala	Val	Ile	Ser	Trp	Thr	Lys	Asp	Gly	Val	His	Leu	Gly
65				70						75					80
Pro	Asn	Asn	Arg	Thr	Val	Leu	Ile	Gly	Glu	Tyr	Leu	Gln	Ile	Lys	Gly
			85					90						95	
Ala	Thr	Pro	Arg	Asp	Ser	Gly	Leu	Tyr	Ala	Cys	Thr	Ala	Ser	Arg	Thr
		100					105						110		
Val	Asp	Ser	Glu	Thr	Trp	Tyr	Phe	Met	Val	Asn	Val	Thr	Asp	Ala	Ile
	115					120						125			
Ser	Ser	Gly	Asp	Asp	Glu	Asp	Asp	Thr	Asp	Gly	Ala	Glu	Asp	Phe	Val
	130					135					140				
Ser	Glu	Asn	Ser	Asn	Asn	Lys	Arg	Ala	Pro	Tyr	Trp	Thr	Asn	Thr	Glu
145				150						155					160
Lys	Met	Glu	Lys	Arg	Leu	His	Ala	Val	Pro	Ala	Ala	Asn	Thr	Val	Lys
			165						170					175	
Phe	Arg	Cys	Pro	Ala	Gly	Gly	Asn	Pro	Met	Pro	Thr	Met	Arg	Trp	Leu
		180					185						190		
Lys	Asn	Gly	Lys	Glu	Phe	Lys	Gln	Glu	His	Arg	Ile	Gly	Gly	Tyr	Lys
	195						200					205			
Val	Arg	Asn	Gln	His	Trp	Ser	Leu	Ile	Met	Glu	Ser	Val	Val	Pro	Ser
	210						215					220			
Asp	Lys	Gly	Asn	Tyr	Thr	Cys	Val	Val	Glu	Asn	Glu	Tyr	Gly	Ser	Ile
225					230					235					240
Asn	His	Thr	Tyr	His	Leu	Asp	Val	Val	Glu	Arg	Ser	Pro	His	Arg	Pro
				245					250					255	
Ile	Leu	Gln	Ala	Gly	Leu	Pro	Ala	Asn	Ala	Ser	Thr	Val	Val	Gly	Gly
		260						265						270	

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Asp	Val	Glu	Phe	Val	Cys	Lys	Val	Tyr	Ser	Asp	Ala	Gln	Pro	His	Ile	275	280	285
Gln	Trp	Ile	Lys	His	Val	Glu	Lys	Asn	Gly	Ser	Lys	Tyr	Gly	Pro	Asp	290	295	300
Gly	Leu	Pro	Tyr	Leu	Lys	Val	Leu	Lys	Ala	Ala	Gly	Val	Asn	Thr	Thr	305	310	315
Asp	Lys	Glu	Ile	Glu	Val	Leu	Tyr	Ile	Arg	Asn	Val	Thr	Phe	Glu	Asp	325	330	335
Ala	Gly	Glu	Tyr	Thr	Cys	Leu	Ala	Gly	Asn	Ser	Ile	Gly	Ile	Ser	Phe	340	345	350
His	Ser	Ala	Trp	Leu	Thr	Val	Leu	Pro	Ala	Pro	Gly	Arg	Glu	Lys	Glu	355	360	365
Ile	Thr	Ala	Ser	Pro	Asp	Tyr	Leu	Glu	Ile	Ala	Ile	Tyr	Cys	Ile	Gly	370	375	380
Val	Phe	Leu	Ile	Ala	Cys	Met	Val	Val	Thr	Val	Ile	Leu	Cys	Arg	Met	385	390	395
Lys	Asn	Thr	Thr	Lys	Lys	Pro	Asp	Phe	Ser	Ser	Gln	Pro	Ala	Val	His	405	410	415
Lys	Leu	Thr	Lys	Arg	Ile	Pro	Leu	Arg	Arg	Gln	Val	Thr	Val	Ser	Ala	420	425	430
Glu	Ser	Ser	Ser	Ser	Met	Asn	Ser	Asn	Thr	Pro	Leu	Val	Arg	Ile	Thr	435	440	445
Thr	Arg	Leu	Ser	Ser	Thr	Ala	Asp	Thr	Pro	Met	Leu	Ala	Gly	Val	Ser	450	455	460
Glu	Tyr	Glu	Leu	Pro	Glu	Asp	Pro	Lys	Trp	Glu	Phe	Pro	Arg	Asp	Lys	465	470	475
Leu	Thr	Leu	Gly	Lys	Pro	Leu	Gly	Glu	Gly	Cys	Phe	Gly	Gln	Val	Val	485	490	495
Met	Ala	Glu	Ala	Val	Gly	Ile	Asp	Lys	Asp	Lys	Pro	Lys	Glu	Ala	Val	500	505	510
Thr	Val	Ala	Val	Lys	Met	Leu	Lys	Asp	Asp	Ala	Thr	Glu	Lys	Asp	Leu	515	520	525
Ser	Asp	Leu	Val	Ser	Glu	Met	Glu	Met	Met	Lys	Met	Ile	Gly	Lys	His	530	535	540
Lys	Asn	Ile	Ile	Asn	Leu	Leu	Gly	Ala	Cys	Thr	Gln	Asp	Gly	Pro	Leu	545	550	555
Tyr	Val	Ile	Val	Glu	Tyr	Ala	Ser	Lys	Gly	Asn	Leu	Arg	Glu	Tyr	Leu	565	570	575
Arg	Ala	Arg	Arg	Pro	Pro	Gly	Met	Glu	Tyr	Ser	Tyr	Asp	Ile	Asn	Arg	580	585	590
Val	Pro	Glu	Glu	Gln	Met	Thr	Phe	Lys	Asp	Leu	Val	Ser	Cys	Thr	Tyr	595	600	605
Gln	Leu	Ala	Arg	Gly	Met	Glu	Tyr	Leu	Ala	Ser	Gln	Lys	Cys	Ile	His	610	615	620
Arg	Asp	Leu	Ala	Ala	Arg	Asn	Val	Leu	Val	Thr	Glu	Asn	Asn	Val	Met	625	630	635
Lys	Ile	Ala	Asp	Phe	Gly	Leu	Ala	Arg	Asp	Ile	Asn	Asn	Ile	Asp	Tyr	645	650	655
Tyr	Lys	Lys	Thr	Thr	Asn	Gly	Arg	Leu	Pro	Val	Lys	Trp	Met	Ala	Pro	660	665	670

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Glu Ala Leu Phe Asp Arg Val Tyr Thr His Gln Ser Asp Val Trp Ser
675 680 685

Phe Gly Val Leu Met Trp Glu Ile Phe Thr Leu Gly Gly Ser Pro Tyr
690 695 700

Pro Gly Ile Pro Val Glu Glu Leu Phe Lys Leu Leu Lys Glu Gly His
705 710 715 720

Arg Met Asp Lys Pro Ala Asn Cys Thr Asn Glu Leu Tyr Met Met Met
725 730 735

Arg Asp Cys Trp His Ala Val Pro Ser Gln Arg Pro Thr Phe Lys Gln
740 745 750

Leu Val Glu Asp Leu Asp Arg Ile Leu Thr Leu Thr Thr Asn Glu Glu
755 760 765

Tyr Leu Asp Leu Ser Gln Pro Leu Glu Gln Tyr Ser Pro Ser Tyr Pro
770 775 780

Asp Thr Arg Ser Ser Cys Ser Ser Gly Asp Asp Ser Val Phe Ser Pro
785 790 795 800

Asp Pro Met Pro Tyr Glu Pro Cys Leu Pro Gln Tyr Pro His Ile Asn
805 810 815

Gly Ser Val Lys Thr
820

<210> SEQ ID NO 72
 <211> LENGTH: 705
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 polynucleotide
 <220> FEATURE:
 <221> NAME/KEY: CDS
 <222> LOCATION: (1)..(705)

<400> SEQUENCE: 72

atg gtg ctg cag acc cag gtg ttc atc tcc ctg ctg ctg tgg atc tcc	48
Met Val Leu Gln Thr Gln Val Phe Ile Ser Leu Leu Leu Trp Ile Ser	
1 5 10 15	
ggc gcg tac ggc gac atc cag atg acc cag agc ccc agc agc ctg agc	96
Gly Ala Tyr Gly Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser	
20 25 30	
gcc agc gtg ggc gac aga gtg acc atc acc tgt cgg gcc agc gag gac	144
Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Asp	
35 40 45	
atc tac agc aac ctg gcc tgg tat cag cag aag ccc ggc aag agc ccc	192
Ile Tyr Ser Asn Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ser Pro	
50 55 60	
cag ctg ctg atc tac gac gcc aac atc ctg gcc gac ggc gtg ccc agc	240
Gln Leu Leu Ile Tyr Asp Ala Asn Ile Leu Ala Asp Gly Val Pro Ser	
65 70 75 80	
aga ttc agc ggc agc ggc tcc ggc acc gac tac acc ctg acc atc tcc	288
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser	
85 90 95	
agc ctg cag ccc gag gac ttc gcc acc tac tac tgc cag cag tac aac	336
Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn	
100 105 110	
aac tac ccc cca ttc acc ttc ggc cag ggc acc aag gtg gaa atc aag	384
Asn Tyr Pro Pro Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys	
115 120 125	

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cgt acg gtg gcc gcc ccc tcc gtg ttc atc ttc ccc ccc tcc gac gag	432
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu	
130 135 140	
cag ctg aag tcc gcc acc gcc tcc gtg gtg tgc ctg ctg aat aac ttc	480
Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe	
145 150 155 160	
tac ccc aga gag gcc aag gtg cag tgg aag gtg gac aac gcc ctg cag	528
Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln	
165 170 175	
tcc ggg aac tcc cag gag agc gtg acc gag cag gac agc aag gac agc	576
Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser	
180 185 190	
acc tac agc ctg agc agc acc ctg acc ctg agc aaa gcc gac tac gag	624
Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu	
195 200 205	
aag cac aag gtg tac gcc tgc gag gtg acc cac cag ggc ctg agc tcc	672
Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser	
210 215 220	
ccc gtc acc aag agc ttc aac agg ggg gag tgt	705
Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys	
225 230 235	

<210> SEQ ID NO 73

<211> LENGTH: 235

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 73

Met Val Leu Gln Thr Gln Val Phe Ile Ser Leu Leu Leu Trp Ile Ser
1 5 10 15

Gly Ala Tyr Gly Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser
20 25 30

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Asp
35 40 45

Ile Tyr Ser Asn Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ser Pro
50 55 60

Gln Leu Leu Ile Tyr Asp Ala Asn Ile Leu Ala Asp Gly Val Pro Ser
65 70 75 80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser
85 90 95

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn
100 105 110

Asn Tyr Pro Pro Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
115 120 125

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
130 135 140

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
145 150 155 160

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
165 170 175

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
180 185 190

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu

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195	200	205	
Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser			
210	215	220	
Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys			
225	230	235	
 <210> SEQ ID NO 74 <211> LENGTH: 1401 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide <220> FEATURE: <221> NAME/KEY: CDS <222> LOCATION: (1) .. (1401) <400> SEQUENCE: 74			
atg aaa cac ctg tgg ttc ttc ctc ctg ctg gtg gca gct ccc aga tgg			48
Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp			
1 5 10 15			
gtg ctg agc cag gtg cag ctg gtg cag tct ggc gcc gaa gtg aag aaa			96
Val Leu Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys			
20 25 30			
cct ggg gct agc gtg aag gtg tcc tgc aag gcc agc ggc ttc acc ttc			144
Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe			
35 40 45			
agc acc agc tat atg agc tgg gtc cgc cag gct cca ggc cag gga ctg			192
Ser Thr Ser Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu			
50 55 60			
gaa tgg atg ggc tgg atc tat gcc ggc gac ggc ggc acc aag tac aac			240
Glu Trp Met Gly Trp Ile Tyr Ala Gly Asp Gly Gly Thr Lys Tyr Asn			
65 70 75 80			
cag aaa ttc aag ggc aga gtg acc ctg acc gtg gac aag agc acc agc			288
Gln Lys Phe Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Thr Ser			
85 90 95			
acc gcc tac atg gaa ctg agc agc ctg cgg agc gag gac acc gcc gtg			336
Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val			
100 105 110			
tac tac tgc gcc acc gac ggc tac ggc gac tgg ttc aca tac tgg ggc			384
Tyr Tyr Cys Ala Thr Asp Gly Tyr Gly Asp Trp Phe Thr Tyr Trp Gly			
115 120 125			
cag ggc acc ctg gtg acc gtg agc tca gcc tcc acc aag ggc cca agc			432
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser			
130 135 140			
gtc ttc ccc ctg gca ccc tcc tcc aag agc acc tct ggc ggc aca gcc			480
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala			
145 150 155 160			
gcc ctg ggc tgc ctg gtc aag gac tac ttc ccc gaa ccc gtg acc gtg			528
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val			
165 170 175			
agc tgg aac tca ggc gcc ctg acc agc ggc gtg cac acc ttc ccc gct			576
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala			
180 185 190			
gtc ctg cag tcc tca gga ctc tac tcc ctc agc agc gtg gtg acc gtg			624
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val			
195 200 205			
ccc tcc agc agc ttg ggc acc cag acc tac atc tgc aac gtg aat cac			672
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His			

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210	215	220	
aag ccc agc aac acc aag gtg gac aag aga gtt gag ccc aaa tct tgt			720
Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys			
225	230	235	240
gac aaa act cac aca tgc cca ccc tgc cca gca cct gaa ctc ctg ggg			768
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly			
	245	250	255
gga ccc tca gtc ttc ctc ttc ccc cca aaa ccc aag gac acc ctc atg			816
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met			
	260	265	270
atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac gtg agc cac			864
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His			
	275	280	285
gaa gac cct gag gtc aag ttc aac tgg tac gtg gac ggc gtg gag gtg			912
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val			
	290	295	300
cat aat gcc aag aca aag ccc cgg gag gag cag tac aac agc acg tac			960
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr			
	305	310	315
cgg gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg aat ggc			1008
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly			
	325	330	335
aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca gcc ccc atc			1056
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile			
	340	345	350
gag aaa acc atc tcc aaa gcc aaa ggc cag ccc cgg gaa cca cag gtg			1104
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val			
	355	360	365
tac acc ctg ccc cca tcc cgg gag gag atg acc aag aac cag gtc agc			1152
Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser			
	370	375	380
ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc gcc gtg gag			1200
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu			
	385	390	400
tgg gag agc aat ggc cag ccc gag aac aac tac aag acc acc cct ccc			1248
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro			
	405	410	415
gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc acc gtg			1296
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val			
	420	425	430
gac aag agc agg tgg cag cag ggc aac gtc ttc tca tgc tcc gtg atg			1344
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met			
	435	440	445
cat gag gct ctg cac aac cac tac acc cag aag agc ctc tcc ctg tct			1392
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser			
	450	455	460
ccc ggc aaa			1401
Pro Gly Lys			
465			

<210> SEQ ID NO 75

<211> LENGTH: 467

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 75

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Met	Lys	His	Leu	Trp	Phe	Phe	Leu	Leu	Leu	Val	Ala	Ala	Pro	Arg	Trp	1	5	10	15
Val	Leu	Ser	Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	20	25	30	
Pro	Gly	Ala	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Phe	Thr	Phe	35	40	45	
Ser	Thr	Ser	Tyr	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	50	55	60	
Glu	Trp	Met	Gly	Trp	Ile	Tyr	Ala	Gly	Asp	Gly	Gly	Thr	Lys	Tyr	Asn	65	70	75	80
Gln	Lys	Phe	Lys	Gly	Arg	Val	Thr	Leu	Thr	Val	Asp	Lys	Ser	Thr	Ser	85	90	95	
Thr	Ala	Tyr	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	100	105	110	
Tyr	Tyr	Cys	Ala	Thr	Asp	Gly	Tyr	Gly	Asp	Trp	Phe	Thr	Tyr	Trp	Gly	115	120	125	
Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	130	135	140	
Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	145	150	155	160
Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	165	170	175	
Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	180	185	190	
Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	195	200	205	
Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	210	215	220	
Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	225	230	235	240
Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	245	250	255	
Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	260	265	270	
Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	275	280	285	
Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	290	295	300	
His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	305	310	315	320
Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	325	330	335	
Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	340	345	350	
Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	355	360	365	
Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	370	375	380	
Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	385	390	395	400

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Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro
			405					410						415	
Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val
			420				425						430		
Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met
		435					440					445			
His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser
	450				455						460				
Pro	Gly	Lys													
465															

<210> SEQ ID NO 76
<211> LENGTH: 1401
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(1401)

