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(12) **United States Patent**
Bedi et al.(10) **Patent No.:** **US 8,993,524 B2**
(45) **Date of Patent:** **Mar. 31, 2015**(54) **COMPOSITIONS AND METHODS FOR
TARGETED IMMUNOMODULATORY
ANTIBODIES AND FUSION PROTEINS**2319/00 (2013.01); A61K 2039/505 (2013.01);
C07K 2317/73 (2013.01); C07K 2317/76
(2013.01)(75) Inventors: **Atul Bedi**, Timonium, MD (US); **Rajani
Ravi**, Ruxton, MD (US)USPC ... **514/19.2**; 514/21.2; 424/178.1; 424/185.1;
424/192.1; 424/194.1; 530/39.1; 530/391.7;
530/391.9; 530/350(73) Assignee: **The Johns Hopkins University**,
Baltimore, MD (US)(58) **Field of Classification Search**

None

See application file for complete search history.

(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.(56) **References Cited**

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(2), (4) Date: **Oct. 17, 2012**2005/0054832 A1 3/2005 Lazar
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2009/0226435 A1 9/2009 Khare(87) PCT Pub. No.: **WO2011/109789**PCT Pub. Date: **Sep. 9, 2011**

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(65) **Prior Publication Data**

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Supplementary European Search Report regarding Application No.
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24, 2011, provisional application No. 61/311,255,
filed on Mar. 5, 2010.(74) *Attorney, Agent, or Firm* — DLA Piper LLP (US)(51) **Int. Cl.**A61K 38/00 (2006.01)
A61K 38/10 (2006.01)
A61K 39/00 (2006.01)
A61K 39/385 (2006.01)
C07K 16/00 (2006.01)
C07K 1/00 (2006.01)
C07K 14/495 (2006.01)
C07K 14/705 (2006.01)
C07K 14/71 (2006.01)
C07K 16/28 (2006.01)(52) **U.S. Cl.**CPC C07K 14/495 (2013.01); C07K 14/70532
(2013.01); C07K 14/70575 (2013.01); C07K
14/70578 (2013.01); C07K 14/70596 (2013.01);
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C07K 16/2812 (2013.01); C07K 16/2815
(2013.01); C07K 16/2851 (2013.01); C07K(57) **ABSTRACT**

The present invention is based on the seminal discovery that targeted immunomodulatory antibodies and fusion proteins can counter act or reverse immune tolerance of cancer cells. Cancer cells are able to escape elimination by chemotherapeutic agents or tumor-targeted antibodies via specific immunosuppressive mechanisms in the tumor microenvironment and such ability of cancer cells is recognized as immune tolerance. Such immune suppressive mechanisms include immunosuppressive cytokines (for example, Transforming growth factor beta (TGF- β) and regulatory T cells and/or immunosuppressive myeloid dendritic cells (DCs). By counteracting tumor-induced immune tolerance, the present invention provides effective compositions and methods for cancer treatment, optional in combination with another existing cancer treatment. The present invention provides strategies to counteract tumor-induced immune tolerance and enhance the antitumor efficacy of chemotherapy by activating and leveraging T cell-mediated adaptive antitumor immunity against resistant or disseminated cancer cells.

15 Claims, 75 Drawing Sheets

1. Amino acid sequences of transforming growth factor beta receptor type II (TGF- β -RII) or TGF- β -RIIB or a fragment thereof:

(i) Transforming growth factor beta receptor type II (TGF- β -RII) (SEQ ID NO: 79):

MGRGLLRGLW PLHIVLWTRI ASTIPPHVQK SVNNDMIVTD NNGAVKFPQL CKFCDVRFST
CDNQKSCMSN CSITSICEKP QEVCAVWRK NDENITLET CHDPKLPYHD FILEDAASPK
CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EYNTSNPDL LLVIFQVTGI SLLPPLGVAI
SVIIIFYCYR VNRQQLSST WETGKTRKLM EFSEHCAIIL EDDRSDISST CANNINHNT
LLPIELDTLV GKGRFAEVYK AKLKQNTSEQ FETVAVKIFP YEEYASWKTE KDIFSDINLK
HENILQFLTA EERKTELQKQ YWLITAFHAK GNLQEYLTRH VISWEDLRKL GSSLARGIAH
LHSDHTPCGR PKMPIVHRDL KSSNILVKND LTCCLCDFGL SLRLDPTLSV DDLANSQGQVG
TARYMAPEVL ESRMNLENVE SFKQTDVYSM ALVLWEMTSR CNAVGEVKDY EPPFGSKVRE
HPCVESMKDN VLRDRGRPEI PSFWLNHQGI QMVCETLTEC WDHDPEARLT AQCVAERFSE
LEHLDRLSGR SCSEKIPED GSLNTTK

[*Italic* – Extracellular domain of Transforming growth factor beta Receptor II (TGF β RII)]
 [Underlined = TGF β RII Extracellular domain (ECD) region that binds TGF- β]

(ii) Transforming growth factor beta receptor type IIB (TGF- β -RIIB) (SEQ ID NO: 80):

MGRGLLRGLW PLHIVLWTRI ASTIPPHVQK SDVEMEAQKD EIICPSCNRT AHPLRHINND
MIVTDNNGAV KFPQLCKFCD VRFSTCDNQK SCMSNCSITS ICEKPQEVCV AVWRKNDENI
TLETVCHDPK LPYHDFILED AASPKCIMKE KKKPGETFFM CSCSSDECND NIIFSEEYNT
SNPDLLLIVIF QVTGISLLPP LGVAISVIII FYCYRVNRQQ KLSSTWETGK TRKLMEFSEH
CAIILEDERS DISSTCANNI NHNTPELLPIE LDTLVGKGRF AEVYKAKLKQ NTSEQFETVA VKI FP
YEEYASWKTE KDIFSDINLK HENILQFLTA EERKTELQKQ YWLITAFHAK GNLQEYLTRH
VISWEDLRKL GSSLARGIAH LHSDHTPCGR PKMPIVHRDL KSSNILVKND LTCCLCDFGL
SLRLDPTLSV DDLANSQGQVG TARYMAPEVL ESRMNLENVE SFKQTDVYSM ALVLWEMTSR
CNAVGEVKDY EPPFGSKVRE HPCVESMKDN VLRDRGRPEI PSFWLNHQGI QMVCETLTEC
WDHDPEARLT AQCVAERFSE LEHLDRLSGR SCSEKIPED GSLNTTK

[*Italic* – Extracellular domain of Transforming growth factor beta Receptor IIB (TGF β RIIB)]
 [Underlined = TGF β RIIB Extracellular domain (ECD) region that binds TGF- β]

2. Truncated mutants of Transforming growth factor beta Receptor II (TGF- β -RII) or TGF- β -RIIB comprising the Extracellular domain (ECD) region that binds TGF- β

(i) TGF- β R-II (Δ C terminus): TGF β RII lacking the last 38 amino acids from the C-terminus (SEQ ID NO: 81):

MGRGLLRGLW PLHIVLWTRI ASTIPPHVQK SVNNDMIVTD NNGAVKFPQL CKFCDVRFST
CDNQKSCMSN CSITSICEKP QEVCAVWRK NDENITLET CHDPKLPYHD FILEDAASPK
CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EYNTSNPDL LLVIFQVTGI SLLPPLGVAI
SVIIIFYCYR VNRQQLSST WETGKTRKLM EFSEHCAIIL EDDRSDISST CANNINHNT
LLPIELDTLV GKGRFAEVYK AKLKQNTSEQ FETVAVKIFP YEEYASWKTE KDIFSDINLK
HENILQFLTA EERKTELQKQ YWLITAFHAK GNLQEYLTRH VISWEDLRKL GSSLARGIAH
LHSDHTPCGR PKMPIVHRDL KSSNILVKND LTCCLCDFGL SLRLDPTLSV DDLANSQGQVG
TARYMAPEVL ESRMNLENVE SFKQTDVYSM ALVLWEMTSR CNAVGEVKDY EPPFGSKVRE
HPCVESMKDN VLRDRGRPEI PSFWLNHQGI QMVCETLTEC WDHDPEARL

Fig. 1A

TGF- β R-IIb (Δ C terminus): TGF β RIIb lacking the last 38 aa from the C-terminus (SEQ ID NO: 82):

MGRGLLRGLW PLHIVLWTRI ASTIPPHVQK SDVEMEAQKD EIICPSCNRT AHPLRHINND
 MIVTDNNGAV KFPQLCKFCD VRFSTCDNQK SCMSNCSITS ICEKPQEVCV AVWRKNDENI
TLETVCHDPK LPYHDFILED AASPKCIMKE KKKPGETFFM CSCSSDECND NIFSEEYNT
SNPDLLLVIQ QVTGISLLPP LGVAISVIII FYCYRVNRQQ KLSSTWETGK TRKLMEFSEH
 CAIILEDERS DISSTCANNI NHNTELLPIE LDTLVGKGRF AEVYKAKLKQ NTSEQFETVA VKI FP
 YEEYASWKTE KDIFSDINLK HENILQFLTA EERKTELKQ YWLITAFHAK GNLQEYLTRH
 VISWEDLRKL GSSLARGIAH LHSDHTEPCGR PKMPIVHRDL KSSNILVKND LTCCLCDFGL
 SLRLDPTLSV DDLANSQVVG TARYMAPEVL ESRMNLENVE SFKQTDVYSM ALVLWEMTSR
 CNAVGEVKDY EPPFGSKVRE HPCVESMKDN VLRDRGRPEI PSFWLNHQGI QMVCETLTEC
 WDHDPEARL

(ii) TGF- β R-II (Acylt): TGF β RII lacking the kinase domain & juxtamembrane region (SEQ ID NO: 83):

MGRGLLRGLW PLHIVLWTRI ASTIPPHVQK SVNNDMIVTD NNGAVKFPQL CKFCDVRFST
CDNQKSCMSN CSITSICEKP QEVCAVWRK NDENITLETV CHDPKLPYHD FILEDAASPK
CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EYNTSNPD LLVIFQVTGI SLLPPLGVAI
 SVIIIFYCYR VNRQKLLSS

TGF- β R-IIb (Acylt): TGF β RIIb lacking the kinase domain & juxtamembrane region (SEQ ID NO: 84):

MGRGLLRGLW PLHIVLWTRI ASTIPPHVQK SDVEMEAQKD EIICPSCNRT AHPLRHINND
 MIVTDNNGAV KFPQLCKFCD VRFSTCDNQK SCMSNCSITS ICEKPQEVCV AVWRKNDENI
TLETVCHDPK LPYHDFILED AASPKCIMKE KKKPGETFFM CSCSSDECND NIFSEEYNT
SNPDLLLVIQ QVTGISLLPP LGVAISVIII FYCYRVNRQQ KLLSS

(iii) TGF- β R-II containing the N-terminus region including the extracellular domain (SEQ ID NO: 85):

MGRGLLRGLW PLHIVLWTRI ASTIPPHVQK SVNNDMIVTD NNGAVKFPQL CKFCDVRFST
CDNQKSCMSN CSITSICEKP QEVCAVWRK NDENITLETV CHDPKLPYHD FILEDAASPK
CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EYNTSNPD LLVIFQ

TGF- β R-IIb containing the N-terminus region including the extracellular domain (SEQ ID NO: 86):

MGRGLLRGLW PLHIVLWTRI ASTIPPHVQK SDVEMEAQKD EIICPSCNRT AHPLRHINND
 MIVTDNNGAV KFPQLCKFCD VRFSTCDNQK SCMSNCSITS ICEKPQEVCV AVWRKNDENI
TLETVCHDPK LPYHDFILED AASPKCIMKE KKKPGETFFM CSCSSDECND NIFSEEYNT
SNPDLLLVIQ Q

(iv) TGF- β R-II containing the extracellular domain that binds TGF- β (SEQ ID NO: 87):

TIPPHVQK SVNNDMIVTD NNGAVKFPQL CKFCDVRFST CDNQKSCMSN CSITSICEKP
QEVCAVWRK NDENITLETV CHDPKLPYHD FILEDAASPK CIMKEKKKPG ETFFMCSCSS
DECNDNIIFS EYNTSNPD

TGF- β R-IIb containing the extracellular domain that binds TGF- β (SEQ ID NO: 88):

TIPPHVQK SDVEMEAQKD EIICPSCNRT AHPLRHINND MIVTDNNGAV KFPQLCKFCD
VRFSTCDNQK SCMSNCSITS ICEKPQEVCV AVWRKNDENI TLETVCHDPK LPYHDFILED
AASPKCIMKE KKKPGETFFM CSCSSDECND NIFSEEYNT SNPD

(v) TGF- β R-II containing the region of the extracellular domain that binds TGF- β (SEQ ID NO: 89):

PQL CKFCDVRFST CDNQKSCMSN CSITSICEKP QEVCAVWRK NDENITLETV CHDPKLPYHD
FILEDAASPK CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EYNTSNPD

Fig. 1B

3. Kinase-deficient mutants, deletion mutants, or point mutants of Transforming growth factor beta Receptor II (TGF β -RII) or TGF β -RIIB or a fragment thereof which binds TGF β

(i) Transforming growth factor beta Receptor II containing point mutations:

Amino acid sequence of TGF- β R-II (K277R) contains a point mutation in its ATP-binding site and is inactive as a kinase (SEQ ID NO: 90):

MGRGLLRGLW PLHIVLWTRI ASTIPPHVQK SVNNDMIVTD NNGAVKFPQL CKFCDVRFST
 CDNQKSCMSN CSITSICEKP QEVCAVAVWRK NDENITLETV CHDPKLPYHD FILEDAASP
 CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EEYNTSNPDL LLVIFQVTGI SLLPPLGVAI
 SVIIIFYCYR VNRQQLSST WETGKTRKLM EFSEHCAIIL EDDRSDISST CANNINHNT
 LLPIELDTLV GKGRFAEVYK AKLKQNTSEQ FETVAVRIFP YEEYASWKTE KDIFSDINLK
 HENILQFLTA EERKTELQKQ YWLITAFHAK GNLQEYLTRH VISWEDLRKL GSSLARGIAH
 LHSDHTPCGR PKMPIVHRDL KSSNILVKND LTCCLCDFGL SLRLDPTLSV DDLANSQQVG
 TARYMAPEVL ESRMNLNVE SFKQTDVYSM ALVLWEMTSR CNAVGEVKDY EPPFGSKVRE
 LEHLDRLSGR SCSEEEKIPED GSLNNTTK

(ii) Transforming growth factor beta Receptor II containing deletions in the amino acid sequence (deletion mutants): Transforming growth factor beta Receptor II (Δ i)

TGF- β R-II (Δ i2) contains a deletion of amino acids 498 to 508 and is inactive as a kinase (SEQ ID NO: 91):

MGRGLLRGLW PLHIVLWTRI ASTIPPHVQK SVNNDMIVTD NNGAVKFPQL CKFCDVRFST
 CDNQKSCMSN CSITSICEKP QEVCAVAVWRK NDENITLETV CHDPKLPYHD FILEDAASP
 CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EEYNTSNPDL LLVIFQVTGI SLLPPLGVAI
 SVIIIFYCYR VNRQQLSST WETGKTRKLM EFSEHCAIIL EDDRSDISST CANNINHNT
 LLPIELDTLV GKGRFAEVYK AKLKQNTSEQ FETVAVKIFP YEEYASWKTE KDIFSDINLK
 HENILQFLTA EERKTELQKQ YWLITAFHAK GNLQEYLTRH VISWEDLRKL GSSLARGIAH
 LHSDHTPCGR PKMPIVHRDL KSSNILVKND LTCCLCDFGL SLRLDPTLSV DDLANSQQVG
 TARYMAPEVL ESRMNLNVE SFKQTDVYSM ALVLWEMTSR CNAVGEVKDY EPPFGSKVRE
 HPCVESMKDA SGIQMVCELT TECWDHDPEA RLTAQCVAER FSELEHLDR LSGRSCSEKI
 PEDGSLNNTTK

4. Amino acid sequences of transforming growth factor beta receptor type III (TGF- β -RIII) or or a fragment thereof.
5. Hybrid or fusion proteins containing amino acid sequences of transforming growth factor beta receptor type II (TGF- β -RII) and TGF- β -RIII.
6. Hybrid or fusion proteins containing amino acid sequences of transforming growth factor beta receptor type IIB (TGF- β -RIIB) and TGF- β -RIII.

Linker sequence used in fusion proteins (SEQ ID NO: 104):

GGGGSGGGSGGGGS

Fig. 1C

Fusion proteins comprising Anti-HER2/neu antibody and Transforming growth factor-beta receptor II (TGF β -RII) Extracellular domain (ECD).

Anti-HER2/neu heavy chain + TGF β -RII ECD fusion amino acid sequence

(SEQ ID NO: 1):

EVQLVESGGGLVQPGGSLRLSCAASG**FN**KD**TY**IHWVRQAPGKLEWVARIYPTNGYTRYADSVKG
RFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGT**LVTVSSASTKGPSVFPLA**
PSSKSTSGGTAALGCLVKDYFPEP**TV****SWNSGALTSGVHTFPAVLQSSGLYSLSSV****TV****PSSSLGT**
QTYICNVNHKPSNTKVDKKVEPKSCDK**TH****TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC**
VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA
LPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNV**FSCVMHEALHNHYTQKSLSLSPGK**
GGGSGGGSGGGGS **TIPPHVQK** *SVNNDMIVTD* **NNGAVKFPQL** **CKFCDVRFST**
CDNQKSCMSN **CSITSICEKP** **QEVCAVVRK** **NDENITLETV** **CHDPKLPYHD** **FILEDAASPK**
CIMKEKKKPG **ETFFMCSCSS** **DECNDNIIFS** **EEYNTSNPD**

Anti-HER2/neu light chain amino acid sequence (SEQ ID NO: 70):

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFS**SGSR**
SGTDFTLTIS**SLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV**
V**CLLN****FPYPREAKVQWKVDNALQSGNSQESVTEQDSK****STY****SL****SSTLTLSKADYEKHKVYACEVTH**
QGLSSPVTKSFNRGEC

Underlined: Anti-HER2 antibody variable region

Plain: Anti-HER2 antibody constant region

Italic: Linker

Bold: TGF β RII ectodomain

Fig. 2

Fusion proteins comprising Anti-EGFR1 antibody and Transforming growth factor-beta receptor II (TGF β -RII) Extracellular domain (ECD).

Anti-EGFR1 heavy chain + TGF β -RII ECD fusion amino acid sequence
(SEQ ID NO: 2):

QVQLKQSGPGLVQPSSLSITCTVSGFSLTNYGVHWVRQSPGKGLEWLGVIWSSGNTDYNTPFTSR
LSINKDNSKSKQVFFKMNSLQSNDAIYYCARALTYDYEFAYWGQGLVTVSAASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ
TYICNVNHKPSNTKVDKRVKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL
PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVMEALHNHYTQKSLSLSPGK
GGGGSGGGSGGGGS TIPPHVQK SVNNDMIVTD NNGAVKFPQL CKFCDVRFST
CDNQKSCMSN CSITSICEKP QEVCVAVWRK NDENITLETV CHDPKLPYHD FILEDAASPK
CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EYNTSNPD

Anti-EGFR1 light chain amino acid sequence (SEQ ID NO: 71):

DILLTQSPVILSVSPGERVSFSCRASQSIGTNIHWYQQRTNGSPRLLIKYASESISGIPSRFSGSG
SGTDFTLINSVESEDIADYYCQQNNNWPTTFGAGTKLELKRTVAAPSVFI FPPSDEQLKSGTASV
VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYSLSSTLTLSKADYEKHKVYACEVTH
QGLSSPVTKSFNRGEC

Underlined: Anti-EGFR antibody variable region

Plain: Anti-EGFR antibody constant region

Italic: Linker

Bold: TGF β RII ectodomain

Fig. 3

Fusion proteins comprising Anti-CD20 antibody and Transforming growth factor-beta receptor II (TGF β -RII) Extracellular domain (ECD).

Anti-CD20 heavy chain+ TGF β -RII ECD fusion amino acid sequence
(SEQ ID NO: 3):

QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGDTSYNQKFKG
KATLTADKSSSTAYMQLSSLTSEDSAVVYCARSTYYGCDWYFNVWGAGTTVTVSAASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSCVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TQTYICNVNHKPSNTKVKDKAEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTIISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK
GGGGSGGGSGGGGS *TIPPHVQK* *SVNNDMIVTD* *NNGAVKFPQL* *CKFCDVRFST*
CDNQKSCMSN CSITSICEKP QEVCVAVWRK NDENITLETV CHDPKLPYHD FILEDAASPK
CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EYNTSNPD

Anti-CD20 light chain amino acid sequence (SEQ ID NO: 72):

QIVLSQSPAILASAPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWIYATSNLASGVPVRFSGSGS
GTSYSLTISRVEAEDAATYYCQWTSNPPTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYSLSSTLTLSKADYEKHKVYACEVTHQ
GLSSPVTKSFNRGEC

Underlined: Anti-CD20 antibody variable region

Plain: Anti-CD20 antibody constant region

Italic: Linker

Bold: TGF β RII ectodomain

Fig. 4

Fusion proteins comprising anti-VEGF antibody and Transforming growth factor-beta receptor II (TGF β -RII) Extracellular domain (ECD).

Anti-VEGF heavy chain+ TGF β -RII ECD fusion amino acid sequence

(SEQ ID NO: 4):

EVQLVESGGGLVQPGGSLRLSCAASGYTFTNYGMNWRQAPGKGLEWVGWINTYTGEPTYAADFKR
RFTFSLDTSKSTAYLQMNSLRAEDTAVYYCAKYPHYYGSSSHWYFDVWGQGTLLVTVSSASTKGPSVF
PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS
LGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTTTPFLVDSGDGSFFLYSKLTVDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGSGGGGS **TIPPHVQK** *SVNNDMIVTD* **NNGAVKFPQL** **CKFCDVRFST**
CDNQKSCMSN **CSITSICEKP** **QEVCAVWRK** **NDENITLETV** **CHDPKLPYHD** **FILEDAASPK**
CIMKEKKKPG **ETFFMCSCSS** **DECNDNIIFS** **EEYNTSNPD**

Anti-VEGF Light chain sequence (SEQ ID NO: 73):

DIQMTQSPSSLSASVGDRVTITCSASQDISNYLNWYQQKPGKAPKVLITYFTSSLHSGVPSRFRSGSG
SGTDFTLTISSLQPEDFATYYCQQYSTVPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV
VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTH
QGLSSPVTKSFNRGEC

Underlined: Anti-VEGF antibody variable region

Plain: Anti-VEGF antibody constant region

Italic: Linker

Bold: TGF β RII ectodomain

Fig. 5

Fusion proteins comprising anti-human CTLA-4 antibody and Transforming growth factor-beta receptor II (TGF β -RII) Extracellular domain (ECD).

Anti-CTLA-4 heavy chain + TGF β -RII Extracellular domain fusion amino acid sequence
(SEQ ID NO: 5):

QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYTMHWVRQA PGKGLEWVTF ISYDGNKYY
ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAIYYCARTG WLGPFDYWGQ GTLVTVSSAS
TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL
YSLSSVTVTP SSSLGTQTYI CNVNHKPSNT KVDKRVEPKS CDKTHTCPPC PAPELLGGPS
VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST
YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT
KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKITPPVLD SDGSFFLYSK LTVDKSRWQQ
GNVFSCSMVM EALHNHYTQK SLSLSPGK **GGGSGGGSGGGGS** **TIPPHVQK** SVNNDMIVTD
NNGAVKFPQL CKFCDVRFST **CDNQKSCMSN** CSITSICEKP QEVCAVAVWRK NDENITLETV
CHDPKLPYHD FILEDAASPK CIMKEKKKPG **ETFFMCSCSS** DECNDNIIFS EBYNTSNPD

Anti-CTLA-4 light chain (SEQ ID NO: 74):

EIVLTQSPGT LSLSPGERAT LSCRASQSVG SSYLAWYQQK PGQAPRLLIY GAFSRATGIP
DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ QYGSSPWTFG QGTKVEIKRT VAAPSVFIFP
PSDEQLKSGT ASVVCLLNNF YPREAKVQWK VDNALQSGNS QESVTEQDSK DSTYLSSTL
TLISKADYEKH KVIACEVTHQ GLSSPVTKSF NRGEC

Underlined: Anti-CTLA-4 antibody heavy chain variable region

Plain: Anti-CTLA-4 antibody heavy chain constant region

Italic: Linker

Bold: TGF β RII ectodomain

Fig. 6

Fusion proteins comprising IL-2, Fc, and Transforming growth factor-beta receptor II (TGF β -RII) Extracellular domain (ECD).

IL-2 + Fc + TGF β -RII Extracellular domain (SEQ ID NO: 6):

APTSSSTKKTQLQLEHLLLDLQMLNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPL
EEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTL
T *GGGSGGGSGGGGS*
 THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
 REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFSCSVMEALHNHYTQKSLSLSPGK *GGGSGGGSGGGGS* **TIPPHVQK** **SVNNDMIVTD**
NNGAVKFPQL **CKFCDVRFST** **CDNQKSCMSN** **CSITSICEKP** **QEVCAVVRK** **NDENITLETV**
CHDPKLPYHD **FILEDAASP** **CIMKEKKKPG** **ETFFMCSCSS** **DECNDNIIFSEFYNTSNPD**

TGF β -RII Extracellular domain + Fc + IL-2 (SEQ ID NO: 7):

TIPPHVQK **SVNNDMIVTD** **NNGAVKFPQL** **CKFCDVRFST** **CDNQKSCMSN** **CSITSICEKP**
QEVCAVVRK **NDENITLETV** **CHDPKLPYHD** **FILEDAASP** **CIMKEKKKPG** **ETFFMCSCSS**
DECNDNIIFS **EEYNTSNPD** *GGGSGGGSGGGGS*
 THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFSCSVMEALHNHYTQKSLSLSPGK *GGGSGGGSGGGGS*
APTSSSTKKTQLQLEHLLLDLQMLNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPL
EEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTL
T

Bold: TGF β RII ectodomain

Italic: Linker (Optional; other linker sequences)

Plain: Fc

Underlined: IL-2 fragment

(Note: Can replace linker *GGGSGGGSGGGGS* SEQ ID NO: 104 with

EPKSCDK SEQ ID NO: 105)

(Note: Can replace underlined aa in Fc: E with D and M with L in Fc)

Fig. 7

Fusion proteins comprising anti-CD25 antibody and Transforming growth factor-beta receptor II (TGF β -RII) Extracellular domain (ECD).

Anti-CD25 (Daclizumab) heavy chain and TGF β -RII Extracellular domain
(SEQ ID NO: 8):

QVQLVQSGAE VKKPGSSVKV SCKASGYTFT SYRMHWVRQA PGQGLEWIGY INPSTGYTEY
NQKFKDKATI TADESTNTAY MELSSLRSED TAVYYCARGG GVFDYWGQGT LVTVSSASTK
GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS
LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKKVEPKSCD KTHTCPPCPA PELLGGPSVF
LFPPPKPDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR
VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG QPREPQVYTL PPSRDELTKN
QVSLTCLVKG FYPSDIAVEW ESNQGPENNY KTTTPVLDSD GSFFLYSKLT VDKSRWQQGN
VFSCSVMHEA LHNHYTQKSL SLSPGK GGGGSGGGGSGGGGS TIPPHVQK SVNNDMIVTD
NNGAVKFPQL CKFCDVRFST CDNQKSCMSN CSITSICEKP QEVCAVWRK NDENITLETV
CHDPKLPYHD FILEDAASPK CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EEYNTSNPD

Anti-CD25 (Daclizumab) light chain (SEQ ID NO: 75):

DIQMTQSPST LSASVGDRVT ITCSASSSIS YMHWYQQKPG KAPKLLIYTT SNLASGVPAR
FSGSGSGTEF TLTISSLQPD DFATYYCHQR STYPLTFGQG TKVEVKRTVA APSVFIFPPS
DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSSTLT
SKADYEKKHV YACEVTHQGL SSPVTKSPNR GEC

Plain: Anti-CD25 antibody

Italic: Linker

Bold: TGF β RII ectodomain

Fig. 8A

Anti-CD25 (Basiliximab) heavy chain and TGF β -RII Extracellular domain

(SEQ ID NO: 9):

QLQQSGTVLA RPGASVKMSC KASGYSFTRY WMHWIKQRPQ QGLEWIGAIY PGNSDTSYNQ
KFEGKAKLTA VTSASTAYME LSSLTHEDSA VYYCSRDIYGY YFDWQGGTT LTVSSASTKG
PSVFPPLAPSS KSTSGGTAAL GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL
SSVVTVPSSS LGTQTYICNV NHKPSNTKVD KRVEPKSCDK THTCPPCPAP ELLGGPSVFL
FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV
VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLF PSRDELTKNQ
VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV
FSCSVMEAL HNHYTQKSL SLPKG GGGSGGGSGGGGS **TIPPHVQK SVNNDMIVTD**
NNGAVKFPQL CKPCDVRFS **CDNQKSCMSN CSITSICEKP QEVCAVVRK NDENITLET**
CHDPKLPYHD FILEDAASPK CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EEYNTSNPD

Anti-CD25 (Basiliximab) light chain (SEQ ID NO: 76):

QIVSTQSPAI MSASPGEKVT MTCSASSRS YMQWYQQKPG TSPKRWIYDT SKLASGVPAR
FSGSGSGTSY SLTISSMEAE DAATYYCHQR SSYTFGGGTK LEIKRTVAAP SVFIFPPSDE
QLKSGTASVV CLLNMFYPRE AKVQWKVDNA LQSGNSQESV TEQDSKIDSTY SLSSTLTLSK
ADYEKHKVYA CEVTHQGLSS PVTKSFNRGEC

Plain: Anti-CD25 antibody

Italic: Linker

Bold: TGF β RII ectodomain

Fig. 8B

Fusion proteins comprising anti-CD4 antibody and Transforming growth factor-beta receptor II (TGF β -RII) Extracellular domain (ECD).

Anti-CD4 heavy chain and TGF β -RII Extracellular domain (SEQ ID NO: 10):

Heavy chain fusion protein:

QVQLQEAGPGLVKPSETLSLTCSVSGGSISGDYYFWIRQSPGKGLEWIGYIYGSGGGTNYNPSLN
NRVSIISIDTSKNLFSCLKRSVTAADTAVYYCASNILKYLHWLLYWQGVLTVSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPFVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVMEALHNHYTQKSLSLSPGK
GGGSGGGSGGGGS **TIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRF**
STCDNQKSCMSNCSITSICEKPQEVCAVWRKNDENITLETVCHDPKLPYHDFILEDAAAPKICIMK
EKKKPGETFFMCSSSDECNDNIIFSEEYNTSNPD

Anti-CD4 light chain (SEQ ID NO: 77):

Light chain:

SYELSQPRSVSVSPGQTAGFTCGGDNVGRKSVQWYQQKPPQAPVLVIYADSERPSGIPARFSGSNS
GNTATLTISGVEAGDEADYYCQVWDSTADHWVFGGGTRLTVLGRTVAAPSVFIFPPSDEQLKSGTA
SVVCLLNNFYFPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEV
THQGLSSPVTKSFNRGEC

Plain: Anti-CD4 antibody (variable region – underlined)

Italic: Linker

Bold: TGF β RII ectodomain

Fig. 9

Fusion proteins comprising PD-1 Ectodomain, Fc, and Transforming growth factor-beta receptor II (TGF β -RII) Extracellular domain (ectodomain).

PD-1 ectodomain + Fc + TGF β RII ectodomain (SEQ ID NO: 11):

PGWFLDSPDRPWNPTFSPALLVVTEGDNATFTCSFSNTSESFVLNWMSPSNQTDKLAAPEDR
SQPGQDCRFRVTQLPNGRDFHMSVVRARRNDSTYLCGATSLAPKAQIKESLRAELRVTERRAEVP
TAHPSPSPRPAGQFQTLV *GGGGSGGGSGGGGS*
 THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
 REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFSCSVMEALHNHYTQKSLSLSPGK *GGGGSGGGSGGGGS*
TIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCAVW
RKNDENITLETVCHDPKLPYHDFILEDAAAPKICIMKEKKKPGETFFMCSSSDECNDNIIFSEYN
TSNPD

TGF β RII ectodomain + Fc + PD-1 ectodomain (SEQ ID NO: 12):

TIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCAVW
RKNDENITLETVCHDPKLPYHDFILEDAAAPKICIMKEKKKPGETFFMCSSSDECNDNIIFSEYN
TSNPD *GGGGSGGGSGGGGS*
 THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
 REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFSCSVMEALHNHYTQKSLSLSPGK *GGGGSGGGSGGGGS*
PGWFLDSPDRPWNPTFSPALLVVTEGDNATFTCSFSNTSESFVLNWMSPSNQTDKLAAPEDR
SQPGQDCRFRVTQLPNGRDFHMSVVRARRNDSTYLCGATSLAPKAQIKESLRAELRVTERRAEVP
TAHPSPSPRPAGQFQTLV

Underlined: PD-1 ectodomain

Italic: Linkers

Plain: IgG1 Fc

Bold: TGF β RII ectodomain

(Note: The first linker sequence *GGGGSGGGSGGGGS* is optional and may be replaced with *EPKSCDK* SEQ ID NO: 105 or deleted)

Fig. 10

Fusion proteins comprising Transforming growth factor-beta receptor II (TGFβ-RII) ectodomain, Fc, and Receptor activator of nuclear factor-κB (RANK) Ectodomain:

TGFβRII ectodomain – Fc - RANK ectodomain (SEQ. ID. NO: 13):

TIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCAVW
 RKNDENITLETVCHDPKLPYHDFILEDAAAPKICIMKEKKKPGETFFMCSSSDECNDNIIFSEEYN
 TSNPDGGGGSGGGSGGGSGTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
 EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK
 TISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS
 CSMHEALHNHYTQKSLSLSPGK GGGGSGGGSGGGGS QI
APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTSDSVCLP CGPDEYLDW NEEDKCLLHK
VCDTGKALVA VVAGNSTTPR RCACTAGYHW SQDCECCRRN TECAPGLAQ HPLQLNKDTV
CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG

RANK ectodomain – Fc - TGFβRII ectodomain (SEQ. ID. NO: 14):

QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTSDSVCLP CGPDEYLDW NEEDKCLLHK
VCDTGKALVA VVAGNSTTPR RCACTAGYHW SQDCECCRRN TECAPGLAQ HPLQLNKDTV
CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG
 GGGSGGGSGGGSGTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV
 KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
 KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF
 LYSKLTVDKSRWQQGNVFS CSMHEALHNHYTQKSLSLSPGKGGGGSGGGSGGGSGTIPPHVQKS
 VNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCAVWRKNDENITL
 ETVCHDPKLPYHDFILEDAAAPKICIMKEKKKPGETFFMCSSSDECNDNIIFSEEYNTSNPD

Bold: TGFβRII ectodomain

Plain: IgG1 Fc

Italics: Linker

Underlined: RANK ectodomain

(optional linker 1 may be deleted or replaced with another linker such as IEGRDMD (SEQ. ID.

NO:106) or EPKSCDK (SEQ.ID. NO: 105))

Fig. 11

- (i) Full-length PD-1 or fragment thereof (SEQ ID NO: 92):

1 MQIPQAPWPV VWAVLQLGWR PGWFLDSPDR PWNPTTFSPA LLVVTEGDNA TFTCSFSNTS
61 ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRTQL PNGRDFHMSV VRARRNDSGT
121 YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSPMGTS SPARRGSADG PRSAQPLRPE DGHCSWFL

Italic: PD-1 ectodomain

Underlined Italic: ligand-binding domain

- (ii) PD-1 extracellular domain (ectodomain) or fragment thereof
(SEQ ID NO: 93):

PGWFLDSPDR PWNPTTFSPA LLVVTEGDNA TFTCSFSNTS ESFVLNWYRM SPSNQTDKLA
AFPEDRSQPG QDCRFRTQL PNGRDFHMSV VRARRNDSGT YLCGAISLAP KAQIKESLRA
ELRVTERRAE VPTAHPSPSP RPAGQFQTLV

- (iii) PD-1 extracellular domain (ectodomain) ligand-binding region
(SEQ ID NO: 94):

DSPDR PWNPTTFSPA LLVVTEGDNA TFTCSFSNTS ESFVLNWYRM SPSNQTDKLA
AFPEDRSQPG QDCRFRTQL PNGRDFHMSV VRARRNDSGT YLCGAISLAP KAQIKESLRA
ELRVTERRAE VPTAHPSPSP RPAGQFQ

- (iv) Mutant of PD-1 or a fragment thereof which binds Programmed Death-1 ligand
[PD-L1 (B7-H1) or PD-L2 (B7-DC)]

Fig. 12

Fusion proteins comprising Anti-HER2/neu antibody and PD-1 Ectodomain.

Anti-HER2/neu heavy chain + PD-1 ectodomain fusion amino acid sequence
(SEQ ID NO: 15):

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKG
RFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGLTVTVSSASTKGPSVFPLA
PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGT
QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC
VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA
LPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK
GGGGSGGGSGGGGS **PGWFLDSPDR PWNPTTFSPA LLVVTEGDNA TFTCSFSNTS**
ESFVLNWMYR SPSNQTDKLA AFPEDRSQPG QDCRFVTVQL PNGRDFHMSV VRARRNDSGT
YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPPSP RPAGQFQTLV

Anti-HER2/neu light chain amino acid sequence (SEQ ID NO: 70):

DIQMTQSPSSLSASVGDRTTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFVSGVPSRFSGSR
SGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV
VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYSLSSTLTLSKADYEKHKVYACEVTH
QGLSSPVTKSFNRGEC

Underlined: Anti-HER2/neu Variable region

Plain: Anti-HER2/neu Constant region

Italic: Linker

Bold: PD-1 ectodomain

Fig. 13

Fusion proteins comprising Anti-EGFR1 antibody and PD-1 Ectodomain.

Anti-EGFR heavy chain + PD-1 ectodomain fusion amino acid sequence

(SEQ ID NO: 16):

QVQLKQSGPGLVQPSSQLSITCTVSGFSLTNYGVHWVRQSPGKGLEWLGVIWSSGNTDYNTFPFTSR
LSINKDNSKSQVFFKMNSLQSNDAIYVCARALTYDYEFAYWGQGLVTVSAASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVTFSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQ
TYICNVNHKPSNTKVDKRVKPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL
PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNYHTQKSLSLSPGK
GGGGSGGGSGGGGS PGWFLDSPDR PWNPTTFSPA LLVVTEGDNA TFTCSFSNTS
ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT
YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHFSPSP RPAGQFQTLV

Anti-EGFR light chain amino acid sequence (SEQ ID NO: 71):

DILLTQSPVILSVSPGERVSFSCRASQSIGTNIHWYQORTNGSPRLLIKYASESISGIPSRFSGSG
SGTDFTLSINSVESEDIADYYCQQNNNWPTTFGAGTKLELKR
TVAAAPSVFI FPPSDEQLKSGTASV
VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTH
QGLSSPVTKSFNRGEC

Underlined: Anti-EGFR Variable region

Plain: Anti-EGFR Constant region

*Italic: Linker***Bold: PD-1 ectodomain**

Fig. 14

Fusion proteins comprising Anti-CD20 antibody and PD-1 Ectodomain.

Anti-CD20 heavy chain + PD-1 ectodomain fusion amino acid sequence
(SEQ ID NO: 17):

QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGDTSYNQKFKG
KATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAGTTVTVSAASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLG
TQTYICNVNHKPSNTKVDKKAEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVMEALHNHYTQKSLSLSPGK
GGGGSGGGSGGGGS PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS
ESFVLNWMYRM SPSNQTDKLA AFPEDRSQPG QDCRFRTVQL PNGRDFHMSV VRARRNDSGT
YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV

Anti-CD20 light chain amino acid sequence (SEQ ID NO: 72):

QIVLSQSPAILASAPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWYATSNLASGVFVRFSGSGS
GTSYSLTISRVEAEDAATYYCQWTSNPPTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSLSSTLTLSKADYEKHKVYACEVTHQ
GLSSPVTKSFNRGEC

Underlined: Anti-CD20 Variable region

Plain: Anti-CD20 Constant region

Italic: Linker

Bold: PD-1 ectodomain

Fig. 15

Fusion proteins comprising Anti-VEGF antibody and PD-1 Ectodomain.

Anti-VEGF heavy chain + PD-1 ectodomain fusion amino acid sequence
(SEQ ID NO: 18):

EVQLVESGGGLVQPGGSLRLSCAASGYTFTNYGMNWVRQAPGKGLEWVGWINTYTGEPTYAADFKR
RFTFSLDTSKSTAYLQMNSLRAEDTAVYYCAKYPHYGSSHWYFDVWGQGT**LVTVSSASTKGPSVF**
PLAPSSKSTSGGTAALGCLVKDYFPEPVT**TSWNSGALTSGVHTFPAVLQSSGLYSLSSV****TVPS**
SS**LGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE**
VTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNV**FSCSVMEALHNHYTQKSLSLSPGK**
GGGSGGGSGGGSGS **PGWFLDSPDR PWNPTTFSPA LLVVTEGDNA TFTCSFSNTS**
ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRTQL PNGRDFHMSV VRARRNDSGT
YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHFSPSP RPAGQFQTLV

Anti-VEGF Light chain sequence (SEQ ID NO: 73):

DIQMTQSPSSLSASVGDRVTITCSASQDISNYLNWYQQKPGKAPKVLIIYFTSSSLHSGVPSRFS
SGSGSGTDFTLTITSSLPEDFATYYCQQYSTVPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV
VCLLNNFYFPREAKVQWKVDNALQSGNSQESVTEQDSKDS**TYSLSS****TLTSLKADYEKHKVYACEVTH**
QGLSSPVTKSFNRGEC

Underlined: Anti-VEGF Variable region

Plain: Anti-VEGF Constant region

Italic: Linker

Bold: PD-1 ectodomain

Fig. 16

Fusion proteins comprising anti-human CTLA-4 antibody and PD-1 Ectodomain.

Anti-(human CTLA-4) (human γ 1-chain)-PD-1 ectodomain fusion protein, disulfide with human κ -chain, dimer

Anti-CTLA-4 heavy chain + PD-1 ectodomain fusion amino acid sequence

(SEQ ID NO: 19):

QVQLVESGGG VVQPGRLRL SCAASGFTFS SYTMHWVRQA PGKGLEWVTF ISYDGNKYY
ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAIYYCARTG WLGPFDYWGO GTLVTVSSAS
TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL
YSLSSVVTVP SSSLGTQTYI CNVNHKPSNT KVDKRVPEKS CDKTHTCPPC PAPELLGGPS
VFLFPPPKPD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST
YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT
KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTTPVLD SDGSFFLYSK LTVDKSRWQQ
GNVFSCSVMH EALHNHYTQKSLSLSPGK **GGGGSGGGSGGGGS** **PWFLDSPDR**
PWNPTTFSPA **LLVVTEDNA** **TFTCSFNTS** **ESFVLNWYRM** **SPSNQTDKLA** **AFPEDRSQPG**
QDCRFRTQL **PNGRDFHMSV** **VRARRNDSGT** **YLCGAISLAP** **KAQIKESLRA** **ELRVTERRAE**
VPTAHPSPSP **RPAGQFQTLV**

Anti-CTLA-4 light chain (SEQ ID NO: 74):

EIVLTQSPGT LSLSPGERAT LSCRASQSVG SSYLAWYQQK PGQAPRLLIY GAFSRATGIP
DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ QYGSSPWTFG QGTKVEIKRT VAAPSVFIFP
PSDEQLKSGT ASVVCLLNNF YPREAKVQWK VDNALQSGNS QESVTEQDSK DSTYLSSTL
TLISKADYEKH KVYACEVTHQ GLSSPVTKSF NRGEC

Underlined: Anti-CTLA-4 Variable region

Plain: Anti-CTLA-4 Constant region

Italic: Linker

Bold: PD-1 ectodomain

Fig. 17

Fusion proteins comprising anti-CD25 antibody and PD-1 Ectodomain.

Anti-CD25 (Daclizumab) heavy chain and PD-1 ectodomain (SEQ ID NO: 20):

QVQLVQSGAE VKKPGSSVKV SCKASGYTFT SYRMHWVRQA PGQGLEWIGY INPSTGYTEY
NQKFKDKATI TADESTNTAY MELSSLRSED TAVYYCARGG GVFDYWGQGT LVTVSSASTK
GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS
LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKKVEPKSCD KTHTCPPCPA PELLGGPSVF
LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR
VVSVLTVLHQ DWLNGKEYKC KVSNAKALPAP IEKTISKAKG QPREPQVYTL PPSRDELTKN
QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTTPVLDSG GSFFLYSKLT VDKSRWQQGN
VFSCSVMEHA LHNHYTQKSL SLSPGK GGGGSGGGGSGGGGS
PGWFLDSPDRPWNPPTFSPALLVVTEGDNATFTCSFSNT
SESFVLNWMSPSNQTDKLAAPEDRSQPGQDCRFRVTQLPNGRDFHMSVVRAR
RNDSGTYLCGAISLAPKAQIKESLRAELRVTERRAEVPTAHPSPSPRPAGQFQTLV

Anti-CD25 (Daclizumab) light chain (SEQ ID NO: 75):

DIQMTQSPST LSASVGDRVT ITCSASSSIS YMHWYQQKPG KAPKLLIYTT SNLASGVPAR
FSGSGSGTEF TLTISSLQPD DFATYYCHQR STYPLTFGQG TKVEVKRTVA APSVFIFPPS
DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSSTLT
SKADYEKHKV YACEVTHQGL SSPVTKSFNR GEC

Plain: Anti-CD25 antibody

Italic: Linker

Bold: PD-1 ectodomain

Fig. 18A

Anti-CD25 (Basiliximab) heavy chain and PD-1 ectodomain (SEQ ID NO: 21):

QLQQSGTVLA RPGASVKMSC KASGYSFTRY WMHWIKQRPQ QGLEWIGAIY PGNSDTSYNQ
KFEGKAKLTA VTSASTAYME LSSLTHEDSA VYYCSRDIYGY YFDFWGQGT T LTVSSASTKG
PSVFPLAPSS KSTSGGTAAL GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL
SSVVTVPSSS LGTQTYICNV NHKPSNTKVD KRVEPKSCDK THTCPPCPAP ELLGGPSVFL
FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV
VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTL P PSRDELTKNQ
VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV
FSCSVMEAL HNHYTQKSLS LSPGK GGGGSGGGGSGGGGS
PGWFLDSPDRPWNPTTFSPALLVVTEGDNATFTCSFSNT
SESFVLNWRMSPSNQTDKLAFFPEDRSQPGQDCRFRVTQLPNGRDFHMSVVRAR
RNDSGTYLCGAISLAPKAQIKESLRAELRVTERRAEVPTAHPSPSRPAGQFQTLV

Anti-CD25 (Basiliximab) light chain (SEQ ID NO: 76):

QIVSTQSPAI MSASPGEKVT MTCSASSRS YMQWYQQKPG TSPKRWIYDT SKLASGVPAR
FSGSGSGTSY SLTISSMEAE DAATYYCHQR SSYTFGGGTK LEIKRTVAAP SVFI FPPSDE
QLKSGTASVV CLLNNFYPRE AKVQWKVDNA LQSGNSQESV TEQDSKDSTY SLSSTLTLSK
ADYEKHKVYA CEVTHQGLSS PVTKSFNRGEC

Plain: Anti-CD25 antibody

Italic: Linker

Bold: PD-1 ectodomain

Fig. 18B

Fusion proteins comprising IL-2, Fc, and PD-1 ectodomain.

IL-2 + Fc + PD-1 ectodomain (SEQ ID NO: 16):

APTSSSTKKTQLQLEHLLLDLQMLNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPL
EEVLNLAQSKNFHLRPDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTL
T *GGGGSGGGSGGGGS*
 THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
 REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFSCSVSMHEALHNHYTQKSLSLSPGK *GGGGSGGGSGGGGS*
 PGWFLDSPDRPWNPTTFSPALLVTEGDNATFTCSFSNTSESFVLNWMSPSNQTDKLAAPEDR
 SQPGQDCRFRVTQLPNGRDFHMSVVRARRNDSGTYLCAISLAPKAQIKESLRAELRVTERRAEVP
 TAHPSPSRPRAGQFQTLV

PD-1 ectodomain + Fc + IL-2 (SEQ ID NO: 23):

PGWFLDSPDRPWNPTTFSPALLVTEGDNATFTCSFSNTSESFVLNWMSPSNQTDKLAAPEDR
 SQPGQDCRFRVTQLPNGRDFHMSVVRARRNDSGTYLCAISLAPKAQIKESLRAELRVTERRAEVP
 TAHPSPSRPRAGQFQTLV *GGGGSGGGSGGGGS*
 THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
 REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFSCSVSMHEALHNHYTQKSLSLSPGK *GGGGSGGGSGGGGS*
APTSSSTKKTQLQLEHLLLDLQMLNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPL
EEVLNLAQSKNFHLRPDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTL
T

Underlined: IL-2 fragment*Italic: Linker*

Plain: Fc

Bold: human PD-1 ectodomain(Note: Can replace optional linker 1 *GGGGSGGGSGGGGS* SEQ ID NO: 104 with*EPKSCDK* SEQ ID NO: 105)(Note: Can replace underlined aa in Fc: E with D and M with L)

Fig. 19

Fusion proteins comprising anti-CD4 antibody and PD-1 Extracellular domain

Anti-CD4 heavy chain and PD-1 Extracellular domain (SEQ ID NO: 24):

Heavy chain fusion protein:

QVQLQEAGPGLVVKPSETLSLTCSVSGCSISGDYYWFWIRQSPGKGLEWIGYIYGSGGGTNYNPSLN
NRVSISIDTSKNLFLSLKLRSVTAADTAVYYCASNILKYLHWLLYWGGVLTVTSSASTKGPSVFPPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTIISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVMHREALHNYTQKSLSLSPGK
GGGGSGGGGSGGGGS
PGWFLDSPDRPWNPPPTFSPALLVVTGEDNATFTCSFSNTSESFVLNWMSPSNQTDKLAAPFEDR
SQPGQDCRFRTQLPNGRDFHMSVVRARRNDSTYLCGAISLAPKAQIKESLRARLRVTERRAEVP
TAHPSPSPRPAGQFQTLV

Anti-CD4 light chain (SEQ ID NO: 77):

Light chain:

SYELSQPRSVSVSPGQTAGFTCGGDNVGRKSVQWYQQKPPQAPVLVIYADSERPSGIPARFSGSNS
GNTATLTISGVEAGDEADYYCQVWDSTADHWVFGGGTRLTVLGRTVAAPSVFIFPPSDEQLKSGTA
SVVCLLNNFYFPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYSLSSTLTLSKADYEKHKVYACEV
THQGLSSPVTKSFNRGEC

Plain: Anti-CD4 antibody (Variable region – underlined)

Italic: Linker

Bold: PD-1 ectodomain

Fig. 20

Fusion proteins comprising PD-1 Ectodomain, Fc, and Receptor activator of nuclear factor- κ B (RANK) Extracellular domain (ectodomain):

RANK ectodomain – Fc – PD-1 ectodomain (SEQ. ID. NO: 25):

QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP CGPDEYLD SW NEEDKCLLHK
VCDTGKALVA VVAGNSTTPR RCACTAGYHW SQDCECCRRN TECAPGLGAQ HPLQLNKDTV
CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG
GGGSGGGSGGGGS
 THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
 REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFSCSVMEALHNHYTQKSLSLSPGK GGGSGGGSGGGGS
 PGWFLDSPDRPWNPTTFSPALLVVEGDNATFTCSFSNTSESFVLNWRMSPSNQTDKLAAPFEDR
 SQPGQDCRFRTQLPNGRDFHMSVVRARRNDSGYLCAISLAPKAQIKESLRAELRVTERRAEV
 TAHPSPSRPAGQFQTLV

PD-1 ectodomain – Fc – RANK ectodomain (SEQ. ID. NO: 26):

PGWFLDSPDRPWNPTTFSPALLVVEGDNATFTCSFSNTSESFVLNWRMSPSNQTDKLAAPFEDR
 SQPGQDCRFRTQLPNGRDFHMSVVRARRNDSGYLCAISLAPKAQIKESLRAELRVTERRAEV
 TAHPSPSRPAGQFQTLVGGGSGGGSGGGGS
 THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
 REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFSCSVMEALHNHYTQKSLSLSPGK GGGSGGGSGGGGS QI APPCTSEKHY EHLGRCCNKC
EPGKYMSSKC TTTSDSVCLP CGPDEYLD SW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR
RCACTAGYHW SQDCECCRRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR
PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG

Bold: PD-1 ectodomain

Italics: Linker (optional: may delete linker 1 or replace with IEGRDMD or EPKSCDK)

Plain: IgG1 Fc

Underlined: RANK ectodomain

Fig. 21

Moieties that bind Receptor activator of nuclear factor- κ B (RANK) ligand(i) Full-length RANK (TNFRSF11A) or fragment thereof (SEQ. ID. NO. 95):

1 MAPRRRRRRP LFALLLLCAL LARLQVALQI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC
61 TTTSDSVCLP CGPDEYLDW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RACTAGYHW
121 SQDCECCRRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK
181 RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPGLIILLLF ASVALVAAIL FGVCYRKKGK
241 ALTANLWHWI NEACGRLSGD KESSGDSVCS THTANFGQQG ACEGVLLLT EEKTFPEDMC
301 YPDQGGVCQG TCVGGGPYQA GEDARMLSLV SKTEIEEDSF RQMPTEDEYM DRPSQPTDQL
361 LFLTEPGSKS TPFSEPLEV GENDSLSQCF TGTQSTVGSE SCNCTEPLCR TDWTFPMSEN
421 YLQKEVDSGH CPHWAASPSP NWADVCTGCR NPPGEDCEPL VGSPKRGPLP QCAYGMGLFP
481 EEEASRTEAR DQPEDGADGR LPSSARAGAG SGSSPGGQSP ASGNVTGNSN STFISSGQVM
541 NPKGDIIVVY VSQTSQEGAA AAAPMGRPV QRETLLRRDS FAGNGFRFPD PCGGPEGLRE
601 PEKASRPVQE QGGAKA

Bold: RANK extracellular domain (RANK ligand-binding domain)(ii) RANK extracellular domain (ectodomain) or fragment thereof (SEQ. ID. NO. 96):

QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP CGPDEYLDW NEEDKCLLHK VCDTGKALVA
VVAGNSTTPR RACTAGYHW SQDCECCRRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR
PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG

(iii) Peptide sequences in RANKL binding domains of RANK or peptides containing key RANKL-binding residues of RANK (SEQ. ID. NO. 97):

1 MAPRRRRRRP LFALLLLCAL LARLQVALQI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC
61 TTTSDSVCLP CGPDEYLDW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RACTAGYHW
121 SQDCECCRRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK
181 RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG

Bold: RANK extracellular domain (RANK ligand-binding domain)

RANK peptide sequences (Underlined) and residues (Italics) involved in binding RANKL.

(iv) Mutant of RANK or a fragment thereof which binds Receptor activator of nuclear factor- κ B (RANK) ligand (RANKL)(v) Full-length Osteoprotegerin (OPG, TNFRSF11B) or fragment thereof (SEQ. ID. NO. 98):

1 MNKLLCCALV FLDISIKWTT QETFPFKYLH YDEETSHQLL CDKCPFGTYL KQHCTAKWKT
61 VCAPCPDHYH TDSWHTSDEC LYCSPVCKEL QYVKQECNRT HNRVCECKEG RYLEIEFCLK
121 HRSCPPGFGV VOAGTFRNT VCKRCPDGFF SNETSSKAPC RKHTNCSVFG LLLTQKGNAT
181 HDNICSGNSE STQKCGIDVT LCEEAFRFA VPTKFTPNWL SVLVDNLPGT KVNAESVERI
241 KRQHSSQEQT FQLLKLWKHQ NKAQDIVKKI IQDIDLCEHS VQRHIGHANL TFEQLRSLME
301 SLPGKKVGAE DIEKTIKACK PSDQILKLLS LWRIKNGDQD TLKGLMHALK HSKTYHFPKT
361 VTQSLKKTIR FLHSFTMYKL YQKLFLEMIG NQVQSVKISC L

Bold: RANK ligand-binding domain

Fig. 22

Fusion proteins comprising Anti-HER2/neu antibody and Receptor activator of nuclear factor- κ B (RANK) Extracellular domain (ECD).

Anti-HER2/neu heavy chain+ RANK ECD fusion amino acid sequence (SEQ. ID. NO: 27):

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISA
DTSKNTAYLQMNSLRAEDTAVYYCSRNGGDGFYAMDYWGQGTLLVTVSSASTKGPSVFPLAPSSKSTSGGTAA
 LGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDK
 KVEPKSCDKTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
 NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
 MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMH
 EALHNHYTQKSLSLSPGK **GGGGSGGGSGGGGS** **QI** **APPCTSEKHY** **EHLGRCCNKC** **EPGKMSSKC**
TTTSDSVCLP **CGPDEYLDW** **NEEDKCLLHK** **VCDTGKALVA** **VVAGNSTTPR** **RCACTAGYHW**
SQDCECCRRN **TECAPGLGAQ** **HPLQLNKDTV** **CKPCLAGYFS** **DAFSSTDKCR** **PWTNCTFLGK**
RVEHHGTEKS **DAVCSSSLPA** **RKPPNEPHVY** **LPG**

Anti-HER2/neu light chain amino acid sequence (SEQ. ID. NO: 70):

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQOKPGKAPKLLIYSASFYSGVPSRFSGSRSGTDFT
LTISLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA
 KVQWKVDNALQSGNSQESVTEQDSKDSSTLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Underlined: Anti-HER2 antibody variable region

Plain: Anti-HER2 antibody constant region

Italics: Linker

Bold: RANK ectodomain

Fig. 23

Fusion proteins comprising Anti-EGFR1 antibody and Receptor activator of nuclear factor- κ B (RANK) Extracellular domain (ECD).

Anti-EGFR1 heavy chain + RANK ECD fusion amino acid sequence (SEQ. ID. NO: 28):

QVQLKQSGPGLVQPSSQLSITCTVSGFSLTNYGVHWVRQSPGKGLEWLGVIWSSGGNTDYNTPFTSRLSINKD
NSKSQVFFKMNLSQSNDAIYYCARALTYDYEFAYWGQGLVTVSAASTKGPSVFPLAPSSKSTSGGTAAL
 GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKR
 VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN
 AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL
 TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSSVMHE
 ALHNHYTQKSLSLSPGK *GGGSGGGSGGGGS* **QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC**
TTTSDSVCLP CGPDEYLDW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RACTAGYHW
SQDCECCRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK
RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG

Anti-EGFR1 light chain amino acid sequence (SEQ. ID. NO: 71):

DILLTQSPVILSVSPGERVSFSCRASQSIGTNIHWYQQRTNGSPRLLIKYASESISGIPSRFSGSGSDFT
LSINSVESEDIADYYCQQNNWPTTFGAGTKLELKTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA
 KVQWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEEKHKVYACEVTHQGLSPVTKSFNRGEC

Underlined: Anti-EGFR antibody variable region

Plain: Anti-EGFR antibody constant region

Italics: Linker

Bold: RANK ectodomain

Fig. 24

Fusion proteins comprising Anti-CD20 antibody and Receptor activator of nuclear factor- κ B (RANK) Extracellular domain (ECD).

Anti-CD20 heavy chain+ RANK ECD fusion amino acid sequence (SEQ. ID. NO: 29):

QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWICAIYPGNGDTSYNQKFKGKATLTA
DKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAGTTVTVSAASTKGPSVFPLAPSSKSTSGGTA
ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVD
KKAEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV
HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRD
ELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSSVM
HEALHNHYTQKSLSLSPGK *GGGGSGGGSGGGGS* **QI** APPCTSEKHY EHLGRCCNKC EPGKYMSSKC
TTTSDSVCLP CGPDEYLDW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RACTAGYHW
SQDCECCRRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK
RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG

Anti-CD20 light chain amino acid sequence (SEQ. ID. NO: 72):

QIVLSQSPAILLSASPGKVTMTCRASSSVSYIHWFQQKPGSSPKPWIYATSNLASGVPVRFSGSGSGTSYSL
TISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK
VQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEEKHKVYACEVTHQGLSSPVTKSFNRGEC

Underlined: Anti-CD20 antibody variable region

Plain: Anti-CD20 antibody constant region

Italics: Linker

Bold: RANK ectodomain

Fig. 25

Fusion proteins comprising anti-VEGF antibody and Receptor activator of nuclear factor- κ B (RANK) Extracellular domain (ECD).

Anti-VEGF heavy chain+ RANK ECD fusion amino acid sequence (SEQ. ID. NO: 30):

EVQLVESGGGLVQPGGSLRLS**CAASGYFTFTNYGMNWVRQAPGKGLEWVGWINTYTGEPTYAADF**
KRRFTFSLDTSKSTAYLQMN**SLRAEDTAVYYCAKYPHYYGSSHWYFDVWGQGLTLTVSSASTKG**
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTFSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP
 SSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

GGGGSGGGSGGGGS **QI** *APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP*
 CGPDEYLD SW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR R~~CACTAGYHW~~ SQDCECCRRN
 TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTD~~KCR~~ PWTNCTFLGK RVEHHGTEKS
 DAVCSSSLPA RKPPNEPHVY LPG

Anti-VEGF Light chain sequence (SEQ. ID. NO: 73):

DIQMTQSPSSLSASVGDRVTITCSASQDISNYLNWYQQKPGKAPKVL**IYFTSS**SLHSGVPSRFS**SGSGSG**
TDFILTISSLOPEDFATYYCQOYSTVPWTFGQGT**KVEIK**RTVAAPS**VFI**PPSDEQLKSGTASV**VCLL**
 NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Underlined: Anti-VEGF antibody variable region

Plain: Anti-VEGF antibody constant region

Italics: Linker

Bold: RANK ectodomain

Fig. 26

Fusion proteins comprising anti-human CTLA-4 antibody and Receptor activator of nuclear factor- κ B (RANK) Extracellular domain (ECD).

Anti-CTLA-4 heavy chain + RANK ECD fusion sequence (SEQ. ID. NO: 31):

QVQLVESGGG VVQPGRLRL SCAASGFTFS SYTMHWVRQA PGKGLEWVTF ISYDGNKYY
ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAIYYCARTG WLGPFDYWQQ GTLVTVSSAS
TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVTWSN SGALTSGVHT FPAVLQSSGL
YSLSSVVTVP SSSSLGTQTYI CNVNHKPSNT KVDKRVEPKS CDKTHTCPPC PAPELLGGPS
VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST
YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT
KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSERWQQ
GNVFCSCVMH EALHNHYTQK SLSLSPGK GGGGSGGGGSGGGGS **QI** APPCTSEKHY EHLGRCCNKC
EPGKYMSSKC TTTSDSVCLP CGPDEYLDSE NEEDKCLLHK VCDTGKALVA VVAGNSTTPR
RCACTAGYHW SQDCECCRRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR
PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKFPNEPHVY LPG

Anti-CTLA-4 light chain (SEQ. ID. NO: 74):

EIVLTQSPGT LSLSPGERAT LSCRASQSVG SSYLAWYQQK PGQAPRLLIY GAFSRATGIP
DRFGSGSGGT DFTLTISRLE PEDFAVYYCQ QYGSSPWTFG QGTKVEIKRT VAAPSVFIFP
PSDEQLKSGT ASVVCLLNNF YPREAKVQWK VDNALQSGNS QESVTEQDSK DSTYSLSSTL
TLISKADYEKH KVYACEVTHQ GLSSPVTKSF NRGEC

Underlined: Anti-CTLA-4 antibody variable region

Plain: Anti-CTLA-4 antibody constant region

Italics: Linker

Bold: RANK ectodomain

Fig. 27

Fusion proteins comprising anti-CD25 antibody and Receptor activator of nuclear factor- κ B (RANK) Extracellular domain (ECD).

Anti-CD25 and RANK ectodomain - Heavy chain (SEQ. ID. NO: 32):

QVQLVQSGAE VKKPGSSVKV SCKASGYTFT SYRMHWVRQA PGQGLEWIGY INPSTGYTEY
NQKFKDKATI TADESTNTAY MELSSLRSED TAVYYCARGG GVFDYWGQGT LVTVSSASTK
GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS
LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKKVEPKSCD KTHTCPPCPA PELLGGPSVF
LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR
VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG QPREPQVYTL PPSRDELTKN
QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTTPVLDSG GSFFLYSKLT VDKSRWQQGN
VFSCSVMHEA LHNHYTQKSL SLSPGK GGGGSGGGGSGGGGS QI APPCTSEKHY EHLGRCCNKC
EPGKYMSSKC TTTSDSVCLP CGPDEYLDW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR
RCACTAGYHW SQDCECCRRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDCKR
PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG

Anti-CD25 - Light chain (SEQ. ID. NO. 75):

DIQMTQSPST LSASVGDRVT ITCSASSSIS YMHWYQQKPG KAPKLLIYTT SNLASGVPAR
FSGSGSGTEF TLTISSLQPD DFATYYCHQR STYPLTFGQG TKVEVKRTVA APSVFIFPPS
DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSSTLT
SKADYEKHKV YACEVTHQGL SSPVTKSFNR GEC

Plain: Anti-CD25 antibody

Italics: Linker

Bold: RANK ectodomain

Fig. 28A

Fusion proteins comprising anti-CD25 antibody and Receptor activator of nuclear factor- κ B (RANK) Extracellular domain (ECD).

Anti-CD25 and RANK ectodomain - Heavy chain (SEQ. ID. NO: 33):

QLQQSGTVLA RPGASVKMSC KASGYSFTRY WMHWIKQRPQ QGLEWIGAIY PGNSDTSYNQ
KFEGKAKLTA VTSASTAYME LSSLTHEDSA VYYCSRDIYGY YFDWGGQTT LTVSSASTKG
PSVFPLAPSS KSTSGGTAAL GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL
SSVVTVPSSS LGTQTYICNV NHKPSNTKVD KRVEPKSCDK THTCPPCPAP ELLGGPSVFL
FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV
VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLF PSRDELTKNQ
VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV
FSCSVMEHAL HNHYTQKSL SLPK GGGGSGGGGSGGGGS **QI APPCTSEKHY EHLGRCCNKC**
EPGKYMSSKC TTTSDSVCLP CGPDEYLD SW NEEDKCLLHK VCDTGKALVA VVAGNSTTFR
RCACTAGYHW SQDCECCRRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR
PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPFNEPHVY LPG

Anti-CD25 – Light chain (SEQ. ID. NO: 76):

QIVSTQSPAI MSASPGEKVT MTCSASSRS YMQWYQQKPG TSPKRWIYDT SKLASGVPAR
FSGSGSGTSY SLTISSMEAE DAATYYCHQR SSYTFGGGTK LEIKRTVAAP SVFIFPPSDE
QLKSGTASVV CLLNIFYPRE AKVQWKVDNA LQSGNSQESV TEQDSKDSTY SLSSTLTLSK
ADYEKHKVYA CEVTHQGLSS PVTKSFNRGEC

Plain: Anti-CD25 antibody

Italics: Linker

Bold: RANK ectodomain

Fig. 28B

Fusion proteins comprising IL-2, Fc, and Receptor activator of nuclear factor- κ B (RANK) Extracellular domain (ECD).

IL2 – Fc – RANK ECD (SEQ. ID. NO: 34):

APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEVLNL
AQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLTGGGGSGGGSG
 GGGSTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
 PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ
 VSLTCLVKGFPYSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHN
 HYTQKSLSLSPGK GGGGSGGGSGGGGS QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC
 TTTSDSVCLP CGPDEYLDW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RACTAGYHW
 SQDCECCRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK
 RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG

RANK ECD – Fc – IL-2 (SEQ. ID. NO: 35):

QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP CGPDEYLDW NEEDKCLLHK
 VCDTGKALVA VVAGNSTTPR RACTAGYHW SQDCECCRN TECAPGLGAQ HPLQLNKDTV
 CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG
 GGGSGGGSGGGSGSTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV
 DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL
 PPSREEMTKNQVSLTCLVKGFPYSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNV
 FSCVMHEALHNHYTQKSLSLSPGKGGGGSGGGSGGGGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKN
PKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMC
EYADETATIVEFLNRWITFCQSIISTLT

Bold: RANK ectodomain

Italics: Linker (Optional; any linker sequence)

Plain: Fc

Underlined: IL2 fragment that binds CD25 (IL-2R α)

(Can replace linker 1 with EPKSCDK or IEGRDMD)

(Can replace underlined aa in Fc: E with D and M with L)

Fig. 29

Fusion protein comprising anti-CD4 antibody and Receptor activator of nuclear factor- κ B (RANK) Extracellular domain (ECD)

Anti-CD4 heavy chain and RANK Extracellular domain (SEQ ID NO: 36):

Heavy chain fusion protein:

QVQLQEAGPGLVKPSETLSLTCSVSGGSISGDYYWFWIRQSPGKGLEWIGYIYGSGGGTNYNPSLN
NRVSISIDTSKNLFSCLKLRSVTAADTAVYYCASNILKYLHWLLYWGQGVLTIVSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLG
TQTYICNVNHKPSNTKVDKRVPEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGSGGGGS QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP
CGPDEYLD SW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RACTAGYHW SQDCECCRRN
TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS
DAVCSSSLPA RKPPNEPHVY LPG

Anti-CD4 light chain (SEQ ID NO: 77):

Light chain:

SYELSQPRSVSVSPGQTAGFTCGGDNVGRKSVQWYQQKPPQAPVLVIYADSERPSGIPARFSGSNS
GNTATLTISGVEAGDEADYYCQVWDSTADHWVFGGGTRLTVLGRTVAAPSVFIFPPSDEQLKSGTA
SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEV
THQGLSSPVTKSFNRGEC

Underlined: Anti-CD4 antibody variable region

Plain: Anti-CD4 antibody constant region

Italic: Linker

Bold: PD-1 ectodomain

Fig. 30

- (i) Full-length human PD-1 ligand 1 (B7-H1; PDCD1L1; PDL1; CD274) protein or a fragment thereof (SEQ ID NO: 99):

MRIFAVFIFM TYWHLLNAFT VTPPKDLYVV EYGSNMTIEC KFPVEKQLDL AALIVYWEME
DKNIIQFVHG EEDLKVQHSS YRQRARLLKD QLSLGNAALQ ITDVKLQDAG VYRCMISYGG
ADYKRITVKV NAPYNKINQR ILVVDPTSE HELTCQAEY PKAEVIWTSS DHQVLSGKTT
TTNSKREEKL FNVSTLRLIN TTTNEIFYCT FRRLDPEENH TAEVLPELP LAHPPNERTH
LVILGAILLC LGVALTFIFR LRKGRMDVK KCGIQDTNSK KQSDTHLEET

- (ii) PD-L1 extracellular binding domain (ectodomain) or fragment thereof (SEQ ID NO: 100):

AFT VTPPKDLYVV EYGSNMTIEC KFPVEKQLDL AALIVYWEME DKNIIQFVHG
EEDLKVQHSS YRQRARLLKD QLSLGNAALQ ITDVKLQDAG VYRCMISYGG ADYKRITVKV
NAPYNKINQR ILVVDPTSE HELTCQAEY PKAEVIWTSS DHQVLSGKTT TTNSKREEKL
FNVTSTLRLIN TTTNEIFYCT FRRLDPEENH TAELVI

- (iii) Human PD-1 ligand 2 [PD-L2 (B7-DC)] or a fragment thereof.

- (iv) Mutant of Programmed Death-1 ligand [PD-L1 (B7-H1) or PD-L2 (B7-DC)] or a fragment thereof which binds Programmed Death-1 (PD-1).

Sequence used in fusion proteins (SEQ ID NO: 101):

RIFAVFIFM TYWHLLNAFT VTPPKDLYVV EYGSNMTIEC KFPVEKQLDL AALIVYWEME
DKNIIQFVHG EEDLKVQHSS YRQRARLLKD QLSLGNAALQ ITDVKLQDAG VYRCMISYGG
ADYKRITVKV NAPYNKINQR ILVVDPTSE HELTCQAEY PKAEVIWTSS DHQVLSGKTT
TTNSKREEKL FNVSTLRLIN TTTNEIFYCT FRRLDPEENH TAEVLPELP LAHPPNERTH
LVILGAILLC LGVALTFIFR LRKGRMDVK KCGIQDTNSK KQSDTHLEET

Bold: PD-L1 extracellular domain (ectodomain)

Underlined Bold: Ligand Binding domain

Fig. 31

Fusion proteins comprising anti-tumor necrosis factor (TNF α) antibody and PD-1 ligand 1 or PD-1 ligand 2

Anti-TNF α heavy chain + PD-L1 (SEQ ID NO: 37):

EVQLVESGGGLVQPGRSRLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVS
AITWNSGHIDYADSVEGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCALVSYLSTASSLDYWGQGT
LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTV
PSSSLGTQTYICNVNHKPSNTKVD**KKAE****PKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT**
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK
GGGGSGGGSGGGGS
RIFAVFIFMTYWHLLNAFTVTVPKDLVVEYGSNMTIECKFPVEKQLDLAALIVWEMEDKNIIQF
VHGEEDLKVQHSSYRQRARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAP
YNKINQRILVDPVPTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTNSKREEKLFNVTSTLRI
NTTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPNERTHLVILGAILLCLGVALTFIFRLRKGR
MMDVKKCGIQDTNSKKQSDTHLEET

Anti-TNF α light chain (SEQ ID NO: 78):

DIQMTQSPSSLSASVGDRVTITCRASQGI
RNYLAWYQQLP
GKAPKLLIYAAS
TLQSGVPSRFS
SGSGSGTDFTLT
ISSIQPEDVATYYCQRYNRAPYTFGQGT
KVEIKRTVAAPS
VFIFPPSDEQLKSGTASV
VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK
STYLSSTLTLSKADYEKHKVYACEVTH
QGLSSPVTKSFNRGEC

Underlined: anti-TNF α antibody variable region

Plain: anti-TNF α antibody constant region

Italic: Linker

Bold: human PD-1 ligand 1 (PD-L1)

(Note: Fc region **KKAE** SEQ ID NO: 106 can be replaced with **KRVE** SEQ ID NO: 107
or **KKVE** SEQ ID NO: 108)

Fig. 32

Fusion proteins comprising TNFR2 Extracellular ligand binding domain, Fc, and PD-1 ligand: (TNFR2 ECD + IgG C γ 1 + PD-L1)

TNFR2 ECD + IgG C γ 1 + PD-L1 (SEQ ID NO: 38):

LPAQVAFTPYAPEPGSTCRLREYYDQTAQMCCSKCSPGQHAKVFCTKTSDTVCDSCEDSTYTQLWN
WVPECLSCGSRSSDQVETQACTREQNRICTCRPGWYCALSKQEGCRLCAPLRKCRPGFGVARPGT
ETSDVVCKPCAPGTFSNTTSSSTDICRPHQICNVVAIPGNASMDAVCTSTSPTRSMAPGAVHLPQPV
STRSQHTQPTPEPSTAPSTSFLPMGSPSPAEGSTGD *EPKSCDK*
 THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
 REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFSCSVMHAEALHNHYTQKSLSLSPGK *GGGGSGGGSGGGGS*
 RIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVWEMEDKNIIQF
 VHGEEDLKVQHSSYRQRARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNA
 YNKINQRIILVDPVPTSEHELTCQAEQYPAEVIWTSDDHQLVSGKTTTTNSKREEKLFNVTSTLRI
 NTTTNEIFYCTFRRLDPEENHTAELVPELPLAHPNERTHLVILGAILLCLGVALTFIFRLRKGR
 MMDVKKCGIQDTNSKKQSDTHLEET

Fusion proteins comprising PD-1 ligand, Fc, and TNFR2 Extracellular ligand binding domain: (PD-L1 + IgG C γ 1 + TNFR2 ECD)

PD-L1 + IgG C γ 1 + TNFR2 ECD (SEQ ID NO: 39):

MRIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVWEMEDKNIIQ
 FVHGEEDLKVQHSSYRQRARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNA
 PYNKINQRIILVDPVPTSEHELTCQAEQYPAEVIWTSDDHQLVSGKTTTTNSKREEKLFNVTSTLRI
 INTTNEIFYCTFRRLDPEENHTAELVPELPLAHPNERTHLVILGAILLCLGVALTFIFR
 LRKGRMMDVKKCGIQDTNSKKQSDTHLEET *GGGGSGGGSGGGGS* *EPKSCDK*
 THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
 REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFSCSVMHAEALHNHYTQKSLSLSPGK *GGGGSGGGSGGGGS*
LPAQVAFTPYAPEPGSTCRLREYYDQTAQMCCSKCSPGQHAKVFCTKTSDTVCDSCEDSTYTQLWN
WVPECLSCGSRSSDQVETQACTREQNRICTCRPGWYCALSKQEGCRLCAPLRKCRPGFGVARPGT
ETSDVVCKPCAPGTFSNTTSSSTDICRPHQICNVVAIPGNASMDAVCTSTSPTRSMAPGAVHLPQPV
STRSQHTQPTPEPSTAPSTSFLPMGSPSPAEGSTGD

Underlined: TNFR2 ligand-binding domain

Plain: human IgG1 heavy chain constant region (IgG C γ 1 domain = H, CH2, CH3)

Italic: Linker (Linker 1 is optional and may be replaced with another linker such as EPKSCDK or GGGSGGGSGGGGS)

Bold: human PD-1 ligand 1 or extracellular binding domain of PD-L1

Fig. 33

Fusion proteins comprising anti-CD20 antibody and PD-1 ligand 1 (PD-L1).

