



US009441044B2

(12) **United States Patent**
Bedi et al.

(10) **Patent No.:** **US 9,441,044 B2**
(45) **Date of Patent:** **Sep. 13, 2016**

(54) **COMPOSITIONS AND METHODS FOR
TARGETED IMMUNOMODULATORY
ANTIBODIES AND FUSION PROTEINS**

- (71) Applicant: **The Johns Hopkins University**,
Baltimore, MD (US)
- (72) Inventors: **Atul Bedi**, Timonium, MD (US);
Rajani Ravi, Ruxton, MD (US)
- (73) Assignee: **The Johns Hopkins University**,
Baltimore, MD (US)
- (*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

(21) Appl. No.: **14/645,282**

(22) Filed: **Mar. 11, 2015**

(65) **Prior Publication Data**

US 2015/0183881 A1 Jul. 2, 2015

Related U.S. Application Data

- (63) Continuation of application No. 13/582,717, filed as
application No. PCT/US2011/027317 on Mar. 4,
2011, now Pat. No. 8,993,524.
- (60) Provisional application No. 61/435,671, filed on Jan.
24, 2011, provisional application No. 61/311,255,
filed on Mar. 5, 2010.

(51) **Int. Cl.**

C07K 16/00 (2006.01)
C07K 16/28 (2006.01)
C07K 14/495 (2006.01)
C07K 14/705 (2006.01)
C07K 14/71 (2006.01)
A61K 39/395 (2006.01)
A61K 45/06 (2006.01)
A61K 47/48 (2006.01)
A61K 39/00 (2006.01)

(52) **U.S. Cl.**

CPC **C07K 16/2863** (2013.01); **A61K 39/3955**
(2013.01); **A61K 45/06** (2013.01); **A61K**
47/48384 (2013.01); **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); **C07K 14/71** (2013.01);
C07K 16/28 (2013.01); **C07K 16/2812**
(2013.01); **C07K 16/2815** (2013.01); **C07K**
16/2851 (2013.01); **A61K 2039/505** (2013.01);
C07K 2317/622 (2013.01); **C07K 2317/73**
(2013.01); **C07K 2317/76** (2013.01); **C07K**
2319/00 (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

7,317,091 B2	1/2008	Lazar et al.	
7,527,791 B2	5/2009	Adams et al.	
7,795,389 B2	9/2010	Sun et al.	
7,803,378 B2	9/2010	Tranchand-Bunel	
7,820,165 B2 *	10/2010	McKenna	C07K 16/22 424/134.1
8,399,618 B2	3/2013	Lazar et al.	
8,815,247 B2	8/2014	Govindappa et al.	
2005/0054832 A1	3/2005	Lazar et al.	
2006/0135459 A1	6/2006	Epstein et al.	
2006/0263368 A1	11/2006	Rosenblum et al.	
2007/0212337 A1	9/2007	Bedi et al.	
2007/0244042 A1	10/2007	Sun et al.	
2008/0075717 A1	3/2008	Tranchand-Bunel	
2009/0053240 A1	2/2009	Lazar et al.	
2009/0226435 A1	9/2009	Khare	
2011/0052585 A1 *	3/2011	Scaria	C07K 14/7155 424/134.1

OTHER PUBLICATIONS

Zhang et al. 2009. Prog in Nat Sci. 19:1197-1200.*
Supplementary European Search Report from Related International
Application No. EP 11 75 1481.
Zhang et al. "Expression of a Soluble TGF- β Receptor by Tumor
Cells Enhances Dendritic Cell/Tumor Fusion Vaccine Efficacy¹"; J.
Immunology, 2008, 181, pp. 3690-3697.
Kwiatkowska et al.: "Expression of soluble recombinant TGF- β
type II receptor fused with the Fc portion of human IgG1 (sT β II-Fc)
in NSO cells"; *Acta Biochimica Polonica*, 2006, 53(2), pp. 361-369.

* cited by examiner

Primary Examiner — Shulamith H Shafer

(74) Attorney, Agent, or Firm — DLA Piper LLP (US)

(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 chemothera-
peutic agents or tumor-targeted antibodies via specific
immunosuppressive mechanisms in the tumor microenvi-
ronment and such ability of cancer cells is recognized as
immune tolerance. Such immunosuppressive mechanisms
include immunosuppressive cytokines (for example, Trans-
forming growth factor beta (TGF- β)) and regulatory T cells
and/or immunosuppressive myeloid dendritic cells (DCs).
By counteracting tumor-induced immune tolerance, the pre-
sent 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 antitu-
mor immunity against resistant or disseminated cancer cells.

10 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* *QEVCAVVRK* *NDENITLETV* *CHDPKLPYHD* *FILEDAASPK*
CIMKEKKKPG *ETFFMCSCSS* *DECNDNIIFS* *EEYNTSNPDL* *LLVIFQVTGI* *SLLPPLGVAI*
SVIIIFYCYR VNRQQLSST WETGKTRKLM EFSEHCAIIL EDDRSDISST CANNINHNT
LLPIELDTLV GKGRFAEVYK AKLKQNTSEQ FETVAVKIFP YEEYASWKTE KDIFSDINLK
HENILQFLTA EERKTELGKQ YWLITAFHAK GNLQEYLTRH VISWEDLRKL GSSLARGIAH
LHSDHTPCGR PKMPIVHRDL KSSNILVKND LTCCLCDFGL SLRLDPTLSV DDLANSQVVG
TARYMAPEVL ESRMNLNVE SFKQTDVYSM ALVLWEMTSR CNAVGEVKDY EPPFGSKVRE
HPCVESMKDN VLRDRGRPEI PSFWLNHQGI QMVCETLTEC WDHDPEARLT AQCVAERFSE
LEHLDRLSGR SCSEEKIPED GSLNNTTK

[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* *ICEKPQEVCAV* *AVVRKNDENI*
TLETVCHDPK *LPYHDFILED* *AASPKCIMKE* *KKKPGETFFM* *CSCSSDECND* *NIIFSEEYNT*
SNPDLLLVIF *QVTGISLLPP* *LGVAISVII* *FYCYRVNRQQ* *KLSTWETGK* *TRKLMEFSEH*
CAIILEDERS DISSTCANNI NHNTPELLIE LDTLVGKGRF AEVYKAKLKQ NTSEQFETVA VKI FP
YEEYASWKTE KDIFSDINLK HENILQFLTA EERKTELGKQ YWLITAFHAK GNLQEYLTRH
VISWEDLRKL GSSLARGIAH LHSDHTPCGR PKMPIVHRDL KSSNILVKND LTCCLCDFGL
SLRLDPTLSV DDLANSQVVG TARYMAPEVL ESRMNLNVE SFKQTDVYSM ALVLWEMTSR
CNAVGEVKDY EPPFGSKVRE HPCVESMKDN VLRDRGRPEI PSFWLNHQGI QMVCETLTEC
WDHDPEARLT AQCVAERFSE LEHLDRLSGR SCSEEKIPED GSLNNTTK

[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* *QEVCAVVRK* *NDENITLETV* *CHDPKLPYHD* *FILEDAASPK*
CIMKEKKKPG *ETFFMCSCSS* *DECNDNIIFS* *EEYNTSNPDL* *LLVIFQVTGI* *SLLPPLGVAI*
SVIIIFYCYR VNRQQLSST WETGKTRKLM EFSEHCAIIL EDDRSDISST CANNINHNT
LLPIELDTLV GKGRFAEVYK AKLKQNTSEQ FETVAVKIFP YEEYASWKTE KDIFSDINLK
HENILQFLTA EERKTELGKQ YWLITAFHAK GNLQEYLTRH VISWEDLRKL GSSLARGIAH
LHSDHTPCGR PKMPIVHRDL KSSNILVKND LTCCLCDFGL SLRLDPTLSV DDLANSQVVG
TARYMAPEVL ESRMNLNVE SFKQTDVYSM ALVLWEMTSR CNAVGEVKDY EPPFGSKVRE
HPCVESMKDN VLRDRGRPEI PSFWLNHQGI QMVCETLTEC WDHDPEARLT

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 NIIFSEEYNT
SNPDLLLVI F QVTGISLEPP LGVAISVIII FYCYRVNRQQ KLSSTWETGK TRKLMEFSEH
 CAIILEDERS DISSTCANNI NHNTELLPIE LDTLVGKGRF AEVYKAKLKQ NTSEQFETVA VKI FP
 YEEYASWKTE KDIFSDINLK HENILQFLTA EERKTELQKQ YWLITAFHAK GNLOEYLTRH
 VISWEDLRKL GSSLARGIAH LHSHTPCGR PKMPIVHRDL KSSNILVKND LTCCLCDFGL
 SLRLDPTLSV DDLANSQVG TARYMAPEVL ESRMNLNVE SFKQTDVYSM ALVLWEMTSR
 CNAVGEVKDY EPPFGSKVRE HPCVESMKDN VLRDRGRPEI PSFWLNHQGI QMVCETLTEC
 WDHDPEARL

(ii) TGF- β R-II (Δ cyt): 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 ETTFCSCSS DECNDNIIFS EYNTSNPD LLVIFQVTGI SLPLPGVAI
 SVIIIFCYR VNRQQLSS

TGF- β R-IIB (Δ cyt): 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 NIIFSEEYNT
SNPDLLLVI F QVTGISLEPP LGVAISVIII FYCYRVNRQQ KLSS

(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 ETTFCSCSS 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 NIIFSEEYNT
SNPDLLLVI F 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 ETTFCSCSS
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 NIIFSEEYNT 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 ETTFCSCSS 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 QEVCAVWRK NDNITLETV CHDPKLPYHD FILEDAASPK
 CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EYNTSNPDL LLVIFQVTGI SLLPPLGVAI
 SVIIIFYCYR VNRQQLSST WETGKTRKLM EFSEHCAIIL EDDRSDISST CANNINHNT
 LLPIELDTLV GKGRFAEVYK AKLKQNTSEQ FETVAVRIFP YEEYASWKTE KDIFSDINLK
 HENILQFLTA EERKTELGKQ YWLITAFHAK GNLQEYLTRH VISWEDLRKL GSSLARGIAH
 LHS DHTPCGR PKMPFIVHRDL KSSNIVKND LTCCLCDFGL SLRLDPTLSV DDLANSQVVG
 TARYMAPEVL ESRMNLENVE SFKQTDVYSM ALVLWEMTSR CNAVGEVKDY EPPFGSKVRE
 LEHLDRLSGR SCSEEEKIPED GSLN'TTK

(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 QEVCAVWRK NDNITLETV CHDPKLPYHD FILEDAASPK
 CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EYNTSNPDL LLVIFQVTGI SLLPPLGVAI
 SVIIIFYCYR VNRQQLSST WETGKTRKLM EFSEHCAIIL EDDRSDISST CANNINHNT
 LLPIELDTLV GKGRFAEVYK AKLKQNTSEQ FETVAVKIFP YEEYASWKTE KDIFSDINLK
 HENILQFLTA EERKTELGKQ YWLITAFHAK GNLQEYLTRH VISWEDLRKL GSSLARGIAH
 LHS DHTPCGR PKMPFIVHRDL KSSNIVKND LTCCLCDFGL SLRLDPTLSV DDLANSQVVG
 TARYMAPEVL ESRMNLENVE SFKQTDVYSM ALVLWEMTSR CNAVGEVKDY EPPFGSKVRE
 HPCVESMKDA SGIQMV CETL TECWDHDEA RLTAQCVAER FSELEHLDRL SGRSCSEKI
 PEDGSLN'TTK