<400> SEQUENCE: 76

atg	aaa	cac	ctg	tgg	ttc	ttc	ctc	ctg	ctg	gtg	gca	gct	ccc	aga	tgg	48
Met	Lys	His	Leu	Trp	Phe	Phe	Leu	Leu	Val	Ala	Ala	Pro	Arg	Trp		
1			5					10					15			
gtg	ctg	agc	cag	gtg	cag	ctg	gtg	cag	tct	ggc	gcc	gaa	gtg	aag	aaa	96
Val	Leu	Ser	Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	
			20				25					30				
cct	ggg	gct	agc	gtg	aag	gtg	tcc	tgc	aag	gcc	agc	ggc	ttc	acc	ttc	144
Pro	Gly	Ala	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Phe	Thr	Phe	
		35				40					45					
agc	acc	agc	tat	atg	agc	tgg	gtc	cgc	cag	gct	cca	ggc	cag	gga	ctg	192
Ser	Thr	Ser	Tyr	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	
	50				55				60							
gaa	tgg	atg	ggc	tgg	atc	tat	gcc	ggc	gac	ggc	ggc	acc	aag	tac	aac	240
Glu	Trp	Met	Gly	Trp	Ile	Tyr	Ala	Gly	Asp	Gly	Gly	Thr	Lys	Tyr	Asn	
65				70				75						80		
cag	aaa	ttc	aag	ggc	aga	gtg	acc	ctg	acc	gcc	gac	aag	agc	acc	agc	288
Gln	Lys	Phe	Lys	Gly	Arg	Val	Thr	Leu	Thr	Ala	Asp	Lys	Ser	Thr	Ser	
			85					90					95			
acc	gcc	tac	atg	gaa	ctg	agc	agc	ctg	cgg	agc	gag	gac	acc	gcc	gtg	336
Thr	Ala	Tyr	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	
			100				105					110				
tac	tac	tgc	gcc	acc	gac	ggc	tac	ggc	gac	tgg	ttc	aca	tac	tgg	ggc	384
Tyr	Tyr	Cys	Ala	Thr	Asp	Gly	Tyr	Gly	Asp	Trp	Phe	Thr	Tyr	Trp	Gly	
		115				120						125				
cag	ggc	acc	ctg	gtg	acc	gtg	agc	tca	gcc	tcc	acc	aag	ggc	cca	agc	432
Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	
	130				135					140						
gtc	ttc	ccc	ctg	gca	ccc	tcc	tcc	aag	agc	acc	tct	ggc	ggc	aca	gcc	480
Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	
145				150					155					160		
gcc	ctg	ggc	tgc	ctg	gtc	aag	gac	tac	ttc	ccc	gaa	ccc	gtg	acc	gtg	528
Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	
			165					170					175			
agc	tgg	aac	tca	ggc	gcc	ctg	acc	agc	ggc	gtg	cac	acc	ttc	ccc	gct	576
Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	
		180					185					190				

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gtc ctg cag tcc tca gga ctc tac tcc ctc agc agc gtg gtg acc gtg Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val 195 200 205	624
ccc tcc agc agc ttg ggc acc cag acc tac atc tgc aac gtg aat cac Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His 210 215 220	672
aag ccc agc aac acc aag gtg gac aag aga gtt gag ccc aaa tct tgt Lys Pro Ser Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys 225 230 235 240	720
gac aaa act cac aca tgc cca ccc tgc cca gca cct gaa ctc ctg ggg Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly 245 250 255	768
gga ccc tca gtc ttc ctc ttc ccc cca aaa ccc aag gac acc ctc atg Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met 260 265 270	816
atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac gtg agc cac Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His 275 280 285	864
gaa gac cct gag gtc aag ttc aac tgg tac gtg gac ggc gtg gag gtg Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val 290 295 300	912
cat aat gcc aag aca aag ccc cgg gag gag cag tac aac agc acg tac His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr 305 310 315 320	960
cgg gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg aat ggc Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly 325 330 335	1008
aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca gcc ccc atc Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile 340 345 350	1056
gag aaa acc atc tcc aaa gcc aaa ggc cag ccc cgg gaa cca cag gtg Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val 355 360 365	1104
tac acc ctg ccc cca tcc cgg gag gag atg acc aag aac cag gtc agc Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser 370 375 380	1152
ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc gcc gtg gag Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu 385 390 395 400	1200
tgg gag agc aat ggc cag ccc gag aac aac tac aag acc acc cct ccc Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro 405 410 415	1248
gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc acc gtg Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val 420 425 430	1296
gac aag agc agg tgg cag cag ggc aac gtc ttc tca tgc tcc gtg atg Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met 435 440 445	1344
cat gag gct ctg cac aac cac tac acc cag aag agc ctc tcc ctg tct His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser 450 455 460	1392
ccc ggc aaa Pro Gly Lys 465	1401

<210> SEQ ID NO 77

<211> LENGTH: 467

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
        polypeptide

<400> SEQUENCE: 77

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
1      5      10      15
Val Leu Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20      25      30
Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe
35      40      45
Ser Thr Ser Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
50      55      60
Glu Trp Met Gly Trp Ile Tyr Ala Gly Asp Gly Gly Thr Lys Tyr Asn
65      70      75      80
Gln Lys Phe Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser
85      90      95
Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
100     105     110
Tyr Tyr Cys Ala Thr Asp Gly Tyr Gly Asp Trp Phe Thr Tyr Trp Gly
115     120     125
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
130     135     140
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
145     150     155     160
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
165     170     175
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
180     185     190
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
195     200     205
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
210     215     220
Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
225     230     235     240
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
245     250     255
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
260     265     270
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
275     280     285
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
290     295     300
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
305     310     315     320
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
325     330     335
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
340     345     350
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
355     360     365

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Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
370 375 380

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
385 390 395 400

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
405 410 415

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
420 425 430

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
435 440 445

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
450 455 460

Pro Gly Lys
465

<210> SEQ ID NO 78
<211> LENGTH: 1401
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polynucleotide
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(1401)

<400> SEQUENCE: 78

atg aaa cac ctg tgg ttc ttc ctc ctg ctg gtg gca gct ccc aga tgg	48
Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp	
1 5 10 15	
gtg ctg agc cag gtg cag ctg gtg cag tct ggc gcc gaa gtg aag aaa	96
Val Leu Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys	
20 25 30	
cct ggg gct agc gtg aag gtg tcc tgc aag gcc agc ggc ttc acc ttc	144
Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe	
35 40 45	
agc acc agc tat atg agc tgg gtc cgc cag gct cca ggc ccc agc acc	192
Ser Thr Ser Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Pro Ser Thr	
50 55 60	
gaa tgg atg ggc tgg atc tat gcc ggc gac ggc ggc acc aag tac aac	240
Glu Trp Met Gly Trp Ile Tyr Ala Gly Asp Gly Gly Thr Lys Tyr Asn	
65 70 75 80	
cag aaa ttc aag ggc aga gtg acc ctg acc gtg gac aag agc acc agc	288
Gln Lys Phe Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Thr Ser	
85 90 95	
acc gcc tac atg gaa ctg agc agc ctg cgg agc gag gac acc gcc gtg	336
Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val	
100 105 110	
tac tac tgc gcc acc gac ggc tac ggc gac tgg ttc aca tac tgg ggc	384
Tyr Tyr Cys Ala Thr Asp Gly Tyr Gly Asp Trp Phe Thr Tyr Trp Gly	
115 120 125	
cag ggc acc ctg gtg acc gtg agc tca gcc tcc acc aag ggc cca agc	432
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser	
130 135 140	
gtc ttc ccc ctg gca ccc tcc tcc aag agc acc tct ggc ggc aca gcc	480
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala	
145 150 155 160	

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gcc ctg ggc tgc ctg gtc aag gac tac ttc ccc gaa ccc gtg acc gtg	528
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val	
165 170 175	
agc tgg aac tca ggc gcc ctg acc agc ggc gtg cac acc ttc ccc gct	576
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala	
180 185 190	
gtc ctg cag tcc tca gga ctc tac tcc ctc agc agc gtg gtg acc gtg	624
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val	
195 200 205	
ccc tcc agc agc ttg ggc acc cag acc tac atc tgc aac gtg aat cac	672
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His	
210 215 220	
aag ccc agc aac acc aag gtg gac aag aga gtt gag ccc aaa tct tgt	720
Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys	
225 230 235 240	
gac aaa act cac aca tgc cca ccc tgc cca gca cct gaa ctc ctg ggg	768
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly	
245 250 255	
gga ccc tca gtc ttc ctc ttc ccc cca aaa ccc aag gac acc ctc atg	816
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met	
260 265 270	
atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac gtg agc cac	864
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His	
275 280 285	
gaa gac cct gag gtc aag ttc aac tgg tac gtg gac ggc gtg gag gtg	912
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val	
290 295 300	
cat aat gcc aag aca aag ccc cgg gag gag cag tac aac agc acg tac	960
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr	
305 310 315 320	
cgg gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg aat ggc	1008
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly	
325 330 335	
aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca gcc ccc atc	1056
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile	
340 345 350	
gag aaa acc atc tcc aaa gcc aaa ggc cag ccc cgg gaa cca cag gtg	1104
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val	
355 360 365	
tac acc ctg ccc cca tcc cgg gag gag atg acc aag aac cag gtc agc	1152
Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser	
370 375 380	
ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc gcc gtg gag	1200
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu	
385 390 395 400	
tgg gag agc aat ggc cag ccc gag aac aac tac aag acc acc cct ccc	1248
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro	
405 410 415	
gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc acc gtg	1296
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val	
420 425 430	
gac aag agc agg tgg cag cag ggc aac gtc ttc tca tgc tcc gtg atg	1344
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met	
435 440 445	
cat gag gct ctg cac aac cac tac acc cag aag agc ctc tcc ctg tct	1392
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser	
450 455 460	

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ccc ggc aaa 1401
Pro Gly Lys
465

<210> SEQ ID NO 79
<211> LENGTH: 467
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 79

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
1 5 10 15
Val Leu Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20 25 30
Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe
35 40 45
Ser Thr Ser Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Pro Ser Thr
50 55 60
Glu Trp Met Gly Trp Ile Tyr Ala Gly Asp Gly Gly Thr Lys Tyr Asn
65 70 75 80
Gln Lys Phe Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Thr Ser
85 90 95
Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
100 105 110
Tyr Tyr Cys Ala Thr Asp Gly Tyr Gly Asp Trp Phe Thr Tyr Trp Gly
115 120 125
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
130 135 140
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
145 150 155 160
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
165 170 175
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
180 185 190
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
195 200 205
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
210 215 220
Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
225 230 235 240
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
245 250 255
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
260 265 270
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
275 280 285
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
290 295 300
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
305 310 315 320
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly

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325										330										335									
Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile														
			340					345						350															
Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val														
		355					360						365																
Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser														
	370					375					380																		
Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu														
385					390					395					400														
Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro														
			405						410						415														
Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val														
		420						425						430															
Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met														
		435					440					445																	
His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser														
	450					455						460																	
Pro	Gly	Lys																											
465																													
<210> SEQ ID NO 80																													
<211> LENGTH: 1401																													
<212> TYPE: DNA																													
<213> ORGANISM: Artificial Sequence																													
<220> FEATURE:																													
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic																													
polynucleotide																													
<220> FEATURE:																													
<221> NAME/KEY: CDS																													
<222> LOCATION: (1)..(1401)																													
<400> SEQUENCE: 80																													
atg	aaa	cac	ctg	tgg	ttc	ttc	ctc	ctg	ctg	gtg	gca	gct	ccc	aga	tgg				48										
Met	Lys	His	Leu	Trp	Phe	Phe	Leu	Leu	Leu	Val	Ala	Ala	Pro	Arg	Trp														
1			5						10					15															
gtg	ctg	agc	cag	gtg	cag	ctg	gtg	cag	tct	ggc	gcc	gaa	gtg	aag	aaa				96										
Val	Leu	Ser	Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys														
			20				25						30																
cct	ggg	gct	agc	gtg	aag	gtg	tcc	tgc	aag	gcc	agc	ggc	ttc	acc	ttc				144										
Pro	Gly	Ala	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Phe	Thr	Phe														
		35					40					45																	
agc	acc	agc	tat	atg	agc	tgg	gtc	cgc	cag	gct	cca	ggc	ccc	agc	atc				192										
Ser	Thr	Ser	Tyr	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Pro	Ser	Ile														
		50				55					60																		
gaa	tgg	atg	ggc	tgg	atc	tat	gcc	ggc	gac	ggc	ggc	acc	aag	tac	aac				240										
Glu	Trp	Met	Gly	Trp	Ile	Tyr	Ala	Gly	Asp	Gly	Gly	Thr	Lys	Tyr	Asn														
65					70				75					80															
cag	aaa	ttc	aag	ggc	aga	gtg	acc	ctg	acc	gtg	gac	aag	agc	acc	agc				288										
Gln	Lys	Phe	Lys	Gly	Arg	Val	Thr	Leu	Thr	Val	Asp	Lys	Ser	Thr	Ser														
			85						90					95															
acc	gcc	tac	atg	gaa	ctg	agc	agc	ctg	cgg	agc	gag	gac	acc	gcc	gtg				336										
Thr	Ala	Tyr	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val														
			100					105						110															
tac	tac	tgc	gcc	acc	gac	ggc	tac	ggc	gac	tgg	ttc	gcc	tac	tgg	ggc				384										
Tyr	Tyr	Cys	Ala	Thr	Asp	Gly	Tyr	Gly	Asp	Trp	Phe	Ala	Tyr	Trp	Gly														
		115				120						125																	
cag	ggc	acc	ctg	gtg	acc	gtg	agc	tca	gcc	tcc	acc	aag	ggc	cca	agc				432										

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Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	
130						135					140					
gtc	ttc	ccc	ctg	gca	ccc	tcc	tcc	aag	agc	acc	tct	ggc	ggc	aca	gcc	480
Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	
145					150					155					160	
gcc	ctg	ggc	tgc	ctg	gtc	aag	gac	tac	ttc	ccc	gaa	ccc	gtg	acc	gtg	528
Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	
				165					170					175		
agc	tgg	aac	tca	ggc	gcc	ctg	acc	agc	ggc	gtg	cac	acc	ttc	ccc	gct	576
Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	
			180					185					190			
gtc	ctg	cag	tcc	tca	gga	ctc	tac	tcc	ctc	agc	agc	gtg	gtg	acc	gtg	624
Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	
	195						200					205				
ccc	tcc	agc	agc	ttg	ggc	acc	cag	acc	tac	atc	tgc	aac	gtg	aat	cac	672
Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	
	210					215					220					
aag	ccc	agc	aac	acc	aag	gtg	gac	aag	aga	gtt	gag	ccc	aaa	tct	tgt	720
Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	
	225				230					235					240	
gac	aaa	act	cac	aca	tgc	cca	ccc	tgc	cca	gca	cct	gaa	ctc	ctg	ggg	768
Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	
				245					250					255		
gga	ccc	tca	gtc	ttc	ctc	ttc	ccc	cca	aaa	ccc	aag	gac	acc	ctc	atg	816
Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	
			260					265					270			
atc	tcc	cgg	acc	cct	gag	gtc	aca	tgc	gtg	gtg	gtg	gac	gtg	agc	cac	864
Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	
	275						280					285				
gaa	gac	cct	gag	gtc	aag	ttc	aac	tgg	tac	gtg	gac	ggc	gtg	gag	gtg	912
Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	
	290					295					300					
cat	aat	gcc	aag	aca	aag	ccc	cgg	gag	gag	cag	tac	aac	agc	acg	tac	960
His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	
	305				310					315					320	
cgg	gtg	gtc	agc	gtc	ctc	acc	gtc	ctg	cac	cag	gac	tgg	ctg	aat	ggc	1008
Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	
				325					330					335		
aag	gag	tac	aag	tgc	aag	gtc	tcc	aac	aaa	gcc	ctc	cca	gcc	ccc	atc	1056
Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	
			340					345					350			
gag	aaa	acc	atc	tcc	aaa	gcc	aaa	ggc	cag	ccc	cgg	gaa	cca	cag	gtg	1104
Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	
	355					360						365				
tac	acc	ctg	ccc	cca	tcc	cgg	gag	gag	atg	acc	aag	aac	cag	gtc	agc	1152
Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	
	370					375						380				
ctg	acc	tgc	ctg	gtc	aaa	ggc	ttc	tat	ccc	agc	gac	atc	gcc	gtg	gag	1200
Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	
	385				390					395				400		
tgg	gag	agc	aat	ggc	cag	ccc	gag	aac	aac	tac	aag	acc	acc	cct	ccc	1248
Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	
			405					410						415		
gtg	ctg	gac	tcc	gac	ggc	tcc	ttc	ttc	ctc	tac	agc	aag	ctc	acc	gtg	1296
Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	
			420					425						430		
gac	aag	agc	agg	tgg	cag	cag	ggc	aac	gtc	ttc	tca	tgc	tcc	gtg	atg	1344