Anti-CD20 heavy chain + PD-L1 sequence (SEQ ID NO: 40):

QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGDTSYNQKFKG
KATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAGTTVTVSAASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFPSSSLG
TQTYICNVNHKPSNTKVDKKAEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVSCFSVMHEALHNHYTQKSLSLSPGK
GGGSGGGSGGGGS
RIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIQF
VHGEEDLKVQHSSYRQRARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAP
YNKINQRILVVDPVTSEHELTCQAEQYPAEVIWTSSDHQVLSGKTTTNSKREEKLFNVTSTLRI
NTTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPPNERHLVILGAILLCLGVALTFIFRLRKGR
MMDVKKCGIQDTNSKKQSDTHLEET

Anti-CD20 light chain sequence (SEQ ID NO: 72):

QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFOQKPGSSPKPWYATSNLASGVFVRFSGSGS
GTSYSLTISRVEAEDAATYYCQQTSTNPPTFGGCTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYSLSSTLTLSKADYEKHKVYACEVTHQ
GLSSPVTKSFNRGEC

Underlined: anti-CD20 antibody variable region

Plain: anti-CD20 antibody constant region

*Italic: Linker***Bold: human PD-1 ligand 1 or extracellular binding domain of PD-L1**

Fig. 34

Fusion proteins comprising anti-CD25 antibody and PD-1 ligand 1 (PD-L1).

Anti-CD25 (Daclizumab) heavy chain and PD-L1 (SEQ ID NO: 41):

QVQLVQSGAE VKKPGSSVKV SCKASGYTFT SYRMHWVRQA PGQGLEWIGY INPSTGYTEY
NQKFKDKATI TADESTNTAY MELSSLRSED TAVYYCARGG GVFDYWGQGT LVTVSSASTK
GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS
LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKKVEPKSCD KHTCPCCPA PELLGGPSVF
LFPFKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR
VVSVLTVLHQ DWLNGKEYKC KVSNAKALPAP IEKTISKAKG QPREPQVYTL PPSRDELTKN
QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTTPVLDSD GSFFLYSKLT VDKSRWQQGN
VFSCSVMHEA LHNHYTQKSL SLSPGK GGGGSGGGGSGGGGS
RIFAVFIFMTYWHLNAFTVTVPKDLYVVEYGSNMTIECK
FPVEKQLDLAALIVWEMEDKNIQFVHGEEEDLKVQHSSYRQRARLLKDQLSLGNA
ALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRILVVDPVTSEHEL
TCQAEQYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLRINTTTNEIFYC
TFRRLDPEENHTAELVPELPLAHPPNERHLVILGAILLCLGVALTFIFRLRKGR
MMDVKKCGIQDTNSKKQSDTHLEET

Anti-CD25 (Daclizumab) light chain (SEQ ID NO: 75):

DIQMTQSPST LSASVGDRVIT ITCSASSSIS YMHWYQKPG KAPKLLIYTT SNLASGVPAR
FSGSGSGTEF TLTISSLQPD DFATYYCHQR STYPLTFGQG TKVEVKRTVA APSVFIFPPS
DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSSTLT
SKADYEKHKV YACEVTHQGL SSPVTKSFNR GEC

Plain: anti-CD25 antibody

Italic: Linker (optional and may be replaced)**Bold: human PD-1 ligand 1 or extracellular binding domain of PD-L1 (underlined)**

Fig. 35A

Fusion proteins comprising IL-2, Fc, and PD-1 ligand 1 (PD-L1)

Fusion protein: hPD-1 ligand 1 + Fc + IL-2 (SEQ ID NO: 43):

MRIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVWEMEDKNIIQFVHGEE
DLKVQHSSYRQARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKV
NAPYKNINQRILVVDPVTSEHETCQAEGYPKAEVIWTSSDHQVLSGKTTTNSKREEKLFNVTSTLRINTT
TNEIFYCTFRRLDPEENHTAELVIPELPLAHPNERTHLVILGAILLCLGVALTFIFR
 LRGKRMMDVKKCGIQDTNSKKQSDTHLEET GGGGSGGGSGGGGS
 THTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE
 QYNSTYRVVSVLTVTLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLT
 CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVSCFVSVMHEALHNHYTQ
 KSLSLSPGK GGGGSGGGSGGGGS
APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNL
AQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEEFLNRWITFCQSIISTLT

Fusion protein: IL-2 + Fc + PD-1 ligand 1 (SEQ ID NO: 44):

APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNL
AQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEEFLNRWITFCQSIISTLT
 GGGGSGGGSGGGGS
 THTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE
 QYNSTYRVVSVLTVTLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLT
 CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVSCFVSVMHEALHNHYTQ
 KSLSLSPGK GGGGSGGGSGGGGS
RIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVWEMEDKNIIQFVHGEE
LKVQHSSYRQARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAPYKNINQRILVV
PVTSEHETCQAEGYPKAEVIWTSSDHQVLSGKTTTNSKREEKLFNVTSTLRINTTTNEIFYCTFRRLDPE
ENHTAELVIPELPLAHPNERTHLVILGAILLCLGVALTFIFRLRGKRMMDVKKCGIQDTNSKKQSDTHLEE
 T

Underlined: IL-2 fragment*Italic: Linker (optional)*

Plain: Fc

Bold: human PD-1 ligand 1 or extracellular binding domain of PD-1L (underlined)

(Note: Can replace linker 1 GGGGSGGGSGGGGS SEQ ID NO: 104 with

EPKSCDK SEQ ID NO: 105)

(Note: Can replace underlined aa in Fc: E with D and M with L)

Fig. 36

Fusion protein comprising anti-CD4 antibody and PD-1 ligand 1 (PD-L1)

Anti-CD4 heavy chain and PD-1 ligand 1 (SEQ ID NO: 45)

Heavy chain fusion protein:

QVQLQEAGPGLVKPSETLSLTCSVSGGSISGDYYWFWIRQSPGKGLEWIGYIYGSGGGTNYNPSLN
NRVSISIDTSKNLFSCLKRSVTAADTAVYYCASNILKYLHWLLYWGGVLTSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLG
TQTYICNVNHKPSNTKVDKRVKPKCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNYHTQKSLSLSPGK
GGGGSGGGSGGGGS
RIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVWEMEDKNIIQF
VHGEEDLKVQHSSYRQRARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAF
YNKINQRIILVDPVTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTNSKREEKLFNVTSTLRI
NTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPNERTHLVILGAILLCLGVALTFIFRLRKGR
MMDVKKCGIQDTNSKKQSDTHLEET

Anti-CD4 light chain (SEQ ID NO: 77)

Light chain:

SYELSQPRSVSVSPGQTAGFTCGGDNVGRKSVQWYQQKPPQAPVLVIYADSERPSGIPARFSGSNS
GNTATLTISGVEAGDEADYYCQVWDSTADHWVFGGGTRLTVLGRTVAAPSVFIFPPSDEQLKSGTA
SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEV
THQGLSSPVTKSFNRGEC

Underlined: Anti-CD4 antibody variable region

Plain: Anti-CD4 antibody constant region

*Italic: Linker***Bold: human PD-1 ligand 1 or extracellular binding domain of PD-1L (underlined)**

Fig. 37

Fusion proteins comprising the extracellular domain of CTLA-4, Immunoglobulin Fc (IgG C γ 1), and a sequence from PD-1 ligand (PD-L1)

Oncostatin M signal peptide + CTLA-4 ECD + IgG C γ 1 + PD-L1 (SEQ ID NO: 46):

MGVLLTQRTLLSLVLALLFPSMASMAMHVAQPAVVLASSRGIASFVCEYASPGKATEVRVTVLVRQA
DSQVTEVCAATYMMGNELTFLDDSICTGTSSGNQVNLTIQGLRAMDTGLYICKVELMYPFYYLGI
GNGTQIYVIDPEPCPDSD QEPKSCDKTHTCPPCPAPELLGGPSVFLFPPPKPKDTLM
 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE
 YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN
 GQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSVMSVHEALHNHYTQKSLSLSPGK
 GGGGSGGGGSGGGGS
 RIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTECKFPVEKQLDLAALIVWEMEDKNIIQF
 VHGEEEDLKVQHSSYRQARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAP
 YNKINQRIILVVDPTSEHELTCAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLR
 NTTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPNERTHLVILGAILLCLGVALTFIFRLRKGR
 MMDVKKCGIQDTNSKKQSDTHLEET

Fusion proteins comprising the extracellular domain of PD-1 ligand (PD-L1), Immunoglobulin Fc (IgG C γ 1), and a sequence from the extracellular domain of CTLA-4.

PD-L1 + IgG C γ 1 + CTLA-4 ECD (SEQ ID NO: 47):

MRIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTECKFPVEKQLDLAALIVWEMEDKNIIQ
FVHGEEEDLKVQHSSYRQARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAP
PYNKINQRIILVVDPTSEHELTCAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLR
INTTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPNERTHLVILGAILLCLGVALTFIFR
LRKGRMMDVKKCGIQDTNSKKQSDTHLEET GGGGSGGGGSGGGGS
QEPKSCDKTHTCPPCPAPELLGGPSVFLFPPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
 GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP
 QVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTV
 DKSRWQQGNVFSVMSVHEALHNHYTQKSLSLSPGK GGGGSGGGGSGGGGS
AMHVAQPAVVLASSRGIASFVCEYASPGKATEVRVTVLVRQADSQVTEVCAATYMMGNELTFLDDSI
CTGTSSGNQVNLTIQGLRAMDTGLYICKVELMYPFYYLGIGNGTQIYVIDPEPCPDSD

Underlined Italic: Oncostatin M Signal Peptide (-25 to -1)

Underlined: CTLA-4 extracellular domain (1-125)

Plain: human IgG1 heavy chain constant region (IgG C γ 1 domain = H, CH2, CH3)

Italic: Linker (optional)

Underlined: human PD-1 ligand 1 (PD-1L) or extracellular binding domain of PD-1L (underlined)

(Note: Optional C to S conversion in IgG sequence (bold underlined))

(Note: The linker QEPKSCDK SEQ ID NO: 110 can be replaced with EPKSCDK SEQ ID NO: 105 or another linker sequence)

Fig. 38

Fusion proteins comprising a sequence of transforming growth factor- β (TGF- β), Immunoglobulin Fc (IgG C β 1), and a sequence of PD-1 ligand (PD-L1)

TGF- β -1 + Fc + PD-L1 (SEQ ID NO: 48):

ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
 QHNPASAAAPCCVPQALEPLPIVYVGRKPKVEQLSNMIVRSCKCS GGGGSGGGSGGGGS
 THTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
 REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFSCSVMEALHNHYTQKSLSLSPGK GGGGSGGGSGGGGS
 RIFAVFIFMTYWHLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVWEMEDKNIIQF
 VHGEEDLKVQHSSYRQARLLKDKQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNA
 YNKINQRLVVDPTSEHELTCAEGYPKAEVIWTSSDHQVLSGKTTTNSKREEKLFNVTSTLRI
 NTTTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPNERTHLVILGAILLCLGVALTFIFRLRKGR
 MMDVKKCGIQDTNSKKQSDTHLEET

Fusion protein comprising a sequence of PD-1 ligand (PD-L1), Immunoglobulin Fc (IgG C γ 1), and a sequence of Transforming growth factor beta (TGF- β)

PD-L1 + Fc + TGF β -1 (SEQ ID NO: 49):

MRIFAVFIFMTYWHLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVWEMEDKNIIQ
 FVHGEEDLKVQHSSYRQARLLKDKQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNA
 PYNKINQRLVVDPTSEHELTCAEGYPKAEVIWTSSDHQVLSGKTTTNSKREEKLFNVTSTLRI
 INTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPNERTHLVILGAILLCLGVALTFIFRLRKGR
 RMDVKKCGIQDTNSKKQSDTHLEET GGGGSGGGSGGGGS
 THTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
 REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFSCSVMEALHNHYTQKSLSLSPGK GGGGSGGGSGGGGS
 ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
 QHNPASAAAPCCVPQALEPLPIVYVGRKPKVEQLSNMIVRSCKCS

Underlined: TGF β -1

Italic: Linker (optional)

Plain: Fc

Bold: human PD-1 ligand 1 or extracellular binding domain of PD-1L (underlined)

(Note: Can replace linker GGGGSGGGSGGGGS SEQ ID NO: 104 with

EPKSCDK SEQ ID NO: 105)

(Note: Can replace underlined aa in Fc: E with D and M with L)

Fig. 39

(i) Transforming growth factor-beta (TGF- β 1, TGF- β 2, or TGF- β 3 or a fragment thereof:

TGF- β 1 full sequence (SEQ ID NO: 102):

1 MPPSGLRLLP LLLPLLRLLV LTPGRFAAGL STCKTIDMEL VKRKRIEAIR GQILSKLRLS
61 SPSPQGEVPP VPLPEAVLAL YNSTRDRVAG ESAEPEPEPE ADYYAKEVTR VLMVENTNKI
121 YEKVKKSPHS IYMLFNTSEL REAVPEPVLL SRAELRLLRL KLKAEQHVEL YQKYSNDSWR
181 YLSNRLLAPS DTPEWLSFDV TGVVRQWLSH GGEVEGFRLS AHCSCDSKDN TLQVDINGFS
241 SSRRGDLATI HGMNRPFLLL MATPLERAQH LHSSRQRRAL DTNYCFSSTE KNCCVRQLYI
301 DFRKDLGWKW IHEPKGYHAN FCLGPCPYIW SLDTQYSKVL ALYNQHNPQA SAAPCCVPQA
361 LEPLPIVYYV GRKPKVEQLS NMIVRSCKCS

Underlined: Mature (active) TGF- β 1 sequence (Ala 279 – Ser 390; 112 aa).

(ii) Mature (active) TGF- β 1 sequence (Ala 279 – Ser 390; 112 aa)

(SEQ ID NO: 103):

AL DTNYCFSSTE KNCCVRQLYI DFRKDLGWKW IHEPKGYHAN FCLGPCPYIW
SLDTQYSKVL ALYNQHNPQA SAAPCCVPQA LEPLPIVYYV GRKPKVEQLS NMIVRSCKCS

Fig. 40

Fusion proteins comprising an antibody that binds TNF- α , and a sequence of transforming growth factor- β (TGF- β).

Anti-TNF α heavy chain + TGF- β 1 (SEQ ID NO: 50):

EVQLVESGGGLVQPGRSRLRLSCAASGFTTFDDYAMHWVRQAPGKGLEWVSAITWNSGHIDYADSV
EG
RFTISRDNAKNSLYLQMNSLRAEDTAVYYCALVSYLSTASSLDYWGGQTLVTVSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLG
TQTYICNVNHKPSNTKVD**KKAE**PKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNNHYTQKSLSLSPGK
GGGGSGGGSGGGGS
ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
QHNPGASAAPCCVPQALEPLPIVYYVGRKPKVEQLSNMIVRSCKCS

Anti-TNF α light chain (SEQ ID NO: 77):

DIQMTQSPSSLSASVGDRVTITCRASQGI RNYLAWYQQLPGKAPKLLIYAAS
TLSQSGVPSRFS
SGSGSGTDFTLTITSSLPEDVATYYCQRYNRAPYTFGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV
VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYSLSSTLTLSKADYEKHKVYACEVTH
QGLSSPVTKSFNRGEC

Underlined: anti-TNF α antibody variable region

Plain: anti-TNF α antibody constant region

Italic: Linker

Bold: Mature (active) human TGF- β 1

(Note: **KKAE** SEQ ID NO: 107 can be replaced with **KRVE** SEQ ID NO: 108 or **KKVE** SEQ ID NO: 109)

Fig. 41

Fusion proteins comprising TNFR2 Extracellular ligand binding domain, Fc, and a sequence from transforming growth factor- β (TGF- β)

TNFR2 ECD + IgG C γ 1 + TGF- β 1 (SEQ ID NO: 51):

LPAQVAFTPYAPEPGSTCRLREYYDQTAQMCCSKCSPGQHAKVFCTKTSDTVCDSCEDSTYTQLWN
WVPECLSCGSRCSDDQVETQACTREQNRICRPGWYCALSKQEGCRLCAPLRKCRPGFGVARPGT
ETSDVVKPCAPGTFSNTTSSTDICRPHQICNVVAIPGNASMDAVCTSTSPTRSMAPGAVHLPQPV
STRSQHTQPTPEPSTAPSTSFLPMGPSPPAEGSTGD *EPKSCDK*
 THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVVSVLTVTLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFSCSVMEALHNHYTQKSLSLSPGK *GGGGSGGGSGGGGS*
 ALDTNYCFSSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
 QHNPAGASAAPCCVPQALEPLPIVYVGRKPKVEQLSNMIVRSCKCS

Fusion proteins comprising a sequence from transforming growth factor- β (TGF- β), Fc, and TNFR2 Extracellular ligand binding domain:

TGF- β 1 + IgG C γ 1 + TNFR2 ECD (SEQ ID NO: 52):

ALDTNYCFSSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
 QHNPAGASAAPCCVPQALEPLPIVYVGRKPKVEQLSNMIVRSCKCS *GGGGSGGGSGGGGS*
 THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHED
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVTLHQDWLNGKEYKCKVSNKALPAPIEKT
 ISKAKGQPREPQVYTLPPS**REEM**TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSD
 GSFFLYSKLTVDKSRWQQGNVFSVMHEALHNHYTQKSLSLSPGK *GGGGSGGGSGGGGS*
LPAQVAFTPYAPEPGSTCRLREYYDQTAQMCCSKCSPGQHAKVFCTKTSDTVCDSCEDSTYTQLWN
WVPECLSCGSRCSDDQVETQACTREQNRICRPGWYCALSKQEGCRLCAPLRKCRPGFGVARPGT
ETSDVVKPCAPGTFSNTTSSTDICRPHQICNVVAIPGNASMDAVCTSTSPTRSMAPGAVHLPQPV
STRSQHTQPTPEPSTAPSTSFLPMGPSPPAEGSTGD

Underlined: TNFR2 ligand-binding domain

Plain: human IgG1 heavy chain constant region (IgG C γ 1 domain = H, CH2, CH3)

Italic: Linker

Bold: Mature (active) human TGF- β 1

(Note: Can replace linker 1 with *GGGGSGGGSGGGGS* SEQ ID NO: 104 or *EPKSCDK* SEQ ID NO: 105)

(Note: Can replace underlined aa in Fc: **E** with D and **M** with L)

Fig. 42

Fusion proteins comprising anti-CD20 antibody and a sequence from transforming growth factor- β (TGF- β)

Anti-CD20 heavy chain + mature TGF β 1 sequence (SEQ ID NO: 53):

QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPCNGDTSYNQKFKG
KATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAGTTVTVSAASTKGPSVFPPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLG
TQTYICNVNHKPSNTKVDKKAEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK
GGGGSGGGSGGGGS
ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
QHNPGASAAPCCVPQALEPLPIVYYVGRKPKVEQLSNMIVRSCKCS

Anti-CD20 light chain sequence (SEQ ID NO: 72):

QIVLSQSPAILASAPGEKVTMTCRASSSVSYIHWFAQKPGSSPKPWIIYATSNLASGVFVRFSGSGS
GTSYSLTISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSTLSSTLTLSKADYEKHKVYACEVTHQ
GLSSPVTKSFNRGEC

Underlined: anti-CD20 antibody variable region

Plain: anti-CD20 antibody constant region

Italic: Linker

Bold: Mature (active) human TGF- β 1

Fig. 43

Fusion proteins comprising anti-CD25 antibody and a sequence from transforming growth factor- β (TGF- β).

Anti-CD25 (Daclizumab) heavy chain and TGF- β 1 (SEQ ID NO: 54):

QVQLVQSGAE VKKPGSSVKV SCKASGYTFT SYRMHWVRQA PGQGLEWIGY INPSTGYTEY
NQKFQDKATI TADESTNTAY MELSSLRSED TAVYYCARGG GVFDYWGQGT LVTVSSASTK
GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS
LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKKVEPKSCD KTHTCP PCA PELLGGPSVF
LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR
VVSVLTVLHQ DWLNGKEYKC KVS NKALPAP IEKTISKAKG QPREPQVYTL PPSRDELTKN
QVSLTCLVKG FYP SDIAVEW ESNGQPENNY K TPPVLDSG GSFFLYSKLT VDKSRWQQGN
VFSCSV MHEA LHNHYTQKSL SLSPGK **GGGSGGGSGGGGS** **ALDTNYCFSS**TEKNCCVRQLY
IDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYNQHNP GASAAPCCVPQALEPLP
IVYYVGRKPKVEQLSNMIVRSCKCS

Anti-CD25 (Daclizumab) light chain (SEQ ID NO: 75):

DIQMTQSPST LSASVGDRVT ITCSASSSIS YMHWYQQKPG KAPKLLIYTT SNLASGVPAR
FSGSGSGTEF TLTISSLQPD DFATYYCHQR STYPLTFGQG TKVEVKRTVA APSVFIFPPS
DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSSLTTL
SKADYEKHKV YACEVTHQGL SSPVTKSFNR GEC

Plain: anti-CD25 antibody

Italic: Linker

Bold: Mature (active) human TGF- β 1

Fig. 44A

Anti-CD25 (Basiliximab) heavy chain and TGF- β 1 (SEQ ID NO: 55):

QLQQSGTVLA RPGASVKMSC KASGYSFTRY WMHWIKQRPG QGLEWIGAIY PGNSDTSYNQ
KFEGKAKLTA VTSASTAYME LSSLTHEDSA VYYCSRDIYGY YDFWQCGTT LTVSSASTKG
PSVFPLAPSS KSTSGGTAAL GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL
SSVVTVPSSS LGTQTYICNV NHKPSNTKVD KRVEPKSCDK THTCPPCPAP ELLGGPSVFL
FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV
VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLT PSRDELTKNQ
VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV
FSCSVMEAL HNHYTQKSLS LSPGK GGGGSGGGGSGGGGS
ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHAN
FCLGPCPYIWSLDTQYSKVLALYNQHNPGASAAPCCVPQALEPLPIVYVGRKPKVEQ
LSNMIVRSCKCS

Anti-CD25 (Basiliximab) light chain (SEQ ID NO: 76):

QIVSTQSPAI MSASPGEKVT MTCSASSRS YMOWYQQKPG TSPKRWIYDT SKLASGVPAR
FSGSGSGTSY SLTISSMEAE DAATYYCHQR SSYTFGGGTK LEIKRTVAAP SVFIFPPSDE
QLKSGTASVV CLLNFPYPRE AKVQWKVDNA LQSGNSQESV TEQDSKIDSTY SLSTLTLSK
ADYEKHKVYA CEVTHQGLSS PVTKSFNRGEC

Plain: anti-CD25 antibody

Italic: Linker

Bold: Mature (active) human TGF- β 1

Fig. 44B

Fusion proteins comprising IL-2, Fc, and a sequence from transforming growth factor- β (TGF- β).

TGF- β 1 + Fc + IL-2 (SEQ ID NO: 56):

ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
 QHNPGASAAPCCVPQALEPLPIVYYVGRKPKVEQLSNMIVRSCKCS *GGGSGGGSGGGGS*
 THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
 REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFSCSVMEALHNHYTQKSLSLSPGK *GGGSGGGSGGGGS*
APTSSSTKKTQLQLEHLLLDLQMLNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPL
EEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTL
T

IL-2 + Fc + TGF- β 1 (SEQ ID NO: 57):

APTSSSTKKTQLQLEHLLLDLQMLNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPL
EEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTL
T *GGGSGGGSGGGGS*
 THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
 REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFSCSVMEALHNHYTQKSLSLSPGK *GGGSGGGSGGGGS*
 ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
 QHNPGASAAPCCVPQALEPLPIVYYVGRKPKVEQLSNMIVRSCKCS

Underlined: IL-2 fragment

Italic: Linker (optional)

Plain: Fc

Bold: Mature (active) human TGF- β 1

(Note: Can replace linker 1 *GGGSGGGSGGGGS* SEQ ID NO: 104 with

EPKCDK SEQ ID NO: 105)

(Note: Can replace underlined aa in Fc: E with D and M with L)

Fig. 45

Fusion protein comprising anti-CD4 antibody and a sequence from transforming growth factor- β (TGF- β).

Anti-CD4 heavy chain and TGF- β 1 (SEQ ID NO: 58)

Heavy chain fusion protein:

QVQLQEAGPGLVKPSETLSLTCSVSGGSISGDYYWFWIRQSPGKGLEWIGYIYGSGGGTNYNPSLN
NRVSI SIDTSKNLFSLKLRSVTAADTAVYYCASNILKYLHWLLYWGQGVLT VSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLG
TQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK
GGGSGGGSGGGGS
ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
QHNPGASAAPCCVPQALEPLPIVYYVGRKPKVEQLSNMIVRSCKCS

Anti-CD4 light chain (SEQ ID NO: 77)

Light chain:

SYELSQPRSVSVSPGQTAGFTCGGDNVGRKSVQWYQQKPPQAPVLVIYADSERPSGIPARFSGSNS
GNTATLTISGVEAGDEADYYCQVWDSTADHWVFVGGGTRLTLVLRGRTVAAPSVFI FPPSDEQLKSGTA
SVVCLLN NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYSLSSTLTLSKADYEKHKVYACEV
THQGLSSPVTKSFNRGEC

Underlined: Anti-CD4 antibody variable region

Plain: Anti-CD4 antibody constant region

Italic: Linker

Bold: Mature (active) human TGF- β 1

Fig. 46

Fusion proteins comprising the extracellular domain of CTLA-4, Immunoglobulin Fc (IgG C γ 1), and a sequence from a sequence from transforming growth factor- β (TGF- β)

Oncostatin M signal peptide + CTLA-4 ECD + IgG C γ 1 + TGF- β 1 (SEQ ID NO: 59):

MGVLLTQRTLLSLVLALLFPSMASMAMHVAQPAVVLASSRGIASFVCEYASPGKATEVRVTVLRQA
DSQVTEVCAATYMMGNELTFLDDSICTGTSSGNQVNLTIQGLRAMDTGLYICKVELMYPPPYLGI
GNGTQIYVIDPEPCPDSDQEPKSCDK THTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN
GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCVMHEALHNHYTQKSLSLSPGK
GGGGSGGGSGGGGS
ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
QHNPGASAAPCCVPQALEPLPIVYVGRKPKVEQLSNMIVRSCKCS

Fusion proteins comprising a sequence from transforming growth factor- β (TGF- β), Immunoglobulin Fc (IgG C γ 1), and a sequence from the extracellular domain of CTLA-4

TGF- β 1 + IgG C γ 1 + CTLA-4 ECD (SEQ ID NO: 60):

ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
QHNPGASAAPCCVPQALEPLPIVYVGRKPKVEQLSNMIVRSCKCS EPKSCDK
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
RDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCVMHEALHNHYTQKSLSLSPGK GGGGSGGGSGGGGS
AMHVAQPAVVLASSRGIASFVCEYASPGKATEVRVTVLRQADSQVTEVCAATYMMGNELTFLDDSI
CTGTSSGNQVNLTIQGLRAMDTGLYICKVELMYPPPYLGIGNGTQIYVIDPEPCPDS

Underlined Italic: Oncostatin M Signal Peptide (-25 to -1)

Underlined: CTLA-4 extracellular domain (1-125)

Plain: human IgG1 heavy chain constant region (IgG C γ 1 domain = H, CH2, CH3)

Italic: Linker (optional)

Bold: Mature (active) human TGF- β 1

(Note: Optional C to S conversion in IgG sequence (bold underlined))

(Note: The linker QEPKSCDK SEQ ID NO: 110 can be replaced with EPKSCDK SEQ ID NO: 105 or another linker sequence)

Fig. 47

Fusion proteins comprising an antibody that binds TNF- α , and a RANKL-binding sequence of receptor activator of nuclear factor-kB (RANK)

Anti-TNF α heavy chain + RANK ectodomain (SEQ ID NO: 61):

EVQLVESGGGLVQPGKSLRLSCAASGFTFDDYAMHWVRQAPGKLEWVSAITWNSGHIDYADSV
EG
RFTISRDNAKNSLYLQMNSLRAEDTAVYYCALVSYLSTASSLDYWGQGT
LVTVSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTV
TPSSSLG
TQTYICNVNHKPSNTKVD**KKAE**PKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

GGGGSGGGSGGGGS QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP
CGPDEYLD SW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RACTAGYHW SQDCECCRRN
TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS
DAVCSSSLPA RKPPNEPHVY LPG

Anti-TNF α light chain (SEQ ID NO: 78):

DIQMTQSPSSLSASVGDRVTITCRASQGIRNYLAWYQQLPGPAPKLLIYAASTLQSGVPSRFSGSG
SGTDFTLTISSLPEDVATYYCQRYNRPYTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV
VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKVYACEVTH
QGLSSPVTKSFNRGEC

Underlined: anti-TNF α antibody variable region

Plain: anti-TNF α antibody constant region

Italic: Linker

Bold: RANK ectodomain

(Note: **KKAE** SEQ ID NO: 107 can be replaced with **KRVE** SEQ ID NO: 108 or **KKVE** SEQ ID NO: 109)

Fig. 48

Fusion proteins comprising TNFR2 Extracellular ligand binding domain, Fc, and a RANKL-binding sequence of receptor activator of nuclear factor- κ B (RANK)
TNFR2 ECD + IgG C γ 1 + RANK ectodomain (SEQ ID NO: 62):

LPAQVAFTPYAPEPGSTCRLREYYDQTAQMCCSKCSPGQHAQVFCTKTSDTVCDSCEDSTYTQLWN
WVPECLSCGSRCSDDQVETQACTREQNRICTRPGWYCALSKQEGCRLCAPLRKCRPGFGVARPGT
ETSDVVCKPCAPGTFSTNTSSTDI CRPHQICNVVAIPGNASMDAVCTSTSPTRSMAPGAVHLPQPV
STRSQHTQPTPEPSTAPSTSFLLPMGPPPAEGSTGD *EPKSCDK*
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHREALHNHYTQKSLSLSPGK *GGGSGGGSGGGSGGGS* QI APPCTSEKHY
EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP CGPDEYLDW NEEDKCLLHK VCDTGKALVA
VVAGNSTTPR RCACTAGYHW SQDCECCRRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS
DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG

Fusion proteins comprising a RANKL-binding sequence of receptor activator of nuclear factor- κ B (RANK), Fc, and TNFR2 Extracellular ligand binding domain:

RANK ectodomain + IgG C γ 1 + TNFR2 ECD (SEQ ID NO: 63):

QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP CGPDEYLDW
NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RCACTAGYHW SQDCECCRRN TECAPGLGAQ
HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA
RKPPNEPHVY LPG
GGGSGGGSGGGSGGGS THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT
ISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
GSFFLYSKLTVDKSRWQQGNVFSQSVMHREALHNHYTQKSLSLSPGK *GGGSGGGSGGGSGGGS*
LPAQVAFTPYAPEPGSTCRLREYYDQTAQMCCSKCSPGQHAQVFCTKTSDTVCDSCEDSTYTQLWN
WVPECLSCGSRCSDDQVETQACTREQNRICTRPGWYCALSKQEGCRLCAPLRKCRPGFGVARPGT
ETSDVVCKPCAPGTFSTNTSSTDI CRPHQICNVVAIPGNASMDAVCTSTSPTRSMAPGAVHLPQPV
STRSQHTQPTPEPSTAPSTSFLLPMGPPPAEGSTGD

Underlined: TNFR2 ligand-binding domain

Plain: human IgG1 heavy chain constant region (IgG C γ 1 domain = H, CH2, CH3)

Italic: Linker

Bold: RANK ectodomain

(Note: Can replace linker 1 with *GGGSGGGSGGGSGGGS* SEQ ID NO: 104 or *EPKSCDK* SEQ ID NO: 105)

(Note: Can replace underlined aa in Fc: E with D and M with L)

Fig. 49

Fusion proteins comprising the extracellular domain of CTLA-4, Immunoglobulin Fc (IgG C γ 1), and a RANKL-binding sequence of receptor activator of nuclear factor- κ B (RANK)

Oncostatin M signal peptide + CTLA-4 ECD + IgG C γ 1 + RANK ectodomain (SEQ ID NO: 64):

MGVLLTQRTLLSLVLALLFPSMASMAMHVAQPAVVLASSRGIASFVCEYASPGKATEVRVTVLRQA
DSQVTEVCAATYMMGNELTFLLDDSICTGTSSGNQVNLTIQGLRAMDTGLYICKVELMYPPPYYLGIG
NGTQIYVIDPEPCPDSDQEPKSCDK THTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNATKPREEQYNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN
GQPENNYKTTPPVLSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGGSGGGGSGGGG QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP
CGPDEYLDSW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RCACTAGYHW SQDCECCRRN
TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS
DAVCSSSLPA RKPPNEPHVY LPG

Fusion proteins comprising a RANKL-binding sequence of receptor activator of nuclear factor- κ B (RANK), Immunoglobulin Fc (IgG C γ 1), and a sequence from the extracellular domain of CTLA-4

RANK ectodomain + IgG C γ 1 + CTLA-4 ECD (SEQ ID NO: 65):

QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP CGPDEYLDSW
NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RCACTAGYHW SQDCECCRRN TECAPGLGAQ
HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA
RKPPNEPHVY LPG EPKSCDK
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGEYKCKVSNKALPAPIEKTISKAGQPREPQVYTLPPS
RDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLSDGSFFLYSKLTVDKSRWQQ
NVFSCSVMHEALHNHYTQKSLSLSPGK GGGGSGGGGSGGGGSGGGG
AMHVAQPAVVLASSRGIASFVCEYASPGKATEVRVTVLRQADSQVTEVCATYMMGNELTFLDDSI
CTGTSSGNQVNLTIQGLRAMDTGLYICKVELMYPPPYLGIGNGTQIYVIDPEPCPDSD

Underlined Italic: Oncostatin M Signal Peptide (-25 to -1)

Underlined: CTLA-4 extracellular domain (1-125)

Plain: human IgG1 heavy chain constant region (IgG C γ 1 domain = H, CH2, CH3)

Italic: Linker (optional)

Bold: RANK ectodomain

(Note: Optional C to S conversion in IgG sequence (bold underlined))

(Note: The linker *QEPKSCDK* SEQ ID NO: 110 can be replaced with *EPKSCDK* SEQ ID NO: 105 or another linker sequence)

Fig. 50

Fusion proteins comprising a RANKL-binding sequence of receptor activator of nuclear factor- κ B (RANK), Fc, and a sequence from transforming growth factor- β (TGF- β).

TGF- β 1 + Fc + RANK ectodomain (SEQ ID NO: 66):

ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
QHNPGASAAAPCCVPQALEPLPIVYYVGRKPKVEQLSNMIVRSCKCS GGGGSGGGSGGGGS
 THTCPFCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
 REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFSCSVMEALHNHYTQKSLSLSPGK GGGGSGGGSGGGGS QI APPCTSEKHY
 EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP CGPDEYLDW NEEDKCLLHK VCDTGKALVA
 VVAGNSTTPR RCTAGYHW SQDCECCRN TECAPGLAQ HPLQLNKDTV CKPCLAGYFS
 DAFSSDKCR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG

RANK ectodomain + Fc + TGF- β 1 (SEQ ID NO: 67):

QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP CGPDEYLDW
 NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RCTAGYHW SQDCECCRN TECAPGLAQ
 HPLQLNKDTV CKPCLAGYFS DAFSSDKCR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA
 RKPPNEPHVY LPG GGGGSGGGSGGGGS
 THTCPFCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
 REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFSCSVMEALHNHYTQKSLSLSPGK GGGGSGGGSGGGGS
ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
QHNPGASAAAPCCVPQALEPLPIVYYVGRKPKVEQLSNMIVRSCKCS

Underlined: Mature (active) human TGF- β 1

Italic: Linker (optional)

Plain: Fc

Bold: RANK ectodomain

(Note: Can replace linker 1 GGGGSGGGSGGGGS SEQ ID NO: 104 with

EPKSCDK SEQ ID NO: 105)

(Note: Can replace underlined aa in Fc: E with D and M with L)

Fig. 51

Fusion proteins comprising a RANKL-binding sequence of receptor activator of nuclear factor-κB (RANK), Fc, and a sequence from PD-1 ligand 1

PD-1L1 + Fc + RANK ectodomain (SEQ ID NO: 68):

RIFAVFIFMTYWHLLNAFTVTVPKDLVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIQFVHGEEED
LKVQHSSYRQRARLLKDLQSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRILVVD
PVTSEHELTCAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLRINTTTNEIFYCTFRRLDPE
ENHTAELVIPELPLAHPNERTHLVILGAILLCLGVALTFIFRLRKGRMDVKKCGIQDTNSKKQSDTHLEE
 T GGGGSGGGSGGGGS
 THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE
 QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR**E**MTKNQVSLT
 CLVKGFPYSPDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVMEALHNHYTQ
 KSLSLSPGK GGGGSGGGSGGGGS QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP
CGPDEYLDSW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RACTAGYHW SQDCECCRRN
TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDCKR PWTNCTFLGK RVEHHGTEKS
DAVCSSSLPA RKPPNEPHVY LPG

RANK ectodomain + Fc + PD-1L1 (SEQ ID NO: 69):

QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP CGPDEYLDSW NEEDKCLLHK
VCDTGKALVA VVAGNSTTPR RACTAGYHW SQDCECCRRN TECAPGLGAQ HPLQLNKDTV
CKPCLAGYFS DAFSSTDCKR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG
 GGGGSGGGSGGGGS
 THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE
 QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR**E**MTKNQVSLT
 CLVKGFPYSPDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVMEALHNHYTQ
 KSLSLSPGK GGGGSGGGSGGGGS
RIFAVFIFMTYWHLLNAFTVTVPKDLVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIQFVHGEEED
LKVQHSSYRQRARLLKDLQSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRILVVD
PVTSEHELTCAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLRINTTTNEIFYCTFRRLDPE
ENHTAELVIPELPLAHPNERTHLVILGAILLCLGVALTFIFRLRKGRMDVKKCGIQDTNSKKQSDTHLEE
 T

Bold: PD-1L1 (May use PD-1L1 extracellular domain – underlined)

Italic: Linker (optional)

Plain: Fc

Underlined: RANK ectodomain

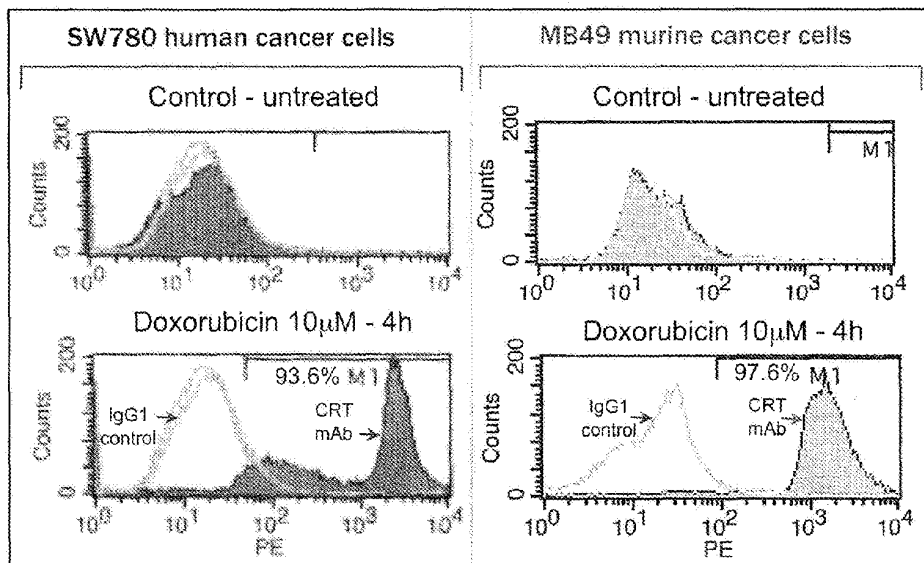
(Note: Can replace linker 1 GGGGSGGGSGGGGS SEQ ID NO: 104 with

EPKSCDK SEQ ID NO: 105)

(Note: Can replace underlined aa in Fc: E with D and M with L)

Fig. 52

A



B

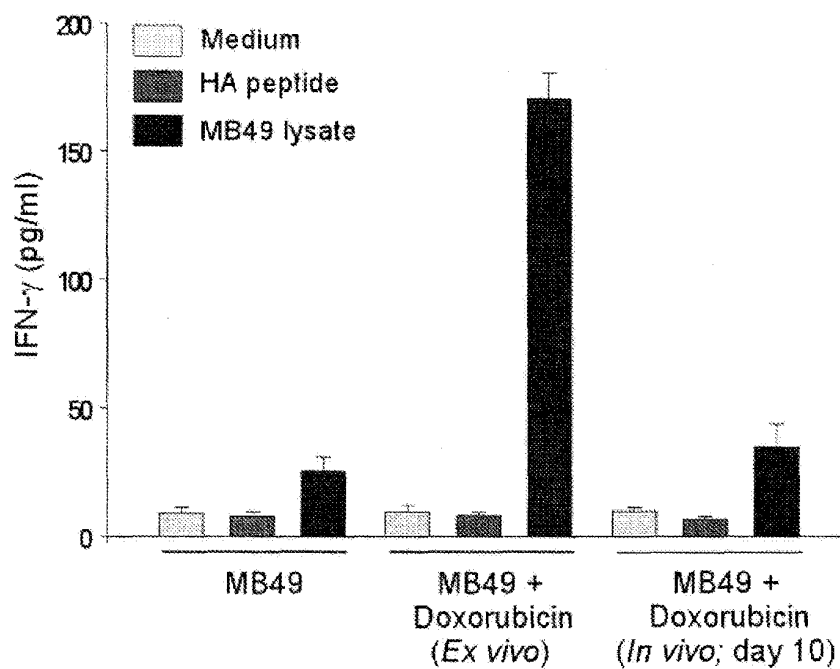
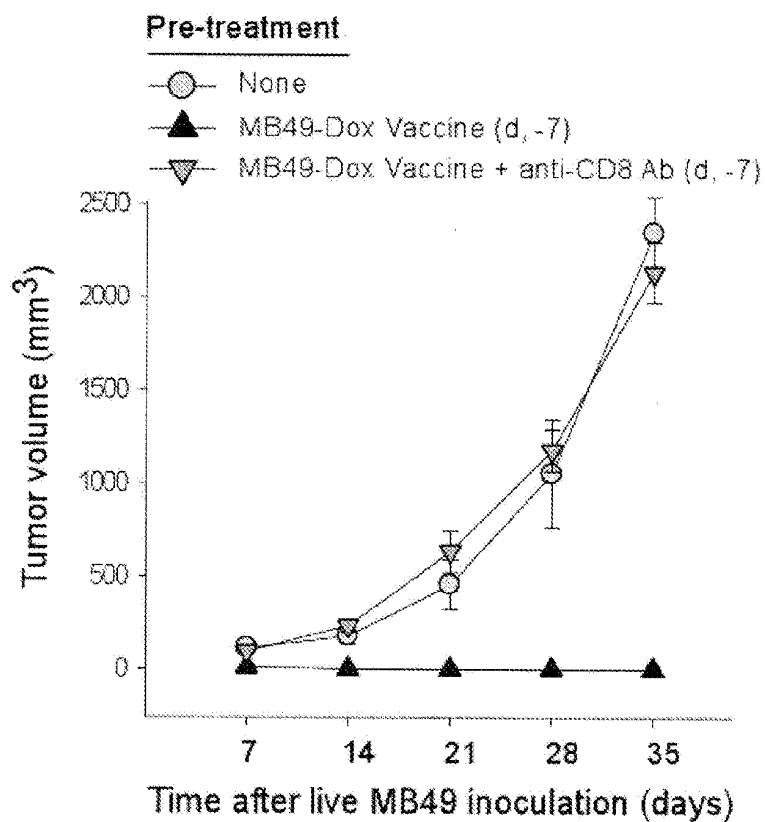


Fig. 53 A & B

C



D

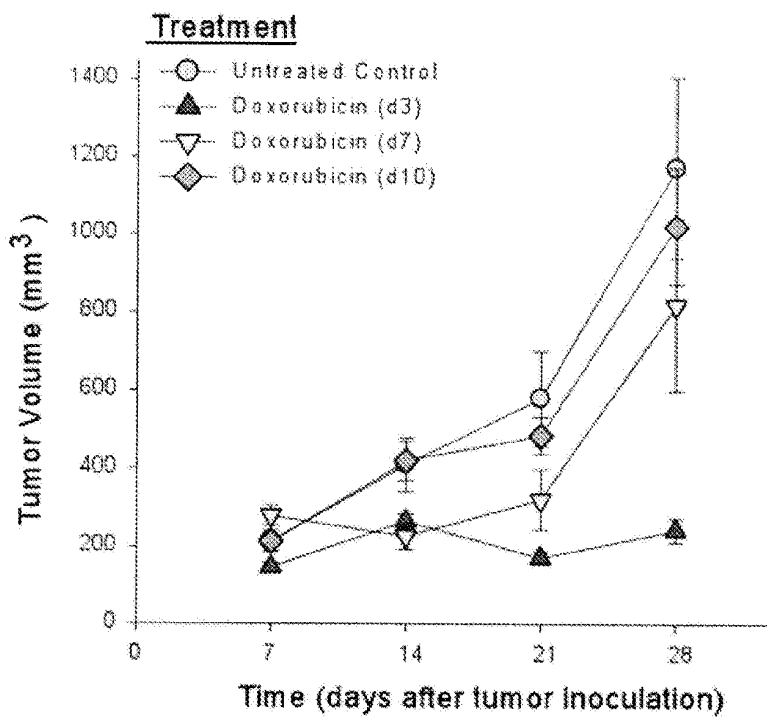
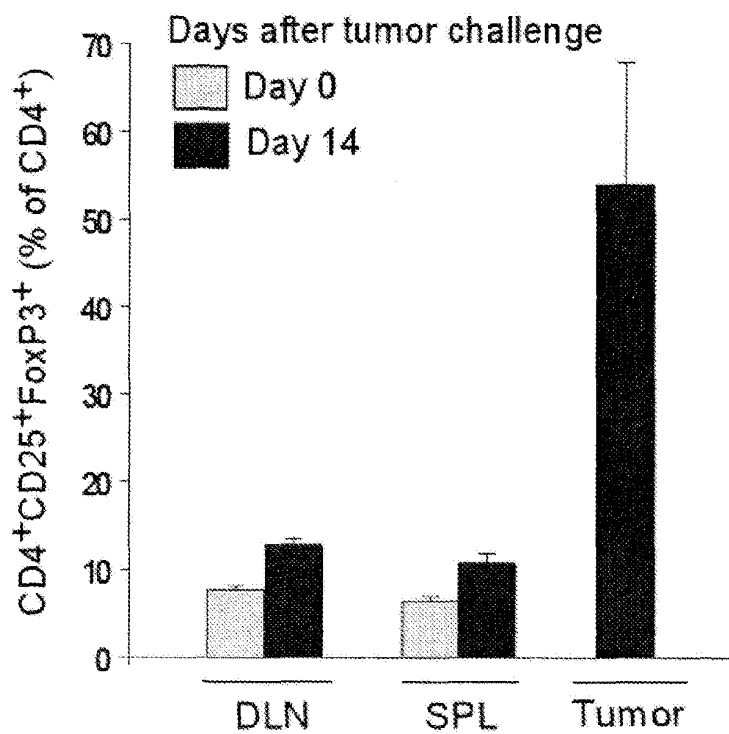


Fig. 53 C & D

E



F

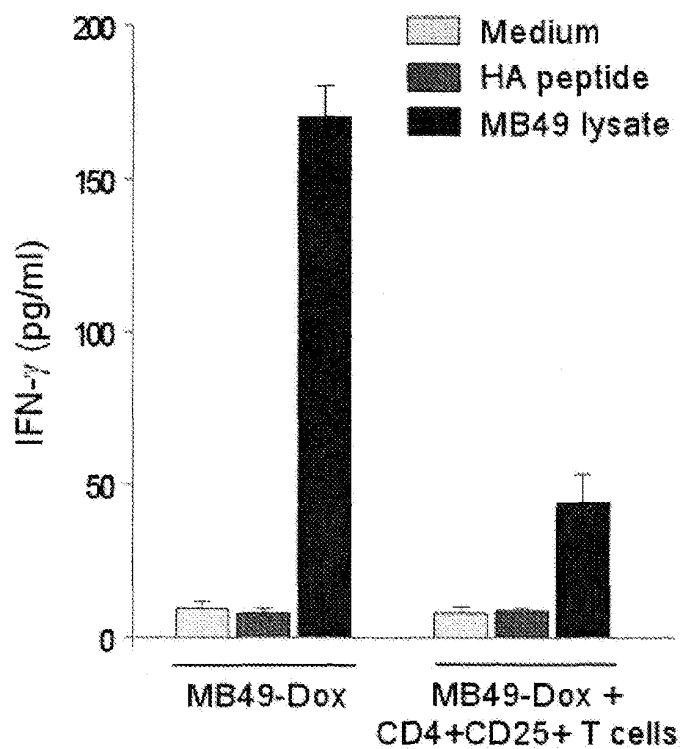


Fig. 53 E & F

G

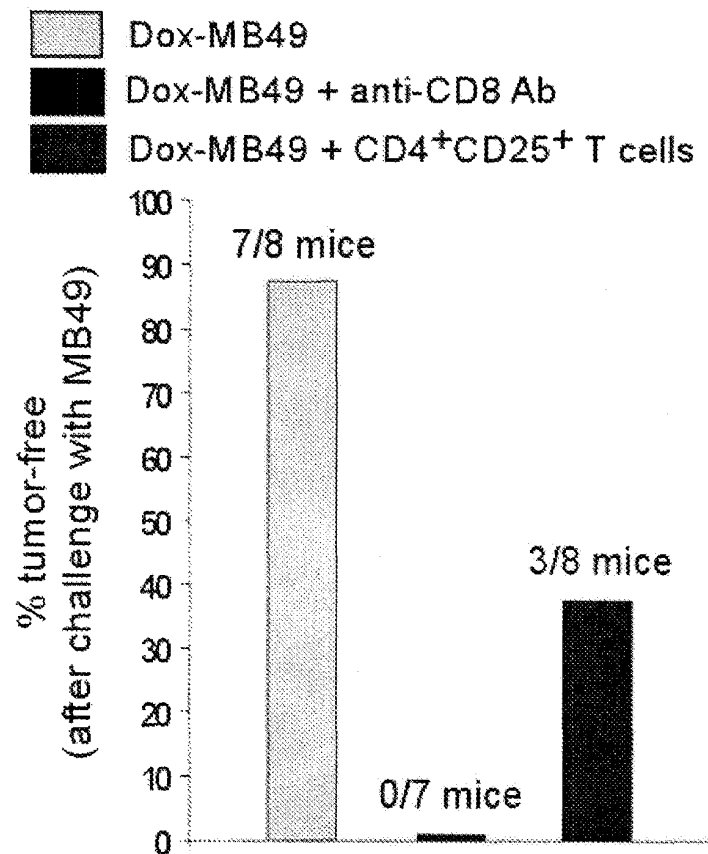


Fig. 53G

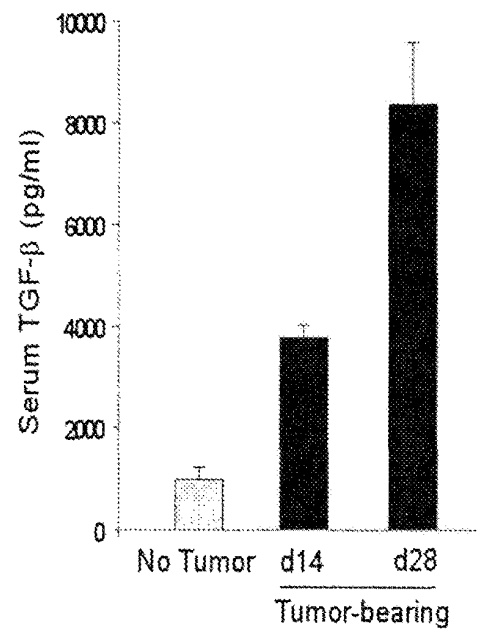
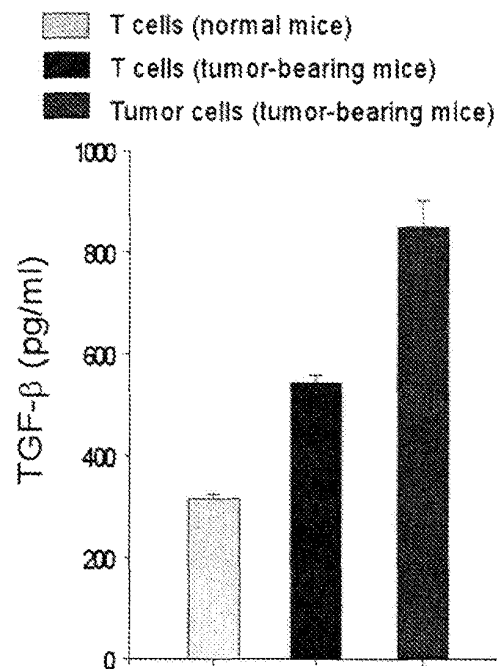
A**B**

Fig. 54 A & B

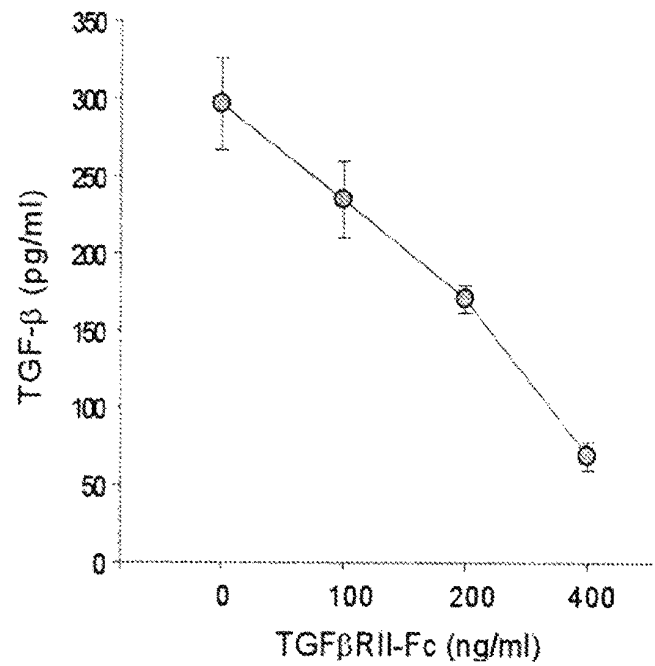
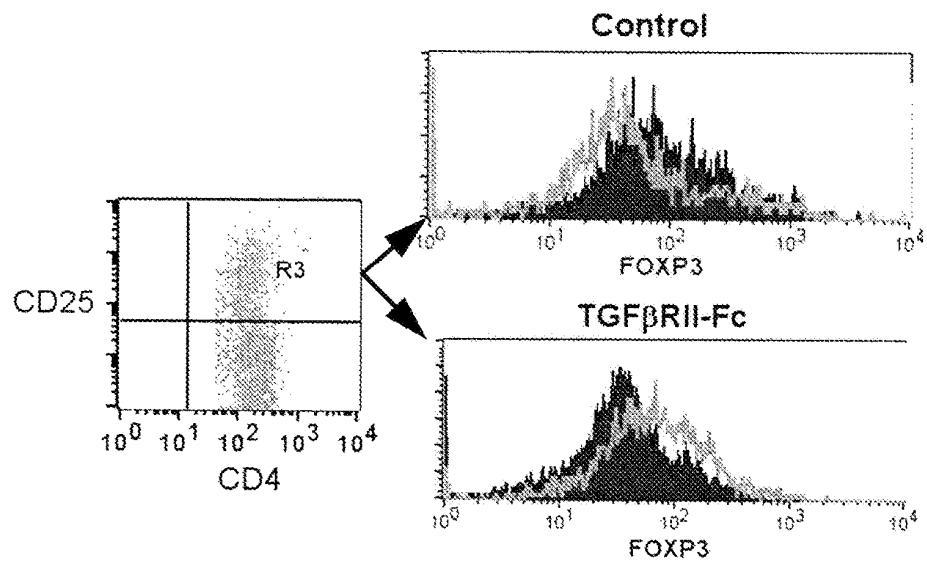
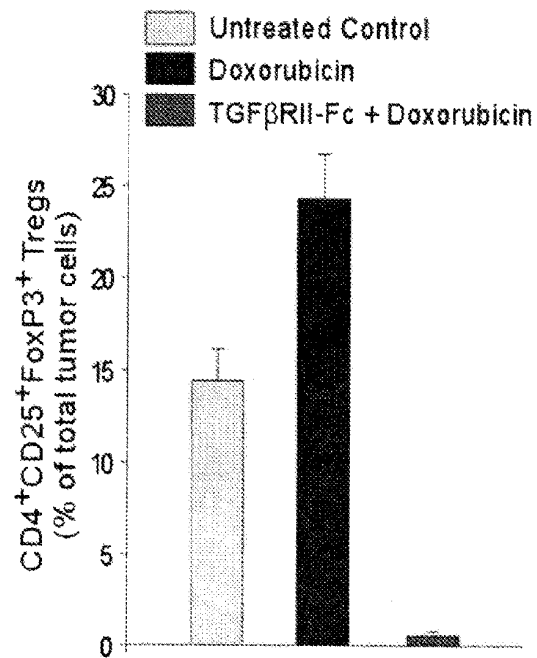
C**D**

Fig. 54 C & D

E



F

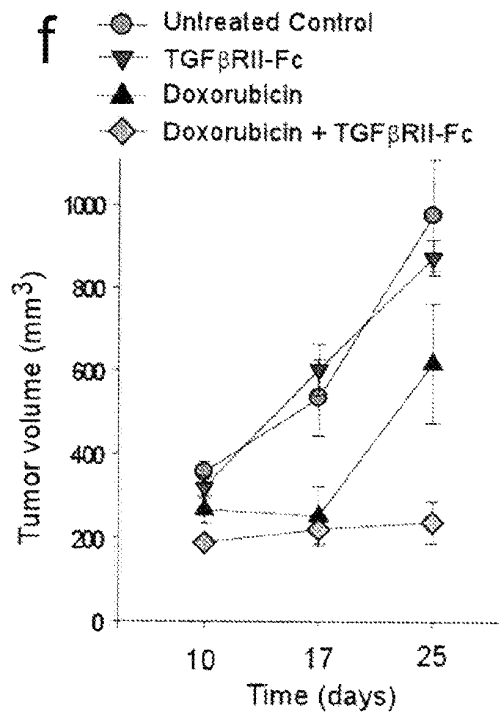


Fig. 54 E & F

A

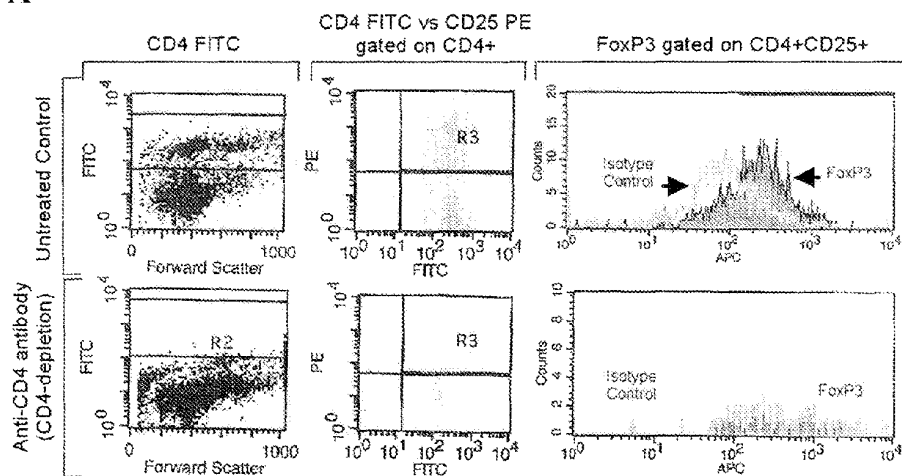
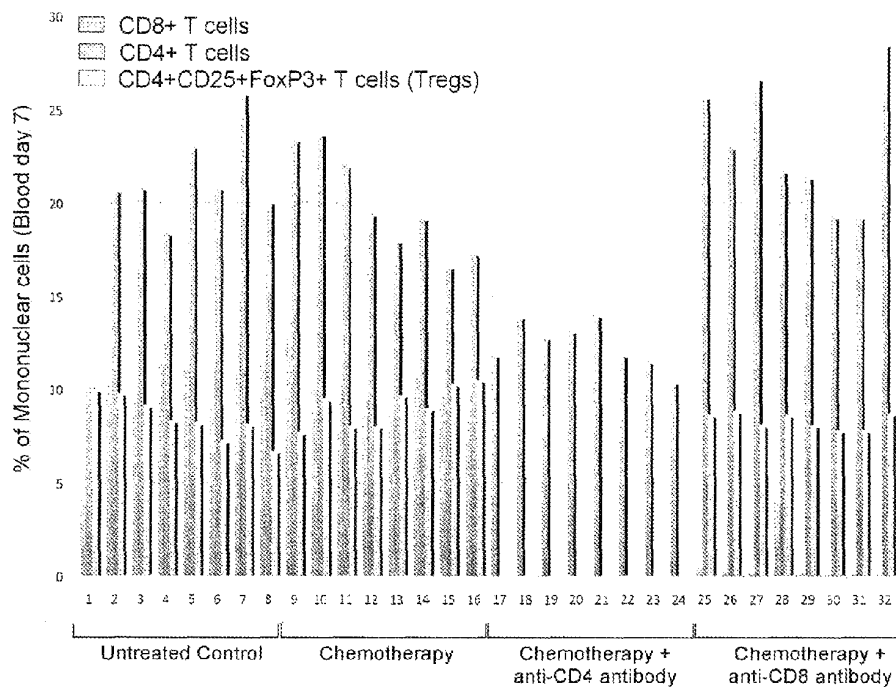
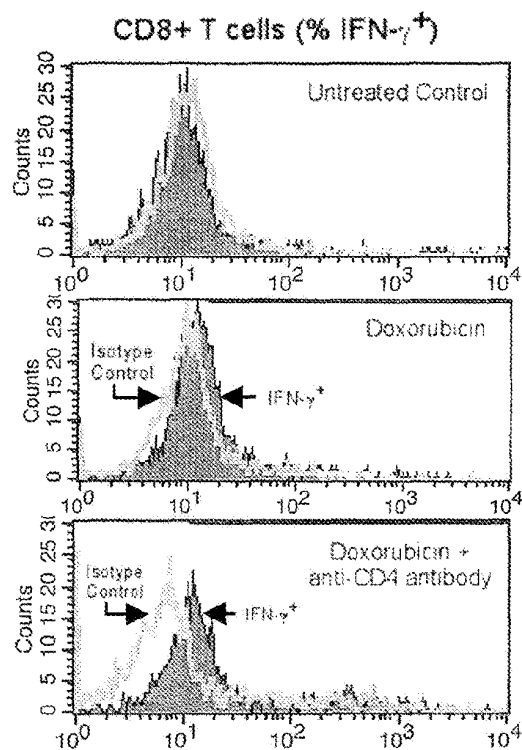
**B**

Fig. 55 A & B

C



D

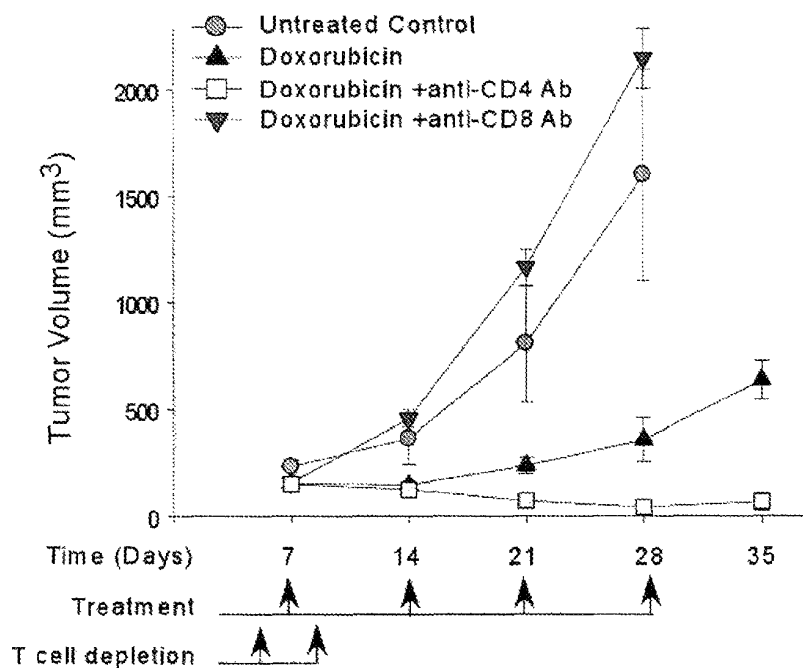
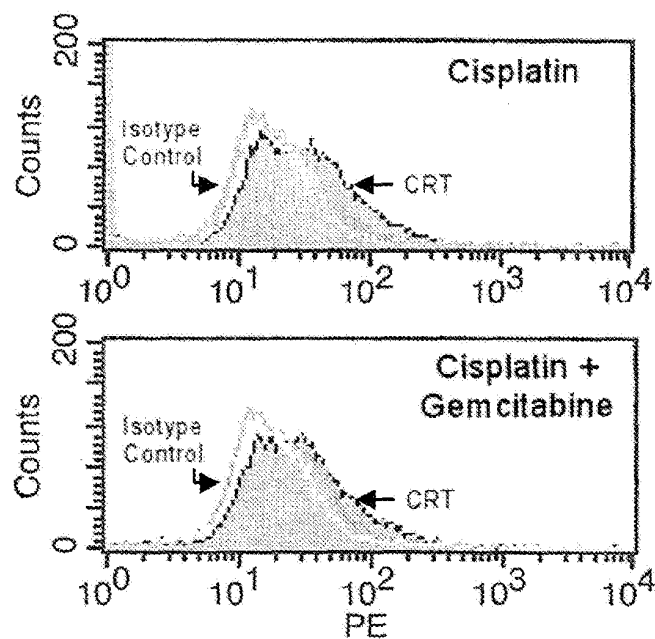


Fig. 55 C & D

A



B

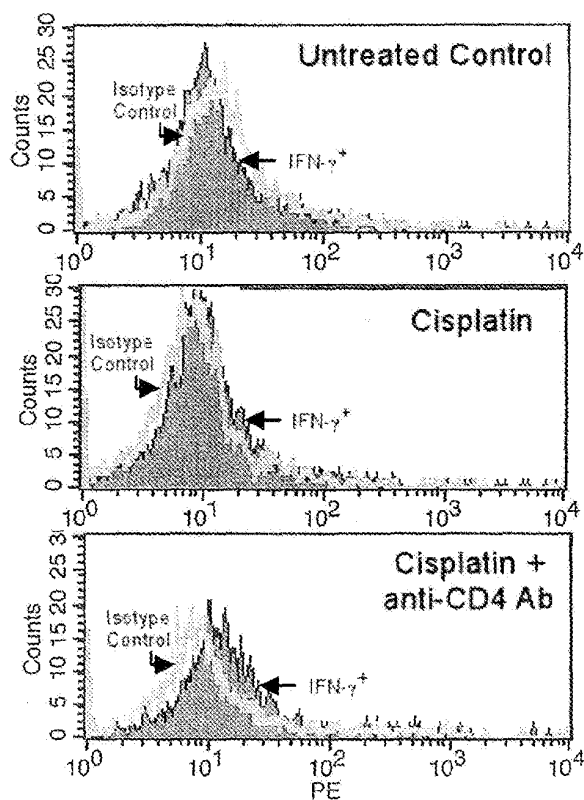


Fig. 56 A & B

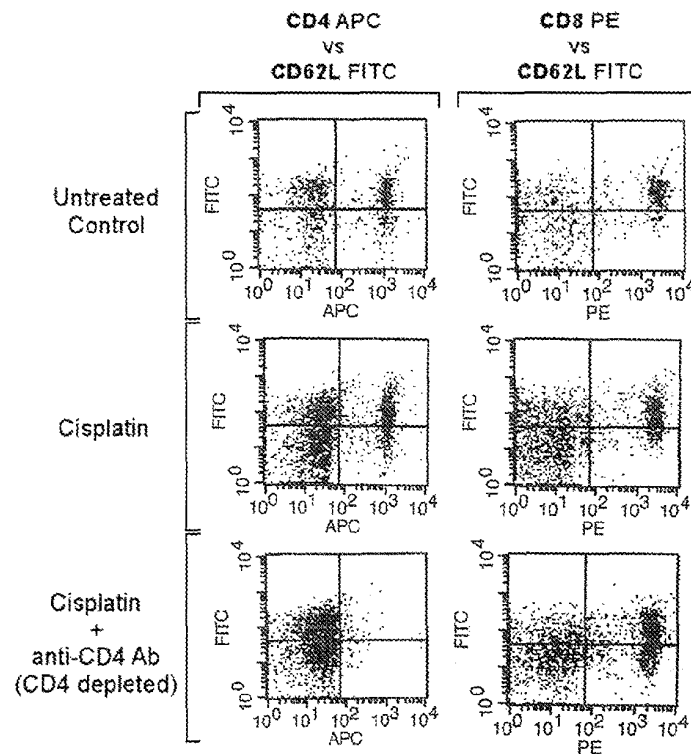
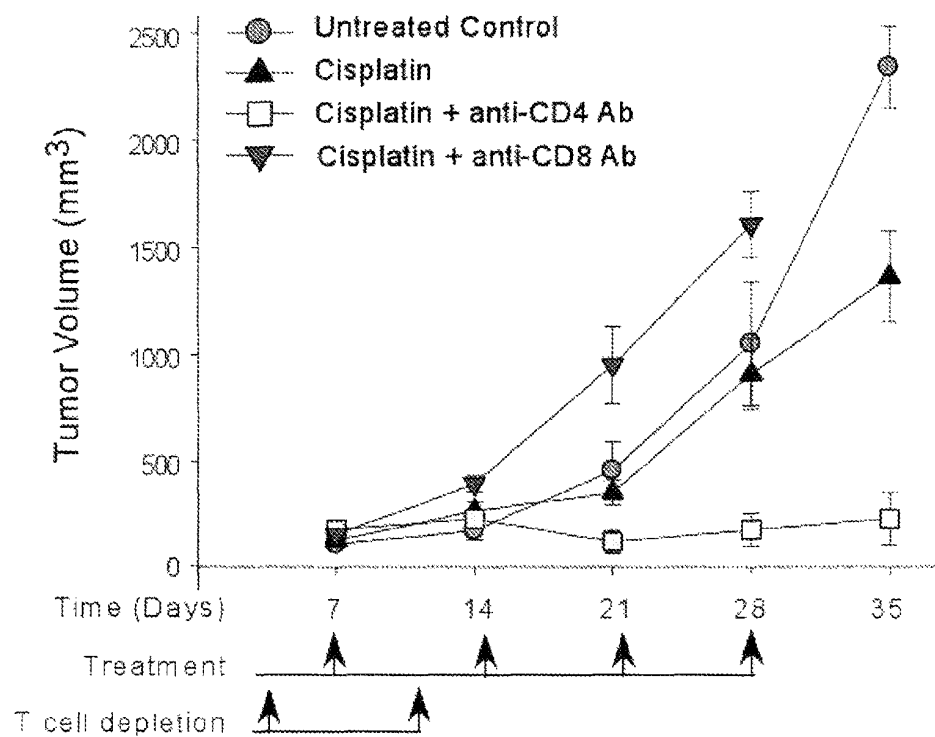
C**D**

Fig. 56 C & D

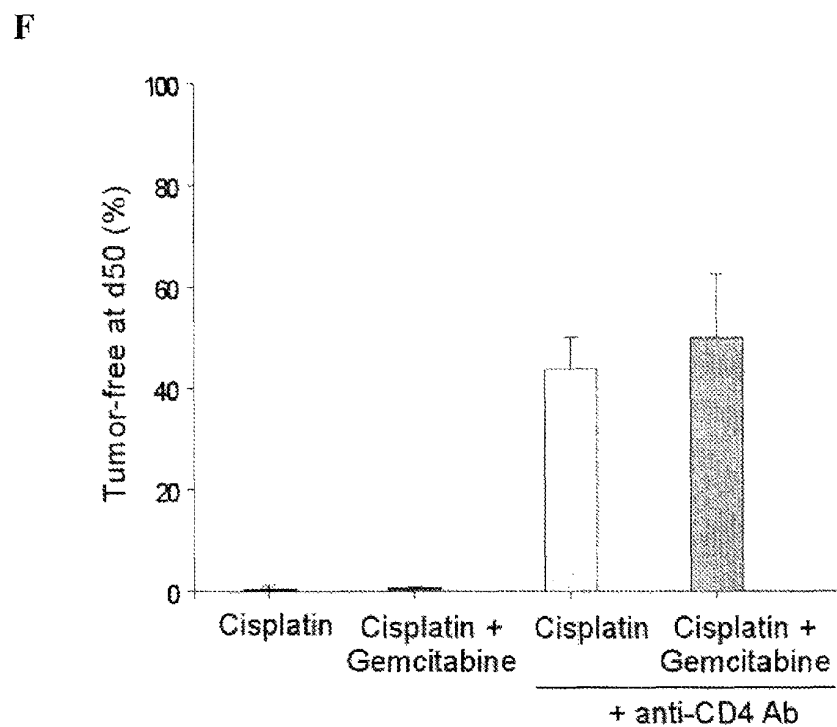
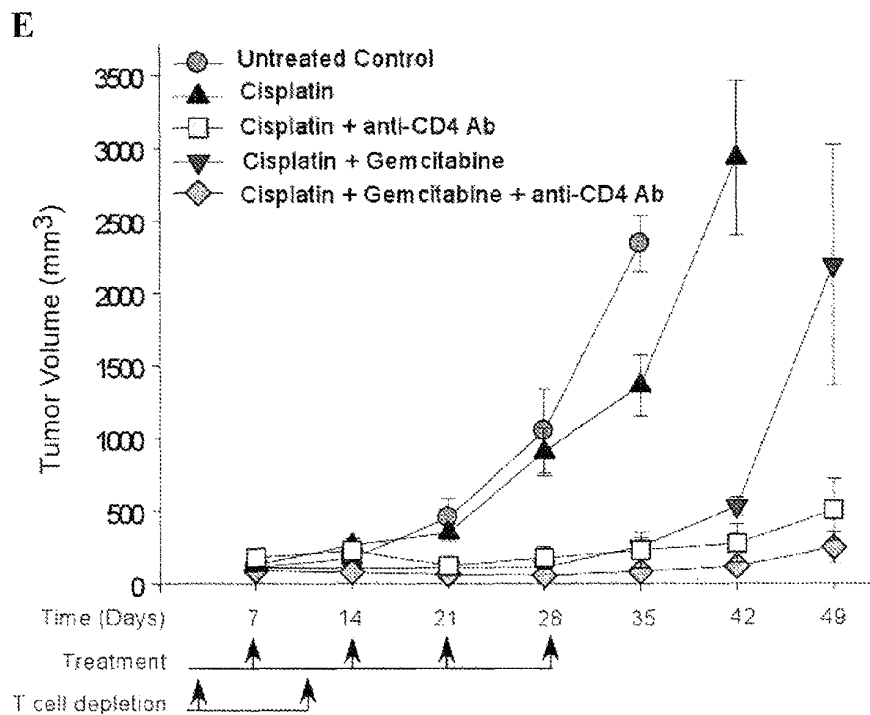
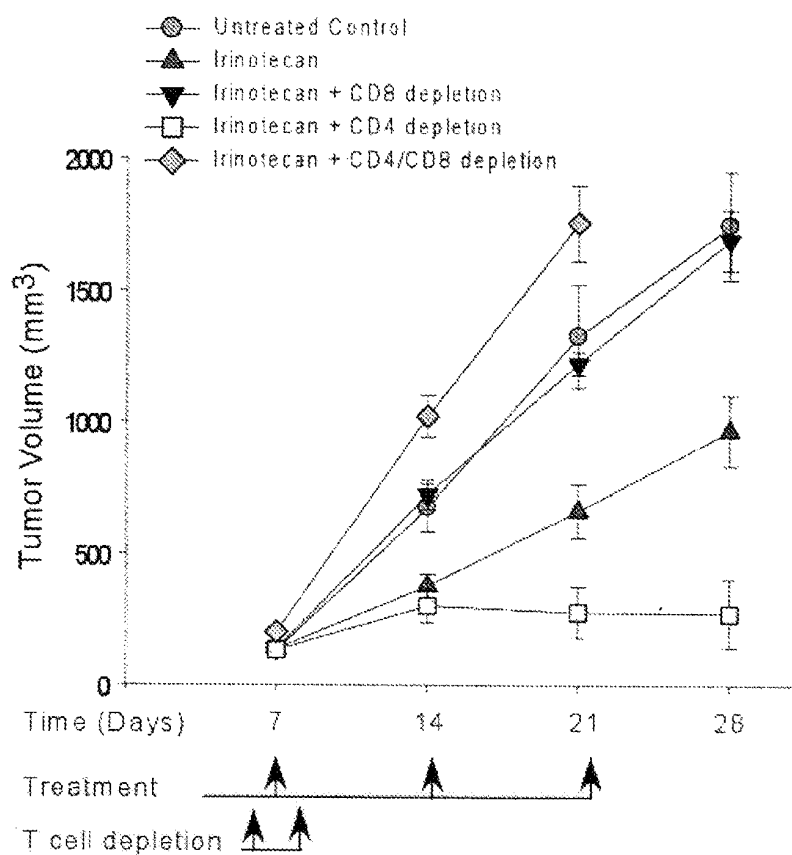