4. Amino acid sequences of transforming growth factor beta receptor type III (TGF- β -RIII) 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**IKDTYIH**WVRQAPGKGLEW**VARIYPTNGYTRYADSVKGR
FTISADTSKNTAYLQMNSLRAEDTAVYYCSR**WGGDGFYAMDYWGQ**GLTVTVSSASTKGPSVFPLA
PSSKSTSGGTAALGCLVKDYFPEP**TVSVNSGALTSGVHTFPAVLQSSGLYSLSSVTVFSSSLGT**
QTYICNVNHKPSNTKVDKKVEPKSCDK**TH**TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC
VVVDVSHEDPEVKFNWYVDGVEVHNA**TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA**
LPAPIEKTI**SKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT**
TPPVLDSDGSFFLYSKLTVDKSRWQQGNV**FSCSVMEALHNHYTQKSLSLSPGK**
GGGGSGGGSGGGGS TIPPHVQK SVNNDMIVTD NNGAVKFPQL CKFCDVREFT
CDNQKSCMSN CSITSICEKP QEVCAVWRK NDENITLETV CHDPKLPYHD FILEDAASPK
CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EYNTSNPD

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

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFS**SGSR**
SGTDFTLT**ISSLPEDFATYYCQQHYTTPPTFGQG**TKVEIKRTVAAPSVFIFPPSDEQLKSGTASV
VCLLNNFYFPREAKVQWKVDNALQSGNSQESVTEQDSK**DSTYLSSTLTLSKADYEKHKVYACEVTH**
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):

QVQLKQSGPGLVQPSSQLSITCTVSGFSLTNYGVHWVRQSPGKGLEWLGVIWSGGNTDYNTPTTSR
LSINKDNSKSQVFFKMNSLQSNDAIYYCARALTYDYEFAYWGQGLTVTVSAASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ
TYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL
PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK
GGGGSGGGSGGGGS TIPPHVQK SVNNDMIVTD NNGAVKFPQL CKFCDVRFST
CDNQKSCMSN CSITSICEKP QEVCAVWRK NDENITLETV CHDPKLPYHD FILEDAASPK
CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EYNTSNPD

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

DILLTQSPVILSVSPGERVSFSCRASQSIGTNIHWYQRTNGSPRLLIKYASESISGIPSRFSGSG
SGTDFTLSINSVESEDIADYYCQQNNNWPTTFGAGTKLELKR
TVAAAPSVFIFPPSDEQLKSGTASV
VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYSLSSTLTLSKADYEEKHKVYACEVTH
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
KATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAGTTVTVSAASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLG
TQTYICNVNHKPSNTKVDKKAEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGSGGGGS **TIPPHVQK** **SVNNDMIVTD** **NNGAVKFPQL** **CKFCDVRFST**
CDNQKSCMSN **CSITSICEKP** **QEVCAVWRK** **NDENITLETV** **CHDPKLPYHD** **FILEDAASPK**
CIMKEKKKPG **ETFFMCSCSS** **DECNDNIIFS** **EEYNTSNPD**

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

QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWIYATSNLASGVPVRFSGSGS
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):

EVQLVESGGGLVQPGGSLRLSCAASGYTFTNYGMNWVRQAPGKGLEWVGWINTYTGEPTYAADFKR
RFTFSLDTSKSTAYLQMNSLRAEDTAVYYCAKYPHYYGSSHWYFDVWGQGTLVTVSSASTKGPSVF
PLAPSSKSTSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPS
SSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHCTCPPCPAPELLGGPSVFLFPPKPKDTL
MISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN
KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA
VEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS
LSSPGK
GGGGSGGGSGGGGS **TIPPHVQK** **SVNNDMIVTD** **NNGAVKFPQL** **CKFCDVRFST**
CDNQKSCMSN **CSITSICEKP** **QEVCAVWRK** **NDENITLETV** **CHDPKLPYHD** **FILEDAASPK**
CIMKEKKKPG **ETFFMCSCSS** **DECNDNIIFS** **EEYNTSNPD**

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

DIQMTQSPSSLSASVGDRVTITCSASQDISNYLNWYQQKPGKAPKVLIYFTSSLHSGVPSR
FSGSGSGTDFTLTISSLPEDFATYYCQYSTVPWTFGQGTKVEIKRTVAAPS
VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLS
SSTLTLSKADYEKHKVYACEVTH
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 ISYDGNNKYY
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 NYKTTTPVLD SDGSFFLYSK LTVDKSRWQQ
GNVFSCSVMH EALHNHYTQK SLSLSPGK GGGGSGGGGSGGGGS **TIPPHVQK SVNNDMIVTD**
NNGAVKFPQL CKFCDVRFST CDNQKSCMSN CSITSICEKP QEVCAVVRK NDENITLETV
CHDPKLPYHD FILEDAASPK CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EYNTSNPD

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

EIVLTQSPGT LSLSPGERAT LSCRASQSVG SSYLAWYQQK PGQAPRLLIY GAFSRATGIP
DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ QYGSSPWTFG QGTKVEIKRT VAAPSVFIFP
PSDEQLKSGT ASVVCLLNMF YPREAKVQWK VDNALQSGNS QESVTEQDSK DSTYSLSSTL
TLSKADYEKH KVYACEVTHQ 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):

APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPL
EEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTL
T GGGGSGGGSGGGGS
 THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
 REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFSCSVMEALHNHYTQKSLSLSPGK GGGGSGGGSGGGGS **TIPPHVQK SVNNDMIVTD**
NNGAVKFPQL CKFCDVRFST CDNQKSCMSN CSITSICEKP QEVCVAVWRK NDENITLETV
CHDPKLPYHD FILEDAASPK CIMKEKKKPG ETFFMCSCSS DECNDNIIFSEEYNTSNPD

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

TIPPHVQK SVNNDMIVTD NNGAVKFPQL CKFCDVRFST CDNQKSCMSN CSITSICEKP
QEVCVAVWRK NDENITLETV CHDPKLPYHD FILEDAASPK CIMKEKKKPG ETFFMCSCSS
DECNDNIIFS EEYNTSNPD GGGGSGGGSGGGGS
 THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
 REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFSCSVMEALHNHYTQKSLSLSPGK GGGGSGGGSGGGGS
APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPL
EEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTL
T

Bold: TGF β RII ectodomain

Italic: Linker (Optional; other linker sequences)

Plain: Fc

Underlined: IL-2 fragment

(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 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
NQKFQDKATI 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 ENSGQPENNY KITPPVLDSG GSFFLYSKLT VDKSRWQQGN
VFSCSVMHEA LHNHYTQKSL SLSPGK *GGGGSGGGSGGGGS* **TIPPHVQK SVNNDMIVTD**
NNGAVKFPQL CKFCDVRFST CDNQKSCMSN CSITSICEKP QEVCVAVWRK NDENITLETV
CHDPKLPYHD FILEDAASPK CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EEYNTSNPD

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

DIQMTQSPST LSASVGDRVIT TCSASSSIS YMHWYQQKPG KAPKLLIYTT SNLASGVPAR
FSGSGSGTEF TLTISSLQPD DFATYYCHQR STYPLTFGQG TKVEVKRTVA APSVFIFPPS
DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSSTLTTL
SKADYEKHKV YACEVTHQGL SSPVTKSFNR 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 YDFDWGQGT LTVSSASTKG
PSVFPLAPSS KSTSGGTAAL GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL
SSVVTVPSSS LGTQTYICNV NHKPSNTKVD KRVEPKSCDK THTCPPCPAP ELLGGPSVFL
FFPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV
VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLPSRDELTKNQ
VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV
FSCSVMEAL HNHYTQKSL LSPGK **GGGGSGGGSGGGGS** **TIPPHVQK SVNNDMIVTD**
NNGAVKFPQL CKFCDVRFST CDNQKSCMSN CSITSICEKP QEVCAVVRK NDENITLETV
CHDPKLPYHD FILEDAASPK CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EYNTSNPD

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

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

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:

QVQLQEAGPGLVKPSETLSLTCSVSGGSISGDYYWFWIRQSPGKGLEWIGYIYGSGGGTNYNPSLN
NRVSISIDTSKNLFSKLRSVTAADTAVYYCASNILKYLHWLLYWCQGVLTVSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLG
TQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK
GGGSGGGSGGGGS **TIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRF**
STCDNQKSCMSNCSITSICEKPQEVCAVVRKNDENITLETVCHDPKLPYHDFILEDAAAPKCI
MK
EKKKPGETFFMCSSSDECNDNIIFSEEYNTSNPD

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

Light chain:

SYELSQPRSVSVSPGQTAGFTCGGDNVGRKSVQWYQQKPPQAPVLVIYADSERPSGIPARFSGSNS
GNTATLTISGVEAGDEADYYCQVWDSTADHWVFGGGTRLTVLGRTVAAPSVFIFPPSDEQLKSGTA
SVVCLLNNFYFPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYSLSSTLTLSKADYEKHKVYACEV
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):

PGWFLDSPDRPWNPTTFSPALLVVTEDGNATFTCSFSNTSESFVLNWYRMSPSNQTDKLAAFPEDR
SQPGQDCRFRVTQLPNGRDFHMSVVRARRNDSTYLCGAISLAPKAQIKESLRAELRVTERRAEVP
TAHPSPSPRPAGQFQTLV *GGGSGGGSGGGGS*
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVSVLTIVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMEALHNHYTQKSLSLSPGK *GGGSGGGSGGGGS*
TIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCAVW
RKNDENITLETVCHDPKLPYHDFILEDAAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYN
TSNPD

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

TIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCAVW
RKNDENITLETVCHDPKLPYHDFILEDAAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYN
TSNPD *GGGSGGGSGGGGS*
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVSVLTIVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMEALHNHYTQKSLSLSPGK *GGGSGGGSGGGGS*
PGWFLDSPDRPWNPTTFSPALLVVTEDGNATFTCSFSNTSESFVLNWYRMSPSNQTDKLAAFPEDR
SQPGQDCRFRVTQLPNGRDFHMSVVRARRNDSTYLCGAISLAPKAQIKESLRAELRVTERRAEVP
TAHPSPSPRPAGQFQTLV

Underlined: PD-1 ectodomain*Italic: Linkers*

Plain: IgG1 Fc

Bold: TGF β RII ectodomain(Note: The first linker sequence *GGGSGGGSGGGGS* 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 (TGF β -RII) ectodomain, Fc, and Receptor activator of nuclear factor- κ B (RANK) Ectodomain:

TGF β RII ectodomain – Fc – RANK ectodomain (SEQ. ID. NO: 13):

TIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCAVAV
RKNDENITLETVCHDPKLPYHDFILEDAAAPKCIIMKEKKKPGETFFMCSSSDECNDNIIFSEEYN
TSNPDGGGGSGGGSGGGSTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSH
EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK
TISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF
FLYSKLTVDKSRWQQGNVVFSCSVMEALHNHYTQKSLSLSPGK GGGGSGGGSGGGGS QI
APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP CGPDEYLDW NEEDKCLLHK
VCDTGKALVA VVAGNSTTPR RACTAGYHW SQDCECCRN TECAPGLGAQ HPLQLNKDTV
CKPCLAGYFS DAFSSTDCKR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG

RANK ectodomain – Fc – TGF β RII ectodomain (SEQ. ID. NO: 14):

QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP CGPDEYLDW NEEDKCLLHK
VCDTGKALVA VVAGNSTTPR RACTAGYHW SQDCECCRN TECAPGLGAQ HPLQLNKDTV
CKPCLAGYFS DAFSSTDCKR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG
GGGGSGGGSGGGSTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEV
KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF
LYSKLTVDKSRWQQGNVVFSCSVMEALHNHYTQKSLSLSPGKGGGGSGGGSGGGST**TIPPHVQKS**
VNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCAVAVWRKN
ENITLETVCHDPKLPYHDFILEDAAAPKCIIMKEKKKPGETFFMCSSSDECNDNIIFSEEYNTSNPD

Bold: TGF β RII 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 MQIPQAFWPV VWAVLQLGWR PGWFLDSPDR PWNPTTFSPA LLVVTEGDNA TFTCSFSNTS
61 ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT
121 YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHFSPSP RPAGQFQTLV VGVVGGGLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDFSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS 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 QDCRFRVTQL PNGRDFHMSV VRARRNDSGT YLCGAISLAP KAQIKESLRA
ELRVTERRAE VPTAHFSPSP RPAGQFQTLV