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Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	
	435						440					445				
cat	gag	gct	ctg	cac	aac	cac	tac	acc	cag	aag	agc	ctc	tcc	ctg	tct	1392
His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	
	450					455					460					
ccc	ggc	aaa														1401
Pro	Gly	Lys														
465																
 <210> SEQ ID NO 81 <211> LENGTH: 467 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide <400> SEQUENCE: 81																
Met	Lys	His	Leu	Trp	Phe	Phe	Leu	Leu	Leu	Val	Ala	Ala	Pro	Arg	Trp	
1			5						10					15		
Val	Leu	Ser	Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	
			20					25					30			
Pro	Gly	Ala	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Phe	Thr	Phe	
		35					40					45				
Ser	Thr	Ser	Tyr	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Pro	Ser	Ile	
	50				55					60						
Glu	Trp	Met	Gly	Trp	Ile	Tyr	Ala	Gly	Asp	Gly	Gly	Thr	Lys	Tyr	Asn	
65					70				75						80	
Gln	Lys	Phe	Lys	Gly	Arg	Val	Thr	Leu	Thr	Val	Asp	Lys	Ser	Thr	Ser	
			85					90						95		
Thr	Ala	Tyr	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	
		100						105					110			
Tyr	Tyr	Cys	Ala	Thr	Asp	Gly	Tyr	Gly	Asp	Trp	Phe	Ala	Tyr	Trp	Gly	
		115				120					125					
Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	
		130				135					140					
Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	
145					150					155					160	
Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	
			165					170						175		
Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	
		180						185					190			
Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	
		195				200						205				
Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	
		210				215					220					
Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	
225					230					235					240	
Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	
				245					250					255		
Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	
			260					265					270			
Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	
		275					280					285				

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Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	
290						295					300					
His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	
305					310					315					320	
Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	
				325					330					335		
Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	
			340					345					350			
Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	
		355					360					365				
Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	
	370					375					380					
Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	
385					390					395					400	
Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	
			405						410					415		
Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	
		420						425					430			
Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	
	435					440						445				
His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	
	450				455						460					
Pro	Gly	Lys														
465																

<210> SEQ ID NO 82
<211> LENGTH: 1401
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(1401)

<400> SEQUENCE: 82

atg	aaa	cac	ctg	tgg	ttc	ttc	ctc	ctg	ctg	gtg	gca	gct	ccc	aga	tgg	48
Met	Lys	His	Leu	Trp	Phe	Phe	Leu	Leu	Val	Ala	Ala	Pro	Arg	Trp		
1			5					10					15			
gtg	ctg	agc	cag	gtg	cag	ctg	gtg	cag	tct	ggc	gcc	gaa	gtg	aag	aaa	96
Val	Leu	Ser	Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	
			20					25					30			
cct	ggg	gct	agc	gtg	aag	gtg	tcc	tgc	aag	gcc	agc	ggc	ttc	acc	ttc	144
Pro	Gly	Ala	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Phe	Thr	Phe	
		35				40						45				
agc	acc	agc	tat	atg	agc	tgg	gtc	cgc	cag	gct	cca	ggc	ccc	agc	acc	192
Ser	Thr	Ser	Tyr	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Pro	Ser	Thr	
		50				55					60					
gaa	tgg	atg	ggc	tgg	atc	tat	gcc	ggc	gac	ggc	ggc	acc	aag	tac	aac	240
Glu	Trp	Met	Gly	Trp	Ile	Tyr	Ala	Gly	Asp	Gly	Gly	Thr	Lys	Tyr	Asn	
65					70				75					80		
cag	aaa	ttc	aag	ggc	aga	gtg	acc	ctg	acc	gtg	gac	aag	agc	acc	agc	288
Gln	Lys	Phe	Lys	Gly	Arg	Val	Thr	Leu	Thr	Val	Asp	Lys	Ser	Thr	Ser	
				85					90					95		
acc	gcc	tac	atg	gaa	ctg	agc	agc	ctg	cgg	agc	gag	gac	acc	gcc	gtg	336
Thr	Ala	Tyr	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	

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100	105	110	
tac tac tgc gcc acc gag ggc tac ggc gac tgg ttc aca tac tgg ggc			384
Tyr Tyr Cys Ala Thr Glu Gly Tyr Gly Asp Trp Phe Thr Tyr Trp Gly			
115	120	125	
cag ggc acc ctg gtg acc gtg agc tca gcc tcc acc aag ggc cca agc			432
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser			
130	135	140	
gtc ttc ccc ctg gca ccc tcc tcc aag agc acc tct ggc ggc aca gcc			480
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala			
145	150	155	160
gcc ctg ggc tgc ctg gtc aag gac tac ttc ccc gaa ccc gtg acc gtg			528
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val			
165	170	175	
agc tgg aac tca ggc gcc ctg acc agc ggc gtg cac acc ttc ccc gct			576
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala			
180	185	190	
gtc ctg cag tcc tca gga ctc tac tcc ctc agc agc gtg gtg acc gtg			624
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val			
195	200	205	
ccc tcc agc agc ttg ggc acc cag acc tac atc tgc aac gtg aat cac			672
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His			
210	215	220	
aag ccc agc aac acc aag gtg gac aag aga gtt gag ccc aaa tct tgt			720
Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys			
225	230	235	240
gac aaa act cac aca tgc cca ccc tgc cca gca cct gaa ctc ctg ggg			768
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly			
245	250	255	
gga ccc tca gtc ttc ctc ttc ccc cca aaa ccc aag gac acc ctc atg			816
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met			
260	265	270	
atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac gtg agc cac			864
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His			
275	280	285	
gaa gac cct gag gtc aag ttc aac tgg tac gtg gac ggc gtg gag gtg			912
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val			
290	295	300	
cat aat gcc aag aca aag ccc cgg gag gag cag tac aac agc acg tac			960
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr			
305	310	315	320
cgg gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg aat ggc			1008
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly			
325	330	335	
aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca gcc ccc atc			1056
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile			
340	345	350	
gag aaa acc atc tcc aaa gcc aaa ggc cag ccc cgg gaa cca cag gtg			1104
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val			
355	360	365	
tac acc ctg ccc cca tcc cgg gag gag atg acc aag aac cag gtc agc			1152
Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser			
370	375	380	
ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc gcc gtg gag			1200
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu			
385	390	395	400
tgg gag agc aat ggc cag ccc gag aac aac tac aag acc acc cct ccc			1248
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro			

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405	410	415	
gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc acc gtg			1296
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val			
420	425	430	
gac aag agc agg tgg cag cag ggc aac gtc ttc tca tgc tcc gtg atg			1344
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met			
435	440	445	
cat gag gct ctg cac aac cac tac acc cag aag agc ctc tcc ctg tct			1392
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser			
450	455	460	
ccc ggc aaa			1401
Pro Gly Lys			
465			
<210> SEQ ID NO 83			
<211> LENGTH: 467			
<212> TYPE: PRT			
<213> ORGANISM: Artificial Sequence			
<220> FEATURE:			
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic			
polypeptide			
<400> SEQUENCE: 83			
Met Lys His Leu Trp Phe Phe Leu Leu Val Ala Ala Pro Arg Trp			
1 5 10 15			
Val Leu Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys			
20 25 30			
Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe			
35 40 45			
Ser Thr Ser Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Pro Ser Thr			
50 55 60			
Glu Trp Met Gly Trp Ile Tyr Ala Gly Asp Gly Gly Thr Lys Tyr Asn			
65 70 75 80			
Gln Lys Phe Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Thr Ser			
85 90 95			
Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val			
100 105 110			
Tyr Tyr Cys Ala Thr Glu Gly Tyr Gly Asp Trp Phe Thr Tyr Trp Gly			
115 120 125			
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser			
130 135 140			
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala			
145 150 155 160			
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val			
165 170 175			
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala			
180 185 190			
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val			
195 200 205			
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His			
210 215 220			
Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys			
225 230 235 240			
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly			
245 250 255			

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<400> SEQUENCE: 84

atg	aaa	cac	ctg	tgg	ttc	ttc	ctc	ctg	ctg	gtg	gca	gct	ccc	aga	tgg	48
Met	Lys	His	Leu	Trp	Phe	Phe	Leu	Leu	Leu	Val	Ala	Ala	Pro	Arg	Trp	
1			5						10					15		
gtg	ctg	agc	cag	gtg	cag	ctg	gtg	cag	tct	ggc	gcc	gaa	gtg	aag	aaa	96
Val	Leu	Ser	Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	
			20					25					30			
cct	ggg	gct	agc	gtg	aag	gtg	tcc	tgc	aag	gcc	agc	ggc	ttc	acc	ttc	144
Pro	Gly	Ala	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Phe	Thr	Phe	
		35					40					45				
agc	acc	agc	tat	atg	agc	tgg	gtc	cgc	cag	gct	cca	ggc	ccc	agc	acc	192
Ser	Thr	Ser	Tyr	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Pro	Ser	Thr	
		50				55					60					
gaa	tgg	atg	ggc	tgg	atc	tat	gcc	ggc	gac	ggc	ggc	acc	aag	tac	aac	240
Glu	Trp	Met	Gly	Trp	Ile	Tyr	Ala	Gly	Asp	Gly	Gly	Thr	Lys	Tyr	Asn	
65					70					75				80		

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cag aaa ttc aag ggc aga gtg acc ctg acc gtg gac aag agc acc agc Gln Lys Phe Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Thr Ser 85 90 95	288
acc gcc tac atg gaa ctg agc agc ctg cgg agc gag gac acc gcc gtg Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val 100 105 110	336
tac tac tgc gcc acc gac gcc tac ggc gac tgg ttc aca tac tgg ggc Tyr Tyr Cys Ala Thr Asp Ala Tyr Gly Asp Trp Phe Thr Tyr Trp Gly 115 120 125	384
cag ggc acc ctg gtg acc gtg agc tca gcc tcc acc aag ggc cca agc Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser 130 135 140	432
gtc ttc ccc ctg gca ccc tcc tcc aag agc acc tct ggc ggc aca gcc Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala 145 150 155 160	480
gcc ctg ggc tgc ctg gtc aag gac tac ttc ccc gaa ccc gtg acc gtg Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val 165 170 175	528
agc tgg aac tca ggc gcc ctg acc agc ggc gtg cac acc ttc ccc gct Ser Trp Asn Ser Gly Ala Leu Thr Ser Ser Gly Val His Thr Phe Pro Ala 180 185 190	576
gtc ctg cag tcc tca gga ctc tac tcc ctc agc agc gtg gtg acc gtg Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val 195 200 205	624
ccc tcc agc agc ttg ggc acc cag acc tac atc tgc aac gtg aat cac Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His 210 215 220	672
aag ccc agc aac acc aag gtg gac aag aga gtt gag ccc aaa tct tgt Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys 225 230 235 240	720
gac aaa act cac aca tgc cca ccc tgc cca gca cct gaa ctc ctg ggg Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly 245 250 255	768
gga ccc tca gtc ttc ctc ttc ccc cca aaa ccc aag gac acc ctc atg Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met 260 265 270	816
atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac gtg agc cac Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His 275 280 285	864
gaa gac cct gag gtc aag ttc aac tgg tac gtg gac ggc gtg gag gtg Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val 290 295 300	912
cat aat gcc aag aca aag ccc cgg gag gag cag tac aac agc acg tac His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr 305 310 315 320	960
cgg gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg aat ggc Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly 325 330 335	1008
aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca gcc ccc atc Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile 340 345 350	1056
gag aaa acc atc tcc aaa gcc aaa ggc cag ccc cgg gaa cca cag gtg Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val 355 360 365	1104
tac acc ctg ccc cca tcc cgg gag gag atg acc aag aac cag gtc agc Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser 370 375 380	1152

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ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc gcc gtg gag	1200
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu	
385 390 395 400	
tggtg gag agc aat ggc cag ccc gag aac aac tac aag acc acc cct ccc	1248
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro	
405 410 415	
gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc acc gtg	1296
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val	
420 425 430	
gac aag agc agg tgg cag cag ggc aac gtc ttc tca tgc tcc gtg atg	1344
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met	
435 440 445	
cat gag gct ctg cac aac cac tac acc cag aag agc ctc tcc ctg tct	1392
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser	
450 455 460	
ccc ggc aaa	1401
Pro Gly Lys	
465	

<210> SEQ ID NO 85

<211> LENGTH: 467

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 85

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
1 5 10 15

Val Leu Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20 25 30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe
35 40 45

Ser Thr Ser Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Pro Ser Thr
50 55 60

Glu Trp Met Gly Trp Ile Tyr Ala Gly Asp Gly Gly Thr Lys Tyr Asn
65 70 75 80

Gln Lys Phe Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Thr Ser
85 90 95

Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Thr Asp Ala Tyr Gly Asp Trp Phe Thr Tyr Trp Gly
115 120 125

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
130 135 140

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
145 150 155 160

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
165 170 175

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
180 185 190

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
195 200 205

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His

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210	215	220
Lys Pro Ser Asn Thr	Lys Val Asp Lys Arg Val	Glu Pro Lys Ser Cys
225	230	235 240
Asp Lys Thr His Thr	Cys Pro Pro Cys Pro Ala Pro	Glu Leu Leu Gly
	245	250 255
Gly Pro Ser Val Phe Leu Phe Pro	Pro Lys Pro Lys Asp Thr	Leu Met
	260	265 270
Ile Ser Arg Thr Pro Glu Val Thr	Cys Val Val Val Asp Val Ser His	
	275	280 285
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val	Asp Gly Val Glu Val	
	290	295 300
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr		
305	310	315 320
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly		
	325	330 335
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile		
	340	345 350
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val		
	355	360 365
Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser		
	370	375 380
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu		
385	390	395 400
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro		
	405	410 415
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val		
	420	425 430
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met		
	435	440 445
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser		
	450	455 460
Pro Gly Lys		
465		

<210> SEQ ID NO 86

<211> LENGTH: 1401

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<220> FEATURE:

<221> NAME/KEY: CDS

<222> LOCATION: (1)..(1401)

<400> SEQUENCE: 86

atg aaa cac ctg tgg ttc ttc ctc ctg ctg gtg gca gct ccc aga tgg	48
Met Lys His Leu Trp Phe Phe Leu Leu Val Ala Ala Pro Arg Trp	
1 5 10 15	
gtg ctg agc cag gtg cag ctg gtg cag tct ggc gcc gaa gtg aag aaa	96
Val Leu Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys	
20 25 30	
cct ggg gct agc gtg aag gtg tcc tgc aag gcc agc ggc ttc acc ttc	144
Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe	
35 40 45	

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agc acc agc tat atg agc tgg gtc cgc cag gct cca ggc ccc agc acc	192
Ser Thr Ser Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Pro Ser Thr	
50 55 60	
gaa tgg atg ggc tgg atc tat gcc ggc gac ggc ggc acc aag tac aac	240
Glu Trp Met Gly Trp Ile Tyr Ala Gly Asp Gly Gly Thr Lys Tyr Asn	
65 70 75 80	
cag aaa ttc aag ggc aga gtg acc ctg acc gtg gac aag agc acc agc	288
Gln Lys Phe Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Thr Ser	
85 90 95	
acc gcc tac atg gaa ctg agc agc ctg cgg agc gag gac acc gcc gtg	336
Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val	
100 105 110	
tac tac tgc gcc acc gac gag tac ggc gac tgg ttc aca tac tgg ggc	384
Tyr Tyr Cys Ala Thr Asp Glu Tyr Gly Asp Trp Phe Thr Tyr Trp Gly	
115 120 125	
cag ggc acc ctg gtg acc gtg agc tca gcc tcc acc aag ggc cca agc	432
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser	
130 135 140	
gtc ttc ccc ctg gca ccc tcc tcc aag agc acc tct ggc ggc aca gcc	480
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala	
145 150 155 160	
gcc ctg ggc tgc ctg gtc aag gac tac ttc ccc gaa ccc gtg acc gtg	528
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val	
165 170 175	
agc tgg aac tca ggc gcc ctg acc agc ggc gtg cac acc ttc ccc gct	576
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala	
180 185 190	
gtc ctg cag tcc tca gga ctc tac tcc ctc agc agc gtg gtg acc gtg	624
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val	
195 200 205	
ccc tcc agc agc ttg ggc acc cag acc tac atc tgc aac gtg aat cac	672
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His	
210 215 220	
aag ccc agc aac acc aag gtg gac aag aga gtt gag ccc aaa tct tgt	720
Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys	
225 230 235 240	
gac aaa act cac aca tgc cca ccc tgc cca gca cct gaa ctc ctg ggg	768
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly	
245 250 255	
gga ccc tca gtc ttc ctc ttc ccc cca aaa ccc aag gac acc ctc atg	816
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met	
260 265 270	
atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac gtg agc cac	864
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His	
275 280 285	
gaa gac cct gag gtc aag ttc aac tgg tac gtg gac ggc gtg gag gtg	912
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val	
290 295 300	
cat aat gcc aag aca aag ccc cgg gag gag cag tac aac agc acg tac	960
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr	
305 310 315 320	
cgg gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg aat ggc	1008
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly	
325 330 335	
aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca gcc ccc atc	1056
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile	
340 345 350	