Fig. 56 E & F

A



B

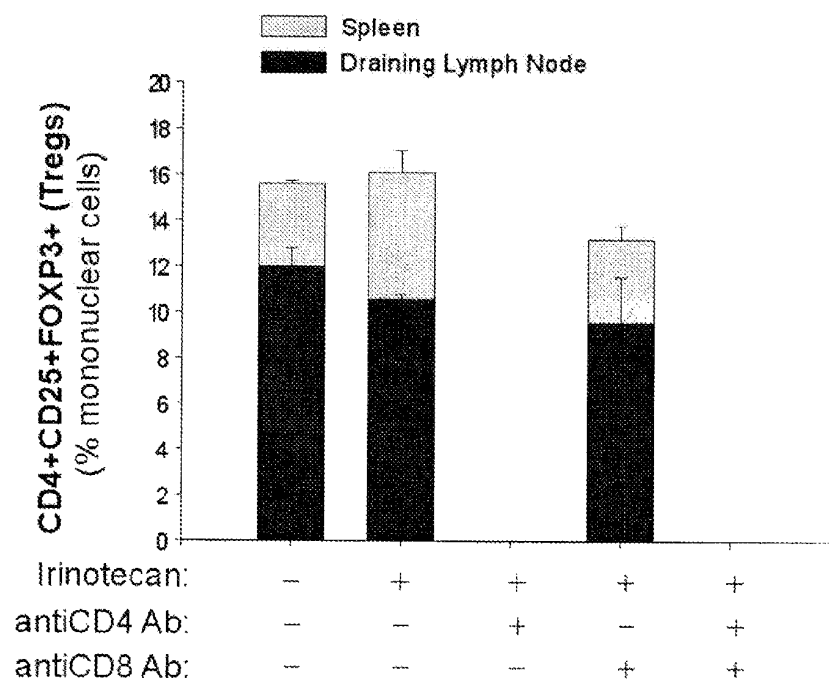


Fig. 57 A & B

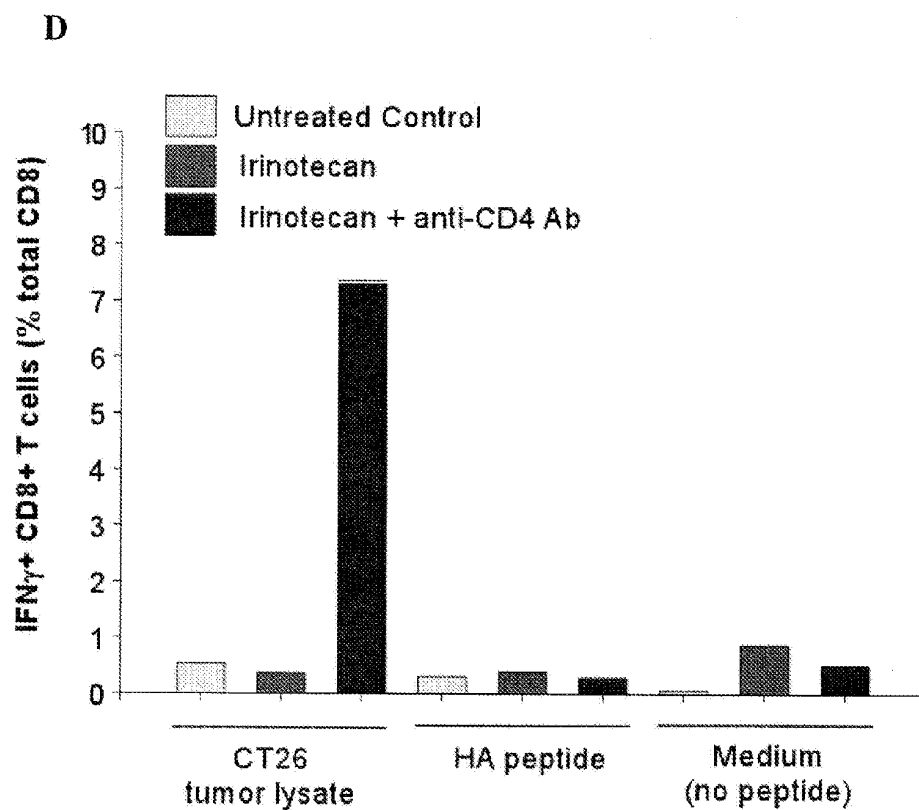
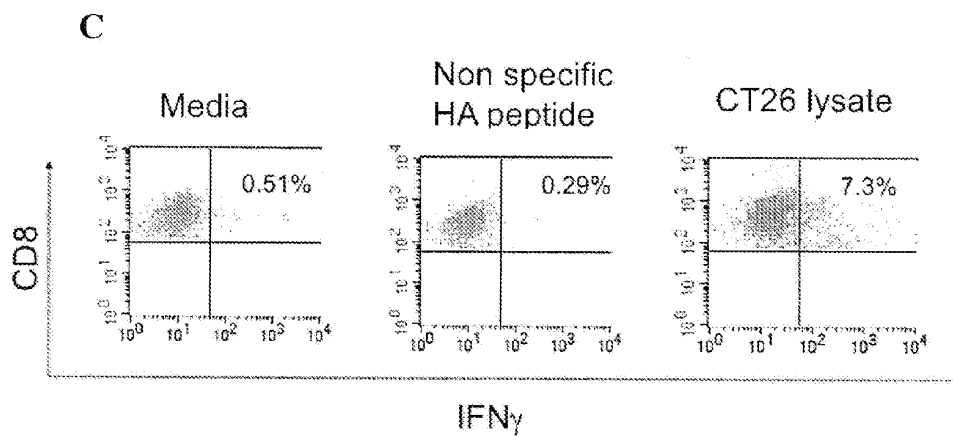


Fig. 57 C & D

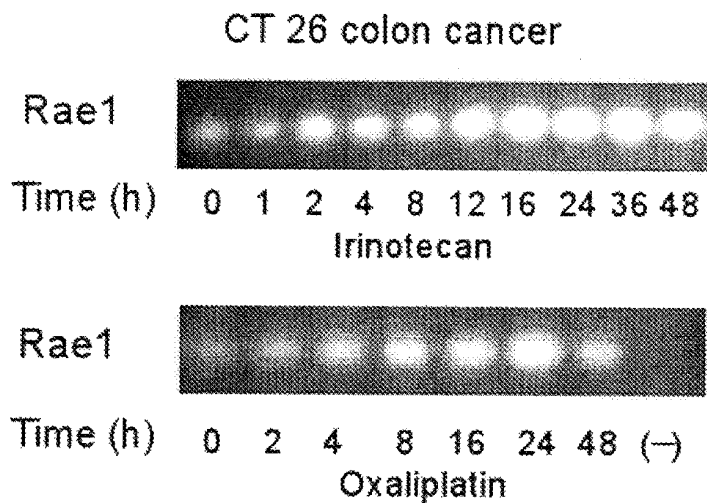
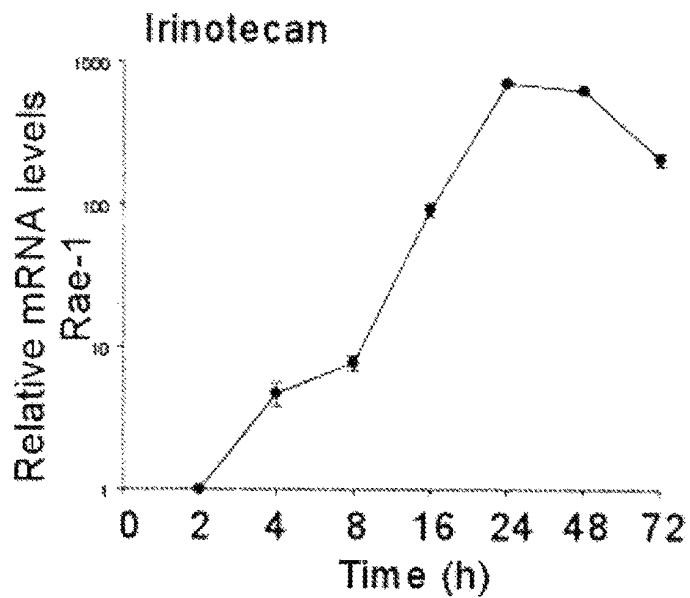
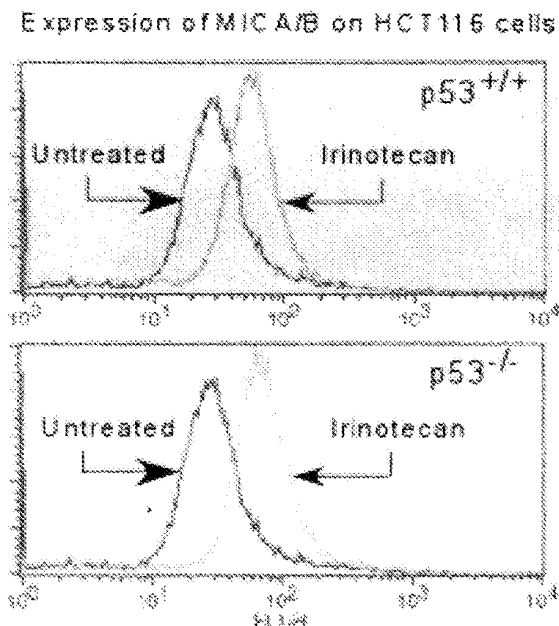
E**F**

Fig. 57 E & F

G



H

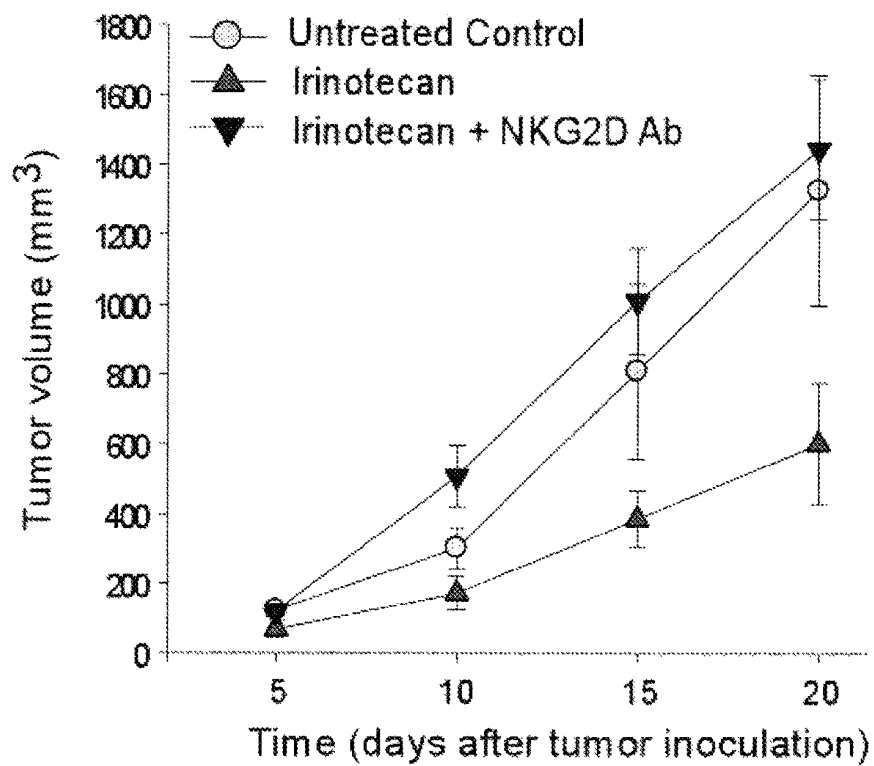


Fig. 57 G & H

COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a 35 USC §371 National Stage application of International Application No. PCT/US2011/027317 filed Mar. 4, 2011, now pending; which claims the benefit under 35 USC §119(e) to U.S. Application Ser. No. 61/435,671 filed Jan. 24, 2011 and to U.S. Application Ser. No. 61/311,255 filed Mar. 5, 2010. The disclosure of each of the prior applications is considered part of and is incorporated by reference in the disclosure of this application.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates generally to the field of targeted immunomodulatory antibodies and fusion proteins for cancer therapy and more specifically to composition and methods for targeted immunostimulatory or immunosuppressive antibodies and fusion proteins to counteract or induce immune tolerance of cancer cells.

2. Background Information

The immune system provides the human body with a means to recognize and defend itself against microorganisms and substances recognized as foreign or potentially harmful. While passive immunotherapy of cancer with monoclonal antibodies and passive transfer of T cells to attack tumor cells have demonstrated clinical efficacy, the goal of active therapeutic vaccination to induce these immune effectors and establish immunological memory against tumor cells has remained challenging. Several tumor-specific and tumor-associated antigens have been identified, yet these antigens are generally weakly immunogenic and tumors employ diverse mechanisms to create a tolerogenic environment that allows them to evade immunologic attack. Strategies to overcome such immune tolerance and activating robust levels of antibody and/or T cell responses hold the key to effective cancer immunotherapy.

SUMMARY OF THE INVENTION

The present invention is based on the seminal discovery that targeted immunomodulatory antibodies and fusion proteins can counteract or reverse immune tolerance of cancer cells. Cancer cells are able to escape elimination by chemotherapeutic agents or tumor-targeted antibodies via specific immunosuppressive mechanisms in the tumor microenvironment and such ability of cancer cells is recognized as immune tolerance. Such immunosuppressive mechanisms include immunosuppressive cytokines (for example, Transforming growth factor beta (TGF- β)) and regulatory T cells and/or immunosuppressive, myeloid dendritic cells (DCs). By counteracting tumor-induced immune tolerance, the present invention provides effective compositions and methods for cancer treatment, optional in combination with another existing cancer treatment. The present invention provides strategies to counteract tumor-induced immune tolerance and enhance the antitumor efficacy of chemotherapy by activating and leveraging T cell-mediated adaptive antitumor immunity against resistant or disseminated cancer cells.

In one embodiment, the present invention provides a molecule including a targeting moiety fused with an immunomodulatory moiety. The targeting moiety specifically binds a

target molecule, and the immunomodulatory moiety specifically binds one of the following molecules: (i) Transforming growth factor-beta (TGF- β); (ii) Programmed death-1 ligand 1 (PD-L1) or Programmed death-1 ligand 2 (PD-L2); (iii) Receptor activator of nuclear factor- κ B (RANK) ligand (RANKL); (iv) Transforming growth factor-beta receptor (TGF- β R); (v) Programmed death-1 (PD-1); and (vi) Receptor activator of nuclear factor- κ B (RANK).

In one aspect, the targeting moiety includes an antibody, antibody fragment, scFv, or Fc-containing polypeptide that specifically binds a component of a tumor cell, tumor antigen, tumor vasculature, tumor microenvironment, or tumor-infiltrating immune cell. In one aspect, the targeting moiety specifically binds epidermal growth factor receptor (EGFR1, Erb-91), HER2/neu (Erb-92), CD20, Vascular endothelial growth factor (VEGF), insulin-like growth factor receptor (IGF-1R), TRAIL-receptor, epithelial cell adhesion molecule, carcino-embryonic antigen, Prostate-specific membrane antigen, Mucin-1, CD30, CD33, or CD40.

In one aspect, the targeting moiety specifically binds a component of a regulatory T cell, myeloid suppressor cell, or dendritic cell. In another aspect, the targeting moiety specifically binds one of the following molecules: (i) CD4; (ii) CD25 (IL-2 α receptor; IL-2 α R); (iii) cytotoxic T-lymphocyte antigen-4 (CTLA-4; CD152); (iv) Interleukin-10 (IL-10); (v) Transforming growth factor-beta receptor (TGF- β R); (vi) Transforming growth factor-beta (TGF- β), (vii) Programmed Death-1 (PD-1); (viii) Programmed death-1 ligand (PD-L1 or PD-L2); (ix) Receptor activator of nuclear factor- κ B (RANK); or (x) Receptor activator of nuclear factor- κ B (RANK) ligand (RANKL).

In one aspect, the immunomodulatory moiety specifically binds one of the following molecules: (i) Transforming growth factor-beta (TGF- β); (ii) Programmed death-1 ligand (PD-L1 or PD-L2); or (iii) Receptor activator of nuclear factor- κ B (RANK) ligand (RANKL).

In one aspect, the immunomodulatory moiety includes a molecule that binds TGF- β . In another aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain of Transforming growth factor-beta receptor TGF- β RII, TGF- β RIIb, or TGF- β RIII. In another aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain of TGF- β RII. In an additional aspect, the immunomodulatory moiety inhibits the activity or function of TGF- β .

In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to HER2/neu, EGFR1, CD20, vascular endothelial growth factor (VEGF), cytotoxic T-lymphocyte antigen-4 (CTLA-4), CD25 (IL-2 α receptor; IL-20), or CD4. In an additional aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain of TGF- β RII. In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10.

In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to Programmed Death-1 (PD-1), Programmed death-1 ligand 1 (PD-L1), or Programmed death-1 ligand 2 (PD-L2). In another aspect, the targeting moiety includes an extracellular ligand-binding domain or ectodomain of Programmed Death-1 (PD-1). In an additional aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain of TGF- β RII. In another aspect, the molecule includes PD-1 ectodomain, immunoglobulin Fc region, and TGF β RII ectodomain. In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO 11 or 12.

In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to Receptor activator of nuclear factor- κ B (RANK) or Receptor activator of nuclear factor- κ B ligand (RANKL). In another aspect, the targeting moiety includes an extracellular ligand-binding domain or ectodomain of Receptor activator of nuclear factor- κ B (RANK). In an additional aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain of TGF- β RII. In another aspect, the molecule includes RANK ectodomain, immunoglobulin Fc region, and TGF β RII ectodomain. In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO 13 or 14.

In one aspect, the immunomodulatory moiety includes a molecule that specifically binds to Programmed death-1 ligand 1 (PD-L1) or Programmed death-1 ligand 2 (PD-L2). In another aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain or ectodomain of Programmed Death-1 (PD-1). In an additional aspect, the immunomodulatory moiety inhibits the activity or function of Programmed death-1 ligand 1 (PD-L1).

In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to HER2/neu, EGFR1, CD20, vascular endothelial growth factor (VEGF), cytotoxic T-lymphocyte antigen-4 (CTLA-4), CD25 (IL-2 α receptor; IL-2 α R), or CD4. In an additional aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain or ectodomain of Programmed Death-1 (PD-1). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24.

In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to Receptor activator of nuclear factor- κ B (RANK) or Receptor activator of nuclear factor- κ B ligand (RANKL). In another aspect, the targeting moiety includes an extracellular ligand-binding domain or ectodomain of Receptor activator of nuclear factor- κ B (RANK). In an additional aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain of Programmed Death-1 (PD-1). In another aspect, the molecule includes RANK ectodomain, immunoglobulin Fc region, and PD-1 ectodomain. In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 25 or 26.

In one aspect, the immunomodulatory moiety includes a molecule that specifically binds to Receptor activator of nuclear factor- κ B ligand (RANKL). In another aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain or ectodomain of Receptor activator of nuclear factor- κ B (RANK). In an additional aspect, the immunomodulatory moiety inhibits the activity or function of Receptor activator of nuclear factor- κ B ligand (RANKL).

In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to HER2/neu, EGFR1, CD20, vascular endothelial growth factor (VEGF), cytotoxic T-lymphocyte antigen-4 (CTLA-4), CD25 (IL-2 α receptor; IL-2 α R), or CD4. In an additional aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain or ectodomain of Receptor activator of nuclear factor- κ B (RANK). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36.

In one aspect, the immunomodulatory moiety includes a sequence from Programmed death-1 ligand 1 (PD-L1) or Programmed death-1 ligand 2 (PD-L2). In an additional aspect, the immunomodulatory moiety increases the function of PD-1.

In one aspect, the targeting moiety specifically binds to Tumor Necrosis Factor- α (TNF- α), and the immunomodulatory moiety includes a sequence from Programmed death-1 ligand 1 (PD-L1) or Programmed death-1 ligand 2 (PD-L2). In an additional aspect, the targeting moiety includes an antibody that binds TNF- α , and the immunomodulatory moiety includes a sequence from PD-1 ligand 1 (PD-L1 or B7-H1). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 37. In another aspect, the targeting moiety includes an extracellular ligand-binding domain of tumor necrosis factor receptor 2 (TNFR2), and the immunomodulatory moiety includes a sequence from PD-1 ligand 1 (PD-L1 or B7-H1). In another aspect, the molecule includes TNFR2 Extracellular ligand binding domain, immunoglobulin Fc region, and a sequence from PD-L1. In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO 38 or 39.

In one aspect, the targeting moiety includes an antibody or antibody fragment that specifically binds to CD20, CD25, or CD4, and the immunomodulatory moiety includes a sequence from Programmed death-1 ligand 1 (PD-L1) or Programmed death-1 ligand 2 (PD-L2). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 40, 41, 42, 43, 44 or 45.

In one aspect, the targeting moiety includes the extracellular domain of CTLA-4 and immunoglobulin Fc region (IgG C γ 1), and the immunomodulatory moiety includes a sequence from Programmed death-1 ligand 1 (PD-L1) or Programmed death-1 ligand 2 (PD-L2). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 46 or 47.

In one aspect, the targeting moiety includes transforming growth factor- β (TGF- β) and immunoglobulin Fc region (IgG C γ 1), and the immunomodulatory moiety includes a sequence from Programmed death-1 ligand 1 (PD-L1) or Programmed death-1 ligand 2 (PD-L2). In an additional aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 48 or 49.

In one aspect, the immunomodulatory moiety includes a sequence from transforming growth factor- β (TGF- β). In an additional aspect, the immunomodulatory moiety activates the signaling function of transforming growth factor- β (TGF- β) receptor.

In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to Tumor Necrosis Factor- α (TNF- α), and the immunomodulatory moiety includes a sequence from transforming growth factor- β (TGF- β). In an additional aspect, the targeting moiety includes an antibody that binds TNF- α , and the immunomodulatory moiety includes a sequence from TGF- β . In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 50. In one aspect, the targeting moiety includes an extracellular ligand-binding domain of tumor necrosis factor receptor 2 (TNFR2). In another aspect, the molecule includes TNFR2 Extracellular ligand binding domain, immunoglobulin Fc region, and a sequence from transforming growth factor- β (TGF- β). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 51 or 52.

In one aspect, the targeting moiety includes an antibody or antibody fragment that specifically binds to CD20, CD25 (IL-2 α receptor; IL-2 α R), or CD4, and the immunomodulatory moiety includes a sequence from transforming growth factor- β (TGF- β). In an additional aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 53, 54, 55, 56, 57 or 58.

In one aspect, the targeting moiety includes an extracellular domain of CTLA-4 and immunoglobulin Fc region (IgG C γ 1), and the immunomodulatory moiety includes a sequence from transforming growth factor- β (TGF- β). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO 59 or 60.

In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to Tumor Necrosis Factor- α (TNF- α), and the immunomodulatory moiety includes an extracellular RANKL-binding domain or ectodomain of Receptor activator of nuclear factor- κ B (RANK). In an additional aspect, the targeting moiety includes an antibody that binds TNF- α , and the immunomodulatory moiety includes a sequence from an extracellular RANKL-binding domain or ectodomain of RANK. In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 61. In one aspect, the targeting moiety includes an extracellular ligand-binding domain of tumor necrosis factor receptor 2 (TNFR2). In another aspect, the molecule includes TNFR2 Extracellular ligand binding domain, immunoglobulin Fc region, and a sequence from an extracellular RANK-binding domain or ectodomain of RANK. In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 62 or 63.

In one aspect, the targeting moiety includes an extracellular domain of CTLA-4 and immunoglobulin Fc region (IgG C γ 1), and the immunomodulatory moiety includes an extracellular RANKL-binding domain or ectodomain of Receptor activator of nuclear factor- κ B (RANK). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 64 or 65.

In one aspect, the targeting moiety includes a sequence from transforming growth factor- β (TGF- β) and immunoglobulin Fc region (IgG C γ 1), and the immunomodulatory moiety includes an extracellular RANKL-binding domain or ectodomain of Receptor activator of nuclear factor- κ B (RANK). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO 66 or 67.

In one aspect, the targeting moiety includes a sequence from Programmed death-1 ligand 1 (PD-L1) and immunoglobulin Fc region (IgG C γ 1), and the immunomodulatory moiety includes an extracellular RANKL-binding domain or ectodomain of Receptor activator of nuclear factor- κ B (RANK). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 68 or 69.

In various aspects, the molecule is fused or directly linked to one or more antigen, antigenic determinant, or epitope.

In another embodiment, the present invention, provides a composition including the molecule of the invention and a cell, wherein the cell is a tumor cell, immune cell, or dendritic cell.

In another embodiment, the present invention provides a method of counteracting or overcoming immune tolerance. The method includes administering to a subject in need thereof one or more molecule of the invention.

In another embodiment, the present invention provides a method of preventing or treating a neoplastic disease. The method includes administration to a subject in need thereof one or more molecule of the invention. In various aspects, the subject is administered one or more molecule of the invention in combination with another anticancer therapy. In one aspect, the anticancer therapy includes a chemotherapeutic molecule, antibody, small molecule kinase inhibitor, hormonal agent or cytotoxic agent. In another aspect, the anticancer therapy includes ionizing radiation, ultraviolet radiation, cryoablation, thermal ablation, or radiofrequency ablation.

In another embodiment, the present invention provides a method of preventing or treating a neoplastic disease. The method includes administration to a subject in need thereof an antibody that targets and depletes CD44+ regulatory T cells (Tregs) in combination with another cytotoxic anticancer therapy. In one aspect, the antibody that targets and depletes Tregs is an anti-CD4 antibody. In various aspects, the cytotoxic anticancer therapy includes a chemotherapeutic molecule, tumor-targeted antibody, small molecule kinase inhibitor, hormonal agent or tumor-targeted cytotoxic agent. In another aspect, the cytotoxic anticancer therapy includes ionizing radiation, ultraviolet radiation, cryoablation, thermal ablation, or radiofrequency ablation.

In another embodiment, the subject is administered one or more molecule of the invention in combination with any vaccine. In another aspect, the vaccine includes a tumor antigen, tumor-associated antigen, tumor epitope, tumor antigen-containing fusion protein, tumor cell, or dendritic cell. In another aspect, the vaccine includes a pathogen antigen, pathogen-associated antigen, pathogen epitope, or pathogen antigen-containing fusion protein.

In another embodiment, the present invention provides a method for treating immune cells wherein the cells are contacted ex vivo or in vitro with a molecule of the invention. In another embodiment, the present invention provides a method of treatment of a neoplastic disease. The method includes administering to a subject in need thereof a composition of immune cells contacted with a molecule of the invention.

In another embodiment, the present invention provides a method of inducing or promoting immune tolerance. The method includes administering to a subject in need thereof one or more molecule of the invention.

In another embodiment, the present invention provides a method of preventing or treating an autoimmune or inflammatory disease including administering to a subject in need thereof one or more molecule of the invention. In one aspect, the subject is administered one or more molecule of the invention in combination with another anti-inflammatory or immunosuppressive therapy. In another embodiment, the present invention provides a method of treatment of immune cells wherein the cells are contacted ex vivo or in vitro with a molecule of the invention. In another embodiment, the present invention provides a method of treating an autoimmune or inflammatory disease or preventing rejection of grafted cells or tissue. The method includes administering to a subject in need thereof a composition of immune cells contacted with a molecule of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows exemplary amino acid sequences of transforming growth factor beta receptor type II (TGF- β -RID or TGF- β -RIIB or a fragment thereof, including (i) Transforming growth factor beta receptor type II (TGF- β -RII) (SEQ ID NO 79), and (ii) Transforming growth factor beta receptor type IIB (TGF- β -RIIB) (SEQ ID NO 80).

Also shown in FIG. 1 are exemplary truncated mutants of Transforming growth factor beta Receptor II (TGF- β -RII) or TGF- β -RIIB including the Extracellular domain (ECD) region that binds TGF- β , including (i) TGF- β R-II (Δ C terminus): TGF β RII lacking the last 38 amino acids from the C-terminus (SEQ ID NO: 81) and TGF- β R-IIB (Δ C terminus): TGF β RIIB lacking the last 38 as from the C-terminus (SEQ ID NO: 82); (ii) (Δ cyt): TGF β RII lacking the kinase domain & juxtamembrane region (SEQ ID NO: 83) and TGF- β RIIB (Δ cyt): TGF β RIIB lacking the kinase domain & juxtamembrane region (SEQ ID NO: 84); (iii) TGF- β R-II con-

taining the N-terminus region including the extracellular domain (SEQ ID NO: 85) and TGF- β R-II containing the N-terminus region including the extracellular domain (SEQ ID NO: 86); (iv) TGF- β R-III containing the extracellular domain that binds TGF- β (SEQ ID NO: 87) and TGF- β R-II containing the extracellular domain that binds TGF- β (SEQ ID NO: 88); and (v) TGF- β R-II containing the region of the extracellular domain that binds TGF- β (SEQ ID NO: 89).

In addition, FIG. 1 also shows exemplary kinase-deficient mutants, deletion mutants, or point mutants of Transforming growth factor beta Receptor II (TGF β -RII) or TGF β -RIIB or a fragment thereof which binds TGF- β , including (i) Transforming growth factor beta Receptor II containing point mutations-amino acid sequence of TGF- β R-II (K277R) contains a point mutation in its ATP-binding site and is inactive as a kinase (SEQ ID NO: 90); and (ii) Transforming growth factor beta Receptor II containing deletions in the amino acid sequence (deletion mutants)—Transforming growth factor beta Receptor II (Δ i)-TGF- β R-II (Δ i2) contains a deletion of amino acids 498 to 508 and is inactive as a kinase (SEQ ID NO: 91).

FIG. 2 shows exemplary fusion proteins including anti-HER2/neu antibody and Transforming growth factor-beta receptor II (TGF β -RII) Extracellular domain (ECD), including anti-HER2/neu heavy chain+TGF β -RII ECD fusion amino acid sequence (SEQ ID NO 1) and anti-HER2/neu light chain amino acid sequence (SEQ ID NO 70).

FIG. 3 shows exemplary fusion proteins including anti-EGFR1 antibody and Transforming growth factor-beta receptor II (TGF β -RII) Extracellular domain (ECD), including anti-EGFR1 heavy chain+TGF β -RII ECD fusion amino acid sequence (SEQ ID NO 2) and anti-EGFR1 light chain amino acid sequence (SEQ ID NO 71).

FIG. 4 shows exemplary fusion proteins including anti-CD20 antibody and Transforming growth factor-beta receptor II (TGF β -RII) Extracellular domain (ECD), including anti-CD20 heavy chain+TGF β -RII ECD fusion amino acid sequence (SEQ ID NO: 3) and anti-CD20 light chain amino acid sequence (SEQ ID NO: 72).

FIG. 5 shows exemplary fusion proteins including anti-VEGF antibody and Transforming growth factor-beta receptor II (TGF β -RII) Extracellular domain (ECD), including anti-VEGF heavy chain+TGF β -RII ECD fusion amino acid sequence (SEQ ID NO: 4) and anti-VEGF Light chain sequence (SEQ ID NO 73).

FIG. 6 shows exemplary fusion proteins including anti-human CTLA-4 antibody and Transforming growth factor-beta receptor II (TGF β -RII) Extracellular domain (ECD), including Anti-CTLA-4 heavy chain+TGF β -RII Extracellular domain fusion amino acid sequence (SEQ ID NO 5) and Anti-CTLA-4 light chain (SEQ ID NO 74).

FIG. 7 shows exemplary fusion proteins including IL-2, Fc, and Transforming growth factor-beta receptor II (TGF β -RII) Extracellular domain (ECD), including IL-2+Fc+TGF β -RII Extracellular domain (SEQ ID NO: 6) and TGF β -RII Extracellular domain+Fc+IL-2 (SEQ ID NO: 7). The linker GGGGSGGGGSGGGGS (SEQ ID NO: 104) is optional and can be replaced with EPKSCDK (SEQ ID NO: 105) or another linker sequence well known in the art. Certain amino acid sequences can be replaced in Fc, including underlined E with D and underlined M with L.

FIG. 8 shows exemplary fusion proteins including anti-CD25 antibody and Transforming growth factor-beta receptor II (TGF β -RII) Extracellular domain (ECD), including anti-CD25 (Daclizumab) heavy chain and TGF β -RII Extracellular domain (SEQ ID NO 8) and anti-CD25 (Daclizumab) light chain (SEQ ID NO: 75) (FIG. 8A); and anti-CD25

(Basiliximab) heavy chain and TGF β -RII Extracellular domain (SEQ ID NO: 9) and anti-CD25 (Basiliximab) light chain (SEQ ID NO: 76).

FIG. 9 shows exemplary fusion proteins including anti-CD4 antibody and Transforming growth factor-beta receptor II (TGF β -RII) Extracellular domain (ECD), including anti-CD4 heavy chain and TGF β -RII Extracellular domain (SEQ ID NO: 10) and anti-CD4 light chain (SEQ ID NO: 77).

FIG. 10 shows exemplary fusion proteins including Programmed Death-1 (PD-1) Ectodomain, Fc, and Transforming growth factor-beta receptor II (TGF β -RII) Extracellular domain (ectodomain), including PD-1 ectodomain+Fc+TGF β -RII ectodomain (SEQ ID NO: 11) and TGF β -RII ectodomain+Fc+PD-1 ectodomain (SEQ ID NO: 12). The linker sequence EPKSCDK (SEQ ID NO 105) is optional and can be deleted or replaced with another linker.

FIG. 11 shows exemplary fusion proteins including Receptor activator of nuclear factor-kB (RANK) Ectodomain, Fc, and Transforming growth factor-beta receptor II (TGF β -RII) Extracellular domain (ectodomain), including RANK ectodomain+Fc+TGF β -RII ectodomain (SEQ ID NO: 13) and TGF β -RII ectodomain+Fc+RANK ectodomain (SEQ ID NO: 14). The linker sequence EPKSCDK (SEQ ID NO: 105) is optional and can be deleted or replaced with another linker.

FIG. 12 shows exemplary immunomodulatory moiety that binds Programmed Death-1 ligand 1 (PD-L1 or B7-H1) or Programmed Death-1 ligand 2 (PD-L2 or B7-DC), including full-length PD-1 or fragment thereof (SEQ ID NO: 92), PD-1 extracellular domain (ectodomain) or fragment thereof (SEQ ID NO: 93), and PD-1 extracellular domain (ectodomain) ligand-binding region (SEQ ID NO 94).

FIG. 13 shows exemplary fusion proteins including anti-HER2/neu antibody and PD-1 Ectodomain, including anti-HER2/neu heavy chain+PD-1 ectodomain fusion amino acid sequence (SEQ ID NO: 15) and anti-HER2/neu light chain amino acid sequence (SEQ ID NO: 70).

FIG. 14 shows exemplary fusion proteins including anti-EGFR1 antibody and PD-1 Ectodomain, including anti-EGFR heavy chain+PD-1 ectodomain fusion amino acid sequence (SEQ ID NO 16) and anti-EGFR light chain amino acid sequence (SEQ ID NO 71).

FIG. 15 shows exemplary fusion proteins including anti-CD20 antibody and PD-1 Ectodomain, including anti-CD20 heavy chain+PD-1 ectodomain fusion amino acid sequence (SEQ ID NO 17) and anti-CD20 light chain amino acid sequence (SEQ ID NO 72).

FIG. 16 shows exemplary fusion proteins including anti-VEGF antibody and PD-1 Ectodomain, including anti-VEGF heavy chain+PD-1 ectodomain fusion amino acid sequence (SEQ ID NO 18) and anti-VEGF Light chain sequence (SEQ ID NO 73).

FIG. 17 shows exemplary fusion proteins including anti-human CTLA-4 antibody and PD-1 Ectodomain, including anti-CTLA-4 heavy chain+PD-1 ectodomain fusion amino acid sequence (SEQ ID NO 19) and anti-CTLA-4 light chain (SEQ ID NO 74).

FIG. 18 shows exemplary fusion proteins including anti-CD25 antibody and PD-1 Ectodomain, including anti-CD25 (Daclizumab) heavy chain and PD-1 ectodomain (SEQ ID NO: 20) and anti-CD25 (Daclizumab) light chain (SEQ ID NO: 75) (FIG. 18A), and anti-CD25 (Basiliximab) heavy chain and PD-1 ectodomain (SEQ ID NO: 21) and anti-CD25 (Basiliximab) light chain (SEQ ID NO: 76) (FIG. 18B).

FIG. 19 shows exemplary fusion proteins including IL-2, Fc, and PD-1 ectodomain, including IL-2+Fc+PD-1 ectodomain (SEQ ID NO: 22) and PD-1 ectodomain+Fc+IL-2 (SEQ ID NO: 23). The linker GGGGSGGGGSGGGGS

SEQ ID NO: 104 is optional and can be replaced with EPK-SCDK SEQ ID NO: 105 or another linker sequence well known in the art. Certain amino acid sequences can be replaced in Fc, including underlined E with D and underlined M with L.

FIG. 20 shows exemplary fusion proteins including anti-CD4 antibody and PD-1 ectodomain, including anti-CD4 heavy chain and PD-1 ectodomain (SEQ ID NO: 24) and anti-CD4 light chain (SEQ ID NO: 77).

FIG. 21 shows exemplary fusion proteins including Receptor activator of nuclear factor- κ B (RANK) Ectodomain, Fc, and PD-1 ectodomain, including RANK ectodomain+Fc+PD-1 ectodomain (SEQ ID NO: 25) and PD-1 ectodomain+Fc+RANK ectodomain (SEQ ID NO: 26). The linker sequence EPKSCDK (SEQ ID NO 105) is optional and can be deleted or replaced with another linker.

FIG. 22 shows exemplary immunomodulatory moiety that binds Receptor activator of nuclear factor- κ B (RANK) ligand (RANKL) including full-length RANK or fragment thereof (SEQ ID NO: 95), extracellular ligand-binding domain or ectodomain of RANK (SEQ ID NO: 96), RANKL-binding sequences or residues of RANK (SEQ ID NO: 93), or RANKL-binding sequences of Osteoprotegerin (OPG) (SEQ ID NO 98).

FIG. 23 shows exemplary fusion proteins including anti-HER2/neu antibody and RANK Ectodomain, including anti-HER2/neu heavy chain+RANK ectodomain fusion amino acid sequence (SEQ ID NO: 27) and anti-HER2/neu light chain amino acid sequence (SEQ ID NO: 70).

FIG. 24 shows exemplary fusion proteins including anti-EGFR1 antibody and RANK Ectodomain, including anti-EGFR heavy chain+RANK ectodomain fusion amino acid sequence (SEQ ID NO: 28) and anti-EGFR light chain amino acid sequence (SEQ ID NO: 71).

FIG. 25 shows exemplary fusion proteins including anti-CD20 antibody and RANK Ectodomain, including anti-CD20 heavy chain+RANK ectodomain fusion amino acid sequence (SEQ ID NO 29) and anti-CD20 light chain amino acid sequence (SEQ ID NO 72).

FIG. 26 shows exemplary fusion proteins including anti-VEGF antibody and RANK Ectodomain, including anti-VEGF heavy chain+RANK ectodomain fusion amino acid sequence (SEQ ID NO 30) and anti-VEGF Light chain sequence (SEQ ID NO 73).

FIG. 27 shows exemplary fusion proteins including anti-human CTLA-4 antibody and RANK Ectodomain, including anti-CTLA-4 heavy chain+RANK ectodomain fusion amino acid sequence (SEQ ID NO 31) and anti-CTLA-4 light chain (SEQ ID NO 74).

FIG. 28 shows exemplary fusion proteins including anti-CD25 antibody and RANK Ectodomain, including anti-CD25 (Daclizumab) heavy chain and RANK ectodomain (SEQ ID NO 32) and anti-CD25 (Daclizumab) light chain (SEQ ID NO 75) (FIG. 28A), and anti-CD25 (Basiliximab) heavy chain and RANK ectodomain (SEQ ID NO: 33) and anti-CD25 (Basiliximab) light chain (SEQ ID NO 76) (FIG. 28B).

FIG. 29 shows exemplary fusion proteins including IL-2, Fc, and RANK ectodomain, including IL-2+Fc+RANK ectodomain (SEQ ID NO: 34) and RANK ectodomain+Fc+IL-2 (SEQ ID NO: 35). The linker GGGGSGGGGSGGGGS SEQ ID NO: 104 is optional and can be replaced with EPK-SCDK SEQ ID NO: 105 or another linker sequence well known in the art. Certain amino acid sequences can be replaced in Fc, including underlined E with D and underlined M with L.

FIG. 30 shows exemplary fusion proteins including anti-CD4 antibody and RANK ectodomain, including anti-CD4 heavy chain and RANK ectodomain (SEQ ID NO: 36) and anti-CD4 light chain (SEQ ID NO: 77).

FIG. 31 shows exemplary immunomodulatory moiety that binds Programmed Death-1 (PD-1) including a PD-1 ligand 1 (PD-L1 or B7-H1) or PD-1 ligand 2 (PD-L2 or B7-DC) or a fragment thereof (for example, SEQ ID NO: 101), full-length human PD-1 ligand 1 (B7-H1; PDCD1L1; PD-L1; or CD274) protein or a fragment thereof (SEQ ID NO: 99), and PD-L1 extracellular binding domain (ectodomain) or fragment thereof (SEQ ID NO: 100).

FIG. 32 shows exemplary fusion proteins including anti-tumor necrosis factor (TNF α) antibody and PD-1 ligand, including anti-TNF α heavy chain+PD-IL (SEQ ID NO: 37) and anti-TNF α light chain (SEQ ID NO: 78). The sequence KKAE (SEQ ID NO: 107) can be replaced with KRVE (SEQ ID NO 108) or KKVE (SEQ ID NO 109).

FIG. 33 shows exemplary fusion proteins including TNFR2 Extracellular ligand binding domain, Fc, and PD-1 ligand, including TNFR2 ECD+IgG C γ 1+PD-L1 (SEQ ID NO: 38) and PD-L1+IgG C γ 1-TNFR2 ECD (SEQ ID NO: 39).

FIG. 34 shows exemplary fusion proteins including anti-CD20 antibody and PD-1 ligand 1 (PD-L1), including anti-CD20 heavy chain+PD-L1 sequence (SEQ ID NO 40) and anti-CD20 light chain sequence (SEQ ID NO: 72).

FIG. 35 shows exemplary fusion proteins including anti-CD25 antibody and PD-1 ligand 1 (PD-L1), including anti-CD25 (Daclizumab) heavy chain and PD-L1 (SEQ ID NO: 41) and anti-CD25 (Daclizumab) light chain (SEQ ID NO 75) (FIG. 35A), and anti-CD25 (Basiliximab) heavy chain and PD-1 ectodomain (SEQ ID NO: 42) and anti-CD25 (Basiliximab) light chain (SEQ ID NO 76) (FIG. 35B).

FIG. 36 shows exemplary fusion proteins including IL-2, Fc, and PD-1 ligand 1 (PD-L1), including fusion protein hPD-1 ligand 1+Fc+IL-2 (SEQ ID NO: 43) and fusion protein IL-2+Fc+PD-1 ligand 1 (SEQ ID NO: 44). The linker GGGGSGGGGSGGGGS SEQ ID NO: 104 is optional and can be replaced with EPKSCDK SEQ ID NO: 105 or another linker sequence well known in the art. Certain amino acid sequences can be replaced in Fc, including underlined E with D and underlined M with L.

FIG. 37 shows exemplary fusion proteins including anti-CD4 antibody and PD-1 ligand 1 (PD-L1), including anti-CD4 heavy chain and PD-1 ligand 1 (PD-L1) (SEQ ID NO: 45) and anti-CD4 light chain (SEQ ID NO 77).

FIG. 38 shows exemplary fusion proteins including the extracellular domain of CTLA-4, Immunoglobulin Fc (IgG C γ 1), and a sequence from PD-1 ligand (PD-L1) including Oncostatin M signal peptide+CTLA-4 ECD+IgG C γ 1+PD-L1 (SEQ ID NO: 46) and PD-1L1+IgG C γ 1+CTLA-4 ECD (SEQ ID NO: 47). The IgG sequence shown can have optional C to S conversion in (bold underlined). The linker QEPK-SCDK SEQ ID NO: 110 is optional and can be replaced with EPKSCDK SEQ ID NO 105 or another linker sequence.

FIG. 39 shows exemplary fusion proteins including a sequence of transforming growth factor- β (TGF- β), Immunoglobulin Fc (IgG C γ 1), and a sequence of PD-1 ligand (PD-L1) including TGF β -1+Fc+PD-L1 (SEQ ID NO: 48), and PD-1L1+Fc+TGF β -1 (SEQ ID NO: 49). The linker GGGGSGGGGSGGGGS SEQ ID NO: 104 is optional and can be replaced with EPKSCDK SEQ ID NO: 105 or another linker sequence well known in the art. Certain amino acid sequences can be replaced in Fc, including underlined E with D and underlined M with L.

11

FIG. 40 shows exemplary immunomodulatory moiety that binds Transforming growth factor-beta receptor (TGF- β R) including Transforming growth factor-beta (TGF- β 1, TGF- β 2, or TGF- β 3 or a fragment thereof, TGF- β 1 full sequence (SEQ ID NO: 102), and mature (active) TGF- β 1 sequence (Ala 279-Ser 390, 112 amino acids) (SEQ ID NO 103).

FIG. 41 shows exemplary fusion proteins including an antibody that binds TNF- α , and a sequence of transforming growth factor- β (TGF- β), including anti-TNF α heavy chain+TGF- β 1 (SEQ ID NO: 50) and anti-TNF α light chain (SEQ ID NO: 78). The sequence KKAE (SEQ ID NO: 107) can be replaced with KRVE (SEQ ID NO: 108) or KKVE (SEQ ID NO: 109).

FIG. 42 shows exemplary fusion proteins including TNFR2 Extracellular ligand binding domain (TNFR2 ECD), immunoglobulin Fc (IgG C γ 1), and a sequence from transforming growth factor- β (TGF- β) including TNFR2 ECD+IgG C γ 1+TGF- β 1 (SEQ ID NO: 51), and TGF- β 1+IgG C γ 1+TNFR2 ECD (SEQ ID NO: 52).

FIG. 43 shows exemplary fusion proteins including anti-CD20 antibody and a sequence from transforming growth factor- β (TGF- β), including anti-CD20 heavy chain+mature TGF β 1 sequence (SEQ ID NO: 53) and anti-CD20 light chain sequence (SEQ ID NO: 72).

FIG. 44 shows exemplary fusion proteins including anti-CD25 antibody and a sequence from transforming growth factor- β (TGF- β), including anti-CD25 (Daclizumab) heavy chain and TGF- β 1 (SEQ ID NO: 54) and anti-CD25 (Daclizumab) light chain (SEQ ID NO: 75) (FIG. 44A), and anti-CD25 (Basiliximab) heavy chain and TGF- β 1 (SEQ ID NO: 55) and anti-CD25 (Basiliximab) light chain (SEQ ID NO 76) (FIG. 44B).

FIG. 45 shows exemplary fusion proteins including IL-2, Fc, and a sequence from transforming growth factor- β (TGF- β), including TGF- β 1+Fc+IL-2 (SEQ ID NO: 56) and IL-2+Fc+TGF- β 1 (SEQ ID NO: 57). The linker GGGGSGGGGSGGGGS SEQ ID NO 104 is optional and can be replaced with EPKSCDK SEQ ID NO: 105 or another linker sequence well known in the art. Certain amino acid sequences can be replaced in Fc, including underlined E with D and underlined M with L.

FIG. 46 shows exemplary fusion proteins including anti-CD4 antibody and a sequence from transforming growth factor- β (TGF- β), including anti-CD4 heavy chain and TGF- β 1 (SEQ ID NO 58) and anti-CD4 light chain (SEQ ID NO 77).

FIG. 47 shows exemplary Fusion proteins including the extracellular domain of CTLA-4, Immunoglobulin Fc (IgG C γ 1), and a sequence from transforming growth factor- β (TGF- β) including Oncostatin M signal peptide+CTLA-4 ECD+IgG C γ 1+TGF- β 1 (SEQ ID NO: 59), and TGF- β 1+IgG C γ 1+CTLA-4 ECD (SEQ ID NO 60). The IgG sequence shown can have optional C to S conversion in (bold underlined). The linker QEPKSCDK SEQ ID NO: 110 is optional and can be replaced with EPKSCDK SEQ ID NO: 105 or another linker sequence.

FIG. 48 shows exemplary fusion proteins including an antibody that binds TNF- α , and a sequence of RANK ectodomain, including anti-TNF α heavy chain+RANK ectodomain (SEQ ID NO: 61) and anti-TNF α light chain (SEQ ID NO: 78). The sequence KKAE (SEQ ID NO 107) can be replaced with KRVE (SEQ ID NO 108) or KKVE (SEQ ID NO 109).

FIG. 49 shows exemplary fusion proteins including TNFR2 Extracellular ligand binding domain (TNFR2 ECD), immunoglobulin Fc (IgG C γ 1), and a sequence from RANK ectodomain including TNFR2 ECD+IgG C γ 1+RANK

12

ectodomain (SEQ ID NO: 62), and RANK ectodomain+IgG C γ 1+TNFR2 ECD (SEQ ID NO: 63).

FIG. 50 shows exemplary Fusion proteins including the extracellular domain of CTLA-4, Immunoglobulin Fc (IgG C γ 1), and a sequence from RANK ectodomain including Oncostatin M signal peptide+CTLA-4 ECD+IgG C γ 1+RANK ectodomain (SEQ ID NO: 64), and RANK ectodomain+IgG C γ 1+CTLA-4 ECD (SEQ ID NO: 65). The IgG sequence shown can have optional C to S conversion in (bold underlined). The linker QEPKSCDK SEQ ID NO: 110 is optional and can be replaced with EPKSCDK SEQ ID NO: 105 or another linker sequence.

FIG. 51 shows exemplary fusion proteins including a sequence from transforming growth factor- β (TGF- β), immunoglobulin Fc (IgG C γ 1), and a sequence from RANK ectodomain including TGF- β -F IgG C γ 1+RANK ectodomain (SEQ ID NO: 66), and RANK ectodomain+IgG C γ 1+TGF- β (SEQ ID NO: 67).

FIG. 52 shows exemplary fusion proteins including a sequence from PD-1 ligand (PD-L1), immunoglobulin Fc (IgG C γ 1), and a sequence from RANK ectodomain including PD-L1+IgG C γ 1+RANK ectodomain (SEQ ID NO: 68), and RANK ectodomain+IgG C γ 1+PD-L1 (SEQ ID NO: 69).

FIG. 53 shows Regulatory T cells (Treg) accumulate in the tumor microenvironment and counteract the ability of chemotherapy to activate CD8 $^{+}$ T cell-mediated antitumor immunity. (a) Surface exposure of calreticulin (CRT) in response to treatment of human (SW780) and murine (MB49) cancer cells with doxorubicin (10 μ M) for 4 h. The surface exposure of CRT was determined by immunofluorescence cytometry of untreated control or doxorubicin-treated cells stained with Dylight-labeled anti-CRT antibody or an isotype control (IgG1) antibody. (b) Priming of tumor-reactive immune responses by MB49 tumor cells treated with doxorubicin ex vivo or in vivo. 5×10^6 MB49 cells that were pre-treated ex vivo with doxorubicin (10 μ M) for 4 h were injected into one flank of syngeneic immunocompetent C57BL/6 mice. Alternatively, C57BL/6 mice were injected with 5×10^5 live MB49 tumor cells and then administered intratumoral doxorubicin (10 μ g) at 10 d following tumor inoculation. Tumor-reactive immune responses were determined by measuring production of IFN- γ by draining lymph node (DLN) cells in response to in vitro re-challenge with either MB49 cell lysates, an irrelevant peptide (Hemagglutinin-HA), or medium alone. (c) Vaccination with doxorubicin-treated tumor cells induces CD8 $^{+}$ T cell-mediated antitumor immunity that prevents tumor formation following re-challenge with live tumor cells. MB49 cells (5×10^6) that were pre-treated in vitro with doxorubicin (10 μ M) for 4 h were injected subcutaneously into one flank of syngeneic immunocompetent C57BL/6 mice. Naïve or vaccinated mice were challenged with untreated live MB49 tumor cells injected into the opposite flank with or without pre-treatment with an anti-CD8 antibody (Clone GK2.43) (5 μ g $\times$ 2 doses, iv) to deplete CD8 $^{+}$ T cells. (d) Delayed administration of chemotherapy in mice with pre-established tumors decreases its immunogenicity and antitumor efficacy. C57BL/6 mice were injected with 5×10^5 live syngeneic MB49 tumor cells and then administered intratumoral doxorubicin (10 μ g) at d3, d7, or d10 following tumor inoculation. (e) Tumors foster the accumulation of CD4 $^{+}$ CD25 $^{+}$ FoxP3 $^{+}$ cells (Tregs) in their microenvironment. Flow cytometric analyses of the percentage of CD4 $^{+}$ CD25 $^{+}$ FoxP3 $^{+}$ cells (Tregs) among CD4 $^{+}$ T lymphocytes isolated from the spleen, draining lymph nodes (DLN), and tumors of immunocompetent C57BL/6 mice at d0 and d14 after subcutaneous inoculation of 5×10^5 live MB49 tumor cells. (f) Tregs infiltrating the tumor microenvironment

suppress priming of tumor-reactive immune responses by doxorubicin-treated tumor cells. Naïve C57BL/6 mice were vaccinated with 5×10^6 doxorubicin-killed MB49 cells with or without intravenous adoptive transfer of 5×10^6 CD4⁺CD25⁺ cells isolated from tumors and DLN of tumor-bearing mice via immunomagnetic separation. Tumor-reactive immune responses were determined by measuring production of IFN- γ by draining lymph node (DLN) cells in response to in vitro re-challenge with either MB49 cell lysates, an irrelevant peptide (Hemagglutinin-HA), or medium alone. (g) Tregs infiltrating the tumor microenvironment suppress the activation of adaptive antitumor immunity in response to chemotherapy-induced tumor cell death. Naïve C57BL/6 mice were vaccinated with 5×10^6 doxorubicin-killed MB49 cells (left flank) with or without pre-treatment with either an anti-CD8 antibody (Clone GK2.43) ($5 \mu\text{g} \times 2$ doses, iv) to deplete CD8⁺ T cells or adoptive transfer of 5×10^6 CD4⁺CD25⁺ cells isolated from tumors and DLN of tumor-bearing mice. Protective antitumor immunity in vaccinated mice was determined by assessment of tumor growth upon challenge with untreated live MB49 tumor cells injected into the opposite flank.

FIG. 54 shows inhibition of TGF- β in the tumor microenvironment reduces 'adaptive' FoxP3⁺ regulatory T cells and enhances the antitumor efficacy chemotherapy. (a) Tumor growth results in a progressive increase in the level of serum TGF- β . Levels of TGF- β in serum of mice at d0, d14, and d28 following inoculation of 5×10^5 live MB49 tumor cells were evaluated utilizing ELISA. (b) Tumor cell-autonomous expression of TGF- β is the dominant source of elevated TGF- β in tumor-bearing mice. Tumor cells or draining lymph node cells isolated from either tumor-bearing mice or their tumor-free counterparts were cultured ex vivo in serum-free medium for 24 h and the amount of TGF- β /10⁶ cells in supernatants was measured by ELISA. (c) TGF β RII:Fc sequesters TGF- β in supernatants of MB49 tumor cells in a concentration-dependent manner. MB49 tumor cells were cultured in the presence of graded concentrations of TGF β RII:Fc (0-400 ng/ml) for 24 h followed by measurement of TGF- β (pg/ml/10⁶ cells) in supernatants via ELISA. (d) TGF- β induces 'adaptive' FoxP3⁺ regulatory T cells in the tumor microenvironment. At 5 d following inoculation of MB49 tumor cells, mice were either left untreated (control) or treated with TGF- β RII:Fc (1 μg intratumoral; twice weekly) for 3 weeks followed by flow cytometric analyses of intracellular FoxP3 expression in CD4⁺CD25⁺ T cells infiltrating the tumors. (e, f) Sequestration of intratumoral TGF- β with TGF β RII:Fc reduces CD4⁺CD25⁺FoxP3⁺ Tregs in tumor tissue and improves the antitumor efficacy of doxorubicin. MB49 tumor-bearing mice were administered doxorubicin (5 mg/kg i.p. weekly $\times 3$) with or without twice weekly treatment with TGF β RII:Fc (1 μg intratumoral). The percentage of CD4⁺CD25⁺FoxP3⁺ cells (Tregs) among tumor cells was assessed by flow cytometry (e), and tumor volume was monitored to determine the effect of counteracting tumor-induced TGF- β -mediated immune tolerance on the in vivo antitumor efficacy of doxorubicin (f).

FIG. 55 shows that anti-CD4 antibody-mediated depletion of CD4⁺ regulatory T cells facilitates chemotherapy-induced activation of tumor-reactive CD8⁺ T cells and enhances the antitumor efficacy of chemotherapy. (a) In vivo depletion of tumor-infiltrating CD4⁺CD25⁺FoxP3⁺ T cells by treatment of tumor-bearing mice with anti-CD4 antibody. C57BL/6 mice injected with 5×10^5 MB49 tumor cells s.c. were left untreated (control) or administered an anti-CD4 antibody (Clone GK1.5) i.p. at 5 d and 9 d following tumor challenge. CD4⁺CD25⁺FoxP3⁺ T cells infiltrating tumors isolated from mice at d16 following tumor challenge were detected by flow

cytometry. (b) Target-specific depletion of either CD4⁺ T cells, CD4⁺CD25⁺FoxP3⁺ T cells, or CD8⁺ T cells by treatment of tumor-bearing mice with anti-CD4 antibody or anti-CD8 antibody. C57BL/6 mice injected s.c. with 5×10^5 MB49 tumor cells were left untreated or treated with doxorubicin (5 mg/kg i.p. weekly $\times 3$) beginning at d7 following tumor inoculation, with or without administration of either anti-CD4 antibody (Clone GK1.5) or anti-CD8 antibody (Clone GK2.43) at d5 and d9 following tumor inoculation. Flow cytometric analyses of peripheral blood mononuclear cells isolated from mice at d16 following tumor challenge determined the percentage of CD4⁺ T cells or CD8⁺ T cells among total mononuclear cells, and the percentage of CD4⁺CD25⁺FoxP3⁺ T cells among total CD4⁺ T cells. (c) Depletion of CD4 regulatory T cells facilitates chemotherapy-induced activation of tumor-reactive CD8⁺ T cells. C57BL/6 mice injected s.c. with 5×10^5 MB49 tumor cells were left untreated or treated with doxorubicin (5 mg/kg i.p. weekly $\times 3$) beginning at d7 following tumor inoculation, with or without administration of anti-CD4 antibody (Clone GK1.5) at d5 and d9 following tumor inoculation. Tumor-reactive immune responses were determined by flow cytometric analyses of IFN- γ expression in CD8⁺ T cells from the tumor and draining lymph node in response to in vitro stimulation with MB49 cell lysates. (d) Depletion of CD4⁺ regulatory T cells augments the in vivo antitumor efficacy of chemotherapy via activation of tumor-reactive CD8⁺ T cells. C57BL/6 mice injected s.c. with 5×10^5 MB49 tumor cells were left untreated or treated with doxorubicin (5 mg/kg i.p. weekly $\times 3$) beginning at d7 following tumor inoculation, with or without administration of either anti-CD4 antibody (Clone GK1.5) or anti-CD8 antibody (Clone GK2.43) at d5 and d9 following tumor inoculation. Tumor volume was monitored to determine the effect of depleting either CD4⁺ T cells or CD8⁺ T cells on the in vivo antitumor efficacy of doxorubicin.

FIG. 56 shows anti-CD4 antibody-mediated depletion of CD4⁺ regulatory T cells augments and sustains the antitumor effect of chemotherapy by enabling activation of adaptive antitumor immunity. (a) Surface exposure of calreticulin (CRT) in response to treatment of MB49 cancer cells with either cisplatin or the combination of cisplatin and gemcitabine for 4 h. The surface exposure of CRT was determined by immunofluorescence cytometry of untreated control or chemotherapy-treated cells stained with DyLight-labeled anti-CRT antibody or an isotype control (IgG1) antibody. (b,c) Depletion of CD4⁺ regulatory T cells enables cisplatin-induced activation of tumor-reactive IFN- γ ⁺CD8⁺ T cells and effector memory (CD8⁺CD62L⁺) T cells. C57BL/6 mice injected s.c. with 5×10^5 MB49 tumor cells were left untreated or treated with cisplatin (0.5 mg/kg i.p. weekly $\times 4$) beginning at d7 following tumor inoculation, with or without administration of anti-CD4 antibody (Clone GK1.5) at d5 and d9 following tumor inoculation. Tumor-reactive immune responses were determined by flow cytometric analyses of IFN- γ expression in CD8⁺ T cells from the tumor and draining lymph node (DLN) in response to in vitro stimulation with MB49 cell lysates (b). The percentage of effector memory T_{EM} cells was determined by flow cytometric analyses of CD8⁺CD62L⁺ cells (c). (d,e,f) Depletion of CD4⁺ regulatory T cells augments the in vivo antitumor efficacy of chemotherapy via activation of tumor-reactive CD8⁺ T cells. C57BL/6 mice injected s.c. with 5×10^5 MB49 tumor cells were left untreated or treated with either cisplatin (0.5 mg/kg) or the combination of cisplatin and gemcitabine (i.p. weekly $\times 4$) beginning at d7 following tumor inoculation, with or without administration of either anti-CD4 antibody (Clone GK1.5) or anti-CD8 antibody (Clone GK2.43) at d5 and d9

following tumor inoculation. Tumor volume was monitored to determine the effect of depleting either CD4⁺ T cells or CD8⁺ T cells on the in vivo antitumor efficacy of chemotherapy and the percentage of mice exhibiting complete tumor-regression by d50 following tumor inoculation. Establishment of adaptive antitumor immunity following regression of primary tumors was determined by re-challenging mice with live MB49 tumor cells in the opposite flank.

FIG. 57 shows that Chemotherapy-induced expression of NKG2D ligands on tumor cells cooperates with depletion of CD4⁺ regulatory T cells to stimulate CD8⁺ T cell-mediated tumor regression. (a) Genotoxic chemotherapeutic agents induce expression of mouse NKG2D ligands (Rae-1) on cancer cells. Kinetics of the upregulation of Rae1 transcripts in mouse CT26 colon cancer cells was determined by quantitative real-time PCR following treatment with irinotecan (25 µg/ml) or oxaliplatin (10 µg/ml). Quantitative RT-PCR was carried out using, Rae-1 specific primers [sense, 5'-CTAGT-GCCACCTGGGAATTCA-3' (SEQ ID NO: 111); anti-sense, 5'-CATCATTAGCTGATCTCCAGCTCA-3' (SEQ ID NO: 112)] and probe [5'-6-FAM-CATCAGTGACAGTTACTTCTTCACCTTCTACACAGAGA-Tamra-3" (SEQ ID NO: 113)]. (b) Genotoxic chemotherapeutic agents induce p53-independent cell surface expression of human NKG2D ligands (MHC-1-related A and B molecules—MICA/MICB) on cancer cells. Isogenic p53-proficient (p53^{+/+}) or p53-deficient (p53^{-/-}) HCT116 cells were treated with irinotecan (25 µg/ml) for 16 h or left untreated. Irinotecan-induced upregulation of cell surface expression of MICA/B was determined by flow cytometric analysis of tumor cells labeled with an anti-human MICA/B MAb (R&D Systems). (c) & (d) Induction of NKG2D ligands contributes to the antitumor effect of chemotherapy in vivo. Immunocompetent Balb/C mice injected s.c. with 2×10⁵ syngeneic CT26 tumor cells were treated with irinotecan (50 mg/kg i.p weekly×3) beginning at d5 following tumor inoculation, with or without pre-treatment with an NKG2D blocking antibody (CX5, eBioscience) (200 µg i.p.) at 16 h before each dose of chemotherapy. Tumor volume was monitored to determine the effect of NKG2D blockade on the in vivo antitumor efficacy of irinotecan. (e) In vivo depletion of CD4⁺CD25⁺FoxP3⁺ T cells by treatment of tumor-bearing mice with anti-CD4 antibody. Balb/C mice injected with 2×10⁵ CT26 tumor cells s.c. were left untreated or treated with irinotecan (50 mg/kg i.p weekly×3) beginning at d7 following tumor inoculation, with or without administration of anti-CD4 antibody (Clone GK1.5) at d5 and d9 following tumor inoculation. CD4⁺CD25⁺FoxP3⁺ T cells in spleen and draining lymph node isolated from mice at d16 following tumor challenge were detected by flow cytometry. (f) Depletion of CD4⁺ regulatory T cells facilitates irinotecan-induced activation of tumor-reactive IFN-γ⁺CD8⁺ T cells. Balb/C mice injected with 2×10⁵ CT26 tumor cells s.c. were left untreated or treated with irinotecan (50 mg/kg i.p weekly×3) beginning at d7 following tumor inoculation, with or without administration of anti-CD4 antibody (Clone GK1.5) at d5 and d9 following tumor inoculation. Tumor-reactive immune responses were determined by flow cytometric analyses of IFN-γ expression in CD8⁺ T cells from the tumor and draining lymph node (DLN) in response to in vitro stimulation with either CT26 cell lysates, an irrelevant peptide (Hemagglutinin-HA), or medium alone. (g) & (h) Chemotherapy-induced expression of NKG2D ligands on tumor cells cooperates with depletion of CD4⁺ regulatory T cells to stimulate CD8⁺ T cell-mediated tumor regression. Balb/C mice injected with 2×10⁵ CT26 tumor cells s.c. were left untreated or treated with irinotecan (50 mg/kg i.p weekly×3) beginning at d7 following tumor

inoculation, with or without administration of anti-CD4 antibody (Clone GK1.5) and/or anti-CD8 antibody (Clone GK2.43) at d5 and d9 following tumor inoculation. Tumor volume was monitored to determine the effect of depleting CD4⁺ T cells and/or CD8⁺ T cells on the in vivo antitumor efficacy of irinotecan.

DETAILED DESCRIPTION OF THE INVENTION

Targeted immunostimulatory antibodies and/or fusion proteins for prevention or treatment of cancer: Chemotherapy is a cornerstone of systemic treatment of patients with most common types of advanced cancers. The vast majority of human cancers harbor genetic alterations and signaling mechanisms that impair the direct death signaling pathways entrained by chemotherapeutic agents. Although chemotherapeutic agents employ diverse mechanisms to directly kill tumor cells, the present invention provides that these agents have immuno-adjuvant effects which activate innate and adaptive antitumor immune responses that are crucial for their antitumor efficacy in vivo. The present invention also provides that antitumor CD8⁺ T cells play an instrumental role in the in vivo response of tumors to diverse cytotoxic chemotherapeutic agents. Although chemotherapeutic agents can induce "immunogenic" tumor cell death and facilitate cross-presentation of antigens by dendritic cells, tumors create a tolerogenic environment that allows them to suppress the activation of innate and adaptive immune responses and evade immunologic attack by immune effector cells. The present invention provides that strategies to counteract tumor-induced immune tolerance in the tumor microenvironment can enhance the antitumor efficacy of chemotherapy by activating and leveraging T cell-mediated adaptive antitumor immunity against disseminated cancer cells.

The present invention is based on the seminal discovery that targeted immunomodulatory antibodies and fusion proteins can counteract or reverse immune tolerance of cancer cells. Cancer cells are able to escape elimination by chemotherapeutic agents or tumor-targeted antibodies via specific immunosuppressive mechanisms in, the tumor microenvironment and such ability of cancer cells is recognized as immune tolerance. By counteracting tumor-induced immune tolerance, the present invention provides effective compositions and methods for cancer treatment, optional in combination with another existing cancer treatment.

The present invention provides compositions and methods for targeted immunostimulatory antibodies and fusion proteins that counteract immune tolerance in the tumor microenvironment and promote T cell-mediated adaptive antitumor immunity for maintenance of durable long-term protection against recurrent or disseminated cancers. These tumor-targeted immunostimulatory molecules are designed to facilitate effective long term T cell-mediated immune responses against tumor cells by at least one of the following:

- (i) promoting death of tumor cells via enhancement of antibody-dependent cellular cytotoxicity (ADCC);
- (ii) facilitating effective cross-presentation of tumor antigen(s) from dying tumor cells by augmenting maturation of dendritic cells (DCs); and
- (iii) increasing activation and proliferation of antitumor CD8⁺ T cells by negating immune suppression mediated by regulatory T cells and myeloid suppressor cells. These antitumor immune responses may be activated in tandem with the sensitization of tumor cells to immune effector-mediated cytotoxicity, thereby establishing a positive feedback loop that augments tumor cytorreduction and reinforces adaptive antitumor immunity. The tumor-targeted immunostimulatory

monoclonal antibodies (mAbs) of the present invention provides the ability to generate and boost antitumor immunity to multiple cross-presented tumor antigens obtained from endogenous tumor cells during the course of therapy (as an, in situ tumor vaccine), while simultaneously leveraging the antitumor immune response to eliminate disseminated cancer cells. Accordingly, the targeted immunostimulatory antibodies and fusion proteins of the invention can integrate the hitherto distinct fields of passive and active immunotherapy and provide a novel platform for simultaneously leveraging the synergistic benefits of these strategies to entrain effective innate and adaptive immune responses against targeted cancers.

While passive immunotherapy of cancer with tumor-targeted monoclonal antibodies has demonstrated clinical efficacy, the goal of active therapeutic vaccination to induce T cell-mediated immunity and establish immunological memory against tumor cells has remained challenging. Several tumor-specific and tumor-associated antigens have been identified, yet tumors employ diverse mechanisms to create a tolerogenic environment that allows them to suppress the activation of a T cell-mediated antitumor immune response. The tumor-targeted immunostimulatory antibodies and/or fusion proteins of the invention are designed to overcome such immune tolerance in the tumor microenvironment and activate robust levels of T cell responses for effective cancer immunotherapy or chemo-immunotherapy. Accordingly, the tumor-targeted immunostimulatory antibodies and/or fusion proteins of the invention have broad clinical relevance for advancing the treatment of many types of human cancers.

The tumor-targeted immunostimulatory mAbs and/or fusion proteins of the invention provide their ability to generate and boost antitumor immunity to multiple cross-presented tumor antigens obtained from endogenous tumor cells during the course of therapy (as an in situ tumor vaccine), while simultaneously leveraging the antitumor immune response to eliminate disseminated cancer cells. Accordingly, the tumor-targeted immunostimulatory antibodies and/or fusion proteins of the invention can integrate the hitherto distinct fields of passive and active immunotherapy and provide a novel platform for simultaneously leveraging the synergistic benefits of these strategies to entrain effective innate and adaptive immune responses against targeted cancers. This approach of the present invention is distinguished from and superior to conventional tumor antigen-, allogeneic tumor cell- or DC-based vaccines in at least one of the following aspects: (i) There is no a priori requirement to define, clone and purify individual tumor antigens, since the patient's tumor itself is the in vivo source of antigens; (ii) Multivalent antitumor immune responses that are naturally tailored against antigens from the patient's own tumor are less likely to allow immune escape than a pre-selected tumor antigen; (iii) The activation of antitumor immune responses by the immuno-adjuvant effects of tumor-targeted immunostimulatory antibodies or fusion proteins occurs in tandem with the sensitization of tumor cells to immune effector-mediated cytotoxicity, thereby establishing a positive feedback loop that augments tumor cytorreduction and reinforces adaptive antitumor immunity; and (iv) The molecules of the invention have broad clinical relevance for advancing the treatment of many types of human cancers.

In addition, the targeted immunostimulatory antibodies and/or fusion proteins of the invention are distinguished from and superior to existing therapeutic molecules in at least one of the following aspects: (i) To counteract immune tolerance in the tumor microenvironment and promote T cell-mediated adaptive antitumor immunity for maintenance of long-term

protection against recurrent or disseminated cancers (for prevention or treatment of diverse cancers); (ii) To produce immune cell compositions for adoptive cellular therapy of diverse cancers; and (iii) To serve as immune adjuvants or vaccines for prophylaxis of diverse cancers or infectious diseases.

The targeted immunostimulatory antibodies and/or fusion proteins of the invention provide the ability to disrupt immunosuppressive networks in the tumor microenvironment. Tumors employ a wide array of regulatory mechanisms to avoid or suppress the immune response. Cancer cells actively promote immune tolerance in the tumor microenvironment via the expression of cytokines and molecules that inhibit the differentiation and maturation of antigen-presenting dendritic cells. The immunosuppressive cytokines and ligands produced by tumor cells include the following: (i) Transforming growth factor-beta (TGF- β); (ii) Programmed death-1 ligand 1 (PD-L1; B7-H1); (iii) Vascular endothelial growth factor (VEGF); and (iv) Interleukin-10 (IL-10). In addition to blocking dendritic cell (DC) maturation, these molecules promote the development of specialized subsets of immunosuppressive CD4⁺ T cells (regulatory T cells; Treg cells) and myeloid-derived suppressor cells (MDSC). Tregs are a minority sub-population of CD4⁺ T cells that constitutively express CD25 [the interleukin-2 (IL-2) receptor α -chain] and the forkhead box P3 (FOXP3) transcription factor. Tregs (CD4+CD25+FoxP3+ cells) maintain immune tolerance by restraining the activation, proliferation, and effector functions of a wide range of immune cells, including CD4⁺ and CD8⁺ T cells, natural killer (NK) and NKT cells. B cells and antigen presenting cells (APCs) in vitro and in vivo. The accumulation of Treg cells in the tumor microenvironment re-inforces tumor immune tolerance and facilitates tumor progression and metastases. The increased expression of immunosuppressive cytokines (TGF- β ; PD-L1) and tumor-infiltrating Tregs is correlated with a reduction of survival of patients with diverse types of cancers. The present invention provides that tumor-induced immune tolerance mediated via Tregs is a crucial determinant of the resistance of cancers to cytotoxic chemotherapeutic agents and tumor-targeted antibodies. The targeted immunostimulatory antibodies and/or fusion proteins of the invention inhibit key immunosuppressive molecules expressed by the targeted tumor cell or tumor-infiltrating Treg cells and myeloid suppressor cells (DCs or MDSC). As such, they provide the targeted ability to inhibit the development or function of Tregs within the tumor microenvironment. In another aspect, they provide the ability to counteract Treg-induced immune suppression in the tumor microenvironment.