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

DSPDR PWNPTTFSPA LLVVTEGDNA TFTCSFSNTS ESFVLNWYRM SPSNQTDKLA
AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT YLCGAISLAP KAQIKESLRA
ELRVTERRAE VPTAHFSPSP 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):

EVQLVESGGGLVQPGGSLRLSCAASGFNIRKDTYIHWRQAPGKGLEWVARIYPTNGYTRYADSVKG
RFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLLTVSSASTKGPSVFPLA
PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGT
QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC
VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA
LPAPIEKTIISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

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

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

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFVLYSGVPSRFSGSR
SGTDFTLTITSSLPEDFATYYCQQHYTTPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV
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):

QVQLKQSGPGLVQPSSQLSITCTVSGFSLTNYGVHWVRQSPGKGLEWLGVIWSSGNTDYNTPFTSR
LSINKDNSKSKQVFFKMNSLQSNDAIYYCARALTYDYEFAYWGQGTLLVTVSAASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ
TYICNVNHKPSNTKVDKRVKPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL
PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFFFLYSKLTVDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGSGGGGS **PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS**
ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRTQL PNGRDFHMSV VRARRNDSGT
YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV

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

DILLTQSPVILSVSPGERVSFSCRASQSIGTNIHWYQQRTNGSPRLLIKYASESISGIPSRFSGSG
SGTDFTLISINSVESEDIADYYCQQNNNWPTTFGAGTKLELKRITVAAPSVEFI FPPSDEQLKSGTASV
VCLLNNEYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYSLSSTLTLSKADYEKHKVYACEVTH
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
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TQTYICNVNHKPSNTKVDKKAEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELITKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

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

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

QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFAQKPGSSPKPWIYATSNLASGVFVRFSGSGS
GTSYSLTISRVEAEDAATYYCQWTSNPPTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYFPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHKVYACEVTHQ
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
RFTFSLDTSKSTAYLQMNSLRAEDTAVYYCAKYPHYYGSSHWYFDVWGQGTLVTVSSASTKGPSVF
FLAPSSKSTSGGTAALGCLVKDYFPEPVTSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPS
LGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMEALHNHYTQKSLSLSPGK
GGGGSGGGSGGGGS PGWFLDSPDR PWNPTTFSPA LLVVTEGDNA TFTCSFSNTS
ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT
YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPPSP RPAGQFQTLV

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

DIQMTQSPSSLSASVGDRVTITCSASQDISNYLNWYQQKPGKAPKVLIIYFTSSLHSGVPSRFSGSG
SGTDFTLTITSSLPEDFATYYCQQYSTVPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV
VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEDSKDSTYLSLSTLTLSKADYEKHKVYACEVTH
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 VVQPGKSLRL SCAASGFTFS SYTMHWVRQA PGKGLEWVTF ISYDGNKYY
ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAIYYCARTG WLGPFDDYWGQ GTLTVTSSAS
TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL
YSLSSVVTVP SSSLGTQTYI CNVNHKPSNT KVDKRVEPKS CDKTHTCPPC PAPELLGGPS
VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST
YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT
KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTTPVLD SDGSFFLYSK LTVDKSRWQQ
GNVFSCSVMH EALHNHYTQKSLSLSPGK **GGGSGGGSGGGGS** **PGWFLDSPDR**
PWNPTFSPA LLVVTEGDNA TFTCSFSNTS ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG
QDCRFRVTQL 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 DSTYSLSSSTL
TLISKADYEH KVIACEVTHQ GLSSPVTKSF NRGEK

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
VVSVLTFLHQ DWLNGKEYKC KVSNAKALPAP IEKTISKAKG QPREPQVYTL PPSRDELTKN
QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTTPVLDSG GSFFLYSKLT VDKSRWQQGN
VFSCSVMEHA LHNHYTQKSL SLSPGK GGGGSGGGGSGGGGS

PGWFLDSPDRPWNPPTFSPALLVTEGDNATFTCSFSNT**SESFVLNWMSPSNQTDKLAAPEDRSQPGQDCRFRVTQLPNGRDFHMSVVRAR****RNDSGTYLCGAISLAPKAQIKESLRAELRVTERRAEVPTAHPSPSRPAGQFQTLV**

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 TYSLSTLTTL
SKADYEEKHKV 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 WMHWIKQRPG QGLEWIGAIY PGNSDTSYNQ
KFEGKAKLTA VTSASTAYME LSSLTHEDSA VYYCSRDIYGY YFDWVGQGT 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
FSCVMHEAL HNHYTQKSLS LSPGK GGGGSGGGGSGGGGS
PGWFLDSPDRPWNPPTFSPALLVVTEGDNATFTCSFSNT
SESFVLNWRMSPSNQTDKLAAPEDRSQPGQDCRFRVTQLPNGRDFHMSVVRAR
RNDSGTYLCGAISLAPKAQIKESLRAELRVTERRAEVPTAHPSPSPRPAGQFQTLV

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

QIVSTQSPAI MSASPGEKVT MTCSASSSRS YMQWYQQKPG TSPKRWIYDT SKLASGVPAR
FSGSGSGTSY SLTISSMEAE DAATYYCHQR SSYTFGGGTK LEIKRTVAAP SVFIFPPSDE
QLKSGTASVV CLLNMFYPRE AKVQWKVDNA LQSGNSQESV TEQDSKDSTY SLSSTLTLSK
ADYERHKVYA CEVTHQGLSS PVTKSFNRGE

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: 22):

APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPL
EEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTL
T *GGGGSGGGSGGGGS*
 THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
 REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFSCSVMEALHNHYTQKSLSLSPGK *GGGGSGGGSGGGGS*
PGWFLDSPDRPWNPTTFSPALLVVTEGDNATFTCSFSNTSESFVLNWYRMSPSNQTDKLAAFPEDR
SQPGQDCRFRVTQLPNGRDFHMSVVRARRNDSGYLCAISLAPKAQIKESLRAELRVTERRAEVP
TAHPSPSPRPAGQFQTLV

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

PGWFLDSPDRPWNPTTFSPALLVVTEGDNATFTCSFSNTSESFVLNWYRMSPSNQTDKLAAFPEDR
SQPGQDCRFRVTQLPNGRDFHMSVVRARRNDSGYLCAISLAPKAQIKESLRAELRVTERRAEVP
TAHPSPSPRPAGQFQTLV *GGGGSGGGSGGGGS*
 THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
 REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFSCSVMEALHNHYTQKSLSLSPGK *GGGGSGGGSGGGGS*
APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPL
EEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTL
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:

QVQLQEAGPGLVKPSETLSLTCSVSGGSISGDYYWFWIRQSPGKGLEWIGYIYGSGGGTNYNPSLN
NRVSISIDTSKNLFSKLRSVTAADTAVYYCASNILKYLHWLLYWGQGLVLTVSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLG
TQTYICNVNHKPSNTKVDKRVKPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSVMSVHEALHNHYTQKSLSLSPGK

GGGGSGGGSGGGGS

PGWFLDSPDRPNPPTFSPALLVVTEGDNATFTCSFSNTSESFVLNWYRMSPSNQTDKLAAFPEDR
SQPGQDCRFRVTQLPNGRDFHMSVVRARRNDSTYLCGAISLAPKAQIKESLRAELRVTERRAEVP
TAHPSPSPRPAGQFQTLV

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

Light chain:

SYELSQPRSVSVSPGQTAGFTCGGDNVGRKSVQWYQQKPPQAPVLVIYADSERPSGIPARFSGSNS
GNTATLTISGVEAGDEADYYCQVWDSTADHWVFGGGTRLTLVLGRTVAAPSVFIFPPSDEQLKSGTA
SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEV
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 CGPDEYLDSW NEEDKCLLHK
VCDTGKALVA VVAGNSTTPR RCTAGYHW SDCCECCRN TECAPGLGAQ HPLQLNKDTV
CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG
GGGGSGGGSGGGGS
 THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
 REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFSCSVMEALHNHYTQKSLSLSPGK GGGGSGGGSGGGGS
PGWFLDSPDRPWNPTTFSPALLVTEGDNATFTCSFSNTSESFVLNWMSPSNQTDKLAFFPEDR
SQPGQDCFRVFTQLPNGRDFHMSVVRARRNDSTYLCAISLAPKAQIKESLRAELRVTERRAEVP
TAHPSPSPRPAGQFQTLV

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

PGWFLDSPDRPWNPTTFSPALLVTEGDNATFTCSFSNTSESFVLNWMSPSNQTDKLAFFPEDR
SQPGQDCFRVFTQLPNGRDFHMSVVRARRNDSTYLCAISLAPKAQIKESLRAELRVTERRAEVP
TAHPSPSPRPAGQFQTLVGGGGSGGGSGGGGS
 THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
 REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFSCSVMEALHNHYTQKSLSLSPGK GGGGSGGGSGGGGS QI APPCTSEKHY EHLGRCCNKC
EPGKYMSSKC TTTSDSVCLP CGPDEYLDSW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR
RCCTAGYHW SDCCECCRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR
PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG

Bold: PD-1 ectodomain

Italics: Linker (optional: may delete linker 1 or replace with IEGRDMD (SEQ. ID. NO: 106) or
EPKSCDK (SEQ. ID. NO: 105))

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 CGPDEYLD SW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RACTAGYHW
 121 SQDCECCRRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK
 181 RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPGLIILLLF ASVALVAII FGVCYRKKGK
 241 ALFANLWUWI NEACGRISGD KESSGDSCVS THTANFGQQG ACEGVLLLTLE EETFPEDMC
 301 YPDQGGVCQG TCVGGGPYAQ GEDARMLSLV SKTEIEEDSF ROMPTEDSYM DRFSQPTDQL
 361 LFLTEPGSKS TPFSEPLEV GENDSLSQCF TGTQSTVGSE SCNCTEPLCR TDWTPMSEN
 421 YLQKEVDSGH CPHWAASPSP NWADVCTGCR NPPGEDCEPL VGSPKRGPLP QCAYGMGLPP
 481 EEEASRTEAR DQPEDGADGR LPSSARAGAG SGSSPGGQSP ASGNVTGNSN STFISSGQVM
 541 NFKGDIIVVY VSQTSQEGAA AAAEPMGRPV QEETLARRDS FAGNGPRFPD 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 CGPDEYLD SW 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 CGPDEYLD SW 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 QETFPKYLH YDEETSHQLL CDKCPPGYL KQHCTAKWKT
 61 VCAPCPDHYY TDSWHTSDEC LYCSPVCKEL QYVKQECNRT HNRVCECKEG RYLEIEFCLK
 121 HRSCPPGFGV VQAGTPERNT VCKRCPDGFF SNETSSKAPC RKHTNCSVFG LLLTQKGNAT
 181 HDNICSGNSE STQKCGIDVT LCEEAFRRFA VPTKFTPNWL SVLVDNLPGT KVNAESVERI
 241 KRQHSSEQET FQLKLWKHQ NKAQDIVKKI IQDIDLCEMS 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
DTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQCTLVTVSSASTKGPSVFPLAPSSKSTSGGTAA
LGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKVDK
KVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMH
EALHNHYTQKSLSLSPGK *GGGGSGGGSGGGGS* **QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC**
TTTSDSVCLP CGPDEYLDW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RCTAGYHW
SQDCECCRRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK
RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG

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

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFRSGSRSGTDF
LTISLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA
KVQWKVDNALQSGNSQESVTEQDSKDSTYLSLSSTLTLSKADYEEKHKVYACEVTHQGLSSPVTKSFNRGEC

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):

QVQLKQSGPGLVQPSSQLSITCTVSGFSLTNYGVHWVRQSPGKGLEWLGVIWSGGNTDYNTPFTSRLSINKD
NSKSQVFEFKMNSLQSNDAIYYCARALTYDYEFAYWGQGLVTVSAASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKR
VEPKSCDKTHTCTPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN
AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHE
ALHNHYTQKSLSLSPGK *GGGGSGGGSGGGGS* **QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC**
TTTSDSVCLP CGPDEYLDW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RACTAGYHW
SQDCECCRRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK
RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG

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

DILLTQSPVILSVSPGERVSFSCRASQSIGTNIHWYQQRTNGSPRLIKYASESISGIPSRFSGSGSGTDEFT
LSINSVESEDIADYYCQQNNNWPTTFGAGTKLELKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA
KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

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):

QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGDTSYNQKFKGKATLTA
DKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAGTTVTVSAASTKGPSVFPLAPSSKSTSGGTA
ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVD
KKAEPKSCDKTHTCPPCPAPELLGGPSVFLFPPPKPDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV
HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRD
ELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLESDGSFFLYSKLTVDKSRWQQGNVFSQSV
HEALHNHYTQKSLSLSPGK *GGGGSGGGSGGGGS* **QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC**
TTTSDSVCLP CGPDEYLDW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RCTAGTYHW
SQDCECCRRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK
RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG

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

QIVLSQSPAILASAPGEKVTMTCRASSSVSYIHWFQQKPGSSPKFWIYATSNLASGVFVRFSGSGSGTSYSL
TISRVEAEDAATYYCQWTSNPPTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK
VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKKHKVYACEVTHQGLSSPVTKSFNRGEC

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):

EVQLVESGGGLVQPGGSLRLSCAASGYTFTNYGMNWVRQAPGKGLEWVGWINTYTGEPTYAADF
KRRFTFSLDTSKSTAYLQMNSLRAEDTAVYYCAKYPHYGSSHWYFDVWGQGLTVTVSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTP
 SSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
 CTVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP
 APIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDS
 DGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNIHYTQKSLSLSPGKGGGSGGGSGGGGS **QI**
APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP
CGPDEYLDW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RCTAGYHW SQDCECCRRN
TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS
DAVCSSSLPA RKPPNEPHVY LPG

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

DIQMTQSPSSLSASVGDRVTITCSASQDISNYLNWYQQKPGKAPKVLIIYFTSSLHSGVPSRFSGSGSG
TDFTLTISSLQPEDFATYYCQYSTVPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL
 NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSTLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

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 VVQPGRSLRL SCAASGFTFS SYTMHWVRQA PGKGLEWVTF ISYDGMNKYY
ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAIYYCARTG WLGPFDYWGQ GTLVTVSSAS
TKGPSVFPLA PSSKSTSGGT AALCCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL
YSLSSVVTVP SSSLGTQTYI CNVNHKPSNT KVDKRVEPKS CDKTHTCPPC PAPELLGGPS
VFLEPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST
YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT
KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTTPVLD SDGSFFLYSK LTVDKSRWQQ
GNVFSCSVMH EALHNHYTQK SLSLSPGK **GGGGSGGGSGGGGS** **QI APPCTSEKHY EHLGRCCNKC**
EPGKYMSSKC TTTSDSVCLP CGPDEYLD SW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR
RCACTAGYHW SQDCECCRRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR
PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG

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

EIVLTQSPGT LSLSPGERAT LSCRASQSVG SSYLAWYQQK PGQAPRLLIY GAFSRATGIP
DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ QYGSSPWTFG QGTKVEIKRT VAAPSVFIFP
PSDEQLKSGT ASVVCLLNMF YPREAKVQWK VDNALQSGNS QESVTEQDSK DSTYSLSTL
TLISKADYEKH KVIACEVTHQ 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
VFSCSVMEHA LHNHYTQKSL SLSPGK GGGSGGGSGGGGS **QI APPCTSEKHY EHLGRCCNKC**
EPGKMSSKC TTTSDSVCLP CGPDEYLDW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR
RCACTAGYHW SQDCECCRRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR
PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG

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

DIQMTQSPST LSASVGDRVT ITCSASSSIS YMHWYQQKPG KAPKLLIYTT SNLASGVPAR
FSGSGSGTEF TLTISLQPD 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 WMHWIKQRPG QGLEWIGAIY PGNSDTSYNQ
KFEGKAKLTA VTSASTAYME LSSLTHEDSA VYYCSRDIYGY YFDWFGQGT LTSSASTKG
PSVFPLAPSS KSTSGGTAAL GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL
SSVVTVPSSS LGTQFYICNV NHKPSNTKVD KRVEPKSCDK THTCPPCPAP ELLGGPSVFL
FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV
VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLF PSRDELTKNQ
VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV
FSCSVMHEAL HNHYTQKSLS LSPGK **GGGGSGGGSGGGGS** **QI APPCTSEKHY EHLGRCCNKC**
EPGKMSSKC **TTTSDSVCLP** **CGPDEYLDW** **NEEDKCLLHK** **VCDTGKALVA** **VVAGNSTTPR**
RCACTAGYHW **SQDCECCRRN** **TECAPGLGAQ** **HPLQLNKDTV** **CKPCLAGYFS** **DAFSSTDKCR**
PWTNCTFLGK **RVEHHGTEKS** **DAVCSSSLPA** **RKPPNEPHVY** **LPG**

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

QIVSTQSPAI MSASPGKVT MTCSASSRS YMQWYQQKPG TSPKRWIYDT SKLASGVPAR
FSGSGSGTSY SLTISSMEAE DAATYYCHQR SSYTFGGGTK LEIKRTVAAP SVFIFPPSDE
QLKSGTASVV CLLNFFYPRE 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):

APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEELKPLEEVNL
AQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLTGGGGSGGGSG
 GGGSTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
 PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ
 VSLTCLVKGFIYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVSCSVMHEALHN
 HYTQKSLSLSPGK GGGGSGGGSGGGGS **QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC**
TTTSDSVCLP CGPDEYLDW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RACTAGYHW
SQDCECCRRN 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 SQDCECCRRN TECAPGLGAQ HPLQLNKDTV
CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG
GGGGSGGGSGGGSGSTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV
DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL
PPSREEMTKNQVSLTCLVKGFIYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVF
SCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGSGGGGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKN
PKLTRMLTFKFYMPKKATELKHLCLEELKPLEEVNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMC
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 (SEQ. ID. NO: 105) or IEGRDMD (SEQ. ID. NO: 106))

(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
NRVSISIDTSKNLFSCLKRSVTAADTAVYYCASNILKYLHWLLYWGQGVLVTVSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLG
TQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNYHTQKSLSLSPGK
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
SVVCLLNNFYFPREAKVQWKVDNALQSGNSQESVTEQDSKSTYSLSSTLTLSKADYEKHKVYACEV
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 FNVSTLRIN TTTNEIFYCT FRRLDPEENH TAEIPELP LAHPNERTH
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
FNVSTLRIN TTTNEIFYCT FRRLDPEENH TAEI

- (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 FNVSTLRIN TTTNEIFYCT FRRLDPEENH TAEIPELP LAHPNERTH
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):

EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSAITWNSGHIDYADSVEG
RFTISRDNAKNSLYLQMNSLRAEDTAVYYCALVSYLSTASSLDYWGQGLVTVSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLG
TQTYICNVNHKPSNTKVD**KKAE**PKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGSGGGGS
RIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVWEMEDKNIIQF
VHGEEDLKVQHSSYRQARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAP
YNKINQRILVVDVPTSEHELTCQAEGYPKAEVIWTS**SDHQVLSGKTTTTNSKREEKLFNVTSTLRI**
NTTTNEIFYCTFRRLDPEENHTAELVIP**ELPLAHPNERTHLVILGAILLCLGVALTFIFRLRKGR**
MMDVKKCGIQDTNSKKQSDTHLEET

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

DIQMTQSPSSLSASVGDRVTITCRASQGIRNYLAWYQQLPGKAPKLLIYAASTLQSGVPSRFSSGSG
SGTDEFTLTISSLQPEDVATYYCQRYNRAPYTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV
VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTH
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: 107 can be replaced with **KRVE** SEQ ID NO: 108
or **KKVE** SEQ ID NO: 109)

FIG. 32

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
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLG
TQTYICNVNHKPSNTKVDKKAEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

GGGGSGGGSGGGGS

RIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVWEMEDKNIIQF
VHGEEDLKVQHSSYRQARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAP
YNKINQRIILVVDVPTSEHELTCAEGYPKAEVIWTS SDHQVLSGKTTTTNSKREEKLFNVTSTLRI
NTTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPPNERTHLVILGAILLCLGVALTFIFRLRKGR
MMDVKKCGIQDTNSKKQSDTHLEET

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

QIVLSQSPAILLSASPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWYATSNLASGVPVRFSGSGS
GTSYSLTISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNFPYFREAKVQWKVDNALQSGNSQESVTEQDSKDSYSTLSSTLTLSKADYEKHKVYACEVTHQ
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 KTHTCPPCPA PELLGGPSVF
LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR
VVSVLTVLHQ DWLNGKEYKC KVSNAKALPAP IEKTISKAKG QPREPQVYTL PPSRDELTKN
QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTTPVLDSD GSFFLYSKLT VDKSRWQQGN
VFSCSVMHEA LHNHYTQKSL SLSPGK GGGGSGGGGSGGGGS

RIFAVFIFMTYWHLNNAFTVTVPKDLYVVEYGSNMTIECK

FPVEKQLDLAALIVWEMEDKNIIQFVHGEECLKVQHSSYRQRARLLKDQLSLGNA

ALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRILVVDVPTSEHEL

TCQAEQPKAEVIWTSDDHQVLSGKTTTTNSKREEKLEFNVSTLRLNTTNEIFYC

TFRRLDPEENHTAELVIPELPLAHPNERTHLVILGAILLCLGVALTFIFRLRKGR

MMDVKKCGIQDTNSKKQSDTHLEET

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 TYSLSSTLTL
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

Anti-CD25 (Basiliximab) heavy chain and PD-1 ectodomain (SEQ ID NO: 42)

QLQQSGTVLA RPGASVKMSC KASGYSFTRY WMHWIKQRPQ QGLEWIGAIY PGNSDTSYNQ
KFEGKAKLTA VTSASTAYME LSSLTHEDSA VYYCSRDIYGY YPFEWGQGT LTVSSASTKG
PSVFPLAPSS KSTSGGTAAL GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL
SSVVTVPSSS LGTQTYICNV NHKPSNTKVD KRVEPKSCDK THTCPPCPAP ELLGGPSVFL
FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV
VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTL PPSRDELTKNQ
VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRRWQQGNV
FSCSVMEAL HNHYTQKSL LSPGK GGGGSGGGSGGGGS
RIFAVFIFMTYWHLNAFTVTVPKDLVVEYGSNMTIECK
FPVEKQLDLAALIVWEMEDKNIIQFVHGEEEDLKVQHSSYRQARLLKDQLSLGNA
ALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRILVVDPTSEHEL
TCQAEQYPKAEVIWTSSDHQVLSGKTTTNSKREEKLFNVTSTLRINTTTNEIFYC
TFRRLDPEENHTAELVIPELPLAHPNERTHLVILGAILLCLGVALTFIFRLRKGR
MMDVKKCGIQDTNSKKQSDTHLEET

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

QIVSTQSPAI MSASPGEKVT MTCSASSRS YMOWYQQKPG TSPKRWIYDT SKLASGVPAR
FSGSGSGTSY SLTISSMEAE DAATYYCHQR SSYTFGGGTK LEIKRTVAAP SVFIFPPSDE
QLKSGTASVV CLLNFFPRE AKVQWKVDNA LQSGNSQESV TEQDSKSTY SLSSTLTLSK
ADYEKHKVYA CEVTHQGLSS PVTKSFNRRGE

Plain: anti-CD25 antibody

Italic: Linker

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

FIG. 35B

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):

MRIFAVFIFMTYWHLNNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIQFVHGEE
DLKVQHSSSYRQRARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKV
NAPYNKINQRIILVVDPVTSEHELTCQAEQYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLRINTT
TNEIFYCTFRRLDPEENHTAELVIPELPLAHPNERTHLVILGAILLCLGVALTFIFR
 LRKGRMMDVKKCGIQDTNSKKQSDTHLEET GGGGSGGGSGGGGS
 THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE
 QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLT
 CLVKGFPYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQ
 KSLSLSPGK GGGGSGGGSGGGGS
 APTSSSTKKTQLQLEHLLLDLQMI LGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEELKPLEEVLNL
 AQSKNFHLRPRDLISINIVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT

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

APTSSSTKKTQLQLEHLLLDLQMI LGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEELKPLEEVLNL
 AQSKNFHLRPRDLISINIVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
 GGGGSGGGSGGGGS
 THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE
 QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLT
 CLVKGFPYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQ
 KSLSLSPGK GGGGSGGGSGGGGS
RIFAVFIFMTYWHLNNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIQFVHGEE
LKVQHSSSYRQRARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRIILVVD
PVTSEHELTCQAEQYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLRINTTTNEIFYCTFRRLDPE
ENHTAELVIPELPLAHPNERTHLVILGAILLCLGVALTFIFRLRGRMMDVKKCGIQDTNSKKQSDTHLEE
 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
NRVSIIDTSKNLFSKLRSVTAADTAVYYCASNILKYLHWLLYWGQGVLTVSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLG
TQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGSGGGGS
RIFAVFIFMTYWHLLNAFTVTVPKDLVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNI IQF
VHGEEDLKVQHSSYRQRARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAP
YNKINQIRILVDPVPTSEHELTCAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLRI
NTTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPNERTHLVILGAILLCLGVALTFIFRLRKGR
MMDVKKCGIQDTNSKKQSDTHLEET

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

Light chain:

SYELSQPRSVSVSPGQTAGFTCGGDNVGRKSVQWYQQKPPQAPVLVIYADSERPSGIPARFSGSNS
GNTATLTISGVEAGDEADYYCQVWDSTADHWVFGGGTRLTVLGRTVAAPSVFIFPPSDEQLKSGTA
SVVCLLNIFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS'TYSLSSSTLTLSKADYERHKVYACEV
THQGLSSPVTKSFNREGC

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):

MGVLLTQRTLLSLVLALLFPSMASMAMHVAQPAVVLASSRGIASFVCEYASPGKATEVRVTVLRQA
DSQVTEVCAATYMMGNELTFLDDSICTGTSSGNQVNLTIQGLRAMDTGLYICKVELMYPPPYLGI
GNGTQIYVIDPEPCPDSD QEPKSCDKTHTCPPCPAPPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE
 YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN
 GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK
 GGGGSGGGGSGGGGS
RIFAVFIFMTYWHL**NAFTVTVPKDLYVVEYGSNMTIECKFPVEKQDLAALIVWEMEDKNIIQF**
VHGEEDLKVQHSSYRQ**RARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNA**
YNKINQ**RILVDPVTSEH****ELTCQAEGYPKAEVIWTS****SDHQVLSGKTTTNSKREEKLFNVTSTLRI**
NTTTNEIF**YCTFRRLDPEENHTAELVIPELPLAHPN****ERTHLVILGAILLCLGVALTFIFRLRKG**
RMMDVKKCGIQDTNSKKQSDTHLEET

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):

MRIFAVFIFMTYWHL**NAFTVTVPKDLYVVEYGSNMTIECKFPVEKQDLAALIVWEMEDKNIIQ**
FVHGEEDLKVQHSSYRQ**RARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNA**
PYNKINQ**RILVDPVTSEH****ELTCQAEGYPKAEVIWTS****SDHQVLSGKTTTNSKREEKLFNVTSTLRI**
INTTTNEIF**YCTFRRLDPEENHTAELVIPELPLAHPN****ERTHLVILGAILLCLGVALTFIFR**
LRKGRMMDVKKCGIQDTNSKKQSDTHLEET GGGGSGGGGSGGGGS
QEPKSCDKTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP
QVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD
DKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK GGGGSGGGGSGGGGS
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)

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

(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
 QHNPGASAAPCCVPQALEPLPIVYVGRKPKVEQLSNMIVRSCKCS *GGGSGGGSGGGGS*
 THTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFSCSVMEALHNHYTQKSLSLSPGK *GGGSGGGSGGGGS*
RIFAVFIFMTYWHLNNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIOF
VHGEEDLKVOHSSYRQARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNA
YNKINQIRILVVDPVTSEHELTCQAEQYPAEVIWTSDDHQVLSGKTTTNSKREEKLFNVTSTLR
INTTTNEIFYCTFRRLDPEENHTAELVPELPLAHPPNERTHLVILGAILLCLGVALTFIFRLRKG
RMDVKKCGIQDTNSKKQSDTHLEET

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):

MRIFAVFIFMTYWHLNNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIO
FVHGEEDLKVOHSSYRQARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNA
PYNKINQIRILVVDPVTSEHELTCQAEQYPAEVIWTSDDHQVLSGKTTTNSKREEKLFNVTSTLR
INTTTNEIFYCTFRRLDPEENHTAELVPELPLAHPPNERTHLVILGAILLCLGVALTFIFRLRKG
RMDVKKCGIQDTNSKKQSDTHLEET *GGGSGGGSGGGGS*
 THTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFSCSVMEALHNHYTQKSLSLSPGK *GGGSGGGSGGGGS*
 ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
 QHNPGASAAPCCVPQALEPLPIVYVGRKPKVEQLSNMIVRSCKCS

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 *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)

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 LLLPLRLLV LTPGRPAAGL STCKTIDMEL VKRKRIEAIR GQILSKLRLS
61 SPSPQGEVPP VPLPEAVLAL YNSTRDRVAG ESAEPEPEPE ADYYAKEVTR VLMVENTNKI
121 YEKVKKSPHS IYMLFNTSEL REAVPEPVLL SRAELRLLRL KLAEQHVEL YQKYSNDSWR
181 YLSNRLAPS DTPWLSFDV TGVVRQWLSH GGEVEGFRLS AHCSCDSKDN TLQVDINGFS
241 SSRGDLATI 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):

EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSAITWNSGHIDYADSVEG
RFTISRDNAKNSLYLQMNSLRAEDTAVYYCALVSYLSTASSLDYWGQGLVTVSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLG
TQTYICNVNHKPSNTKVD**KKAE**PKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMEALHNHYTQKSLSLSPGK
GGGGSGGGSGGGGS
ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
QHNP**GASAAPCCVPQALEPLPIVYYVGRKPKVEQLSNMIVRSCKCS**

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

DIQMTQSPSSLSASVGDRVTITCRASQGIRNYLAWYQQLPGKAPKLLIYAASTLQSGVPSRFSGSG
SGTDFTLTISSLPEDVATYYCQRYNRAPYTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV
VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKVYACEVTH
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
WVPECLSCGSRCSDDQVETQACTREQNRICTCRPGWYCALSKEGCRLCAPLRKCRPGFGVARPGT
ETSDVVCKPCAPGTFSNTTSSTDICRPHQICNVVAIPGNASMDAVCTSTSPTRSMAPGAVHLPQPV
STRSQHTQPTPEPSTAPSTSFLLLPMGPSPPAEGSTGD *EPKSCDK*
 THTCPPCPAPELLGGPSVFLFPPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
 R**EEM**TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFSCSVMEALHNHYTQKSLSLSPGK *GGGGSGGGSGGGGS*
ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
QHNPASAAAPCCVPQALEPLPIVYYVGRKPKVEQLSNMIVRSCKCS

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):

ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
QHNPASAAAPCCVPQALEPLPIVYYVGRKPKVEQLSNMIVRSCKCS *GGGGSGGGSGGGGS*
 THTCPPCPAPELLGGPSVFLFPPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
 R**EEM**TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFSCSVMEALHNHYTQKSLSLSPGK *GGGGSGGGSGGGGS*
LPAQVAFTPYAPEPGSTCRLREYYDQTAQMCCSKCSPGQHAKVFCTKTSDTVCDSCEDSTYTQLWN
WVPECLSCGSRCSDDQVETQACTREQNRICTCRPGWYCALSKEGCRLCAPLRKCRPGFGVARPGT
ETSDVVCKPCAPGTFSNTTSSTDICRPHQICNVVAIPGNASMDAVCTSTSPTRSMAPGAVHLPQPV
STRSQHTQPTPEPSTAPSTSFLLLPMGPSPPAEGSTGD

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):

QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGDTSYNQKFKG
KATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAGTTTVSAASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TQTYICNVNHKPSNTKVDKKAEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGSGGGGS
ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
QHNPGASAAPCCVPQALEPLPIVYYVGRKPKVEQLSNMIVRSCKCS

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

QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQKQKPGSSPKPWYATSNLASGVPVRFSGSGS
GTSYSLTISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYLSLSSTLTLSKADYEKHKVYACEVTHQ
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
NQKFKDKATI TADESTNTAY MELSSLRSED TAVYYCARGG GVFDYWGQGT LVTVSSASTK
GPSVFEPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS
LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKKVEPKSCD KTHTCPPCPA PELLGGPSVF
LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR
VVSVLTVLHQ DWLNGKEYKC KVSNAKLPAP IEKTISKAKG QPREPQVYTL PPSRDELTKN
QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTTPVLDSG GSFFLYSKLT VDKSRWQQGN
VFSCSVMHEA LHNHYTQKSL SLSPGK GGGGSGGGGSGGGGS **ALDTNYCFSSTEKNCCVRQLY**
IDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYNQHNP
GASAAAPCCVPQALEPLP
IVYYVGRKPKVEQLSNMIVRSCKCS

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

DIQMTQSPST LSASVGDRVIT ITCSASSSIS YMHYQQKPG KAPKLLIYTT SNLASGVPAR
FSGSGSGTEF TLTISSLQPD DFATYYCHQR STYPLTFGQG TKVEVKRTVA APSVFIFPPS
DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSTLTLL
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 WMHWIKQRPQ QGLEWIGAIY FGNSDTSYNQ
KFEGKAKLTA VTSASTAYME LSSLTHEDSA VYYCSRDIYGY YDFFWGQGT LTVSSASTKG
PSVFPLAPSS KSTSGGTAAL GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL
SSVVTVPSSS LGTQTYICNV NHKPSNTKVD KRVEPKSCDK THTCPPCPAP ELLGGPSVFL
FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV
VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLPSRDELTKNQ
VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRRWQQGNV
FSCSVMEAL HNHYTQKSLS LSPGK GGGGSGGGGSGGGGS

ALDTNYCFSSSTEKNCCVRQLYIDFRKDLGKWIIHEPKGYHAN

FCLGPCPYIWSLDTQYSKVLALYNQHNPASAAPCCVPQALEPLPIVYVGRKPKVEQ

LSNMIVRSCKCS

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

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

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):

ALDTNYCFSSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
QHNP*GASAA***PCCVPQALEPLPIVYYVGRKPKVEQLSNMIVRSCKCS** *GGGSGGGSGGGGS*
 THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFSCSVMEALHNHYTQKSLSLSPGK *GGGSGGGSGGGGS*
APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPL
EEVLNLAQSKNFHLRPRDLISNINVIVELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTL
T

IL-2 + Fc + TGF- β 1 (SEQ ID NO: 57):

APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPL
EEVLNLAQSKNFHLRPRDLISNINVIVELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTL
T *GGGSGGGSGGGGS*
 THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFSCSVMEALHNHYTQKSLSLSPGK *GGGSGGGSGGGGS*
ALDTNYCFSSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
QHNP*GASAA***PCCVPQALEPLPIVYYVGRKPKVEQLSNMIVRSCKCS**

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
EPKSCDK 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:

QVQLQEAGPGLVKPSETLSLTCSVSGGSISGDYYWFWIRQSPGKGLEWIGYIYSGGGTNYNPSLN
NRVSISIDTSKNLFSCLKLRSVTAADTAVYYCASNILKYLHWLLYWQGVLTVSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLG
TQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVMEALAHNHYTQKSLSLSPGK

GGGGSGGGSGGGGS

ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
QHNPGASAAPCCVPQALEPLPIVYYVGRKPKVEQLSNMIVRSCKCS

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

Light chain:

SYELSQPRSVSVSPGQTAGFTCGGDNVGRKSVQWYQQKPPQAPVLVIYADSERPSGIPARFSGSNS
GNTATLTISGVEAGDEADYYCQVWDSTADHWVFGGGTRLTLVLGRTVAAPSVFIFPPSDEQLKSGTA
SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYSLSSTLTLSKADYEKHKVYACEV
THQGLSPVTKSFNRGEC

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):

MGVLLTQRTLLSLVLALLFPSMASMAMHVAQPAVVASSRGIASFVCEYASPGKATEVRVTVLRQA
DSQVTEVCAATYMMGNELTFLDDSICTGTSSGNQVNLTIQGLRAMDTGLYICKVELMYPPPYLGI
 GNGTQIYVIDPEPCPDSQEPKSCDK THTCPCPPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE
 YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN
 GQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK
 GGGGSGGGGSGGGGS
ALDTNYCFSSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
QHNPGASAAAPCCVPQALEPLPIVYYVGRKPKVEQLSNMIVRSCKCS

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):

ALDTNYCFSSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
QHNPGASAAAPCCVPQALEPLPIVYYVGRKPKVEQLSNMIVRSCKCS EPKSCDK
 THTCPCPPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
 RDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFCSCVMHEALHNHYTQKSLSLSPGK GGGGSGGGGSGGGGS
AMHVAQPAVVASSRGIASFVCEYASPGKATEVRVTVLRQADSQVTEVCAATYMMGNELTFLDDSI
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):

EVQLVESGGGLVQPGRSRLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSAITWNSGHIDYADSV
EG
RFTISRDNAKNSLYLQMNSLRAEDTAVYYCALVSYLSTASSLDYWGQGTLVTVSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLG
TQTYICNVNHKPSNTKVD**KKAE**PKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGSGGGGS **QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP**
CGPDEYLDW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RCACTAGYHW SQDCECCRRN
TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS
DAVCSSSLPA RKPPNEPHVY LPG

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

DIQMTQSPSSLSASVGDRVTITCRASQGIRNYLAWYQQLPQKAPKLLIYAASTLQSGVPSRFSGSG
SGTDFTLTITSSLPEDVATYYCQRYNRAPYTFGGGTKVEIKRTVAAPSVEIFPPSDEQLKSGTASV
VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTH
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 γ 1 + RANK ectodomain (SEQ ID NO: 62):

LPAQVAFTPYAPEPGSTCRLREYYDQTAQMCCSKCSPGQHAKVFCTKTSDTVCDSCEDSTYTQLWN
WVPECLSCGSRCSDDQVETQACTREQNRICTCRPGWYCALSKQEGCRLCAPLRKCRPGFGVARPGT
ETSDVVCKPCAPGTFSNTTSSTDICRPHQICNVVAIPGNASMDAVCTSTSPTRSMAPGAVHLPQPV
STRSQHTQPTPEPSTAPSTSFLPMGPSPPAEGSTGD *EPKSCDK*
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMEALHNHYTQKSLSLSPGK *GGGGSGGGSGGGGS* **QI APPCTSEKHY**
EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP CGPDEYLDSW NEEDKCLLHK VCDTGKALVA
VVAGNSTTPR RCACTAGYHW **SQDCECCRN 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 γ 1 + TNFR2 ECD (SEQ ID NO: 63):

QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP CGPDEYLDSW
NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RCACTAGYHW **SQDCECCRN TECAPGLGAQ**
HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA
RKPPNEPHVY LPG
GGGGSGGGSGGGGS THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHED
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT
ISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
GSFFLYSKLTVDKSRWQQGNVSCSVMEALHNHYTQKSLSLSPGK *GGGGSGGGSGGGGS*
LPAQVAFTPYAPEPGSTCRLREYYDQTAQMCCSKCSPGQHAKVFCTKTSDTVCDSCEDSTYTQLWN
WVPECLSCGSRCSDDQVETQACTREQNRICTCRPGWYCALSKQEGCRLCAPLRKCRPGFGVARPGT
ETSDVVCKPCAPGTFSNTTSSTDICRPHQICNVVAIPGNASMDAVCTSTSPTRSMAPGAVHLPQPV
STRSQHTQPTPEPSTAPSTSFLPMGPSPPAEGSTGD

Underlined: TNFR2 ligand-binding domain

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

Italic: Linker

Bold: RANK ectodomain

(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. 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
DSQVTEVCAATYMMGNELTFLDDSICTGTSSGNQVNLTIQGLRAMDTGLYICKVELMYPPPYYLGI
GNGTQIYVIDPEPCPDSQEPKSCDK **THT**CPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE
 YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN
 GQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK
 GGGGSGGGGSGGGGS **QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTSDSVCLP**
CGPDEYLD SW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RACTAGYHW 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 TTSDSVCLP CGPDEYLD SW
NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RACTAGYHW SQDCECCRRN TECAPGLGAQ
HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA
RKPPNEPHVY LPG *EPKSCDK*
 THT**CPPC**PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
 RDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFCSCVMHEALHNHYTQKSLSLSPGK GGGGSGGGGSGGGGS
AMHVAQPAVVLASSRGIASFVCEYASPGKATEVRVTVLRQADSQVTEVCAATYMMGNELTFLDDSI
CTGTSSGNQVNLTIQGLRAMDTGLYICKVELMYPPPYYLGIGNGTQIYVIDPEPCPDS

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
QHNPGASAAPCCVPQALEPLPIVYYVGRKPKVEQLSNMIVRSCKCS GGGGSGGGGSGGGGS
 THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFSCSVMEALHNHYTQKSLSLSPGK GGGGSGGGGSGGGGS **QI APPCTSEKHY**
EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP CGPDEYLDW NEEDKCLLHK VCDTGKALVA
VVAGNSTTPR RACTAGYHW SQDCECCRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS
DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG

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

QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP CGPDEYLDW
NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RACTAGYHW SQDCECCRN TECAPGLGAQ
HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA
RKPPNEPHVY LPG GGGGSGGGGSGGGGS
 THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQG
 NVFSCSVMEALHNHYTQKSLSLSPGK GGGGSGGGGSGGGGS
ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
QHNPGASAAPCCVPQALEPLPIVYYVGRKPKVEQLSNMIVRSCKCS

Underlined: Mature (active) human TGF- β 1

Italic: Linker (optional)

Plain: Fc

Bold: RANK ectodomain

(Note: Can replace linker 1 GGGGSGGGGSGGGGS 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- κ B (RANK), Fc, and a sequence from PD-1 ligand 1

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

RIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIQFVHGEED
LKVQHSSYRQRARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRILVVD
PVTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLRINTTTNEIFYCTFRRLDPE
ENHTAELVIPELPLAHPNERTHLVILGAILLCLGVALTFIFRLRKGRMMDVKKCGIQDTNSKKQSDTHLEE
T *GGGGSGGGSGGGGS*
 THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE
 QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLT
 CLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSVMSVHEALHNHYTQ
 KSLSLSPGK *GGGGSGGGSGGGGS* QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTSDSVCLP
CGPDEYLDW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RACTAGYHW SQDCECCRN
TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS
DAVCSSSLPA RKPPNEPHVY LPG

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

QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTSDSVCLP CGPDEYLDW NEEDKCLLHK
VCDTGKALVA VVAGNSTTPR RACTAGYHW SQDCECCRN TECAPGLGAQ HPLQLNKDTV
CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG
GGGGSGGGSGGGGS
 THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE
 QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLT
 CLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSVMSVHEALHNHYTQ
 KSLSLSPGK *GGGGSGGGSGGGGS*
RIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIQFVHGEED
LKVQHSSYRQRARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRILVVD
PVTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLRINTTTNEIFYCTFRRLDPE
ENHTAELVIPELPLAHPNERTHLVILGAILLCLGVALTFIFRLRKGRMMDVKKCGIQDTNSKKQSDTHLEE
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