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gag aaa acc atc tcc aaa gcc aaa ggc cag ccc cgg gaa cca cag gtg	1104
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val	
355 360 365	
tac acc ctg ccc cca tcc cgg gag gag atg acc aag aac cag gtc agc	1152
Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser	
370 375 380	
ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc gcc gtg gag	1200
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu	
385 390 395 400	
tgg gag agc aat ggc cag ccc gag aac aac tac aag acc acc cct ccc	1248
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro	
405 410 415	
gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc acc gtg	1296
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val	
420 425 430	
gac aag agc agg tgg cag cag ggc aac gtc ttc tca tgc tcc gtg atg	1344
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met	
435 440 445	
cat gag gct ctg cac aac cac tac acc cag aag agc ctc tcc ctg tct	1392
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser	
450 455 460	
ccc gcc aaa	1401
Pro Gly Lys	
465	

<210> SEQ ID NO 87

<211> LENGTH: 467

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 87

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp	
1 5 10 15	
Val Leu Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys	
20 25 30	
Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe	
35 40 45	
Ser Thr Ser Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Pro Ser Thr	
50 55 60	
Glu Trp Met Gly Trp Ile Tyr Ala Gly Asp Gly Gly Thr Lys Tyr Asn	
65 70 75 80	
Gln Lys Phe Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Thr Ser	
85 90 95	
Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val	
100 105 110	
Tyr Tyr Cys Ala Thr Asp Glu Tyr Gly Asp Trp Phe Thr Tyr Trp Gly	
115 120 125	
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser	
130 135 140	
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala	
145 150 155 160	
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val	
165 170 175	

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Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	
		180						185					190			
Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	
		195					200					205				
Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	
		210				215					220					
Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	
	225				230					235					240	
Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	
			245						250					255		
Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	
			260					265					270			
Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	
		275					280					285				
Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	
		290				295					300					
His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	
	305				310					315					320	
Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	
			325						330					335		
Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	
			340					345					350			
Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	
		355					360					365				
Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	
		370				375					380					
Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	
	385				390					395					400	
Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	
			405						410					415		
Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	
			420					425					430			
Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	
		435					440					445				
His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	
		450				455					460					
Pro	Gly	Lys														
		465														

<210> SEQ ID NO 88
<211> LENGTH: 1401
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(1401)

<400> SEQUENCE: 88

atg	aaa	cac	ctg	tgg	ttc	ttc	ctc	ctg	ctg	gtg	gca	gct	ccc	aga	tgg	48
Met	Lys	His	Leu	Trp	Phe	Phe	Leu	Leu	Val	Ala	Ala	Pro	Arg	Trp		
1			5					10					15			
gtg	ctg	agc	cag	gtg	cag	ctg	gtg	cag	tct	ggc	gcc	gaa	gtg	aag	aaa	96

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Val	Leu	Ser	Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	
			20					25					30			
cct	ggg	gct	agc	gtg	aag	gtg	tcc	tgc	aag	gcc	agc	ggc	ttc	acc	ttc	144
Pro	Gly	Ala	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Phe	Thr	Phe	
		35					40					45				
agc	acc	agc	tat	atg	agc	tgg	gtc	cgc	cag	gct	cca	ggc	ccc	agc	acc	192
Ser	Thr	Ser	Tyr	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Pro	Ser	Thr	
		50				55				60						
gaa	tgg	atg	ggc	tgg	atc	tat	gcc	ggc	gac	ggc	ggc	acc	aag	tac	aac	240
Glu	Trp	Met	Gly	Trp	Ile	Tyr	Ala	Gly	Asp	Gly	Gly	Thr	Lys	Tyr	Asn	
65					70				75						80	
cag	aaa	ttc	aag	ggc	aga	gtg	acc	ctg	acc	gtg	gac	aag	agc	acc	agc	288
Gln	Lys	Phe	Lys	Gly	Arg	Val	Thr	Leu	Thr	Val	Asp	Lys	Ser	Thr	Ser	
				85					90					95		
acc	gcc	tac	atg	gaa	ctg	agc	agc	ctg	cgg	agc	gag	gac	acc	gcc	gtg	336
Thr	Ala	Tyr	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	
			100					105					110			
tac	tac	tgc	gcc	acc	gac	ttc	tac	ggc	gac	tgg	ttc	aca	tac	tgg	ggc	384
Tyr	Tyr	Cys	Ala	Thr	Asp	Phe	Tyr	Gly	Asp	Trp	Phe	Thr	Tyr	Trp	Gly	
		115					120					125				
cag	ggc	acc	ctg	gtg	acc	gtg	agc	tca	gcc	tcc	acc	aag	ggc	cca	agc	432
Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	
		130				135					140					
gtc	ttc	ccc	ctg	gca	ccc	tcc	tcc	aag	agc	acc	tct	ggc	ggc	aca	gcc	480
Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	
145					150					155					160	
gcc	ctg	ggc	tgc	ctg	gtc	aag	gac	tac	ttc	ccc	gaa	ccc	gtg	acc	gtg	528
Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	
				165				170					175			
agc	tgg	aac	tca	ggc	gcc	ctg	acc	agc	ggc	gtg	cac	acc	ttc	ccc	gct	576
Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	
		180						185					190			
gtc	ctg	cag	tcc	tca	gga	ctc	tac	tcc	ctc	agc	agc	gtg	gtg	acc	gtg	624
Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	
		195					200					205				
ccc	tcc	agc	agc	ttg	ggc	acc	cag	acc	tac	atc	tgc	aac	gtg	aat	cac	672
Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	
		210				215					220					
aag	ccc	agc	aac	acc	aag	gtg	gac	aag	aga	gtt	gag	ccc	aaa	tct	tgt	720
Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	
225					230					235				240		
gac	aaa	act	cac	aca	tgc	cca	ccc	tgc	cca	gca	cct	gaa	ctc	ctg	ggg	768
Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	
				245				250						255		
gga	ccc	tca	gtc	ttc	ctc	ttc	ccc	cca	aaa	ccc	aag	gac	acc	ctc	atg	816
Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	
			260					265					270			
atc	tcc	cgg	acc	cct	gag	gtc	aca	tgc	gtg	gtg	gtg	gac	gtg	agc	cac	864
Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	
		275					280					285				
gaa	gac	cct	gag	gtc	aag	ttc	aac	tgg	tac	gtg	gac	ggc	gtg	gag	gtg	912
Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	
		290				295					300					
cat	aat	gcc	aag	aca	aag	ccc	cgg	gag	gag	cag	tac	aac	agc	acg	tac	960
His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	
305					310					315					320	
cgg	gtg	gtc	agc	gtc	ctc	acc	gtc	ctg	cac	cag	gac	tgg	ctg	aat	ggc	1008

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Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly		
				325					330					335			
aag	gag	tac	aag	tgc	aag	gtc	tcc	aac	aaa	gcc	ctc	cca	gcc	ccc	atc		1056
Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile		
			340					345					350				
gag	aaa	acc	atc	tcc	aaa	gcc	aaa	ggc	cag	ccc	cgg	gaa	cca	cag	gtg		1104
Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val		
			355				360					365					
tac	acc	ctg	ccc	cca	tcc	cgg	gag	gag	atg	acc	aag	aac	cag	gtc	agc		1152
Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser		
			370			375					380						
ctg	acc	tgc	ctg	gtc	aaa	ggc	ttc	tat	ccc	agc	gac	atc	gcc	gtg	gag		1200
Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu		
			385		390				395					400			
tgg	gag	agc	aat	ggc	cag	ccc	gag	aac	aac	tac	aag	acc	acc	cct	ccc		1248
Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro		
			405					410						415			
gtg	ctg	gac	tcc	gac	ggc	tcc	ttc	ttc	ctc	tac	agc	aag	ctc	acc	gtg		1296
Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val		
			420				425						430				
gac	aag	agc	agg	tgg	cag	cag	ggc	aac	gtc	ttc	tca	tgc	tcc	gtg	atg		1344
Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met		
			435			440						445					
cat	gag	gct	ctg	cac	aac	cac	tac	acc	cag	aag	agc	ctc	tcc	ctg	tct		1392
His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser		
			450		455						460						
ccc	ggc	aaa															1401
Pro	Gly	Lys															
			465														

<210> SEQ ID NO 89

<211> LENGTH: 467

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 89

Met	Lys	His	Leu	Trp	Phe	Phe	Leu	Leu	Val	Ala	Ala	Pro	Arg	Trp
1			5					10				15		

Val	Leu	Ser	Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys
		20			25							30			

Pro	Gly	Ala	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Phe	Thr	Phe
	35				40						45				

Ser	Thr	Ser	Tyr	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Pro	Ser	Thr
	50				55				60						

Glu	Trp	Met	Gly	Trp	Ile	Tyr	Ala	Gly	Asp	Gly	Gly	Thr	Lys	Tyr	Asn
65				70				75						80	

Gln	Lys	Phe	Lys	Gly	Arg	Val	Thr	Leu	Thr	Val	Asp	Lys	Ser	Thr	Ser
		85					90						95		

Thr	Ala	Tyr	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val
	100						105						110		

Tyr	Tyr	Cys	Ala	Thr	Asp	Phe	Tyr	Gly	Asp	Trp	Phe	Thr	Tyr	Trp	Gly
	115					120						125			

Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser
	130					135					140				

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Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala
145					150					155					160
Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val
			165						170					175	
Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala
		180						185					190		
Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val
	195						200					205			
Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His
	210					215					220				
Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys
225					230					235					240
Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly
				245					250					255	
Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met
			260					265					270		
Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His
	275						280					285			
Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val
	290					295					300				
His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr
305					310					315					320
Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly
				325					330					335	
Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile
			340					345					350		
Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val
		355					360					365			
Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser
	370					375					380				
Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu
385					390					395					400
Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro
			405						410					415	
Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val
		420						425					430		
Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met
		435					440					445			
His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser
	450					455					460				
Pro	Gly	Lys													
465															

<210> SEQ ID NO 90

<211> LENGTH: 1401

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<220> FEATURE:

<221> NAME/KEY: CDS

<222> LOCATION: (1)..(1401)

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<400> SEQUENCE: 90

atg aaa cac ctg tgg ttc ttc ctc ctg ctg gtg gca gct ccc aga tgg	48
Met Lys His Leu Trp Phe Phe Leu Leu Val Ala Ala Pro Arg Trp	
1 5 10 15	
gtg ctg agc cag gtg cag ctg gtg cag tct ggc gcc gaa gtg aag aaa	96
Val Leu Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys	
20 25 30	
cct ggg gct agc gtg aag gtg tcc tgc aag gcc agc ggc ttc acc ttc	144
Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe	
35 40 45	
agc acc agc tat atg agc tgg gtc cgc cag gct cca ggc ccc agc acc	192
Ser Thr Ser Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Pro Ser Thr	
50 55 60	
gaa tgg atg ggc tgg atc tat gcc ggc gac ggc ggc acc aag tac aac	240
Glu Trp Met Gly Trp Ile Tyr Ala Gly Asp Gly Gly Thr Lys Tyr Asn	
65 70 75 80	
cag aaa ttc aag ggc aga gtg acc ctg acc gtg gac aag agc acc agc	288
Gln Lys Phe Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Thr Ser	
85 90 95	
acc gcc tac atg gaa ctg agc agc ctg cgg agc gag gac acc gcc gtg	336
Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val	
100 105 110	
tac tac tgc gcc acc gac cac tac ggc gac tgg ttc aca tac tgg ggc	384
Tyr Tyr Cys Ala Thr Asp His Tyr Gly Asp Trp Phe Thr Tyr Trp Gly	
115 120 125	
cag ggc acc ctg gtg acc gtg agc tca gcc tcc acc aag ggc cca agc	432
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser	
130 135 140	
gtc ttc ccc ctg gca ccc tcc tcc aag agc acc tct ggc ggc aca gcc	480
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala	
145 150 155 160	
gcc ctg ggc tgc ctg gtc aag gac tac ttc ccc gaa ccc gtg acc gtg	528
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val	
165 170 175	
agc tgg aac tca ggc gcc ctg acc agc ggc gtg cac acc ttc ccc gct	576
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala	
180 185 190	
gtc ctg cag tcc tca gga ctc tac tcc ctc agc agc gtg gtg acc gtg	624
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val	
195 200 205	
ccc tcc agc agc ttg ggc acc cag acc tac atc tgc aac gtg aat cac	672
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His	
210 215 220	
aag ccc agc aac acc aag gtg gac aag aga gtt gag ccc aaa tct tgt	720
Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys	
225 230 235 240	
gac aaa act cac aca tgc cca ccc tgc cca gca cct gaa ctc ctg ggg	768
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly	
245 250 255	
gga ccc tca gtc ttc ctc ttc ccc cca aaa ccc aag gac acc ctc atg	816
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met	
260 265 270	
atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac gtg agc cac	864
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His	
275 280 285	
gaa gac cct gag gtc aag ttc aac tgg tac gtg gac ggc gtg gag gtg	912
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val	

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290	295	300	
cat aat gcc aag aca aag ccc cgg gag gag cag tac aac agc acg tac			960
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr			
305	310	315	320
cgg gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg aat ggc			1008
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly			
	325	330	335
aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca gcc ccc atc			1056
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile			
	340	345	350
gag aaa acc atc tcc aaa gcc aaa ggc cag ccc cgg gaa cca cag gtg			1104
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Thr Gln Val			
	355	360	365
tac acc ctg ccc cca tcc cgg gag gag atg acc aag aac cag gtc agc			1152
Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser			
	370	375	380
ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc gcc gtg gag			1200
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu			
	385	390	400
tgg gag agc aat ggc cag ccc gag aac aac tac aag acc acc cct ccc			1248
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro			
	405	410	415
gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc acc gtg			1296
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val			
	420	425	430
gac aag agc agg tgg cag cag ggc aac gtc ttc tca tgc tcc gtg atg			1344
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met			
	435	440	445
cat gag gct ctg cac aac cac tac acc cag aag agc ctc tcc ctg tct			1392
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser			
	450	455	460
ccc ggc aaa			1401
Pro Gly Lys			
465			

<210> SEQ ID NO 91

<211> LENGTH: 467

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 91

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
1 5 10 15Val Leu Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20 25 30Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe
35 40 45Ser Thr Ser Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Pro Ser Thr
50 55 60Glu Trp Met Gly Trp Ile Tyr Ala Gly Asp Gly Gly Thr Lys Tyr Asn
65 70 75 80Gln Lys Phe Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Thr Ser
85 90 95

Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val

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100					105					110					
Tyr	Tyr	Cys	Ala	Thr	Asp	His	Tyr	Gly	Asp	Trp	Phe	Thr	Tyr	Trp	Gly
		115					120					125			
Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser
		130					135					140			
Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala
		145					150					155			160
Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val
				165								170			175
Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala
			180						185					190	
Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val
		195					200					205			
Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His
				210			215					220			
Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys
				225			230					235			240
Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly
				245					250						255
Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met
			260						265					270	
Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His
			275				280					285			
Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val
			290				295					300			
His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr
				305			310					315			320
Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly
				325					330					335	
Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile
			340						345					350	
Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val
			355				360					365			
Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser
				370			375					380			
Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu
				385			390					395			400
Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro
				405					410					415	
Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val
				420					425					430	
Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met
				435			440					445			
His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser
				450			455					460			
Pro	Gly	Lys													
				465											

<210> SEQ ID NO 92

<211> LENGTH: 1401

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(1401)