The targeted immunostimulatory antibodies and/or fusion proteins of the invention provide the ability to inhibit the development or function of Tregs and myeloid suppressor cells (DCs or MDSC) within the tumor microenvironment. Tregs (CD4+CD25+FoxP3+ cells) express an array of immunosuppressive cytokines and molecules which act in concert to induce immune tolerance and promote tumor progression and metastases. These include: (1) Cytotoxic T-lymphocyte associated protein 4 (CTLA-4; CD152), a co-inhibitory receptor that binds to the ligands CD80 (B7-1) or CD86 (B7-2) on the antigen presenting cell (APC) and inhibits co-stimulation of T cells; (ii) Programmed death-1 ligand 1 (PD-L1; B7-H1), a ligand which engages the co-inhibitory receptor Programmed death-1 (PD-1) and inhibits T cell activation and proliferation. (iii) Transforming growth factor-beta (TGF- β), a cytokine which regulates immune responses by restricting the maturation and antigen-presenting function of dendritic cells, inhibiting the proliferation and activation of

naïve T cells, suppressing the expression of cytotoxic molecules (Granzyme A/B, FasL, Apo2L/TRAIL, IFN- γ) in immune effector cells, and promoting the development and function of Tregs; (iv) Receptor activator of nuclear factor- κ B ligand (RANKL), a ligand which engages Receptor activator of nuclear factor- κ B (RANK) and promotes osteoclast differentiation. Treg development, and tumor metastases. In addition, Tregs express other surface molecules; (v) LAG-3, a CD4-related molecule that hinders MHC class II (vi) glucocorticoid-induced tumor necrosis factor receptor family-related gene (GITR; TNFRSF18); and (vii) IL-10. The targeted immunostimulatory antibodies and/or fusion proteins of the invention provide the ability to bind a targeted molecule expressed by Tregs or myeloid suppressor cells while concurrently sequestering and inhibiting one or more immunosuppressive molecule that promotes their development, survival or function. In one aspect, the targeted immunostimulatory antibodies and/or fusion proteins directly deplete the number of Tregs.

In one embodiment, the present invention provides a molecule including a targeting moiety fused with an immunomodulatory moiety. The targeting moiety specifically binds a target molecule on the tumor cell or tumor microenvironment (tumor stroma, tumor vasculature, or tumor infiltrating immune cell), and the immunomodulatory moiety specifically binds an immunosuppressive molecule expressed by the targeted tumor cell or tumor-infiltrating Treg cells and myeloid suppressor cells (DC or MDSC).

In one embodiment, the present invention provides a molecule including a targeting moiety fused with an immunomodulatory moiety. The targeting moiety specifically binds a target molecule expressed by Treg cells, myeloid suppressor cells (MDSC), or dendritic cells (DC), and the immunomodulatory moiety specifically binds an immunosuppressive molecule that promotes their development, survival or function.

In one embodiment, the present invention provides a molecule including a targeting moiety fused with an immunomodulatory moiety. The targeting moiety specifically binds a target molecule, and the immunomodulatory moiety specifically binds one of the following molecules: (i) Transforming growth factor-beta (TGF- β); (ii) Programmed death-1 ligand 1 (PD-L1) or Programmed death-1 ligand 2 (PD-L2); (iii) Receptor activator of nuclear factor- κ B (RANK) ligand (RANKL); (iv) Vascular endothelial growth factor (VEGF); (v) Transforming growth factor-beta receptor (TGF- β R); (vi) Programmed death-1 (PD-1); and (vii) Receptor activator of nuclear factor- κ B (RANK).

In one aspect, the targeting moiety includes an antibody, antibody fragment, scFv, or Fc-containing polypeptide that specifically binds a component of a tumor cell, tumor antigen, tumor vasculature, tumor microenvironment, or tumor-infiltrating immune cell. In one aspect, the targeting moiety specifically binds epidermal growth factor receptor (EGFR1, Erb-B1), HER2/neu (Erb-B2), CD20, Vascular endothelial growth factor (VEGF), insulin-like growth factor receptor (IGF-1R), TRAIL-receptor, epithelial cell adhesion molecule, carcino-embryonic antigen, Prostate-specific membrane antigen, Mucin-1, CD30, CD33, or CD40.

In one aspect, the targeting moiety specifically binds a component of a regulatory T cell myeloid suppressor cell or dendritic cell. In another aspect, the targeting moiety specifically binds one of the following molecules: (i) CD4; (ii) CD25 (IL-2 α receptor; IL-2 α R); (iii) cytotoxic T-lymphocyte antigen-4 (CTLA-4; CD152); (iv) Interleukin-10 (IL-10); (v) Transforming growth factor-beta receptor (TGF- β R); (vi) Transforming growth factor-beta (TGF- β); (vii) Programmed Death-1 (PD-1); (viii) Programmed death-1 ligand

(PD-L1 or PD-L2); (ix) Receptor activator of nuclear factor- κ B (RANK); (x) Receptor activator of nuclear factor- κ B (RANK) ligand (RANKL); (xi) LAG-3; or ND glucocorticoid-induced tumor necrosis factor receptor family-related gene (GITR; TNFRSF18).

In one aspect, the immunomodulatory moiety specifically binds one of the following molecules: (i) Transforming growth factor-beta (TGF- β); (ii) Programmed death-1 ligand (PD-L1 or PD-L2); (iii) Receptor activator of nuclear factor- κ B (RANK) ligand (RANKL); or (iv) vascular endothelial growth factor (VEGF).

In one aspect, the immunomodulatory moiety includes a molecule that binds TGF- β . In another aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain of Transforming growth factor-beta receptor TGF- β R1, TGF- β R2, or TGF- β R3. In another aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain of TGF- β R1. In another aspect, the molecule includes a TGF- β -binding amino acid sequence corresponding to SEQ ID NOs: 79-91. In an additional aspect, the immunomodulatory moiety inhibits the activity or function of TGF- β .

In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to HER2/neu, EGFR1, CD20, vascular endothelial growth factor (VEGF), cytotoxic T-lymphocyte antigen-4 (CTLA-4), CD25 (IL-2 α receptor; IL-2 α R), or CD4. In an additional aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain of TGF- β R1. In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10.

In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to Programmed Death-1 (PD-1), Programmed death-1 ligand 1 (PD-L1), or Programmed death-1 ligand 2 (PD-L2). In another aspect the targeting moiety includes an extracellular ligand-binding domain or ectodomain of Programmed Death-1 (PD-1). In an additional aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain of TGF- β R1. In another aspect, the molecule includes PD-1 ectodomain, immunoglobulin Fc region, and TGF β R1 ectodomain. In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO 11 or 12.

In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to Receptor activator of nuclear factor- κ B (RANK) or Receptor activator of nuclear factor- κ B ligand (RANKL). In another aspect, the targeting moiety includes an extracellular ligand-binding domain or ectodomain of Receptor activator of nuclear factor- κ B (RANK). In an additional aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain of TGF- β R1. In another aspect, the molecule includes RANK ectodomain, immunoglobulin Fc region, and TGF β R1 ectodomain. In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO 13 or 14.

In one aspect, the immunomodulatory moiety includes a molecule that specifically binds to Programmed death-1 ligand 1 (PD-L1) or Programmed death-1 ligand 2 (PD-L2). In another aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain or ectodomain of Programmed Death-1 (PD-1). In another aspect, the molecule includes a PD-L1-binding amino acid sequence corresponding to SEQ ID NO: 92, 93, or 94. In an additional aspect, the immunomodulatory moiety inhibits the activity or function of Programmed death-1 ligand 1 (PD-L1).

In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to HER2/neu, EGFR1, CD20, vascular endothelial growth factor (VEGF), cytotoxic T-lymphocyte antigen-4 (CTLA-4), CD25 (IL-2 α receptor; IL-2 α R), or CD4. In an additional aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain or ectodomain of Programmed Death-1 (PD-1). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24.

In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to Receptor activator of nuclear factor- κ B (RANK) or Receptor activator of nuclear factor- κ B ligand (RANKL). In another aspect the targeting moiety includes an extracellular ligand-binding domain or ectodomain of Receptor activator of nuclear factor- κ B (RANK). In an additional aspect the immunomodulatory moiety includes an extracellular ligand-binding domain of Programmed Death-1 (PD-1). In another aspect, the molecule includes RANK ectodomain, immunoglobulin Fc region, and PD-1 ectodomain. In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO 25 or 26.

In one aspect, the immunomodulatory moiety includes a molecule that specifically binds to Receptor activator of nuclear factor- κ B ligand (RANKL). In another aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain or ectodomain of Receptor activator of nuclear factor- κ B (RANK). In another aspect, the molecule includes a RANKL-binding amino acid sequence corresponding to SEQ ID NO: 95, 96, 97, or 98. In an additional aspect, the immunomodulatory moiety inhibits the activity or function of Receptor activator of nuclear factor- κ B ligand (RANKL).

In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to HER2/neu, EGFR1, CD20, vascular endothelial growth factor (VEGF), cytotoxic T-lymphocyte antigen-4 (CTLA-4), CD25 (IL-2 α receptor; IL-2 α R), or CD4. In an additional aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain or ectodomain of Receptor activator of nuclear factor- κ B (RANK). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36.

The present invention provides novel targeted immunosuppressive antibodies and fusion proteins that induce or promote immune tolerance by at least one of the following:

- (i) inhibiting the activation of dendritic cells, T cells, and/or B cells; and
- (ii) promoting the development and/or suppressor function of regulatory T cells and immunosuppressive myeloid DCs. These targeted immunosuppressive molecules of the invention are designed to suppress unwanted or excessive immune or inflammatory responses in order to treat autoimmune or inflammatory diseases or prevent the rejection of a transplanted cell, tissue, or organ.

Targeted immunosuppressive antibodies and/or fusion proteins: The aberrant activation of self-reactive T cells and/or breakdown of the mechanisms of immune tolerance promotes the development of autoimmunity that results in various diseases including type I diabetes mellitus, multiple sclerosis, systemic lupus erythematosus, inflammatory bowel disease, and rheumatoid arthritis. The targeted immunosuppressive antibodies and/or fusion proteins of the invention are designed to suppress unwanted or excessive immune or inflammatory responses and restore or promote immune tolerance. Accordingly, the compositions and methods of the

invention have broad clinical relevance for the treatment of diverse autoimmune or inflammatory diseases and preventing the rejection of a transplanted cell, tissue, or organ grafts.

The targeted immunosuppressive antibodies and/or fusion proteins of the invention provides their ability to inhibit the activity of targeted pro-inflammatory cytokines or immune cells while simultaneously promoting immune tolerance via the targeted delivery of immunosuppressive molecules that facilitate the development and/or function of regulatory T cells. These molecules of the present invention are distinguished from and superior to existing therapeutic molecules in at least one of the following aspects: (i) The molecules of the invention enable targeted delivery of immunosuppressive molecules to immune cells or pro-inflammatory molecules in the milieu of the affected cell, tissue or organ; (ii) The molecules of the invention can couple the inhibition of the targeted pro-inflammatory molecule or immune cell with the simultaneous delivery of an immunosuppressive molecule that promotes immune tolerance, thereby improving the suppression of immune effector cells; and (iii) The molecules of the invention can provide a mechanism of simultaneously engaging two independent or synergistic mechanisms of immune tolerance or immune suppression.

Further, the targeted immunosuppressive antibodies and/or fusion proteins of the invention are distinguished from and superior to existing therapeutic molecules in at least one of the following aspects: (i) To suppress unwanted or excessive immune or inflammatory responses in order to treat autoimmune or inflammatory diseases; and (ii) To prevent the rejection of a transplanted cell, tissue, or organ grafts.

In one aspect, the immunomodulatory moiety includes a sequence from Programmed death-1 ligand 1 (PD-L1) or Programmed death-1 ligand 2 (PD-L2). In another aspect, the molecule includes a PD-1-binding amino acid sequence corresponding to SEQ ID NO 99, 100, or 101. In an additional aspect, the immunomodulatory moiety increases the function of PD-1.

In one aspect, the targeting moiety specifically binds to Tumor Necrosis Factor- α (TNF- α), and the immunomodulatory moiety includes a sequence from Programmed death-1 ligand 1 (PD-L1) or Programmed death-1 ligand 2 (PD-L2). In an additional aspect, the targeting moiety includes an antibody that binds TNF- α , and the immunomodulatory moiety includes a sequence from PD-1 ligand 1 (PD-L1 or B7-H1). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO 37. In another aspect, the targeting moiety includes an extracellular ligand-binding domain of tumor necrosis factor receptor 2 (TNFR2), and the immunomodulatory moiety includes a sequence from PD-1 ligand 1 (PD-L1 or B7-H1). In another aspect, the molecule includes TNFR2 Extracellular ligand binding domain, immunoglobulin Fc region, and a sequence from PD-L1. In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 38 or 39.

In one aspect, the targeting moiety includes an antibody or antibody fragment that specifically binds to CD20, CD25, or CD4, and the immunomodulatory moiety includes a sequence from Programmed death-1 ligand 1 (PD-L1) or Programmed death-1 ligand 2 (PD-L2). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO 40, 41, 42, 43, 44, or 45.

In one aspect, the targeting moiety includes the extracellular domain of CTLA-4 and immunoglobulin Fc region (IgG C γ 1), and the immunomodulatory moiety includes a sequence from Programmed death-1 ligand 1 (PD-L1) or

Programmed death-1 ligand 2 (PD-L2). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO 46 or 47.

In one aspect, the targeting moiety includes transforming growth factor- β (TGF- β) and immunoglobulin Fc region (IgG C γ 1), and the immunomodulatory moiety includes a sequence from Programmed death-1 ligand 1 (PD-L1) or Programmed death-1 ligand 2 (PD-L2). In an additional aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 48 or 49.

In one aspect, the immunomodulatory moiety includes a sequence from transforming growth factor- β (TGF- β). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO 99, 100, or 101. In an additional aspect, the immunomodulatory moiety activates the signaling function of transforming growth factor- β (TGF- β) receptor.

In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to Tumor Necrosis Factor- α (TNF- α), and the immunomodulatory moiety includes a sequence from transforming growth factor- β (TGF- β). In an additional aspect, the targeting moiety includes an antibody that binds TNF- α , and the immunomodulatory moiety includes a sequence from TGF- β . In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 50. In one aspect, the targeting moiety includes an extracellular ligand-binding domain of tumor necrosis factor receptor 2 (TNFR2). In another aspect, the molecule includes TNFR2 Extracellular ligand binding domain, immunoglobulin Fc region, and a sequence from transforming growth factor- β (TGF- β). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 51 or 52.

In one aspect, the targeting moiety includes an antibody or antibody fragment that specifically binds to CD20, CD25 (IL-2 α receptor; IL-2 α R), or CD4, and the immunomodulatory moiety includes a sequence from transforming growth factor- β (TGF- β). In an additional aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 53, 54, 55, 56, 57 or 58.

In one aspect, the targeting moiety includes an extracellular domain of CTLA-4 and immunoglobulin Fc region (IgG C γ 1), and the immunomodulatory moiety includes a sequence from transforming growth factor- β (TGF- β). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 59 or 60.

In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to Tumor Necrosis Factor- α (TNF- α), and the immunomodulatory moiety includes an extracellular RANKL-binding domain or ectodomain of Receptor activator of nuclear factor- κ B (RANK) or Osteoprotegerin (OPG). In an additional aspect, the targeting moiety includes an antibody that binds TNF- α , and the immunomodulatory moiety includes a sequence from an extracellular RANKL-binding domain or ectodomain of RANK. In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 61. In one aspect, the targeting moiety includes an extracellular ligand-binding domain of tumor necrosis factor receptor 2 (TNFR2). In another aspect, the molecule includes TNFR2 Extracellular ligand binding domain, immunoglobulin Fc region, and a sequence from an extracellular RANK-binding domain or ectodomain of RANK. In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 62 or 63.

In one aspect, the targeting moiety includes an extracellular domain of CTLA-4 and immunoglobulin Fc region (IgG C γ 1), and the immunomodulatory moiety includes an extra-

cellular RANKL-binding domain or ectodomain of Receptor activator of nuclear factor- κ B (RANK) or Osteoprotegerin (OPG). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 64 or 65.

In one aspect, the targeting moiety includes a sequence from transforming growth factor- β (TGF- β) and immunoglobulin Fc region (IgG C γ 1), and the immunomodulatory moiety includes an extracellular RANKL-binding domain or ectodomain of Receptor activator of nuclear factor- κ B (RANK). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO 66 or 67.

In one aspect, the targeting moiety includes a sequence from Programmed death-1 ligand 1 (PD-L1) and immunoglobulin Fc region (IgG C γ 1), and the immunomodulatory moiety includes an extracellular RANKL-binding domain or ectodomain of Receptor activator of nuclear factor- κ B (RANK). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 68 or 69.

In various aspects, the molecule is fused or directly linked to one or more antigen, antigenic determinant, or epitope.

In another embodiment, the present invention provides a composition including the molecule of the invention and a cell, wherein the cell is a tumor cell, immune cell, or dendritic cell.

In another embodiment, the present invention provides a method of counteracting or overcoming immune tolerance. The method includes administering to a subject in need thereof one or more molecule of the invention.

In another embodiment, the present invention provides a method of preventing or treating a neoplastic disease. In one aspect, the neoplastic disease is a non-T cell malignancy which does not express CD4 on the tumor cell. In one embodiment, the method includes administration to a subject in need thereof an antibody that targets and depletes CD4⁺ regulatory T cells (Tregs) in combination with a cytotoxic anticancer therapy. In one aspect, the antibody that targets and depletes Tregs is an anti-CD4 antibody. In various aspects, the cytotoxic anticancer therapy includes a chemotherapeutic molecule, tumor-targeted antibody, small molecule kinase inhibitor, hormonal agent, or tumor-targeted cytotoxic agent, anti-angiogenic agent or any combination thereof. In another aspect, the cytotoxic anticancer therapy includes ionizing radiation, ultraviolet radiation, cryoablation, thermal ablation, or radiofrequency ablation.

In another embodiment, the method includes administration to a subject in need thereof an antibody or molecule that targets and depletes CD4⁺ regulatory T cells (Tregs) in combination with an immunostimulatory antibody, fusion protein, peptide or ligand that targets CTLA-4, PD1, PD-1L, RANKL, TGF- β , GITR, 4-1BB, OX-40, or Toll-like receptors (TLR 1-10). In one aspect, the TLR-agonist comprises an activator of TLR-8 or TLR-9. In one aspect, the TLR agonist comprises an immunostimulatory nucleic acid sequence containing CpG nucleotides. In one aspect, the antibody that targets and depletes Tregs is an anti-CD4 antibody.

In another embodiment, the present invention provides a method of preventing or treating a neoplastic disease. The method includes administration to a subject in need thereof one or more molecule of the invention. In various aspects, the subject is administered one or more molecule of the invention in combination with another anticancer therapy. In one aspect, the anticancer therapy includes a chemotherapeutic molecule, antibody, small molecule kinase inhibitor, hormonal agent, cytotoxic agent, targeted therapeutic agent, or anti-angiogenic agent. In another aspect, the anticancer therapy includes ionizing radiation, ultraviolet radiation, cryoablation, thermal ablation, or radiofrequency ablation. In

another aspect, the subject is administered one or more molecule of the invention in combination with an antibody or molecule that inhibits the production or function of regulatory T cells (Tregs) or depletes the number of Tregs. In one aspect, the antibody that targets and depletes Tregs is an anti-CD4 antibody. In another aspect, the molecule that counteracts the function of Tregs is an antibody, fusion protein, peptide or ligand that targets CTLA-4, PD1, PD-1L, RANKL, TGF- β , GITR. In another aspect, the molecule that counteracts the function of Tregs is an antibody or fusion protein or ligand that targets 4-1BB or OX-40. In another aspect, the molecule that counteracts the function of Tregs is an agonist of Toll-like receptors (TLR 1-10). In one aspect, the TLR-agonist comprises an activator of TLR-8 or TLR-9. In one aspect, the TLR agonist is an immunostimulatory nucleic acid sequence containing CpG nucleotides.

In one aspect the chemotherapeutic agent is a topoisomerase-interacting agent, anthracycline, doxorubicin, mitoxantrone, camptothecin, camptothecin analogue, irinotecan, epipodophylotoxin, etoposide, alkylating agent, cyclophosphamide, cisplatin, cisplatin analogue, oxaliplatin, antimetabolite, fluoropyrimidine analogue, 5-fluorouracil, gemcitabine, azacytidine, antimicrotubule agent, taxane, paclitaxel, or docetaxel.

In another embodiment, the subject is administered one or more molecule of the invention in combination with any vaccine. In another aspect, the vaccine includes a tumor antigen, tumor-associated antigen, tumor epitope, tumor antigen-containing fusion protein, tumor cell, or dendritic cell. In another aspect, the vaccine includes a pathogen antigen, pathogen-associated antigen, pathogen epitope, or pathogen antigen-containing fusion protein. In one aspect, the vaccine includes a surrogate CD4+ T cell helper epitope from tetanus toxin. In one aspect, the CD4+ T helper sequence contains a domain of tetanus toxin fragment C (pDOM1). In one aspect, the pDOM sequence is fused to a cell-permeabilizing cationic polypeptide (e.g. Arginine-9). In another aspect, the Arg9-pDOM sequence is fused to a specific antigen comprising the vaccine.

In another embodiment, the present invention provides a method for treating immune cells wherein the cells are contacted ex vivo or in vitro with a molecule of the invention. In another embodiment, the present invention provides a method of treatment of a neoplastic disease. The method includes administering to a subject in need thereof a composition of immune cells contacted with a molecule of the invention.

In another embodiment, the present invention provides a method of inducing or promoting immune tolerance. The method includes administering to a subject in need thereof one or more molecule of the invention.

In another embodiment, the present invention provides a method of preventing or treating an autoimmune or inflammatory disease including administering to a subject in need thereof one or more molecule of the invention. In one aspect, the subject is administered one or more molecule of the invention in combination with another anti-inflammatory or immunosuppressive therapy. In another embodiment, the present invention provides a method of treatment of immune cells wherein the cells are contacted ex vivo or in vitro with a molecule of the invention. In another embodiment, the present invention provides a method of treating an autoimmune or inflammatory disease or preventing rejection of grafted cells or tissue. The method includes administering to a subject in need thereof a composition of immune cells contacted with a molecule of the invention.

All publications, patents, and patent applications mentioned in this specification are herein incorporated by refer-

ence to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

As used in this specification and the appended claims, the singular forms “a,” “an,” and “the” include plural references unless the context clearly dictates otherwise. Thus, for example, references to “the method” includes one or more methods, and/or steps of the type described herein which will become apparent to those persons skilled in the art upon reading this disclosure and so forth.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, the preferred methods and materials are now described.

As used herein “immune cells” or “immune effector cells” include T lymphocytes, B lymphocytes, natural killer (NK) cells, NKT cells, monocytes, macrophages, dendritic cells (DC), antigen presenting cells (APC).

As used herein, “neoplasm” or “tumor” including grammatical variations thereof, means new and abnormal growth of tissue, which may be benign or cancerous. In a related aspect, the neoplasm is indicative of a neoplastic disease or disorder, including but not limited, to various cancers. For example, such cancers can include prostate, pancreatic, biliary, colon, rectal, liver, kidney, lung, testicular, breast, ovarian, pancreatic, brain, and head and neck cancers, melanoma, sarcoma, multiple myeloma, leukemia, lymphoma, and the like.

As used herein, “subject,” including grammatical variations thereof, means a human or vertebrate animal including a dog, cat, horse, cow, pig, sheep, goat, chicken, monkey, rat, and mouse.

As used herein, “targeting moiety” refers to a molecule that has the ability to localize and bind to a specific molecule or cellular component. The targeting moiety can be an antibody, antibody fragment, scFv, Fc-containing polypeptide, fusion antibody, polypeptide, peptide, aptamer, ligand, nucleic acid, or any combination thereof. In one embodiment, a targeting moiety can bind to a molecule present in a cell or tissue. In one aspect, the targeting moiety can bind a molecule in a diseased cell or tissue, such as a cancer cell or tumor. In, another aspect, the targeting molecule can bind a normal cell or tissue, such as an immune cell. In another aspect, the targeting moiety can bind a cellular or extracellular molecule that modulates the immune response. In another aspect, the targeting moiety binds a growth factor receptor, growth factor, cytokine receptor, cytokine, or cell surface molecule.

In another embodiment, the targeting moiety is a tumor-targeting moiety. The tumor-targeting moiety can bind a component of a tumor cell or bind in the vicinity of a tumor cell (e.g., tumor vasculature or tumor microenvironment). In one embodiment, the tumor targeting moiety binds to a component of a tumor cell, tumor microenvironment, tumor vasculature, tumor-associated lymphocyte, tumor antigen, tumor-associated antigen, tumor cell surface molecule, tumor antigenic determinant, tumor antigen-containing fusion protein, tumor-associated cell, tumor-associated immune cell, or tumor vaccine.

For example, in various embodiments, a targeting moiety is specific for or binds to a molecule or component, which includes but is not limited to, epidermal growth factor receptor (EGFR, EGFR1, ErbB-1, HER1). ErbB-2 (HER2/neu), ErbB-3/HER3. ErbB-4/HER4, EGFR ligand family; insulin-like growth factor receptor (IGFR) family, IGF-binding pro-

teins (IGFBPs), IGF ligand family (IGF-1R); platelet derived growth factor receptor (PDGFR) family, PDGFR ligand family; fibroblast growth factor receptor (FGFR) family, FGFR ligand family, vascular endothelial growth factor receptor (VEGFR) family, VEGF family; HGF receptor family; TRK receptor family; ephrin (EPH) receptor family; AXL receptor family; leukocyte tyrosine kinase (LTK) receptor family; TIE receptor family, angiopoietin 1, 2; receptor tyrosine kinase-like orphan receptor (ROR) receptor family; discoidin domain receptor (DDR) family; RET receptor family; KLG receptor family; RYK receptor family; MusK receptor family; Transforming growth factor alpha (TGF- α), TGF- α receptor; Transforming growth factor-beta (TGF- β), TGF- β receptor; Interleukin β receptor alpha2 chain (IL13Ralpha2), Interleukin-6 (IL-6), IL-6 receptor, interleukin-4, IL-4 receptor, Cytokine receptors, Class I (hematopoietin family) and Class II (interferon/IL-10 family) receptors, tumor necrosis factor (TNF) family, TNF- α , tumor necrosis factor (TNF) receptor superfamily (TNFRSF), death receptor family, TRAIL-receptor; cancer-testis (CT) antigens, lineage-specific antigens, differentiation antigens, alpha-actinin-4, ARTC1, breakpoint cluster region-Abelson (Bcr-abl) fusion products, B-RAF, caspase-5 (CASP-5), caspase-8 (CASP-8), beta-catenin (CTNNB1), cell division cycle 27 (CDC27), cyclin-dependent kinase 4 (CDK4), CDKN2A, COA-1, dek-can fusion protein, EFTUD-2. Elongation factor 2 (ELF2), Ets variant gene 6/acute myeloid leukemia 1 gene ETS (ETC6-AML1) fusion protein, fibronectin (FN), GPNMB, low density lipid receptor/GDP-L fucose: beta-Dgalactose 2-alpha-L-fucosyltransferase (LDLR/FUT) fusion protein. HLA-A2, arginine to isoleucine exchange at residue 170 of the alpha-helix of the alpha2-domain in the HLA-A2 gene (HLA-A*201-R170I), M.L.A-A11, heat shock protein 70-2 mutated (HSP70-2M), KIAA0205, MART2, melanoma ubiquitous mutated 1, 2, 3 (MUM-1, 2, 3), prostatic acid phosphatase (PAP), neo-PAP, Myosin class 1, NFYC, OGT, OS-9, pml-RARalpha fusion protein, PRDX5, PTPRK, K-ras (KRAS2), N-ras (NRAS), HRAS, RBAF600, SIRT2, SNRPD1, SYT-SSX1 or -SSX2 fusion protein, Triosephosphate Isomerase, BAGE, BAGE-1, BAGE-2, 3, 4, 5, GAGE-1, 2, 3, 4, 5, 6, 7, 8, GnT-V (aberrant N-acetyl glucosaminyl transferase V, MGAT5), HERV-K MEL, KK-LC, KM-HN-1, LAGE, LAGE-1, CTL-recognized antigen on melanoma (CAMEL), MAGE-A1 (MAGE-1), MAGE-A2, MAGE-A3, MAGE-A4, MAGE-AS, MAGE-A6, MAGE-A8, MAGE-A9, MAGE-A10, MAGE-A11, MAGE-A12, MAGE-3, MAGE-B1, MAGE-B2, MAGE-B5, MAGE-B6, MAGE-C1, MAGE-C2, mucin 1 (MUC1), MART-1/Melan-A (MLANA), gp100, gp100/Pmel117 (SILV), tyrosinase (TYR), TRP-1, HAGE, NA-88, NY-ESO-1, NY-ESO-1/LAGE-2, SAGE, Sp17, SSX-1, 2, 3, 4, TRP2-INT2, carcinoembryonic antigen (CEA), Kallikrein 4, mammaglobin-A, OA1, prostate specific antigen (PSA), prostate specific membrane antigen, TRP-1/, 75. TRP-2 adipophilin, interferon inducible protein absent in melanoma 2 (AIM-2), BING-4, CPSF, cyclin D1, epithelial cell adhesion molecule (EpCAM), EpcA3, fibroblast growth factor-5 (FGF-5), glycoprotein 250 (gp250) intestinal carboxyl esterase (iCE), alpha-feto protein (AFP), M-CSF, mdm-2, MUC1, p53 (TP53), PBF, FRAME, PSMA, RAGE-1, RNF43, RU2AS, SOX10, STEAP1, survivin (BIRC5), human telomerase reverse transcriptase (hTERT), telomerase, Wilms' tumor gene (WT1), SYCP1, BRD1, SPANX, XAGE, ADAM2, PAGE-5, LIP1, CTAGE-1, CSAGE, MMA1, CAGE, BORIS, HOM-TES-85, AF15q14, HCA661, LDHC, MORC, SGY-1, SPO11, TPX1, NY-SAR-35, FTHL17, NXF2 TDRD1, TEX 15, FATE, TPTE, immunoglobulin idiotypes, Bence-Jones protein,

estrogen receptors (ER), androgen receptors (AR), CD40, CD30, CD20, CD19, CD33, CD4, CD25, CD3, cancer antigen 72-4 (CA 72-4), cancer antigen 15-3 (CA 15-3), cancer antigen 27-29 (CA 27-29), cancer antigen 125 (CA 125), cancer antigen 19-9 (CA 19-9), beta-human chorionic gonadotropin, 1-2 microglobulin, squamous cell carcinoma antigen, neuron-specific enolase, heat shock protein gp96, GM2, sargramostim, CTLA-4, 707 alanine proline (707-AP), adenocarcinoma antigen recognized by T cells 4 (ART-4), carcinoembryonic antigen peptide-1 (CAP-1), calcium-activated chloride channel-2 (CLCA2), cyclophilin B (Cyp-B), human signet ring tumor-2 (HST-2), Human papilloma virus (HPV) proteins (HPV-E6, HPV-E7, major or minor capsid antigens, others), Epstein-Barr virus (EBV) proteins (EBV latent membrane proteins—LMP1, LMP2; others), Hepatitis B or C virus proteins, and HIV proteins. A composition of the invention can further include the foregoing as a peptide/polypeptide and/or encoding the same.

In one aspect, the targeting moiety includes an antibody, antibody fragment, scFv, or Fc-containing polypeptide that specifically binds a component of a tumor cell, tumor antigen, tumor vasculature, tumor microenvironment, or tumor-infiltrating immune cell. In one aspect, the targeting moiety specifically binds epidermal growth factor receptor (EGFR1, Erb-B1), HER2/neu (Erb-B2), CD20. Vascular endothelial growth factor (VEGF), insulin-like growth factor receptor (IGF-1R). TRAIL-receptor, epithelial cell adhesion molecule, carcino-embryonic antigen, Prostate-specific membrane antigen. Mucin-1, CD30, CD33, CD40, or a combination thereof.

Examples of antibodies which can be incorporated into compositions and methods disclosed herein include, but are not limited, to antibodies such as trastuzumab (anti-HER2/neu antibody); Pertuzumab (anti-HER2 mAb); cetuximab (chimeric monoclonal antibody to epidermal growth factor receptor EGFR); panitumumab (anti-EGFR antibody); nimotuzumab (anti-EGFR antibody); Zalutuzumab (anti-EGFR mAb); Necitumumab (anti-EGFR mAb); MDX-210 (humanized anti-HER-2 bispecific antibody); MDX-210 (humanized anti-HER-2 bispecific antibody); MDX-447 (humanized anti-EGF receptor bispecific antibody); Rituximab (chimeric murine/human anti-CD20 mAb); Obinutuzumab (anti-CD20 mAb); Ofatumumab (anti-CD20 mAb); Tositumumab-1131 (anti-CD20 mAb); Ibritumomab tiuxetan (anti-CD20 mAb); Bevacizumab (anti-VEGF mAb); Ramucirumab (anti-VEGFR2 mAb); Ranibizumab (anti-VEGF mAb); Aflibercept (extracellular domains of VEGFR1 and VEGFR2 fused to IgG1 Fc); AMG386 (angiopoietin-1 and -2 binding peptide fused to IgG1 Fc); Dalotuzumab (anti-IGF-1R mAb); Gemtuzumab ozogamicin (anti-CD33 mAb); Alemtuzumab (anti-Campath-1/CD52 mAb); Brentuximab vedotin (anti-CD30 mAb); Catumaxomab (bispecific mAb that targets epithelial cell adhesion molecule and CD3); Naptumomab (anti-5T4 mAb); Girentuximab (anti-Carbonic anhydrase ix); or Farletuzumab (anti-folate receptor). Other examples include antibodies such as Panorex™ (17-1A) (murine monoclonal antibody); Panorex (@17-1A) (chimeric murine monoclonal antibody); BEC2 (anti-idiotypic mAb, mimics the GD epitope) (with BCG); Oncolym (Lym-1 monoclonal antibody); SMART M195 Ab, humanized 13' 1 LYM-1 (Oncolym). Ovarex (B43.13, anti-idiotypic mouse mAb); 3622W94 mAb that binds to EGP40 (17-1A) pancarcinoma antigen on adenocarcinomas; Zenapax (SMART Anti-Tac (IL-2 receptor); SMART M195 Ab, humanized Ab, humanized); NovoMab-G2 (pancarcinoma specific Ab); TNT (chimeric mAb to histone antigens); TNT (chimeric mAb to histone antigens); Gliomab-H (Monoclonals—Humanized Abs);

GNI-250 Mab; EMD-72000 (chimeric-EGF antagonist); LymphoCide (humanized IL-2 antibody); and MDX-260 bispecific, targets GD-2, ANA Ab, SMART IDIO Ab, SMART ABL 364 Ab or ImmurAIT-CEA. Examples of antibodies include those disclosed in U.S. Pat. No. 5,736,167. U.S. Pat. No. 7,060,808, and U.S. Pat. No. 5,821,337.

In one embodiment, the targeting moiety specifically binds a component of a regulatory T cell, myeloid suppressor cell, or dendritic cell. In another aspect, the targeting moiety specifically binds one of the following molecules: CD4; CD25 (IL-2 α receptor; IL-2 α R); cytotoxic T-lymphocyte antigen-4 (CTLA-4; CD152); Interleukin-10 (IL-10); Transforming growth factor-beta receptor (TGF- β R); Transforming growth factor-beta (TGF- β); Programmed Death-1 (PD-1); Programmed death-1 ligand (PD-L1 or PD-L2); Receptor activator of nuclear factor- κ B (RANK); Receptor activator of nuclear factor- κ B (RANK) ligand (RANKL); LAG-3; glucocorticoid-induced tumor necrosis factor receptor family-related gene (GITR; TNFRSF18); or Interleukin-4 receptor (IL-4R). In one aspect, the targeting moiety is an agonist that increases the function of the targeted molecule. In another aspect, the targeting moiety is an antagonist that inhibits the function of the targeted molecule.

In one aspect, the targeting moiety binds a specific cytokine, cytokine receptor, co-stimulatory molecule, co-inhibitory molecule, or immunomodulatory receptor that modulates the immune system. In another aspect, the targeting moiety specifically binds one of the following molecules: tumor necrosis factor (TNF) superfamily; tumor necrosis factor- α (TNF- α); tumor necrosis factor receptor (TNFR) superfamily; Interleukin-12 (IL-12); IL-12 receptor; 4-1BB (CD137); 4-1BB ligand (4-1BBL; CD137L); OX40 (CD134; TNR4); OX40 ligand (OX40L; CD40; CD40 ligand (CD40L); CTLA-4; Programmed death-1 (PD-1); PD-1 ligand 1 (PD-L1; B7-H1); or PD-1 ligand 2 (PD-L2; B7-DC); B7 family; B7-1 (CD80); B7-2 (CD86); B7-H3; B7-H4; GITR/AITR; GITRL/AITRL; BTLA; CD70; CD27; LIGHT; HVEM; Toll-like receptor (TLR) (TLR 1, 2, 3, 4, 5, 6, 7, 8, 9, 10). In one aspect, the targeting moiety is an agonist that increases the function of the targeted molecule. In another aspect, the targeting moiety is an antagonist that inhibits the function of the targeted molecule.

In one aspect, the targeting moiety includes an antibody, antibody fragment, scFv, Fc-containing polypeptide, or peptide that specifically binds a component of a regulatory T cell, myeloid suppressor cell, or dendritic cell. In another aspect, the targeting moiety includes an antibody, antibody fragment, scFv, or Fc-containing polypeptide that specifically binds a cytokine, cytokine receptor, co-stimulatory molecule, or co-inhibitory molecule that modulates the immune system. In another aspect, the targeting moiety specifically binds one of the following molecules: CD4; CD25 (IL-2 α receptor; IL-2 α R); cytotoxic T-lymphocyte antigen-4 (CTLA-4; CD152); Interleukin-10 (IL-10); Transforming growth factor-beta receptor (TGF- β R); Transforming growth factor-beta (TGF- β); Programmed Death-1 (PD-1); PD-1 ligand 1 (PD-L1; B7-H1); PD-1 ligand 2 (PD-L2; B7-DC); Receptor activator of nuclear factor- κ B (RANK); Receptor activator of nuclear factor- κ B (RANK) ligand (RANKL); LAG-3; glucocorticoid-induced tumor necrosis factor receptor family-related gene (GITR; TNFRSF18); Interleukin-4 receptor (IL-4R); tumor necrosis factor (TNF) superfamily; tumor necrosis factor- α (TNF- α); tumor necrosis factor receptor (TNFR) superfamily; interleukin-12 (IL-12); IL-12 receptor; 4-1BB (CD137); 4-1BB ligand (4-1BBL; CD137L); OX40 (CD134; TNR4); OX40 ligand (OX40L; CD40; CD40 ligand (CD40L); CTLA-4; B7 family; B7-1 (CD80); B7-2 (CD86);

B7-H3; B7-H4; GITR/AITR; GITRL/AITRL; BTLA; CD70; CD27; LIGHT; or HVEM. In one aspect, the targeting moiety is an agonist that increases the function of the targeted molecule, in another aspect, the targeting moiety is an antagonist that inhibits the function of the targeted molecule.

Examples of antibodies which can be incorporated into compositions and methods disclosed herein include, but are not limited, to antibodies such as Zanulimumab (anti-CD4 mAb), Keliximab (anti-CD4 mAb); Ipilimumab (MDX-101; anti-CTLA-4 mAb); Tremilimumab (anti-CTLA-4 mAb); (Daclizumab (anti-CD25/IL-2R mAb); Basiliximab (anti-CD25/IL-2R mAb); MDX-1106 (anti-PD1 mAb); antibody to GITR; GC1008 (anti-TGF- β antibody); metelimumab/CAT-192 (anti-TGF- β antibody); Ierdelimumab/CAT-152 (anti-TGF- β antibody); ID11 (anti-TGF- β antibody); Denosumab (anti-RANKL mAb); BMS-663513 (humanized anti-4-1BB mAb); SGN-40 (humanized anti-CD40 mAb); CP870,893 (human anti-CD40 mAb); Infliximab (chimeric anti-TNF mAb; Adalimumab (human anti-TNF mAb); Certolizumab (humanized Fab anti-TNF); Golimumab (anti-TUNE); Etanercept (Extracellular domain of TNFR fused to IgG1 Fc); Belatacept (Extracellular domain of CTLA-4 fused to Fc); Abatacept (Extracellular domain of CTLA-4 fused to Fc); Belimumab (anti-B Lymphocyte stimulator); Muromonab-CD3 (anti-CD3 mAb); Otelixizumab (anti-CD3 mAb); Teplizumab (anti-CD3 mAb); Tocilizumab (anti-IL6R mAb); REGN88 (anti-IL6R mAb); Ustekinumab (anti-IL-12/23 mAb); Briakinumab (anti-IL-12/23 mAb); Natalizumab (anti- α 4 integrin); Vedolizumab (anti- α 4 β 7 integrin mAb); T1h (anti-CD6 mAb); Epratuzumab (anti-CD22 mAb); Efalizumab (anti-CD11a mAb); and Atacicept (extracellular domain of transmembrane activator and calcium-modulating ligand interactor fused with Fe).

In one embodiment, the present invention provides a molecule including a targeting moiety fused with an "immunomodulatory moiety". As used herein, "immunomodulatory moiety" refers to a ligand peptide, polypeptide, or Fc-containing polypeptide that binds a specific component of a regulatory T cell, myeloid suppressor cell, or dendritic cell and modulates the number or function of Tregs or myeloid suppressor cells. In an additional aspect, the "immunomodulatory moiety" specifically binds a cytokine, cytokine receptor, co-stimulatory molecule, or co-inhibitory molecule that modulates the immune system. In another aspect, the immunomodulatory moiety specifically binds one of the following molecules: Transforming growth factor-beta receptor (TGF- β R); Transforming growth factor-beta (TGF- β); Programmed Death-1 (PD-1); PD-1 ligand 1 (PD-L1; B7-H1); PD-1 ligand 2 (PD-L2; B7-DC); Receptor activator of nuclear factor- κ B (RANK); or Receptor activator of nuclear factor- κ B (RANK) ligand (RANKL); or vascular endothelial growth factor (VEGF). In another aspect, the immunomodulatory moiety specifically binds one of the following molecules: glucocorticoid-induced tumor necrosis factor receptor family-related gene (GITR; AITR; TNFRSF18); GITRL/AITRL; 4-1BB (CD137); 4-1BB ligand (4-1BBL; CD137L); OX40 (CD134; TNR4); OX40 ligand (OX40L); B7-H3; B7-H4; BTLA; CD40; CD40 ligand (CD40L); CD70; CD27; LIGHT; or HVEM. In another aspect, the immunomodulatory moiety specifically binds one of the following molecules: tumor necrosis factor- α (TNF- α); Interleukin-12 (IL-12); IL-12R; Interleukin-10 (IL-10); IL-10R. In another aspect, the immunomodulatory moiety comprises an extracellular domain of CTLA-4. In one aspect, the immunomodulatory moiety is an agonist that increases the function of the bound

molecule. In another aspect, the immunomodulatory moiety is an antagonist that inhibits the function of the targeted molecule.

In another aspect, the immunomodulatory moiety comprises an extracellular domain or ligand-binding sequence of one of the following receptors: Transforming growth factor-beta receptor (TGF- β RII, TGF- β RIIb, or TGF- β RIII); Programmed Death-1 (PD-1); Receptor activator of nuclear factor- κ B (RANK); vascular endothelial growth factor receptor (VEGFR1 or VEGFR2); or IL-10R. In another aspect, the immunomodulatory moiety comprises an extracellular domain or ligand-binding sequence of one of the following receptors: tumor necrosis factor receptor 2 (TNFR2); 4-1BB (CD137); OX40 (CD134; TNR4); CD40; IL-12R; or glucocorticoid-induced tumor necrosis factor receptor family-related gene (GITR; AITR; TNFRSF18). In an additional aspect, the extracellular domain of the specific receptor binds the cognate ligand and inhibits the interaction of the ligand with its native receptor.

In another aspect, the immunomodulatory moiety comprises one or more of the following ligands or active ligand fragments: Transforming growth factor-beta (TGF- β); PD-1 ligand 1 (PD-L1); PD-1 ligand 2 (PD-L2); or IL-10. In another aspect, the immunomodulatory moiety comprises one or more of the following ligands or active ligand fragments: 4-1BB ligand (4-1BBL; CD137L); OX40 ligand (OX40L); IL-12; CD40L; or GITRL/AITRL.

In another aspect, the immunomodulatory moiety is fused to the C-terminus of the targeting moiety. In another aspect, the immunomodulatory moiety is fused to the N-terminus of the targeting moiety. In one aspect, the fusion molecule is represented by X-Fc-Y, wherein X is the targeting moiety, Fc is an immunoglobulin Fc region, and Y is the immunomodulatory moiety. In another aspect, the fusion molecule is represented by Y-Fc-X, wherein X is the targeting moiety, and Y is the immunomodulatory moiety. In one aspect, the targeting moiety may additionally be an immunomodulatory moiety.

In one aspect, the targeting moiety includes an antibody, antibody fragment, scFv, or Fc-containing polypeptide that specifically binds a component of a tumor cell, tumor antigen, tumor vasculature, tumor microenvironment, or tumor-infiltrating immune cell, and the immunomodulatory moiety comprises an extracellular domain or ligand-binding sequence of one of the following receptors: Transforming growth factor-beta receptor (TGF- β RII, TGF- β RIIb, or TGF- β RIII); Programmed Death-1 (PD-1); Receptor activator of nuclear factor- κ B (RANK); vascular endothelial growth factor receptor (VEGFR1 or VEGFR2); or IL-10R.

In one aspect, the targeting moiety includes an antibody, antibody fragment, scFv, or Fc-containing polypeptide that specifically binds a component of a tumor cell, tumor antigen, tumor vasculature, tumor microenvironment, or tumor-infiltrating immune cell, and the immunomodulatory moiety comprises one or more of the following ligands or active ligand fragments: 4-1BB ligand (4-1BBL; CD137L); OX40 ligand (OX40L); IL-12; CD40L; or GITRL/AITRL.

In another aspect, the targeting moiety includes an antibody, antibody fragment, scFv, Fc-containing polypeptide or ligand that binds a specific component of a regulatory T cell, myeloid suppressor cell, or dendritic cell, and the immunomodulatory moiety comprises an extracellular domain or ligand-binding sequence of one of the following receptors: Transforming growth factor-beta receptor (TGF- β RII, TGF- β RIIb, or TGF- β RIII); Programmed Death-1 (PD-1); Receptor activator of nuclear factor- κ B (RANK); or IL-10R. In another aspect, the immunomodulatory moiety comprises one or more of the following ligands or active ligand frag-

ments: 4-1BB ligand (4-1BBL; CD137L); OX40 ligand (OX40L); IL-12; CD40L; or GITRL/AITRL. In another aspect, the specific targeted component of a regulatory T cell, myeloid suppressor cell, or dendritic cell is one of the following molecules: CD4; CD25 (IL-2 α receptor; IL-2 α R); cytotoxic T-lymphocyte antigen-4 (CTLA-4; CD152); Interleukin-10 (IL-10); Transforming growth factor-beta (TGF- β); Programmed Death-1 (PD-1); Programmed death-1 ligand (PD-L1 or PD-L2); Receptor activator of nuclear factor- κ B (RANK) ligand (RANKL); LAG-3; glucocorticoid-induced tumor necrosis factor receptor family-related gene (GITR; TNFRSF18); or Interleukin-4 receptor (IL-4R).

In another aspect, the targeting moiety includes an antibody, antibody fragment, scFv, Fc-containing polypeptide or ligand that binds one of the following: CTLA-4; 4-1BB (CD137); OX40 (CD134; TNR4); CD40; IL-12R; or glucocorticoid-induced tumor necrosis factor receptor family-related gene (GITR; AITR; TNFRSF18); and the immunomodulatory moiety comprises a different molecule selected from the following: (i) an extracellular domain or ligand-binding sequence of one of the following receptors: Transforming growth factor-beta receptor (TGF- β RII, TGF- β RIIb, or TGF- β RIII); Programmed Death-1 (PD-1); Receptor activator of nuclear factor- κ B (RANK); or IL-10R; or (ii) Fc-containing polypeptide or ligand that binds one of the following: CTLA-4; 4-1BB (CD137); OX40 (CD134; TNR4); CD40; IL-12R; or GITR (AITR; TNFRSF18).

In another aspect, the targeting moiety and immunomodulatory moiety are two different molecules selected from any of the following: an antibody, antibody fragment, scFv, Fc-containing polypeptide or ligand that binds TGF- β , CTLA-4, PD-1, 4-1BB (CD137), OX40 (CD134; TNR4), CD40; IL-12R, or GITR/AITR (TNFRSF18), or Toll-like receptor (TLR); an extracellular domain or ligand-binding sequence of Transforming growth factor-beta receptor (TGF- β RII, TGF- β RIIb, or TGF- β RIII), Programmed Death-1 (PD-1), Receptor activator of nuclear factor- κ B (RANK), or IL-10R. In one aspect the fusion molecule is represented by X-Fc-Y, wherein X is an immunomodulatory targeting moiety and Y is a different immunomodulatory moiety.

In another aspect, the targeting moiety includes an antibody, antibody fragment, scFv, Fc-containing polypeptide that binds one of the following molecules: CD4; CD25 (IL-2 α receptor; IL-2 α R); or CD20; and the immunomodulatory moiety comprises one of the following ligands or active ligand fragments: Transforming growth factor-beta (TGF- β); PD-1 ligand 1 (PD-L1); PD-1 ligand 2 (PD-L2); or IL-10.

In another aspect, the targeting moiety includes an antibody, antibody fragment, scFv, Fc-containing polypeptide that binds tumor necrosis factor- α (TNF- α), Interleukin-12 (IL-12), IL-6R, B-lymphocyte stimulator, CD11a, CD6, or CD22; and the immunomodulatory moiety comprises one of the following: (i) ligands or active ligand fragments of Transforming growth factor-beta (TGF- β). PD-1 ligand 1 (PD-L1), or IL-10; or (ii) an extracellular domain or ligand-binding fragment of RANK, 4-1BB (CD137), OX40 (CD134; TNR4), CD40, IL-12R or GITR/AITR (TNFRSF18).

In another aspect, the targeting moiety comprises the extracellular domain of CTLA-4 fused to immunoglobulin Fc, and the immunomodulatory moiety comprises one of the following: (i) ligands or active ligand fragments of Transforming growth factor-beta (TGF- β). PD-1 ligand 1 (PD-L1), or IL-10; or (ii) ligand-binding fragment of TNFR2, RANK, 4-1BB (CD137), OX40 (CD134; TNR4), CD40, IL-12R or GITR/AITR (TNFRSF18).

In another aspect, the targeting moiety and immunomodulatory moiety are two different molecules selected from any

of the following: an antibody, antibody fragment, scFv, Fc-containing polypeptide that binds tumor necrosis factor- α (TNF- α), interleukin-12 (IL-12), IL-6R. B-lymphocyte stimulator, CD11a, CD6, or CD22; a ligand-binding fragment of TNFR2, RANK, 4-1BB (CD137), OX40 (CD134; TNFR4), CD40, IL-12R or GITR/AITR (TNFRSF18); ligands or active ligand fragments of Transforming growth factor-beta (TGF- β), PD-1 ligand 1 (PD-L1), or IL-10; or CTLA-4-Fc. In one aspect, the fusion molecule is represented by X-Fc-Y, wherein X is the immunomodulatory targeting moiety and Y is a different immunomodulatory moiety.

Antibodies: In one embodiment, the targeting moiety or fusion protein is an immunoglobulin. As used herein, the term "immunoglobulin" includes natural or artificial mono- or polyvalent antibodies including, but not limited to polyclonal, monoclonal, multispecific, human, humanized or chimeric antibodies, single chain antibodies. Fab fragments. F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the invention), and epitope-binding fragments of any of the above. The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that immunospecifically binds an antigen. The immunoglobulin ion can be of any type (e.g., IgG, IgE, IgM, IgD, IgA, and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2) or subclass of immunoglobulin molecule.

An antibody as disclosed herein includes an antibody fragment, such as, but not limited to, Fab, Fab' and F(ab')₂, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments including either a VL or VH domain. In one embodiment, the targeting moiety is an antibody or scFv.

An antigen-binding antibody fragment, including single-chain antibody, may include the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains. An antigen-binding fragment can also include any combination of variable region(s) with a hinge region, CH1, CH2, and CH3 domains. Also included is a Fc fragment, antigen-Fc fusion proteins, and Fc-targeting moiety. The antibody may be from any animal origin including birds and mammals. In one aspect, the antibody is, or derived from, a human, murine (e.g., mouse and rat), donkey, sheep, rabbit, goat, guinea pig, camel, horse, or chicken. Further, such antibody may be a humanized version of an antibody. The antibody may be monospecific, bispecific, trispecific, or of greater multispecificity.

The antibody herein specifically include a "chimeric" antibody in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (U.S. Pat. No. 4,816,567; and Morrison et al (1984) Proc. Natl. Acad. Sci. USA. 81:6851-6855). A chimeric antibody of interest herein includes "primatized" antibodies including variable domain antigen-binding sequences derived from a non-human primate (e.g., Old World Monkey, Ape etc) and human constant region sequences.

Various methods have been employed to produce antibodies. Hybridoma technology, which refers to a cloned cell line

that produces a single type of antibody, uses the cells of various species, including mice (murine), hamsters, rats, and humans. Another method to prepare an antibody uses genetic engineering including recombinant DNA techniques. For example, antibodies made from these techniques include, among others, chimeric antibodies and humanized antibodies. A chimeric antibody combines DNA encoding regions from more than one type of species. For example, a chimeric antibody may derive the variable region from a mouse and the constant region from a human. A humanized antibody comes predominantly from a human, even though it contains non-human portions. Like a chimeric antibody, a humanized antibody may contain a completely human constant region. But unlike a chimeric antibody, the variable region may be partially derived from a human. The nonhuman, synthetic portions of a humanized antibody often come from CDRs in murine antibodies. In any event, these regions are crucial to allow the antibody to recognize and bind to a specific antigen.

In one embodiment, a hybridoma can produce a targeted fusion protein comprising a targeting moiety and an immunomodulatory moiety. In one embodiment, a targeting moiety comprising an antibody, antibody fragment, or polypeptide is linked or fused to an immunomodulatory moiety consisting of a polypeptide, with a linker or without a linker. The linker can be an amino acid linker. In one embodiment, a linker is (GGGGS)_n wherein n is 1, 2, 3, 4, 5, 6, 7, or 8. For example, GGGSGGGSGGGGS (SEQ ID NO: 104). In another embodiment, a linker is EPKSCDK (SEQ ID NO: 105). In another embodiment, a linker is IEGRDMD (SEQ. ID. NO: 106). In various aspects, the length of the linker may be modified to optimize binding of the target moiety or the function of the immunomodulatory moiety. In various aspects, the immunomodulatory moiety is a polypeptide that is fused to the C-terminus of the Fc region of the heavy chain of a targeting antibody or Fc-containing fusion protein. In another aspect, the immunomodulatory moiety is a polypeptide that is fused to the C-terminus of the light chain of a targeting antibody. In another aspect, the fusion protein comprises an X-Fc-Y sequence, wherein X is a targeting polypeptide and Y is an immunomodulatory polypeptide.

For example, a hybridoma can produce the polypeptides corresponding to SEQ. ID. NO: 1-69.

An antibody fragment can include a portion of an intact antibody, e.g. including the antigen-binding or variable region thereof. Examples of antibody fragments include Fab, Fab', F(ab')₂, and Fv fragments; Fc fragments or Fc-fusion products; diabodies; linear antibodies; single-chain antibody molecules; and multispecific antibodies formed from antibody fragment(s).

An intact antibody is one which includes an antigen-binding variable region as well as a light chain constant domain (CL) and heavy chain constant domains, CH1, CH2 and CH3. The constant domains may be native sequence constant domains (e.g. human native sequence constant domains) or amino acid sequence variant thereof for any other modified Fc (e.g. glycosylation or other engineered Fc).

The intact antibody may have one or more "effector functions" which refer to those biological activities attributable to the Fc region (a native sequence Fc region or amino acid sequence variant Fc region or any other modified Fc region) of an antibody. Examples of antibody effector functions include C1q binding; complement dependent cytotoxicity; Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell surface receptors (e.g., B cell receptor (BCR)); and cross-presentation of antigens by antigen presenting cells or dendritic cells. In one embodiment, the targeting antibody or Fc-containing

fusion protein facilitates focused or preferential delivery of an immunomodulatory moiety to a target cell. In another aspect, a targeting antibody can induce death of the targeted cell or sensitize it to immune cell-mediated cytotoxicity. In another aspect, the Fc-fusion protein or antibody can facilitate delivery of the immunomodulatory moiety or immunogenic apoptotic material from antibody-bound tumor targets, or both, to an antigen presenting cells (APC) via interactions between their Fc and Fc receptors (on APC).

Depending on the amino acid sequence of the constant domain of their heavy chains, intact antibodies can be assigned to different "classes." There are five major classes of intact antibodies: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into "subclasses" (isotypes), e.g., IgG1, IgG2, IgC3, IgG4, IgA, and IgA2. The heavy-chain constant domains (that correspond to the different classes of antibodies are called alpha (α), delta (δ), epsilon (ϵ), gamma (γ), and mu (μ) respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

Peptides: In some aspects of the invention the targeting, moiety or immunomodulatory moiety is a peptide or polypeptide. A peptide includes any analog, fragment or chemical derivative of a peptide whose amino acid residue sequence is shown herein. Therefore, a present peptide can be subject to various changes, substitutions, insertions, and deletions where such changes provide for certain advantages in its use. In this regard, a peptide of this invention corresponds to, rather than is identical to, the sequence of a recited peptide where one or more changes are made and it retains the ability to function as the unmodified peptide in one or more of the assays.

The term "analog" includes any peptide having an amino acid residue sequence substantially identical to a sequence specifically shown herein in which one or more residues have been conservatively substituted with a functionally similar residue and which displays the activity as described herein. Examples of conservative substitutions include the substitution of one non-polar (hydrophobic) residue such as isoleucine, valine, leucine or methionine for another, the substitution of one polar (hydrophilic) residue for another such as between arginine and lysine, between glutamine and asparagine, between glycine and serine, the substitution of one basic residue such as lysine, arginine or histidine for another, or the substitution of one acidic residue, such as aspartic acid or glutamic acid for another.

The term "fragment" refers to any subject polypeptide having an amino acid residue sequence shorter than that of a polypeptide whose amino acid residue sequence is disclosed herein.

As used herein "a tumor targeting peptide" includes polymers containing fewer than 100 amino acids, where the polymer specifically binds to a cellular component of a tumor cell, tumor vasculature, and/or a component of a tumor microenvironment.

A peptide of the present invention can be synthesized by any of the techniques that are known to those skilled in "the polypeptide art, including recombinant DNA techniques. Synthetic chemistry techniques, such as a solid-phase Merrifield-type synthesis, are preferred for reasons of purity, antigenic specificity, freedom from undesired side products, ease of production and the like. An excellent summary of the many techniques available can be found in Steward et al., "Solid Phase Peptide Synthesis"* W. H. Freeman Co., San Francisco, 1969; Bodanszky, et al., "Peptide Synthesis", John Wiley & Sons, Second Edition, 1976; J. Meienhofer, "Hormonal Proteins and Peptides". Vol. 2. p. 46, Academic Press

(New York), 1983; Merrifield, Adv. Enzymol., 32:221-96, 1969; Fields et al. Int. J. Peptide Protein Res., 35:161-214, 1990; and U.S. Pat. No. 4,244,946 for solid phase peptide synthesis, and Schroder et al. "The Peptides", Vol. 1, Academic Press (New York), 1965 for classical solution synthesis. Appropriate protective groups usable in such synthesis are described in the above texts and in J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, New York, 1973.

Aptamers: In one aspect of the invention, the targeting moiety is an aptamer. In various embodiments, an aptamer is specific for a molecule on a tumor cell, tumor vasculature, and/or a tumor microenvironment. The term "aptamer" includes DNA, RNA or peptides that are selected based on specific binding properties to a particular molecule. For example, an aptamer(s) can be selected for binding a particular gene product in a tumor cell, tumor vasculature, tumor microenvironment, and/or an immune cell, as disclosed herein, where selection is made by methods known in the art and familiar to one of skill in the art. Subsequently, said aptamer(s) can be administered to a subject to modulate or regulate an immune response.

Some aptamers having affinity to a specific protein, DNA, amino acid and nucleotides have been described (e.g., K. Y. Wang, et al., Biochemistry 32:1899-1904 (1993); Pitney et al., U.S. Pat. No. 5,691,145; Gold, et al. Ann. Rev. Biochem. 64:763-797 (1995); Szostak et al., U.S. Pat. No. 5,631,146). High affinity and high specificity binding aptamers have been derived from combinatorial libraries (supra, Gold, et al.). Aptamers may have high affinities, with equilibrium dissociation constants ranging from micromolar to sub-nanomolar depending on the selection used, aptamers may also exhibit high selectivity, for example, showing a thousand fold, discrimination between 7-methyl G and G (Haller and Sarnow, Proc. Natl. Acad. Sci. USA 94:8521-8526 (1997)) or between D and L-tryptophan (supra, Gold et al.). An aptamer can be selected based on the particular molecule targeted (e.g., aptamer targeting EGFR or other cancer markers). Standard procedures for in vitro selection are known, such as SELEX experiments, described at Science 249 (4968) 505-510 (1990), and Nature (London), 346 (6287) 818-822 (1990) which can be followed throughout, or with modifications and improvements known in the art.

The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The terms "administration of" and or "administering" should be understood to mean providing a composition in a therapeutically effective amount to the individual in need of treatment. Administration can be intratumoral or systemic (intravenous) administration. Furthermore, in conjunction with vaccination of recipient with pathogen antigen vaccine (e.g. tetanus toxoid). In addition, in conjunction with agent to deplete or inactivate regulatory T cells (e.g. cyclophosphamide) or myeloid suppressor cells (e.g. gemcitabine). In a further example, ex vivo treatment of immune cells and tumor cells for generation of tumor reactive or pathogen antigen reactive immune cells—for adoptive cellular immunotherapy. Administration can be intradermal or subcutaneous.

Furthermore, administration can be in combination with one or more additional therapeutic agents deplete or inacti-

vate regulatory T cells (cyclophosphamide) or myeloid suppressor cells (e.g. gemcitabine). The pharmaceutical compositions of the invention identified herein are useful for parenteral topical, oral, nasal (or otherwise inhaled), rectal, or local administration, such as by aerosol or transdermally, for prophylactic and/or therapeutic treatment of one or more of the pathologies/indications described herein (e.g., cancer, pathogenic infectious agents, associated conditions thereof). The pharmaceutical compositions can be administered in a variety of unit dosage forms depending upon the method of administration. Suitable unit dosage forms, include, but are not limited to powders, tablets, pills, capsules, lozenges, suppositories, patches, nasal sprays, injectables, implantable sustained-release formulations, lipid complexes, etc.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, as it will be understood that modifications and variations are encompassed within the spirit and scope of the instant disclosure.

The following examples are provided to further illustrate the embodiments of the present invention, but are not intended to limit the scope of the invention. While they are typical of those that might be used, other procedures, methodologies, or techniques known to those skilled in the art may alternatively be used.

EXAMPLE 1

Counteracting Tumor Immune Tolerance Via Antibody-Mediated Depletion of CD4⁺ Regulatory T Cells Facilitates the Activation of Tumor-Reactive CD8⁺ T Cells and Enhances the In Vivo Antitumor Efficacy of Cytotoxic Anticancer Agents

Immunogenic death of tumor cells by chemotherapeutic agents can induce CD8⁺ T cell-mediated antitumor immunity. In response to specific chemotherapeutic agents, tumor cells exhibit the rapid translocation of intracellular calreticulin (CRT) to the cell surface where its aggregation provides a signal for the recognition and engulfment of dying tumor cells by antigen presenting dendritic cells (DCs). Treatment of mouse MB49 or human SW780 bladder cancer cells with doxorubicin, an anthracycline chemotherapeutic agent, induced rapid surface exposure of CRT that was detected by immunofluorescence cytometry of cells stained with Dylight 488-labeled anti-CRT antibody (FIG. 1a). To determine whether ex vivo treatment with doxorubicin induced an immunogenic death of tumor cells, either untreated live MB49 cells or an equivalent number of MB49 cells that were pre-treated in vitro with doxorubicin were injected into one flank of syngeneic immunocompetent C57BL/6 mice. Unlike mice injected with live tumor cells, mice injected with doxorubicin-treated tumor cells exhibited increased production of IFN- γ by draining lymph node (DLN) cells in response to in vitro re-challenge with MB49 cell lysates (FIG. 1b). Vaccination with doxorubicin-killed MB49 cells generated a tumor-specific immune response since no corresponding increase in IFN- γ secretion by DLN cells was observed following in vitro exposure to an irrelevant peptide (Hemagglutinin-HA). Injection of doxorubicin-treated MB49 tumor cells protected mice against tumor growth upon challenge with untreated live MB49 tumor cells injected into the opposite flank. (FIG. 1c). The protection against tumor growth by vaccination with doxorubicin-treated tumor cells was not

observed in mice that were depleted of CD8⁺ T cells with an anti-CD8 antibody before challenge with live tumor cells (FIG. 1c). These observations indicate that ex vivo treatment with chemotherapeutic agents can induce an immunogenic death of tumor cells that generates CD8⁺ T cell-mediated adaptive antitumor immunity.

Tumor-induced immune tolerance inhibits activation of CD8⁺ T cells in response to chemotherapy. To examine whether in vivo treatment with chemotherapeutic agents can activate CD8⁺ T cell-mediated immune responses in mice with pre-established tumors, C57BL/6 mice were injected with live syngeneic MB49 tumor cells and then administered intratumoral doxorubicin at various time points following tumor inoculation. In contrast to vaccination of naïve mice with doxorubicin-killed MB49 cells, in vivo treatment of mice with established MB49 tumors at d10 following tumor inoculation failed to induce a corresponding increase in IFN- γ secretion by DLN cells in response to in vitro re-challenge with MB49 cell lysates (FIG. 1b). Whereas treatment with doxorubicin on d3 following tumor inoculation was able to arrest tumor growth, delayed administration of the same dose of doxorubicin on d10 failed to inhibit the progressive growth of established MB49 tumors (FIG. 1d). These results indicate that tumor-induced immune tolerance in the microenvironment of established cancers counteracts the activation of adaptive antitumor immunity in response to chemotherapy-induced tumor cell death.

Regulatory T cells (Treg) accumulate in the tumor microenvironment and counteract the ability of chemotherapy to activate CD8⁺ T cell mediated antitumor immunity. To investigate whether FoxP3⁺ Tregs are involved in enforcing immune tolerance in the tumor microenvironment, we examined the percentage of CD4⁺CD25⁺FoxP3⁺ cells (Tregs) among CD4⁺ T lymphocytes in the spleen, draining lymph nodes (DLN), and tumors of immunocompetent C57BL/6 mice at d0 and d14 after tumor inoculation. Whereas tumor-bearing mice exhibited only a minor increase in the percentage of Tregs among CD4⁺ T cells in the spleen and DLN at d14 following tumor inoculation, a majority of tumor-infiltrating CD4⁺ T cells at this time were CD4⁺CD25⁺FoxP3⁺ cells (FIG. 1e). To investigate whether Tregs infiltrating the tumor microenvironment can suppress the activation of adaptive antitumor immunity in response to chemotherapy-induced tumor cell death, CD4⁺CD25⁺ cells isolated from tumors and DLN of tumor-bearing mice were adoptively transferred into syngeneic C57BL/6 naïve mice before vaccination with doxorubicin-killed MB49 cells. The adoptive transfer of tumor-infiltrating CD4⁺CD25⁺ cells into naïve mice inhibited the ability of subsequent in vivo vaccination with doxorubicin-treated MB49 tumor cells to increase production of IFN- γ by draining lymph node (DLN) cells in response to in vitro re-challenge with MB49 cell lysates (FIG. 1f). Consistent with the ability of tumor-infiltrating CD4⁺CD25⁺ cells to suppress the tumor-specific immune response, the adoptive transfer of these cells counteracted the protection conferred by vaccination with doxorubicin-treated MB49 cells against tumor growth upon challenge with untreated live MB49 tumor cells (FIG. 1g). These results indicate that the tumor microenvironment fosters the accumulation of FoxP3⁺ Tregs which counteract the activation of CD8⁺ T cell mediated antitumor immunity in response to chemotherapy-induced tumor cell death.

Inhibition of TGF- β in the tumor microenvironment reduces tumor-infiltrating FoxP3⁺ regulatory T cells and enhances the antitumor efficacy chemotherapy. TGF- β induces FoxP3 expression in naïve peripheral CD4⁺CD25⁺FoxP3⁺ T cells and facilitates their conversion into 'adaptive'

FoxP3⁺ Tregs that share the immunosuppressive ability of natural FoxP3⁺ Tregs generated in the thymus. Since human cancers frequently become refractory to the growth-inhibitory effect of TGF- β and acquire an ability to increase expression and secretion of TGF- β , we investigated whether this switch enables tumor cells to increase the number of adaptive Tregs in the tumor microenvironment. Examination of serum levels of TGF- β in mice at d0, d14, and d28 following inoculation of live MB49 tumor cells demonstrated that, tumor growth resulted in a progressive increase in the level of serum TGF- β (FIG. 2a). To assess the precise source of TGF- β in tumor-bearing mice, the total amount of TGF- β in supernatants of tumor cells or draining lymph node cells isolated from tumor-bearing mice were measured following ex vivo culture in serum-free medium for 24 h. Measurement of the level of TGF- β /10⁶ cells showed that tumor cells were the dominant source of the increased level of TGF- β in tumor-bearing mice (FIG. 2b). In addition to tumor cell-autonomous expression of TGF- β , T cells from tumor-bearing mice also expressed higher levels of TGF- β compared to their counterparts from tumor-free mice (FIG. 2b). To determine whether the elevation of TGF- β is responsible for the upregulation of Tregs in the tumor microenvironment, tumor-bearing mice were treated with a soluble chimeric protein comprising the extracellular domain of TGF β RII and the Fc portion of the murine IgG1 heavy chain (TGF β RII:Fc). This fusion protein interferes with the binding of TGF- β to endogenous TGF β RII and functions as a stable TGF- β antagonist. ELISA assays confirmed the ability of TGF β RII:Fc to sequester TGF- β in supernatants of MB49 tumor cells in a concentration-dependent manner (FIG. 2c). At 5 d following inoculation of MB49 tumor cells, mice were either left untreated or treated with TGF β RII:Fc (1 μ g intratumoral; twice weekly) for 3 weeks followed by flow cytometric analyses of intracellular FoxP3 expression in CD4⁺CD25⁺ T cells infiltrating the tumors. In vivo treatment of tumors with TGF β RII:Fc resulted in a significant decline in FoxP3 expression in tumor-infiltrating CD4⁺ T cells (FIG. 2d) and a dramatic reduction of CD4⁺CD25⁺FoxP3⁺ Tregs in tumor tissue (FIG. 2e). To determine whether inhibition of TGF- β in the tumor microenvironment can improve the antitumor efficacy of chemotherapy, MB49 tumor-bearing mice were administered doxorubicin (5 mg/kg i.p. weekly $\times$ 3) with or without twice weekly treatment with TGF β RII:Fc (1 μ g intratumoral). In contrast to treatment with either doxorubicin or TGF β RII:Fc alone, combined treatment with both agents was able to arrest the growth of MB49 tumors. These results indicate that tumor cell autonomous expression of TGF- β in the tumor microenvironment induces 'adaptive' FoxP3⁺ Tregs and that counteracting tumor-induced TGF- β -mediated immune tolerance enhances the antitumor efficacy of chemotherapy.

Anti-CD4 antibody-mediated depletion of CD4⁺ regulatory T cells facilitates chemotherapy-induced activation of tumor-reactive CD8⁺ T cells and enhances the antitumor efficacy of chemotherapy. To determine whether depletion of CD4⁺ regulatory T cells can improve the antitumor efficacy of chemotherapy by enhancing the activity of CD8⁺ T cells in the tumor microenvironment, immunocompetent mice bearing syngeneic tumors were administered an anti-CD4 antibody (Clone GK1.5) to deplete CD4⁺ T cells or an anti-CD8 antibody (Clone GK2.43) to deplete CD8⁺ T cells and then treated with specific chemotherapeutic agents. Flow cytometric analyses of peripheral blood mononuclear cells from MB49 tumor-bearing mice at d7 following administration of anti-CD4 antibody or anti-CD8 antibody confirmed the target-specific depletion of either CD4⁺ T cells or CD8⁺ T cells, respectively (FIG. 3a). Mice treated with anti-CD4 antibody

showed loss of CD4⁺CD25⁺FoxP3⁺ T cells in the peripheral blood as well as among tumor-infiltrating cells (FIG. 3a, b). To determine whether antibody-mediated depletion of CD4⁺CD25⁺FoxP3⁺ cells facilitates chemotherapy-induced activation of tumor-reactive CD8⁺ T cells in the tumor microenvironment, we evaluated the expression of IFN- γ in CD8⁺ T cells extracted from the tumor and draining lymph node of MB49 tumor-bearing mice that were left untreated or treated with doxorubicin (with or without anti-CD4 antibody). Flow cytometric analyses showed that CD8⁺ T cells from untreated mice did not express IFN- γ in response to in vitro re-challenge with MB49 cell lysates (FIG. 3c). Whereas IFN- γ CD8⁺ T cells became evident in mice treated with doxorubicin alone, antibody-mediated depletion of CD4⁺ T cells further enhanced the percentage of tumor-reactive CD8⁺ T cells that expressed IFN- γ in doxorubicin-treated animals (FIG. 3c). To directly evaluate whether the activation of tumor-reactive CD8⁺ T cells determines the in vivo antitumor efficacy of chemotherapy, we examined the effect of antibody-mediated depletion of CD8⁺ T cells or CD4⁺ T cells on the response of MB49 tumor-bearing mice to systemic treatment with doxorubicin (5 mg/kg). Treatment with doxorubicin alone inhibited the growth of MB49 tumors but failed to arrest tumor progression. Whereas depletion of CD8⁺ T cells completely impaired the in vivo antitumor efficacy of doxorubicin, depletion of CD4⁺ T cells enhanced the response to doxorubicin and resulted in tumor regression (FIG. 3d).

Anti-CD4 antibody-mediated depletion of CD4⁺ regulatory T cells augments and sustains the antitumor effect of chemotherapy by enabling activation of adaptive antitumor immunity. Whereas tumor cells treated with anthracyclins, such as doxorubicin, are particularly effective in eliciting an antitumor immune response, other chemotherapeutic agents are less effective in inducing immunogenic tumor cell death. The surface exposure of calreticulin is a key determinant of the immunogenicity of tumor cell death in response to chemotherapeutic agents. Compared to the efficient translocation of CRT to the cell surface in response to treatment with doxorubicin (FIG. 1a), treatment of MB49 tumor cells with equitoxic doses of either cisplatin or the combination of cisplatin and gemcitabine was less effective in increasing CRT exposure (FIG. 4a). Whereas tumor-reactive IFN- γ CD8⁺ T cells were evident in tumors of MB49 tumor-bearing mice treated with doxorubicin (FIG. 3c), treatment with cisplatin was unable to induce a corresponding elevation of IFN- γ expression in CD8⁺ T cells in response to in vitro re-challenge with MB49 cell lysates (FIG. 4b). To examine whether counteraction of Treg-mediated immune tolerance enables the activation of antitumor immunity by cisplatin, immunocompetent tumor-bearing mice were treated with cisplatin following depletion of Tregs with anti-CD4 antibody. Antibody-mediated depletion of CD4⁺ T cells enhanced the percentage of tumor-reactive IFN- γ CD8⁺ T cells as well as CD8⁺CD62L⁻ T cells in cisplatin-treated animals (FIG. 4b,c). Treatment of MB49 tumor-bearing mice with cisplatin partially inhibited tumor growth but failed to arrest tumor progression. Whereas depletion of CD8⁺ T cells completely negated the in vivo antitumor effect of cisplatin, depletion of CD4⁺ T cells enhanced the response to cisplatin and arrested tumor growth (FIG. 4d). Although treatment of tumor-bearing mice with the combination of cisplatin and gemcitabine was also able to arrest tumor growth, tumor growth rapidly resumed following termination of therapy with none of the animals (0/8) being tumor-free at d50 following tumor inoculation (FIG. 4e). In contrast, mice depleted of CD4⁺ T cells exhibited a more sustained response to either single agent or combination chemotherapy, with 7/16 mice exhibiting com-

plete tumor regression. The complete regression of tumors was attended with establishment of adaptive antitumor immunity since none of the cured mice (7/7) developed tumors when re-challenged with live MB49 tumor cells in the opposite flank.