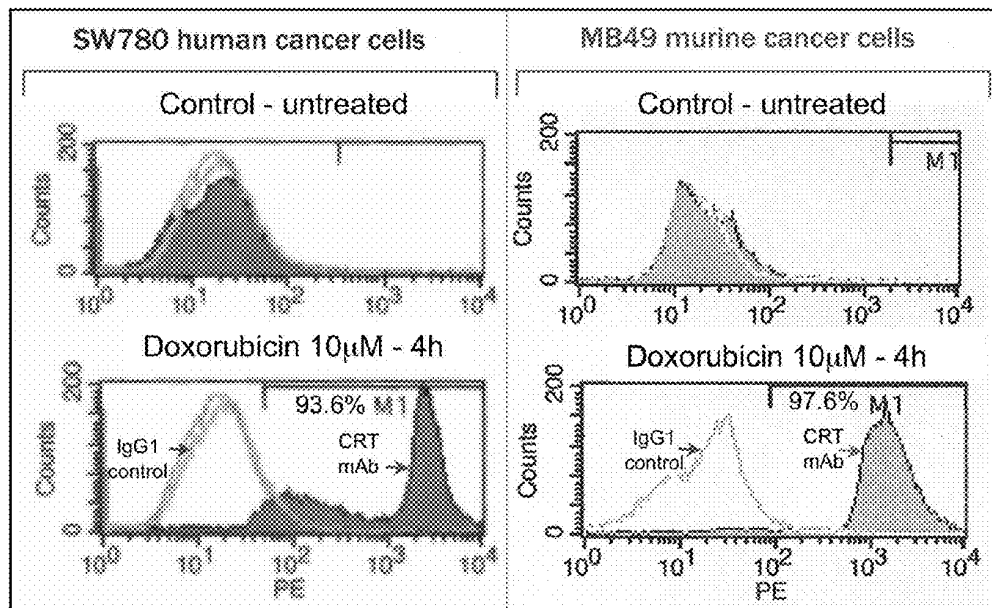


FIG. 53A

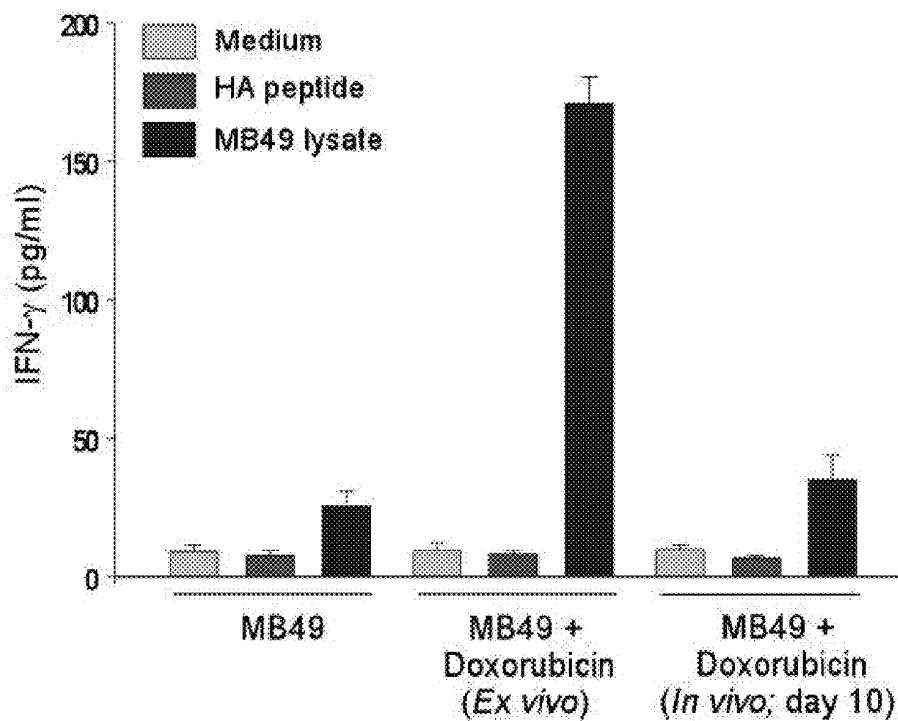


FIG. 53B

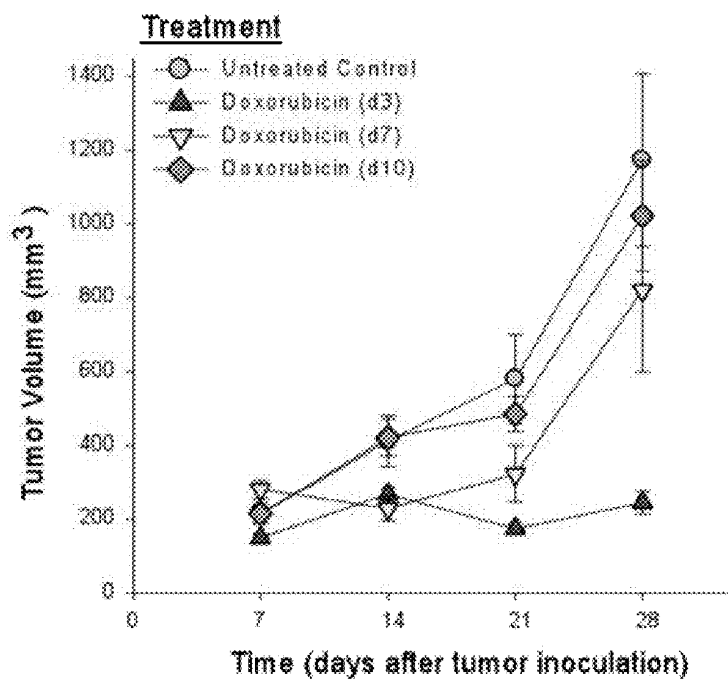
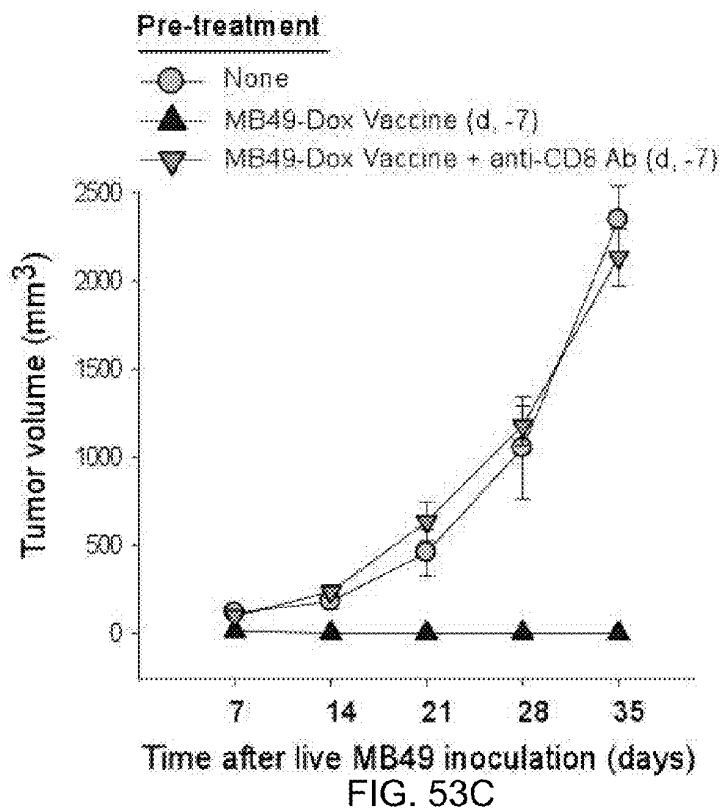