<400> SEQUENCE: 92

atg	aaa	cac	ctg	tgg	ttc	ttc	ctc	ctg	ctg	gtg	gca	gct	ccc	aga	tgg	48
Met	Lys	His	Leu	Trp	Phe	Phe	Leu	Leu	Leu	Val	Ala	Ala	Pro	Arg	Trp	
1			5					10						15		
gtg	ctg	agc	cag	gtg	cag	ctg	gtg	cag	tct	ggc	gcc	gaa	gtg	aag	aaa	96
Val	Leu	Ser	Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	
			20					25					30			
cct	ggg	gct	agc	gtg	aag	gtg	tcc	tgc	aag	gcc	agc	ggc	ttc	acc	ttc	144
Pro	Gly	Ala	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Phe	Thr	Phe	
			35				40					45				
agc	acc	agc	tat	atg	agc	tgg	gtc	cgc	cag	gct	cca	ggc	ccc	agc	acc	192
Ser	Thr	Ser	Tyr	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Pro	Ser	Thr	
			50				55				60					
gaa	tgg	atg	ggc	tgg	atc	tat	gcc	ggc	gac	ggc	ggc	acc	aag	tac	aac	240
Glu	Trp	Met	Gly	Trp	Ile	Tyr	Ala	Gly	Asp	Gly	Gly	Thr	Lys	Tyr	Asn	
65					70				75					80		
cag	aaa	ttc	aag	ggc	aga	gtg	acc	ctg	acc	gtg	gac	aag	agc	acc	agc	288
Gln	Lys	Phe	Lys	Gly	Arg	Val	Thr	Leu	Thr	Val	Asp	Lys	Ser	Thr	Ser	
			85					90						95		
acc	gcc	tac	atg	gaa	ctg	agc	agc	ctg	cgg	agc	gag	gac	acc	gcc	gtg	336
Thr	Ala	Tyr	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	
			100					105					110			
tac	tac	tgc	gcc	acc	gac	atc	tac	ggc	gac	tgg	ttc	aca	tac	tgg	ggc	384
Tyr	Tyr	Cys	Ala	Thr	Asp	Ile	Tyr	Gly	Asp	Trp	Phe	Thr	Tyr	Trp	Gly	
			115				120					125				
cag	ggc	acc	ctg	gtg	acc	gtg	agc	tca	gcc	tcc	acc	aag	ggc	cca	agc	432
Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	
			130				135				140					
gtc	ttc	ccc	ctg	gca	ccc	tcc	tcc	aag	agc	acc	tct	ggc	ggc	aca	gcc	480
Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	
145					150					155				160		
gcc	ctg	ggc	tgc	ctg	gtc	aag	gac	tac	ttc	ccc	gaa	ccc	gtg	acc	gtg	528
Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	
			165					170					175			
agc	tgg	aac	tca	ggc	gcc	ctg	acc	agc	ggc	gtg	cac	acc	ttc	ccc	gct	576
Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	
			180					185					190			
gtc	ctg	cag	tcc	tca	gga	ctc	tac	tcc	ctc	agc	agc	gtg	gtg	acc	gtg	624
Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	
			195				200					205				
ccc	tcc	agc	agc	ttg	ggc	acc	cag	acc	tac	atc	tgc	aac	gtg	aat	cac	672
Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	
			210				215				220					
aag	ccc	agc	aac	acc	aag	gtg	gac	aag	aga	gtt	gag	ccc	aaa	tct	tgt	720
Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	
225					230					235				240		
gac	aaa	act	cac	aca	tgc	cca	ccc	tgc	cca	gca	cct	gaa	ctc	ctg	ggg	768
Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	
			245					250					255			
gga	ccc	tca	gtc	ttc	ctc	ttc	ccc	cca	aaa	ccc	aag	gac	acc	ctc	atg	816
Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	
			260					265					270			

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atc tcc cgg acc cct gag gtc aca tgc gtg gtg gac gtg agc cac      864
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
      275              280              285

gaa gac cct gag gtc aag ttc aac tgg tac gtg gac ggc gtg gag gtg      912
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
      290              295              300

cat aat gcc aag aca aag ccc cgg gag gag cag tac aac agc acg tac      960
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
      305              310              315              320

cgg gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg aat ggc      1008
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
      325              330              335

aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca gcc ccc atc      1056
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
      340              345              350

gag aaa acc atc tcc aaa gcc aaa ggc cag ccc cgg gaa cca cag gtg      1104
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
      355              360              365

tac acc ctg ccc cca tcc cgg gag gag atg acc aag aac cag gtc agc      1152
Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
      370              375              380

ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc gcc gtg gag      1200
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
      385              390              395              400

tgg gag agc aat ggc cag ccc gag aac aac tac aag acc acc cct ccc      1248
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
      405              410              415

gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc acc gtg      1296
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
      420              425              430

gac aag agc agg tgg cag cag ggc aac gtc ttc tca tgc tcc gtg atg      1344
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
      435              440              445

cat gag gct ctg cac aac cac tac acc cag aag agc ctc tcc ctg tct      1392
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
      450              455              460

ccc ggc aaa
Pro Gly Lys
465

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<210> SEQ ID NO 93

<211> LENGTH: 467

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 93

```

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
1              5              10              15

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Val Leu Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20              25              30

```

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Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe
35              40              45

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Ser Thr Ser Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Pro Ser Thr
50              55              60

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Glu	Trp	Met	Gly	Trp	Ile	Tyr	Ala	Gly	Asp	Gly	Gly	Thr	Lys	Tyr	Asn	65	70	75	80
Gln	Lys	Phe	Lys	Gly	Arg	Val	Thr	Leu	Thr	Val	Asp	Lys	Ser	Thr	Ser	85	90	95	
Thr	Ala	Tyr	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	100	105	110	
Tyr	Tyr	Cys	Ala	Thr	Asp	Ile	Tyr	Gly	Asp	Trp	Phe	Thr	Tyr	Trp	Gly	115	120	125	
Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	130	135	140	
Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	145	150	155	160
Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	165	170	175	
Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	180	185	190	
Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	195	200	205	
Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	210	215	220	
Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	225	230	235	240
Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	245	250	255	
Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	260	265	270	
Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	275	280	285	
Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	290	295	300	
His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	305	310	315	320
Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	325	330	335	
Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	340	345	350	
Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	355	360	365	
Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	370	375	380	
Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	385	390	395	400
Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	405	410	415	
Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	420	425	430	
Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	435	440	445	
His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	450	455	460	
Pro	Gly	Lys																	

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<210> SEQ ID NO 94
<211> LENGTH: 1401
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(1401)

<400> SEQUENCE: 94

atg aaa cac ctg tgg ttc ttc ctc ctg ctg gtg gca gct ccc aga tgg      48
Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
 1             5             10             15

gtg ctg agc cag gtg cag ctg gtg cag tct ggc gcc gaa gtg aag aaa      96
Val Leu Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
      20             25             30

cct ggg gct agc gtg aag gtg tcc tgc aag gcc agc ggc ttc acc ttc     144
Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe
      35             40             45

agc acc agc tat atg agc tgg gtc cgc cag gct cca ggc ccc agc acc     192
Ser Thr Ser Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Pro Ser Thr
      50             55             60

gaa tgg atg ggc tgg atc tat gcc ggc gac ggc ggc acc aag tac aac     240
Glu Trp Met Gly Trp Ile Tyr Ala Gly Asp Gly Gly Thr Lys Tyr Asn
 65             70             75             80

cag aaa ttc aag ggc aga gtg acc ctg acc gtg gac aag agc acc agc     288
Gln Lys Phe Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Thr Ser
      85             90             95

acc gcc tac atg gaa ctg agc agc ctg cgg agc gag gac acc gcc gtg     336
Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
      100            105            110

tac tac tgc gcc acc gac aag tac ggc gac tgg ttc aca tac tgg ggc     384
Tyr Tyr Cys Ala Thr Asp Lys Tyr Gly Asp Trp Phe Thr Tyr Trp Gly
      115            120            125

cag ggc acc ctg gtg acc gtg agc tca gcc tcc acc aag ggc cca agc     432
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
      130            135            140

gtc ttc ccc ctg gca ccc tcc tcc aag agc acc tct ggc ggc aca gcc     480
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
      145            150            155            160

gcc ctg ggc tgc ctg gtc aag gac tac ttc ccc gaa ccc gtg acc gtg     528
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
      165            170            175

agc tgg aac tca ggc gcc ctg acc agc ggc gtg cac acc ttc ccc gct     576
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
      180            185            190

gtc ctg cag tcc tca gga ctc tac tcc ctc agc agc gtg gtg acc gtg     624
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
      195            200            205

ccc tcc agc agc ttg ggc acc cag acc tac atc tgc aac gtg aat cac     672
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
      210            215            220

aag ccc agc aac acc aag gtg gac aag aga gtt gag ccc aaa tct tgt     720
Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
      225            230            235            240
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gac aaa act cac aca tgc cca ccc tgc cca gca cct gaa ctc ctg ggg	768
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly	
245 250 255	
gga ccc tca gtc ttc ctc ttc ccc cca aaa ccc aag gac acc ctc atg	816
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met	
260 265 270	
atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac gtg agc cac	864
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His	
275 280 285	
gaa gac cct gag gtc aag ttc aac tgg tac gtg gac ggc gtg gag gtg	912
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val	
290 295 300	
cat aat gcc aag aca aag ccc cgg gag gag cag tac aac agc acg tac	960
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr	
305 310 315 320	
cgg gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg aat ggc	1008
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly	
325 330 335	
aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca gcc ccc atc	1056
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile	
340 345 350	
gag aaa acc atc tcc aaa gcc aaa ggc cag ccc cgg gaa cca cag gtg	1104
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val	
355 360 365	
tac acc ctg ccc cca tcc cgg gag gag atg acc aag aac cag gtc agc	1152
Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser	
370 375 380	
ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc gcc gtg gag	1200
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu	
385 390 395 400	
tgg gag agc aat ggc cag ccc gag aac aac tac aag acc acc cct ccc	1248
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro	
405 410 415	
gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc acc gtg	1296
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val	
420 425 430	
gac aag agc agg tgg cag cag ggc aac gtc ttc tca tgc tcc gtg atg	1344
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met	
435 440 445	
cat gag gct ctg cac aac cac tac acc cag aag agc ctc tcc ctg tct	1392
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser	
450 455 460	
ccc ggc aaa	1401
Pro Gly Lys	
465	

<210> SEQ ID NO 95

<211> LENGTH: 467

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 95

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
1 5 10 15

Val Leu Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20 25 30

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Pro	Gly	Ala	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Phe	Thr	Phe
35							40					45			
Ser	Thr	Ser	Tyr	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Pro	Ser	Thr
50						55					60				
Glu	Trp	Met	Gly	Trp	Ile	Tyr	Ala	Gly	Asp	Gly	Gly	Thr	Lys	Tyr	Asn
65					70					75					80
Gln	Lys	Phe	Lys	Gly	Arg	Val	Thr	Leu	Thr	Val	Asp	Lys	Ser	Thr	Ser
				85					90					95	
Thr	Ala	Tyr	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val
				100				105					110		
Tyr	Tyr	Cys	Ala	Thr	Asp	Lys	Tyr	Gly	Asp	Trp	Phe	Thr	Tyr	Trp	Gly
		115					120					125			
Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser
130						135					140				
Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala
145					150					155					160
Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val
				165					170					175	
Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala
		180						185					190		
Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val
195						200						205			
Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His
210						215					220				
Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys
225					230					235					240
Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly
				245					250					255	
Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met
				260				265					270		
Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His
		275					280					285			
Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val
290						295					300				
His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr
305					310					315					320
Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly
				325					330					335	
Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile
				340				345					350		
Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val
		355					360					365			
Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser
370						375					380				
Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu
385					390										

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Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
435 440 445

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
450 455 460

Pro Gly Lys
465

<210> SEQ ID NO 96
<211> LENGTH: 1401
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polynucleotide
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(1401)

<400> SEQUENCE: 96

atg aaa cac ctg tgg ttc ttc ctc ctg ctg gtg gca gct ccc aga tgg	48
Met Lys His Leu Trp Phe Phe Leu Leu Val Ala Ala Pro Arg Trp	
1 5 10 15	
gtg ctg agc cag gtg cag ctg gtg cag tct ggc gcc gaa gtg aag aaa	96
Val Leu Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys	
20 25 30	
cct ggg gct agc gtg aag gtg tcc tgc aag gcc agc ggc ttc acc ttc	144
Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe	
35 40 45	
agc acc agc tat atg agc tgg gtc cgc cag gct cca ggc ccc agc acc	192
Ser Thr Ser Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Pro Ser Thr	
50 55 60	
gaa tgg atg ggc tgg atc tat gcc ggc gac ggc ggc acc aag tac aac	240
Glu Trp Met Gly Trp Ile Tyr Ala Gly Asp Gly Gly Thr Lys Tyr Asn	
65 70 75 80	
cag aaa ttc aag ggc aga gtg acc ctg acc gtg gac aag agc acc agc	288
Gln Lys Phe Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Thr Ser	
85 90 95	
acc gcc tac atg gaa ctg agc agc ctg cgg agc gag gac acc gcc gtg	336
Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val	
100 105 110	
tac tac tgc gcc acc gac ctg tac ggc gac tgg ttc aca tac tgg ggc	384
Tyr Tyr Cys Ala Thr Asp Leu Tyr Gly Asp Trp Phe Thr Tyr Trp Gly	
115 120 125	
cag ggc acc ctg gtg acc gtg agc tca gcc tcc acc aag ggc cca agc	432
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser	
130 135 140	
gtc ttc ccc ctg gca ccc tcc tcc aag agc acc tct ggc ggc aca gcc	480
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala	
145 150 155 160	
gcc ctg ggc tgc ctg gtc aag gac tac ttc ccc gaa ccc gtg acc gtg	528
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val	
165 170 175	
agc tgg aac tca ggc gcc ctg acc agc ggc gtg cac acc ttc ccc gct	576
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala	
180 185 190	
gtc ctg cag tcc tca gga ctc tac tcc ctc agc agc gtg gtg acc gtg	624
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val	
195 200 205	
ccc tcc agc agc ttg ggc acc cag acc tac atc tgc aac gtg aat cac	672

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Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	
210						215					220					
aag	ccc	agc	aac	acc	aag	gtg	gac	aag	aga	gtt	gag	ccc	aaa	tct	tgt	720
Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	
225					230					235					240	
gac	aaa	act	cac	aca	tgc	cca	ccc	tgc	cca	gca	cct	gaa	ctc	ctg	ggg	768
Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	
				245					250					255		
gga	ccc	tca	gtc	ttc	ctc	ttc	ccc	cca	aaa	ccc	aag	gac	acc	ctc	atg	816
Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	
			260					265					270			
atc	tcc	cgg	acc	cct	gag	gtc	aca	tgc	gtg	gtg	gtg	gac	gtg	agc	cac	864
Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	
		275					280					285				
gaa	gac	cct	gag	gtc	aag	ttc	aac	tgg	tac	gtg	gac	ggc	gtg	gag	gtg	912
Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	
	290					295				300						
cat	aat	gcc	aag	aca	aag	ccc	cgg	gag	gag	cag	tac	aac	agc	acg	tac	960
His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	
305					310					315					320	
cgg	gtg	gtc	agc	gtc	ctc	acc	gtc	ctg	cac	cag	gac	tgg	ctg	aat	ggc	1008
Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	
				325					330					335		
aag	gag	tac	aag	tgc	aag	gtc	tcc	aac	aaa	gcc	ctc	cca	gcc	ccc	atc	1056
Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	
		340						345					350			
gag	aaa	acc	atc	tcc	aaa	gcc	aaa	ggc	cag	ccc	cgg	gaa	cca	cag	gtg	1104
Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	
		355					360					365				
tac	acc	ctg	ccc	cca	tcc	cgg	gag	gag	atg	acc	aag	aac	cag	gtc	agc	1152
Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	
		370				375				380						
ctg	acc	tgc	ctg	gtc	aaa	ggc	ttc	tat	ccc	agc	gac	atc	gcc	gtg	gag	1200
Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	
				385		390				395				400		
tgg	gag	agc	aat	ggc	cag	ccc	gag	aac	aac	tac	aag	acc	acc	cct	ccc	1248
Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	
			405						410					415		
gtg	ctg	gac	tcc	gac	ggc	tcc	ttc	ttc	ctc	tac	agc	aag	ctc	acc	gtg	1296
Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	
			420					425					430			
gac	aag	agc	agg	tgg	cag	cag	ggc	aac	gtc	ttc	tca	tgc	tcc	gtg	atg	1344
Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	
			435				440					445				
cat	gag	gct	ctg	cac	aac	cac	tac	acc	cag	aag	agc	ctc	tcc	ctg	tct	1392
His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	
		450				455					460					
ccc	ggc	aaa														1401
Pro	Gly	Lys														
465																

<210> SEQ ID NO 97

<211> LENGTH: 467

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

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<400> SEQUENCE: 97

Met	Lys	His	Leu	Trp	Phe	Phe	Leu	Leu	Leu	Val	Ala	Ala	Pro	Arg	Trp
1			5						10					15	
Val	Leu	Ser	Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys
			20					25					30		
Pro	Gly	Ala	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Phe	Thr	Phe
		35					40					45			
Ser	Thr	Ser	Tyr	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Pro	Ser	Thr
	50					55					60				
Glu	Trp	Met	Gly	Trp	Ile	Tyr	Ala	Gly	Asp	Gly	Gly	Thr	Lys	Tyr	Asn
65					70				75						80
Gln	Lys	Phe	Lys	Gly	Arg	Val	Thr	Leu	Thr	Val	Asp	Lys	Ser	Thr	Ser
			85						90					95	
Thr	Ala	Tyr	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val
			100					105					110		
Tyr	Tyr	Cys	Ala	Thr	Asp	Leu	Tyr	Gly	Asp	Trp	Phe	Thr	Tyr	Trp	Gly
		115				120						125			
Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser
	130					135						140			
Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala
145					150					155					160
Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val
			165						170					175	
Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala
		180						185					190		
Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val
	195					200						205			
Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His
	210				215						220				
Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys
225					230					235					240
Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly
			245						250					255	
Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met
			260					265					270		
Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His
	275						280					285			
Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val
	290					295					300				
His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr
305					310					315					320
Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly
			325						330					335	
Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile
			340					345					350		
Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val
		355					360					365			
Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser
	370					375					380				
Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu
385					390					395					400

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Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
405 410 415