Chemotherapy-induced expression of NKG2D ligands on tumor cells cooperates with depletion of CD⁴⁺ regulatory T cells to stimulate CD⁸⁺ T cell-mediated tumor regression. NKG2D (NK group 2, member D) is a lectin-like type II transmembrane stimulatory receptor used by NK cells, $\gamma\delta$ -TC^{R+} T cells and $\alpha\beta$ -TC^{R+} T cells for immune surveillance of tumors. Expression of mouse and human ligands for NKG2D is upregulated in transformed epithelial cell lines in response to genotoxic stress or stalled DNA replication, via activation of a DNA damage checkpoint pathway initiated by ATM (ataxia telangiectasia, mutated) or ATR (ATM- and Rad3-related) protein kinases. Treatment of CT26 mouse colon cancer cells with genotoxic chemotherapeutic agents resulted in upregulation of mouse NKG2D ligands of the retinoic acid inducible gene family (Rae1) (FIG. 5a). RT-PCR showed that Rae1 mRNA was induced in CT26 cells by 2-4-h, reached a plateau after 16-24 h, and began to decline after 48 h of treatment with either the irinotecan or oxaliplatin (FIG. 5a). Flow cytometric analysis demonstrated that cell surface expression of human NKG2D ligands (MHC-1-related A and B molecules—MICA, MICB) was also upregulated on human colorectal cancer cells (HCT116) in response to treatment with irinotecan (FIG. 1b). Isogenic HCT116 cells that differ only in their p53 status demonstrated that p53 is not required for irinotecan-induced upregulation of MICA/B (FIG. 1b). To examine whether the induction of NKG2D ligands contributes to the antitumor effect of chemotherapy in vivo, immunocompetent Balb/C mice inoculated with syngeneic CT26 tumor cells were treated with irinotecan (50 mg/kg i.p.) with or without pre-treatment with an NKG2D blocking antibody (200 μ g i.p.). Whereas treatment with irinotecan alone inhibited the growth of CT26 tumors, the antitumor effect of irinotecan was negated by pre-treatment with the NKG2D blocking antibody (FIG. 1c). Since engagement of NKG2D by its ligands provides a costimulatory signal for the activation of CD⁸⁺ T cells, we investigated whether DNA damage-induced expression of NKG2D ligands on tumor cells cooperates with depletion of CD⁴⁺ regulatory T cells to stimulate CD⁸⁺ T cell-mediated tumor regression. Balb/C mice bearing CT26 tumors were administered an anti-CD4 antibody (Clone GK1.5) to deplete CD⁴⁺ T cells and/or an anti-CD8 antibody (Clone GK2.43) to deplete CD⁸⁺ T cells and then treated with irinotecan. Flow cytometric analyses confirmed the loss of CD⁴⁺CD2⁵⁺FoxP3⁺ T cells in the spleen and draining lymph node of mice treated with anti-CD4 antibody (FIG. 5d). Antibody-mediated depletion of CD⁴⁺ T cells enhanced the percentage of tumor-reactive IFN- γ ⁺CD⁸⁺ T cells in irinotecan-treated animals (FIG. 5e). Whereas treatment of CT26 tumor-bearing mice with irinotecan only slowed tumor growth, depletion of CD⁴⁺ T cells enhanced the response to irinotecan and arrested tumor growth (FIG. 5f). The ability of CD⁴⁺ T cell depletion to augment the antitumor efficacy of irinotecan was mediated by CD⁸⁺ T cells since antibody-mediated depletion of CD⁸⁺ T cells completely negated the in vivo antitumor effect of chemotherapy in CD⁴⁺ T cell-depleted mice (FIG. 5g).

These data provide the following insights: (i) activation of tumor-reactive CD8⁺ T cells in response to immunogenic tumor cell death is a crucial determinant of the antitumor efficacy of chemotherapy in vivo; (ii) tumor-induced Tregs impair the antitumor efficacy of chemotherapy by inhibiting the activation of CD8⁺ T cells in the tumor microenviron-

ment; and (iii) Counteracting tumor-induced immune tolerance via antibody-mediated depletion of CD4⁺ regulatory T cells facilitates chemotherapy-induced activation of antitumor immunity with memory, thereby enhancing the antitumor efficacy of chemotherapy; (iv) Strategies to decrease the number or function of CD4⁺ regulatory T cells in the tumor microenvironment can increase the activation of CD8⁺ T cells and improve the response of tumors to cytotoxic anticancer agents (chemotherapy, tumor-targeted antibodies, targeted therapeutics, kinase inhibitors) or chemimmunotherapy (combination of chemotherapeutic agent with immunotherapeutic agents).

EXAMPLE 2

Exemplary Targeted Immunomodulatory Antibodies & Fusion Proteins

A targeting moiety, including an antibody, can be coupled to an immunomodulatory moiety including a polypeptide derived from the extracellular domain of TGFBR2. Crosslinkers or activating agents for such coupling or conjugation are well known in the art. Alternatively, the fusion proteins of the invention can be synthesized using recombinant DNA technology well known in the art where the coding sequences of various portions of the fusion proteins can be linked together at the nucleic acid level. Subsequently the fusion proteins of the invention can be produced using a host cell well known in the art. Examples of targeted immunomodulatory antibodies and fusion proteins are shown in FIGS. 1-33 and briefly described below.

In one embodiment, the present invention provides a molecule including a targeting moiety fused with an immunomodulatory moiety, wherein the targeting moiety specifically binds to a target molecule, and the immunomodulatory moiety specifically binds to Transforming growth factor-beta (TGF- β). SEQ ID NO: 1 provides a fusion protein including anti-HER2/neu antibody and Transforming growth factor-beta receptor II (TGF β -RII) Extracellular domain (ECD) (FIG. 2). SEQ ID NO: 2 provides a fusion protein including anti-EGFR1 antibody and Transforming growth factor-beta receptor II (TGF β -RII) Extracellular domain (ECD) (FIG. 3). SEQ ID NO: 3 provides a fusion protein including anti-CD20 antibody and Transforming growth factor-beta receptor II (TGF β -RII) Extracellular domain (ECD) (FIG. 4). SEQ ID NO: 4 provides a fusion protein including anti-VEGF antibody and Transforming growth factor-beta receptor II (TGF β -RII) Extracellular domain (ECD) (FIG. 5). SEQ ID NO: 5 provides a fusion protein including anti-human CTLA-4 antibody and Transforming growth factor-beta receptor II (TGF β -RII) Extracellular domain (ECD) (FIG. 6). SEQ ID NO: 6 provides a fusion protein including IL-2, Fc, and Transforming growth factor-beta receptor II (TGF β -RII) Extracellular domain (ECD) (FIG. 7). SEQ ID NO: 7 provides a fusion protein including Transforming growth factor-beta receptor II (TGF β -RII) Extracellular domain (ECD), Fc, and IL-2 (FIG. 7). SEQ ID NO 8 provides a fusion protein including anti-CD25 antibody and Transforming growth factor-beta receptor II (TGF β -RII) Extracellular domain (ECD) (FIG. 8A). SEQ ID NO: 9 provides a fusion protein including anti-CD25 antibody and Transforming growth factor-beta receptor II (TGF β -RII) Extracellular domain (ECD) (FIG. 8B). SEQ ID NO: 10 provides a fusion protein including anti-CD4 antibody and Transforming growth factor-beta receptor II (TGF β -RII) Extracellular domain (ECD) (FIG. 9). SEQ ID NO: 11 provides a fusion protein including PD-1 Ectodomain, Fc, and Transforming growth factor-beta recep-

tor II (TGF β -RII) Extracellular domain (ectodomain) (PD-1 ectodomain+Fc+TGF β RII ectodomain; FIG. 10). SEQ ID NO: 12 provides a fusion protein including Transforming growth factor-beta receptor II (TGF β -RII) Extracellular domain (ectodomain), Fc, and PD-1 Ectodomain (TGF β -RII ectodomain+Fc+PD-1 ectodomain; FIG. 10). SEQ ID NO: 13 provides a fusion protein including RANK Ectodomain, Fc, and Transforming growth factor-beta receptor (TGF β -RII) Extracellular domain (ectodomain) (RANK ectodomain+Fc+TGF β RII ectodomain; FIG. 11). SEQ ID NO: 14 provides a fusion protein including Transforming growth factor-beta receptor II (TGF β -RII) Extracellular domain (ectodomain), Fc, and RANK Ectodomain (TGF β RII ectodomain+Fc+RANK ectodomain; FIG. 11).

In another embodiment, the present invention provides a molecule including a targeting moiety fused with an immunomodulatory moiety, wherein the targeting moiety specifically binds to a target molecule, and the immunomodulatory moiety is a molecule that specifically binds to Programmed Death-1 ligand 1 (PD-L1 or B7-H1) or Programmed Death-1 ligand 2 (PD-L2 or B7-DC). SEQ ID NO 15 provides a fusion protein including anti-HER2/neu antibody and PD-1 Ectodomain (FIG. 13). SEQ ID NO 16 provides a fusion protein including anti-EGFR1 antibody and PD-1 Ectodomain (FIG. 14). SEQ ID NO 17 provides a fusion protein including anti-CD20 antibody and PD-1 Ectodomain (FIG. 15). SEQ ID NO 18 provides a fusion protein including anti-VEGF antibody and PD-1 Ectodomain (FIG. 16). SEQ ID NO: 19 provides a fusion protein including anti-human CTLA-4 antibody and PD-1 Ectodomain (FIG. 17). SEQ ID NO: 20 provides a fusion protein including anti-CD25 antibody and PD-1 Ectodomain (FIG. 18A). SEQ ID NO: 21 provides a fusion protein including anti-CD25 antibody and PD-1 Ectodomain (FIG. 18B). SEQ ID NO: 22 provides a fusion protein including IL-2, Fc, and PD-1 ectodomain (IL-2+Fc+PD-1 ectodomain; FIG. 19). SEQ ID NO: 23 provides a fusion protein including PD-1 ectodomain, Fc, and IL-2 (PD-1 ectodomain+Fc+IL-2; FIG. 19). SEQ ID NO: 24 provides a fusion protein including anti-CD4 antibody and PD-1 Ectodomain (FIG. 20). SEQ ID NO: 25 provides a fusion protein including RANK Ectodomain, Fc, and PD-1 ectodomain (RANK ectodomain+Fc+PD-1 ectodomain; FIG. 21). SEQ ID NO: 26 provides a fusion protein including PD-1 ectodomain, Fc, and RANK Ectodomain (PD-1 ectodomain+Fc+RANK ectodomain; FIG. 21).

In another embodiment, the present invention provides a molecule including a targeting moiety fused with an immunomodulatory moiety, wherein the targeting moiety specifically binds to a target molecule, and the immunomodulatory moiety is a molecule that specifically binds to Receptor activator of NF- κ B ligand (RANKL). SEQ ID NO: 27 provides a fusion protein including anti-HER2/neu antibody and RANK Ectodomain (FIG. 23). SEQ ID NO: 28 provides a fusion protein including anti-EGFR1 antibody and RANK Ectodomain (FIG. 24). SEQ ID NO: 29 provides a fusion protein including anti-CD20 antibody and RANK Ectodomain (FIG. 25). SEQ ID NO: 30 provides a fusion protein including anti-VEGF antibody and RANK Ectodomain (FIG. 26). SEQ ID NO: 31 provides a fusion protein including anti-human CTLA-4 antibody and RANK Ectodomain (FIG. 27). SEQ ID NO: 32 provides a fusion protein including anti-CD25 antibody and RANK Ectodomain (FIG. 28A). SEQ ID NO: 33 provides a fusion protein including anti-CD25 antibody and RANK Ectodomain (FIG. 28B). SEQ ID NO: 34 provides a fusion protein including IL-2, Fc, and RANK ectodomain (IL-2+Fc+RANK ectodomain; FIG. 29). SEQ ID NO: 35 provides a

fusion protein including RANK ectodomain, Fc, and IL-2 (RANK ectodomain+Fc+IL-2; FIG. 29). SEQ ID NO: 36 provides a fusion protein including anti-CD4 antibody and RANK Ectodomain (FIG. 30).

In another embodiment, the present invention provides a molecule including a targeting moiety fused with an immunomodulatory moiety, wherein the targeting moiety specifically binds to a target molecule, and the immunomodulatory moiety includes a molecule that specifically binds to Programmed death-1 (PD-1). SEQ ID NO: 37 provides a fusion protein including anti-tumor necrosis factor (TNF α) antibody and PD-1 ligand 1 (FIG. 32). SEQ ID NO: 38 provides a fusion protein including TNFR2 Extracellular ligand binding domain, Fc, and PD-1 ligand: (TNFR2 ECD+IgG C γ 1+PD-L1; FIG. 33). SEQ ID NO: 39 provides a fusion protein including PD-1 ligand, Fc, and TNFR2 Extracellular ligand binding domain: (PD-L1+IgG C γ 1-TNFR2 ECD; FIG. 33). SEQ ID NO: 40 provides a fusion protein including anti-CD20 antibody and PD-1 ligand 1 (PD-L1) (FIG. 34). SEQ ID NO: 41 provides a fusion protein including anti-CD25 antibody and PD-1 ligand 1 (PD-L1) (FIG. 35A). SEQ ID NO: 42 provides a fusion protein including anti-CD25 antibody and PD-1 ligand 1 (PD-L1) (FIG. 35B). SEQ ID NO: 43 provides a fusion protein including PD-1 ligand 1 (PD-L1), Fc, and IL-2 (PD-L1-Fc-IL2; FIG. 36). SEQ ID NO: 44 provides a fusion protein including IL-2, Fc, and PD-1 ligand 1 (PD-L1) (IL-2-Fc-PD-L1; FIG. 36). SEQ ID NO: 45 provides a fusion protein including anti-CD4 antibody and PD-1 ligand 1 (PD-L1) (FIG. 37). SEQ ID NO: 46 provides a fusion protein including the extracellular domain of CTLA-4, Immunoglobulin Fc (IgG C γ 1), and a sequence from PD-1 ligand (PD-L1) (Oncostatin M signal peptide+CTLA-4 ECD+IgG C γ 1+PD-L1; FIG. 38). SEQ ID NO: 47 provides a fusion protein including the extracellular domain of PD-1 ligand (PD-L1), immunoglobulin Fc (IgG C γ 1), and a sequence from the extracellular domain of CTLA-4: (PD-L1+IgG C γ 1+CTLA-4 ECD; FIG. 38). SEQ ID NO: 48 provides a fusion protein including Transforming growth factor- β (TGF- β), immunoglobulin Fc (IgG1), and a sequence from PD-1 ligand 1 (PD-L1) (TGF- β -1+Fc+PD-L1; FIG. 39). SEQ ID NO: 49 provides a fusion protein including a sequence from PD-1 ligand 1 (PD-L1), immunoglobulin Fc (IgG C γ 1), and Transforming growth factor beta (TGF- β) (PD-L1+Fc+TGF-1; FIG. 39).

In another embodiment, the present invention provides a molecule including a targeting moiety fused with an immunomodulatory moiety, wherein the targeting moiety specifically binds to a target molecule, and the immunomodulatory moiety includes a molecule that specifically binds to Transforming growth factor-beta receptor (TGF- β R). SEQ ID NO 50 provides a fusion protein including an antibody that binds TNF- α , and a sequence from Transforming growth factor- β (TGF- β) (FIG. 41). SEQ ID NO: 51 provides a fusion protein including TNFR2 Extracellular ligand binding domain, Fc, and a sequence from Transforming growth factor- β (TGF- β) (TNFR2 ECD+IgG C γ 1+TGF- β ; FIG. 42). SEQ ID NO 52 provides a fusion protein including a sequence from Transforming growth factor- β (TGF- β), Fc, and TNFR2 Extracellular ligand binding domain: (TGF- β +IgG C γ 1+TNFR2 ECD; FIG. 42). SEQ ID NO: 53 provides a fusion protein including anti-CD20 antibody and a sequence from Transforming growth factor- β (TGF- β) (FIG. 43). SEQ ID NO: 54 provides a fusion protein including anti-CD25 antibody and a sequence from transforming growth factor- β (TGF- β) (FIG. 44A). SEQ ID NO: 55 provides a fusion protein including anti-CD25 antibody and a sequence from transforming growth factor- β (TGF- β) (FIG. 44B). SEQ ID NO: 56 pro-

vides a fusion protein including a sequence from Transforming growth factor- β (TGF- β), Fc, and IL-2 (TGF- β +Fc+IL-2; FIG. 45). SEQ ID NO: 57 provides a fusion protein including IL-2, Fc, and Transforming growth factor- β (TGF- β) (IL-2+Fc+TGF- β ; FIG. 45). SEQ ID NO: 58 provides a fusion protein including anti-CD4 antibody and a sequence from transforming growth factor-3 (TGF- β) (FIG. 46). SEQ ID NO: 59 provides a fusion protein including the extracellular domain of CTLA-4, immunoglobulin Fc (IgG C γ 1), and a sequence from a sequence from transforming growth factor- β (TGF- β) (Oncostatin M signal peptide+CTLA-4 ECD+IgG C γ 1+TGF-1; FIG. 47). SEQ ID NO: 60 provides a fusion protein including a sequence from Transforming growth factor-3 (TGF-13, immunoglobulin Fc (IgG C γ 1), and a sequence from the extracellular domain of CTLA-4: (TGF- β 1+IgG C γ 1+CTLA-4 ECD) (FIG. 47).

In another embodiment, the present invention provides a molecule including a targeting moiety fused with an immunomodulatory moiety, wherein the targeting moiety specifically binds to a target molecule, and the immunomodulatory moiety is a molecule that specifically binds to Receptor activator of NF- κ B ligand (RANKL). SEQ ID NO: 61 provides a fusion protein including an antibody that binds TNF- α , and a sequence from RANK Ectodomain (FIG. 48). SEQ ID NO: 62 provides a fusion protein including TNFR2 Extracellular ligand binding domain, Fc, and a sequence from RANK Ectodomain (TNFR2 ECD+IgG C γ 1+RANK Ectodomain; FIG. 49). SEQ ID NO: 63 provides a fusion protein including a sequence from RANK Ectodomain, Fc, and TNFR2 Extracellular ligand binding domain: (RANK Ectodomain+IgG C γ 1+TNFR2 ECD; FIG. 49). SEQ ID NO: 64 provides a

fusion protein including the extracellular domain of CTLA-4, immunoglobulin Fc (IgG C γ 1), and a sequence from a sequence from RANK Ectodomain (Oncostatin M signal peptide+CTLA-4 ECD+IgG C γ 1+RANK Ectodomain; FIG. 50). SEQ ID NO: 65 provides a fusion protein including a sequence from RANK Ectodomain, immunoglobulin Fc (IgG C γ 1), and a sequence from the extracellular domain of CTLA-4: (RANK Ectodomain+IgG C γ 1+CTLA-4 ECD) (FIG. 50). SEQ ID NO: 66 provides a fusion protein including a sequence from transforming growth factor- β (TGF- β), immunoglobulin Fc region (IgG C γ 1), and an extracellular ligand-binding domain or ectodomain of Receptor activator of nuclear factor- κ B (RANK) (TGF- β +IgG C γ 1+RANK Ectodomain; FIG. 51). SEQ ID NO: 67 provides a fusion protein including a sequence from RANK Ectodomain, immunoglobulin Fc (IgG C γ 1), and a sequence from transforming growth factor- β (TGF- β): (RANK Ectodomain+IgG C γ 1+TGF- β) (FIG. 51). SEQ ID NO: 68 provides a fusion protein including a sequence from Programmed death-1 ligand 1 (PD-L1), immunoglobulin Fc region (IgG C γ 1), and an extracellular ligand-binding domain or ectodomain of Receptor activator of nuclear factor- κ B (RANK) (PD-L1+IgG C γ 1+RANK Ectodomain; FIG. 52). SEQ ID NO: 69 provides a fusion protein including a sequence from RANK Ectodomain, immunoglobulin Fc (IgG C γ 1), and a sequence from Programmed death-1 ligand 1 (PD-L1): (RANK Ectodomain+IgG C γ 1+PD-L1) (FIG. 52).

Although the invention has been described with reference to the above example, it will be understood that modifications and variations are encompassed within the spirit and scope of the invention. Accordingly, the invention is limited only by the following claims.

SEQUENCE LISTING

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<210> SEQ ID NO 1

<211> LENGTH: 602

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

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Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
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Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
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Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser

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Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro	180	185	190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys	195	200	205
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp	210	215	220
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly	225	230	235
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile	245	250	255
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu	260	265	270
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His	275	280	285
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg	290	295	300
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys	305	310	315
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu	325	330	335
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr	340	345	350
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu	355	360	365
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp	370	375	380
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val	385	390	395
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp	405	410	415
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His	420	425	430
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro	435	440	445
Gly Lys Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly	450	455	460
Ser Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile	465	470	475
Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe	485	490	495
Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser	500	505	510
Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val	515	520	525
Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys	530	535	540
His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala	545	550	555
Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe	565	570	575

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Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe
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Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
595 600

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<211> LENGTH: 601
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 2

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Gly Val His Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Val Ile Trp Ser Gly Gly Asn Thr Asp Tyr Asn Thr Pro Phe Thr
50 55 60

Ser Arg Leu Ser Ile Asn Lys Asp Asn Ser Lys Ser Gln Val Phe Phe
65 70 75 80

Lys Met Asn Ser Leu Gln Ser Asn Asp Thr Ala Ile Tyr Tyr Cys Ala
85 90 95

Arg Ala Leu Thr Tyr Tyr Asp Tyr Glu Phe Ala Tyr Trp Gly Gln Gly
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Thr Leu Val Thr Val Ser Ala Ala Ser Thr Lys Gly Pro Ser Val Phe
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Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
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Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
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Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
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Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
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Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys
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Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
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Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
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Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
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Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
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Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
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Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr

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Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
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Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
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Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys
			405						410					415	
Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
	420						425						430		
Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly
	435						440					445			
Lys	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser
	450					455					460				
Thr	Ile	Pro	Pro	His	Val	Gln	Lys	Ser	Val	Asn	Asn	Asp	Met	Ile	Val
465					470					475					480
Thr	Asp	Asn	Asn	Gly	Ala	Val	Lys	Phe	Pro	Gln	Leu	Cys	Lys	Phe	Cys
				485					490					495	
Asp	Val	Arg	Phe	Ser	Thr	Cys	Asp	Asn	Gln	Lys	Ser	Cys	Met	Ser	Asn
			500					505					510		
Cys	Ser	Ile	Thr	Ser	Ile	Cys	Glu	Lys	Pro	Gln	Glu	Val	Cys	Val	Ala
	515						520					525			
Val	Trp	Arg	Lys	Asn	Asp	Glu	Asn	Ile	Thr	Leu	Glu	Thr	Val	Cys	His
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Asp	Pro	Lys	Leu	Pro	Tyr	His	Asp	Phe	Ile	Leu	Glu	Asp	Ala	Ala	Ser
545					550					555					560
Pro	Lys	Cys	Ile	Met	Lys	Glu	Lys	Lys	Lys	Pro	Gly	Glu	Thr	Phe	Phe
			565						570					575	
Met	Cys	Ser	Cys	Ser	Ser	Asp	Glu	Cys	Asn	Asp	Asn	Ile	Ile	Phe	Ser
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Glu	Glu	Tyr	Asn	Thr	Ser	Asn	Pro	Asp							
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<211> LENGTH: 603

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 3

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Asn	Met	His	Trp	Val	Lys	Gln	Thr	Pro	Gly	Arg	Gly	Leu	Glu	Trp	Ile
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Gly	Ala	Ile	Tyr	Pro	Gly	Asn	Gly	Asp	Thr	Ser	Tyr	Asn	Gln	Lys	Phe
	50				55				60						
Lys	Gly	Lys	Ala	Thr	Leu	Thr	Ala	Asp	Lys	Ser	Ser	Ser	Thr	Ala	Tyr
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Met	Gln	Leu	Ser	Ser	Leu	Thr	Ser	Glu	Asp	Ser	Ala	Val	Tyr	Tyr	Cys
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Ala	Arg	Ser	Thr	Tyr	Tyr	Gly	Gly	Asp	Trp	Tyr	Phe	Asn	Val	Trp	Gly
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Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val
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Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala
				165					170					175	
Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val
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Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His
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Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Ala	Glu	Pro	Lys	Ser	Cys
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Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly
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Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met
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Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly
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Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile
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Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val
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Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser
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Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val
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Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met
			420					425					430		
His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser
		435					440					445			
Pro	Gly	Lys	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly
	450					455					460				
Gly	Ser	Thr	Ile	Pro	Pro	His	Val	Gln	Lys	Ser	Val	Asn	Asn	Asp	Met
	465				470					475				480	
Ile	Val	Thr	Asp	Asn	Asn	Gly	Ala	Val	Lys	Phe	Pro	Gln	Leu	Cys	Lys
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Phe	Cys	Asp	Val	Arg	Phe	Ser	Thr	Cys	Asp	Asn	Gln	Lys	Ser	Cys	Met
		500						505					510		
Ser	Asn	Cys	Ser	Ile	Thr	Ser	Ile	Cys	Glu	Lys	Pro	Gln	Glu	Val	Cys
		515					520					525			
Val	Ala	Val	Trp	Arg	Lys	Asn	Asp	Glu	Asn	Ile	Thr	Leu	Glu	Thr	Val

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545	550	555 560
Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr		
	565	570 575
Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile		
	580	585 590
Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp		
595	600	
<210> SEQ ID NO 4		
<211> LENGTH: 605		
<212> TYPE: PRT		
<213> ORGANISM: Homo sapiens		
<400> SEQUENCE: 4		
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly		
1	5	10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Asn Tyr		
	20	25 30
Gly Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val		
	35	40 45
Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Ala Asp Phe		
	50	55 60
Lys Arg Arg Phe Thr Phe Ser Leu Asp Thr Ser Lys Ser Thr Ala Tyr		
	65	70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys		
	85	90 95
Ala Lys Tyr Pro His Tyr Tyr Gly Ser Ser His Trp Tyr Phe Asp Val		
	100	105 110
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly		
	115	120 125
Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly		
	130	135 140
Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val		
	145	150 155 160
Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe		
	165	170 175
Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val		
	180	185 190
Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val		
	195	200 205
Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys		
	210	215 220
Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu		
	225	230 235 240
Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr		
	245	250 255
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val		
	260	265 270
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val		
	275	280 285
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser		
	290	295 300

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Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
 305 310 315 320
 Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
 325 330 335
 Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
 340 345 350
 Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
 355 360 365
 Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
 370 375 380
 Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
 385 390 395 400
 Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
 405 410 415
 Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
 420 425 430
 Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
 435 440 445
 Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
 450 455 460
 Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn
 465 470 475 480
 Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu
 485 490 495
 Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser
 500 505 510
 Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu
 515 520 525
 Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu
 530 535 540
 Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu
 545 550 555 560
 Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly
 565 570 575
 Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn
 580 585 590
 Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
 595 600 605

<210> SEQ ID NO 5
 <211> LENGTH: 600
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 5

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Thr Phe Ile Ser Tyr Asp Gly Asn Asn Lys Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

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Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
 85 90 95
 Ala Arg Thr Gly Trp Leu Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr
 100 105 110
 Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
 115 120 125
 Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
 130 135 140
 Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
 145 150 155 160
 Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
 165 170 175
 Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
 180 185 190
 Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
 195 200 205
 Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
 210 215 220
 His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
 225 230 235 240
 Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
 245 250 255
 Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
 260 265 270
 Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
 275 280 285
 Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
 290 295 300
 Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
 305 310 315 320
 Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
 325 330 335
 Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
 340 345 350
 Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
 355 360 365
 Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
 370 375 380
 Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
 385 390 395 400
 Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
 405 410 415
 Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
 420 425 430
 Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 435 440 445
 Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Thr
 450 455 460
 Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr
 465 470 475 480
 Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp
 485 490 495

Ala 1	Pro	Thr	Ser 5	Ser	Thr	Lys	Lys 10	Thr	Gln	Leu	Gln	Leu	Glu	His 15
Leu	Leu	Leu	Asp 20	Leu	Gln	Met	Ile	Leu 25	Asn	Gly	Ile	Asn	Asn	Tyr 30
Asn	Pro	Lys 35	Leu	Thr	Arg	Met	Leu 40	Thr	Phe	Lys	Phe	Tyr 45	Met	Pro 50
Lys 50	Ala	Thr	Glu	Leu	Lys 55	His	Leu	Gln	Cys	Leu	Glu 60	Glu	Glu	Leu 65
Pro 65	Leu	Glu	Glu	Val	Leu 70	Asn	Leu	Ala	Gln	Ser 75	Lys	Asn	Phe	His 80
Arg	Pro	Arg	Asp 85	Leu	Ile	Ser	Asn	Ile 90	Asn	Val	Ile	Val	Leu	Glu 95
Lys	Gly	Ser	Glu 100	Thr	Thr	Phe	Met	Cys 105	Glu	Tyr	Ala	Asp	Glu 110	Thr 115
Thr 115	Ile	Val	Glu	Phe	Leu	Asn	Arg 120	Trp	Ile	Thr	Phe	Cys 125	Gln	Ser 130
Ile 130	Ser	Thr	Leu	Thr	Gly 135	Gly	Gly	Gly	Ser	Gly	Gly 140	Gly	Gly	Ser 145
Gly 145	Gly	Gly	Ser	Thr	His 150	Thr	Cys	Pro	Pro	Cys 155	Pro	Ala	Pro	Glu 160
Leu	Gly	Gly	Pro	Ser 165	Val	Phe	Leu	Phe 170	Pro	Pro	Lys	Pro	Lys	Asp 175
Leu	Met	Ile	Ser 180	Arg	Thr	Pro	Glu	Val 185	Thr	Cys	Val	Val	Val	Asp 190
Ser	His	Glu 195	Asp	Pro	Glu	Val	Lys 200	Phe	Asn	Trp	Tyr 205	Val	Asp	Gly 210
Glu 210	Val	His	Asn	Ala	Lys 215	Thr	Lys	Pro	Arg	Glu	Glu 220	Gln	Tyr	Asn 225
Thr 225	Tyr	Arg	Val	Val	Ser 230	Val	Leu	Thr	Val	Leu	His 235	Gln	Asp	Trp 240
Asn	Gly	Lys	Glu	Tyr 245	Lys	Cys	Lys	Val	Ser 250	Asn	Lys	Ala	Leu	Pro 255
Pro	Ile	Glu 260	Lys	Thr	Ile	Ser	Lys 265	Ala	Lys	Gly	Gln	Pro	Arg	Glu 270

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Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
 275 280 285
 Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
 290 295 300
 Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
 305 310 315 320
 Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
 325 330 335
 Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
 340 345 350
 Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
 355 360 365
 Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
 370 375 380
 Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn
 385 390 395 400
 Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu
 405 410 415
 Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser
 420 425 430
 Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu
 435 440 445
 Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu
 450 455 460
 Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu
 465 470 475 480
 Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly
 485 490 495
 Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn
 500 505 510
 Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
 515 520 525

 <210> SEQ ID NO 7
 <211> LENGTH: 525
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

 <400> SEQUENCE: 7

 Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val
 1 5 10 15
 Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys
 20 25 30
 Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn
 35 40 45
 Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala
 50 55 60
 Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His
 65 70 75 80
 Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser
 85 90 95
 Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe
 100 105 110
 Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser

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115					120					125					
Glu	Glu	Tyr	Asn	Thr	Ser	Asn	Pro	Asp	Gly	Gly	Gly	Gly	Ser	Gly	Gly
130						135					140				
Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro
145					150					155					160
Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys
					165				170					175	
Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val
			180					185					190		
Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr
		195					200					205			
Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu
	210					215					220				
Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His
225					230					235					240
Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys
			245						250					255	
Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln
			260					265					270		
Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met
		275					280					285			
Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro
	290					295					300				
Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn
305					310					315					320
Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu
			325						330				335		
Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val
			340					345					350		
Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln
		355					360					365			
Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys	Gly	Gly	Gly	Gly	Ser	Gly	Gly
	370					375					380				
Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Ala	Pro	Thr	Ser	Ser	Ser	Thr	Lys
385					390					395					400
Lys	Thr	Gln	Leu	Gln	Leu	Glu	His	Leu	Leu	Leu	Asp	Leu	Gln	Met	Ile
			405						410					415	
Leu	Asn	Gly	Ile	Asn	Asn	Tyr	Lys	Asn	Pro	Lys	Leu	Thr	Arg	Met	Leu
			420					425					430		
Thr	Phe	Lys	Phe	Tyr	Met	Pro	Lys	Lys	Ala	Thr	Glu	Leu	Lys	His	Leu
		435					440					445			
Gln	Cys	Leu	Glu	Glu	Glu	Leu	Lys	Pro	Leu	Glu	Glu	Val	Leu	Asn	Leu
		450				455					460				
Ala	Gln	Ser	Lys	Asn	Phe	His	Leu	Arg	Pro	Arg	Asp	Leu	Ile	Ser	Asn
465					470					475					480
Ile	Asn	Val	Ile	Val	Leu	Glu	Leu	Lys	Gly	Ser	Glu	Thr	Thr	Phe	Met
			485						490					495	
Cys	Glu	Tyr	Ala	Asp	Glu	Thr	Ala	Thr	Ile	Val	Glu	Phe	Leu	Asn	Arg
		500						505					510		
Trp	Ile	Thr	Phe	Cys	Gln	Ser	Ile	Ile	Ser	Thr	Leu	Thr			
		515					520					525			

<210> SEQ ID NO 8

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<211> LENGTH: 598
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1      5      10      15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20     25     30
Arg Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35     40     45
Gly Tyr Ile Asn Pro Ser Thr Gly Tyr Thr Glu Tyr Asn Gln Lys Phe
50     55     60
Lys Asp Lys Ala Thr Ile Thr Ala Asp Glu Ser Thr Asn Thr Ala Tyr
65     70     75     80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85     90     95
Ala Arg Gly Gly Gly Val Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100    105    110
Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115    120    125
Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130    135    140
Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145    150    155    160
Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165    170    175
Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180    185    190
Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195    200    205
Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210    215    220
Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
225    230    235    240
Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245    250    255
Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260    265    270
Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275    280    285
Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290    295    300
Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305    310    315    320
Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325    330    335
Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340    345    350
Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355    360    365
Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370    375    380
Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp

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385	390	395	400
Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp	405	410	415
Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His	420	425	430
Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly	435	440	445
Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Thr Ile Pro	450	455	460
Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn	465	470	475
Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg	485	490	495
Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile	500	505	510
Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg	515	520	525
Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys	530	535	540
Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys	545	550	555
Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser	565	570	575
Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr	580	585	590
Asn Thr Ser Asn Pro Asp	595		

<210> SEQ ID NO 9
 <211> LENGTH: 597
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 9

Gln Leu Gln Gln Ser Gly Thr Val Leu Ala Arg Pro Gly Ala Ser Val	1	5	10	15
Lys Met Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Arg Tyr Trp Met	20	25	30	
His Trp Ile Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Ala	35	40	45	
Ile Tyr Pro Gly Asn Ser Asp Thr Ser Tyr Asn Gln Lys Phe Glu Gly	50	55	60	
Lys Ala Lys Leu Thr Ala Val Thr Ser Ala Ser Thr Ala Tyr Met Glu	65	70	75	80
Leu Ser Ser Leu Thr His Glu Asp Ser Ala Val Tyr Tyr Cys Ser Arg	85	90	95	
Asp Tyr Gly Tyr Tyr Phe Asp Phe Trp Gly Gln Gly Thr Thr Leu Thr	100	105	110	
Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro	115	120	125	
Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val	130	135	140	
Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala	145	150	155	160

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580	585	590
Thr Ser Asn Pro Asp		
595		
 <210> SEQ ID NO 10		
<211> LENGTH: 603		
<212> TYPE: PRT		
<213> ORGANISM: Homo sapiens		
 <400> SEQUENCE: 10		
Gln Val Gln Leu Gln Glu Ala Gly Pro Gly Leu Val Lys Pro Ser Glu		
1 5 10 15		
Thr Leu Ser Leu Thr Cys Ser Val Ser Gly Gly Ser Ile Ser Gly Asp		
20 25 30		
Tyr Tyr Trp Phe Trp Ile Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp		
35 40 45		
Ile Gly Tyr Ile Tyr Gly Ser Gly Gly Gly Thr Asn Tyr Asn Pro Ser		
50 55 60		
Leu Asn Asn Arg Val Ser Ile Ser Ile Asp Thr Ser Lys Asn Leu Phe		
65 70 75 80		
Ser Leu Lys Leu Arg Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr		
85 90 95		
Cys Ala Ser Asn Ile Leu Lys Tyr Leu His Trp Leu Leu Tyr Trp Gly		
100 105 110		
Gln Gly Val Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser		
115 120 125		
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala		
130 135 140		
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val		
145 150 155 160		
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala		
165 170 175		
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val		
180 185 190		
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His		
195 200 205		
Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys		
210 215 220		
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly		
225 230 235 240		
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met		
245 250 255		
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His		
260 265 270		
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val		
275 280 285		
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr		
290 295 300		
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly		
305 310 315 320		
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile		
325 330 335		
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val		
340 345 350		

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Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
 355 360 365
 Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
 370 375 380
 Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
 385 390 395 400
 Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
 405 410 415
 Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
 420 425 430
 His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
 435 440 445
 Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
 450 455 460
 Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met
 465 470 475 480
 Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys
 485 490 495
 Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met
 500 505 510
 Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys
 515 520 525
 Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val
 530 535 540
 Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala
 545 550 555 560
 Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr
 565 570 575
 Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile
 580 585 590
 Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
 595 600

<210> SEQ ID NO 11
 <211> LENGTH: 542
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11

Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp Asn Pro Pro Thr
 1 5 10 15
 Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp Asn Ala Thr Phe
 20 25 30
 Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val Leu Asn Trp Tyr
 35 40 45
 Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala Ala Phe Pro Glu
 50 55 60
 Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg Val Thr Gln Leu
 65 70 75 80
 Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg Ala Arg Arg Asn
 85 90 95
 Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu Ala Pro Lys Ala
 100 105 110
 Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val Thr Glu Arg Arg
 115 120 125

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Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro Arg Pro Ala Gly
 130 135 140
 Gln Phe Gln Thr Leu Val Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
 145 150 155 160
 Gly Gly Gly Gly Ser Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
 165 170 175
 Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
 180 185 190
 Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
 195 200 205
 Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
 210 215 220
 Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
 225 230 235 240
 Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
 245 250 255
 Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
 260 265 270
 Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
 275 280 285
 Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
 290 295 300
 Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
 305 310 315 320
 Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
 325 330 335
 Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
 340 345 350
 Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
 355 360 365
 Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
 370 375 380
 Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
 385 390 395 400
 Gly Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Val Asn
 405 410 415
 Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln
 420 425 430
 Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys
 435 440 445
 Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln
 450 455 460
 Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu
 465 470 475 480
 Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu
 485 490 495
 Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro
 500 505 510
 Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp
 515 520 525
 Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
 530 535 540

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<210> SEQ ID NO 12
<211> LENGTH: 542
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12

Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val
1           5           10           15

Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys
          20           25           30

Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn
          35           40           45

Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala
          50           55           60

Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His
          65           70           75           80

Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser
          85           90           95

Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe
          100          105          110

Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser
          115          120          125

Glu Glu Tyr Asn Thr Ser Asn Pro Asp Gly Gly Gly Gly Ser Gly Gly
          130          135          140

Gly Gly Ser Gly Gly Gly Gly Ser Thr His Thr Cys Pro Pro Cys Pro
          145          150          155          160

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
          165          170          175

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
          180          185          190

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
          195          200          205

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
          210          215          220

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
          225          230          235          240

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
          245          250          255

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
          260          265          270

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
          275          280          285

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
          290          295          300

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
          305          310          315          320

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
          325          330          335

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
          340          345          350

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
          355          360          365

Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly
          370          375          380

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Gly Gly Ser Gly Gly Gly Gly Ser Pro Gly Trp Phe Leu Asp Ser Pro
 385 390 395 400
 Asp Arg Pro Trp Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val
 405 410 415
 Thr Glu Gly Asp Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser
 420 425 430
 Glu Ser Phe Val Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr
 435 440 445
 Asp Lys Leu Ala Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp
 450 455 460
 Cys Arg Phe Arg Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met
 465 470 475 480
 Ser Val Val Arg Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly
 485 490 495
 Ala Ile Ser Leu Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala
 500 505 510
 Glu Leu Arg Val Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro
 515 520 525
 Ser Pro Ser Pro Arg Pro Ala Gly Gln Phe Gln Thr Leu Val
 530 535 540

<210> SEQ ID NO 13
 <211> LENGTH: 577
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 13

Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val
 1 5 10 15
 Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys
 20 25 30
 Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn
 35 40 45
 Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala
 50 55 60
 Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His
 65 70 75 80
 Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser
 85 90 95
 Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe
 100 105 110
 Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser
 115 120 125
 Glu Glu Tyr Asn Thr Ser Asn Pro Asp Gly Gly Gly Gly Ser Gly Gly
 130 135 140
 Gly Gly Ser Gly Gly Gly Gly Ser Thr His Thr Cys Pro Pro Cys Pro
 145 150 155 160
 Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
 165 170 175
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
 180 185 190
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
 195 200 205
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu

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210	215	220
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His		
225	230	235 240
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys		
	245	250 255
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln		
	260	265 270
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met		
	275	280 285
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro		
	290	295 300
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn		
305	310	315 320
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu		
	325	330 335
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val		
	340	345 350
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln		
	355	360 365
Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly		
	370	375 380
Gly Gly Ser Gly Gly Gly Ser Gln Ile Ala Pro Pro Cys Thr Ser		
385	390	395 400
Glu Lys His Tyr Glu His Leu Gly Arg Cys Cys Asn Lys Cys Glu Pro		
	405	410 415
Gly Lys Tyr Met Ser Ser Lys Cys Thr Thr Thr Ser Asp Ser Val Cys		
	420	425 430
Leu Pro Cys Gly Pro Asp Glu Tyr Leu Asp Ser Trp Asn Glu Glu Asp		
	435	440 445
Lys Cys Leu Leu His Lys Val Cys Asp Thr Gly Lys Ala Leu Val Ala		
	450	455 460
Val Val Ala Gly Asn Ser Thr Thr Pro Arg Arg Cys Ala Cys Thr Ala		
465	470	475 480
Gly Tyr His Trp Ser Gln Asp Cys Glu Cys Cys Arg Arg Asn Thr Glu		
	485	490 495
Cys Ala Pro Gly Leu Gly Ala Gln His Pro Leu Gln Leu Asn Lys Asp		
	500	505 510
Thr Val Cys Lys Pro Cys Leu Ala Gly Tyr Phe Ser Asp Ala Phe Ser		
	515	520 525
Ser Thr Asp Lys Cys Arg Pro Trp Thr Asn Cys Thr Phe Leu Gly Lys		
	530	535 540
Arg Val Glu His His Gly Thr Glu Lys Ser Asp Ala Val Cys Ser Ser		
545	550	555 560
Ser Leu Pro Ala Arg Lys Pro Pro Asn Glu Pro His Val Tyr Leu Pro		
	565	570 575

Gly

<210> SEQ ID NO 14
 <211> LENGTH: 577
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 14

Gln Ile Ala Pro Pro Cys Thr Ser Glu Lys His Tyr Glu His Leu Gly

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1	5	10	15
Arg Cys Cys Asn Lys Cys Glu Pro Gly Lys Tyr Met Ser Ser Lys Cys	20	25	30
Thr Thr Thr Ser Asp Ser Val Cys Leu Pro Cys Gly Pro Asp Glu Tyr	35	40	45
Leu Asp Ser Trp Asn Glu Glu Asp Lys Cys Leu Leu His Lys Val Cys	50	55	60
Asp Thr Gly Lys Ala Leu Val Ala Val Val Ala Gly Asn Ser Thr Thr	65	70	75
Pro Arg Arg Cys Ala Cys Thr Ala Gly Tyr His Trp Ser Gln Asp Cys	85	90	95
Glu Cys Cys Arg Arg Asn Thr Glu Cys Ala Pro Gly Leu Gly Ala Gln	100	105	110
His Pro Leu Gln Leu Asn Lys Asp Thr Val Cys Lys Pro Cys Leu Ala	115	120	125
Gly Tyr Phe Ser Asp Ala Phe Ser Ser Thr Asp Lys Cys Arg Pro Trp	130	135	140
Thr Asn Cys Thr Phe Leu Gly Lys Arg Val Glu His His Gly Thr Glu	145	150	155
Lys Ser Asp Ala Val Cys Ser Ser Ser Leu Pro Ala Arg Lys Pro Pro	165	170	175
Asn Glu Pro His Val Tyr Leu Pro Gly Gly Gly Gly Ser Gly Gly	180	185	190
Gly Gly Ser Gly Gly Gly Gly Ser Thr His Thr Cys Pro Pro Cys Pro	195	200	205
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys	210	215	220
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val	225	230	235
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr	245	250	255
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu	260	265	270
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His	275	280	285
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys	290	295	300
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln	305	310	315
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met	325	330	335
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro	340	345	350
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn	355	360	365
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu	370	375	380
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val	385	390	395
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln	405	410	415
Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly	420	425	430

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Gly Gly Ser Gly Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys
 435 440 445
 Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys
 450 455 460
 Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp
 465 470 475 480
 Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu
 485 490 495
 Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn
 500 505 510
 Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp
 515 520 525
 Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys
 530 535 540
 Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu
 545 550 555 560
 Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro
 565 570 575

Asp

<210> SEQ ID NO 15
 <211> LENGTH: 615
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 15

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
 20 25 30
 Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
 115 120 125
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
 130 135 140
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
 145 150 155 160
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
 165 170 175
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 180 185 190
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
 195 200 205
 Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
 210 215 220

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Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
 225 230 235 240
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
 245 250 255
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
 260 265 270
 Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
 275 280 285
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
 290 295 300
 Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
 305 310 315 320
 Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
 325 330 335
 Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
 340 345 350
 Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
 355 360 365
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
 370 375 380
 Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
 385 390 395 400
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
 405 410 415
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
 420 425 430
 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
 435 440 445
 Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
 450 455 460
 Ser Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp Asn Pro Pro
 465 470 475 480
 Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp Asn Ala Thr
 485 490 495
 Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val Leu Asn Trp
 500 505 510
 Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala Ala Phe Pro
 515 520 525
 Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg Val Thr Gln
 530 535 540
 Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg Ala Arg Arg
 545 550 555 560
 Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu Ala Pro Lys
 565 570 575
 Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val Thr Glu Arg
 580 585 590
 Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro Arg Pro Ala
 595 600 605
 Gly Gln Phe Gln Thr Leu Val
 610 615

<210> SEQ ID NO 16

<211> LENGTH: 614

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 16

Gln Val Gln Leu Lys Gln Ser Gly Pro Gly Leu Val Gln Pro Ser Gln
1          5          10          15
Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Asn Tyr
20          25          30
Gly Val His Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Leu
35          40          45
Gly Val Ile Trp Ser Gly Gly Asn Thr Asp Tyr Asn Thr Pro Phe Thr
50          55          60
Ser Arg Leu Ser Ile Asn Lys Asp Asn Ser Lys Ser Gln Val Phe Phe
65          70          75          80
Lys Met Asn Ser Leu Gln Ser Asn Asp Thr Ala Ile Tyr Tyr Cys Ala
85          90          95
Arg Ala Leu Thr Tyr Tyr Asp Tyr Glu Phe Ala Tyr Trp Gly Gln Gly
100         105         110
Thr Leu Val Thr Val Ser Ala Ala Ser Thr Lys Gly Pro Ser Val Phe
115         120         125
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130         135         140
Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145         150         155         160
Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165         170         175
Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180         185         190
Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195         200         205
Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys
210         215         220
Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225         230         235         240
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245         250         255
Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260         265         270
Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275         280         285
Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290         295         300
Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305         310         315         320
Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325         330         335
Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340         345         350
Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
355         360         365
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370         375         380
Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385         390         395         400

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Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
 405 410 415
 Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
 420 425 430
 Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
 435 440 445
 Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser
 450 455 460
 Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp Asn Pro Pro Thr
 465 470 475 480
 Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp Asn Ala Thr Phe
 485 490 495
 Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val Leu Asn Trp Tyr
 500 505 510
 Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala Ala Phe Pro Glu
 515 520 525
 Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg Val Thr Gln Leu
 530 535 540
 Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg Ala Arg Arg Asn
 545 550 555 560
 Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu Ala Pro Lys Ala
 565 570 575
 Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val Thr Glu Arg Arg
 580 585 590
 Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro Arg Pro Ala Gly
 595 600 605
 Gln Phe Gln Thr Leu Val
 610

<210> SEQ ID NO 17
 <211> LENGTH: 616
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 17

Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala
 1 5 10 15
 Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30
 Asn Met His Trp Val Lys Gln Thr Pro Gly Arg Gly Leu Glu Trp Ile
 35 40 45
 Gly Ala Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe
 50 55 60
 Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
 65 70 75 80
 Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ser Thr Tyr Tyr Gly Gly Asp Trp Tyr Phe Asn Val Trp Gly
 100 105 110
 Ala Gly Thr Thr Val Thr Val Ser Ala Ala Ser Thr Lys Gly Pro Ser
 115 120 125
 Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
 130 135 140
 Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val

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145	150	155	160
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala	165	170	175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val	180	185	190
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His	195	200	205
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Ala Glu Pro Lys Ser Cys	210	215	220
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly	225	230	235
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met	245	250	255
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His	260	265	270
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val	275	280	285
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr	290	295	300
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly	305	310	315
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile	325	330	335
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val	340	345	350
Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser	355	360	365
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu	370	375	380
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro	385	390	395
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val	405	410	415
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met	420	425	430
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser	435	440	445
Pro Gly Lys Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly	450	455	460
Gly Ser Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp Asn Pro	465	470	475
Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp Asn Ala	485	490	495
Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val Leu Asn	500	505	510
Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala Ala Phe	515	520	525
Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg Val Thr	530	535	540
Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg Ala Arg	545	550	555
Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu Ala Pro	565	570	575

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Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val Thr Glu
580 585 590

Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro Arg Pro
595 600 605

Ala Gly Gln Phe Gln Thr Leu Val
610 615

<210> SEQ ID NO 18
 <211> LENGTH: 618
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Ala Asp Phe
50 55 60

Lys Arg Arg Phe Thr Phe Ser Leu Asp Thr Ser Lys Ser Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Tyr Pro His Tyr Tyr Gly Ser Ser His Trp Tyr Phe Asp Val
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
115 120 125

Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
130 135 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145 150 155 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
165 170 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
180 185 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
195 200 205

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
210 215 220

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
225 230 235 240

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
245 250 255

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
260 265 270

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
275 280 285

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
290 295 300

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
305 310 315 320

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala

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Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Ile	Tyr	Tyr	Cys
			85						90					95	
Ala	Arg	Thr	Gly	Trp	Leu	Gly	Pro	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Thr
			100					105					110		
Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro
			115				120					125			
Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly
	130				135						140				
Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn
	145			150						155					160
Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln
			165						170					175	
Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser
			180					185					190		
Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser
	195						200					205			
Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr
	210					215					220				
His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser
	225				230					235					240
Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg
			245						250					255	
Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro
			260					265					270		
Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala
	275						280					285			
Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val
	290				295						300				
Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr
	305			310					315						320
Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr
			325					330					335		
Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu
			340				345						350		
Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys
		355					360					365			
Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser
	370					375					380				
Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp
	385				390					395					400
Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser
			405						410				415		
Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala
			420					425					430		
Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys
		435					440					445			
Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Pro
	450					455					460				
Gly	Trp	Phe	Leu	Asp	Ser	Pro	Asp	Arg	Pro	Trp	Asn	Pro	Pro	Thr	Phe
	465				470					475					480
Ser	Pro	Ala	Leu	Leu	Val	Val	Thr	Glu	Gly	Asp	Asn	Ala	Thr	Phe	Thr
			485					490					495		
Cys	Ser	Phe	Ser	Asn	Thr	Ser	Glu	Ser	Phe	Val	Leu	Asn	Trp	Tyr	Arg

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500										505										510									
Met	Ser	Pro	Ser	Asn	Gln	Thr	Asp	Lys	Leu	Ala	Ala	Phe	Pro	Glu	Asp														
		515						520							525														
Arg	Ser	Gln	Pro	Gly	Gln	Asp	Cys	Arg	Phe	Arg	Val	Thr	Gln	Leu	Pro														
		530					535								540														
Asn	Gly	Arg	Asp	Phe	His	Met	Ser	Val	Val	Arg	Ala	Arg	Arg	Asn	Asp														
		545			550						555				560														
Ser	Gly	Thr	Tyr	Leu	Cys	Gly	Ala	Ile	Ser	Leu	Ala	Pro	Lys	Ala	Gln														
				565					570					575															
Ile	Lys	Glu	Ser	Leu	Arg	Ala	Glu	Leu	Arg	Val	Thr	Glu	Arg	Arg	Ala														
				580				585						590															
Glu	Val	Pro	Thr	Ala	His	Pro	Ser	Pro	Ser	Pro	Arg	Pro	Ala	Gly	Gln														
		595					600							605															
Phe	Gln	Thr	Leu	Val																									
				610																									

<210> SEQ ID NO 20
 <211> LENGTH: 611
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 20

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ser
1			5						10					15	
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Ser	Tyr
			20					25					30		
Arg	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile
		35					40					45			
Gly	Tyr	Ile	Asn	Pro	Ser	Thr	Gly	Tyr	Thr	Glu	Tyr	Asn	Gln	Lys	Phe
		50				55					60				
Lys	Asp	Lys	Ala	Thr	Ile	Thr	Ala	Asp	Glu	Ser	Thr	Asn	Thr	Ala	Tyr
				70					75						80
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85				90						95	
Ala	Arg	Gly	Gly	Gly	Val	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val
			100					105					110		
Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala
			115				120						125		
Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu
			130			135					140				
Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly
				150					155					160	
Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser
				165				170						175	
Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu
			180				185						190		
Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr
		195					200					205			
Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr
			210			215					220				
Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe
					230						235				240
Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro
				245					250					255	

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Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
 260 265 270
 Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
 275 280 285
 Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
 290 295 300
 Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
 305 310 315 320
 Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
 325 330 335
 Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
 340 345 350
 Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
 355 360 365
 Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
 370 375 380
 Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
 385 390 395 400
 Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
 405 410 415
 Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
 420 425 430
 Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly
 435 440 445
 Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Pro Gly Trp
 450 455 460
 Phe Leu Asp Ser Pro Asp Arg Pro Trp Asn Pro Pro Thr Phe Ser Pro
 465 470 475 480
 Ala Leu Leu Val Val Thr Glu Gly Asp Asn Ala Thr Phe Thr Cys Ser
 485 490 495
 Phe Ser Asn Thr Ser Glu Ser Phe Val Leu Asn Trp Tyr Arg Met Ser
 500 505 510
 Pro Ser Asn Gln Thr Asp Lys Leu Ala Ala Phe Pro Glu Asp Arg Ser
 515 520 525
 Gln Pro Gly Gln Asp Cys Arg Phe Arg Val Thr Gln Leu Pro Asn Gly
 530 535 540
 Arg Asp Phe His Met Ser Val Val Arg Ala Arg Arg Asn Asp Ser Gly
 545 550 555 560
 Thr Tyr Leu Cys Gly Ala Ile Ser Leu Ala Pro Lys Ala Gln Ile Lys
 565 570 575
 Glu Ser Leu Arg Ala Glu Leu Arg Val Thr Glu Arg Arg Ala Glu Val
 580 585 590
 Pro Thr Ala His Pro Ser Pro Ser Pro Arg Pro Ala Gly Gln Phe Gln
 595 600 605
 Thr Leu Val
 610

<210> SEQ ID NO 21

<211> LENGTH: 610

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

Gln Leu Gln Gln Ser Gly Thr Val Leu Ala Arg Pro Gly Ala Ser Val
 1 5 10 15

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Lys	Met	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ser	Phe	Thr	Arg	Tyr	Trp	Met	
			20				25							30		
His	Trp	Ile	Lys	Gln	Arg	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile	Gly	Ala	
			35				40							45		
Ile	Tyr	Pro	Gly	Asn	Ser	Asp	Thr	Ser	Tyr	Asn	Gln	Lys	Phe	Glu	Gly	
			50				55							60		
Lys	Ala	Lys	Leu	Thr	Ala	Val	Thr	Ser	Ala	Ser	Thr	Ala	Tyr	Met	Glu	
			65				70							75		
Leu	Ser	Ser	Leu	Thr	His	Glu	Asp	Ser	Ala	Val	Tyr	Tyr	Cys	Ser	Arg	
			85				90							95		
Asp	Tyr	Gly	Tyr	Tyr	Phe	Asp	Phe	Trp	Gly	Gln	Gly	Thr	Thr	Leu	Thr	
			100				105							110		
Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	
			115				120							125		
Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	
			130				135							140		
Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	
			145				150							155		
Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	
			165				170							175		
Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	
			180				185							190		
Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	
			195				200							205		
Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	
			210				215							220		
Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	
			225				230							235		
Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	
			245				250							255		
Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	
			260				265							270		
Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	
			275				280							285		
Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	
			290				295							300		
Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	
			305				310							315		
Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	
			325				330							335		
Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	
			340				345							350		
Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	
			355				360							365		
Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	
			370				375							380		
Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	
			385				390							395		
Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	

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His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly
 435 440 445
 Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Pro Gly Trp Phe
 450 455 460
 Leu Asp Ser Pro Asp Arg Pro Trp Asn Pro Pro Thr Phe Ser Pro Ala
 465 470 475 480
 Leu Leu Val Val Thr Glu Gly Asp Asn Ala Thr Phe Thr Cys Ser Phe
 485 490 495
 Ser Asn Thr Ser Glu Ser Phe Val Leu Asn Trp Tyr Arg Met Ser Pro
 500 505 510
 Ser Asn Gln Thr Asp Lys Leu Ala Ala Phe Pro Glu Asp Arg Ser Gln
 515 520 525
 Pro Gly Gln Asp Cys Arg Phe Arg Val Thr Gln Leu Pro Asn Gly Arg
 530 535 540
 Asp Phe His Met Ser Val Val Arg Ala Arg Arg Asn Asp Ser Gly Thr
 545 550 555 560
 Tyr Leu Cys Gly Ala Ile Ser Leu Ala Pro Lys Ala Gln Ile Lys Glu
 565 570 575
 Ser Leu Arg Ala Glu Leu Arg Val Thr Glu Arg Arg Ala Glu Val Pro
 580 585 590
 Thr Ala His Pro Ser Pro Ser Pro Arg Pro Ala Gly Gln Phe Gln Thr
 595 600 605
 Leu Val
 610

<210> SEQ ID NO 22

<211> LENGTH: 538

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His
 1 5 10 15
 Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys
 20 25 30
 Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys
 35 40 45
 Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu Glu Leu Lys
 50 55 60
 Pro Leu Glu Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu
 65 70 75 80
 Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu
 85 90 95
 Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala
 100 105 110
 Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe Cys Gln Ser Ile
 115 120 125
 Ile Ser Thr Leu Thr Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
 130 135 140
 Gly Gly Gly Ser Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
 145 150 155 160
 Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
 165 170 175
 Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
 180 185 190

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Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
 195 200 205
 Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
 210 215 220
 Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
 225 230 235 240
 Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
 245 250 255
 Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
 260 265 270
 Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
 275 280 285
 Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
 290 295 300
 Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
 305 310 315 320
 Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
 325 330 335
 Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
 340 345 350
 Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
 355 360 365
 Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly
 370 375 380
 Gly Gly Gly Ser Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
 385 390 395 400
 Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
 405 410 415
 Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
 420 425 430
 Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
 435 440 445
 Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
 450 455 460
 Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
 465 470 475 480
 Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
 485 490 495
 Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
 500 505 510
 Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
 515 520 525
 Arg Pro Ala Gly Gln Phe Gln Thr Leu Val
 530 535

<210> SEQ ID NO 23
 <211> LENGTH: 538
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 23

Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp Asn Pro Pro Thr
 1 5 10 15
 Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp Asn Ala Thr Phe

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20				25				30			
Thr	Cys	Ser	Phe	Ser	Asn	Thr	Ser	Glu	Ser	Phe	Val
	35						40				45
Arg	Met	Ser	Pro	Ser	Asn	Gln	Thr	Asp	Lys	Leu	Ala
	50				55					60	
Asp	Arg	Ser	Gln	Pro	Gly	Gln	Asp	Cys	Arg	Phe	Arg
65					70					75	
Pro	Asn	Gly	Arg	Asp	Phe	His	Met	Ser	Val	Val	Arg
			85					90			95
Asp	Ser	Gly	Thr	Tyr	Leu	Cys	Gly	Ala	Ile	Ser	Leu
	100						105				110
Gln	Ile	Lys	Glu	Ser	Leu	Arg	Ala	Glu	Leu	Arg	Val
	115						120				125
Ala	Glu	Val	Pro	Thr	Ala	His	Pro	Ser	Pro	Ser	Pro
	130					135					140
Gln	Phe	Gln	Thr	Leu	Val	Gly	Gly	Gly	Ser	Gly	Gly
145				150					155		
Gly	Gly	Gly	Gly	Ser	Thr	His	Thr	Cys	Pro	Pro	Cys
				165				170			
Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro
	180						185				
Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys
	195						200				205
Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp
	210					215					220
Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu
225				230					235		
Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu
			245					250			
Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn
	260						265				270
Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly
	275						280				285
Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu
	290					295				300	
Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr
305				310					315		
Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn
			325					330			
Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe
			340					345			
Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn
	355						360				365
Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr
	370					375					380
Ser	Leu	Ser	Pro	Gly	Lys	Gly	Gly	Gly	Ser	Gly	Gly
385				390					395		
Gly	Gly	Gly	Gly	Ser	Ala	Pro	Thr	Ser	Ser	Ser	Thr
			405					410			
Leu	Gln	Leu	Glu	His	Leu	Leu	Leu	Asp	Leu	Gln	Met
	420							425			
Ile	Asn	Asn	Tyr	Lys	Asn	Pro	Lys	Leu	Thr	Arg	Met
	435						440				445

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Phe Tyr Met Pro Lys Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu
 450 455 460
 Glu Glu Glu Leu Lys Pro Leu Glu Glu Val Leu Asn Leu Ala Gln Ser
 465 470 475 480
 Lys Asn Phe His Leu Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val
 485 490 495
 Ile Val Leu Glu Leu Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr
 500 505 510
 Ala Asp Glu Thr Ala Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr
 515 520 525
 Phe Cys Gln Ser Ile Ile Ser Thr Leu Thr
 530 535

<210> SEQ ID NO 24
 <211> LENGTH: 616
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24

Gln Val Gln Leu Gln Glu Ala Gly Pro Gly Leu Val Lys Pro Ser Glu
 1 5 10 15
 Thr Leu Ser Leu Thr Cys Ser Val Ser Gly Gly Ser Ile Ser Gly Asp
 20 25 30
 Tyr Tyr Trp Phe Trp Ile Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp
 35 40 45
 Ile Gly Tyr Ile Tyr Gly Ser Gly Gly Gly Thr Asn Tyr Asn Pro Ser
 50 55 60
 Leu Asn Asn Arg Val Ser Ile Ser Ile Asp Thr Ser Lys Asn Leu Phe
 65 70 75 80
 Ser Leu Lys Leu Arg Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
 85 90 95
 Cys Ala Ser Asn Ile Leu Lys Tyr Leu His Trp Leu Leu Tyr Trp Gly
 100 105 110
 Gln Gly Val Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
 115 120 125
 Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
 130 135 140
 Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
 145 150 155 160
 Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
 165 170 175
 Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
 180 185 190
 Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
 195 200 205
 Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
 210 215 220
 Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
 225 230 235 240
 Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
 245 250 255
 Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
 260 265 270
 Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val

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Thr	Thr	Thr	Ser	Asp	Ser	Val	Cys	Leu	Pro	Cys	Gly	Pro	Asp	Glu	Tyr
		35					40					45			
Leu	Asp	Ser	Trp	Asn	Glu	Glu	Asp	Lys	Cys	Leu	Leu	His	Lys	Val	Cys
	50					55					60				
Asp	Thr	Gly	Lys	Ala	Leu	Val	Ala	Val	Val	Ala	Gly	Asn	Ser	Thr	Thr
65					70					75					80
Pro	Arg	Arg	Cys	Ala	Cys	Thr	Ala	Gly	Tyr	His	Trp	Ser	Gln	Asp	Cys
			85						90					95	
Glu	Cys	Cys	Arg	Arg	Asn	Thr	Glu	Cys	Ala	Pro	Gly	Leu	Gly	Ala	Gln
			100					105					110		
His	Pro	Leu	Gln	Leu	Asn	Lys	Asp	Thr	Val	Cys	Lys	Pro	Cys	Leu	Ala
		115					120					125			
Gly	Tyr	Phe	Ser	Asp	Ala	Phe	Ser	Ser	Thr	Asp	Lys	Cys	Arg	Pro	Trp
	130						135				140				
Thr	Asn	Cys	Thr	Phe	Leu	Gly	Lys	Arg	Val	Glu	His	His	Gly	Thr	Glu
145					150					155					160
Lys	Ser	Asp	Ala	Val	Cys	Ser	Ser	Ser	Leu	Pro	Ala	Arg	Lys	Pro	Pro
			165						170					175	
Asn	Glu	Pro	His	Val	Tyr	Leu	Pro	Gly	Gly	Gly	Gly	Gly	Ser	Gly	Gly
			180					185					190		
Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro
		195					200					205			
Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys
	210					215					220				
Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val
225					230					235					240
Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr
			245						250					255	
Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu
	260							265					270		
Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His
	275						280						285		
Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys
	290					295					300				
Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln
305					310					315					320
Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met
			325						330					335	
Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro
		340						345					350		
Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn
	355						360					365			
Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu
	370					375					380				
Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val
385				390						395					400
Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln
			405						410					415	
Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys	Gly	Gly	Gly	Gly	Ser	Gly	Gly
		420						425					430		
Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Pro	Gly	Trp	Phe	Leu	Asp	Ser	Pro
	435						440					445			
Asp	Arg	Pro	Trp	Asn	Pro	Pro	Thr	Phe	Ser	Pro	Ala	Leu	Leu	Val	Val

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450	455	460
Thr Glu Gly Asp Asn Ala	Thr Phe Thr Cys Ser Phe	Ser Asn Thr Ser
465	470	475
Glu Ser Phe Val Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr		495
485	490	
Asp Lys Leu Ala Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp		510
500	505	
Cys Arg Phe Arg Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met		525
515	520	
Ser Val Val Arg Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly		540
530	535	
Ala Ile Ser Leu Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala		560
545	550	555
Glu Leu Arg Val Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro		575
565	570	
Ser Pro Ser Pro Arg Pro Ala Gly Gln Phe Gln Thr Leu Val		590
580	585	
<210> SEQ ID NO 26		
<211> LENGTH: 590		
<212> TYPE: PRT		
<213> ORGANISM: Homo sapiens		
<400> SEQUENCE: 26		
Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp Asn Pro Pro Thr		
1	5	10
Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp Asn Ala Thr Phe		
20	25	30
Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val Leu Asn Trp Tyr		
35	40	45
Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala Ala Phe Pro Glu		
50	55	60
Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg Val Thr Gln Leu		
65	70	75
Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg Ala Arg Arg Asn		
85	90	95
Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu Ala Pro Lys Ala		
100	105	110
Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val Thr Glu Arg Arg		
115	120	125
Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro Arg Pro Ala Gly		
130	135	140
Gln Phe Gln Thr Leu Val Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser		
145	150	155
Gly Gly Gly Gly Ser Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu		
165	170	175
Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp		
180	185	190
Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp		
195	200	205
Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly		
210	215	220
Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn		
225	230	235
		240

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Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp
			245					250						255	
Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro
		260					265						270		
Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu
		275					280					285			
Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn
	290					295					300				
Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile
305					310					315					320
Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr
			325						330						335
Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys
			340					345					350		
Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys
	355						360					365			
Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu
	370					375					380				
Ser	Leu	Ser	Pro	Gly	Lys	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser
385					390					395					400
Gly	Gly	Gly	Gly	Ser	Gln	Ile	Ala	Pro	Pro	Cys	Thr	Ser	Glu	Lys	His
				405					410					415	
Tyr	Glu	His	Leu	Gly	Arg	Cys	Cys	Asn	Lys	Cys	Glu	Pro	Gly	Lys	Tyr
			420					425					430		
Met	Ser	Ser	Lys	Cys	Thr	Thr	Thr	Ser	Asp	Ser	Val	Cys	Leu	Pro	Cys
	435						440					445			
Gly	Pro	Asp	Glu	Tyr	Leu	Asp	Ser	Trp	Asn	Glu	Glu	Asp	Lys	Cys	Leu
	450					455					460				
Leu	His	Lys	Val	Cys	Asp	Thr	Gly	Lys	Ala	Leu	Val	Ala	Val	Val	Ala
465					470					475					480
Gly	Asn	Ser	Thr	Thr	Pro	Arg	Arg	Cys	Ala	Cys	Thr	Ala	Gly	Tyr	His
			485						490					495	
Trp	Ser	Gln	Asp	Cys	Glu	Cys	Cys	Arg	Arg	Asn	Thr	Glu	Cys	Ala	Pro
			500					505					510		
Gly	Leu	Gly	Ala	Gln	His	Pro	Leu	Gln	Leu	Asn	Lys	Asp	Thr	Val	Cys
	515						520					525			
Lys	Pro	Cys	Leu	Ala	Gly	Tyr	Phe	Ser	Asp	Ala	Phe	Ser	Ser	Thr	Asp
	530					535					540				
Lys	Cys	Arg	Pro	Trp	Thr	Asn	Cys	Thr	Phe	Leu	Gly	Lys	Arg	Val	Glu
545					550					555					560
His	His	Gly	Thr	Glu	Lys	Ser	Asp	Ala	Val	Cys	Ser	Ser	Ser	Leu	Pro
			565						570					575	
Ala	Arg	Lys	Pro	Pro	Asn	Glu	Pro	His	Val	Tyr	Leu	Pro	Gly		
			580				585						590		

<210> SEQ ID NO 27

<211> LENGTH: 650

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly
1			5						10					15	

Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Asn	Ile	Lys	Asp	Thr
	20							25					30		

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Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
 115 120 125
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
 130 135 140
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
 145 150 155 160
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
 165 170 175
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 180 185 190
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
 195 200 205
 Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
 210 215 220
 Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
 225 230 235 240
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
 245 250 255
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
 260 265 270
 Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
 275 280 285
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
 290 295 300
 Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
 305 310 315 320
 Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
 325 330 335
 Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
 340 345 350
 Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
 355 360 365
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
 370 375 380
 Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
 385 390 395 400
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
 405 410 415
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
 420 425 430
 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
 435 440 445

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Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
 450 455 460
 Ser Gln Ile Ala Pro Pro Cys Thr Ser Glu Lys His Tyr Glu His Leu
 465 470 475 480
 Gly Arg Cys Cys Asn Lys Cys Glu Pro Gly Lys Tyr Met Ser Ser Lys
 485 490 495
 Cys Thr Thr Thr Ser Asp Ser Val Cys Leu Pro Cys Gly Pro Asp Glu
 500 505 510
 Tyr Leu Asp Ser Trp Asn Glu Glu Asp Lys Cys Leu Leu His Lys Val
 515 520 525
 Cys Asp Thr Gly Lys Ala Leu Val Ala Val Val Ala Gly Asn Ser Thr
 530 535 540
 Thr Pro Arg Arg Cys Ala Cys Thr Ala Gly Tyr His Trp Ser Gln Asp
 545 550 555 560
 Cys Glu Cys Cys Arg Arg Asn Thr Glu Cys Ala Pro Gly Leu Gly Ala
 565 570 575
 Gln His Pro Leu Gln Leu Asn Lys Asp Thr Val Cys Lys Pro Cys Leu
 580 585 590
 Ala Gly Tyr Phe Ser Asp Ala Phe Ser Ser Thr Asp Lys Cys Arg Pro
 595 600 605
 Trp Thr Asn Cys Thr Phe Leu Gly Lys Arg Val Glu His His Gly Thr
 610 615 620
 Glu Lys Ser Asp Ala Val Cys Ser Ser Ser Leu Pro Ala Arg Lys Pro
 625 630 635 640
 Pro Asn Glu Pro His Val Tyr Leu Pro Gly
 645 650

<210> SEQ ID NO 28

<211> LENGTH: 649

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

Gln Val Gln Leu Lys Gln Ser Gly Pro Gly Leu Val Gln Pro Ser Gln
 1 5 10 15
 Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Asn Tyr
 20 25 30
 Gly Val His Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Leu
 35 40 45
 Gly Val Ile Trp Ser Gly Gly Asn Thr Asp Tyr Asn Thr Pro Phe Thr
 50 55 60
 Ser Arg Leu Ser Ile Asn Lys Asp Asn Ser Lys Ser Gln Val Phe Phe
 65 70 75 80
 Lys Met Asn Ser Leu Gln Ser Asn Asp Thr Ala Ile Tyr Tyr Cys Ala
 85 90 95
 Arg Ala Leu Thr Tyr Tyr Asp Tyr Glu Phe Ala Tyr Trp Gly Gln Gly
 100 105 110
 Thr Leu Val Thr Val Ser Ala Ala Ser Thr Lys Gly Pro Ser Val Phe
 115 120 125
 Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
 130 135 140
 Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
 145 150 155 160
 Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
 165 170 175

Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser
			180				185						190		
Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro
			195				200						205		
Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys
			210				215						220		
Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro
			225				230						235		
Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
			245				250						255		
Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp
			260				265						270		
Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
			275				280						285		
Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val
			290				295						300		
Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
			305				310						315		
Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys
			325				330						335		
Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
			340				345						350		
Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
			355				360						365		
Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
			370				375						380		
Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
			385				390						395		
Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys
			405				410						415		
Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
			420				425						430		
Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly
			435				440						445		
Lys	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser
			450				455						460		
Gln	Ile	Ala	Pro	Pro	Cys	Thr	Ser	Glu	Lys	His	Tyr	Glu	His	Leu	Gly
			465				470						475		
Arg	Cys	Cys	Asn	Lys	Cys	Glu	Pro	Gly	Lys	Tyr	Met	Ser	Ser	Lys	Cys
			485				490						495		
Thr	Thr	Thr	Ser	Asp	Ser	Val	Cys	Leu	Pro	Cys	Gly	Pro	Asp	Glu	Tyr
			500				505						510		
Leu	Asp	Ser	Trp	Asn	Glu	Glu	Asp	Lys	Cys	Leu	Leu	His	Lys	Val	Cys
			515				520						525		
Asp	Thr	Gly	Lys	Ala	Leu	Val	Ala	Val	Val	Ala	Gly	Asn	Ser	Thr	Thr
			530				535						540		
Pro	Arg	Arg	Cys	Ala	Cys	Thr	Ala	Gly	Tyr	His	Trp	Ser	Gln	Asp	Cys
			545				550						555		
Glu	Cys	Cys	Arg	Arg	Asn	Thr	Glu	Cys	Ala	Pro	Gly	Leu	Gly	Ala	Gln
			565				570						575		
His	Pro	Leu	Gln	Leu	Asn	Lys	Asp	Thr	Val	Cys	Lys	Pro	Cys	Leu	Ala
			580												

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Gly Tyr Phe Ser Asp Ala Phe Ser Ser Thr Asp Lys Cys Arg Pro Trp
 595 600 605

Thr Asn Cys Thr Phe Leu Gly Lys Arg Val Glu His His Gly Thr Glu
 610 615 620

Lys Ser Asp Ala Val Cys Ser Ser Ser Leu Pro Ala Arg Lys Pro Pro
 625 630 635 640

Asn Glu Pro His Val Tyr Leu Pro Gly
 645

<210> SEQ ID NO 29
 <211> LENGTH: 651
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 29

Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30

Asn Met His Trp Val Lys Gln Thr Pro Gly Arg Gly Leu Glu Trp Ile
 35 40 45

Gly Ala Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe
 50 55 60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
 65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Ser Thr Tyr Tyr Gly Gly Asp Trp Tyr Phe Asn Val Trp Gly
 100 105 110

Ala Gly Thr Thr Val Thr Val Ser Ala Ala Ser Thr Lys Gly Pro Ser
 115 120 125

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
 130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
 145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
 165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
 180 185 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
 195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Ala Glu Pro Lys Ser Cys
 210 215 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
 225 230 235 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
 245 250 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
 260 265 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
 275 280 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
 290 295 300