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
420 425 430

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
435 440 445

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
450 455 460

Pro Gly Lys
465

<210> SEQ ID NO 98
<211> LENGTH: 1401
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polynucleotide
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(1401)

<400> SEQUENCE: 98

atg aaa cac ctg tgg ttc ttc ctc ctg ctg gtg gca gct ccc aga tgg	48
Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp	
1 5 10 15	
gtg ctg agc cag gtg cag ctg gtg cag tct ggc gcc gaa gtg aag aaa	96
Val Leu Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys	
20 25 30	
cct ggg gct agc gtg aag gtg tcc tgc aag gcc agc ggc ttc acc ttc	144
Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe	
35 40 45	
agc acc agc tat atg agc tgg gtc cgc cag gct cca ggc ccc agc acc	192
Ser Thr Ser Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Pro Ser Thr	
50 55 60	
gaa tgg atg ggc tgg atc tat gcc ggc gac ggc ggc acc aag tac aac	240
Glu Trp Met Gly Trp Ile Tyr Ala Gly Asp Gly Gly Thr Lys Tyr Asn	
65 70 75 80	
cag aaa ttc aag ggc aga gtg acc ctg acc gtg gac aag agc acc agc	288
Gln Lys Phe Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Thr Ser	
85 90 95	
acc gcc tac atg gaa ctg agc agc ctg cgg agc gag gac acc gcc gtg	336
Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val	
100 105 110	
tac tac tgc gcc acc gac atg tac ggc gac tgg ttc aca tac tgg ggc	384
Tyr Tyr Cys Ala Thr Asp Met Tyr Gly Asp Trp Phe Thr Tyr Trp Gly	
115 120 125	
cag ggc acc ctg gtg acc gtg agc tca gcc tcc acc aag ggc cca agc	432
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser	
130 135 140	
gtc ttc ccc ctg gca ccc tcc tcc aag agc acc tct ggc ggc aca gcc	480
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala	
145 150 155 160	
gcc ctg ggc tgc ctg gtc aag gac tac ttc ccc gaa ccc gtg acc gtg	528
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val	
165 170 175	
agc tgg aac tca ggc gcc ctg acc agc ggc gtg cac acc ttc ccc gct	576
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala	

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180	185	190	
gtc ctg cag tcc tca gga ctc tac tcc ctc agc agc gtg gtg acc gtg			624
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val			
195	200	205	
ccc tcc agc agc ttg ggc acc cag acc tac atc tgc aac gtg aat cac			672
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His			
210	215	220	
aag ccc agc aac acc aag gtg gac aag aga gtt gag ccc aaa tct tgt			720
Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys			
225	230	235	240
gac aaa act cac aca tgc cca ccc tgc cca gca cct gaa ctc ctg ggg			768
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly			
245	250	255	
gga ccc tca gtc ttc ctc ttc ccc cca aaa ccc aag gac acc ctc atg			816
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met			
260	265	270	
atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac gtg agc cac			864
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His			
275	280	285	
gaa gac cct gag gtc aag ttc aac tgg tac gtg gac ggc gtg gag gtg			912
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val			
290	295	300	
cat aat gcc aag aca aag ccc cgg gag gag cag tac aac agc acg tac			960
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr			
305	310	315	320
cgg gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg aat ggc			1008
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly			
325	330	335	
aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca gcc ccc atc			1056
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile			
340	345	350	
gag aaa acc atc tcc aaa gcc aaa ggc cag ccc cgg gaa cca cag gtg			1104
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val			
355	360	365	
tac acc ctg ccc cca tcc cgg gag gag atg acc aag aac cag gtc agc			1152
Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser			
370	375	380	
ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc gcc gtg gag			1200
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu			
385	390	395	400
tgg gag agc aat ggc cag ccc gag aac aac tac aag acc acc cct ccc			1248
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro			
405	410	415	
gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc acc gtg			1296
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val			
420	425	430	
gac aag agc agg tgg cag cag ggc aac gtc ttc tca tgc tcc gtg atg			1344
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met			
435	440	445	
cat gag gct ctg cac aac cac tac acc cag aag agc ctc tcc ctg tct			1392
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser			
450	455	460	
ccc ggc aaa			1401
Pro Gly Lys			
465			

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<211> LENGTH: 467
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 99

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
1 5 10 15

Val Leu Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20 25 30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe
35 40 45

Ser Thr Ser Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Pro Ser Thr
50 55 60

Glu Trp Met Gly Trp Ile Tyr Ala Gly Asp Gly Gly Thr Lys Tyr Asn
65 70 75 80

Gln Lys Phe Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Thr Ser
85 90 95

Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Thr Asp Met Tyr Gly Asp Trp Phe Thr Tyr Trp Gly
115 120 125

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
130 135 140

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
145 150 155 160

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
165 170 175

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
180 185 190

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
195 200 205

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
210 215 220

Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
225 230 235 240

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
245 250 255

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
260 265 270

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
275 280 285

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
290 295 300

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
305 310 315 320

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
325 330 335

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
340 345 350

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val

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355	360	365	
Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser			
370	375	380	
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu			
385	390	395	400
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro			
	405	410	415
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val			
	420	425	430
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met			
	435	440	445
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser			
	450	455	460
Pro Gly Lys			
465			
 <210> SEQ ID NO 100 <211> LENGTH: 1401 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide <220> FEATURE: <221> NAME/KEY: CDS <222> LOCATION: (1)..(1401) <400> SEQUENCE: 100			
atg aaa cac ctg tgg ttc ttc ctc ctg ctg gtg gca gct ccc aga tgg			48
Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp			
1 5 10 15			
gtg ctg agc cag gtg cag ctg gtg cag tct ggc gcc gaa gtg aag aaa			96
Val Leu Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys			
20 25 30			
cct ggg gct agc gtg aag gtg tcc tgc aag gcc agc ggc ttc acc ttc			144
Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe			
35 40 45			
agc acc agc tat atg agc tgg gtc cgc cag gct cca ggc ccc agc acc			192
Ser Thr Ser Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Pro Ser Thr			
50 55 60			
gaa tgg atg ggc tgg atc tat gcc ggc gac ggc ggc acc aag tac aac			240
Glu Trp Met Gly Trp Ile Tyr Ala Gly Asp Gly Gly Thr Lys Tyr Asn			
65 70 75 80			
cag aaa ttc aag ggc aga gtg acc ctg acc gtg gac aag agc acc agc			288
Gln Lys Phe Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Thr Ser			
85 90 95			
acc gcc tac atg gaa ctg agc agc ctg cgg agc gag gac acc gcc gtg			336
Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val			
100 105 110			
tac tac tgc gcc acc gac cag tac ggc gac tgg ttc aca tac tgg ggc			384
Tyr Tyr Cys Ala Thr Asp Gln Tyr Gly Asp Trp Phe Thr Tyr Trp Gly			
115 120 125			
cag ggc acc ctg gtg acc gtg agc tca gcc tcc acc aag ggc cca agc			432
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser			
130 135 140			
gtc ttc ccc ctg gca ccc tcc tcc aag agc acc tct ggc ggc aca gcc			480
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala			
145 150 155 160			

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gcc ctg ggc tgc ctg gtc aag gac tac ttc ccc gaa ccc gtg acc gtg	528
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val	
165 170 175	
agc tgg aac tca ggc gcc ctg acc agc ggc gtg cac acc ttc ccc gct	576
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala	
180 185 190	
gtc ctg cag tcc tca gga ctc tac tcc ctc agc agc gtg gtg acc gtg	624
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val	
195 200 205	
ccc tcc agc agc ttg ggc acc cag acc tac atc tgc aac gtg aat cac	672
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His	
210 215 220	
aag ccc agc aac acc aag gtg gac aag aga gtt gag ccc aaa tct tgt	720
Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys	
225 230 235 240	
gac aaa act cac aca tgc cca ccc tgc cca gca cct gaa ctc ctg ggg	768
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly	
245 250 255	
gga ccc tca gtc ttc ctc ttc ccc cca aaa ccc aag gac acc ctc atg	816
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met	
260 265 270	
atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac gtg agc cac	864
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His	
275 280 285	
gaa gac cct gag gtc aag ttc aac tgg tac gtg gac ggc gtg gag gtg	912
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val	
290 295 300	
cat aat gcc aag aca aag ccc cgg gag gag cag tac aac agc acg tac	960
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr	
305 310 315 320	
cgg gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg aat ggc	1008
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly	
325 330 335	
aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca gcc ccc atc	1056
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile	
340 345 350	
gag aaa acc atc tcc aaa gcc aaa ggc cag ccc cgg gaa cca cag gtg	1104
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val	
355 360 365	
tac acc ctg ccc cca tcc cgg gag gag atg acc aag aac cag gtc agc	1152
Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser	
370 375 380	
ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc gcc gtg gag	1200
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu	
385 390 395 400	
tgg gag agc aat ggc cag ccc gag aac aac tac aag acc acc cct ccc	1248
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro	
405 410 415	
gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc acc gtg	1296
Val Leu Asp Ser Asp Gly Ser Phe Leu Tyr Ser Lys Leu Thr Val	
420 425 430	
gac aag agc agg tgg cag cag ggc aac gtc ttc tca tgc tcc gtg atg	1344
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met	
435 440 445	
cat gag gct ctg cac aac cac tac acc cag aag agc ctc tcc ctg tct	1392
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser	
450 455 460	

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ccc ggc aaa 1401
Pro Gly Lys
465

<210> SEQ ID NO 101
<211> LENGTH: 467
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polypeptide

<400> SEQUENCE: 101

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
1 5 10 15
Val Leu Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20 25 30
Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe
35 40 45
Ser Thr Ser Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Pro Ser Thr
50 55 60
Glu Trp Met Gly Trp Ile Tyr Ala Gly Asp Gly Gly Thr Lys Tyr Asn
65 70 75 80
Gln Lys Phe Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Thr Ser
85 90 95
Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
100 105 110
Tyr Tyr Cys Ala Thr Asp Gln Tyr Gly Asp Trp Phe Thr Tyr Trp Gly
115 120 125
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
130 135 140
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
145 150 155 160
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
165 170 175
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
180 185 190
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
195 200 205
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
210 215 220
Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
225 230 235 240
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
245 250 255
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
260 265 270
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
275 280 285
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
290 295 300
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
305 310 315 320

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Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	
				325					330					335		
Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	
			340					345					350			
Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	
		355					360					365				
Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	
	370					375					380					
Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	
385					390					395					400	
Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	
			405					410						415		
Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	
		420						425					430			
Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	
	435					440						445				
His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	
	450				455						460					
Pro	Gly	Lys														
465																

<210> SEQ ID NO 102

<211> LENGTH: 1401

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<220> FEATURE:

<221> NAME/KEY: CDS

<222> LOCATION: (1)..(1401)

<400> SEQUENCE: 102

atg	aaa	cac	ctg	tgg	ttc	ttc	ctc	ctg	ctg	gtg	gca	gct	ccc	aga	tgg	48
Met	Lys	His	Leu	Trp	Phe	Phe	Leu	Leu	Val	Ala	Ala	Pro	Arg	Trp		
1			5					10					15			
gtg	ctg	agc	cag	gtg	cag	ctg	gtg	cag	tct	ggc	gcc	gaa	gtg	aag	aaa	96
Val	Leu	Ser	Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	
			20				25					30				
cct	ggg	gct	agc	gtg	aag	gtg	tcc	tgc	aag	gcc	agc	ggc	ttc	acc	ttc	144
Pro	Gly	Ala	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Phe	Thr	Phe	
		35				40					45					
agc	acc	agc	tat	atg	agc	tgg	gtc	cgc	cag	gct	cca	ggc	ccc	agc	acc	192
Ser	Thr	Ser	Tyr	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Pro	Ser	Thr	
	50				55					60						
gaa	tgg	atg	ggc	tgg	atc	tat	gcc	ggc	gac	ggc	ggc	acc	aag	tac	aac	240
Glu	Trp	Met	Gly	Trp	Ile	Tyr	Ala	Gly	Asp	Gly	Gly	Thr	Lys	Tyr	Asn	
65				70				75					80			
cag	aaa	ttc	aag	ggc	aga	gtg	acc	ctg	acc	gtg	gac	aag	agc	acc	agc	288
Gln	Lys	Phe	Lys	Gly	Arg	Val	Thr	Leu	Thr	Val	Asp	Lys	Ser	Thr	Ser	
			85				90						95			
acc	gcc	tac	atg	gaa	ctg	agc	agc	ctg	cgg	agc	gag	gac	acc	gcc	gtg	336
Thr	Ala	Tyr	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	
		100					105					110				
tac	tac	tgc	gcc	acc	gac	cgg	tac	ggc	gac	tgg	ttc	aca	tac	tgg	ggc	384
Tyr	Tyr	Cys	Ala	Thr	Asp	Arg	Tyr	Gly	Asp	Trp	Phe	Thr	Tyr	Trp	Gly	
	115					120					125					

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cag ggc acc ctg gtg acc gtg agc tca gcc tcc acc aag ggc cca agc Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser 130 135 140	432
gtc ttc ccc ctg gca ccc tcc tcc aag agc acc tct ggc ggc aca gcc Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala 145 150 155 160	480
gcc ctg ggc tgc ctg gtg aag gac tac ttc ccc gaa ccc gtg acc gtg Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val 165 170 175	528
agc tgg aac tca ggc gcc ctg acc agc ggc gtg cac acc ttc ccc gct Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala 180 185 190	576
gtc ctg cag tcc tca gga ctc tac tcc ctc agc agc gtg gtg acc gtg Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val 195 200 205	624
ccc tcc agc agc ttg ggc acc cag acc tac atc tgc aac gtg aat cac Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His 210 215 220	672
aag ccc agc aac acc aag gtg gac aag aga gtt gag ccc aaa tct tgt Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys 225 230 235 240	720
gac aaa act cac aca tgc cca ccc tgc cca gca cct gaa ctc ctg ggg Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly 245 250 255	768
gga ccc tca gtc ttc ctc ttc ccc cca aaa ccc aag gac acc ctc atg Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met 260 265 270	816
atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac gtg agc cac Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His 275 280 285	864
gaa gac cct gag gtc aag ttc aac tgg tac gtg gac ggc gtg gag gtg Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val 290 295 300	912
cat aat gcc aag aca aag ccc cgg gag gag cag tac aac agc acg tac His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr 305 310 315 320	960
cgg gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg aat ggc Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly 325 330 335	1008
aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca gcc ccc atc Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile 340 345 350	1056
gag aaa acc atc tcc aaa gcc aaa ggc cag ccc cgg gaa cca cag gtg Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val 355 360 365	1104
tac acc ctg ccc cca tcc cgg gag gag atg acc aag aac cag gtc agc Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser 370 375 380	1152
ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc gcc gtg gag Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu 385 390 395 400	1200
tgg gag agc aat ggc cag ccc gag aac aac tac aag acc acc cct ccc Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro 405 410 415	1248
gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc acc gtg Val Leu Asp Ser Asp Gly Ser Phe Leu Tyr Ser Lys Leu Thr Val 420 425 430	1296

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gac aag agc agg tgg cag cag ggc aac gtc ttc tca tgc tcc gtg atg	1344
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met	
435 440 445	
cat gag gct ctg cac aac cac tac acc cag aag agc ctc tcc ctg tct	1392
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser	
450 455 460	
ccc ggc aaa	1401
Pro Gly Lys	
465	

<210> SEQ ID NO 103
<211> LENGTH: 467
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 103

Met Lys His Leu Trp Phe Phe Leu Leu Val Ala Ala Pro Arg Trp	
1 5 10 15	
Val Leu Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys	
20 25 30	
Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe	
35 40 45	
Ser Thr Ser Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Pro Ser Thr	
50 55 60	
Glu Trp Met Gly Trp Ile Tyr Ala Gly Asp Gly Gly Thr Lys Tyr Asn	
65 70 75 80	
Gln Lys Phe Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Thr Ser	
85 90 95	
Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val	
100 105 110	
Tyr Tyr Cys Ala Thr Asp Arg Tyr Gly Asp Trp Phe Thr Tyr Trp Gly	
115 120 125	
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser	
130 135 140	
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala	
145 150 155 160	
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val	
165 170 175	
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala	
180 185 190	
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val	
195 200 205	
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His	
210 215 220	
Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys	
225 230 235 240	
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly	
245 250 255	
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met	
260 265 270	
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His	
275 280 285	

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Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
290 295 300
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
305 310 315 320
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
325 330 335
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
340 345 350
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
355 360 365
Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
370 375 380
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
385 390 395 400
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
405 410 415
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
420 425 430
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
435 440 445
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
450 455 460
Pro Gly Lys
465

<210> SEQ ID NO 104
<211> LENGTH: 1401
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polynucleotide
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(1401)

<400> SEQUENCE: 104

atg aaa cac ctg tgg ttc ttc ctc ctg ctg gtg gca gct ccc aga tgg	48
Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp	
1 5 10 15	
gtg ctg agc cag gtg cag ctg gtg cag tct ggc gcc gaa gtg aag aaa	96
Val Leu Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys	
20 25 30	
cct ggg gct agc gtg aag gtg tcc tgc aag gcc agc ggc ttc acc ttc	144
Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe	
35 40 45	
agc acc agc tat atg agc tgg gtc cgc cag gct cca ggc ccc agc acc	192
Ser Thr Ser Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Pro Ser Thr	
50 55 60	
gaa tgg atg ggc tgg atc tat gcc ggc gac ggc ggc acc aag tac aac	240
Glu Trp Met Gly Trp Ile Tyr Ala Gly Asp Gly Gly Thr Lys Tyr Asn	
65 70 75 80	
cag aaa ttc aag ggc aga gtg acc ctg acc gtg gac aag agc acc agc	288
Gln Lys Phe Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Thr Ser	
85 90 95	
acc gcc tac atg gaa ctg agc agc ctg cgg agc gag gac acc gcc gtg	336

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Thr	Ala	Tyr	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	
			100					105					110			
tac	tac	tgc	gcc	acc	gac	gtg	tac	ggc	gac	tgg	ttc	aca	tac	tgg	ggc	384
Tyr	Tyr	Cys	Ala	Thr	Asp	Val	Tyr	Gly	Asp	Trp	Phe	Thr	Tyr	Trp	Gly	
		115					120					125				
cag	ggc	acc	ctg	gtg	acc	gtg	agc	tca	gcc	tcc	acc	aag	ggc	cca	agc	432
Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	
		130					135				140					
gtc	ttc	ccc	ctg	gca	ccc	tcc	tcc	aag	agc	acc	tct	ggc	ggc	aca	gcc	480
Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	
		145			150					155					160	
gcc	ctg	ggc	tgc	ctg	gtc	aag	gac	tac	ttc	ccc	gaa	ccc	gtg	acc	gtg	528
Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	
				165					170					175		
agc	tgg	aac	tca	ggc	gcc	ctg	acc	agc	ggc	gtg	cac	acc	ttc	ccc	gct	576
Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	
		180						185					190			
gtc	ctg	cag	tcc	tca	gga	ctc	tac	tcc	ctc	agc	agc	gtg	gtg	acc	gtg	624
Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	
		195					200					205				
ccc	tcc	agc	agc	ttg	ggc	acc	cag	acc	tac	atc	tgc	aac	gtg	aat	cac	672
Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	
		210					215				220					
aag	ccc	agc	aac	acc	aag	gtg	gac	aag	aga	gtt	gag	ccc	aaa	tct	tgt	720
Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	
		225			230				235						240	
gac	aaa	act	cac	aca	tgc	cca	ccc	tgc	cca	gca	cct	gaa	ctc	ctg	ggg	768
Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	
				245					250					255		
gga	ccc	tca	gtc	ttc	ctc	ttc	ccc	cca	aaa	ccc	aag	gac	acc	ctc	atg	816
Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	
			260					265					270			
atc	tcc	cgg	acc	cct	gag	gtc	aca	tgc	gtg	gtg	gtg	gac	gtg	agc	cac	864
Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	
		275					280					285				
gaa	gac	cct	gag	gtc	aag	ttc	aac	tgg	tac	gtg	gac	ggc	gtg	gag	gtg	912
Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	
		290				295					300					
cat	aat	gcc	aag	aca	aag	ccc	cgg	gag	gag	cag	tac	aac	agc	acg	tac	960
His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	
		305				310				315					320	
cgg	gtg	gtc	agc	gtc	ctc	acc	gtc	ctg	cac	cag	gac	tgg	ctg	aat	ggc	1008
Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	
				325					330					335		
aag	gag	tac	aag	tgc	aag	gtc	tcc	aac	aaa	gcc	ctc	cca	gcc	ccc	atc	1056
Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	
			340					345					350			
gag	aaa	acc	atc	tcc	aaa	gcc	aaa	ggc	cag	ccc	cgg	gaa	cca	cag	gtg	1104
Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	
		355					360					365				
tac	acc	ctg	ccc	cca	tcc	cgg	gag	gag	atg	acc	aag	aac	cag	gtc	agc	1152
Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	
		370					375					380				
ctg	acc	tgc	ctg	gtc	aaa	ggc	ttc	tat	ccc	agc	gac	atc	gcc	gtg	gag	1200
Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	
		385				390				395				400		
tgg	gag	agc	aat	ggc	cag	ccc	gag	aac	aac	tac	aag	acc	acc	cct	ccc	1248

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Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro		
				405					410					415			
gtg	ctg	gac	tcc	gac	ggc	tcc	ttc	ctc	tac	agc	aag	ctc	acc	gtg		1296	
Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val		
			420					425					430				
gac	aag	agc	agg	tgg	cag	cag	ggc	aac	gtc	ttc	tca	tgc	tcc	gtg	atg	1344	
Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met		
			435				440					445					
cat	gag	gct	ctg	cac	aac	cac	tac	acc	cag	aag	agc	ctc	tcc	ctg	tct	1392	
His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser		
			450			455					460						
ccc	ggc	aaa														1401	
Pro	Gly	Lys															
465																	

<210> SEQ ID NO 105

<211> LENGTH: 467

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 105

Met	Lys	His	Leu	Trp	Phe	Phe	Leu	Leu	Leu	Val	Ala	Ala	Pro	Arg	Trp		
1			5						10					15			
Val	Leu	Ser	Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys		
			20					25					30				
Pro	Gly	Ala	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Phe	Thr	Phe		
		35				40						45					
Ser	Thr	Ser	Tyr	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Pro	Ser	Thr		
	50				55				60								
Glu	Trp	Met	Gly	Trp	Ile	Tyr	Ala	Gly	Asp	Gly	Gly	Thr	Lys	Tyr	Asn		
65				70				75						80			
Gln	Lys	Phe	Lys	Gly	Arg	Val	Thr	Leu	Thr	Val	Asp	Lys	Ser	Thr	Ser		
			85					90						95			
Thr	Ala	Tyr	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val		
		100					105						110				
Tyr	Tyr	Cys	Ala	Thr	Asp	Val	Tyr	Gly	Asp	Trp	Phe	Thr	Tyr	Trp	Gly		
	115					120						125					
Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser		
	130				135						140						
Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala		
145				150						155					160		
Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val		
			165					170						175			
Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala		
		180					185						190				
Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val		
	195					200						205					
Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His		
	210				215					220							
Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys		
225				230					235					240			
Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly		

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																245				250				255							
Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met																
			260				265						270																		
Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His																
			275				280						285																		
Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val																
			290	295									300																		
His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr																
305			310						315						320																
Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly																
			325						330						335																
Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile																
			340			345						350																			
Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val																
			355			360						365																			
Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser																
			370			375						380																			
Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu																
385			390						395			400																			
Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro																
			405						410						415																
Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val																
			420						425						430																
Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met																
			435			440						445																			
His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser																
450			455									460																			
Pro Gly Lys																															
465																															
<210> SEQ ID NO 106																															
<211> LENGTH: 1401																															
<212> TYPE: DNA																															
<213> ORGANISM: Artificial Sequence																															
<220> FEATURE:																															
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide																															
<220> FEATURE:																															
<221> NAME/KEY: CDS																															
<222> LOCATION: (1)..(1401)																															
<400> SEQUENCE: 106																															
atg	aaa	cac	ctg	tgg	ttc	ttc	ctc	ctg	ctg	gtg	gca	gct	ccc	aga	tgg	48															
Met	Lys	His	Leu	Trp	Phe	Phe	Leu	Leu	Leu	Val	Ala	Ala	Pro	Arg	Trp																
1			5			10						15																			
gtg	ctg	agc	cag	gtg	cag	ctg	gtg	cag	tct	ggc	gcc	gaa	gtg	aag	aaa	96															
Val	Leu	Ser	Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys																
			20			25						30																			
cct	ggg	gct	agc	gtg	aag	gtg	tcc	tgc	aag	gcc	agc	ggc	ttc	acc	ttc	144															
Pro	Gly	Ala	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Phe	Thr	Phe																
			35			40						45																			
agc	acc	agc	tat	atg	agc	tgg	gtc	cgc	cag	gct	cca	ggc	ccc	agc	acc	192															
Ser	Thr	Ser	Tyr	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Pro	Ser	Thr																
50			55			60																									
gaa	tgg	atg	ggc	tgg	atc	tat	gcc	ggc	gac	ggc	ggc	acc	aag	tac	aac	240															
Glu	Trp	Met	Gly	Trp	Ile	Tyr	Ala	Gly	As																						

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65	70	75	80	
cag aaa ttc aag ggc aga gtg acc ctg acc gtg gac aag agc acc agc				288
Gln Lys Phe Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Thr Ser	85	90	95	
acc gcc tac atg gaa ctg agc agc ctg cgg agc gag gac acc gcc gtg				336
Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val	100	105	110	
tac tac tgc gcc acc gac tgg tac ggc gac tgg ttc aca tac tgg ggc				384
Tyr Tyr Cys Ala Thr Asp Trp Tyr Gly Asp Trp Phe Thr Tyr Trp Gly	115	120	125	
cag ggc acc ctg gtg acc gtg agc tca gcc tcc acc aag ggc cca agc				432
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser	130	135	140	
gtc ttc ccc ctg gca ccc tcc tcc aag agc acc tct ggc ggc aca gcc				480
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala	145	150	155	160
gcc ctg ggc tgc ctg gtc aag gac tac ttc ccc gaa ccc gtg acc gtg				528
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val	165	170	175	
agc tgg aac tca ggc gcc ctg acc agc ggc gtg cac acc ttc ccc gct				576
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala	180	185	190	
gtc ctg cag tcc tca gga ctc tac tcc ctc agc agc gtg gtg acc gtg				624
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val	195	200	205	
ccc tcc agc agc ttg ggc acc cag acc tac atc tgc aac gtg aat cac				672
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His	210	215	220	
aag ccc agc aac acc aag gtg gac aag aga gtt gag ccc aaa tct tgt				720
Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys	225	230	235	240
gac aaa act cac aca tgc cca ccc tgc cca gca cct gaa ctc ctg ggg				768
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly	245	250	255	
gga ccc tca gtc ttc ctc ttc ccc cca aaa ccc aag gac acc ctc atg				816
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met	260	265	270	
atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac gtg agc cac				864
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His	275	280	285	
gaa gac cct gag gtc aag ttc aac tgg tac gtg gac ggc gtg gag gtg				912
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val	290	295	300	
cat aat gcc aag aca aag ccc cgg gag gag cag tac aac agc acg tac				960
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr	305	310	315	320
cgg gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg aat ggc				1008
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly	325	330	335	
aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca gcc ccc atc				1056
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile	340	345	350	
gag aaa acc atc tcc aaa gcc aaa ggc cag ccc cgg gaa cca cag gtg				1104
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val	355	360	365	
tac acc ctg ccc cca tcc cgg gag gag atg acc aag aac cag gtc agc				1152
Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser				

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370	375	380	
ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc gcc gtg gag			1200
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu			
385	390	395	400
tgg gag agc aat ggc cag ccc gag aac aac tac aag acc acc cct ccc			1248
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro			
	405	410	415
gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc acc gtg			1296
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val			
	420	425	430
gac aag agc agg tgg cag cag ggc aac gtc ttc tca tgc tcc gtg atg			1344
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met			
	435	440	445
cat gag gct ctg cac aac cac tac acc cag aag agc ctc tcc ctg tct			1392
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser			
	450	455	460
ccc ggc aaa			1401
Pro Gly Lys			
465			

<210> SEQ ID NO 107

<211> LENGTH: 467

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 107

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Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
1           5           10           15

Val Leu Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20           25           30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe
35           40           45

Ser Thr Ser Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Pro Ser Thr
50           55           60

Glu Trp Met Gly Trp Ile Tyr Ala Gly Asp Gly Gly Thr Lys Tyr Asn
65           70           75           80

Gln Lys Phe Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Thr Ser
85           90           95

Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
100          105          110

Tyr Tyr Cys Ala Thr Asp Trp Tyr Gly Asp Trp Phe Thr Tyr Trp Gly
115          120          125

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
130          135          140

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
145          150          155          160

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
165          170          175

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
180          185          190

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
195          200          205

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Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His
210						215					220				
Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys
225					230					235					240
Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly
				245					250					255	
Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met
			260					265					270		
Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His
		275					280					285			
Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val
	290					295					300				
His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr
305					310					315					320
Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly
				325					330					335	
Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile
			340					345					350		
Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val
		355					360					365			
Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser
		370				375					380				
Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu
385					390					395					400
Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro
			405						410					415	
Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val
			420					425					430		
Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met
		435					440					445			
His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser
	450					455					460				
Pro	Gly	Lys													
465															

<210> SEQ ID NO 108
<211> LENGTH: 1401
<212> TYPE: DNA
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
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Met	Lys	His	Leu	Trp	Phe	Phe	Leu	Leu	Val	Ala	Ala	Pro	Arg	Trp		
1			5					10					15			
gtg	ctg	agc	cag	gtg	cag	ctg	gtg	cag	tct	ggc	gcc	gaa	gtg	aag	aaa	96
Val	Leu	Ser	Gln	Val	Gln	Leu	Val	Ser	Gly	Ala	Glu	Val	Lys	Lys		
			20				25					30				
cct	ggg	gct	agc	gtg	aag	gtg	tcc	tgc	aag	gcc	agc	ggc	ttc	acc	ttc	144
Pro	Gly	Ala	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Phe	Thr	Phe	
		35					40					45				

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agc acc agc tat atg agc tgg gtc cgc cag gct cca ggc ccc agc acc Ser Thr Ser Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Pro Ser Thr 50 55 60	192
gaa tgg atg ggc tgg atc tat gcc ggc gac ggc ggc acc aag tac aac Glu Trp Met Gly Trp Ile Tyr Ala Gly Asp Gly Gly Thr Lys Tyr Asn 65 70 75 80	240
cag aaa ttc aag ggc aga gtg acc ctg acc gtg gac aag agc acc agc Gln Lys Phe Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Thr Ser 85 90 95	288
acc gcc tac atg gaa ctg agc agc ctg cgg agc gag gac acc gcc gtg Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val 100 105 110	336
tac tac tgc gcc acc gac tac tac ggc gac tgg ttc aca tac tgg ggc Tyr Tyr Cys Ala Thr Asp Tyr Tyr Gly Asp Trp Phe Thr Tyr Trp Gly 115 120 125	384
cag ggc acc ctg gtg acc gtg agc tca gcc tcc acc aag ggc cca agc Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser 130 135 140	432
gtc ttc ccc ctg gca ccc tcc tcc aag agc acc tct ggc ggc aca gcc Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala 145 150 155 160	480
gcc ctg ggc tgc ctg gtc aag gac tac ttc ccc gaa ccc gtg acc gtg Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val 165 170 175	528
agc tgg aac tca ggc gcc ctg acc agc ggc gtg cac acc ttc ccc gct Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala 180 185 190	576
gtc ctg cag tcc tca gga ctc tac tcc ctc agc agc gtg gtg acc gtg Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val 195 200 205	624
ccc tcc agc agc ttg ggc acc cag acc tac atc tgc aac gtg aat cac Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His 210 215 220	672
aag ccc agc aac acc aag gtg gac aag aga gtt gag ccc aaa tct tgt Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys 225 230 235 240	720
gac aaa act cac aca tgc cca ccc tgc cca gca cct gaa ctc ctg ggg Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly 245 250 255	768
gga ccc tca gtc ttc ctc ttc ccc cca aaa ccc aag gac acc ctc atg Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met 260 265 270	816
atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac gtg agc cac Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His 275 280 285	864
gaa gac cct gag gtc aag ttc aac tgg tac gtg gac ggc gtg gag gtg Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val 290 295 300	912
cat aat gcc aag aca aag ccc cgg gag gag cag tac aac agc acg tac His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr 305 310 315 320	960
cgg gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg aat ggc Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly 325 330 335	1008
aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca gcc ccc atc Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile 340 345 350	1056

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gag aaa acc atc tcc aaa gcc aaa ggc cag ccc cgg gaa cca cag gtg Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val 355 360 365	1104
tac acc ctg ccc cca tcc cgg gag gag atg acc aag aac cag gtc agc Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser 370 375 380	1152
ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc gcc gtg gag Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu 385 390 395 400	1200
tgg gag agc aat ggc cag ccc gag aac aac tac aag acc acc cct ccc Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro 405 410 415	1248
gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc acc gtg Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val 420 425 430	1296
gac aag agc agg tgg cag cag ggc aac gtc ttc tca tgc tcc gtg atg Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met 435 440 445	1344
cat gag gct ctg cac aac cac tac acc cag aag agc ctc tcc ctg tct His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser 450 455 460	1392
ccc ggc aaa Pro Gly Lys 465	1401

<210> SEQ ID NO 109

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<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