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
 305 310 315 320

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Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
 325 330 335
 Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
 340 345 350
 Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
 355 360 365
 Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
 370 375 380
 Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
 385 390 395 400
 Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
 405 410 415
 Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
 420 425 430
 His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
 435 440 445
 Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
 450 455 460
 Gly Ser Gln Ile Ala Pro Pro Cys Thr Ser Glu Lys His Tyr Glu His
 465 470 475 480
 Leu Gly Arg Cys Cys Asn Lys Cys Glu Pro Gly Lys Tyr Met Ser Ser
 485 490 495
 Lys Cys Thr Thr Thr Ser Asp Ser Val Cys Leu Pro Cys Gly Pro Asp
 500 505 510
 Glu Tyr Leu Asp Ser Trp Asn Glu Glu Asp Lys Cys Leu Leu His Lys
 515 520 525
 Val Cys Asp Thr Gly Lys Ala Leu Val Ala Val Val Ala Gly Asn Ser
 530 535 540
 Thr Thr Pro Arg Arg Cys Ala Cys Thr Ala Gly Tyr His Trp Ser Gln
 545 550 555 560
 Asp Cys Glu Cys Cys Arg Arg Asn Thr Glu Cys Ala Pro Gly Leu Gly
 565 570 575
 Ala Gln His Pro Leu Gln Leu Asn Lys Asp Thr Val Cys Lys Pro Cys
 580 585 590
 Leu Ala Gly Tyr Phe Ser Asp Ala Phe Ser Ser Thr Asp Lys Cys Arg
 595 600 605
 Pro Trp Thr Asn Cys Thr Phe Leu Gly Lys Arg Val Glu His His Gly
 610 615 620
 Thr Glu Lys Ser Asp Ala Val Cys Ser Ser Ser Leu Pro Ala Arg Lys
 625 630 635 640
 Pro Pro Asn Glu Pro His Val Tyr Leu Pro Gly
 645 650

<210> SEQ ID NO 30
 <211> LENGTH: 653
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 30

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
 20 25 30
 Gly Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

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35					40					45					
Gly	Trp	Ile	Asn	Thr	Tyr	Thr	Gly	Glu	Pro	Thr	Tyr	Ala	Ala	Asp	Phe
50						55					60				
Lys	Arg	Arg	Phe	Thr	Phe	Ser	Leu	Asp	Thr	Ser	Lys	Ser	Thr	Ala	Tyr
65					70					75					80
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Ala	Lys	Tyr	Pro	His	Tyr	Tyr	Gly	Ser	Ser	His	Trp	Tyr	Phe	Asp	Val
			100					105					110		
Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly
	115						120					125			
Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly
130						135						140			
Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val
145					150					155					160
Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe
				165					170					175	
Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val
			180					185					190		
Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val
	195						200					205			
Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys
210						215					220				
Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu
225					230					235					240
Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr
			245						250					255	
Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val
			260					265					270		
Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val
	275						280						285		
Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser
290						295					300				
Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu
305					310					315					320
Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala
			325						330					335	
Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro
			340					345					350		
Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln
	355						360					365			
Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala
	370					375					380				
Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr
385					390					395					400
Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu
			405						410					415	
Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser
			420					425					430		
Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser
	435						440					445			
Leu	Ser	Pro	Gly	Lys	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly
450						455					460				

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Gly Gly Gly Ser Gln Ile Ala Pro Pro Cys Thr Ser Glu Lys His Tyr
 465 470 475 480
 Glu His Leu Gly Arg Cys Cys Asn Lys Cys Glu Pro Gly Lys Tyr Met
 485 490 495
 Ser Ser Lys Cys Thr Thr Thr Ser Asp Ser Val Cys Leu Pro Cys Gly
 500 505 510
 Pro Asp Glu Tyr Leu Asp Ser Trp Asn Glu Glu Asp Lys Cys Leu Leu
 515 520 525
 His Lys Val Cys Asp Thr Gly Lys Ala Leu Val Ala Val Val Ala Gly
 530 535 540
 Asn Ser Thr Thr Pro Arg Arg Cys Ala Cys Thr Ala Gly Tyr His Trp
 545 550 555 560
 Ser Gln Asp Cys Glu Cys Cys Arg Arg Asn Thr Glu Cys Ala Pro Gly
 565 570 575
 Leu Gly Ala Gln His Pro Leu Gln Leu Asn Lys Asp Thr Val Cys Lys
 580 585 590
 Pro Cys Leu Ala Gly Tyr Phe Ser Asp Ala Phe Ser Ser Thr Asp Lys
 595 600 605
 Cys Arg Pro Trp Thr Asn Cys Thr Phe Leu Gly Lys Arg Val Glu His
 610 615 620
 His Gly Thr Glu Lys Ser Asp Ala Val Cys Ser Ser Leu Pro Ala
 625 630 635 640
 Arg Lys Pro Pro Asn Glu Pro His Val Tyr Leu Pro Gly
 645 650

<210> SEQ ID NO 31
 <211> LENGTH: 648
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 31

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Thr Phe Ile Ser Tyr Asp Gly Asn Asn Lys Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
 85 90 95
 Ala Arg Thr Gly Trp Leu Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr
 100 105 110
 Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
 115 120 125
 Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
 130 135 140
 Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
 145 150 155 160
 Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
 165 170 175
 Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser

-continued

180							185							190						
Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser					
		195					200					205								
Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr					
		210				215					220									
His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser					
		225			230					235					240					
Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg					
				245					250					255						
Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro					
			260					265					270							
Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala					
		275				280						285								
Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val					
		290				295					300									
Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr					
					310					315					320					
Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr					
				325					330					335						
Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu					
			340					345					350							
Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys					
		355					360					365								
Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser					
		370				375					380									
Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp					
					390					395					400					
Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser					
				405					410					415						
Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala					
			420					425					430							
Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys					
		435				440						445								
Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gln					
		450				455					460									
Ile	Ala	Pro	Pro	Cys	Thr	Ser	Glu	Lys	His	Tyr	Glu	His	Leu	Gly	Arg					
					470					475					480					
Cys	Cys	Asn	Lys	Cys	Glu	Pro	Gly	Lys	Tyr	Met	Ser	Ser	Lys	Cys	Thr					
			485						490					495						
Thr	Thr	Ser	Asp	Ser	Val	Cys	Leu	Pro	Cys	Gly	Pro	Asp	Glu	Tyr	Leu					
			500					505					510							
Asp	Ser	Trp	Asn	Glu	Glu	Asp	Lys	Cys	Leu	Leu	His	Lys	Val	Cys	Asp					
		515					520					525								
Thr	Gly	Lys	Ala	Leu	Val	Ala	Val	Val	Ala	Gly	Asn	Ser	Thr	Thr	Pro					
		530				535						540								
Arg	Arg	Cys	Ala	Cys	Thr	Ala	Gly	Tyr	His	Trp	Ser	Gln	Asp	Cys	Glu					
				550						555					560					
Cys	Cys	Arg	Arg	Asn	Thr	Glu	Cys	Ala	Pro	Gly	Leu	Gly	Ala	Gln	His					
				565					570					575						
Pro	Leu	Gln	Leu	Asn	Lys	Asp	Thr	Val	Cys	Lys	Pro	Cys	Leu	Ala	Gly					
			580					585					590							
Tyr	Phe	Ser	Asp	Ala	Phe	Ser	Ser	Thr	Asp	Lys	Cys	Arg	Pro	Trp	Thr					
		595					600					605								

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Asn Cys Thr Phe Leu Gly Lys Arg Val Glu His His Gly Thr Glu Lys
 610 615 620

Ser Asp Ala Val Cys Ser Ser Ser Leu Pro Ala Arg Lys Pro Pro Asn
 625 630 635 640

Glu Pro His Val Tyr Leu Pro Gly
 645

<210> SEQ ID NO 32
 <211> LENGTH: 646
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 32

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30

Arg Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
 35 40 45

Gly Tyr Ile Asn Pro Ser Thr Gly Tyr Thr Glu Tyr Asn Gln Lys Phe
 50 55 60

Lys Asp Lys Ala Thr Ile Thr Ala Asp Glu Ser Thr Asn Thr Ala Tyr
 65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Gly Gly Gly Val Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
 100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
 115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
 130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
 145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
 165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
 180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
 195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
 210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
 225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
 245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
 260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
 275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
 290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
 305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser

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325					330					335					
Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro
			340					345					350		
Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val
		355					360					365			
Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly
	370					375					380				
Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp
	385			390					395						400
Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp
			405					410						415	
Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His
		420					425					430			
Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys	Gly	Gly
		435					440					445			
Gly	Gly	Ser	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gln	Ile	Ala	
	450					455					460				
Pro	Pro	Cys	Thr	Ser	Glu	Lys	His	Tyr	Glu	His	Leu	Gly	Arg	Cys	Cys
	465			470					475						480
Asn	Lys	Cys	Glu	Pro	Gly	Lys	Tyr	Met	Ser	Ser	Lys	Cys	Thr	Thr	Thr
		485						490						495	
Ser	Asp	Ser	Val	Cys	Leu	Pro	Cys	Gly	Pro	Asp	Glu	Tyr	Leu	Asp	Ser
		500					505						510		
Trp	Asn	Glu	Glu	Asp	Lys	Cys	Leu	Leu	His	Lys	Val	Cys	Asp	Thr	Gly
	515						520					525			
Lys	Ala	Leu	Val	Ala	Val	Val	Ala	Gly	Asn	Ser	Thr	Thr	Pro	Arg	Arg
	530			535							540				
Cys	Ala	Cys	Thr	Ala	Gly	Tyr	His	Trp	Ser	Gln	Asp	Cys	Glu	Cys	Cys
	545			550					555						560
Arg	Arg	Asn	Thr	Glu	Cys	Ala	Pro	Gly	Leu	Gly	Ala	Gln	His	Pro	Leu
		565						570						575	
Gln	Leu	Asn	Lys	Asp	Thr	Val	Cys	Lys	Pro	Cys	Leu	Ala	Gly	Tyr	Phe
		580					585						590		
Ser	Asp	Ala	Phe	Ser	Ser	Thr	Asp	Lys	Cys	Arg	Pro	Trp	Thr	Asn	Cys
	595					600					605				
Thr	Phe	Leu	Gly	Lys	Arg	Val	Glu	His	His	Gly	Thr	Glu	Lys	Ser	Asp
	610			615							620				
Ala	Val	Cys	Ser	Ser	Ser	Leu	Pro	Ala	Arg	Lys	Pro	Pro	Asn	Glu	Pro
	625			630				635						640	
His	Val	Tyr	Leu	Pro	Gly										
			645												

<210> SEQ ID NO 33

<211> LENGTH: 645

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 33

Gln	Leu	Gln	Gln	Ser	Gly	Thr	Val	Leu	Ala	Arg	Pro	Gly	Ala	Ser	Val
1				5						10				15	
Lys	Met	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ser	Phe	Thr	Arg	Tyr	Trp	Met
			20					25					30		
His	Trp	Ile	Lys	Gln	Arg	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile	Gly	Ala
		35					40					45			

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Ile	Tyr	Pro	Gly	Asn	Ser	Asp	Thr	Ser	Tyr	Asn	Gln	Lys	Phe	Glu	Gly
50						55					60				
Lys	Ala	Lys	Leu	Thr	Ala	Val	Thr	Ser	Ala	Ser	Thr	Ala	Tyr	Met	Glu
65					70					75					80
Leu	Ser	Ser	Leu	Thr	His	Glu	Asp	Ser	Ala	Val	Tyr	Tyr	Cys	Ser	Arg
				85					90					95	
Asp	Tyr	Gly	Tyr	Tyr	Phe	Asp	Phe	Trp	Gly	Gln	Gly	Thr	Thr	Leu	Thr
			100					105						110	
Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro
			115					120						125	
Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val
			130					135						140	
Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala
145					150						155				160
Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly
				165						170					175
Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly
			180						185					190	
Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys
			195					200						205	
Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys
			210					215				220			
Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu
225					230					235					240
Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu
				245					250					255	
Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys
			260					265						270	
Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys
			275					280					285		
Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu
						295					300				
Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys
305					310					315					320
Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys
				325						330					335
Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser
				340					345					350	
Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys
			355					360					365		
Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln
			370				375					380			
Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly
385					390					395					400
Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln
				405						410					415
Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn
				420					425					430	
His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys	Gly	Gly	Gly
			435					440					445		
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gln	Ile	Ala	Pro
			450					455				460			
Pro	Cys	Thr	Ser	Glu	Lys	His	Tyr	Glu	His	Leu	Gly	Arg	Cys	Cys	Asn

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465	470	475	480
Lys Cys Glu Pro Gly Lys Tyr Met Ser Ser Lys Cys Thr Thr Thr Ser	485	490	495
Asp Ser Val Cys Leu Pro Cys Gly Pro Asp Glu Tyr Leu Asp Ser Trp	500	505	510
Asn Glu Glu Asp Lys Cys Leu Leu His Lys Val Cys Asp Thr Gly Lys	515	520	525
Ala Leu Val Ala Val Val Ala Gly Asn Ser Thr Thr Pro Arg Arg Cys	530	535	540
Ala Cys Thr Ala Gly Tyr His Trp Ser Gln Asp Cys Glu Cys Cys Arg	545	550	555
Arg Asn Thr Glu Cys Ala Pro Gly Leu Gly Ala Gln His Pro Leu Gln	565	570	575
Leu Asn Lys Asp Thr Val Cys Lys Pro Cys Leu Ala Gly Tyr Phe Ser	580	585	590
Asp Ala Phe Ser Ser Thr Asp Lys Cys Arg Pro Trp Thr Asn Cys Thr	595	600	605
Phe Leu Gly Lys Arg Val Glu His His Gly Thr Glu Lys Ser Asp Ala	610	615	620
Val Cys Ser Ser Ser Leu Pro Ala Arg Lys Pro Pro Asn Glu Pro His	625	630	635
Val Tyr Leu Pro Gly	645		

<210> SEQ ID NO 34

<211> LENGTH: 573

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His	1	5	10	15
Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys	20	25	30	
Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys	35	40	45	
Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys	50	55	60	
Pro Leu Glu Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu	65	70	75	80
Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu	85	90	95	
Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala	100	105	110	
Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe Cys Gln Ser Ile	115	120	125	
Ile Ser Thr Leu Thr Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly	130	135	140	
Gly Gly Gly Ser Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu	145	150	155	160
Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr	165	170	175	
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val	180	185	190	

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Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
  195                                200                                205

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
  210                                215                                220

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
  225                                230                                235                                240

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
  245                                250                                255

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
  260                                265                                270

Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
  275                                280                                285

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
  290                                295                                300

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
  305                                310                                315                                320

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
  325                                330                                335

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
  340                                345                                350

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
  355                                360                                365

Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
  370                                375                                380

Gly Gly Gly Ser Gln Ile Ala Pro Pro Cys Thr Ser Glu Lys His Tyr
  385                                390                                395                                400

Glu His Leu Gly Arg Cys Cys Asn Lys Cys Glu Pro Gly Lys Tyr Met
  405                                410                                415

Ser Ser Lys Cys Thr Thr Thr Ser Asp Ser Val Cys Leu Pro Cys Gly
  420                                425                                430

Pro Asp Glu Tyr Leu Asp Ser Trp Asn Glu Glu Asp Lys Cys Leu Leu
  435                                440                                445

His Lys Val Cys Asp Thr Gly Lys Ala Leu Val Ala Val Val Ala Gly
  450                                455                                460

Asn Ser Thr Thr Pro Arg Arg Cys Ala Cys Thr Ala Gly Tyr His Trp
  465                                470                                475                                480

Ser Gln Asp Cys Glu Cys Cys Arg Arg Asn Thr Glu Cys Ala Pro Gly
  485                                490                                495

Leu Gly Ala Gln His Pro Leu Gln Leu Asn Lys Asp Thr Val Cys Lys
  500                                505                                510

Pro Cys Leu Ala Gly Tyr Phe Ser Asp Ala Phe Ser Ser Thr Asp Lys
  515                                520                                525

Cys Arg Pro Trp Thr Asn Cys Thr Phe Leu Gly Lys Arg Val Glu His
  530                                535                                540

His Gly Thr Glu Lys Ser Asp Ala Val Cys Ser Ser Ser Leu Pro Ala
  545                                550                                555                                560

Arg Lys Pro Pro Asn Glu Pro His Val Tyr Leu Pro Gly
  565                                570

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<210> SEQ ID NO 35
<211> LENGTH: 573
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35

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Gln 1	Ile	Ala	Pro 5	Pro	Cys	Thr	Ser	Glu	Lys 10	His	Tyr	Glu	His	Leu 15	Gly
Arg	Cys	Cys	Asn 20	Lys	Cys	Glu	Pro	Gly 25	Lys	Tyr	Met	Ser	Ser 30	Lys	Cys
Thr	Thr	Thr 35	Ser	Asp	Ser	Val	Cys 40	Leu	Pro	Cys	Gly 45	Pro	Asp	Glu	Tyr
Leu 50	Ser	Trp	Asn	Glu	Glu 55	Asp	Lys	Cys	Leu 60	His	Lys	Val	Cys		
Asp 65	Thr	Gly	Lys	Ala	Leu 70	Val	Ala	Val	Val 75	Ala	Gly	Asn	Ser	Thr	Thr 80
Pro	Arg	Arg	Cys 85	Ala	Cys	Thr	Ala	Gly	Tyr 90	His	Trp	Ser	Gln	Asp 95	Cys
Glu	Cys	Cys	Arg 100	Arg	Asn	Thr	Glu	Cys 105	Ala	Pro	Gly	Leu 110	Gly	Ala	Gln
His 115	Pro	Leu	Gln	Leu	Asn	Lys	Asp 120	Thr	Val	Cys	Lys	Pro 125	Cys	Leu	Ala
Gly 130	Tyr	Phe	Ser	Asp	Ala 135	Phe	Ser	Ser	Thr	Asp	Lys 140	Cys	Arg	Pro	Trp
Thr 145	Asn	Cys	Thr	Phe	Leu 150	Gly	Lys	Arg	Val	Glu 155	His	His	Gly	Thr	Glu 160
Lys	Ser	Asp	Ala 165	Val	Cys	Ser	Ser	Ser	Leu 170	Pro	Ala	Arg	Lys	Pro 175	Pro
Asn	Glu	Pro	His 180	Val	Tyr	Leu	Pro	Gly 185	Gly	Gly	Gly	Gly	Ser 190	Gly	Gly
Gly 195	Ser	Gly	Gly	Gly	Gly	Gly	Ser 200	Thr	His	Thr	Cys 205	Pro	Cys	Pro	
Ala 210	Pro	Glu	Leu	Leu	Gly 215	Gly	Pro	Ser	Val	Phe 220	Leu	Phe	Pro	Pro	Lys
Pro 225	Lys	Asp	Thr	Leu	Met 230	Ile	Ser	Arg	Thr	Pro 235	Glu	Val	Thr	Cys	Val 240
Val	Val	Asp	Val 245	Ser	His	Glu	Asp	Pro	Glu 250	Val	Lys	Phe	Asn	Trp 255	Tyr
Val	Asp	Gly 260	Val	Glu	Val	His	Asn	Ala 265	Lys	Thr	Lys	Pro	Arg	Glu	Glu
Gln 275	Tyr	Asn	Ser	Thr	Tyr	Arg	Val 280	Val	Ser	Val	Leu 285	Thr	Val	Leu	His
Gln 290	Asp	Trp	Leu	Asn	Gly 295	Lys	Glu	Tyr	Lys	Cys 300	Lys	Val	Ser	Asn	Lys
Ala 305	Leu	Pro	Ala	Pro	Ile 310	Glu	Lys	Thr	Ile	Ser 315	Lys	Ala	Lys	Gly	Gln
Pro	Arg	Glu 325	Pro	Gln	Val	Tyr	Thr	Leu 330	Pro	Pro	Ser	Arg	Glu 335	Glu	Met
Thr	Lys	Asn 340	Gln	Val	Ser	Leu	Thr	Cys 345	Leu	Val	Lys	Gly	Phe	Tyr	Pro
Ser	Asp	Ile 355	Ala	Val	Glu	Trp	Glu 360	Ser	Asn	Gly	Gln 365	Pro	Glu	Asn	Asn
Tyr 370	Lys	Thr	Thr	Pro	Pro	Val 375	Leu	Asp	Ser	Asp	Gly 380	Ser	Phe	Phe	Leu
Tyr 385	Ser	Lys	Leu	Thr	Val 390	Asp	Lys	Ser	Arg	Trp 395	Gln	Gln	Gly	Asn	Val 400
Phe	Ser	Cys 405	Ser	Val	Met	His	Glu	Ala 410	Leu	His	Asn	His	Tyr	Thr	Gln

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Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly
 420 425 430
 Gly Gly Ser Gly Gly Gly Gly Ser Ala Pro Thr Ser Ser Ser Thr Lys
 435 440 445
 Lys Thr Gln Leu Gln Leu Glu His Leu Leu Leu Asp Leu Gln Met Ile
 450 455 460
 Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys Leu Thr Arg Met Leu
 465 470 475 480
 Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr Glu Leu Lys His Leu
 485 490 495
 Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu Glu Val Leu Asn Leu
 500 505 510
 Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg Asp Leu Ile Ser Asn
 515 520 525
 Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser Glu Thr Thr Phe Met
 530 535 540
 Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val Glu Phe Leu Asn Arg
 545 550 555 560
 Trp Ile Thr Phe Cys Gln Ser Ile Ile Ser Thr Leu Thr
 565 570

<210> SEQ ID NO 36
 <211> LENGTH: 651
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36

Gln Val Gln Leu Gln Glu Ala Gly Pro Gly Leu Val Lys Pro Ser Glu
 1 5 10 15
 Thr Leu Ser Leu Thr Cys Ser Val Ser Gly Gly Ser Ile Ser Gly Asp
 20 25 30
 Tyr Tyr Trp Phe Trp Ile Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp
 35 40 45
 Ile Gly Tyr Ile Tyr Gly Ser Gly Gly Gly Thr Asn Tyr Asn Pro Ser
 50 55 60
 Leu Asn Asn Arg Val Ser Ile Ser Ile Asp Thr Ser Lys Asn Leu Phe
 65 70 75 80
 Ser Leu Lys Leu Arg Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
 85 90 95
 Cys Ala Ser Asn Ile Leu Lys Tyr Leu His Trp Leu Leu Tyr Trp Gly
 100 105 110
 Gln Gly Val Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
 115 120 125
 Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
 130 135 140
 Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
 145 150 155 160
 Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
 165 170 175
 Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
 180 185 190
 Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
 195 200 205
 Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
 210 215 220

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Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	225	230	235	240
Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	245	250	255	
Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	260	265	270	
Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	275	280	285	
His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	290	295	300	
Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	305	310	315	320
Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	325	330	335	
Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	340	345	350	
Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	355	360	365	
Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	370	375	380	
Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	385	390	395	400
Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	405	410	415	
Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	420	425	430	
His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	435	440	445	
Pro	Gly	Lys	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	450	455	460	
Gly	Ser	Gln	Ile	Ala	Pro	Pro	Cys	Thr	Ser	Glu	Lys	His	Tyr	Glu	His	465	470	475	480
Leu	Gly	Arg	Cys	Cys	Asn	Lys	Cys	Glu	Pro	Gly	Lys	Tyr	Met	Ser	Ser	485	490	495	
Lys	Cys	Thr	Thr	Thr	Ser	Asp	Ser	Val	Cys	Leu	Pro	Cys	Gly	Pro	Asp	500	505	510	
Glu	Tyr	Leu	Asp	Ser	Trp	Asn	Glu	Glu	Asp	Lys	Cys	Leu	Leu	His	Lys	515	520	525	
Val	Cys	Asp	Thr	Gly	Lys	Ala	Leu	Val	Ala	Val	Val	Ala	Gly	Asn	Ser	530	535	540	
Thr	Thr	Pro	Arg	Arg	Cys	Ala	Cys	Thr	Ala	Gly	Tyr	His	Trp	Ser	Gln	545	550	555	560
Asp	Cys	Glu	Cys	Cys	Arg	Arg	Asn	Thr	Glu	Cys	Ala	Pro	Gly	Leu	Gly	565	570	575	
Ala	Gln	His	Pro	Leu	Gln	Leu	Asn	Lys	Asp	Thr	Val	Cys	Lys	Pro	Cys	580	585	590	
Leu	Ala	Gly	Tyr	Phe	Ser	Asp	Ala	Phe	Ser	Ser	Thr	Asp	Lys	Cys	Arg	595	600	605	
Pro	Trp	Thr	Asn	Cys	Thr	Phe	Leu	Gly	Lys	Arg	Val	Glu	His	His	Gly	610	615	620	
Thr	Glu	Lys	Ser	Asp	Ala	Val	Cys	Ser	Ser	Ser	Leu	Pro	Ala	Arg	Lys	625	630	635	640

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Pro Pro Asn Glu Pro His Val Tyr Leu Pro Gly
645 650

<210> SEQ ID NO 37
<211> LENGTH: 755
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 37

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Thr Trp Asn Ser Gly His Ile Asp Tyr Ala Asp Ser Val
50 55 60

Glu Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Leu Val Ser Tyr Leu Ser Thr Ala Ser Ser Leu Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Ala Glu Pro Lys Ser Cys
210 215 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
225 230 235 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
245 250 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
260 265 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
275 280 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
290 295 300

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305 310 315 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
325 330 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
340 345 350

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
355 360 365

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Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
 370 375 380
 Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
 385 390 395 400
 Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
 405 410 415
 Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
 420 425 430
 His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
 435 440 445
 Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
 450 455 460
 Gly Ser Arg Ile Phe Ala Val Phe Ile Phe Met Thr Tyr Trp His Leu
 465 470 475 480
 Leu Asn Ala Phe Thr Val Thr Val Pro Lys Asp Leu Tyr Val Val Glu
 485 490 495
 Tyr Gly Ser Asn Met Thr Ile Glu Cys Lys Phe Pro Val Glu Lys Gln
 500 505 510
 Leu Asp Leu Ala Ala Leu Ile Val Tyr Trp Glu Met Glu Asp Lys Asn
 515 520 525
 Ile Ile Gln Phe Val His Gly Glu Glu Asp Leu Lys Val Gln His Ser
 530 535 540
 Ser Tyr Arg Gln Arg Ala Arg Leu Leu Lys Asp Gln Leu Ser Leu Gly
 545 550 555 560
 Asn Ala Ala Leu Gln Ile Thr Asp Val Lys Leu Gln Asp Ala Gly Val
 565 570 575
 Tyr Arg Cys Met Ile Ser Tyr Gly Gly Ala Asp Tyr Lys Arg Ile Thr
 580 585 590
 Val Lys Val Asn Ala Pro Tyr Asn Lys Ile Asn Gln Arg Ile Leu Val
 595 600 605
 Val Asp Pro Val Thr Ser Glu His Glu Leu Thr Cys Gln Ala Glu Gly
 610 615 620
 Tyr Pro Lys Ala Glu Val Ile Trp Thr Ser Ser Asp His Gln Val Leu
 625 630 635 640
 Ser Gly Lys Thr Thr Thr Thr Asn Ser Lys Arg Glu Glu Lys Leu Phe
 645 650 655
 Asn Val Thr Ser Thr Leu Arg Ile Asn Thr Thr Thr Asn Glu Ile Phe
 660 665 670
 Tyr Cys Thr Phe Arg Arg Leu Asp Pro Glu Glu Asn His Thr Ala Glu
 675 680 685
 Leu Val Ile Pro Glu Leu Pro Leu Ala His Pro Pro Asn Glu Arg Thr
 690 695 700
 His Leu Val Ile Leu Gly Ala Ile Leu Leu Cys Leu Gly Val Ala Leu
 705 710 715 720
 Thr Phe Ile Phe Arg Leu Arg Lys Gly Arg Met Met Asp Val Lys Lys
 725 730 735
 Cys Gly Ile Gln Asp Thr Asn Ser Lys Lys Gln Ser Asp Thr His Leu
 740 745 750
 Glu Glu Thr
 755

<210> SEQ ID NO 38

<211> LENGTH: 771

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 38

Leu Pro Ala Gln Val Ala Phe Thr Pro Tyr Ala Pro Glu Pro Gly Ser
1          5          10          15

Thr Cys Arg Leu Arg Glu Tyr Tyr Asp Gln Thr Ala Gln Met Cys Cys
          20          25          30

Ser Lys Cys Ser Pro Gly Gln His Ala Lys Val Phe Cys Thr Lys Thr
          35          40          45

Ser Asp Thr Val Cys Asp Ser Cys Glu Asp Ser Thr Tyr Thr Gln Leu
          50          55          60

Trp Asn Trp Val Pro Glu Cys Leu Ser Cys Gly Ser Arg Cys Ser Ser
65          70          75          80

Asp Gln Val Glu Thr Gln Ala Cys Thr Arg Glu Gln Asn Arg Ile Cys
          85          90          95

Thr Cys Arg Pro Gly Trp Tyr Cys Ala Leu Ser Lys Gln Glu Gly Cys
          100          105          110

Arg Leu Cys Ala Pro Leu Arg Lys Cys Arg Pro Gly Phe Gly Val Ala
          115          120          125

Arg Pro Gly Thr Glu Thr Ser Asp Val Val Cys Lys Pro Cys Ala Pro
          130          135          140

Gly Thr Phe Ser Asn Thr Thr Ser Ser Thr Asp Ile Cys Arg Pro His
145          150          155          160

Gln Ile Cys Asn Val Val Ala Ile Pro Gly Asn Ala Ser Met Asp Ala
          165          170          175

Val Cys Thr Ser Thr Ser Pro Thr Arg Ser Met Ala Pro Gly Ala Val
          180          185          190

His Leu Pro Gln Pro Val Ser Thr Arg Ser Gln His Thr Gln Pro Thr
          195          200          205

Pro Glu Pro Ser Thr Ala Pro Ser Thr Ser Phe Leu Leu Pro Met Gly
          210          215          220

Pro Ser Pro Pro Ala Glu Gly Ser Thr Gly Asp 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 Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
 465 470 475 480
 Gly Ser Arg Ile Phe Ala Val Phe Ile Phe Met Thr Tyr Trp His Leu
 485 490 495
 Leu Asn Ala Phe Thr Val Thr Val Pro Lys Asp Leu Tyr Val Val Glu
 500 505 510
 Tyr Gly Ser Asn Met Thr Ile Glu Cys Lys Phe Pro Val Glu Lys Gln
 515 520 525
 Leu Asp Leu Ala Ala Leu Ile Val Tyr Trp Glu Met Glu Asp Lys Asn
 530 535 540
 Ile Ile Gln Phe Val His Gly Glu Glu Asp Leu Lys Val Gln His Ser
 545 550 555 560
 Ser Tyr Arg Gln Arg Ala Arg Leu Leu Lys Asp Gln Leu Ser Leu Gly
 565 570 575
 Asn Ala Ala Leu Gln Ile Thr Asp Val Lys Leu Gln Asp Ala Gly Val
 580 585 590
 Tyr Arg Cys Met Ile Ser Tyr Gly Gly Ala Asp Tyr Lys Arg Ile Thr
 595 600 605
 Val Lys Val Asn Ala Pro Tyr Asn Lys Ile Asn Gln Arg Ile Leu Val
 610 615 620
 Val Asp Pro Val Thr Ser Glu His Glu Leu Thr Cys Gln Ala Glu Gly
 625 630 635 640
 Tyr Pro Lys Ala Glu Val Ile Trp Thr Ser Ser Asp His Gln Val Leu
 645 650 655
 Ser Gly Lys Thr Thr Thr Thr Asn Ser Lys Arg Glu Glu Lys Leu Phe
 660 665 670
 Asn Val Thr Ser Thr Leu Arg Ile Asn Thr Thr Thr Asn Glu Ile Phe
 675 680 685
 Tyr Cys Thr Phe Arg Arg Leu Asp Pro Glu Glu Asn His Thr Ala Glu
 690 695 700
 Leu Val Ile Pro Glu Leu Pro Leu Ala His Pro Pro Asn Glu Arg Thr
 705 710 715 720
 His Leu Val Ile Leu Gly Ala Ile Leu Leu Cys Leu Gly Val Ala Leu
 725 730 735
 Thr Phe Ile Phe Arg Leu Arg Lys Gly Arg Met Met Asp Val Lys Lys
 740 745 750
 Cys Gly Ile Gln Asp Thr Asn Ser Lys Lys Gln Ser Asp Thr His Leu
 755 760 765
 Glu Glu Thr
 770

<210> SEQ ID NO 39

<211> LENGTH: 787

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 39

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Met Arg Ile Phe Ala Val Phe Ile Phe Met Thr Tyr Trp His Leu Leu
1           5           10           15
Asn Ala Phe Thr Val Thr Val Pro Lys Asp Leu Tyr Val Val Glu Tyr
20           25           30
Gly Ser Asn Met Thr Ile Glu Cys Lys Phe Pro Val Glu Lys Gln Leu
35           40           45
Asp Leu Ala Ala Leu Ile Val Tyr Trp Glu Met Glu Asp Lys Asn Ile
50           55           60
Ile Gln Phe Val His Gly Glu Glu Asp Leu Lys Val Gln His Ser Ser
65           70           75           80
Tyr Arg Gln Arg Ala Arg Leu Leu Lys Asp Gln Leu Ser Leu Gly Asn
85           90           95
Ala Ala Leu Gln Ile Thr Asp Val Lys Leu Gln Asp Ala Gly Val Tyr
100          105          110
Arg Cys Met Ile Ser Tyr Gly Gly Ala Asp Tyr Lys Arg Ile Thr Val
115          120          125
Lys Val Asn Ala Pro Tyr Asn Lys Ile Asn Gln Arg Ile Leu Val Val
130          135          140
Asp Pro Val Thr Ser Glu His Glu Leu Thr Cys Gln Ala Glu Gly Tyr
145          150          155          160
Pro Lys Ala Glu Val Ile Trp Thr Ser Ser Asp His Gln Val Leu Ser
165          170          175
Gly Lys Thr Thr Thr Thr Asn Ser Lys Arg Glu Glu Lys Leu Phe Asn
180          185          190
Val Thr Ser Thr Leu Arg Ile Asn Thr Thr Thr Asn Glu Ile Phe Tyr
195          200          205
Cys Thr Phe Arg Arg Leu Asp Pro Glu Glu Asn His Thr Ala Glu Leu
210          215          220
Val Ile Pro Glu Leu Pro Leu Ala His Pro Pro Asn Glu Arg Thr His
225          230          235          240
Leu Val Ile Leu Gly Ala Ile Leu Leu Cys Leu Gly Val Ala Leu Thr
245          250          255
Phe Ile Phe Arg Leu Arg Lys Gly Arg Met Met Asp Val Lys Lys Cys
260          265          270
Gly Ile Gln Asp Thr Asn Ser Lys Lys Gln Ser Asp Thr His Leu Glu
275          280          285
Glu Thr Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
290          295          300
Ser Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
305          310          315          320
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
325          330          335
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
340          345          350
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
355          360          365
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
370          375          380
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
385          390          395          400
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
405          410          415

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Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
 420 425 430
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
 435 440 445
 Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
 450 455 460
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
 465 470 475 480
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
 485 490 495
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
 500 505 510
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
 515 520 525
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly
 530 535 540
 Gly Gly Ser Gly Gly Gly Gly Ser Leu Pro Ala Gln Val Ala Phe Thr
 545 550 555 560
 Pro Tyr Ala Pro Glu Pro Gly Ser Thr Cys Arg Leu Arg Glu Tyr Tyr
 565 570 575
 Asp Gln Thr Ala Gln Met Cys Cys Ser Lys Cys Ser Pro Gly Gln His
 580 585 590
 Ala Lys Val Phe Cys Thr Lys Thr Ser Asp Thr Val Cys Asp Ser Cys
 595 600 605
 Glu Asp Ser Thr Tyr Thr Gln Leu Trp Asn Trp Val Pro Glu Cys Leu
 610 615 620
 Ser Cys Gly Ser Arg Cys Ser Ser Asp Gln Val Glu Thr Gln Ala Cys
 625 630 635 640
 Thr Arg Glu Gln Asn Arg Ile Cys Thr Cys Arg Pro Gly Trp Tyr Cys
 645 650 655
 Ala Leu Ser Lys Gln Glu Gly Cys Arg Leu Cys Ala Pro Leu Arg Lys
 660 665 670
 Cys Arg Pro Gly Phe Gly Val Ala Arg Pro Gly Thr Glu Thr Ser Asp
 675 680 685
 Val Val Cys Lys Pro Cys Ala Pro Gly Thr Phe Ser Asn Thr Thr Ser
 690 695 700
 Ser Thr Asp Ile Cys Arg Pro His Gln Ile Cys Asn Val Val Ala Ile
 705 710 715 720
 Pro Gly Asn Ala Ser Met Asp Ala Val Cys Thr Ser Thr Ser Pro Thr
 725 730 735
 Arg Ser Met Ala Pro Gly Ala Val His Leu Pro Gln Pro Val Ser Thr
 740 745 750
 Arg Ser Gln His Thr Gln Pro Thr Pro Glu Pro Ser Thr Ala Pro Ser
 755 760 765
 Thr Ser Phe Leu Leu Pro Met Gly Pro Ser Pro Pro Ala Glu Gly Ser
 770 775 780
 Thr Gly Asp
 785

<210> SEQ ID NO 40
 <211> LENGTH: 755
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 40

Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala
 1 5 10 15
 Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30
 Asn Met His Trp Val Lys Gln Thr Pro Gly Arg Gly Leu Glu Trp Ile
 35 40 45
 Gly Ala Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe
 50 55 60
 Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
 65 70 75 80
 Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ser Thr Tyr Tyr Gly Gly Asp Trp Tyr Phe Asn Val Trp Gly
 100 105 110
 Ala Gly Thr Thr Val Thr Val Ser Ala Ala Ser Thr Lys Gly Pro Ser
 115 120 125
 Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
 130 135 140
 Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
 145 150 155 160
 Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
 165 170 175
 Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
 180 185 190
 Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
 195 200 205
 Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Ala Glu Pro Lys Ser Cys
 210 215 220
 Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
 225 230 235 240
 Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
 245 250 255
 Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
 260 265 270
 Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
 275 280 285
 His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
 290 295 300
 Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
 305 310 315 320
 Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
 325 330 335
 Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
 340 345 350
 Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
 355 360 365
 Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
 370 375 380
 Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
 385 390 395 400
 Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
 405 410 415

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Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
 420 425 430
 His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
 435 440 445
 Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
 450 455 460
 Gly Ser Arg Ile Phe Ala Val Phe Ile Phe Met Thr Tyr Trp His Leu
 465 470 475 480
 Leu Asn Ala Phe Thr Val Thr Val Pro Lys Asp Leu Tyr Val Val Glu
 485 490 495
 Tyr Gly Ser Asn Met Thr Ile Glu Cys Lys Phe Pro Val Glu Lys Gln
 500 505 510
 Leu Asp Leu Ala Ala Leu Ile Val Tyr Trp Glu Met Glu Asp Lys Asn
 515 520 525
 Ile Ile Gln Phe Val His Gly Glu Glu Asp Leu Lys Val Gln His Ser
 530 535 540
 Ser Tyr Arg Gln Arg Ala Arg Leu Leu Lys Asp Gln Leu Ser Leu Gly
 545 550 555 560
 Asn Ala Ala Leu Gln Ile Thr Asp Val Lys Leu Gln Asp Ala Gly Val
 565 570 575
 Tyr Arg Cys Met Ile Ser Tyr Gly Gly Ala Asp Tyr Lys Arg Ile Thr
 580 585 590
 Val Lys Val Asn Ala Pro Tyr Asn Lys Ile Asn Gln Arg Ile Leu Val
 595 600 605
 Val Asp Pro Val Thr Ser Glu His Glu Leu Thr Cys Gln Ala Glu Gly
 610 615 620
 Tyr Pro Lys Ala Glu Val Ile Trp Thr Ser Ser Asp His Gln Val Leu
 625 630 635 640
 Ser Gly Lys Thr Thr Thr Thr Asn Ser Lys Arg Glu Glu Lys Leu Phe
 645 650 655
 Asn Val Thr Ser Thr Leu Arg Ile Asn Thr Thr Thr Asn Glu Ile Phe
 660 665 670
 Tyr Cys Thr Phe Arg Arg Leu Asp Pro Glu Glu Asn His Thr Ala Glu
 675 680 685
 Leu Val Ile Pro Glu Leu Pro Leu Ala His Pro Pro Asn Glu Arg Thr
 690 695 700
 His Leu Val Ile Leu Gly Ala Ile Leu Leu Cys Leu Gly Val Ala Leu
 705 710 715 720
 Thr Phe Ile Phe Arg Leu Arg Lys Gly Arg Met Met Asp Val Lys Lys
 725 730 735
 Cys Gly Ile Gln Asp Thr Asn Ser Lys Lys Gln Ser Asp Thr His Leu
 740 745 750
 Glu Glu Thr
 755

<210> SEQ ID NO 41

<211> LENGTH: 750

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 41

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr

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20					25					30						
Arg	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile	
35					40					45						
Gly	Tyr	Ile	Asn	Pro	Ser	Thr	Gly	Tyr	Thr	Glu	Tyr	Asn	Gln	Lys	Phe	
50					55					60						
Lys	Asp	Lys	Ala	Thr	Ile	Thr	Ala	Asp	Glu	Ser	Thr	Asn	Thr	Ala	Tyr	
65					70					75					80	
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
85					90					95						
Ala	Arg	Gly	Gly	Gly	Val	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	
100					105					110						
Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	
115					120					125						
Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	
130					135					140						
Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	
145					150					155					160	
Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	
165					170					175						
Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	
180					185					190						
Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	
195					200					205						
Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	
210					215					220						
Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	
225					230					235					240	
Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	
245					250					255						
Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	
260					265					270						
Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	
275					280					285						
Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	
290					295					300						
Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	
305					310					315					320	
Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	
325					330					335						
Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	
340					345					350						
Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	
355					360					365						
Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	
370					375					380						
Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	
385					390					395					400	
Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	
405					410					415						
Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	
420					425					430						
Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys	Gly	Gly	
435					440					445						

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Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Arg Ile Phe
 450 455 460
 Ala Val Phe Ile Phe Met Thr Tyr Trp His Leu Leu Asn Ala Phe Thr
 465 470 475 480
 Val Thr Val Pro Lys Asp Leu Tyr Val Val Glu Tyr Gly Ser Asn Met
 485 490 495
 Thr Ile Glu Cys Lys Phe Pro Val Glu Lys Gln Leu Asp Leu Ala Ala
 500 505 510
 Leu Ile Val Tyr Trp Glu Met Glu Asp Lys Asn Ile Ile Gln Phe Val
 515 520 525
 His Gly Glu Glu Asp Leu Lys Val Gln His Ser Ser Tyr Arg Gln Arg
 530 535 540
 Ala Arg Leu Leu Lys Asp Gln Leu Ser Leu Gly Asn Ala Ala Leu Gln
 545 550 555 560
 Ile Thr Asp Val Lys Leu Gln Asp Ala Gly Val Tyr Arg Cys Met Ile
 565 570 575
 Ser Tyr Gly Gly Ala Asp Tyr Lys Arg Ile Thr Val Lys Val Asn Ala
 580 585 590
 Pro Tyr Asn Lys Ile Asn Gln Arg Ile Leu Val Val Asp Pro Val Thr
 595 600 605
 Ser Glu His Glu Leu Thr Cys Gln Ala Glu Gly Tyr Pro Lys Ala Glu
 610 615 620
 Val Ile Trp Thr Ser Ser Asp His Gln Val Leu Ser Gly Lys Thr Thr
 625 630 635 640
 Thr Thr Asn Ser Lys Arg Glu Glu Lys Leu Phe Asn Val Thr Ser Thr
 645 650 655
 Leu Arg Ile Asn Thr Thr Thr Asn Glu Ile Phe Tyr Cys Thr Phe Arg
 660 665 670
 Arg Leu Asp Pro Glu Glu Asn His Thr Ala Glu Leu Val Ile Pro Glu
 675 680 685
 Leu Pro Leu Ala His Pro Pro Asn Glu Arg Thr His Leu Val Ile Leu
 690 695 700
 Gly Ala Ile Leu Leu Cys Leu Gly Val Ala Leu Thr Phe Ile Phe Arg
 705 710 715 720
 Leu Arg Lys Gly Arg Met Met Asp Val Lys Lys Cys Gly Ile Gln Asp
 725 730 735
 Thr Asn Ser Lys Lys Gln Ser Asp Thr His Leu Glu Glu Thr
 740 745 750

<210> SEQ ID NO 42

<211> LENGTH: 749

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 42

Gln Leu Gln Gln Ser Gly Thr Val Leu Ala Arg Pro Gly Ala Ser Val
 1 5 10 15
 Lys Met Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Arg Tyr Trp Met
 20 25 30
 His Trp Ile Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Ala
 35 40 45
 Ile Tyr Pro Gly Asn Ser Asp Thr Ser Tyr Asn Gln Lys Phe Glu Gly
 50 55 60
 Lys Ala Lys Leu Thr Ala Val Thr Ser Ala Ser Thr Ala Tyr Met Glu

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65	70	75	80
Leu Ser Ser Leu Thr His Glu Asp Ser Ala Val Tyr Tyr Cys Ser Arg	85	90	95
Asp Tyr Gly Tyr Tyr Phe Asp Phe Trp Gly Gln Gly Thr Thr Leu Thr	100	105	110
Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro	115	120	125
Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val	130	135	140
Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala	145	150	155
Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly	165	170	175
Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly	180	185	190
Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys	195	200	205
Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys	210	215	220
Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu	225	230	235
Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu	245	250	255
Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys	260	265	270
Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys	275	280	285
Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu	290	295	300
Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys	305	310	315
Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys	325	330	335
Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser	340	345	350
Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys	355	360	365
Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln	370	375	380
Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly	385	390	395
Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln	405	410	415
Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn	420	425	430
His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly	435	440	445
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Arg Ile Phe Ala	450	455	460
Val Phe Ile Phe Met Thr Tyr Trp His Leu Leu Asn Ala Phe Thr Val	465	470	475
Thr Val Pro Lys Asp Leu Tyr Val Val Glu Tyr Gly Ser Asn Met Thr	485	490	495

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Ile Glu Cys Lys Phe Pro Val Glu Lys Gln Leu Asp Leu Ala Ala Leu
 500 505 510
 Ile Val Tyr Trp Glu Met Glu Asp Lys Asn Ile Ile Gln Phe Val His
 515 520 525
 Gly Glu Glu Asp Leu Lys Val Gln His Ser Ser Tyr Arg Gln Arg Ala
 530 535 540
 Arg Leu Leu Lys Asp Gln Leu Ser Leu Gly Asn Ala Ala Leu Gln Ile
 545 550 555 560
 Thr Asp Val Lys Leu Gln Asp Ala Gly Val Tyr Arg Cys Met Ile Ser
 565 570 575
 Tyr Gly Gly Ala Asp Tyr Lys Arg Ile Thr Val Lys Val Asn Ala Pro
 580 585 590
 Tyr Asn Lys Ile Asn Gln Arg Ile Leu Val Val Asp Pro Val Thr Ser
 595 600 605
 Glu His Glu Leu Thr Cys Gln Ala Glu Gly Tyr Pro Lys Ala Glu Val
 610 615 620
 Ile Trp Thr Ser Ser Asp His Gln Val Leu Ser Gly Lys Thr Thr Thr
 625 630 635 640
 Thr Asn Ser Lys Arg Glu Glu Lys Leu Phe Asn Val Thr Ser Thr Leu
 645 650 655
 Arg Ile Asn Thr Thr Thr Asn Glu Ile Phe Tyr Cys Thr Phe Arg Arg
 660 665 670
 Leu Asp Pro Glu Glu Asn His Thr Ala Glu Leu Val Ile Pro Glu Leu
 675 680 685
 Pro Leu Ala His Pro Pro Asn Glu Arg Thr His Leu Val Ile Leu Gly
 690 695 700
 Ala Ile Leu Leu Cys Leu Gly Val Ala Leu Thr Phe Ile Phe Arg Leu
 705 710 715 720
 Arg Lys Gly Arg Met Met Asp Val Lys Lys Cys Gly Ile Gln Asp Thr
 725 730 735
 Asn Ser Lys Lys Gln Ser Asp Thr His Leu Glu Glu Thr
 740 745

<210> SEQ ID NO 43
 <211> LENGTH: 678
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 43

Met Arg Ile Phe Ala Val Phe Ile Phe Met Thr Tyr Trp His Leu Leu
 1 5 10 15
 Asn Ala Phe Thr Val Thr Val Pro Lys Asp Leu Tyr Val Val Glu Tyr
 20 25 30
 Gly Ser Asn Met Thr Ile Glu Cys Lys Phe Pro Val Glu Lys Gln Leu
 35 40 45
 Asp Leu Ala Ala Leu Ile Val Tyr Trp Glu Met Glu Asp Lys Asn Ile
 50 55 60
 Ile Gln Phe Val His Gly Glu Glu Asp Leu Lys Val Gln His Ser Ser
 65 70 75 80
 Tyr Arg Gln Arg Ala Arg Leu Leu Lys Asp Gln Leu Ser Leu Gly Asn
 85 90 95
 Ala Ala Leu Gln Ile Thr Asp Val Lys Leu Gln Asp Ala Gly Val Tyr
 100 105 110
 Arg Cys Met Ile Ser Tyr Gly Gly Ala Asp Tyr Lys Arg Ile Thr Val

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115						120						125					
Lys	Val	Asn	Ala	Pro	Tyr	Asn	Lys	Ile	Asn	Gln	Arg	Ile	Leu	Val	Val		
130						135					140						
Asp	Pro	Val	Thr	Ser	Glu	His	Glu	Leu	Thr	Cys	Gln	Ala	Glu	Gly	Tyr		
145					150					155					160		
Pro	Lys	Ala	Glu	Val	Ile	Trp	Thr	Ser	Ser	Asp	His	Gln	Val	Leu	Ser		
				165					170					175			
Gly	Lys	Thr	Thr	Thr	Thr	Asn	Ser	Lys	Arg	Glu	Glu	Lys	Leu	Phe	Asn		
			180					185					190				
Val	Thr	Ser	Thr	Leu	Arg	Ile	Asn	Thr	Thr	Thr	Asn	Glu	Ile	Phe	Tyr		
	195					200						205					
Cys	Thr	Phe	Arg	Arg	Leu	Asp	Pro	Glu	Glu	Asn	His	Thr	Ala	Glu	Leu		
210						215					220						
Val	Ile	Pro	Glu	Leu	Pro	Leu	Ala	His	Pro	Pro	Asn	Glu	Arg	Thr	His		
225					230						235				240		
Leu	Val	Ile	Leu	Gly	Ala	Ile	Leu	Leu	Cys	Leu	Gly	Val	Ala	Leu	Thr		
			245						250					255			
Phe	Ile	Phe	Arg	Leu	Arg	Lys	Gly	Arg	Met	Met	Asp	Val	Lys	Lys	Cys		
			260					265					270				
Gly	Ile	Gln	Asp	Thr	Asn	Ser	Lys	Lys	Gln	Ser	Asp	Thr	His	Leu	Glu		
	275						280					285					
Glu	Thr	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly		
	290					295					300						
Ser	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly		
305					310					315					320		
Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile		
			325						330					335			
Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu		
			340					345					350				
Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His		
	355					360					365						
Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg		
	370					375					380						
Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys		
385					390					395					400		
Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu		
			405						410					415			
Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr		
			420					425					430				
Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu		
	435						440					445					
Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp		
	450					455					460						
Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val		
465					470					475					480		
Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp		
			485						490					495			
Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His		
			500					505					510				
Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro		
	515						520					525					
Gly	Lys	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly		
530						535					540						

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Ser Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu
545 550 555 560

His Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr
565 570 575

Lys Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro
580 585 590

Lys Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu
595 600 605

Lys Pro Leu Glu Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His
610 615 620

Leu Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu
625 630 635 640

Leu Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr
645 650 655

Ala Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe Cys Gln Ser
660 665 670

Ile Ile Ser Thr Leu Thr
675

<210> SEQ ID NO 44

<211> LENGTH: 677

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 44

Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His
1 5 10 15

Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys
20 25 30

Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys
35 40 45

Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Lys
50 55 60

Pro Leu Glu Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu
65 70 75 80

Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu
85 90 95

Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala
100 105 110

Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe Cys Gln Ser Ile
115 120 125

Ile Ser Thr Leu Thr Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
130 135 140

Gly Gly Gly Ser Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
145 150 155 160

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
165 170 175

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
180 185 190

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
195 200 205

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
210 215 220

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu

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225	230	235	240
Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala	245	250	255
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro	260	265	270
Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln	275	280	285
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala	290	295	300
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr	305	310	315
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu	325	330	335
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser	340	345	350
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser	355	360	365
Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly	370	375	380
Gly Gly Gly Ser Arg Ile Phe Ala Val Phe Ile Phe Met Thr Tyr Trp	385	390	395
His Leu Leu Asn Ala Phe Thr Val Thr Val Pro Lys Asp Leu Tyr Val	405	410	415
Val Glu Tyr Gly Ser Asn Met Thr Ile Glu Cys Lys Phe Pro Val Glu	420	425	430
Lys Gln Leu Asp Leu Ala Ala Leu Ile Val Tyr Trp Glu Met Glu Asp	435	440	445
Lys Asn Ile Ile Gln Phe Val His Gly Glu Glu Asp Leu Lys Val Gln	450	455	460
His Ser Ser Tyr Arg Gln Arg Ala Arg Leu Leu Lys Asp Gln Leu Ser	465	470	475
Leu Gly Asn Ala Ala Leu Gln Ile Thr Asp Val Lys Leu Gln Asp Ala	485	490	495
Gly Val Tyr Arg Cys Met Ile Ser Tyr Gly Gly Ala Asp Tyr Lys Arg	500	505	510
Ile Thr Val Lys Val Asn Ala Pro Tyr Asn Lys Ile Asn Gln Arg Ile	515	520	525
Leu Val Val Asp Pro Val Thr Ser Glu His Glu Leu Thr Cys Gln Ala	530	535	540
Glu Gly Tyr Pro Lys Ala Glu Val Ile Trp Thr Ser Ser Asp His Gln	545	550	555
Val Leu Ser Gly Lys Thr Thr Thr Thr Asn Ser Lys Arg Glu Glu Lys	565	570	575
Leu Phe Asn Val Thr Ser Thr Leu Arg Ile Asn Thr Thr Thr Asn Glu	580	585	590
Ile Phe Tyr Cys Thr Phe Arg Arg Leu Asp Pro Glu Glu Asn His Thr	595	600	605
Ala Glu Leu Val Ile Pro Glu Leu Pro Leu Ala His Pro Pro Asn Glu	610	615	620
Arg Thr His Leu Val Ile Leu Gly Ala Ile Leu Leu Cys Leu Gly Val	625	630	635
Ala Leu Thr Phe Ile Phe Arg Leu Arg Lys Gly Arg Met Met Asp Val	645	650	655

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Lys Lys Cys Gly Ile Gln Asp Thr Asn Ser Lys Lys Gln Ser Asp Thr
660 665 670

His Leu Glu Glu Thr
675

<210> SEQ ID NO 45

<211> LENGTH: 755

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 45

Gln Val Gln Leu Gln Glu Ala Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Ser Val Ser Gly Gly Ser Ile Ser Gly Asp
20 25 30

Tyr Tyr Trp Phe Trp Ile Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp
35 40 45

Ile Gly Tyr Ile Tyr Gly Ser Gly Gly Gly Thr Asn Tyr Asn Pro Ser
50 55 60

Leu Asn Asn Arg Val Ser Ile Ser Ile Asp Thr Ser Lys Asn Leu Phe
65 70 75 80

Ser Leu Lys Leu Arg Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Ser Asn Ile Leu Lys Tyr Leu His Trp Leu Leu Tyr Trp Gly
100 105 110

Gln Gly Val Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
210 215 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
225 230 235 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
245 250 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
260 265 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
275 280 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
290 295 300

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305 310 315 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
325 330 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val

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340						345						350					
Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser		
		355					360					365					
Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu		
		370				375					380						
Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro		
385					390					395					400		
Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val		
				405					410					415			
Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met		
				420					425					430			
His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser		
				435			440					445					
Pro	Gly	Lys	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly		
		450					455					460					
Gly	Ser	Arg	Ile	Phe	Ala	Val	Phe	Ile	Phe	Met	Thr	Tyr	Trp	His	Leu		
465					470					475					480		
Leu	Asn	Ala	Phe	Thr	Val	Thr	Val	Pro	Lys	Asp	Leu	Tyr	Val	Val	Glu		
				485					490					495			
Tyr	Gly	Ser	Asn	Met	Thr	Ile	Glu	Cys	Lys	Phe	Pro	Val	Glu	Lys	Gln		
				500				505					510				
Leu	Asp	Leu	Ala	Ala	Leu	Ile	Val	Tyr	Trp	Glu	Met	Glu	Asp	Lys	Asn		
		515					520					525					
Ile	Ile	Gln	Phe	Val	His	Gly	Glu	Glu	Asp	Leu	Lys	Val	Gln	His	Ser		
		530				535					540						
Ser	Tyr	Arg	Gln	Arg	Ala	Arg	Leu	Leu	Lys	Asp	Gln	Leu	Ser	Leu	Gly		
545					550					555					560		
Asn	Ala	Ala	Leu	Gln	Ile	Thr	Asp	Val	Lys	Leu	Gln	Asp	Ala	Gly	Val		
				565					570					575			
Tyr	Arg	Cys	Met	Ile	Ser	Tyr	Gly	Gly	Ala	Asp	Tyr	Lys	Arg	Ile	Thr		
				580					585					590			
Val	Lys	Val	Asn	Ala	Pro	Tyr	Asn	Lys	Ile	Asn	Gln	Arg	Ile	Leu	Val		
		595					600					605					
Val	Asp	Pro	Val	Thr	Ser	Glu	His	Glu	Leu	Thr	Cys	Gln	Ala	Glu	Gly		
		610					615					620					
Tyr	Pro	Lys	Ala	Glu	Val	Ile	Trp	Thr	Ser	Ser	Asp	His	Gln	Val	Leu		
625					630					635					640		
Ser	Gly	Lys	Thr	Thr	Thr	Thr	Asn	Ser	Lys	Arg	Glu	Glu	Lys	Leu	Phe		
				645					650					655			
Asn	Val	Thr	Ser	Thr	Leu	Arg	Ile	Asn	Thr	Thr	Thr	Asn	Glu	Ile	Phe		
				660				665					670				
Tyr	Cys	Thr	Phe	Arg	Arg	Leu	Asp	Pro	Glu	Glu	Asn	His	Thr	Ala	Glu		
		675					680					685					
Leu	Val	Ile	Pro	Glu	Leu	Pro	Leu	Ala	His	Pro	Pro	Asn	Glu	Arg	Thr		
		690					695					700					
His	Leu	Val	Ile	Leu	Gly	Ala	Ile	Leu	Leu	Cys	Leu	Gly	Val	Ala	Leu		
705					710					715					720		
Thr	Phe	Ile	Phe	Arg	Leu	Arg	Lys	Gly	Arg	Met	Met	Asp	Val	Lys	Lys		
				725					730					735			
Cys	Gly	Ile	Gln	Asp	Thr	Asn	Ser	Lys	Lys	Gln	Ser	Asp	Thr	His	Leu		
				740					745					750			
Glu	Glu	Thr															
		755															

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<210> SEQ ID NO 46
<211> LENGTH: 687
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 46
Met Gly Val Leu Leu Thr Gln Arg Thr Leu Leu Ser Leu Val Leu Ala
1      5      10      15
Leu Leu Phe Pro Ser Met Ala Ser Met Ala Met His Val Ala Gln Pro
20     25     30
Ala Val Val Leu Ala Ser Ser Arg Gly Ile Ala Ser Phe Val Cys Glu
35     40     45
Tyr Ala Ser Pro Gly Lys Ala Thr Glu Val Arg Val Thr Val Leu Arg
50     55     60
Gln Ala Asp Ser Gln Val Thr Glu Val Cys Ala Ala Thr Tyr Met Met
65     70     75     80
Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser Ile Cys Thr Gly Thr Ser
85     90     95
Ser Gly Asn Gln Val Asn Leu Thr Ile Gln Gly Leu Arg Ala Met Asp
100    105    110
Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu Met Tyr Pro Pro Pro Tyr
115    120    125
Tyr Leu Gly Ile Gly Asn Gly Thr Gln Ile Tyr Val Ile Asp Pro Glu
130    135    140
Pro Cys Pro Asp Ser Asp Gln Glu Pro Lys Ser Cys Asp Lys Thr His
145    150    155    160
Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
165    170    175
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
180    185    190
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
195    200    205
Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
210    215    220
Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
225    230    235    240
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
245    250    255
Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
260    265    270
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
275    280    285
Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
290    295    300
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
305    310    315    320
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
325    330    335
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
340    345    350
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
355    360    365
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly

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370					375					380					
Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Arg	Ile
385				390					395						400
Phe	Ala	Val	Phe	Ile	Phe	Met	Thr	Tyr	Trp	His	Leu	Leu	Asn	Ala	Phe
			405						410					415	
Thr	Val	Thr	Val	Pro	Lys	Asp	Leu	Tyr	Val	Val	Glu	Tyr	Gly	Ser	Asn
			420					425					430		
Met	Thr	Ile	Glu	Cys	Lys	Phe	Pro	Val	Glu	Lys	Gln	Leu	Asp	Leu	Ala
		435					440					445			
Ala	Leu	Ile	Val	Tyr	Trp	Glu	Met	Glu	Asp	Lys	Asn	Ile	Ile	Gln	Phe
	450					455					460				
Val	His	Gly	Glu	Glu	Asp	Leu	Lys	Val	Gln	His	Ser	Ser	Tyr	Arg	Gln
465				470					475						480
Arg	Ala	Arg	Leu	Leu	Lys	Asp	Gln	Leu	Ser	Leu	Gly	Asn	Ala	Ala	Leu
			485					490						495	
Gln	Ile	Thr	Asp	Val	Lys	Leu	Gln	Asp	Ala	Gly	Val	Tyr	Arg	Cys	Met
			500					505					510		
Ile	Ser	Tyr	Gly	Gly	Ala	Asp	Tyr	Lys	Arg	Ile	Thr	Val	Lys	Val	Asn
		515					520					525			
Ala	Pro	Tyr	Asn	Lys	Ile	Asn	Gln	Arg	Ile	Leu	Val	Val	Asp	Pro	Val
	530					535					540				
Thr	Ser	Glu	His	Glu	Leu	Thr	Cys	Gln	Ala	Glu	Gly	Tyr	Pro	Lys	Ala
545				550					555						560
Glu	Val	Ile	Trp	Thr	Ser	Ser	Asp	His	Gln	Val	Leu	Ser	Gly	Lys	Thr
			565					570						575	
Thr	Thr	Thr	Asn	Ser	Lys	Arg	Glu	Glu	Lys	Leu	Phe	Asn	Val	Thr	Ser
			580					585					590		
Thr	Leu	Arg	Ile	Asn	Thr	Thr	Thr	Asn	Glu	Ile	Phe	Tyr	Cys	Thr	Phe
	595						600					605			
Arg	Arg	Leu	Asp	Pro	Glu	Glu	Asn	His	Thr	Ala	Glu	Leu	Val	Ile	Pro
	610					615					620				
Glu	Leu	Pro	Leu	Ala	His	Pro	Pro	Asn	Glu	Arg	Thr	His	Leu	Val	Ile
625				630					635						640
Leu	Gly	Ala	Ile	Leu	Leu	Cys	Leu	Gly	Val	Ala	Leu	Thr	Phe	Ile	Phe
			645					650						655	
Arg	Leu	Arg	Lys	Gly	Arg	Met	Met	Asp	Val	Lys	Lys	Cys	Gly	Ile	Gln
		660					665					670			
Asp	Thr	Asn	Ser	Lys	Lys	Gln	Ser	Asp	Thr	His	Leu	Glu	Glu	Thr	
	675					680					685				

<210> SEQ ID NO 47

<211> LENGTH: 678

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 47

Met	Arg	Ile	Phe	Ala	Val	Phe	Ile	Phe	Met	Thr	Tyr	Trp	His	Leu	Leu
1			5						10				15		
Asn	Ala	Phe	Thr	Val	Thr	Val	Pro	Lys	Asp	Leu	Tyr	Val	Val	Glu	Tyr
		20					25					30			
Gly	Ser	Asn	Met	Thr	Ile	Glu	Cys	Lys	Phe	Pro	Val	Glu	Lys	Gln	Leu
	35					40						45			
Asp	Leu	Ala	Ala	Leu	Ile	Val	Tyr	Trp	Glu	Met	Glu	Asp	Lys	Asn	Ile
	50				55					60					

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Ile	Gln	Phe	Val	His	Gly	Glu	Glu	Asp	Leu	Lys	Val	Gln	His	Ser	Ser
65					70					75				80	
Tyr	Arg	Gln	Arg	Ala	Arg	Leu	Leu	Lys	Asp	Gln	Leu	Ser	Leu	Gly	Asn
			85						90					95	
Ala	Ala	Leu	Gln	Ile	Thr	Asp	Val	Lys	Leu	Gln	Asp	Ala	Gly	Val	Tyr
			100					105					110		
Arg	Cys	Met	Ile	Ser	Tyr	Gly	Gly	Ala	Asp	Tyr	Lys	Arg	Ile	Thr	Val
		115				120						125			
Lys	Val	Asn	Ala	Pro	Tyr	Asn	Lys	Ile	Asn	Gln	Arg	Ile	Leu	Val	Val
	130					135					140				
Asp	Pro	Val	Thr	Ser	Glu	His	Glu	Leu	Thr	Cys	Gln	Ala	Glu	Gly	Tyr
145					150					155				160	
Pro	Lys	Ala	Glu	Val	Ile	Trp	Thr	Ser	Ser	Asp	His	Gln	Val	Leu	Ser
			165						170					175	
Gly	Lys	Thr	Thr	Thr	Thr	Asn	Ser	Lys	Arg	Glu	Glu	Lys	Leu	Phe	Asn
			180					185					190		
Val	Thr	Ser	Thr	Leu	Arg	Ile	Asn	Thr	Thr	Thr	Asn	Glu	Ile	Phe	Tyr
		195					200					205			
Cys	Thr	Phe	Arg	Arg	Leu	Asp	Pro	Glu	Glu	Asn	His	Thr	Ala	Glu	Leu
	210					215					220				
Val	Ile	Pro	Glu	Leu	Pro	Leu	Ala	His	Pro	Pro	Asn	Glu	Arg	Thr	His
225				230						235				240	
Leu	Val	Ile	Leu	Gly	Ala	Ile	Leu	Leu	Cys	Leu	Gly	Val	Ala	Leu	Thr
			245						250					255	
Phe	Ile	Phe	Arg	Leu	Arg	Lys	Gly	Arg	Met	Met	Asp	Val	Lys	Lys	Cys
			260					265					270		
Gly	Ile	Gln	Asp	Thr	Asn	Ser	Lys	Lys	Gln	Ser	Asp	Thr	His	Leu	Glu
	275						280					285			
Glu	Thr	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly
	290					295					300				
Ser	Gln	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys
305				310						315				320	
Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro
			325						330					335	
Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys
			340					345					350		
Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp
		355					360					365			
Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu
	370					375					380				
Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu
385				390						395				400	
His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn
			405					410						415	
Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly
			420					425					430		
Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu
		435				440						445			
Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr
	450					455					460				
Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn
465				470						475				480	
Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe

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485				490				495							
Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn
			500											510	
Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr
			515				520							525	
Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys	Gly	Gly	Gly	Gly	Ser	Gly
			530				535							540	
Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Ala	Met	His	Val	Ala	Gln	Pro
			545				550				555				560
Ala	Val	Val	Leu	Ala	Ser	Ser	Arg	Gly	Ile	Ala	Ser	Phe	Val	Cys	Glu
			565								570				575
Tyr	Ala	Ser	Pro	Gly	Lys	Ala	Thr	Glu	Val	Arg	Val	Thr	Val	Leu	Arg
			580								585				590
Gln	Ala	Asp	Ser	Gln	Val	Thr	Glu	Val	Cys	Ala	Ala	Thr	Tyr	Met	Met
			595				600								605
Gly	Asn	Glu	Leu	Thr	Phe	Leu	Asp	Asp	Ser	Ile	Cys	Thr	Gly	Thr	Ser
			610				615								620
Ser	Gly	Asn	Gln	Val	Asn	Leu	Thr	Ile	Gln	Gly	Leu	Arg	Ala	Met	Asp
			625				630				635				640
Thr	Gly	Leu	Tyr	Ile	Cys	Lys	Val	Glu	Leu	Met	Tyr	Pro	Pro	Pro	Tyr
			645								650				655
Tyr	Leu	Gly	Ile	Gly	Asn	Gly	Thr	Gln	Ile	Tyr	Val	Ile	Asp	Pro	Glu
			660								665				670
Pro	Cys	Pro	Asp	Ser	Asp										
			675												

<210> SEQ ID NO 48

<211> LENGTH: 656

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 48

Ala	Leu	Asp	Thr	Asn	Tyr	Cys	Phe	Ser	Ser	Thr	Glu	Lys	Asn	Cys	Cys
1				5						10				15	
Val	Arg	Gln	Leu	Tyr	Ile	Asp	Phe	Arg	Lys	Asp	Leu	Gly	Trp	Lys	Trp
			20					25					30		
Ile	His	Glu	Pro	Lys	Gly	Tyr	His	Ala	Asn	Phe	Cys	Leu	Gly	Pro	Cys
			35				40						45		
Pro	Tyr	Ile	Trp	Ser	Leu	Asp	Thr	Gln	Tyr	Ser	Lys	Val	Leu	Ala	Leu
			50			55					60				
Tyr	Asn	Gln	His	Asn	Pro	Gly	Ala	Ser	Ala	Ala	Pro	Cys	Cys	Val	Pro
			65		70				75						80
Gln	Ala	Leu	Glu	Pro	Leu	Pro	Ile	Val	Tyr	Tyr	Val	Gly	Arg	Lys	Pro
			85					90						95	
Lys	Val	Glu	Gln	Leu	Ser	Asn	Met	Ile	Val	Arg	Ser	Cys	Lys	Cys	Ser
			100				105						110		
Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Thr
			115				120						125		
His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser
			130			135					140				
Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg
			145			150				155					160
Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro
				165					170						175

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Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala
			180					185					190		
Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val
		195					200					205			
Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr
	210					215					220				
Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr
225					230					235					240
Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu
			245						250					255	
Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys
			260					265					270		
Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser
		275					280					285			
Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp
	290					295					300				
Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser
305					310					315					320
Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala
				325					330					335	
Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys
			340					345					350		
Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Arg
		355				360						365			
Ile	Phe	Ala	Val	Phe	Ile	Phe	Met	Thr	Tyr	Trp	His	Leu	Leu	Asn	Ala
	370					375					380				
Phe	Thr	Val	Thr	Val	Pro	Lys	Asp	Leu	Tyr	Val	Val	Glu	Tyr	Gly	Ser
385					390					395					400
Asn	Met	Thr	Ile	Glu	Cys	Lys	Phe	Pro	Val	Glu	Lys	Gln	Leu	Asp	Leu
			405					410						415	
Ala	Ala	Leu	Ile	Val	Tyr	Trp	Glu	Met	Glu	Asp	Lys	Asn	Ile	Ile	Gln
			420					425					430		
Phe	Val	His	Gly	Glu	Glu	Asp	Leu	Lys	Val	Gln	His	Ser	Ser	Tyr	Arg
		435					440					445			
Gln	Arg	Ala	Arg	Leu	Leu	Lys	Asp	Gln	Leu	Ser	Leu	Gly	Asn	Ala	Ala
		450				455					460				
Leu	Gln	Ile	Thr	Asp	Val	Lys	Leu	Gln	Asp	Ala	Gly	Val	Tyr	Arg	Cys
465					470				475						480
Met	Ile	Ser	Tyr	Gly	Gly	Ala	Asp	Tyr	Lys	Arg	Ile	Thr	Val	Lys	Val
			485					490						495	
Asn	Ala	Pro	Tyr	Asn	Lys	Ile	Asn	Gln	Arg	Ile	Leu	Val	Val	Asp	Pro
			500					505					510		
Val	Thr	Ser	Glu	His	Glu	Leu	Thr	Cys	Gln	Ala	Glu	Gly	Tyr	Pro	Lys
		515					520					525			
Ala	Glu	Val	Ile	Trp	Thr	Ser	Ser	Asp	His	Gln	Val	Leu	Ser	Gly	Lys
		530				535					540				
Thr	Thr	Thr	Thr	Asn	Ser	Lys	Arg	Glu	Glu	Lys	Leu	Phe	Asn	Val	Thr
545					550					555					560
Ser	Thr	Leu	Arg	Ile	Asn	Thr	Thr	Thr	Asn	Glu	Ile	Phe	Tyr	Cys	Thr
			565					570						575	
Phe	Arg	Arg	Leu	Asp	Pro	Glu	Glu	Asn	His	Thr	Ala	Glu	Leu	Val	Ile
			580					585					590		
Pro	Glu	Leu	Pro	Leu	Ala	His	Pro	Pro	Asn	Glu	Arg	Thr	His	Leu	Val

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595	600	605
Ile Leu Gly Ala Ile Leu Leu Cys Leu Gly Val Ala Leu Thr Phe Ile 610 615 620		
Phe Arg Leu Arg Lys Gly Arg Met Met Asp Val Lys Lys Cys Gly Ile 625 630 635 640		
Gln Asp Thr Asn Ser Lys Lys Gln Ser Asp Thr His Leu Glu Glu Thr 645 650 655		
 <210> SEQ ID NO 49 <211> LENGTH: 657 <212> TYPE: PRT <213> ORGANISM: Homo sapiens <400> SEQUENCE: 49		
Met Arg Ile Phe Ala Val Phe Ile Phe Met Thr Tyr Trp His Leu Leu 1 5 10 15		
Asn Ala Phe Thr Val Thr Val Pro Lys Asp Leu Tyr Val Val Glu Tyr 20 25 30		
Gly Ser Asn Met Thr Ile Glu Cys Lys Phe Pro Val Glu Lys Gln Leu 35 40 45		
Asp Leu Ala Ala Leu Ile Val Tyr Trp Glu Met Glu Asp Lys Asn Ile 50 55 60		
Ile Gln Phe Val His Gly Glu Glu Asp Leu Lys Val Gln His Ser Ser 65 70 75 80		
Tyr Arg Gln Arg Ala Arg Leu Leu Lys Asp Gln Leu Ser Leu Gly Asn 85 90 95		
Ala Ala Leu Gln Ile Thr Asp Val Lys Leu Gln Asp Ala Gly Val Tyr 100 105 110		
Arg Cys Met Ile Ser Tyr Gly Gly Ala Asp Tyr Lys Arg Ile Thr Val 115 120 125		
Lys Val Asn Ala Pro Tyr Asn Lys Ile Asn Gln Arg Ile Leu Val Val 130 135 140		
Asp Pro Val Thr Ser Glu His Glu Leu Thr Cys Gln Ala Glu Gly Tyr 145 150 155 160		
Pro Lys Ala Glu Val Ile Trp Thr Ser Ser Asp His Gln Val Leu Ser 165 170 175		
Gly Lys Thr Thr Thr Thr Asn Ser Lys Arg Glu Glu Lys Leu Phe Asn 180 185 190		
Val Thr Ser Thr Leu Arg Ile Asn Thr Thr Thr Asn Glu Ile Phe Tyr 195 200 205		
Cys Thr Phe Arg Arg Leu Asp Pro Glu Glu Asn His Thr Ala Glu Leu 210 215 220		
Val Ile Pro Glu Leu Pro Leu Ala His Pro Pro Asn Glu Arg Thr His 225 230 235 240		
Leu Val Ile Leu Gly Ala Ile Leu Leu Cys Leu Gly Val Ala Leu Thr 245 250 255		
Phe Ile Phe Arg Leu Arg Lys Gly Arg Met Met Asp Val Lys Lys Cys 260 265 270		
Gly Ile Gln Asp Thr Asn Ser Lys Lys Gln Ser Asp Thr His Leu Glu 275 280 285		
Glu Thr Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly 290 295 300		
Ser Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly 305 310 315 320		

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Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
 325 330 335
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
 340 345 350
 Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
 355 360 365
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
 370 375 380
 Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
 385 390 395 400
 Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
 405 410 415
 Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
 420 425 430
 Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
 435 440 445
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
 450 455 460
 Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
 465 470 475 480
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
 485 490 495
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
 500 505 510
 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
 515 520 525
 Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
 530 535 540
 Ser Ala Leu Asp Thr Asn Tyr Cys Phe Ser Ser Thr Glu Lys Asn Cys
 545 550 555 560
 Cys Val Arg Gln Leu Tyr Ile Asp Phe Arg Lys Asp Leu Gly Trp Lys
 565 570 575
 Trp Ile His Glu Pro Lys Gly Tyr His Ala Asn Phe Cys Leu Gly Pro
 580 585 590
 Cys Pro Tyr Ile Trp Ser Leu Asp Thr Gln Tyr Ser Lys Val Leu Ala
 595 600 605
 Leu Tyr Asn Gln His Asn Pro Gly Ala Ser Ala Ala Pro Cys Cys Val
 610 615 620
 Pro Gln Ala Leu Glu Pro Leu Pro Ile Val Tyr Tyr Val Gly Arg Lys
 625 630 635 640
 Pro Lys Val Glu Gln Leu Ser Asn Met Ile Val Arg Ser Cys Lys Cys
 645 650 655

Ser

<210> SEQ ID NO 50
 <211> LENGTH: 578
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 50

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
 20 25 30

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Ala	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
	35						40					45			
Ser	Ala	Ile	Thr	Trp	Asn	Ser	Gly	His	Ile	Asp	Tyr	Ala	Asp	Ser	Val
	50				55					60					
Glu	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Ser	Leu	Tyr
65				70					75					80	
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
			85						90					95	
Ala	Leu	Val	Ser	Tyr	Leu	Ser	Thr	Ala	Ser	Ser	Leu	Asp	Tyr	Trp	Gly
			100					105					110		
Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser
		115					120					125			
Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala
	130					135					140				
Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val
145				150					155						160
Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala
			165						170					175	
Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val
		180						185					190		
Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His
	195						200					205			
Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Ala	Glu	Pro	Lys	Ser	Cys
	210					215					220				
Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly
225				230						235					240
Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met
			245						250					255	
Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His
	260							265					270		
Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val
	275						280					285			
His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr
	290					295					300				
Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly
305				310						315					320
Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile
			325						330					335	
Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val
		340						345					350		
Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser
	355						360					365			
Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu
	370					375					380				
Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro
385				390						395					400
Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val
			405						410					415	
Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met
		420						425				430			
His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser
	435						440					445			
Pro	Gly	Lys	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly

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450	455	460
Gly Ser Ala Leu Asp Thr Asn Tyr Cys Phe Ser Ser Thr Glu Lys Asn		
465	470	475 480
Cys Cys Val Arg Gln Leu Tyr Ile Asp Phe Arg Lys Asp Leu Gly Trp		
	485	490 495
Lys Trp Ile His Glu Pro Lys Gly Tyr His Ala Asn Phe Cys Leu Gly		
	500	505 510
Pro Cys Pro Tyr Ile Trp Ser Leu Asp Thr Gln Tyr Ser Lys Val Leu		
	515	520 525
Ala Leu Tyr Asn Gln His Asn Pro Gly Ala Ser Ala Ala Pro Cys Cys		
	530	535 540
Val Pro Gln Ala Leu Glu Pro Leu Pro Ile Val Tyr Tyr Val Gly Arg		
545	550	555 560
Lys Pro Lys Val Glu Gln Leu Ser Asn Met Ile Val Arg Ser Cys Lys		
	565	570 575
Cys Ser		
<210> SEQ ID NO 51		
<211> LENGTH: 594		
<212> TYPE: PRT		
<213> ORGANISM: Homo sapiens		
<400> SEQUENCE: 51		
Leu Pro Ala Gln Val Ala Phe Thr Pro Tyr Ala Pro Glu Pro Gly Ser		
1	5	10 15
Thr Cys Arg Leu Arg Glu Tyr Tyr Asp Gln Thr Ala Gln Met Cys Cys		
	20	25 30
Ser Lys Cys Ser Pro Gly Gln His Ala Lys Val Phe Cys Thr Lys Thr		
	35	40 45
Ser Asp Thr Val Cys Asp Ser Cys Glu Asp Ser Thr Tyr Thr Gln Leu		
	50	55 60
Trp Asn Trp Val Pro Glu Cys Leu Ser Cys Gly Ser Arg Cys Ser Ser		
65	70	75 80
Asp Gln Val Glu Thr Gln Ala Cys Thr Arg Glu Gln Asn Arg Ile Cys		
	85	90 95
Thr Cys Arg Pro Gly Trp Tyr Cys Ala Leu Ser Lys Gln Glu Gly Cys		
	100	105 110
Arg Leu Cys Ala Pro Leu Arg Lys Cys Arg Pro Gly Phe Gly Val Ala		
	115	120 125
Arg Pro Gly Thr Glu Thr Ser Asp Val Val Cys Lys Pro Cys Ala Pro		
	130	135 140
Gly Thr Phe Ser Asn Thr Thr Ser Ser Thr Asp Ile Cys Arg Pro His		
145	150	155 160
Gln Ile Cys Asn Val Val Ala Ile Pro Gly Asn Ala Ser Met Asp Ala		
	165	170 175
Val Cys Thr Ser Thr Ser Pro Thr Arg Ser Met Ala Pro Gly Ala Val		
	180	185 190
His Leu Pro Gln Pro Val Ser Thr Arg Ser Gln His Thr Gln Pro Thr		
	195	200 205
Pro Glu Pro Ser Thr Ala Pro Ser Thr Ser Phe Leu Leu Pro Met Gly		
	210	215 220
Pro Ser Pro Pro Ala Glu Gly Ser Thr Gly Asp 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	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly
	465			470					475					480	
Gly	Ser	Ala	Leu	Asp	Thr	Asn	Tyr	Cys	Phe	Ser	Ser	Thr	Glu	Lys	Asn
			485					490					495		
Cys	Cys	Val	Arg	Gln	Leu	Tyr	Ile	Asp	Phe	Arg	Lys	Asp	Leu	Gly	Trp
		500					505						510		
Lys	Trp	Ile	His	Glu	Pro	Lys	Gly	Tyr	His	Ala	Asn	Phe	Cys	Leu	Gly
		515					520					525			
Pro	Cys	Pro	Tyr	Ile	Trp	Ser	Leu	Asp	Thr	Gln	Tyr	Ser	Lys	Val	Leu
	530					535					540				
Ala	Leu	Tyr	Asn	Gln	His	Asn	Pro	Gly	Ala	Ser	Ala	Ala	Pro	Cys	Cys
	545			550					555					560	
Val	Pro	Gln	Ala	Leu	Glu	Pro	Leu	Pro	Ile	Val	Tyr	Tyr	Val	Gly	Arg
			565					570					575		
Lys	Pro	Lys	Val	Glu	Gln	Leu	Ser	Asn	Met	Ile	Val	Arg	Ser	Cys	Lys
			580				585						590		

Cys Ser

<210> SEQ ID NO 52

<211> LENGTH: 602

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 52

Ala	Leu	Asp	Thr	Asn	Tyr	Cys	Phe	Ser	Ser	Thr	Glu	Lys	Asn	Cys	Cys
1				5					10					15	

Val Arg Gln Leu Tyr Ile Asp Phe Arg Lys Asp Leu Gly Trp Lys Trp

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20								25					30				
Ile	His	Glu	Pro	Lys	Gly	Tyr	His	Ala	Asn	Phe	Cys	Leu	Gly	Pro	Cys		
		35					40					45					
Pro	Tyr	Ile	Trp	Ser	Leu	Asp	Thr	Gln	Tyr	Ser	Lys	Val	Leu	Ala	Leu		
		50			55						60						
Tyr	Asn	Gln	His	Asn	Pro	Gly	Ala	Ser	Ala	Ala	Pro	Cys	Cys	Val	Pro		
65					70					75					80		
Gln	Ala	Leu	Glu	Pro	Leu	Pro	Ile	Val	Tyr	Tyr	Val	Gly	Arg	Lys	Pro		
				85					90					95			
Lys	Val	Glu	Gln	Leu	Ser	Asn	Met	Ile	Val	Arg	Ser	Cys	Lys	Cys	Ser		
		100						105					110				
Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Thr		
		115				120				125							
His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser		
		130				135				140							
Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg		
145					150				155						160		
Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro		
				165				170				175					
Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala		
		180						185			190						
Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val		
		195				200						205					
Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr		
		210				215				220							
Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr		
225					230				235				240				
Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu		
				245				250				255					
Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys		
				260				265				270					
Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser		
		275						280				285					
Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp		
		290				295				300							
Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser		
305					310				315				320				
Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala		
				325				330				335					
Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys		
		340						345				350					
Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Leu		
		355				360				365							
Pro	Ala	Gln	Val	Ala	Phe	Thr	Pro	Tyr	Ala	Pro	Glu	Pro	Gly	Ser	Thr		
		370				375				380							
Cys	Arg	Leu	Arg	Glu	Tyr	Tyr	Asp	Gln	Thr	Ala	Gln	Met	Cys	Cys	Ser		
385					390				395				400				
Lys	Cys	Ser	Pro	Gly	Gln	His	Ala	Lys	Val	Phe	Cys	Thr	Lys	Thr	Ser		
				405				410				415					
Asp	Thr	Val	Cys	Asp	Ser	Cys	Glu	Asp	Ser	Thr	Tyr	Thr	Gln	Leu	Trp		
		420						425				430					
Asn	Trp	Val	Pro	Glu	Cys	Leu	Ser	Cys	Gly	Ser	Arg	Cys	Ser	Ser	Asp		
		435				440				445							

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Gln Val Glu Thr Gln Ala Cys Thr Arg Glu Gln Asn Arg Ile Cys Thr
 450 455 460

Cys Arg Pro Gly Trp Tyr Cys Ala Leu Ser Lys Gln Glu Gly Cys Arg
 465 470 475 480

Leu Cys Ala Pro Leu Arg Lys Cys Arg Pro Gly Phe Gly Val Ala Arg
 485 490 495

Pro Gly Thr Glu Thr Ser Asp Val Val Cys Lys Pro Cys Ala Pro Gly
 500 505 510

Thr Phe Ser Asn Thr Thr Ser Ser Thr Asp Ile Cys Arg Pro His Gln
 515 520 525

Ile Cys Asn Val Val Ala Ile Pro Gly Asn Ala Ser Met Asp Ala Val
 530 535 540

Cys Thr Ser Thr Ser Pro Thr Arg Ser Met Ala Pro Gly Ala Val His
 545 550 555 560

Leu Pro Gln Pro Val Ser Thr Arg Ser Gln His Thr Gln Pro Thr Pro
 565 570 575

Glu Pro Ser Thr Ala Pro Ser Thr Ser Phe Leu Leu Pro Met Gly Pro
 580 585 590

Ser Pro Pro Ala Glu Gly Ser Thr Gly Asp
 595 600

<210> SEQ ID NO 53
 <211> LENGTH: 578
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 53

Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30

Asn Met His Trp Val Lys Gln Thr Pro Gly Arg Gly Leu Glu Trp Ile
 35 40 45

Gly Ala Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe
 50 55 60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
 65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Ser Thr Tyr Tyr Gly Gly Asp Trp Tyr Phe Asn Val Trp Gly
 100 105 110

Ala Gly Thr Thr Val Thr Val Ser Ala Ala Ser Thr Lys Gly Pro Ser
 115 120 125

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
 130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
 145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
 165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
 180 185 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
 195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Ala Glu Pro Lys Ser Cys

-continued

210	215	220
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly 225 230 235 240		
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met 245 250 255		
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His 260 265 270		
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val 275 280 285		
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr 290 295 300		
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly 305 310 315 320		
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile 325 330 335		
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val 340 345 350		
Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser 355 360 365		
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu 370 375 380		
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro 385 390 395 400		
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val 405 410 415		
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met 420 425 430		
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser 435 440 445		
Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly 450 455 460		
Gly Ser Ala Leu Asp Thr Asn Tyr Cys Phe Ser Ser Thr Glu Lys Asn 465 470 475 480		
Cys Cys Val Arg Gln Leu Tyr Ile Asp Phe Arg Lys Asp Leu Gly Trp 485 490 495		
Lys Trp Ile His Glu Pro Lys Gly Tyr His Ala Asn Phe Cys Leu Gly 500 505 510		
Pro Cys Pro Tyr Ile Trp Ser Leu Asp Thr Gln Tyr Ser Lys Val Leu 515 520 525		
Ala Leu Tyr Asn Gln His Asn Pro Gly Ala Ser Ala Ala Pro Cys Cys 530 535 540		
Val Pro Gln Ala Leu Glu Pro Leu Pro Ile Val Tyr Tyr Val Gly Arg 545 550 555 560		
Lys Pro Lys Val Glu Gln Leu Ser Asn Met Ile Val Arg Ser Cys Lys 565 570 575		

Cys Ser

<210> SEQ ID NO 54

<211> LENGTH: 573

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 54

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser

-continued

1	5	10	15
Ser Val Lys	Val Ser Cys Lys	Ala Ser Gly Tyr Thr Phe Thr Ser Tyr	
	20	25	30
Arg Met His	Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile		
	35	40	45
Gly Tyr Ile	Asn Pro Ser Thr Gly Tyr Thr Glu Tyr Asn Gln Lys Phe		
	50	55	60
Lys Asp Lys	Ala Thr Ile Thr Ala Asp Glu Ser Thr Asn Thr Ala Tyr		
	65	70	75
Met Glu Leu	Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys		
	85	90	95
Ala Arg Gly	Gly Gly Val Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val		
	100	105	110
Thr Val Ser	Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala		
	115	120	125
Pro Ser Ser	Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu		
	130	135	140
Val Lys Asp	Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly		
	145	150	155
Ala Leu Thr	Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser		
	165	170	175
Gly Leu Tyr	Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu		
	180	185	190
Gly Thr Gln	Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr		
	195	200	205
Lys Val Asp	Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr		
	210	215	220
Cys Pro Pro	Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe		
	225	230	235
Leu Phe Pro	Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro		
	245	250	255
Glu Val Thr	Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val		
	260	265	270
Lys Phe Asn	Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr		
	275	280	285
Lys Pro Arg	Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val		
	290	295	300
Leu Thr Val	Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys		
	305	310	315
Lys Val Ser	Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser		
	325	330	335
Lys Ala Lys	Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro		
	340	345	350
Ser Arg Asp	Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val		
	355	360	365
Lys Gly Phe	Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly		
	370	375	380
Gln Pro Glu	Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp		
	385	390	395
Gly Ser Phe	Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp		
	405	410	415
Gln Gln Gly	Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His		
	420	425	430

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Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly
 435 440 445
 Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Leu Asp
 450 455 460
 Thr Asn Tyr Cys Phe Ser Ser Thr Glu Lys Asn Cys Cys Val Arg Gln
 465 470 475 480
 Leu Tyr Ile Asp Phe Arg Lys Asp Leu Gly Trp Lys Trp Ile His Glu
 485 490 495
 Pro Lys Gly Tyr His Ala Asn Phe Cys Leu Gly Pro Cys Pro Tyr Ile
 500 505 510
 Trp Ser Leu Asp Thr Gln Tyr Ser Lys Val Leu Ala Leu Tyr Asn Gln
 515 520 525
 His Asn Pro Gly Ala Ser Ala Ala Pro Cys Cys Val Pro Gln Ala Leu
 530 535 540
 Glu Pro Leu Pro Ile Val Tyr Tyr Val Gly Arg Lys Pro Lys Val Glu
 545 550 555 560
 Gln Leu Ser Asn Met Ile Val Arg Ser Cys Lys Cys Ser
 565 570

<210> SEQ ID NO 55

<211> LENGTH: 572

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 55

Gln Leu Gln Gln Ser Gly Thr Val Leu Ala Arg Pro Gly Ala Ser Val
 1 5 10 15
 Lys Met Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Arg Tyr Trp Met
 20 25 30
 His Trp Ile Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Ala
 35 40 45
 Ile Tyr Pro Gly Asn Ser Asp Thr Ser Tyr Asn Gln Lys Phe Glu Gly
 50 55 60
 Lys Ala Lys Leu Thr Ala Val Thr Ser Ala Ser Thr Ala Tyr Met Glu
 65 70 75 80
 Leu Ser Ser Leu Thr His Glu Asp Ser Ala Val Tyr Tyr Cys Ser Arg
 85 90 95
 Asp Tyr Gly Tyr Tyr Phe Asp Phe Trp Gly Gln Gly Thr Thr Leu Thr
 100 105 110
 Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
 115 120 125
 Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
 130 135 140
 Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
 145 150 155 160
 Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
 165 170 175
 Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
 180 185 190
 Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
 195 200 205
 Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
 210 215 220
 Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu

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225	230	235	240
Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu	245	250	255
Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys	260	265	270
Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys	275	280	285
Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu	290	295	300
Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys	305	310	315
Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys	325	330	335
Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser	340	345	350
Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys	355	360	365
Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln	370	375	380
Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly	385	390	395
Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln	405	410	415
Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn	420	425	430
His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly	435	440	445
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Leu Asp Thr	450	455	460
Asn Tyr Cys Phe Ser Ser Thr Glu Lys Asn Cys Cys Val Arg Gln Leu	465	470	475
Tyr Ile Asp Phe Arg Lys Asp Leu Gly Trp Lys Trp Ile His Glu Pro	485	490	495
Lys Gly Tyr His Ala Asn Phe Cys Leu Gly Pro Cys Pro Tyr Ile Trp	500	505	510
Ser Leu Asp Thr Gln Tyr Ser Lys Val Leu Ala Leu Tyr Asn Gln His	515	520	525
Asn Pro Gly Ala Ser Ala Ala Pro Cys Cys Val Pro Gln Ala Leu Glu	530	535	540
Pro Leu Pro Ile Val Tyr Tyr Val Gly Arg Lys Pro Lys Val Glu Gln	545	550	555
Leu Ser Asn Met Ile Val Arg Ser Cys Lys Cys Ser	565	570	

<210> SEQ ID NO 56

<211> LENGTH: 500

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 56

Ala Leu Asp Thr Asn Tyr Cys Phe Ser Ser Thr Glu Lys Asn Cys Cys	1	5	10	15
Val Arg Gln Leu Tyr Ile Asp Phe Arg Lys Asp Leu Gly Trp Lys Trp	20	25	30	

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Ile	His	Glu	Pro	Lys	Gly	Tyr	His	Ala	Asn	Phe	Cys	Leu	Gly	Pro	Cys
	35						40					45			
Pro	Tyr	Ile	Trp	Ser	Leu	Asp	Thr	Gln	Tyr	Ser	Lys	Val	Leu	Ala	Leu
	50					55					60				
Tyr	Asn	Gln	His	Asn	Pro	Gly	Ala	Ser	Ala	Ala	Pro	Cys	Cys	Val	Pro
65					70					75					80
Gln	Ala	Leu	Glu	Pro	Leu	Pro	Ile	Val	Tyr	Tyr	Val	Gly	Arg	Lys	Pro
				85					90					95	
Lys	Val	Glu	Gln	Leu	Ser	Asn	Met	Ile	Val	Arg	Ser	Cys	Lys	Cys	Ser
			100					105					110		
Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Thr
		115					120					125			
His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser
	130					135					140				
Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg
145					150					155					160
Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro
				165					170					175	
Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala
			180					185					190		
Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val
	195						200					205			
Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr
	210					215					220				
Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr
225					230					235					240
Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu
			245						250					255	
Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys
		260						265					270		
Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser
	275						280					285			
Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp
	290					295					300				
Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser
305					310					315					320
Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala
			325						330					335	
Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys
			340					345					350		
Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Ala
		355					360					365			
Pro	Thr	Ser	Ser	Ser	Thr	Lys	Lys	Thr	Gln	Leu	Gln	Leu	Glu	His	Leu
	370					375					380				
Leu	Leu	Asp	Leu	Gln	Met	Ile	Leu	Asn	Gly	Ile	Asn	Asn	Tyr	Lys	Asn
385					390				395						400
Pro	Lys	Leu	Thr	Arg	Met	Leu	Thr	Phe	Lys	Phe	Tyr	Met	Pro	Lys	Lys
			405						410					415	
Ala	Thr	Glu	Leu	Lys	His	Leu	Gln	Cys	Leu	Glu	Glu	Glu	Leu	Lys	Pro
			420					425					430		
Leu	Glu	Glu	Val	Leu	Asn	Leu	Ala	Gln	Ser	Lys	Asn	Phe	His	Leu	Arg
	435						440					445			
Pro	Arg	Asp	Leu	Ile	Ser	Asn	Ile	Asn	Val	Ile	Val	Leu	Glu	Leu	Lys

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450	455	460	
Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr			
465	470	475	480
Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe Cys Gln Ser Ile Ile			
	485	490	495
Ser Thr Leu Thr			
	500		
 <210> SEQ ID NO 57			
<211> LENGTH: 500			
<212> TYPE: PRT			
<213> ORGANISM: Homo sapiens			
 <400> SEQUENCE: 57			
Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His			
1	5	10	15
Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys			
	20	25	30
Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys			
	35	40	45
Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys			
	50	55	60
Pro Leu Glu Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu			
65	70	75	80
Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu			
	85	90	95
Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala			
	100	105	110
Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe Cys Gln Ser Ile			
	115	120	125
Ile Ser Thr Leu Thr Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly			
	130	135	140
Gly Gly Gly Ser Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu			
145	150	155	160
Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr			
	165	170	175
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val			
	180	185	190
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val			
	195	200	205
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser			
	210	215	220
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu			
225	230	235	240
Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala			
	245	250	255
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro			
	260	265	270
Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln			
	275	280	285
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala			
	290	295	300
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr			
305	310	315	320

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Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
 325 330 335

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
 340 345 350

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
 355 360 365

Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
 370 375 380

Gly Gly Gly Ser Ala Leu Asp Thr Asn Tyr Cys Phe Ser Ser Thr Glu
 385 390 395 400

Lys Asn Cys Cys Val Arg Gln Leu Tyr Ile Asp Phe Arg Lys Asp Leu
 405 410 415

Gly Trp Lys Trp Ile His Glu Pro Lys Gly Tyr His Ala Asn Phe Cys
 420 425 430

Leu Gly Pro Cys Pro Tyr Ile Trp Ser Leu Asp Thr Gln Tyr Ser Lys
 435 440 445

Val Leu Ala Leu Tyr Asn Gln His Asn Pro Gly Ala Ser Ala Ala Pro
 450 455 460

Cys Cys Val Pro Gln Ala Leu Glu Pro Leu Pro Ile Val Tyr Tyr Val
 465 470 475 480

Gly Arg Lys Pro Lys Val Glu Gln Leu Ser Asn Met Ile Val Arg Ser
 485 490 495

Cys Lys Cys Ser
 500

<210> SEQ ID NO 58

<211> LENGTH: 578

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 58

Gln Val Gln Leu Gln Glu Ala Gly Pro Gly Leu Val Lys Pro Ser Glu
 1 5 10 15

Thr Leu Ser Leu Thr Cys Ser Val Ser Gly Gly Ser Ile Ser Gly Asp
 20 25 30

Tyr Tyr Trp Phe Trp Ile Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp
 35 40 45

Ile Gly Tyr Ile Tyr Gly Ser Gly Gly Gly Thr Asn Tyr Asn Pro Ser
 50 55 60

Leu Asn Asn Arg Val Ser Ile Ser Ile Asp Thr Ser Lys Asn Leu Phe
 65 70 75 80

Ser Leu Lys Leu Arg Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
 85 90 95

Cys Ala Ser Asn Ile Leu Lys Tyr Leu His Trp Leu Leu Tyr Trp Gly
 100 105 110

Gln Gly Val Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
 115 120 125

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
 130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
 145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
 165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
 180 185 190

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Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
 195                200                205

Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
 210                215                220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
 225                230                235                240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
 245                250                255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
 260                265                270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
 275                280                285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
 290                295                300

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
 305                310                315                320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
 325                330                335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
 340                345                350

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
 355                360                365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
 370                375                380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
 385                390                395                400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
 405                410                415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
 420                425                430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
 435                440                445

Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
 450                455                460

Gly Ser Ala Leu Asp Thr Asn Tyr Cys Phe Ser Ser Thr Glu Lys Asn
 465                470                475                480

Cys Cys Val Arg Gln Leu Tyr Ile Asp Phe Arg Lys Asp Leu Gly Trp
 485                490                495

Lys Trp Ile His Glu Pro Lys Gly Tyr His Ala Asn Phe Cys Leu Gly
 500                505                510

Pro Cys Pro Tyr Ile Trp Ser Leu Asp Thr Gln Tyr Ser Lys Val Leu
 515                520                525

Ala Leu Tyr Asn Gln His Asn Pro Gly Ala Ser Ala Ala Pro Cys Cys
 530                535                540

Val Pro Gln Ala Leu Glu Pro Leu Pro Ile Val Tyr Tyr Val Gly Arg
 545                550                555                560

Lys Pro Lys Val Glu Gln Leu Ser Asn Met Ile Val Arg Ser Cys Lys
 565                570                575

Cys Ser

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<210> SEQ ID NO 59

<211> LENGTH: 510

<212> TYPE: PRT

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 59

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Met Gly Val Leu Leu Thr Gln Arg Thr Leu Leu Ser Leu Val Leu Ala
1      5      10      15
Leu Leu Phe Pro Ser Met Ala Ser Met Ala Met His Val Ala Gln Pro
20      25      30
Ala Val Val Leu Ala Ser Ser Arg Gly Ile Ala Ser Phe Val Cys Glu
35      40      45
Tyr Ala Ser Pro Gly Lys Ala Thr Glu Val Arg Val Thr Val Leu Arg
50      55      60
Gln Ala Asp Ser Gln Val Thr Glu Val Cys Ala Ala Thr Tyr Met Met
65      70      75      80
Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser Ile Cys Thr Gly Thr Ser
85      90      95
Ser Gly Asn Gln Val Asn Leu Thr Ile Gln Gly Leu Arg Ala Met Asp
100     105     110
Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu Met Tyr Pro Pro Pro Tyr
115     120     125
Tyr Leu Gly Ile Gly Asn Gly Thr Gln Ile Tyr Val Ile Asp Pro Glu
130     135     140
Pro Cys Pro Asp Ser Asp Gln Glu Pro Lys Ser Cys Asp Lys Thr His
145     150     155     160
Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
165     170     175
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
180     185     190
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
195     200     205
Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
210     215     220
Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
225     230     235     240
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
245     250     255
Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
260     265     270
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
275     280     285
Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
290     295     300
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
305     310     315     320
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
325     330     335
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
340     345     350
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
355     360     365
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly
370     375     380
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Ala Leu
385     390     395     400

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Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
 275 280 285
 Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
 290 295 300
 Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
 305 310 315 320
 Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
 325 330 335
 Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly
 340 345 350
 Gly Ser Gly Gly Gly Gly Ser Ala Met His Val Ala Gln Pro Ala Val
 355 360 365
 Val Leu Ala Ser Ser Arg Gly Ile Ala Ser Phe Val Cys Glu Tyr Ala
 370 375 380
 Ser Pro Gly Lys Ala Thr Glu Val Arg Val Thr Val Leu Arg Gln Ala
 385 390 395 400
 Asp Ser Gln Val Thr Glu Val Cys Ala Ala Thr Tyr Met Met Gly Asn
 405 410 415
 Glu Leu Thr Phe Leu Asp Asp Ser Ile Cys Thr Gly Thr Ser Ser Gly
 420 425 430
 Asn Gln Val Asn Leu Thr Ile Gln Gly Leu Arg Ala Met Asp Thr Gly
 435 440 445
 Leu Tyr Ile Cys Lys Val Glu Leu Met Tyr Pro Pro Pro Tyr Tyr Leu
 450 455 460
 Gly Ile Gly Asn Gly Thr Gln Ile Tyr Val Ile Asp Pro Glu Pro Cys
 465 470 475 480
 Pro Asp Ser Asp

<210> SEQ ID NO 61
 <211> LENGTH: 651
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 61

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
 20 25 30
 Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Thr Trp Asn Ser Gly His Ile Asp Tyr Ala Asp Ser Val
 50 55 60
 Glu Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Leu Val Ser Tyr Leu Ser Thr Ala Ser Ser Leu Asp Tyr Trp Gly
 100 105 110
 Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
 115 120 125
 Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
 130 135 140
 Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
 145 150 155 160

Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala
				165						170		175			
Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val
				180						185		190			
Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His
				195						200		205			
Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Ala	Glu	Pro	Lys	Ser	Cys
				210						215		220			
Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly
				225						230		235			
Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met
				245						250		255			
Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His
				260						265		270			
Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val
				275						280		285			
His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr
				290						295		300			
Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly
				305						310		315			
Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile
				325						330		335			
Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val
				340						345		350			
Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser
				355						360		365			
Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu
				370						375		380			
Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro
				385						390		395			
Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val
				405						410		415			
Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met
				420						425		430			
His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser
				435						440		445			
Pro	Gly	Lys	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly
				450						455		460			
Gly	Ser	Gln	Ile	Ala	Pro	Pro	Cys	Thr	Ser	Glu	Lys	His	Tyr	Glu	His
				465						470		475			
Leu	Gly	Arg	Cys	Cys	Asn	Lys	Cys	Glu	Pro	Gly	Lys	Tyr	Met	Ser	Ser
				485						490		495			
Lys	Cys	Thr	Thr	Thr	Ser	Asp	Ser	Val	Cys	Leu	Pro	Cys	Gly	Pro	Asp
				500						505		510			
Glu	Tyr	Leu	Asp	Ser	Trp	Asn	Glu	Glu	Asp	Lys	Cys	Leu	Leu	His	Lys
				515						520		525			
Val	Cys	Asp	Thr	Gly	Lys	Ala	Leu	Val	Ala	Val	Val	Ala	Gly	Asn	Ser
				530						535		540			
Thr	Thr	Pro	Arg	Arg	Cys	Ala	Cys	Thr	Ala	Gly	Tyr	His	Trp	Ser	Gln
				545						550		555			
Asp	Cys	Glu	Cys	Cys	Arg	Arg	Asn	Thr	Glu	Cys	Ala	Pro	Gly	Leu	Gly
				565						570		575			

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Ala Gln His Pro Leu Gln Leu Asn Lys Asp Thr Val Cys Lys Pro Cys
 580 585 590

Leu Ala Gly Tyr Phe Ser Asp Ala Phe Ser Ser Thr Asp Lys Cys Arg
 595 600 605

Pro Trp Thr Asn Cys Thr Phe Leu Gly Lys Arg Val Glu His His Gly
 610 615 620

Thr Glu Lys Ser Asp Ala Val Cys Ser Ser Ser Leu Pro Ala Arg Lys
 625 630 635 640

Pro Pro Asn Glu Pro His Val Tyr Leu Pro Gly
 645 650

<210> SEQ ID NO 62
 <211> LENGTH: 667
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 62

Leu Pro Ala Gln Val Ala Phe Thr Pro Tyr Ala Pro Glu Pro Gly Ser
 1 5 10 15

Thr Cys Arg Leu Arg Glu Tyr Tyr Asp Gln Thr Ala Gln Met Cys Cys
 20 25 30

Ser Lys Cys Ser Pro Gly Gln His Ala Lys Val Phe Cys Thr Lys Thr
 35 40 45

Ser Asp Thr Val Cys Asp Ser Cys Glu Asp Ser Thr Tyr Thr Gln Leu
 50 55 60

Trp Asn Trp Val Pro Glu Cys Leu Ser Cys Gly Ser Arg Cys Ser Ser
 65 70 75 80

Asp Gln Val Glu Thr Gln Ala Cys Thr Arg Glu Gln Asn Arg Ile Cys
 85 90 95

Thr Cys Arg Pro Gly Trp Tyr Cys Ala Leu Ser Lys Gln Glu Gly Cys
 100 105 110

Arg Leu Cys Ala Pro Leu Arg Lys Cys Arg Pro Gly Phe Gly Val Ala
 115 120 125

Arg Pro Gly Thr Glu Thr Ser Asp Val Val Cys Lys Pro Cys Ala Pro
 130 135 140

Gly Thr Phe Ser Asn Thr Thr Ser Ser Thr Asp Ile Cys Arg Pro His
 145 150 155 160

Gln Ile Cys Asn Val Val Ala Ile Pro Gly Asn Ala Ser Met Asp Ala
 165 170 175

Val Cys Thr Ser Thr Ser Pro Thr Arg Ser Met Ala Pro Gly Ala Val
 180 185 190

His Leu Pro Gln Pro Val Ser Thr Arg Ser Gln His Thr Gln Pro Thr
 195 200 205

Pro Glu Pro Ser Thr Ala Pro Ser Thr Ser Phe Leu Leu Pro Met Gly
 210 215 220

Pro Ser Pro Pro Ala Glu Gly Ser Thr Gly Asp 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

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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 Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
 465 470 475 480
 Gly Ser Gln Ile Ala Pro Pro Cys Thr Ser Glu Lys His Tyr Glu His
 485 490 495
 Leu Gly Arg Cys Cys Asn Lys Cys Glu Pro Gly Lys Tyr Met Ser Ser
 500 505 510
 Lys Cys Thr Thr Thr Ser Asp Ser Val Cys Leu Pro Cys Gly Pro Asp
 515 520 525
 Glu Tyr Leu Asp Ser Trp Asn Glu Glu Asp Lys Cys Leu Leu His Lys
 530 535 540
 Val Cys Asp Thr Gly Lys Ala Leu Val Ala Val Val Ala Gly Asn Ser
 545 550 555 560
 Thr Thr Pro Arg Arg Cys Ala Cys Thr Ala Gly Tyr His Trp Ser Gln
 565 570 575
 Asp Cys Glu Cys Cys Arg Arg Asn Thr Glu Cys Ala Pro Gly Leu Gly
 580 585 590
 Ala Gln His Pro Leu Gln Leu Asn Lys Asp Thr Val Cys Lys Pro Cys
 595 600 605
 Leu Ala Gly Tyr Phe Ser Asp Ala Phe Ser Ser Thr Asp Lys Cys Arg
 610 615 620
 Pro Trp Thr Asn Cys Thr Phe Leu Gly Lys Arg Val Glu His His Gly
 625 630 635 640
 Thr Glu Lys Ser Asp Ala Val Cys Ser Ser Ser Leu Pro Ala Arg Lys
 645 650 655
 Pro Pro Asn Glu Pro His Val Tyr Leu Pro Gly
 660 665

<210> SEQ ID NO 63

<211> LENGTH: 675

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 63

Gln Ile Ala Pro Pro Cys Thr Ser Glu Lys His Tyr Glu His Leu Gly

-continued

1	5	10	15
Arg Cys Cys Asn Lys Cys Glu Pro Gly Lys Tyr Met Ser Ser Lys Cys	20	25	30
Thr Thr Thr Ser Asp Ser Val Cys Leu Pro Cys Gly Pro Asp Glu Tyr	35	40	45
Leu Asp Ser Trp Asn Glu Glu Asp Lys Cys Leu Leu His Lys Val Cys	50	55	60
Asp Thr Gly Lys Ala Leu Val Ala Val Val Ala Gly Asn Ser Thr Thr	65	70	75
Pro Arg Arg Cys Ala Cys Thr Ala Gly Tyr His Trp Ser Gln Asp Cys	85	90	95
Glu Cys Cys Arg Arg Asn Thr Glu Cys Ala Pro Gly Leu Gly Ala Gln	100	105	110
His Pro Leu Gln Leu Asn Lys Asp Thr Val Cys Lys Pro Cys Leu Ala	115	120	125
Gly Tyr Phe Ser Asp Ala Phe Ser Ser Thr Asp Lys Cys Arg Pro Trp	130	135	140
Thr Asn Cys Thr Phe Leu Gly Lys Arg Val Glu His His Gly Thr Glu	145	150	155
Lys Ser Asp Ala Val Cys Ser Ser Ser Leu Pro Ala Arg Lys Pro Pro	165	170	175
Asn Glu Pro His Val Tyr Leu Pro Gly Gly Gly Gly Ser Gly Gly	180	185	190
Gly Gly Ser Gly Gly Gly Gly Ser Thr His Thr Cys Pro Pro Cys Pro	195	200	205
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys	210	215	220
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val	225	230	235
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr	245	250	255
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu	260	265	270
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His	275	280	285
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys	290	295	300
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln	305	310	315
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met	325	330	335
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro	340	345	350
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn	355	360	365
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu	370	375	380
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val	385	390	395
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln	405	410	415
Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly	420	425	430

-continued

Gly Gly Ser Gly Gly Gly Gly Ser Leu Pro Ala Gln Val Ala Phe Thr
 435 440 445
 Pro Tyr Ala Pro Glu Pro Gly Ser Thr Cys Arg Leu Arg Glu Tyr Tyr
 450 455 460
 Asp Gln Thr Ala Gln Met Cys Cys Ser Lys Cys Ser Pro Gly Gln His
 465 470 475 480
 Ala Lys Val Phe Cys Thr Lys Thr Ser Asp Thr Val Cys Asp Ser Cys
 485 490 495
 Glu Asp Ser Thr Tyr Thr Gln Leu Trp Asn Trp Val Pro Glu Cys Leu
 500 505 510
 Ser Cys Gly Ser Arg Cys Ser Ser Asp Gln Val Glu Thr Gln Ala Cys
 515 520 525
 Thr Arg Glu Gln Asn Arg Ile Cys Thr Cys Arg Pro Gly Trp Tyr Cys
 530 535 540
 Ala Leu Ser Lys Gln Glu Gly Cys Arg Leu Cys Ala Pro Leu Arg Lys
 545 550 555 560
 Cys Arg Pro Gly Phe Gly Val Ala Arg Pro Gly Thr Glu Thr Ser Asp
 565 570 575
 Val Val Cys Lys Pro Cys Ala Pro Gly Thr Phe Ser Asn Thr Thr Ser
 580 585 590
 Ser Thr Asp Ile Cys Arg Pro His Gln Ile Cys Asn Val Val Ala Ile
 595 600 605
 Pro Gly Asn Ala Ser Met Asp Ala Val Cys Thr Ser Thr Ser Pro Thr
 610 615 620
 Arg Ser Met Ala Pro Gly Ala Val His Leu Pro Gln Pro Val Ser Thr
 625 630 635 640
 Arg Ser Gln His Thr Gln Pro Thr Pro Glu Pro Ser Thr Ala Pro Ser
 645 650 655
 Thr Ser Phe Leu Leu Pro Met Gly Pro Ser Pro Pro Ala Glu Gly Ser
 660 665 670
 Thr Gly Asp
 675

<210> SEQ ID NO 64
 <211> LENGTH: 583
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 64

Met Gly Val Leu Leu Thr Gln Arg Thr Leu Leu Ser Leu Val Leu Ala
 1 5 10 15
 Leu Leu Phe Pro Ser Met Ala Ser Met Ala Met His Val Ala Gln Pro
 20 25 30
 Ala Val Val Leu Ala Ser Ser Arg Gly Ile Ala Ser Phe Val Cys Glu
 35 40 45
 Tyr Ala Ser Pro Gly Lys Ala Thr Glu Val Arg Val Thr Val Leu Arg
 50 55 60
 Gln Ala Asp Ser Gln Val Thr Glu Val Cys Ala Ala Thr Tyr Met Met
 65 70 75 80
 Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser Ile Cys Thr Gly Thr Ser
 85 90 95
 Ser Gly Asn Gln Val Asn Leu Thr Ile Gln Gly Leu Arg Ala Met Asp
 100 105 110
 Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu Met Tyr Pro Pro Pro Tyr

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115					120					125					
Tyr	Leu	Gly	Ile	Gly	Asn	Gly	Thr	Gln	Ile	Tyr	Val	Ile	Asp	Pro	Glu
130						135					140				
Pro	Cys	Pro	Asp	Ser	Asp	Gln	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His
145					150					155					160
Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val
				165					170					175	
Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr
			180					185					190		
Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu
	195						200					205			
Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys
210						215						220			
Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser
225					230						235				240
Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys
				245					250					255	
Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile
			260					265						270	
Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro
		275					280					285			
Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu
		290				295						300			
Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn
305					310					315					320
Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser
				325					330					335	
Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg
			340					345					350		
Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu
		355				360						365			
His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys	Gly
	370					375						380			
Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gln	Ile
385					390					395					400
Ala	Pro	Pro	Cys	Thr	Ser	Glu	Lys	His	Tyr	Glu	His	Leu	Gly	Arg	Cys
			405						410					415	
Cys	Asn	Lys	Cys	Glu	Pro	Gly	Lys	Tyr	Met	Ser	Ser	Lys	Cys	Thr	Thr
			420					425					430		
Thr	Ser	Asp	Ser	Val	Cys	Leu	Pro	Cys	Gly	Pro	Asp	Glu	Tyr	Leu	Asp
		435					440					445			
Ser	Trp	Asn	Glu	Glu	Asp	Lys	Cys	Leu	Leu	His	Lys	Val	Cys	Asp	Thr
	450					455					460				
Gly	Lys	Ala	Leu	Val	Ala	Val	Val	Ala	Gly	Asn	Ser	Thr	Thr	Pro	Arg
465				470					475						480
Arg	Cys	Ala	Cys	Thr	Ala	Gly	Tyr	His	Trp	Ser	Gln	Asp	Cys	Glu	Cys
			485					490						495	
Cys	Arg	Arg	Asn	Thr	Glu	Cys	Ala	Pro	Gly	Leu	Gly	Ala	Gln	His	Pro
			500					505					510		
Leu	Gln	Leu	Asn	Lys	Asp	Thr	Val	Cys	Lys	Pro	Cys	Leu	Ala	Gly	Tyr
		515					520					525			
Phe	Ser	Asp	Ala	Phe	Ser	Ser	Thr	Asp	Lys	Cys	Arg	Pro	Trp	Thr	Asn
		530				535					540				

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Cys Thr Phe Leu Gly Lys Arg Val Glu His His Gly Thr Glu Lys Ser
545 550 555 560

Asp Ala Val Cys Ser Ser Ser Leu Pro Ala Arg Lys Pro Pro Asn Glu
565 570 575

Pro His Val Tyr Leu Pro Gly
580

<210> SEQ ID NO 65
<211> LENGTH: 557
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 65

Gln Ile Ala Pro Pro Cys Thr Ser Glu Lys His Tyr Glu His Leu Gly
1 5 10 15

Arg Cys Cys Asn Lys Cys Glu Pro Gly Lys Tyr Met Ser Ser Lys Cys
20 25 30

Thr Thr Thr Ser Asp Ser Val Cys Leu Pro Cys Gly Pro Asp Glu Tyr
35 40 45

Leu Asp Ser Trp Asn Glu Glu Asp Lys Cys Leu Leu His Lys Val Cys
50 55 60

Asp Thr Gly Lys Ala Leu Val Ala Val Val Ala Gly Asn Ser Thr Thr
65 70 75 80

Pro Arg Arg Cys Ala Cys Thr Ala Gly Tyr His Trp Ser Gln Asp Cys
85 90 95

Glu Cys Cys Arg Arg Asn Thr Glu Cys Ala Pro Gly Leu Gly Ala Gln
100 105 110

His Pro Leu Gln Leu Asn Lys Asp Thr Val Cys Lys Pro Cys Leu Ala
115 120 125

Gly Tyr Phe Ser Asp Ala Phe Ser Ser Thr Asp Lys Cys Arg Pro Trp
130 135 140

Thr Asn Cys Thr Phe Leu Gly Lys Arg Val Glu His His Gly Thr Glu
145 150 155 160

Lys Ser Asp Ala Val Cys Ser Ser Ser Leu Pro Ala Arg Lys Pro Pro
165 170 175

Asn Glu Pro His Val Tyr Leu Pro Gly Glu Pro Lys Ser Cys Asp Lys
180 185 190

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
195 200 205

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
210 215 220

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
225 230 235 240

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
245 250 255

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
260 265 270

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
275 280 285

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
290 295 300

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
305 310 315 320

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr

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325					330					335					
Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
			340					345					350		
Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
		355					360					365			
Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys
	370					375					380				
Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
	385			390						395				400	
Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly
			405					410						415	
Lys	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser
		420					425					430			
Ala	Met	His	Val	Ala	Gln	Pro	Ala	Val	Val	Leu	Ala	Ser	Ser	Arg	Gly
	435					440					445				
Ile	Ala	Ser	Phe	Val	Cys	Glu	Tyr	Ala	Ser	Pro	Gly	Lys	Ala	Thr	Glu
	450					455					460				
Val	Arg	Val	Thr	Val	Leu	Arg	Gln	Ala	Asp	Ser	Gln	Val	Thr	Glu	Val
	465			470					475					480	
Cys	Ala	Ala	Thr	Tyr	Met	Met	Gly	Asn	Glu	Leu	Thr	Phe	Leu	Asp	Asp
			485					490						495	
Ser	Ile	Cys	Thr	Gly	Thr	Ser	Ser	Gly	Asn	Gln	Val	Asn	Leu	Thr	Ile
		500					505					510			
Gln	Gly	Leu	Arg	Ala	Met	Asp	Thr	Gly	Leu	Tyr	Ile	Cys	Lys	Val	Glu
	515					520					525				
Leu	Met	Tyr	Pro	Pro	Pro	Tyr	Tyr	Leu	Gly	Ile	Gly	Asn	Gly	Thr	Gln
	530					535			540						
Ile	Tyr	Val	Ile	Asp	Pro	Glu	Pro	Cys	Pro	Asp	Ser	Asp			
	545			550				555							

<210> SEQ ID NO 66

<211> LENGTH: 552

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 66

Ala	Leu	Asp	Thr	Asn	Tyr	Cys	Phe	Ser	Ser	Thr	Glu	Lys	Asn	Cys	Cys
1				5					10				15		
Val	Arg	Gln	Leu	Tyr	Ile	Asp	Phe	Arg	Lys	Asp	Leu	Gly	Trp	Lys	Trp
		20					25					30			
Ile	His	Glu	Pro	Lys	Gly	Tyr	His	Ala	Asn	Phe	Cys	Leu	Gly	Pro	Cys
	35					40					45				
Pro	Tyr	Ile	Trp	Ser	Leu	Asp	Thr	Gln	Tyr	Ser	Lys	Val	Leu	Ala	Leu
	50			55						60					
Tyr	Asn	Gln	His	Asn	Pro	Gly	Ala	Ser	Ala	Ala	Pro	Cys	Cys	Val	Pro
	65			70				75						80	
Gln	Ala	Leu	Glu	Pro	Leu	Pro	Ile	Val	Tyr	Val	Gly	Arg	Lys	Pro	
		85				90						95			
Lys	Val	Glu	Gln	Leu	Ser	Asn	Met	Ile	Val	Arg	Ser	Cys	Lys	Cys	Ser
	100					105						110			
Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Thr
	115					120					125				
His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser
	130				135						140				

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Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg
145					150					155					160
Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro
			165						170					175	
Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala
			180					185					190		
Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val
	195						200					205			
Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr
	210					215					220				
Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr
225					230					235					240
Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu
			245						250					255	
Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys
			260					265					270		
Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser
	275						280					285			
Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp
	290					295					300				
Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser
305				310						315				320	
Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala
			325					330						335	
Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys
		340					345						350		
Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gln
	355					360						365			
Ile	Ala	Pro	Pro	Cys	Thr	Ser	Glu	Lys	His	Tyr	Glu	His	Leu	Gly	Arg
	370					375					380				
Cys	Cys	Asn	Lys	Cys	Glu	Pro	Gly	Lys	Tyr	Met	Ser	Ser	Lys	Cys	Thr
385				390						395					400
Thr	Thr	Ser	Asp	Ser	Val	Cys	Leu	Pro	Cys	Gly	Pro	Asp	Glu	Tyr	Leu
			405						410					415	
Asp	Ser	Trp	Asn	Glu	Glu	Asp	Lys	Cys	Leu	Leu	His	Lys	Val	Cys	Asp
			420				425						430		
Thr	Gly	Lys	Ala	Leu	Val	Ala	Val	Val	Ala	Gly	Asn	Ser	Thr	Thr	Pro
	435					440						445			
Arg	Arg	Cys	Ala	Cys	Thr	Ala	Gly	Tyr	His	Trp	Ser	Gln	Asp	Cys	Glu
	450					455					460				
Cys	Cys	Arg	Arg	Asn	Thr	Glu	Cys	Ala	Pro	Gly	Leu	Gly	Ala	Gln	His
465				470					475					480	
Pro	Leu	Gln	Leu	Asn	Lys	Asp	Thr	Val	Cys	Lys	Pro	Cys	Leu	Ala	Gly
			485					490					495		
Tyr	Phe	Ser	Asp	Ala	Phe	Ser	Ser	Thr	Asp	Lys	Cys	Arg	Pro	Trp	Thr
		500						505					510		
Asn	Cys	Thr	Phe	Leu	Gly	Lys	Arg	Val	Glu	His	His	Gly	Thr	Glu	Lys
		515					520					525			
Ser	Asp	Ala	Val	Cys	Ser	Ser	Ser	Leu	Pro	Ala	Arg	Lys	Pro	Pro	Asn
	530						535				540				
Glu	Pro	His	Val	Tyr	Leu	Pro	Gly								
545					550										

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<210> SEQ ID NO 67
<211> LENGTH: 552
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 67

Gln Ile Ala Pro Pro Cys Thr Ser Glu Lys His Tyr Glu His Leu Gly
1          5          10          15
Arg Cys Cys Asn Lys Cys Glu Pro Gly Lys Tyr Met Ser Ser Lys Cys
20          25          30
Thr Thr Thr Ser Asp Ser Val Cys Leu Pro Cys Gly Pro Asp Glu Tyr
35          40          45
Leu Asp Ser Trp Asn Glu Glu Asp Lys Cys Leu Leu His Lys Val Cys
50          55          60
Asp Thr Gly Lys Ala Leu Val Ala Val Val Ala Gly Asn Ser Thr Thr
65          70          75          80
Pro Arg Arg Cys Ala Cys Thr Ala Gly Tyr His Trp Ser Gln Asp Cys
85          90          95
Glu Cys Cys Arg Arg Asn Thr Glu Cys Ala Pro Gly Leu Gly Ala Gln
100         105         110
His Pro Leu Gln Leu Asn Lys Asp Thr Val Cys Lys Pro Cys Leu Ala
115         120         125
Gly Tyr Phe Ser Asp Ala Phe Ser Ser Thr Asp Lys Cys Arg Pro Trp
130         135         140
Thr Asn Cys Thr Phe Leu Gly Lys Arg Val Glu His His Gly Thr Glu
145         150         155         160
Lys Ser Asp Ala Val Cys Ser Ser Ser Leu Pro Ala Arg Lys Pro Pro
165         170         175
Asn Glu Pro His Val Tyr Leu Pro Gly Gly Gly Gly Gly Ser Gly Gly
180         185         190
Gly Gly Ser Gly Gly Gly Gly Ser Thr His Thr Cys Pro Pro Cys Pro
195         200         205
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
210         215         220
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
225         230         235         240
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
245         250         255
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
260         265         270
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
275         280         285
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
290         295         300
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
305         310         315         320
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
325         330         335
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
340         345         350
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
355         360         365
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
370         375         380

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Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
 385 390 395 400
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
 405 410 415
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly
 420 425 430
 Gly Gly Ser Gly Gly Gly Gly Ser Ala Leu Asp Thr Asn Tyr Cys Phe
 435 440 445
 Ser Ser Thr Glu Lys Asn Cys Cys Val Arg Gln Leu Tyr Ile Asp Phe
 450 455 460
 Arg Lys Asp Leu Gly Trp Lys Trp Ile His Glu Pro Lys Gly Tyr His
 465 470 475 480
 Ala Asn Phe Cys Leu Gly Pro Cys Pro Tyr Ile Trp Ser Leu Asp Thr
 485 490 495
 Gln Tyr Ser Lys Val Leu Ala Leu Tyr Asn Gln His Asn Pro Gly Ala
 500 505 510
 Ser Ala Ala Pro Cys Cys Val Pro Gln Ala Leu Glu Pro Leu Pro Ile
 515 520 525
 Val Tyr Tyr Val Gly Arg Lys Pro Lys Val Glu Gln Leu Ser Asn Met
 530 535 540
 Ile Val Arg Ser Cys Lys Cys Ser
 545 550

<210> SEQ ID NO 68

<211> LENGTH: 729

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 68

Arg Ile Phe Ala Val Phe Ile Phe Met Thr Tyr Trp His Leu Leu Asn
 1 5 10 15
 Ala Phe Thr Val Thr Val Pro Lys Asp Leu Tyr Val Val Glu Tyr Gly
 20 25 30
 Ser Asn Met Thr Ile Glu Cys Lys Phe Pro Val Glu Lys Gln Leu Asp
 35 40 45
 Leu Ala Ala Leu Ile Val Tyr Trp Glu Met Glu Asp Lys Asn Ile Ile
 50 55 60
 Gln Phe Val His Gly Glu Asp Leu Lys Val Gln His Ser Ser Tyr
 65 70 75 80
 Arg Gln Arg Ala Arg Leu Leu Lys Asp Gln Leu Ser Leu Gly Asn Ala
 85 90 95
 Ala Leu Gln Ile Thr Asp Val Lys Leu Gln Asp Ala Gly Val Tyr Arg
 100 105 110
 Cys Met Ile Ser Tyr Gly Gly Ala Asp Tyr Lys Arg Ile Thr Val Lys
 115 120 125
 Val Asn Ala Pro Tyr Asn Lys Ile Asn Gln Arg Ile Leu Val Val Asp
 130 135 140
 Pro Val Thr Ser Glu His Glu Leu Thr Cys Gln Ala Glu Gly Tyr Pro
 145 150 155 160
 Lys Ala Glu Val Ile Trp Thr Ser Ser Asp His Gln Val Leu Ser Gly
 165 170 175
 Lys Thr Thr Thr Thr Asn Ser Lys Arg Glu Glu Lys Leu Phe Asn Val
 180 185 190
 Thr Ser Thr Leu Arg Ile Asn Thr Thr Thr Asn Glu Ile Phe Tyr Cys
 195 200 205

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Thr	Phe	Arg	Arg	Leu	Asp	Pro	Glu	Glu	Asn	His	Thr	Ala	Glu	Leu	Val
210						215					220				
Ile	Pro	Glu	Leu	Pro	Leu	Ala	His	Pro	Pro	Asn	Glu	Arg	Thr	His	Leu
225					230					235					240
Val	Ile	Leu	Gly	Ala	Ile	Leu	Leu	Cys	Leu	Gly	Val	Ala	Leu	Thr	Phe
			245						250					255	
Ile	Phe	Arg	Leu	Arg	Lys	Gly	Arg	Met	Met	Asp	Val	Lys	Lys	Cys	Gly
			260					265					270		
Ile	Gln	Asp	Thr	Asn	Ser	Lys	Lys	Gln	Ser	Asp	Thr	His	Leu	Glu	Glu
		275					280					285			
Thr	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser
	290					295					300				
Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro
305					310					315					320
Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
			325						330					335	
Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp
			340					345					350		
Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
	355					360						365			
Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val
	370					375					380				
Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
385					390					395					400
Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys
			405						410					415	
Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
			420					425					430		
Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
		435					440					445			
Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
	450					455					460				
Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
465					470					475					480
Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys
			485						490					495	
Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
			500					505					510		
Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly
		515					520					525			
Lys	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser
	530					535					540				
Gln	Ile	Ala	Pro	Pro	Cys	Thr	Ser	Glu	Lys	His	Tyr	Glu	His	Leu	Gly
545					550					555					560
Arg	Cys	Cys	Asn	Lys	Cys	Glu	Pro	Gly	Lys	Tyr	Met	Ser	Ser	Lys	Cys
			565						570					575	
Thr	Thr	Thr	Ser	Asp	Ser	Val	Cys	Leu	Pro	Cys	Gly	Pro	Asp	Glu	Tyr
			580					585					590		
Leu	Asp	Ser	Trp	Asn	Glu	Glu	Asp	Lys	Cys	Leu	Leu	His	Lys	Val	Cys
		595					600					605			
Asp	Thr	Gly	Lys	Ala	Leu	Val	Ala	Val	Val	Ala	Gly	Asn	Ser	Thr	Thr
	610					615					620				

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Pro Arg Arg Cys Ala Cys Thr Ala Gly Tyr His Trp Ser Gln Asp Cys
625 630 635 640

Glu Cys Cys Arg Arg Asn Thr Glu Cys Ala Pro Gly Leu Gly Ala Gln
645 650 655

His Pro Leu Gln Leu Asn Lys Asp Thr Val Cys Lys Pro Cys Leu Ala
660 665 670

Gly Tyr Phe Ser Asp Ala Phe Ser Ser Thr Asp Lys Cys Arg Pro Trp
675 680 685

Thr Asn Cys Thr Phe Leu Gly Lys Arg Val Glu His His Gly Thr Glu
690 695 700

Lys Ser Asp Ala Val Cys Ser Ser Ser Leu Pro Ala Arg Lys Pro Pro
705 710 715 720

Asn Glu Pro His Val Tyr Leu Pro Gly
725

<210> SEQ ID NO 69
 <211> LENGTH: 729
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 69

Gln Ile Ala Pro Pro Cys Thr Ser Glu Lys His Tyr Glu His Leu Gly
1 5 10 15

Arg Cys Cys Asn Lys Cys Glu Pro Gly Lys Tyr Met Ser Ser Lys Cys
20 25 30

Thr Thr Thr Ser Asp Ser Val Cys Leu Pro Cys Gly Pro Asp Glu Tyr
35 40 45

Leu Asp Ser Trp Asn Glu Glu Asp Lys Cys Leu Leu His Lys Val Cys
50 55 60

Asp Thr Gly Lys Ala Leu Val Ala Val Val Ala Gly Asn Ser Thr Thr
65 70 75 80

Pro Arg Arg Cys Ala Cys Thr Ala Gly Tyr His Trp Ser Gln Asp Cys
85 90 95

Glu Cys Cys Arg Arg Asn Thr Glu Cys Ala Pro Gly Leu Gly Ala Gln
100 105 110

His Pro Leu Gln Leu Asn Lys Asp Thr Val Cys Lys Pro Cys Leu Ala
115 120 125

Gly Tyr Phe Ser Asp Ala Phe Ser Ser Thr Asp Lys Cys Arg Pro Trp
130 135 140

Thr Asn Cys Thr Phe Leu Gly Lys Arg Val Glu His His Gly Thr Glu
145 150 155 160

Lys Ser Asp Ala Val Cys Ser Ser Ser Leu Pro Ala Arg Lys Pro Pro
165 170 175

Asn Glu Pro His Val Tyr Leu Pro Gly Gly Gly Gly Ser Gly Gly
180 185 190

Gly Gly Ser Gly Gly Gly Gly Ser Thr His Thr Cys Pro Pro Cys Pro
195 200 205

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
210 215 220

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
225 230 235 240

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
245 250 255

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
260 265 270

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Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
 275 280 285
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
 290 295 300
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
 305 310 315 320
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
 325 330 335
 Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
 340 345 350
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
 355 360 365
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
 370 375 380
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
 385 390 395 400
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
 405 410 415
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly
 420 425 430
 Gly Gly Ser Gly Gly Gly Gly Ser Arg Ile Phe Ala Val Phe Ile Phe
 435 440 445
 Met Thr Tyr Trp His Leu Leu Asn Ala Phe Thr Val Thr Val Pro Lys
 450 455 460
 Asp Leu Tyr Val Val Glu Tyr Gly Ser Asn Met Thr Ile Glu Cys Lys
 465 470 475 480
 Phe Pro Val Glu Lys Gln Leu Asp Leu Ala Ala Leu Ile Val Tyr Trp
 485 490 495
 Glu Met Glu Asp Lys Asn Ile Ile Gln Phe Val His Gly Glu Glu Asp
 500 505 510
 Leu Lys Val Gln His Ser Ser Tyr Arg Gln Arg Ala Arg Leu Leu Lys
 515 520 525
 Asp Gln Leu Ser Leu Gly Asn Ala Ala Leu Gln Ile Thr Asp Val Lys
 530 535 540
 Leu Gln Asp Ala Gly Val Tyr Arg Cys Met Ile Ser Tyr Gly Gly Ala
 545 550 555 560
 Asp Tyr Lys Arg Ile Thr Val Lys Val Asn Ala Pro Tyr Asn Lys Ile
 565 570 575
 Asn Gln Arg Ile Leu Val Val Asp Pro Val Thr Ser Glu His Glu Leu
 580 585 590
 Thr Cys Gln Ala Glu Gly Tyr Pro Lys Ala Glu Val Ile Trp Thr Ser
 595 600 605
 Ser Asp His Gln Val Leu Ser Gly Lys Thr Thr Thr Asn Ser Lys
 610 615 620
 Arg Glu Glu Lys Leu Phe Asn Val Thr Ser Thr Leu Arg Ile Asn Thr
 625 630 635 640
 Thr Thr Asn Glu Ile Phe Tyr Cys Thr Phe Arg Arg Leu Asp Pro Glu
 645 650 655
 Glu Asn His Thr Ala Glu Leu Val Ile Pro Glu Leu Pro Leu Ala His
 660 665 670
 Pro Pro Asn Glu Arg Thr His Leu Val Ile Leu Gly Ala Ile Leu Leu
 675 680 685

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Cys Leu Gly Val Ala Leu Thr Phe Ile Phe Arg Leu Arg Lys Gly Arg
690 695 700

Met Met Asp Val Lys Lys Cys Gly Ile Gln Asp Thr Asn Ser Lys Lys
705 710 715 720

Gln Ser Asp Thr His Leu Glu Glu Thr
725

<210> SEQ ID NO 70

<211> LENGTH: 214

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 70

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Asn Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> SEQ ID NO 71

<211> LENGTH: 214

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 71

Asp Ile Leu Leu Thr Gln Ser Pro Val Ile Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Val Ser Phe Ser Cys Arg Ala Ser Gln Ser Ile Gly Thr Asn
20 25 30

Ile His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile
35 40 45

Lys Tyr Ala Ser Glu Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
50 55 60

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Ser Gly Ser Gly Thr Asp Phe Thr Leu Ser Ile Asn Ser Val Glu Ser
 65 70 75 80
 Glu Asp Ile Ala Asp Tyr Tyr Cys Gln Gln Asn Asn Asn Trp Pro Thr
 85 90 95
 Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr Val Ala Ala
 100 105 110
 Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
 115 120 125
 Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
 130 135 140
 Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
 145 150 155 160
 Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
 165 170 175
 Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
 180 185 190
 Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
 195 200 205
 Phe Asn Arg Gly Glu Cys
 210

<210> SEQ ID NO 72
 <211> LENGTH: 213
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 72

Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
 1 5 10 15
 Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Ile
 20 25 30
 His Trp Phe Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
 35 40 45
 Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Val Arg Phe Ser Gly Ser
 50 55 60
 Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
 65 70 75 80
 Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Thr Ser Asn Pro Pro Thr
 85 90 95
 Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro
 100 105 110
 Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
 115 120 125
 Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
 130 135 140
 Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
 145 150 155 160
 Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
 165 170 175
 Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
 180 185 190
 Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
 195 200 205
 Asn Arg Gly Glu Cys
 210

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<210> SEQ ID NO 73
 <211> LENGTH: 214
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 73

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1      5      10      15
Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Gln Asp Ile Ser Asn Tyr
20     25     30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Val Leu Ile
35     40     45
Tyr Phe Thr Ser Ser Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50     55     60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65     70     75     80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Thr Val Pro Trp
85     90     95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100    105    110
Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115    120    125
Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130    135    140
Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145    150    155    160
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165    170    175
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180    185    190
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195    200    205
Phe Asn Arg Gly Glu Cys
210

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<210> SEQ ID NO 74
 <211> LENGTH: 215
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 74

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Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1      5      10      15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Gly Ser Ser
20     25     30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35     40     45
Ile Tyr Gly Ala Phe Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50     55     60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65     70     75     80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
85     90     95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100    105    110

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Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
 115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
 130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
 145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
 165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
 180 185 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
 195 200 205

Ser Phe Asn Arg Gly Glu Cys
 210 215

<210> SEQ ID NO 75
 <211> LENGTH: 213
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 75

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Ile Ser Tyr Met
 20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
 35 40 45

Thr Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
 50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
 65 70 75 80

Asp Phe Ala Thr Tyr Cys His Gln Arg Ser Thr Tyr Pro Leu Thr
 85 90 95

Phe Gly Gln Gly Thr Lys Val Glu Val Lys Arg Thr Val Ala Ala Pro
 100 105 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
 115 120 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
 130 135 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
 145 150 155 160

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
 165 170 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
 180 185 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
 195 200 205

Asn Arg Gly Glu Cys
 210

<210> SEQ ID NO 76
 <211> LENGTH: 210
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 76

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Gln Ile Val Ser Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
 1 5 10 15
 Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Arg Ser Tyr Met
 20 25 30
 Gln Trp Tyr Gln Gln Lys Pro Gly Thr Ser Pro Lys Arg Trp Ile Tyr
 35 40 45
 Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
 50 55 60
 Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu Ala Glu
 65 70 75 80
 Asp Ala Ala Thr Tyr Tyr Cys His Gln Arg Ser Ser Tyr Thr Phe Gly
 85 90 95
 Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val
 100 105 110
 Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser
 115 120 125
 Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln
 130 135 140
 Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val
 145 150 155 160
 Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu
 165 170 175
 Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu
 180 185 190
 Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg
 195 200 205
 Gly Glu
 210

<210> SEQ ID NO 77
 <211> LENGTH: 216
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 77

Ser Tyr Glu Leu Ser Gln Pro Arg Ser Val Ser Val Ser Pro Gly Gln
 1 5 10 15
 Thr Ala Gly Phe Thr Cys Gly Gly Asp Asn Val Gly Arg Lys Ser Val
 20 25 30
 Gln Trp Tyr Gln Gln Lys Pro Pro Gln Ala Pro Val Leu Val Ile Tyr
 35 40 45
 Ala Asp Ser Glu Arg Pro Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser
 50 55 60
 Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Val Glu Ala Gly
 65 70 75 80
 Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Thr Ala Asp His
 85 90 95
 Trp Val Phe Gly Gly Gly Thr Arg Leu Thr Val Leu Gly Arg Thr Val
 100 105 110
 Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys
 115 120 125
 Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg
 130 135 140
 Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn

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145	150	155	160
Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser	165	170	175
Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys	180	185	190
Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr	195	200	205
Lys Ser Phe Asn Arg Gly Glu Cys	210	215	

<210> SEQ ID NO 78
 <211> LENGTH: 214
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 78

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly	1	5	10	15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Tyr	20	25	30	
Leu Ala Trp Tyr Gln Gln Leu Pro Gly Lys Ala Pro Lys Leu Leu Ile	35	40	45	
Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly	50	55	60	
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro	65	70	75	80
Glu Asp Val Ala Thr Tyr Tyr Cys Gln Arg Tyr Asn Arg Ala Pro Tyr	85	90	95	
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala	100	105	110	
Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly	115	120	125	
Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala	130	135	140	
Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln	145	150	155	160
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser	165	170	175	
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr	180	185	190	
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser	195	200	205	
Phe Asn Arg Gly Glu Cys	210			

<210> SEQ ID NO 79
 <211> LENGTH: 567
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 79

Met Gly Arg Gly Leu Leu Arg Gly Leu Trp Pro Leu His Ile Val Leu	1	5	10	15
Trp Thr Arg Ile Ala Ser Thr Ile Pro Pro His Val Gln Lys Ser Val	20	25	30	
Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro				

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35					40					45					
Gln	Leu	Cys	Lys	Phe	Cys	Asp	Val	Arg	Phe	Ser	Thr	Cys	Asp	Asn	Gln
50					55						60				
Lys	Ser	Cys	Met	Ser	Asn	Cys	Ser	Ile	Thr	Ser	Ile	Cys	Glu	Lys	Pro
65					70					75				80	
Gln	Glu	Val	Cys	Val	Ala	Val	Trp	Arg	Lys	Asn	Asp	Glu	Asn	Ile	Thr
			85					90						95	
Leu	Glu	Thr	Val	Cys	His	Asp	Pro	Lys	Leu	Pro	Tyr	His	Asp	Phe	Ile
			100					105					110		
Leu	Glu	Asp	Ala	Ala	Ser	Pro	Lys	Cys	Ile	Met	Lys	Glu	Lys	Lys	Lys
		115						120				125			
Pro	Gly	Glu	Thr	Phe	Phe	Met	Cys	Ser	Cys	Ser	Ser	Asp	Glu	Cys	Asn
	130					135						140			
Asp	Asn	Ile	Ile	Phe	Ser	Glu	Glu	Tyr	Asn	Thr	Ser	Asn	Pro	Asp	Leu
145					150					155					160
Leu	Leu	Val	Ile	Phe	Gln	Val	Thr	Gly	Ile	Ser	Leu	Leu	Pro	Pro	Leu
			165					170						175	
Gly	Val	Ala	Ile	Ser	Val	Ile	Ile	Ile	Phe	Tyr	Cys	Tyr	Arg	Val	Asn
			180					185					190		
Arg	Gln	Gln	Lys	Leu	Ser	Ser	Thr	Trp	Glu	Thr	Gly	Lys	Thr	Arg	Lys
	195						200					205			
Leu	Met	Glu	Phe	Ser	Glu	His	Cys	Ala	Ile	Ile	Leu	Glu	Asp	Asp	Arg
	210					215					220				
Ser	Asp	Ile	Ser	Ser	Thr	Cys	Ala	Asn	Asn	Ile	Asn	His	Asn	Thr	Glu
225					230					235					240
Leu	Leu	Pro	Ile	Glu	Leu	Asp	Thr	Leu	Val	Gly	Lys	Gly	Arg	Phe	Ala
			245					250						255	
Glu	Val	Tyr	Lys	Ala	Lys	Leu	Lys	Gln	Asn	Thr	Ser	Glu	Gln	Phe	Glu
			260					265					270		
Thr	Val	Ala	Val	Lys	Ile	Phe	Pro	Tyr	Glu	Glu	Tyr	Ala	Ser	Trp	Lys
	275					280						285			
Thr	Glu	Lys	Asp	Ile	Phe	Ser	Asp	Ile	Asn	Leu	Lys	His	Glu	Asn	Ile
	290					295					300				
Leu	Gln	Phe	Leu	Thr	Ala	Glu	Glu	Arg	Lys	Thr	Glu	Leu	Gly	Lys	Gln
305					310					315					320
Tyr	Trp	Leu	Ile	Thr	Ala	Phe	His	Ala	Lys	Gly	Asn	Leu	Gln	Glu	Tyr
			325						330					335	
Leu	Thr	Arg	His	Val	Ile	Ser	Trp	Glu	Asp	Leu	Arg	Lys	Leu	Gly	Ser
			340					345					350		
Ser	Leu	Ala	Arg	Gly	Ile	Ala	His	Leu	His	Ser	Asp	His	Thr	Pro	Cys
	355					360						365			
Gly	Arg	Pro	Lys	Met	Pro	Ile	Val	His	Arg	Asp	Leu	Lys	Ser	Ser	Asn
	370					375					380				
Ile	Leu	Val	Lys	Asn	Asp	Leu	Thr	Cys	Cys	Leu	Cys	Asp	Phe	Gly	Leu
385				390						395					400
Ser	Leu	Arg	Leu	Asp	Pro	Thr	Leu	Ser	Val	Asp	Asp	Leu	Ala	Asn	Ser
			405						410					415	
Gly	Gln	Val	Gly	Thr	Ala	Arg	Tyr	Met	Ala	Pro	Glu	Val	Leu	Glu	Ser
			420					425					430		
Arg	Met	Asn	Leu	Glu	Asn	Val	Glu	Ser	Phe	Lys	Gln	Thr	Asp	Val	Tyr
	435						440					445			
Ser	Met	Ala	Leu	Val	Leu	Trp	Glu	Met	Thr	Ser	Arg	Cys	Asn	Ala	Val
	450					455					460				

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Gly Glu Val Lys Asp Tyr Glu Pro Pro Phe Gly Ser Lys Val Arg Glu
 465 470 475 480
 His Pro Cys Val Glu Ser Met Lys Asp Asn Val Leu Arg Asp Arg Gly
 485 490 495
 Arg Pro Glu Ile Pro Ser Phe Trp Leu Asn His Gln Gly Ile Gln Met
 500 505 510
 Val Cys Glu Thr Leu Thr Glu Cys Trp Asp His Asp Pro Glu Ala Arg
 515 520 525
 Leu Thr Ala Gln Cys Val Ala Glu Arg Phe Ser Glu Leu Glu His Leu
 530 535 540
 Asp Arg Leu Ser Gly Arg Ser Cys Ser Glu Glu Lys Ile Pro Glu Asp
 545 550 555 560
 Gly Ser Leu Asn Thr Thr Lys
 565

<210> SEQ ID NO 80
 <211> LENGTH: 592
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 80

Met Gly Arg Gly Leu Leu Arg Gly Leu Trp Pro Leu His Ile Val Leu
 1 5 10 15
 Trp Thr Arg Ile Ala Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp
 20 25 30
 Val Glu Met Glu Ala Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn
 35 40 45
 Arg Thr Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr
 50 55 60
 Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp
 65 70 75 80
 Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys
 85 90 95
 Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val
 100 105 110
 Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp
 115 120 125
 Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro
 130 135 140
 Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met
 145 150 155 160
 Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu
 165 170 175
 Glu Tyr Asn Thr Ser Asn Pro Asp Leu Leu Leu Val Ile Phe Gln Val
 180 185 190
 Thr Gly Ile Ser Leu Leu Pro Pro Leu Gly Val Ala Ile Ser Val Ile
 195 200 205
 Ile Ile Phe Tyr Cys Tyr Arg Val Asn Arg Gln Gln Lys Leu Ser Ser
 210 215 220
 Thr Trp Glu Thr Gly Lys Thr Arg Lys Leu Met Glu Phe Ser Glu His
 225 230 235 240
 Cys Ala Ile Ile Leu Glu Asp Asp Arg Ser Asp Ile Ser Ser Thr Cys
 245 250 255
 Ala Asn Asn Ile Asn His Asn Thr Glu Leu Leu Pro Ile Glu Leu Asp

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260										265					270				
Thr	Leu	Val	Gly	Lys	Gly	Arg	Phe	Ala	Glu	Val	Tyr	Lys	Ala	Lys	Leu				
		275						280				285							
Lys	Gln	Asn	Thr	Ser	Glu	Gln	Phe	Glu	Thr	Val	Ala	Val	Lys	Ile	Phe				
	290					295					300								
Pro	Tyr	Glu	Glu	Tyr	Ala	Ser	Trp	Lys	Thr	Glu	Lys	Asp	Ile	Phe	Ser				
305					310					315					320				
Asp	Ile	Asn	Leu	Lys	His	Glu	Asn	Ile	Leu	Gln	Phe	Leu	Thr	Ala	Glu				
				325					330					335					
Glu	Arg	Lys	Thr	Glu	Leu	Gly	Lys	Gln	Tyr	Trp	Leu	Ile	Thr	Ala	Phe				
		340						345					350						
His	Ala	Lys	Gly	Asn	Leu	Gln	Glu	Tyr	Leu	Thr	Arg	His	Val	Ile	Ser				
		355					360					365							
Trp	Glu	Asp	Leu	Arg	Lys	Leu	Gly	Ser	Ser	Leu	Ala	Arg	Gly	Ile	Ala				
	370					375					380								
His	Leu	His	Ser	Asp	His	Thr	Pro	Cys	Gly	Arg	Pro	Lys	Met	Pro	Ile				
385					390					395					400				
Val	His	Arg	Asp	Leu	Lys	Ser	Ser	Asn	Ile	Leu	Val	Lys	Asn	Asp	Leu				
			405						410					415					
Thr	Cys	Cys	Leu	Cys	Asp	Phe	Gly	Leu	Ser	Leu	Arg	Leu	Asp	Pro	Thr				
		420						425					430						
Leu	Ser	Val	Asp	Asp	Leu	Ala	Asn	Ser	Gly	Gln	Val	Gly	Thr	Ala	Arg				
		435					440					445							
Tyr	Met	Ala	Pro	Glu	Val	Leu	Glu	Ser	Arg	Met	Asn	Leu	Glu	Asn	Val				
	450					455					460								
Glu	Ser	Phe	Lys	Gln	Thr	Asp	Val	Tyr	Ser	Met	Ala	Leu	Val	Leu	Trp				
465					470					475					480				
Glu	Met	Thr	Ser	Arg	Cys	Asn	Ala	Val	Gly	Glu	Val	Lys	Asp	Tyr	Glu				
			485						490					495					
Pro	Pro	Phe	Gly	Ser	Lys	Val	Arg	Glu	His	Pro	Cys	Val	Glu	Ser	Met				
		500						505					510						
Lys	Asp	Asn	Val	Leu	Arg	Asp	Arg	Gly	Arg	Pro	Glu	Ile	Pro	Ser	Phe				
	515						520					525							
Trp	Leu	Asn	His	Gln	Gly	Ile	Gln	Met	Val	Cys	Glu	Thr	Leu	Thr	Glu				
	530				535						540								
Cys	Trp	Asp	His	Asp	Pro	Glu	Ala	Arg	Leu	Thr	Ala	Gln	Cys	Val	Ala				
545				550					555						560				
Glu	Arg	Phe	Ser	Glu	Leu	Glu	His	Leu	Asp	Arg	Leu	Ser	Gly	Arg	Ser				
			565					570						575					
Cys	Ser	Glu	Glu	Lys	Ile	Pro	Glu	Asp	Gly	Ser	Leu	Asn	Thr	Thr	Lys				
		580					585						590						
<210> SEQ ID NO 81																			
<211> LENGTH: 529																			
<212> TYPE: PRT																			
<213> ORGANISM: Homo sapiens																			
<400> SEQUENCE: 81																			
Met	Gly	Arg	Gly	Leu	Leu	Arg	Gly	Leu	Trp	Pro	Leu	His	Ile	Val	Leu				
1			5					10					15						
Trp	Thr	Arg	Ile	Ala	Ser	Thr	Ile	Pro	Pro	His	Val	Gln	Lys	Ser	Val				
		20						25					30						
Asn	Asn	Asp	Met	Ile	Val	Thr	Asp	Asn	Asn	Gly	Ala	Val	Lys	Phe	Pro				
		35					40					45							