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Val Leu Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys 20 25 30
Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe 35 40 45
Ser Thr Ser Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Pro Ser Thr 50 55 60
Glu Trp Met Gly Trp Ile Tyr Ala Gly Asp Gly Gly Thr Lys Tyr Asn 65 70 75 80
Gln Lys Phe Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Thr Ser 85 90 95
Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val 100 105 110
Tyr Tyr Cys Ala Thr Asp Tyr Tyr Gly Asp Trp Phe Thr Tyr Trp Gly 115 120 125
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser 130 135 140
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala 145 150 155 160
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val 165 170 175

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Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
 180 185 190
 Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
 195 200 205
 Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
 210 215 220
 Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
 225 230 235 240
 Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
 245 250 255
 Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
 260 265 270
 Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
 275 280 285
 Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
 290 295 300
 His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
 305 310 315 320
 Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
 325 330 335
 Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
 340 345 350
 Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
 355 360 365
 Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
 370 375 380
 Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
 385 390 395 400
 Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
 405 410 415
 Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
 420 425 430
 Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
 435 440 445
 His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
 450 455 460
 Pro Gly Lys
 465

<210> SEQ ID NO 110
 <211> LENGTH: 39
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 primer

<400> SEQUENCE: 110

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39

<210> SEQ ID NO 111
 <211> LENGTH: 39
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 111

ggtgctggtg ctcttgctcg cggtcagggt cactctgcc 39

<210> SEQ ID NO 112
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 112

ctgtttcaag gtccgagcaa taacaaacgt gcaccgtatt gg 42

<210> SEQ ID NO 113
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 113

cgcaagcttg tcgactcaaa caacatccag atgataggta tg 42

<210> SEQ ID NO 114
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<400> SEQUENCE: 114

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 115

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 116

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<210> SEQ ID NO 117
<211> LENGTH: 27

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<212> TYPE: DNA
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<400> SEQUENCE: 117

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<400> SEQUENCE: 118

gacttctacg gcgactgggt cacatac 27

<210> SEQ ID NO 119
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 119

gaccactacg gcgactgggt cacatac 27

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 120

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<400> SEQUENCE: 121

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<210> SEQ ID NO 122
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 122

gacctgtacg gcgactgggt cacatac 27

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<210> SEQ ID NO 123
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 123

gacatgtacg gcgactgggt cacatac 27

<210> SEQ ID NO 124
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 124

gaccagtacg gcgactgggt cacatac 27

<210> SEQ ID NO 125
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 125

gaccggtacg gcgactgggt cacatac 27

<210> SEQ ID NO 126
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 126

gacgtgtacg gcgactgggt cacatac 27

<210> SEQ ID NO 127
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 127

gactggtacg gcgactgggt cacatac 27

<210> SEQ ID NO 128
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

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<400> SEQUENCE: 128

gactactacg gcgactgggt cacatac

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1. A combination of a first composition comprising an antibody, or a functional fragment thereof, and a second composition comprising a tyrosine kinase inhibitor, wherein the antibody, or functional fragment thereof, has antibody dependent cellular cytotoxic activity and binds to a fibroblast growth factor receptor (FGFR).

2. The combination according to claim 1, wherein the fibroblast growth factor receptor (FGFR) is human FGFR.

3. The combination according to claim 1, wherein the fibroblast growth factor receptor (FGFR) is FGFR2.

4. The combination according to claim 1, wherein the antibody, or functional fragment thereof, binds to human fibroblast growth factor receptor 2 (human FGFR2) IIIb and/or human fibroblast growth factor receptor 2 (human FGFR2) IIIc.

5. The combination according to claim 1, wherein the antibody, or functional fragment thereof, binds to human fibroblast growth factor receptor 2 (human FGFR2) IIIb and human fibroblast growth factor receptor 2 (human FGFR2) IIIc.

6. The combination according to claim 2, wherein the antibody, or functional fragment thereof, binds to one or two or more immunoglobulin-like domains of the human fibroblast growth factor receptor 2.

7. The combination according to claim 2, wherein the antibody, or functional fragment thereof, binds to immunoglobulin-like domain 2 of the human fibroblast growth factor receptor 2.

8. The combination according to claim 2, wherein the antibody, or functional fragment thereof, binds to immunoglobulin-like domain 3 of the human fibroblast growth factor receptor 2.

9. The combination according to claim 5, wherein the antibody, or functional fragment thereof, has neutralizing activity against the human fibroblast growth factor receptor 2 (human FGFR2) IIIb and/or the human fibroblast growth factor receptor 2 (human FGFR2) IIIc.

10. The combination according claim 5, wherein the antibody, or functional fragment thereof, has neutralizing activity against the human fibroblast growth factor receptor 2 (human FGFR2) IIIb and the human fibroblast growth factor receptor 2 (human FGFR2) IIIc.

11. The combination according to claim 1, wherein the antibody, or functional fragment thereof, has antitumor activity.

12. The combination according to claim 11, wherein the antibody, or functional fragment thereof, exhibits antitumor activity in vivo.

13. The combination according claim 1, wherein the antibody comprises a heavy chain comprising CDRH1 consisting of the amino acid sequence represented by SEQ ID NO: 52, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; CDRH2 consisting of the amino acid sequence represented by SEQ ID NO: 53, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two

amino acids; and CDRH3 consisting of the amino acid sequence represented by SEQ ID NO: 54, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; and a light chain comprising CDRL1 consisting of the amino acid sequence represented by SEQ ID NO: 61, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; CDRL2 consisting of the amino acid sequence represented by SEQ ID NO: 62, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; and CDRL3 consisting of the amino acid sequence represented by SEQ ID NO: 63, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; and binds to human FGFR2.

14. The combination according to claim 1, wherein the antibody comprises a heavy chain comprising CDRH1 consisting of the amino acid sequence represented by SEQ ID NO: 55, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; CDRH2 consisting of the amino acid sequence represented by SEQ ID NO: 56, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; and CDRH3 consisting of the amino acid sequence represented by SEQ ID NO: 57, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; and a light chain comprising CDRL1 consisting of the amino acid sequence represented by SEQ ID NO: 64, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; CDRL2 consisting of the amino acid sequence represented by SEQ ID NO: 65, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; and CDRL3 consisting of the amino acid sequence represented by SEQ ID NO: 66, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; and binds to human FGFR2.

15. The combination according to claim 1, wherein the antibody comprises a heavy chain comprising CDRH1 consisting of the amino acid sequence represented by SEQ ID NO: 58, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; CDRH2 consisting of the amino acid sequence represented by SEQ ID NO: 59, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; and CDRH3 consisting of the amino acid sequence represented by SEQ ID NO: 60, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; and a light chain comprising CDRL1 consisting of the amino acid sequence represented by SEQ ID NO: 67, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; CDRL2 consisting of the amino acid sequence represented by SEQ ID NO: 68, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; and CDRL3 con-

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sisting of the amino acid sequence represented by SEQ ID NO: 69, or an amino acid sequence derived from the amino acid sequence by the substitution of one or two amino acids; and binds to human FGFR2.

16. The combination according to claim 15, wherein the CDRH3 consists of an amino acid sequence derived from the amino acid sequence represented by SEQ ID NO: 60 by the substitution of one or two amino acids.

17. The combination according to claim 1, wherein the antibody is a monoclonal antibody.

18. The combination according to claim 1, wherein the antibody is a chimeric antibody.

19. The combination according to claim 1, wherein the antibody is a humanized antibody.

20. The combination according to claim 19, wherein the antibody is selected from the following (i) to (xix):

- (i) a humanized antibody (hFR2-14_H19/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73, and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 97;
- (ii) a humanized antibody (hFR2-14_H12/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73, and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 97;
- (iii) a humanized antibody (hFR2-14_H8/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73, and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 89;
- (iv) a humanized antibody (hFR2-14_H11/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73, and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 95;
- (v) a humanized antibody (hFR2-14_H5/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73, and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 83;
- (vi) a humanized antibody (hFR2-14_H1/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73, and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 75;
- a humanized antibody (hFR2-14_H2/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73, and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 77;
- (viii) a humanized antibody (hFR2-14_H3/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73, and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 79;

- (ix) a humanized antibody (hFR2-14_H4/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73, and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 81;
- (x) a humanized antibody (hFR2-14_H6/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73, and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 85;
- (xi) a humanized antibody (hFR2-14_H7/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73, and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 87;
- (xii) a humanized antibody (hFR2-14_H9/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73, and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 91;
- (xiii) a humanized antibody (hFR2-14_H10/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73, and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 93;
- (xiv) a humanized antibody (hFR2-14_H13/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73, and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 99;
- (xv) a humanized antibody (hFR2-14_H14/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73, and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 101;
- (xvi) a humanized antibody (hFR2-14_H15/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73, and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 103;
- (xvii) a humanized antibody (hFR2-14_H16/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73, and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 105;
- (xviii) a humanized antibody (hFR2-14_H17/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73, and a heavy chain comprising amino acid positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 107;
- (xix) a humanized antibody (hFR2-14_H18/L1) comprising a light chain comprising amino acid positions 21 to 235 of the amino acid sequence represented by SEQ ID NO: 73, and a heavy chain comprising amino acid

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positions 20 to 467 of the amino acid sequence represented by SEQ ID NO: 109.

21. A pharmaceutical composition comprising an antibody, or functional fragment thereof, and a tyrosine kinase inhibitor; wherein the antibody, or functional fragment thereof, has antibody dependent cellular cytotoxic activity and binds to a fibroblast growth factor receptor (FGFR), and wherein the antibody comprises heavy and light chains comprising amino acid sequences having 95% or higher identity to the amino acid sequences of the heavy and light chains, respectively, of an antibody according to claim 20, and binds to human FGFR2.

22. A pharmaceutical composition comprising an antibody, or functional fragment thereof, and a tyrosine kinase inhibitor; wherein the antibody, or functional fragment thereof, has antibody dependent cellular cytotoxic activity and binds to a fibroblast growth factor receptor (FGFR), wherein the antibody, or functional fragment thereof, binds to a site on an antigen recognized by an antibody according to claim 20.

23. A pharmaceutical composition comprising an antibody, or functional fragment thereof, and a tyrosine kinase inhibitor; wherein the antibody, or functional fragment thereof, has antibody dependent cellular cytotoxic activity and binds to a fibroblast growth factor receptor (FGFR), wherein the antibody, or functional fragment thereof, competes with an antibody according to claim 20.

24. The combination according to claim 1, wherein the antibody, or functional fragment thereof, binds to an epitope on human FGFR2, the epitope being constituted by tyrosine (Tyr) at residue 155, threonine (Thr) at residue 157, lysine (Lys) at residue 176, alanine (Ala) at residue 181, glycine (Gly) at residue 182, glycine (Gly) at residue 183, asparagine (Asn) at residue 184, proline (Pro) at residue 185, methionine (Met) at residue 186, threonine (Thr) at residue 188, glutamine (Gln) at residue 200, glutamic acid (Glu) at residue 201, glycine (Gly) at residue 205, glycine (Gly) at residue 206, lysine (Lys) at residue 208, valine (Val) at residue 209, arginine (Arg) at residue 210, asparagine (Asn) at residue 211, glutamine (Gln) at residue 212, histidine (His) at residue 213, tryptophan (Trp) at residue 214, and isoleucine (Ile) at residue 217 of the amino acid sequence represented by SEQ ID NO: 70.

25. The combination according to claim 1, wherein the antibody, or functional fragment thereof, has an interaction distance with each of tyrosine (Tyr) at residue 155, threonine (Thr) at residue 157, lysine (Lys) at residue 176, alanine (Ala) at residue 181, glycine (Gly) at residue 182, glycine (Gly) at residue 183, asparagine (Asn) at residue 184, proline (Pro) at residue 185, methionine (Met) at residue 186, threonine (Thr) at residue 188, glutamine (Gln) at residue 200, glutamic acid (Glu) at residue 201, glycine (Gly) at residue 205, glycine (Gly) at residue 206, lysine (Lys) at residue 208, valine (Val) at residue 209, arginine (Arg) at residue 210, asparagine (Asn) at residue 211, glutamine (Gln) at residue 212, histidine (His) at residue 213, tryptophan (Trp) at residue 214, and isoleucine (Ile) at residue 217 of the amino acid sequence represented by SEQ ID NO: 70.

26. The combination according to claim 25, wherein the interaction distance is 6 angstroms or shorter.

27. The combination according to claim 25, wherein the interaction distance is 4 angstroms or shorter.

28. The combination according to claim 1, wherein the antibody is a human antibody.

29. The combination according to claim 3, wherein the antibody, or functional fragment thereof, inhibits the binding of FGF to human FGFR2.

30. The combination according to claim 1, wherein the antibody, or functional fragment thereof, has antibody dependent cellular cytotoxic activity and/or antibody dependent cell phagocytosis activity.

31. A pharmaceutical composition comprising an antibody, or functional fragment thereof, and a tyrosine kinase inhibitor, wherein the antibody, or functional fragment thereof, is obtained by a method for producing an antibody or a functional fragment thereof, comprising the following steps (i) and (ii):

(i) culturing a cell of the following (1) or (2):

(1) a recombinant cell comprising a recombinant vector having an insert of a nucleotide of any one of the following (a) to (c), or comprising the nucleotide:

a. a nucleotide comprising a nucleotide sequence encoding a partial or whole amino acid sequence of the heavy or light chain of an antibody according to claim 20,

b. a nucleotide consisting of a nucleotide sequence comprising the nucleotide sequence encoding a partial or whole amino acid sequence of the heavy or light chain of an antibody according to claim 20, and

c. a nucleotide consisting of the nucleotide sequence encoding a partial or whole amino acid sequence of the heavy or light chain of an antibody according to claim 20; and

(2) a cell producing an antibody, or a functional fragment thereof, according to claim 20; and

(ii) recovering the antibody, or functional fragment thereof, according to claim 20 from the cultures obtained in the step (i).

32. The combination according to claim 1, wherein 1 to 5 amino acids are deleted from the amino terminus or carboxyl terminus of the heavy or light chain of the antibody.

33. A combination comprising a modified form of the antibody, or functional fragment thereof, according to claim 1 and a tyrosine kinase inhibitor.

34. The combination according to claim 33, wherein the modified form of the antibody, or functional fragment thereof, is a regulated sugar chain modification.

35. The combination according to claim 20, wherein the antibody, or functional fragment thereof, comprises a sugar chain modification.

36. The combination according to claim 1, wherein the combination is used in the treatment or prevention of cancer.

37. The combination according to claim 36, wherein the cancer is FGFR2-positive.

38. The combination according to claim 36, further comprising an additional drug.

39. The combination according to claim 1, wherein the antibody, or functional fragment thereof, is conjugated with an additional compound.

40. The combination according to claim 1, wherein the tyrosine kinase inhibitor is an FGFR tyrosine kinase inhibitor.

41. The combination according to claim 40, wherein the FGFR tyrosine kinase is an FGFR2 inhibitor.

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42. The combination according to claim 41, wherein the FGFR2 inhibitor is one or two or more selected from the group consisting of acylaminopyrazole, a quinolone or quinazoline derivative modified with a phenoxy group or a phenylthio group, BGJ398, LY2874455, brivanib, dovitinib, lenvatinib, masitinib, nintedanib, regorafenib, pazopanib, TSU68, ENMD-2076, and ponatinib.

43. The combination according to claim 41, wherein the FGFR2 inhibitor is AZD4547.

44. The combination according to claim 41, wherein the FGFR2 inhibitor is Ki23057.

45. A pharmaceutical composition comprising an FGFR tyrosine kinase inhibitor combined with an antibody, or a functional fragment thereof, according to claim 1.

46. A pharmaceutical composition comprising an antibody, or a functional fragment thereof, according to claim 33 combined with an FGFR tyrosine kinase inhibitor.

47. A pharmaceutical composition comprising an FGFR tyrosine kinase inhibitor, wherein the pharmaceutical composition enhances the effect of an antibody, or a functional fragment thereof, according to claim 1.

48. A pharmaceutical composition comprising an antibody, or a functional fragment thereof, according to claim 1,

wherein the pharmaceutical composition enhances the effect of an FGFR tyrosine kinase inhibitor.

49. A pharmaceutical composition in which an antibody, or a functional fragment thereof, according to claim 1 is to be administered in combination with an FGFR tyrosine kinase inhibitor.

50. The pharmaceutical composition according to claim 49, wherein the antibody, or functional fragment thereof, and the FGFR tyrosine kinase inhibitor are contained as active ingredients in separate preparations, which are to be administered concurrently or at different times.

51. The pharmaceutical composition according to claim 49, wherein the antibody, or functional fragment thereof, and the FGFR tyrosine kinase inhibitor are contained as active ingredients in a single preparation.

52. The combination of claim 1, wherein the first composition comprising an antibody, or a functional fragment thereof, and the second composition comprising a tyrosine kinase inhibitor are formulated into a single preparation.

53. The combination of claim 1, wherein the first composition comprising an antibody, or a functional fragment thereof, and the second composition comprising a tyrosine kinase inhibitor are formulated into separate preparations.

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