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Gln	Leu	Cys	Lys	Phe	Cys	Asp	Val	Arg	Phe	Ser	Thr	Cys	Asp	Asn	Gln
50						55					60				
Lys	Ser	Cys	Met	Ser	Asn	Cys	Ser	Ile	Thr	Ser	Ile	Cys	Glu	Lys	Pro
65					70					75				80	
Gln	Glu	Val	Cys	Val	Ala	Val	Trp	Arg	Lys	Asn	Asp	Glu	Asn	Ile	Thr
			85						90					95	
Leu	Glu	Thr	Val	Cys	His	Asp	Pro	Lys	Leu	Pro	Tyr	His	Asp	Phe	Ile
			100					105					110		
Leu	Glu	Asp	Ala	Ala	Ser	Pro	Lys	Cys	Ile	Met	Lys	Glu	Lys	Lys	Lys
		115					120					125			
Pro	Gly	Glu	Thr	Phe	Phe	Met	Cys	Ser	Cys	Ser	Ser	Asp	Glu	Cys	Asn
	130					135						140			
Asp	Asn	Ile	Ile	Phe	Ser	Glu	Glu	Tyr	Asn	Thr	Ser	Asn	Pro	Asp	Leu
145					150					155					160
Leu	Leu	Val	Ile	Phe	Gln	Val	Thr	Gly	Ile	Ser	Leu	Leu	Pro	Pro	Leu
			165						170						175
Gly	Val	Ala	Ile	Ser	Val	Ile	Ile	Ile	Phe	Tyr	Cys	Tyr	Arg	Val	Asn
			180					185					190		
Arg	Gln	Gln	Lys	Leu	Ser	Ser	Thr	Trp	Glu	Thr	Gly	Lys	Thr	Arg	Lys
		195					200					205			
Leu	Met	Glu	Phe	Ser	Glu	His	Cys	Ala	Ile	Ile	Leu	Glu	Asp	Asp	Arg
	210					215					220				
Ser	Asp	Ile	Ser	Ser	Thr	Cys	Ala	Asn	Asn	Ile	Asn	His	Asn	Thr	Glu
225					230					235					240
Leu	Leu	Pro	Ile	Glu	Leu	Asp	Thr	Leu	Val	Gly	Lys	Gly	Arg	Phe	Ala
			245					250						255	
Glu	Val	Tyr	Lys	Ala	Lys	Leu	Lys	Gln	Asn	Thr	Ser	Glu	Gln	Phe	Glu
		260						265					270		
Thr	Val	Ala	Val	Lys	Ile	Phe	Pro	Tyr	Glu	Glu	Tyr	Ala	Ser	Trp	Lys
	275						280					285			
Thr	Glu	Lys	Asp	Ile	Phe	Ser	Asp	Ile	Asn	Leu	Lys	His	Glu	Asn	Ile
	290					295					300				
Leu	Gln	Phe	Leu	Thr	Ala	Glu	Glu	Arg	Lys	Thr	Glu	Leu	Gly	Lys	Gln
305					310					315					320
Tyr	Trp	Leu	Ile	Thr	Ala	Phe	His	Ala	Lys	Gly	Asn	Leu	Gln	Glu	Tyr
			325						330					335	
Leu	Thr	Arg	His	Val	Ile	Ser	Trp	Glu	Asp	Leu	Arg	Lys	Leu	Gly	Ser
		340						345					350		
Ser	Leu	Ala	Arg	Gly	Ile	Ala	His	Leu	His	Ser	Asp	His	Thr	Pro	Cys
		355					360					365			
Gly	Arg	Pro	Lys	Met	Pro	Ile	Val	His	Arg	Asp	Leu	Lys	Ser	Ser	Asn
	370					375					380				
Ile	Leu	Val	Lys	Asn	Asp	Leu	Thr	Cys	Cys	Leu	Cys	Asp	Phe	Gly	Leu
385					390					395					400
Ser	Leu	Arg	Leu	Asp	Pro	Thr	Leu	Ser	Val	Asp	Asp	Leu	Ala	Asn	Ser
			405						410					415	
Gly	Gln	Val	Gly	Thr	Ala	Arg	Tyr	Met	Ala	Pro	Glu	Val	Leu	Glu	Ser
		420						425					430		
Arg	Met	Asn	Leu	Glu	Asn	Val	Glu	Ser	Phe	Lys	Gln	Thr	Asp	Val	Tyr
	435						440					445			
Ser	Met	Ala	Leu	Val	Leu	Trp	Glu	Met	Thr	Ser	Arg	Cys	Asn	Ala	Val
	450					455					460				
Gly	Glu	Val	Lys	Asp	Tyr	Glu	Pro	Pro	Phe	Gly	Ser	Lys	Val	Arg	Glu

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465	470	475	480
His Pro Cys Val Glu Ser Met Lys Asp Asn Val Leu Arg Asp Arg Gly	485	490	495
Arg Pro Glu Ile Pro Ser Phe Trp Leu Asn His Gln Gly Ile Gln Met	500	505	510
Val Cys Glu Thr Leu Thr Glu Cys Trp Asp His Asp Pro Glu Ala Arg	515	520	525
Leu			
<210> SEQ ID NO 82			
<211> LENGTH: 554			
<212> TYPE: PRT			
<213> ORGANISM: Homo sapiens			
<400> SEQUENCE: 82			
Met Gly Arg Gly Leu Leu Arg Gly Leu Trp Pro Leu His Ile Val Leu	5	10	15
Trp Thr Arg Ile Ala Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp	20	25	30
Val Glu Met Glu Ala Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn	35	40	45
Arg Thr Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr	50	55	60
Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp	65	70	75
Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys	85	90	95
Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val	100	105	110
Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp	115	120	125
Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro	130	135	140
Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met	145	150	155
Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu	165	170	175
Glu Tyr Asn Thr Ser Asn Pro Asp Leu Leu Leu Val Ile Phe Gln Val	180	185	190
Thr Gly Ile Ser Leu Leu Pro Pro Leu Gly Val Ala Ile Ser Val Ile	195	200	205
Ile Ile Phe Tyr Cys Tyr Arg Val Asn Arg Gln Gln Lys Leu Ser Ser	210	215	220
Thr Trp Glu Thr Gly Lys Thr Arg Lys Leu Met Glu Phe Ser Glu His	225	230	235
Cys Ala Ile Ile Leu Glu Asp Asp Arg Ser Asp Ile Ser Ser Thr Cys	245	250	255
Ala Asn Asn Ile Asn His Asn Thr Glu Leu Leu Pro Ile Glu Leu Asp	260	265	270
Thr Leu Val Gly Lys Gly Arg Phe Ala Glu Val Tyr Lys Ala Lys Leu	275	280	285
Lys Gln Asn Thr Ser Glu Gln Phe Glu Thr Val Ala Val Lys Ile Phe	290	295	300
Pro Tyr Glu Glu Tyr Ala Ser Trp Lys Thr Glu Lys Asp Ile Phe Ser			

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305	310	315	320
Asp Ile Asn Leu Lys His Glu Asn Ile Leu Gln Phe Leu Thr Ala Glu	325	330	335
Glu Arg Lys Thr Glu Leu Gly Lys Gln Tyr Trp Leu Ile Thr Ala Phe	340	345	350
His Ala Lys Gly Asn Leu Gln Glu Tyr Leu Thr Arg His Val Ile Ser	355	360	365
Trp Glu Asp Leu Arg Lys Leu Gly Ser Ser Leu Ala Arg Gly Ile Ala	370	375	380
His Leu His Ser Asp His Thr Pro Cys Gly Arg Pro Lys Met Pro Ile	385	390	395
Val His Arg Asp Leu Lys Ser Ser Asn Ile Leu Val Lys Asn Asp Leu	405	410	415
Thr Cys Cys Leu Cys Asp Phe Gly Leu Ser Leu Arg Leu Asp Pro Thr	420	425	430
Leu Ser Val Asp Asp Leu Ala Asn Ser Gly Gln Val Gly Thr Ala Arg	435	440	445
Tyr Met Ala Pro Glu Val Leu Glu Ser Arg Met Asn Leu Glu Asn Val	450	455	460
Glu Ser Phe Lys Gln Thr Asp Val Tyr Ser Met Ala Leu Val Leu Trp	465	470	475
Glu Met Thr Ser Arg Cys Asn Ala Val Gly Glu Val Lys Asp Tyr Glu	485	490	495
Pro Pro Phe Gly Ser Lys Val Arg Glu His Pro Cys Val Glu Ser Met	500	505	510
Lys Asp Asn Val Leu Arg Asp Arg Gly Arg Pro Glu Ile Pro Ser Phe	515	520	525
Trp Leu Asn His Gln Gly Ile Gln Met Val Cys Glu Thr Leu Thr Glu	530	535	540
Cys Trp Asp His Asp Pro Glu Ala Arg Leu	545	550	

<210> SEQ ID NO 83

<211> LENGTH: 199

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 83

Met Gly Arg Gly Leu Leu Arg Gly Leu Trp Pro Leu His Ile Val Leu	1	5	10	15
Trp Thr Arg Ile Ala Ser Thr Ile Pro Pro His Val Gln Lys Ser Val	20	25	30	
Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro	35	40	45	
Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln	50	55	60	
Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro	65	70	75	80
Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr	85	90	95	
Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile	100	105	110	
Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys	115	120	125	

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Pro	Gly	Glu	Thr	Phe	Phe	Met	Cys	Ser	Cys	Ser	Ser	Asp	Glu	Cys	Asn
130						135					140				
Asp	Asn	Ile	Ile	Phe	Ser	Glu	Glu	Tyr	Asn	Thr	Ser	Asn	Pro	Asp	Leu
145					150					155					160
Leu	Leu	Val	Ile	Phe	Gln	Val	Thr	Gly	Ile	Ser	Leu	Leu	Pro	Pro	Leu
				165					170					175	
Gly	Val	Ala	Ile	Ser	Val	Ile	Ile	Ile	Phe	Tyr	Cys	Tyr	Arg	Val	Asn
			180					185					190		
Arg	Gln	Gln	Lys	Leu	Ser	Ser									
	195														

<210> SEQ ID NO 84
 <211> LENGTH: 224
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 84

Met	Gly	Arg	Gly	Leu	Leu	Arg	Gly	Leu	Trp	Pro	Leu	His	Ile	Val	Leu
1			5						10					15	
Trp	Thr	Arg	Ile	Ala	Ser	Thr	Ile	Pro	Pro	His	Val	Gln	Lys	Ser	Asp
			20					25					30		
Val	Glu	Met	Glu	Ala	Gln	Lys	Asp	Glu	Ile	Ile	Cys	Pro	Ser	Cys	Asn
		35					40					45			
Arg	Thr	Ala	His	Pro	Leu	Arg	His	Ile	Asn	Asn	Asp	Met	Ile	Val	Thr
		50				55					60				
Asp	Asn	Asn	Gly	Ala	Val	Lys	Phe	Pro	Gln	Leu	Cys	Lys	Phe	Cys	Asp
65				70						75					80
Val	Arg	Phe	Ser	Thr	Cys	Asp	Asn	Gln	Lys	Ser	Cys	Met	Ser	Asn	Cys
				85					90					95	
Ser	Ile	Thr	Ser	Ile	Cys	Glu	Lys	Pro	Gln	Glu	Val	Cys	Val	Ala	Val
			100					105					110		
Trp	Arg	Lys	Asn	Asp	Glu	Asn	Ile	Thr	Leu	Glu	Thr	Val	Cys	His	Asp
		115				120						125			
Pro	Lys	Leu	Pro	Tyr	His	Asp	Phe	Ile	Leu	Glu	Asp	Ala	Ala	Ser	Pro
	130					135					140				
Lys	Cys	Ile	Met	Lys	Glu	Lys	Lys	Lys	Pro	Gly	Glu	Thr	Phe	Phe	Met
145				150						155					160
Cys	Ser	Cys	Ser	Ser	Asp	Glu	Cys	Asn	Asp	Asn	Ile	Ile	Phe	Ser	Glu
				165					170					175	
Glu	Tyr	Asn	Thr	Ser	Asn	Pro	Asp	Leu	Leu	Leu	Val	Ile	Phe	Gln	Val
				180				185					190		
Thr	Gly	Ile	Ser	Leu	Leu	Pro	Pro	Leu	Gly	Val	Ala	Ile	Ser	Val	Ile
		195				200						205			
Ile	Ile	Phe	Tyr	Cys	Tyr	Arg	Val	Asn	Arg	Gln	Gln	Lys	Leu	Ser	Ser
	210					215					220				

<210> SEQ ID NO 85
 <211> LENGTH: 166
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 85

Met	Gly	Arg	Gly	Leu	Leu	Arg	Gly	Leu	Trp	Pro	Leu	His	Ile	Val	Leu
1				5					10					15	
Trp	Thr	Arg	Ile	Ala	Ser	Thr	Ile	Pro	Pro	His	Val	Gln	Lys	Ser	Val
			20					25					30		

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Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro
 35 40 45
 Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln
 50 55 60
 Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro
 65 70 75 80
 Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr
 85 90 95
 Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile
 100 105 110
 Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys
 115 120 125
 Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn
 130 135 140
 Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Leu
 145 150 155 160
 Leu Leu Val Ile Phe Gln
 165

<210> SEQ ID NO 86
 <211> LENGTH: 191
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 86

Met Gly Arg Gly Leu Leu Arg Gly Leu Trp Pro Leu His Ile Val Leu
 1 5 10 15
 Trp Thr Arg Ile Ala Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp
 20 25 30
 Val Glu Met Glu Ala Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn
 35 40 45
 Arg Thr Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr
 50 55 60
 Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp
 65 70 75 80
 Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys
 85 90 95
 Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val
 100 105 110
 Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp
 115 120 125
 Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro
 130 135 140
 Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met
 145 150 155 160
 Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu
 165 170 175
 Glu Tyr Asn Thr Ser Asn Pro Asp Leu Leu Leu Val Ile Phe Gln
 180 185 190

<210> SEQ ID NO 87
 <211> LENGTH: 137
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 87

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Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val
 1 5 10 15

Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys
 20 25 30

Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn
 35 40 45

Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala
 50 55 60

Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His
 65 70 75 80

Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser
 85 90 95

Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe
 100 105 110

Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser
 115 120 125

Glu Glu Tyr Asn Thr Ser Asn Pro Asp
 130 135

<210> SEQ ID NO 88
 <211> LENGTH: 162
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 88

Thr Ile Pro Pro His Val Gln Lys Ser Asp Val Glu Met Glu Ala Gln
 1 5 10 15

Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr Ala His Pro Leu
 20 25 30

Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val
 35 40 45

Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys
 50 55 60

Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys
 65 70 75 80

Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu
 85 90 95

Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His
 100 105 110

Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu
 115 120 125

Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp
 130 135 140

Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn
 145 150 155 160

Pro Asp

<210> SEQ ID NO 89
 <211> LENGTH: 112
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 89

Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn
 1 5 10 15

Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys

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20					25					30					
Pro	Gln	Glu	Val	Cys	Val	Ala	Val	Trp	Arg	Lys	Asn	Asp	Glu	Asn	Ile
	35						40					45			
Thr	Leu	Glu	Thr	Val	Cys	His	Asp	Pro	Lys	Leu	Pro	Tyr	His	Asp	Phe
	50					55					60				
Ile	Leu	Glu	Asp	Ala	Ala	Ser	Pro	Lys	Cys	Ile	Met	Lys	Glu	Lys	Lys
	65					70					75				80
Lys	Pro	Gly	Glu	Thr	Phe	Phe	Met	Cys	Ser	Cys	Ser	Ser	Asp	Glu	Cys
			85					90					95		
Asn	Asp	Asn	Ile	Ile	Phe	Ser	Glu	Glu	Tyr	Asn	Thr	Ser	Asn	Pro	Asp
			100					105					110		
<210> SEQ ID NO 90															
<211> LENGTH: 507															
<212> TYPE: PRT															
<213> ORGANISM: Homo sapiens															
<400> SEQUENCE: 90															
Met	Gly	Arg	Gly	Leu	Leu	Arg	Gly	Leu	Trp	Pro	Leu	His	Ile	Val	Leu
	1			5					10					15	
Trp	Thr	Arg	Ile	Ala	Ser	Thr	Ile	Pro	Pro	His	Val	Gln	Lys	Ser	Val
			20					25					30		
Asn	Asn	Asp	Met	Ile	Val	Thr	Asp	Asn	Asn	Gly	Ala	Val	Lys	Phe	Pro
		35					40					45			
Gln	Leu	Cys	Lys	Phe	Cys	Asp	Val	Arg	Phe	Ser	Thr	Cys	Asp	Asn	Gln
	50					55					60				
Lys	Ser	Cys	Met	Ser	Asn	Cys	Ser	Ile	Thr	Ser	Ile	Cys	Glu	Lys	Pro
	65					70					75				80
Gln	Glu	Val	Cys	Val	Ala	Val	Trp	Arg	Lys	Asn	Asp	Glu	Asn	Ile	Thr
			85					90						95	
Leu	Glu	Thr	Val	Cys	His	Asp	Pro	Lys	Leu	Pro	Tyr	His	Asp	Phe	Ile
			100					105					110		
Leu	Glu	Asp	Ala	Ala	Ser	Pro	Lys	Cys	Ile	Met	Lys	Glu	Lys	Lys	Lys
		115					120					125			
Pro	Gly	Glu	Thr	Phe	Phe	Met	Cys	Ser	Cys	Ser	Ser	Asp	Glu	Cys	Asn
		130					135					140			
Asp	Asn	Ile	Ile	Phe	Ser	Glu	Glu	Tyr	Asn	Thr	Ser	Asn	Pro	Asp	Leu
				150					155					160	
Leu	Leu	Val	Ile	Phe	Gln	Val	Thr	Gly	Ile	Ser	Leu	Leu	Pro	Pro	Leu
			165					170						175	
Gly	Val	Ala	Ile	Ser	Val	Ile	Ile	Ile	Phe	Tyr	Cys	Tyr	Arg	Val	Asn
			180					185					190		
Arg	Gln	Gln	Lys	Leu	Ser	Ser	Thr	Trp	Glu	Thr	Gly	Lys	Thr	Arg	Lys
		195					200					205			
Leu	Met	Glu	Phe	Ser	Glu	His	Cys	Ala	Ile	Ile	Leu	Glu	Asp	Asp	Arg
		210					215					220			
Ser	Asp	Ile	Ser	Ser	Thr	Cys	Ala	Asn	Asn	Ile	Asn	His	Asn	Thr	Glu
				230					235					240	
Leu	Leu	Pro	Ile	Glu	Leu	Asp	Thr	Leu	Val	Gly	Lys	Gly	Arg	Phe	Ala
			245					250						255	
Glu	Val	Tyr	Lys	Ala	Lys	Leu	Lys	Gln	Asn	Thr	Ser	Glu	Gln	Phe	Glu
			260					265						270	
Thr	Val	Ala	Val	Arg	Ile	Phe	Pro	Tyr	Glu	Glu	Tyr	Ala	Ser	Trp	Lys
			275				280							285	

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Thr Glu Lys Asp Ile Phe Ser Asp Ile Asn Leu Lys His Glu Asn Ile
 290 295 300
 Leu Gln Phe Leu Thr Ala Glu Glu Arg Lys Thr Glu Leu Gly Lys Gln
 305 310 315 320
 Tyr Trp Leu Ile Thr Ala Phe His Ala Lys Gly Asn Leu Gln Glu Tyr
 325 330 335
 Leu Thr Arg His Val Ile Ser Trp Glu Asp Leu Arg Lys Leu Gly Ser
 340 345 350
 Ser Leu Ala Arg Gly Ile Ala His Leu His Ser Asp His Thr Pro Cys
 355 360 365
 Gly Arg Pro Lys Met Pro Ile Val His Arg Asp Leu Lys Ser Ser Asn
 370 375 380
 Ile Leu Val Lys Asn Asp Leu Thr Cys Cys Leu Cys Asp Phe Gly Leu
 385 390 395 400
 Ser Leu Arg Leu Asp Pro Thr Leu Ser Val Asp Asp Leu Ala Asn Ser
 405 410 415
 Gly Gln Val Gly Thr Ala Arg Tyr Met Ala Pro Glu Val Leu Glu Ser
 420 425 430
 Arg Met Asn Leu Glu Asn Val Glu Ser Phe Lys Gln Thr Asp Val Tyr
 435 440 445
 Ser Met Ala Leu Val Leu Trp Glu Met Thr Ser Arg Cys Asn Ala Val
 450 455 460
 Gly Glu Val Lys Asp Tyr Glu Pro Pro Phe Gly Ser Lys Val Arg Glu
 465 470 475 480
 Leu Glu His Leu Asp Arg Leu Ser Gly Arg Ser Cys Ser Glu Glu Lys
 485 490 495
 Ile Pro Glu Asp Gly Ser Leu Asn Thr Thr Lys
 500 505

<210> SEQ ID NO 91
 <211> LENGTH: 550
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 91

Met Gly Arg Gly Leu Leu Arg Gly Leu Trp Pro Leu His Ile Val Leu
 1 5 10 15
 Trp Thr Arg Ile Ala Ser Thr Ile Pro Pro His Val Gln Lys Ser Val
 20 25 30
 Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro
 35 40 45
 Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln
 50 55 60
 Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro
 65 70 75 80
 Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr
 85 90 95
 Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile
 100 105 110
 Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys
 115 120 125
 Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn
 130 135 140
 Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Leu
 145 150 155 160

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Leu Leu Val Ile Phe Gln Val Thr Gly Ile Ser Leu Leu Pro Pro Leu
 165 170 175
 Gly Val Ala Ile Ser Val Ile Ile Ile Phe Tyr Cys Tyr Arg Val Asn
 180 185 190
 Arg Gln Gln Lys Leu Ser Ser Thr Trp Glu Thr Gly Lys Thr Arg Lys
 195 200 205
 Leu Met Glu Phe Ser Glu His Cys Ala Ile Ile Leu Glu Asp Asp Arg
 210 215 220
 Ser Asp Ile Ser Ser Thr Cys Ala Asn Asn Ile Asn His Asn Thr Glu
 225 230 235 240
 Leu Leu Pro Ile Glu Leu Asp Thr Leu Val Gly Lys Gly Arg Phe Ala
 245 250 255
 Glu Val Tyr Lys Ala Lys Leu Lys Gln Asn Thr Ser Glu Gln Phe Glu
 260 265 270
 Thr Val Ala Val Lys Ile Phe Pro Tyr Glu Glu Tyr Ala Ser Trp Lys
 275 280 285
 Thr Glu Lys Asp Ile Phe Ser Asp Ile Asn Leu Lys His Glu Asn Ile
 290 295 300
 Leu Gln Phe Leu Thr Ala Glu Glu Arg Lys Thr Glu Leu Gly Lys Gln
 305 310 315 320
 Tyr Trp Leu Ile Thr Ala Phe His Ala Lys Gly Asn Leu Gln Glu Tyr
 325 330 335
 Leu Thr Arg His Val Ile Ser Trp Glu Asp Leu Arg Lys Leu Gly Ser
 340 345 350
 Ser Leu Ala Arg Gly Ile Ala His Leu His Ser Asp His Thr Pro Cys
 355 360 365
 Gly Arg Pro Lys Met Pro Ile Val His Arg Asp Leu Lys Ser Ser Asn
 370 375 380
 Ile Leu Val Lys Asn Asp Leu Thr Cys Cys Leu Cys Asp Phe Gly Leu
 385 390 395 400
 Ser Leu Arg Leu Asp Pro Thr Leu Ser Val Asp Asp Leu Ala Asn Ser
 405 410 415
 Gly Gln Val Gly Thr Ala Arg Tyr Met Ala Pro Glu Val Leu Glu Ser
 420 425 430
 Arg Met Asn Leu Glu Asn Val Glu Ser Phe Lys Gln Thr Asp Val Tyr
 435 440 445
 Ser Met Ala Leu Val Leu Trp Glu Met Thr Ser Arg Cys Asn Ala Val
 450 455 460
 Gly Glu Val Lys Asp Tyr Glu Pro Pro Phe Gly Ser Lys Val Arg Glu
 465 470 475 480
 His Pro Cys Val Glu Ser Met Lys Asp Ala Ser Gly Ile Gln Met Val
 485 490 495
 Cys Glu Thr Leu Thr Glu Cys Trp Asp His Asp Pro Glu Ala Arg Leu
 500 505 510
 Thr Ala Gln Cys Val Ala Glu Arg Phe Ser Glu Leu Glu His Leu Asp
 515 520 525
 Arg Leu Ser Gly Arg Ser Cys Ser Glu Glu Lys Ile Pro Glu Asp Gly
 530 535 540
 Ser Leu Asn Thr Thr Lys
 545 550

<210> SEQ ID NO 92

<211> LENGTH: 288

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 92
Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1          5          10          15
Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
          20          25          30
Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
          35          40          45
Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
          50          55          60
Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65          70          75          80
Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
          85          90          95
Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
          100          105          110
Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
          115          120          125
Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
          130          135          140
Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145          150          155          160
Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
          165          170          175
Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
          180          185          190
Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
          195          200          205
Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
          210          215          220
Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225          230          235          240
Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
          245          250          255
Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
          260          265          270
Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
          275          280          285

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<210> SEQ ID NO 93
<211> LENGTH: 150
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 93
Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp Asn Pro Pro Thr
1          5          10          15
Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp Asn Ala Thr Phe
          20          25          30
Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val Leu Asn Trp Tyr
          35          40          45
Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala Ala Phe Pro Glu
          50          55          60

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Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg Val Thr Gln Leu
 65 70 75 80
 Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg Ala Arg Arg Asn
 85 90 95
 Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu Ala Pro Lys Ala
 100 105 110
 Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val Thr Glu Arg Arg
 115 120 125
 Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro Arg Pro Ala Gly
 130 135 140
 Gln Phe Gln Thr Leu Val
 145 150

<210> SEQ ID NO 94
 <211> LENGTH: 142
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 94

Asp Ser Pro Asp Arg Pro Trp Asn Pro Pro Thr Phe Ser Pro Ala Leu
 1 5 10 15
 Leu Val Val Thr Glu Gly Asp Asn Ala Thr Phe Thr Cys Ser Phe Ser
 20 25 30
 Asn Thr Ser Glu Ser Phe Val Leu Asn Trp Tyr Arg Met Ser Pro Ser
 35 40 45
 Asn Gln Thr Asp Lys Leu Ala Ala Phe Pro Glu Asp Arg Ser Gln Pro
 50 55 60
 Gly Gln Asp Cys Arg Phe Arg Val Thr Gln Leu Pro Asn Gly Arg Asp
 65 70 75 80
 Phe His Met Ser Val Val Arg Ala Arg Arg Asn Asp Ser Gly Thr Tyr
 85 90 95
 Leu Cys Gly Ala Ile Ser Leu Ala Pro Lys Ala Gln Ile Lys Glu Ser
 100 105 110
 Leu Arg Ala Glu Leu Arg Val Thr Glu Arg Arg Ala Glu Val Pro Thr
 115 120 125
 Ala His Pro Ser Pro Ser Pro Arg Pro Ala Gly Gln Phe Gln
 130 135 140

<210> SEQ ID NO 95
 <211> LENGTH: 616
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 95

Met Ala Pro Arg Ala Arg Arg Arg Arg Pro Leu Phe Ala Leu Leu Leu
 1 5 10 15
 Leu Cys Ala Leu Leu Ala Arg Leu Gln Val Ala Leu Gln Ile Ala Pro
 20 25 30
 Pro Cys Thr Ser Glu Lys His Tyr Glu His Leu Gly Arg Cys Cys Asn
 35 40 45
 Lys Cys Glu Pro Gly Lys Tyr Met Ser Ser Lys Cys Thr Thr Thr Ser
 50 55 60
 Asp Ser Val Cys Leu Pro Cys Gly Pro Asp Glu Tyr Leu Asp Ser Trp
 65 70 75 80
 Asn Glu Glu Asp Lys Cys Leu Leu His Lys Val Cys Asp Thr Gly Lys
 85 90 95

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Ala	Leu	Val	Ala	Val	Val	Ala	Gly	Asn	Ser	Thr	Thr	Pro	Arg	Arg	Cys	
		100						105					110			
Ala	Cys	Thr	Ala	Gly	Tyr	His	Trp	Ser	Gln	Asp	Cys	Glu	Cys	Cys	Arg	
	115						120					125				
Arg	Asn	Thr	Glu	Cys	Ala	Pro	Gly	Leu	Gly	Ala	Gln	His	Pro	Leu	Gln	
	130					135					140					
Leu	Asn	Lys	Asp	Thr	Val	Cys	Lys	Pro	Cys	Leu	Ala	Gly	Tyr	Phe	Ser	
145					150					155					160	
Asp	Ala	Phe	Ser	Ser	Thr	Asp	Lys	Cys	Arg	Pro	Trp	Thr	Asn	Cys	Thr	
			165						170					175		
Phe	Leu	Gly	Lys	Arg	Val	Glu	His	His	Gly	Thr	Glu	Lys	Ser	Asp	Ala	
		180						185					190			
Val	Cys	Ser	Ser	Ser	Leu	Pro	Ala	Arg	Lys	Pro	Pro	Asn	Glu	Pro	His	
	195						200					205				
Val	Tyr	Leu	Pro	Gly	Leu	Ile	Ile	Leu	Leu	Leu	Phe	Ala	Ser	Val	Ala	
	210					215					220					
Leu	Val	Ala	Ala	Ile	Ile	Phe	Gly	Val	Cys	Tyr	Arg	Lys	Lys	Gly	Lys	
225				230						235					240	
Ala	Leu	Thr	Ala	Asn	Leu	Trp	His	Trp	Ile	Asn	Glu	Ala	Cys	Gly	Arg	
			245					250						255		
Leu	Ser	Gly	Asp	Lys	Glu	Ser	Ser	Gly	Asp	Ser	Cys	Val	Ser	Thr	His	
		260						265					270			
Thr	Ala	Asn	Phe	Gly	Gln	Gln	Gly	Ala	Cys	Glu	Gly	Val	Leu	Leu	Leu	
	275						280					285				
Thr	Leu	Glu	Glu	Lys	Thr	Phe	Pro	Glu	Asp	Met	Cys	Tyr	Pro	Asp	Gln	
	290					295					300					
Gly	Gly	Val	Cys	Gln	Gly	Thr	Cys	Val	Gly	Gly	Gly	Pro	Tyr	Ala	Gln	
305				310					315						320	
Gly	Glu	Asp	Ala	Arg	Met	Leu	Ser	Leu	Val	Ser	Lys	Thr	Glu	Ile	Glu	
		325							330					335		
Glu	Asp	Ser	Phe	Arg	Gln	Met	Pro	Thr	Glu	Asp	Glu	Tyr	Met	Asp	Arg	
		340						345					350			
Pro	Ser	Gln	Pro	Thr	Asp	Gln	Leu	Leu	Phe	Leu	Thr	Glu	Pro	Gly	Ser	
		355					360						365			
Lys	Ser	Thr	Pro	Pro	Phe	Ser	Glu	Pro	Leu	Glu	Val	Gly	Glu	Asn	Asp	
	370					375					380					
Ser	Leu	Ser	Gln	Cys	Phe	Thr	Gly	Thr	Gln	Ser	Thr	Val	Gly	Ser	Glu	
385				390						395					400	
Ser	Cys	Asn	Cys	Thr	Glu	Pro	Leu	Cys	Arg	Thr	Asp	Trp	Thr	Pro	Met	
			405						410					415		
Ser	Ser	Glu	Asn	Tyr	Leu	Gln	Lys	Glu	Val	Asp	Ser	Gly	His	Cys	Pro	
		420						425					430			
His	Trp	Ala	Ala	Ser	Pro	Ser	Pro	Asn	Trp	Ala	Asp	Val	Cys	Thr	Gly	
		435					440					445				
Cys	Arg	Asn	Pro	Pro	Gly	Glu	Asp	Cys	Glu	Pro	Leu	Val	Gly	Ser	Pro	
	450					455					460					
Lys	Arg	Gly	Pro	Leu	Pro	Gln	Cys	Ala	Tyr	Gly	Met	Gly	Leu	Pro	Pro	
465				470						475				480		
Glu	Glu	Glu	Ala	Ser	Arg	Thr	Glu	Ala	Arg	Asp	Gln	Pro	Glu	Asp	Gly	
			485						490					495		
Ala	Asp	Gly	Arg	Leu	Pro	Ser	Ser	Ala	Arg	Ala	Gly	Ala	Gly	Ser	Gly	
		500						505					510			
Ser	Ser	Pro	Gly	Gly	Gln	Ser	Pro	Ala	Ser	Gly	Asn	Val	Thr	Gly	Asn	

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515	520	525
Ser Asn Ser Thr Phe Ile Ser Ser Gly Gln Val Met Asn Phe Lys Gly		
530	535	540
Asp Ile Ile Val Val Tyr Val Ser Gln Thr Ser Gln Glu Gly Ala Ala		
545	550	555
		560
Ala Ala Ala Glu Pro Met Gly Arg Pro Val Gln Glu Glu Thr Leu Ala		
565	570	575
Arg Arg Asp Ser Phe Ala Gly Asn Gly Pro Arg Phe Pro Asp Pro Cys		
580	585	590
Gly Gly Pro Glu Gly Leu Arg Glu Pro Glu Lys Ala Ser Arg Pro Val		
595	600	605
Gln Glu Gln Gly Gly Ala Lys Ala		
610	615	

<210> SEQ ID NO 96

<211> LENGTH: 185

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 96

Gln Ile Ala Pro Pro Cys Thr Ser Glu Lys His Tyr Glu His Leu Gly		
1	5	10
Arg Cys Cys Asn Lys Cys Glu Pro Gly Lys Tyr Met Ser Ser Lys Cys		
20	25	30
Thr Thr Thr Ser Asp Ser Val Cys Leu Pro Cys Gly Pro Asp Glu Tyr		
35	40	45
Leu Asp Ser Trp Asn Glu Glu Asp Lys Cys Leu Leu His Lys Val Cys		
50	55	60
Asp Thr Gly Lys Ala Leu Val Ala Val Val Ala Gly Asn Ser Thr Thr		
65	70	75
Pro Arg Arg Cys Ala Cys Thr Ala Gly Tyr His Trp Ser Gln Asp Cys		
85	90	95
Glu Cys Cys Arg Arg Asn Thr Glu Cys Ala Pro Gly Leu Gly Ala Gln		
100	105	110
His Pro Leu Gln Leu Asn Lys Asp Thr Val Cys Lys Pro Cys Leu Ala		
115	120	125
Gly Tyr Phe Ser Asp Ala Phe Ser Ser Thr Asp Lys Cys Arg Pro Trp		
130	135	140
Thr Asn Cys Thr Phe Leu Gly Lys Arg Val Glu His His Gly Thr Glu		
145	150	155
Lys Ser Asp Ala Val Cys Ser Ser Ser Leu Pro Ala Arg Lys Pro Pro		
165	170	175
Asn Glu Pro His Val Tyr Leu Pro Gly		
180	185	

<210> SEQ ID NO 97

<211> LENGTH: 213

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 97

Met Ala Pro Arg Ala Arg Arg Arg Arg Pro Leu Phe Ala Leu Leu Leu		
1	5	10
Leu Cys Ala Leu Leu Ala Arg Leu Gln Val Ala Leu Gln Ile Ala Pro		
20	25	30
Pro Cys Thr Ser Glu Lys His Tyr Glu His Leu Gly Arg Cys Cys Asn		

-continued

35					40					45					
Lys	Cys	Glu	Pro	Gly	Lys	Tyr	Met	Ser	Ser	Lys	Cys	Thr	Thr	Thr	Ser
50					55					60					
Asp	Ser	Val	Cys	Leu	Pro	Cys	Gly	Pro	Asp	Glu	Tyr	Leu	Asp	Ser	Trp
65					70					75					80
Asn	Glu	Glu	Asp	Lys	Cys	Leu	Leu	His	Lys	Val	Cys	Asp	Thr	Gly	Lys
				85					90					95	
Ala	Leu	Val	Ala	Val	Val	Ala	Gly	Asn	Ser	Thr	Thr	Pro	Arg	Arg	Cys
				100				105					110		
Ala	Cys	Thr	Ala	Gly	Tyr	His	Trp	Ser	Gln	Asp	Cys	Glu	Cys	Cys	Arg
				115			120					125			
Arg	Asn	Thr	Glu	Cys	Ala	Pro	Gly	Leu	Gly	Ala	Gln	His	Pro	Leu	Gln
				130		135					140				
Leu	Asn	Lys	Asp	Thr	Val	Cys	Lys	Pro	Cys	Leu	Ala	Gly	Tyr	Phe	Ser
145					150					155					160
Asp	Ala	Phe	Ser	Ser	Thr	Asp	Lys	Cys	Arg	Pro	Trp	Thr	Asn	Cys	Thr
				165					170					175	
Phe	Leu	Gly	Lys	Arg	Val	Glu	His	His	Gly	Thr	Glu	Lys	Ser	Asp	Ala
				180				185						190	
Val	Cys	Ser	Ser	Ser	Leu	Pro	Ala	Arg	Lys	Pro	Pro	Asn	Glu	Pro	His
				195			200					205			
Val	Tyr	Leu	Pro	Gly											
				210											

<210> SEQ ID NO 98

<211> LENGTH: 401

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 98

Met	Asn	Lys	Leu	Leu	Cys	Cys	Ala	Leu	Val	Phe	Leu	Asp	Ile	Ser	Ile
1				5					10					15	
Lys	Trp	Thr	Thr	Gln	Glu	Thr	Phe	Pro	Pro	Lys	Tyr	Leu	His	Tyr	Asp
			20					25					30		
Glu	Glu	Thr	Ser	His	Gln	Leu	Leu	Cys	Asp	Lys	Cys	Pro	Pro	Gly	Thr
		35					40					45			
Tyr	Leu	Lys	Gln	His	Cys	Thr	Ala	Lys	Trp	Lys	Thr	Val	Cys	Ala	Pro
	50				55						60				
Cys	Pro	Asp	His	Tyr	Tyr	Thr	Asp	Ser	Trp	His	Thr	Ser	Asp	Glu	Cys
65				70					75					80	
Leu	Tyr	Cys	Ser	Pro	Val	Cys	Lys	Glu	Leu	Gln	Tyr	Val	Lys	Gln	Glu
			85					90						95	
Cys	Asn	Arg	Thr	His	Asn	Arg	Val	Cys	Glu	Cys	Lys	Glu	Gly	Arg	Tyr
			100				105						110		
Leu	Glu	Ile	Glu	Phe	Cys	Leu	Lys	His	Arg	Ser	Cys	Pro	Pro	Gly	Phe
	115						120					125			
Gly	Val	Val	Gln	Ala	Gly	Thr	Pro	Glu	Arg	Asn	Thr	Val	Cys	Lys	Arg
	130					135					140				
Cys	Pro	Asp	Gly	Phe	Phe	Ser	Asn	Glu	Thr	Ser	Ser	Lys	Ala	Pro	Cys
145				150					155					160	
Arg	Lys	His	Thr	Asn	Cys	Ser	Val	Phe	Gly	Leu	Leu	Leu	Thr	Gln	Lys
			165					170						175	
Gly	Asn	Ala	Thr	His	Asp	Asn	Ile	Cys	Ser	Gly	Asn	Ser	Glu	Ser	Thr
			180				185						190		

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Gln Lys Cys Gly Ile Asp Val Thr Leu Cys Glu Glu Ala Phe Phe Arg
 195 200 205

Phe Ala Val Pro Thr Lys Phe Thr Pro Asn Trp Leu Ser Val Leu Val
 210 215 220

Asp Asn Leu Pro Gly Thr Lys Val Asn Ala Glu Ser Val Glu Arg Ile
 225 230 235 240

Lys Arg Gln His Ser Ser Gln Glu Gln Thr Phe Gln Leu Leu Lys Leu
 245 250 255

Trp Lys His Gln Asn Lys Ala Gln Asp Ile Val Lys Lys Ile Ile Gln
 260 265 270

Asp Ile Asp Leu Cys Glu Asn Ser Val Gln Arg His Ile Gly His Ala
 275 280 285

Asn Leu Thr Phe Glu Gln Leu Arg Ser Leu Met Glu Ser Leu Pro Gly
 290 295 300

Lys Lys Val Gly Ala Glu Asp Ile Glu Lys Thr Ile Lys Ala Cys Lys
 305 310 315 320

Pro Ser Asp Gln Ile Leu Lys Leu Leu Ser Leu Trp Arg Ile Lys Asn
 325 330 335

Gly Asp Gln Asp Thr Leu Lys Gly Leu Met His Ala Leu Lys His Ser
 340 345 350

Lys Thr Tyr His Phe Pro Lys Thr Val Thr Gln Ser Leu Lys Lys Thr
 355 360 365

Ile Arg Phe Leu His Ser Phe Thr Met Tyr Lys Leu Tyr Gln Lys Leu
 370 375 380

Phe Leu Glu Met Ile Gly Asn Gln Val Gln Ser Val Lys Ile Ser Cys
 385 390 395 400

Leu

<210> SEQ ID NO 99
 <211> LENGTH: 290
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 99

Met Arg Ile Phe Ala Val Phe Ile Phe Met Thr Tyr Trp His Leu Leu
 1 5 10 15

Asn Ala Phe Thr Val Thr Val Pro Lys Asp Leu Tyr Val Val Glu Tyr
 20 25 30

Gly Ser Asn Met Thr Ile Glu Cys Lys Phe Pro Val Glu Lys Gln Leu
 35 40 45

Asp Leu Ala Ala Leu Ile Val Tyr Trp Glu Met Glu Asp Lys Asn Ile
 50 55 60

Ile Gln Phe Val His Gly Glu Glu Asp Leu Lys Val Gln His Ser Ser
 65 70 75 80

Tyr Arg Gln Arg Ala Arg Leu Leu Lys Asp Gln Leu Ser Leu Gly Asn
 85 90 95

Ala Ala Leu Gln Ile Thr Asp Val Lys Leu Gln Asp Ala Gly Val Tyr
 100 105 110

Arg Cys Met Ile Ser Tyr Gly Gly Ala Asp Tyr Lys Arg Ile Thr Val
 115 120 125

Lys Val Asn Ala Pro Tyr Asn Lys Ile Asn Gln Arg Ile Leu Val Val
 130 135 140

Asp Pro Val Thr Ser Glu His Glu Leu Thr Cys Gln Ala Glu Gly Tyr
 145 150 155 160

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Pro Lys Ala Glu Val Ile Trp Thr Ser Ser Asp His Gln Val Leu Ser
 165 170 175

Gly Lys Thr Thr Thr Thr Asn Ser Lys Arg Glu Glu Lys Leu Phe Asn
 180 185 190

Val Thr Ser Thr Leu Arg Ile Asn Thr Thr Thr Asn Glu Ile Phe Tyr
 195 200 205

Cys Thr Phe Arg Arg Leu Asp Pro Glu Glu Asn His Thr Ala Glu Leu
 210 215 220

Val Ile Pro Glu Leu Pro Leu Ala His Pro Pro Asn Glu Arg Thr His
 225 230 235 240

Leu Val Ile Leu Gly Ala Ile Leu Leu Cys Leu Gly Val Ala Leu Thr
 245 250 255

Phe Ile Phe Arg Leu Arg Lys Gly Arg Met Met Asp Val Lys Lys Cys
 260 265 270

Gly Ile Gln Asp Thr Asn Ser Lys Lys Gln Ser Asp Thr His Leu Glu
 275 280 285

Glu Thr
 290

<210> SEQ ID NO 100

<211> LENGTH: 209

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 100

Ala Phe Thr Val Thr Val Pro Lys Asp Leu Tyr Val Val Glu Tyr Gly
 1 5 10 15

Ser Asn Met Thr Ile Glu Cys Lys Phe Pro Val Glu Lys Gln Leu Asp
 20 25 30

Leu Ala Ala Leu Ile Val Tyr Trp Glu Met Glu Asp Lys Asn Ile Ile
 35 40 45

Gln Phe Val His Gly Glu Glu Asp Leu Lys Val Gln His Ser Ser Tyr
 50 55 60

Arg Gln Arg Ala Arg Leu Leu Lys Asp Gln Leu Ser Leu Gly Asn Ala
 65 70 75 80

Ala Leu Gln Ile Thr Asp Val Lys Leu Gln Asp Ala Gly Val Tyr Arg
 85 90 95

Cys Met Ile Ser Tyr Gly Gly Ala Asp Tyr Lys Arg Ile Thr Val Lys
 100 105 110

Val Asn Ala Pro Tyr Asn Lys Ile Asn Gln Arg Ile Leu Val Val Asp
 115 120 125

Pro Val Thr Ser Glu His Glu Leu Thr Cys Gln Ala Glu Gly Tyr Pro
 130 135 140

Lys Ala Glu Val Ile Trp Thr Ser Ser Asp His Gln Val Leu Ser Gly
 145 150 155 160

Lys Thr Thr Thr Thr Asn Ser Lys Arg Glu Glu Lys Leu Phe Asn Val
 165 170 175

Thr Ser Thr Leu Arg Ile Asn Thr Thr Thr Asn Glu Ile Phe Tyr Cys
 180 185 190

Thr Phe Arg Arg Leu Asp Pro Glu Glu Asn His Thr Ala Glu Leu Val
 195 200 205

Ile

<210> SEQ ID NO 101

<211> LENGTH: 289

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 101

Arg Ile Phe Ala Val Phe Ile Phe Met Thr Tyr Trp His Leu Leu Asn
1           5           10           15
Ala Phe Thr Val Thr Val Pro Lys Asp Leu Tyr Val Val Glu Tyr Gly
20           25           30
Ser Asn Met Thr Ile Glu Cys Lys Phe Pro Val Glu Lys Gln Leu Asp
35           40           45
Leu Ala Ala Leu Ile Val Tyr Trp Glu Met Glu Asp Lys Asn Ile Ile
50           55           60
Gln Phe Val His Gly Glu Glu Asp Leu Lys Val Gln His Ser Ser Tyr
65           70           75           80
Arg Gln Arg Ala Arg Leu Leu Lys Asp Gln Leu Ser Leu Gly Asn Ala
85           90           95
Ala Leu Gln Ile Thr Asp Val Lys Leu Gln Asp Ala Gly Val Tyr Arg
100          105          110
Cys Met Ile Ser Tyr Gly Gly Ala Asp Tyr Lys Arg Ile Thr Val Lys
115          120          125
Val Asn Ala Pro Tyr Asn Lys Ile Asn Gln Arg Ile Leu Val Val Asp
130          135          140
Pro Val Thr Ser Glu His Glu Leu Thr Cys Gln Ala Glu Gly Tyr Pro
145          150          155          160
Lys Ala Glu Val Ile Trp Thr Ser Ser Asp His Gln Val Leu Ser Gly
165          170          175
Lys Thr Thr Thr Thr Asn Ser Lys Arg Glu Glu Lys Leu Phe Asn Val
180          185          190
Thr Ser Thr Leu Arg Ile Asn Thr Thr Thr Asn Glu Ile Phe Tyr Cys
195          200          205
Thr Phe Arg Arg Leu Asp Pro Glu Glu Asn His Thr Ala Glu Leu Val
210          215          220
Ile Pro Glu Leu Pro Leu Ala His Pro Pro Asn Glu Arg Thr His Leu
225          230          235          240
Val Ile Leu Gly Ala Ile Leu Leu Cys Leu Gly Val Ala Leu Thr Phe
245          250          255
Ile Phe Arg Leu Arg Lys Gly Arg Met Met Asp Val Lys Lys Cys Gly
260          265          270
Ile Gln Asp Thr Asn Ser Lys Lys Gln Ser Asp Thr His Leu Glu Glu
275          280          285

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Thr

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<210> SEQ ID NO 102
<211> LENGTH: 390
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 102

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Met Pro Pro Ser Gly Leu Arg Leu Leu Pro Leu Leu Leu Pro Leu Leu
1           5           10           15
Arg Leu Leu Val Leu Thr Pro Gly Arg Pro Ala Ala Gly Leu Ser Thr
20           25           30
Cys Lys Thr Ile Asp Met Glu Leu Val Lys Arg Lys Arg Ile Glu Ala
35           40           45
Ile Arg Gly Gln Ile Leu Ser Lys Leu Arg Leu Ser Ser Pro Pro Ser

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50					55					60					
Gln	Gly	Glu	Val	Pro	Pro	Val	Pro	Leu	Pro	Glu	Ala	Val	Leu	Ala	Leu
65					70					75					80
Tyr	Asn	Ser	Thr	Arg	Asp	Arg	Val	Ala	Gly	Glu	Ser	Ala	Glu	Pro	Glu
				85					90					95	
Pro	Glu	Pro	Glu	Ala	Asp	Tyr	Tyr	Ala	Lys	Glu	Val	Thr	Arg	Val	Leu
			100					105					110		
Met	Val	Glu	Asn	Thr	Asn	Lys	Ile	Tyr	Glu	Lys	Val	Lys	Lys	Ser	Pro
			115				120					125			
His	Ser	Ile	Tyr	Met	Leu	Phe	Asn	Thr	Ser	Glu	Leu	Arg	Glu	Ala	Val
			130				135					140			
Pro	Glu	Pro	Val	Leu	Leu	Ser	Arg	Ala	Glu	Leu	Arg	Leu	Leu	Arg	Leu
145					150					155					160
Lys	Leu	Lys	Ala	Glu	Gln	His	Val	Glu	Leu	Tyr	Gln	Lys	Tyr	Ser	Asn
			165						170					175	
Asp	Ser	Trp	Arg	Tyr	Leu	Ser	Asn	Arg	Leu	Leu	Ala	Pro	Ser	Asp	Thr
			180					185					190		
Pro	Glu	Trp	Leu	Ser	Phe	Asp	Val	Thr	Gly	Val	Val	Arg	Gln	Trp	Leu
			195				200					205			
Ser	His	Gly	Gly	Glu	Val	Glu	Gly	Phe	Arg	Leu	Ser	Ala	His	Cys	Ser
			210				215					220			
Cys	Asp	Ser	Lys	Asp	Asn	Thr	Leu	Gln	Val	Asp	Ile	Asn	Gly	Phe	Ser
225					230					235					240
Ser	Ser	Arg	Arg	Gly	Asp	Leu	Ala	Thr	Ile	His	Gly	Met	Asn	Arg	Pro
			245						250					255	
Phe	Leu	Leu	Leu	Met	Ala	Thr	Pro	Leu	Glu	Arg	Ala	Gln	His	Leu	His
			260					265					270		
Ser	Ser	Arg	Gln	Arg	Arg	Ala	Leu	Asp	Thr	Asn	Tyr	Cys	Phe	Ser	Ser
			275				280					285			
Thr	Glu	Lys	Asn	Cys	Cys	Val	Arg	Gln	Leu	Tyr	Ile	Asp	Phe	Arg	Lys
			290				295					300			
Asp	Leu	Gly	Trp	Lys	Trp	Ile	His	Glu	Pro	Lys	Gly	Tyr	His	Ala	Asn
305					310					315					320
Phe	Cys	Leu	Gly	Pro	Cys	Pro	Tyr	Ile	Trp	Ser	Leu	Asp	Thr	Gln	Tyr
			325						330					335	
Ser	Lys	Val	Leu	Ala	Leu	Tyr	Asn	Gln	His	Asn	Pro	Gly	Ala	Ser	Ala
			340				345						350		
Ala	Pro	Cys	Cys	Val	Pro	Gln	Ala	Leu	Glu	Pro	Leu	Pro	Ile	Val	Tyr
			355				360					365			
Tyr	Val	Gly	Arg	Lys	Pro	Lys	Val	Glu	Gln	Leu	Ser	Asn	Met	Ile	Val
			370				375					380			
Arg	Ser	Cys	Lys	Cys	Ser										
385					390										

<210> SEQ ID NO 103
 <211> LENGTH: 112
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 103

Ala	Leu	Asp	Thr	Asn	Tyr	Cys	Phe	Ser	Ser	Thr	Glu	Lys	Asn	Cys	Cys
1				5					10					15	
Val	Arg	Gln	Leu	Tyr	Ile	Asp	Phe	Arg	Lys	Asp	Leu	Gly	Trp	Lys	Trp
			20					25					30		

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```

Ile His Glu Pro Lys Gly Tyr His Ala Asn Phe Cys Leu Gly Pro Cys
    35                      40                      45

Pro Tyr Ile Trp Ser Leu Asp Thr Gln Tyr Ser Lys Val Leu Ala Leu
    50                      55                      60

Tyr Asn Gln His Asn Pro Gly Ala Ser Ala Ala Pro Cys Cys Val Pro
    65                      70                      75                      80

Gln Ala Leu Glu Pro Leu Pro Ile Val Tyr Tyr Val Gly Arg Lys Pro
    85                      90                      95

Lys Val Glu Gln Leu Ser Asn Met Ile Val Arg Ser Cys Lys Cys Ser
    100                      105                      110

```

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<210> SEQ ID NO 104
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct

```

```

<400> SEQUENCE: 104

```

```

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1          5          10          15

```

```

<210> SEQ ID NO 105
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct

```

```

<400> SEQUENCE: 105

```

```

Glu Pro Lys Ser Cys Asp Lys
1          5

```

```

<210> SEQ ID NO 106
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct

```

```

<400> SEQUENCE: 106

```

```

Ile Glu Gly Arg Asp Met Asp
1          5

```

```

<210> SEQ ID NO 107
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct

```

```

<400> SEQUENCE: 107

```

```

Lys Lys Ala Glu
1

```

```

<210> SEQ ID NO 108
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct

```

```

<400> SEQUENCE: 108

```

```

Lys Arg Val Glu
1

```

-continued

<210> SEQ ID NO 109
 <211> LENGTH: 4
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic construct

<400> SEQUENCE: 109

Lys Lys Val Glu
 1

<210> SEQ ID NO 110
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic construct

<400> SEQUENCE: 110

Gln Glu Pro Lys Ser Cys Asp Lys
 1 5

<210> SEQ ID NO 111
 <211> LENGTH: 21
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Primer

<400> SEQUENCE: 111

ctagtgccac ctgggaattc a 21

<210> SEQ ID NO 112
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Primer

<400> SEQUENCE: 112

catcattagc tgatctccag ctca 24

<210> SEQ ID NO 113
 <211> LENGTH: 38
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic construct

<400> SEQUENCE: 113

catcagtgac agttacttct tcaccttcta cacagaga 38

<210> SEQ ID NO 114
 <211> LENGTH: 1821
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 114

gagctcgagg tgcagctggg ggaatccggc ggaggactgg tgcagcctgg cggatccctg 60

agactgtctt gcgcgcctc cggttcaac atcaaggaca cctacatcca ctgggtgcga 120

caggccctg gcaagggact ggaatgggtg gcccgatct accccaccaa cggtacacc 180

agatacgccg actccgtgaa gggccgggtc accatctccg ccgacacctc caagaacacc 240

- continued

gectacctgc agatgaactc cctgcggggc gaggacaccg ccgtgtacta ctgetccaga	300
tggggaggcg acggcttcta cgccatggac tactggggcc agggcaccct ggtgacagtg	360
tcctctgect ccaccaaggg cccctctgtg ttccctctgg ccccttccag caagtccaca	420
tctggcgcca ccgcccgtct gggtgcctg gtgaaagact acttcccga gcccgtagcc	480
gtgtcctgga actctggcgc cctgacctcc ggctgcaca cctttccage cgtgctgcag	540
tcctccggcc tgtaactcct gtctccgtg gtgacctgac cctccagctc tctgggcacc	600
cagacctaca tctgcaactg gaaccacaag ccctccaaca ccaaggtgga caagaaggtg	660
gaaccaagt cctgcgacaa gaccacacc tgccccctt gccctgctcc tgaactgctg	720
ggcggaccct ccgtgttctt gtcccccca aagcccaagg acacctgat gatctcccg	780
acccccgaag tgacctgcgt ggtggtggac gtgtccacg aggacctga agtgaagttc	840
aattggtatg tggacggcgt ggaagtgcac aacccaaga ccaagcccag agaggacag	900
tacaactcca cctaccgggt ggtgtctgtg ctgacctgac tgcaccagga ctggctgaac	960
ggcaaagagt acaagtgcga ggtgtccaac aaggccctgc ctgccccat cgaaaagacc	1020
atctccaagg ccaagggcga gcctcgcgag cctcaggtgt acacactgcc ccctagccgg	1080
gaagagatga ccaagaacca ggtgtccctg acctgtctgg tgaaaggctt ctaccctcc	1140
gatatcgccg tggaatggga gtccaacggc cagcccgaga acaactacaa gaccaccccc	1200
cctgtgctgg actccgacgg ctcatcttct ctgtactcca agctgacctg ggacaagtcc	1260
cgggtggcagc agggcaactg gttctcctgc tccgtgatgc acgaggccct gcacaaccac	1320
tacaccaga agtcctctgc cctgagccct ggaaaggcg gaggcggctc tgggtggtgga	1380
ggctctggag gcggaggctc taccatccct ccacacgtgc agaaatccgt gaacaacgac	1440
atgatcgtga ccgacaacaa cggcgccgtg aagttcccc agctgtgcaa gttctgacg	1500
gtgcggttct ctacctgcga caaccagaaa tctgcatgt ccaactgctc catcacctcc	1560
atctgcgaga agccccagga agtgtgcgtg gccgtgtggc ggaagaacga cgagaacatc	1620
acctggaaa ccgtgtgcca cgaccccaag ctgccctacc acgattcat cctggaagat	1680
gccgcctccc ccaagtgcac catgaaggaa aagaagaagc ccggcgagac attcttcatg	1740
tgcagctgct cctccgacga gtgcaacgac aacatcatct tctccgaaga gtacaacacc	1800
tccaaccccg actgaggtac c	1821

<210> SEQ ID NO 115

<211> LENGTH: 657

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 115

gagctcgaca tccagatgac ccagtcccc tccagcctgt ccgcctctgt gggcgacaga	60
gtgacctca cctgtcgggc ctctcaggac gtgaacaccg ccgtggcctg gtatcagcag	120
aagcctggca agggccccaa gctgctgac tactccgect ccttctctga ctccgggggtg	180
ccatcccggg tctccggctc tagatccggc accgacttca ccctgacct ctccagcctg	240
cagcccgagg acttcgccac ctactactgc cagcagcact acaccacccc cctacacctc	300
ggccagggca ccaaggtgga aatcaagcgg accgtggcgg ctccctccgt gtteatcttc	360
ccaccctccg acgagcagct gaagtctggc accgcctccg tcgtgtgcct gctgaacaac	420
ttctaccccc gcgaggccaa ggtgcagtgg aaggtggaca acgcctgca gtccggcaac	480
tcccaggaat ccgtgacga gcaggactcc aaggacagca cctactcctt gtctccacc	540

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ctgacctgt ccaaggccga ctacgagaag cacaaggtgt acgctgcga agtgaccac	600
caggcctgt ccagccccgt gaccaagtcc ttcaaccggg gcgagtgtg aggtacc	657

<210> SEQ ID NO 116
 <211> LENGTH: 1818
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 116

gagctccagg tgcagctgaa gcagtcggc ccaggactgg tgcagccttc ccagtcctg	60
tccatcacct gtaccgtgtc cggcttctcc ctgaccaact acggcgtgca ctgggtccga	120
cagtcctcag gcaaggccct ggaatggctg ggagtgttt ggagcggcgg caacaccgac	180
tacaacaccc ccttcacctc cgggtgttcc atcaacaagg acaactcaa gtcccagggtg	240
ttcttcaaga tgaactccct gcagtcacac gacaccgcca tctactactg cgccagagcc	300
ctgacctact atgactacga gttcgcctac tggggacagg gcacctggt caccgtgtct	360
gccgcctcta ccaaggcccc ctccgtgttt cccctggccc cctccagcaa gtccacatct	420
ggcggcaccg ccgctctggg ctgcctgttc aaggactact tccccgagcc cgtgaccgtg	480
tcctggaact ctggcgccct gacctccggc gtgcacacct ttccagccgt gctgcagtcc	540
tcggcctgt actccctgtc ctccgtcgtg accgtgccct ccagctctct gggcaccag	600
acctacatct gcaacgtgaa ccacaagccc tccaacacca aggtggacaa gcgggtggaa	660
cccaagtcct gcgacaagac ccacacctgt cccccctgcc ctgcccctga actgctggga	720
ggcccttcctg tgttccctgt cccccaaaag cccaaggaca ccctgatgat ctcccgacc	780
cccgaagtga cctgcgtggt ggtggacgtg tccacgagg accctgaagt gaagtcaat	840
tggtacgtgg acggcgtgga agtgacacac gccaaagacca agcccagaga ggaacagtac	900
aactccacct accgggtggt gtccgtgtg accgtgtgtc accaggactg gctgaacggc	960
aaagagtaca agtgcaaggt ctccaacaag gcctgcctg ccccatcga aaagaccatc	1020
tccaaggcca agggccagcc ccgcgagcct caggtgtaca ctctgcctcc cagccgggac	1080
gagctgacca agaaccaggt gtccctgacc tgtctgttca agggcttcta cccctccgat	1140
atcgccgtgg aatgggagtc caacggccag cccgagaaca actacaagac cccccccct	1200
gtgctggact ccgacggctc attcttctg tactccaagc tgaccgtgga caagtcccg	1260
tggcagcagg gcaacgtgtt ctctgtctcc gtgatgcac aggcctgca caaccactac	1320
accagaagt cctgtctct gagccccgc aaggcggag gcggtctgg tgggtgtggc	1380
tctggtggcg gaggctctac catccctcca cagtgacaga aatccgtgaa caacgacatg	1440
atcgtgaccg acaacaacgg cgccgtgaag ttccccagc tgtgcaagtt ctgacgctg	1500
cggttctcta cctgcgacaa ccagaaatcc tgcattgtca actgtccat cactccatc	1560
tgcgagaagc cccaggaagt gtgcgtcgcc gtctggcgga agaacgacga gaacatcacc	1620
ctgaaaaccg tgtgccacga ccccaagctg ccctaccacg atttcatcct ggaagatgcc	1680
gcctccccca agtgatcat gaaggaaaag aagaagccg gcgagacttt cttcatgtgc	1740
agctgtctct ccgacgagtg caacgacac atcatcttct ccgaagagta caacacctcc	1800
aacccccgact gaggtacc	1818

<210> SEQ ID NO 117
 <211> LENGTH: 657
 <212> TYPE: DNA

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 117

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gagctcgata tectgetgac ccagtcctcc gtgatcctgt ccgtgtctcc tggcgagcgg      60
gtgtccttct cctgccgggc ctcccagtc atcggcacca acatccactg gtatcagcag      120
cggaccaacg gctcccctcg gctgctgatt aagtacgcct ccgagtctat ctccggcatc      180
ccctcccggt tctccggctc tggctccggc accgacttca ccctgtccat caactccgtg      240
gaatccgagg atatgcgga ctactactgc cagcagaaca acaactggcc caccaccttc      300
ggcgctggca ccaagctgga actgaagcgg accgtggccg ctccctccgt gttcatcttc      360
ccacctcccg acgagcagct gaagtccggc accgcctccg tcgtgtgcct gctgaacaac      420
ttctaccccc gcgaggccaa ggtgcagtgg aaggtggaca acgccttgca gtccggcaac      480
tcccaggaat ccgtcacga gcaggactcc aaggacagca cctactccct gtccctccacc      540
ctgacctgtg ccaaggccga ctacgagaag cacaaggtgt acgcctgcga agtgacccac      600
cagggcctgt ccagccccgt gaccaagtc ttcaaccggg gcgagtgtg aggtacc      657

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<210> SEQ ID NO 118

<211> LENGTH: 1824

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 118

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gagctccagg tgcagctgca gcagcctggc gccgagctgg tcaagcctgg cgcttccgtg      60
aagatgtcct gcaaggcctc cggtacacc ttaccagct acaacatgca ctgggtcaag      120
cagacccccg gcagaggcct ggaatggatc ggcccatct ccccgccaa cggcgacacc      180
tcctacaacc agaagttaa gggaaaggcc accctgaccg ccgacaagtc ctctccacc      240
gcctacatgc agctgtctc cctgacctcc gaggaactcc ccgtgtacta ctgcgcccg      300
tccacctact acggcggcga ctggtacttc aacgtgtggg gcgctggcac caccgtgacc      360
gtgtctgccg cctctaccaa gggccctcc gtgtttcccc tggcccccct cagcaagtc      420
acatctggcg gcaccggcgc tctgggtgc ctggtcaagg actacttccc cgagcccgtg      480
acagtgtcct ggaactctgg cgcctgacc agcggcgtgc acacettcc agccgtgctg      540
cagtcctctg gcctgtactc cctgtccagc gtcgtgaccg tgcctccag ctctctgggc      600
acccagacct acatctgcaa cgtgaaccac aagccctcca acaccaaggt ggacaagaag      660
gccgagccca agtctctgga caagaccac acctgtcccc cctgccctgc cctgaaactg      720
ctgggaggcc cttctgtgtt cctgttcccc ccaaagccca aggacacct gatgatctcc      780
cggacccccg aagtgacctg cgtggtggtg gacgtgtccc acgaggacce tgaagtgaag      840
ttcaattggt acgtggacgg cgtggaagtg cacaacgcca agaccaagcc cagagaggaa      900
cagtacaact ccacctaccg ggtggtgtcc gtgctgaccg tgctgcacca ggactggctg      960
aacggcaaaag agtacaagtg caagggtgcc aacaaggccc tgccctgccc catcgaaaag      1020
accatctcca aggccaaagg ccagccccgc gagcctcagg tgtacactct gcctcccagc      1080
cgggacgagc tgaccaagaa ccagggtgcc ctgacctgtc tggccaaggg cttctacccc      1140
tccgatatcg ccgtggaatg ggagtccaac ggccagcccg agaacaacta caagaccacc      1200
ccccctgtgc tggactccga cggtcattc ttctgtact ccaagctgac cgtggacaag      1260
tcccgggtgc agcaggccaa cgtgttctcc tgctccgtga tgcacgaggc cctgcacaac      1320
cactacaccc agaagtccct gtccctgagc cccggaaagg gcggaggcgg atctggtggt      1380

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ggaggatcag gcggcggagg ctctaccatc cccccacacg tgcagaaatc cgtgaacaac 1440
gacatgatcg tgaccgacaa caacggcgcc gtgaagttcc ccagctgtg caagttctgc 1500
gacgtgcggt tctctacctg cgacaaccag aaatcctgca tgtccaactg ctccatcacc 1560
tccatctgcg agaagcccca ggaagtgtgc gtcgccgtct ggcggaagaa cgacgagAAC 1620
atcaccttgg aaacctgtg ccacgacccc aagctgccct accacgactt catcctggaa 1680
gatgccgctt cccccaaagt catcatgaag gaaaagaaga agccccggcga gactttcttc 1740
atgtgctctt gctcctccga cgagtgcAAC gacaacatca tcttctccga agagtacaac 1800
acctccaacc ccgactgagg tacc 1824

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```

<210> SEQ ID NO 119
<211> LENGTH: 654
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

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<400> SEQUENCE: 119
gagctccaga tcgtgctgtc ccagtccccc gccatcctgt ctgctagccc tggcgagaaa 60
gtgacaatga cctgcggggc ctctcctccc gtgtcctaca tccactggtt ccagcagaag 120
cccggtccca gcccgaagcc ctggatctac gccacctcca acctggcctc cggcggtgcca 180
gtgcggttct ctggctccgg ctccggcacc tctactccc tgaccatctc ccgggtggaa 240
gccgaggacg ccggcaccta ctactgccag cagtggacct ccaaccccc cacttttggc 300
ggaggcacca agctggaat caagcggacc gtggccgctc cctccgtgtt catcttccca 360
ccctccgacg agcagctgaa gtccggcacc gcctccgtcg tgtgcctgct gaacaacttc 420
taccgccgag aggccaaagt gcagtggaag gtggacaacg ccctgcagtc cggcaactcc 480
caggaatccg tcaccgagca ggactccaag gacagcacct acagcctgtc ctccacctg 540
acctgtcca aggccgacta cgagaagcac aaggtgtacg cctgcgaagt gaccaccag 600
ggcctgtcca gccccgtgac caagtccttc aaccggggcg agtgcagagg tacc 654

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```

<210> SEQ ID NO 120
<211> LENGTH: 1830
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 120
gagctcgagg tgcagctggt ggaatccggc ggaggcctgg tccagcctgg cggatccctg 60
agactgtcct gtgccgcctc cggtacacc ttcaccaact acgcatgaa ctgggtccga 120
caggcccttg gcaagggcct ggaatgggtc ggatggatca acacctacac cggcgagccc 180
acctacgccc ccgacttcaa gcggcgggtc accttctccc tggacacctc caagtcacc 240
gectacctgc agatgaactc cctgcgggcc gaggacaccg ccgtgtacta ctgcgccaag 300
taccacctact actacggctc ctccactgg tacttcgacg tgtggggcca gggcaccctg 360
gtcacctgtt cctccgcctc taccaggggc ccctccgtgt tccctctggc cccctccagc 420
aagtcacat ctggcggcac cgccgctctg ggctgcctgg tcaaggacta cttccccgag 480
cccgtgaccg tgtcctggaa ctctggcgcc ctgacctccg gcgtgcacac ctttccagcc 540
gtgtgcagct cctccggcct gtactccctg tctccgtcg tgacctgcc ctccagctct 600
ctgggcaccc agacctacat ctgcaacgtg aaccacaagc cctccaacac caaggtggac 660
aagaaggtgg aaccgaagtc ctgcgacaag acccacacct gtccccctg cctgcccct 720

```

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gaactgctgg gaggcctag cgtgttctg tccccccaa agcccaagga caccctgatg	780
atctcccga cccccaagt gacctgcgtg gtggtggacg tgtcccacga ggacctgaa	840
gtgaagtcca attggtacgt ggacggcgtg gaagtgcaca acgccaagac caagcccaga	900
gaggaacagt acaactccac ctaccgggtg gtgtccgtgc tgacctgct gcaccaggac	960
tggtgaacg gcaaagagta caagtgcaag gtgtccaaca aggcctgccc tgccccatc	1020
gaaaagacca tctccaaggc caaggccag ccccgcgagc ctcagggtga cactctgccc	1080
cctagccggg aagagatgac caagaaccag gtgtccctga cctgtctggt caagggttc	1140
tacctctccg atatcgccgt ggaatgggag tccaacggcc agcccagaaa caactacaag	1200
accaccccc ctgtgctgga ctccgacggc tcattcttcc tgtactcaa gctgacctg	1260
gacaagtccc ggtggcagca gggaacgtg ttctctgct ccgtgatgca cgaggccctg	1320
cacaaccact acaccagaa gtccctgtcc ctgagcccag gcaagggcgg aggcggatct	1380
ggtggtggag gatcaggcgg cggaggtct accatcccc cacacgtgca gaaatccgtg	1440
aacaacgaca tgatcgtgac cgacaacaac ggcgccgtga agttcccca gctgtgcaag	1500
ttctgcgacg tgccgttctc tacctgcgac aaccagaaat cctgcatgtc caactgctcc	1560
atcacctcca tctgcgagaa gcccaggaa gtgtgcgtcg ccgtctggcg gaagaacgac	1620
gagaacatca ccttggaac cgtgtgccac gacccaagc tgccctacca cgacttcac	1680
ctggaagatg ccgcctcccc caagtgcac atgaaggaaa agaagaagcc cggcgagact	1740
ttcttcatgt gcagctgctc ctccgacgag tgcaacgaca acatcatctt ctccgaagag	1800
tacaacacct ccaaccccga ctgaggtacc	1830

<210> SEQ ID NO 121
 <211> LENGTH: 657
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 121

gagctcgata tccagatgac ccagtcctcc tccagcctgt ccgcctctgt gggcgacaga	60
gtgacctca cctgttccgc cagccaggac atctccaact acctgaactg gtatcagcag	120
aagcccgga aggcctctaa ggtgctgac tacttcacct cctccctgca ctccggcgtg	180
ccctccagat tctccggctc tggtccggc accgacttta cctgacct ctccagcctg	240
cagcccgagg acttcgccac ctactactgc cagcagtaact ccacgtgcc ctggaccttc	300
ggccagggca ccaaggtgga aatcaagcgg accgtggccg ctccctccgt gttcatcttc	360
ccaccctccg acgagcagct gaagtccggc accgcctccg tcgtgtgcct gctgaacaac	420
ttctaccccc gcgaggccaa ggtgcagtgg aaggtggaca acgcctgca gtccggcaac	480
tcccaggaat ccgtcaccga gcaggactcc aaggacagca cctactccct gtctccacc	540
ctgacctgt ccaaggccga ctacgagaag cacaaggtgt acgcctgcga agtgacctac	600
cagggcctgt ccagcccccgt gaccaagtcc ttcaaccggg gcgagtgtg aggtacc	657

<210> SEQ ID NO 122
 <211> LENGTH: 40
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic construct

<400> SEQUENCE: 122

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly

- continued

1	5	10	15
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly			
	20	25	30
Gly Gly Ser Gly Gly Gly Gly Ser			
	35	40	

What is claimed is:

1. An isolated molecule comprising a targeting moiety fused with an immunomodulatory moiety, wherein:

- (a) the targeting moiety specifically binds Cytotoxic T-lymphocyte associated antigen-4 (CTLA-4); and
- (b) the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain of Transforming growth factor-beta receptor (TGF- β R).

2. The molecule of claim 1, wherein the targeting moiety comprises an antibody, antibody fragment, scFv, or Fc-containing polypeptide that specifically binds CTLA-4.

3. The molecule of claim 1, wherein the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain of Transforming growth factor-beta receptor selected from the group consisting of SEQ ID NO: 79-91.

4. The molecule of claim 3, wherein the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain of Transforming growth factor-beta receptor II (TGF- β RII).

5. The molecule of claim 4, wherein the immunomodulatory moiety comprises the amino acid sequence corresponding to SEQ ID NO: 87 or a binding fragment thereof.

6. The molecule of claim 5, wherein the molecule comprises the amino acid sequence corresponding to SEQ ID NO: 5 or a binding fragment thereof.

7. The molecule of claim 6, wherein the molecule comprises the amino acid sequence corresponding to SEQ ID NO:

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5 or a binding fragment thereof and the amino acid sequence corresponding to SEQ ID NO: 74 or a binding fragment thereof.

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8. A method of treating a neoplastic disease comprising: administration to a subject in need thereof one or more molecules of claim 1, wherein the neoplastic disease is bladder cancer or melanoma.

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9. The method of claim 8, wherein the subject is administered in combination with another anticancer therapy.

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10. The method of claim 8, wherein the anticancer therapy comprises a chemotherapeutic molecule, antibody, small molecule kinase inhibitor, hormonal agent, ionizing radiation, ultraviolet radiation, cryoablation, thermal ablation, or radiofrequency ablation.

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11. The method of claim 8, wherein the subject is administered in combination with a vaccine.

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12. The method of claim 8, wherein the subject is human.

13. The isolated molecule of claim 1, further comprising a linker at the C_H3 region of the Fc.

14. The isolated molecule of claim 13, wherein the linker is (GGGS)_n (SEQ ID NO:104), and wherein n is 1, 2, 3, 4, 5, 6, 7 or 8.

15. The isolated molecule of claim 13, wherein the linker comprises the amino acid sequence GGGGSGGGGSGGGGS (SEQ ID NO:104).

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