FIG. 53D

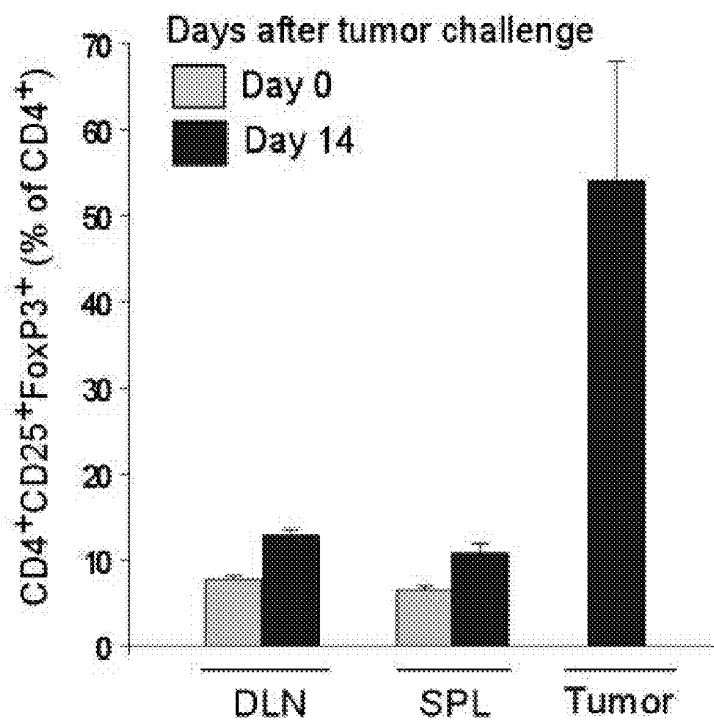


FIG. 53E

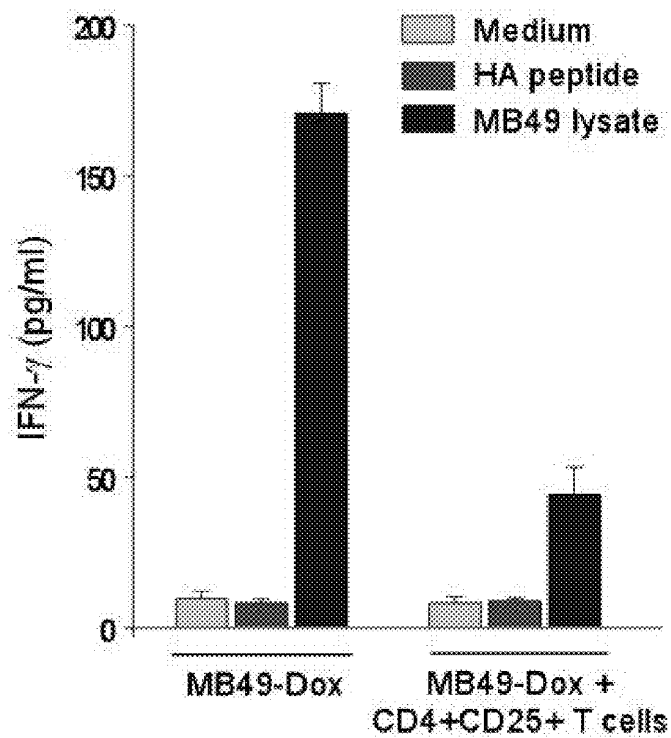


FIG. 53F

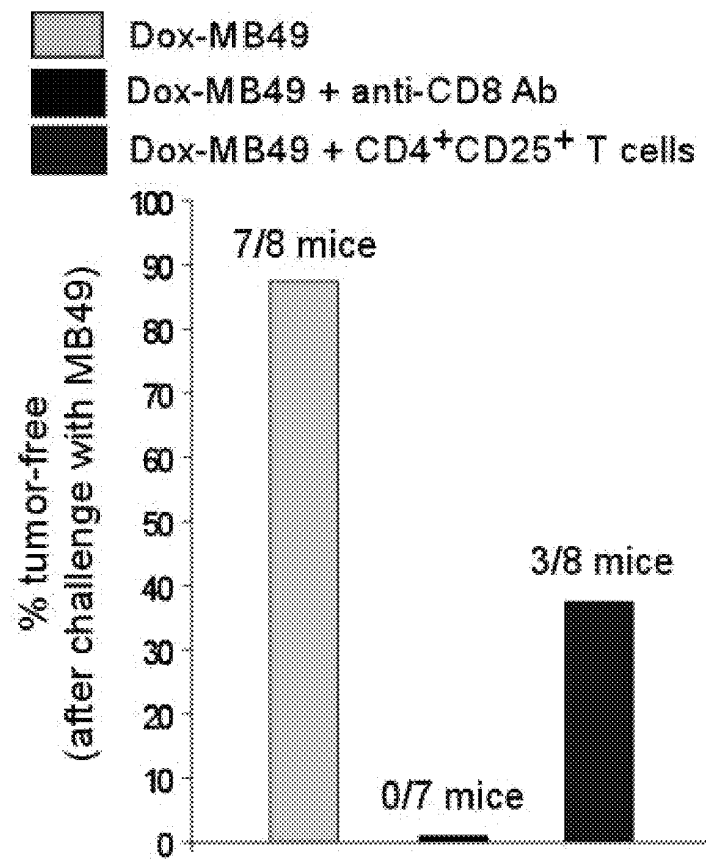


FIG. 53G

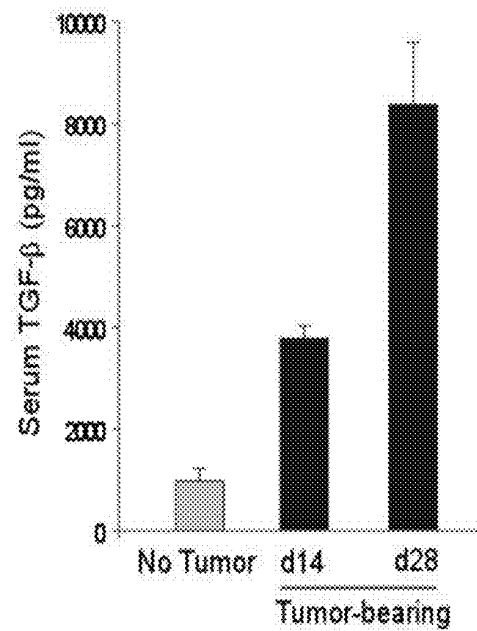


FIG. 54A

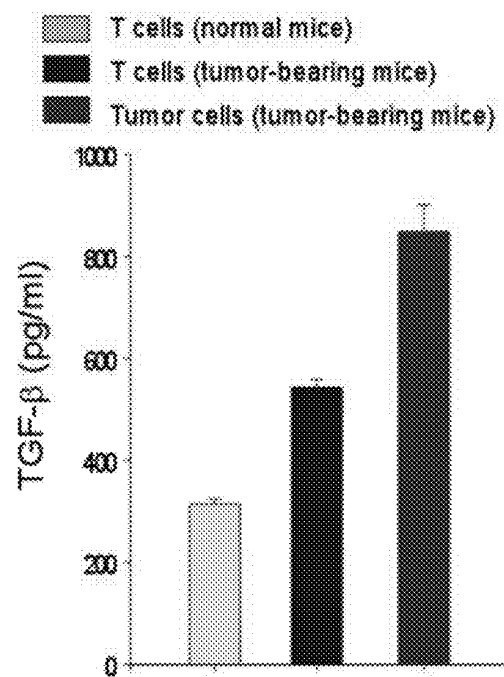


FIG. 54B

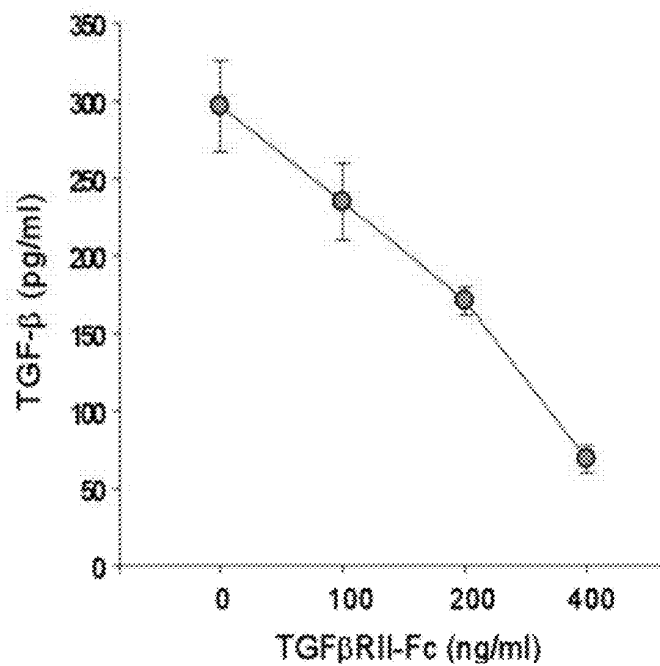


FIG. 54C

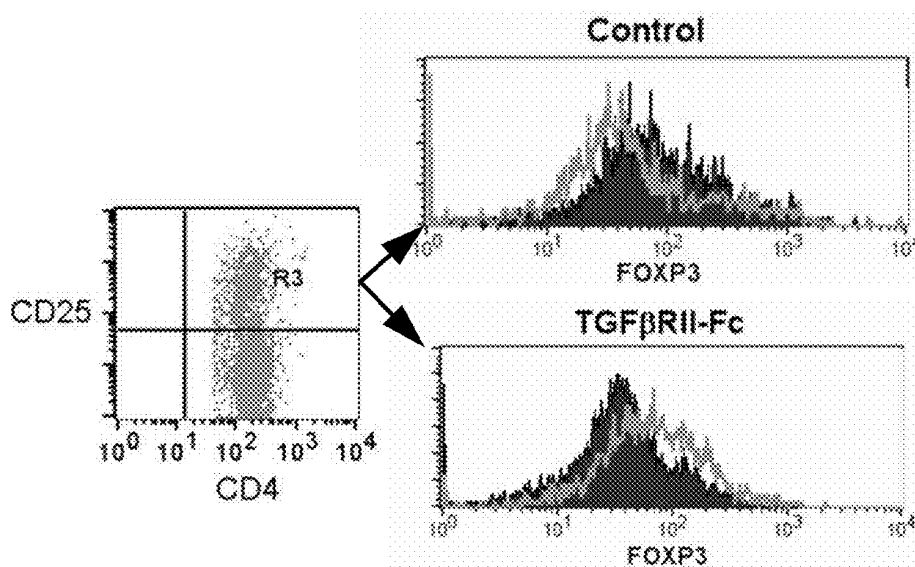


FIG. 54D

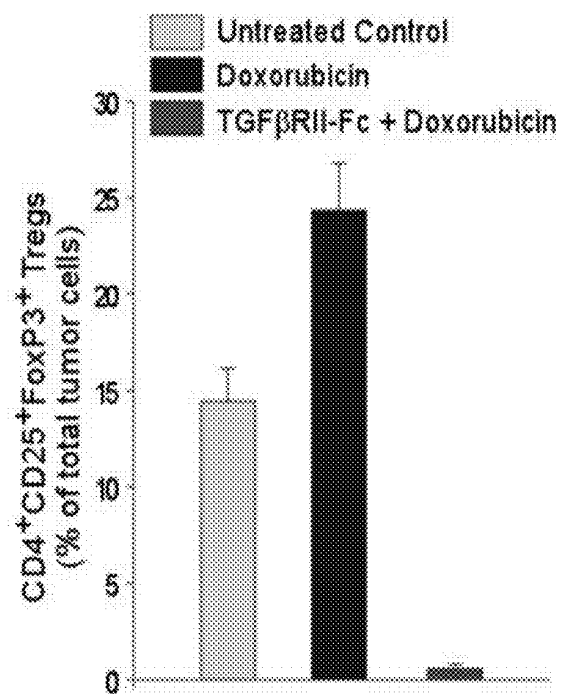


FIG. 54E

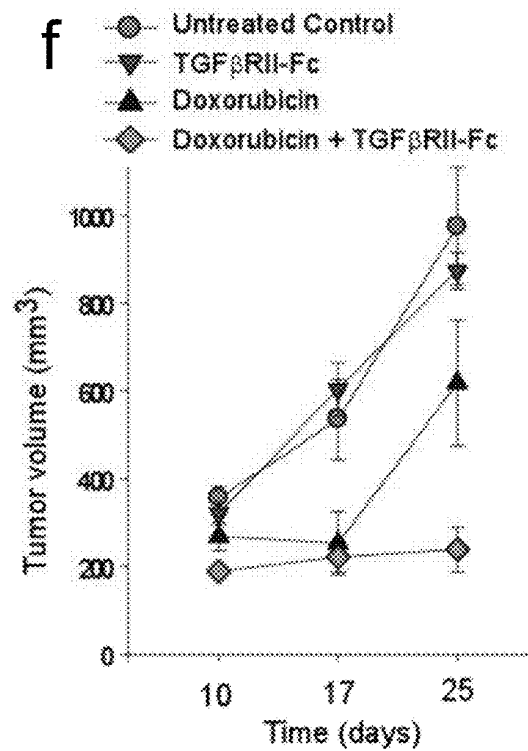


FIG. 54F

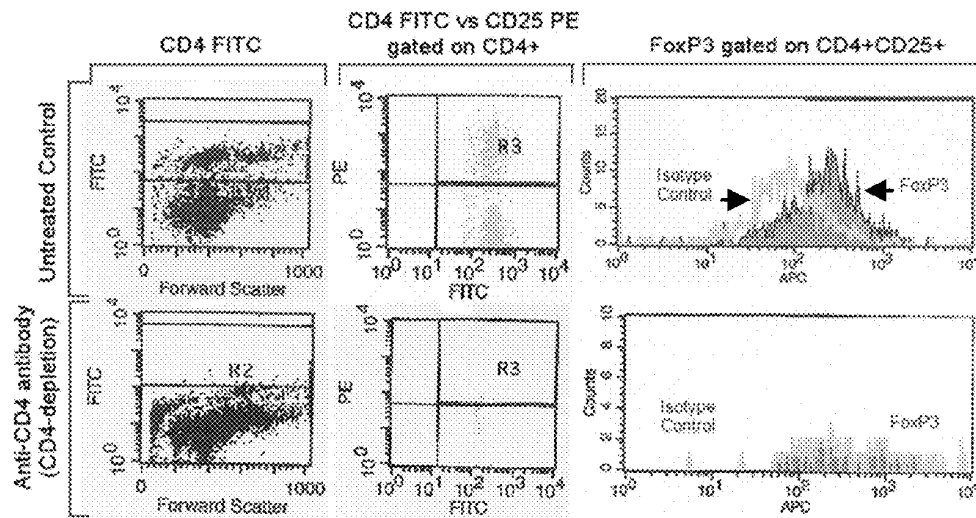


FIG. 55A

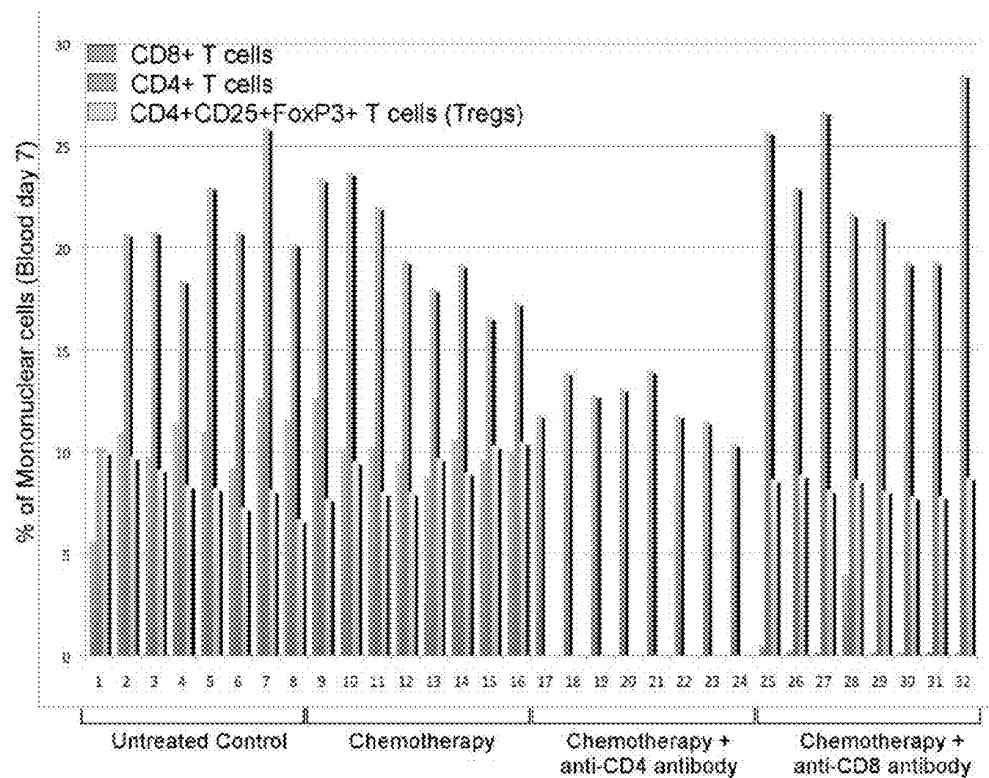


FIG. 55B

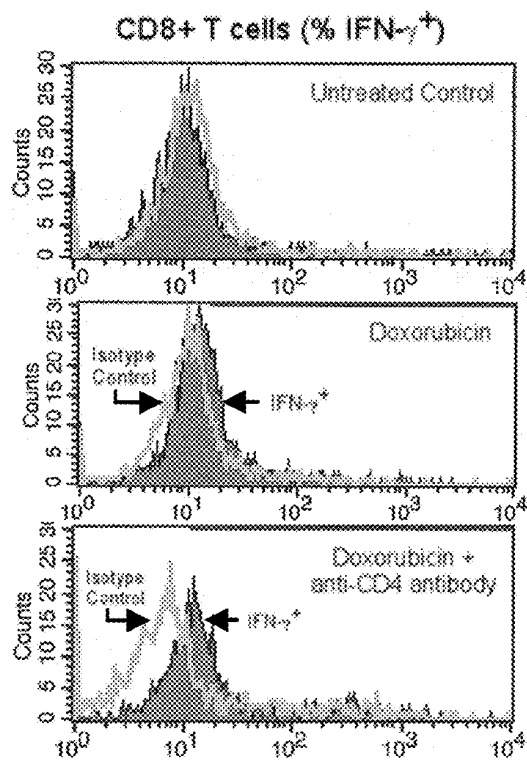


FIG. 55C

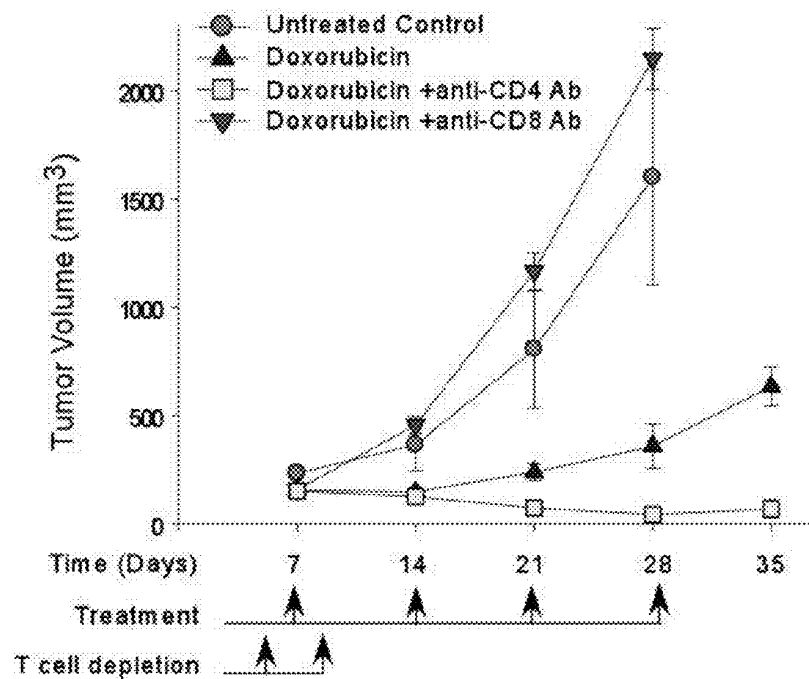


FIG. 55D

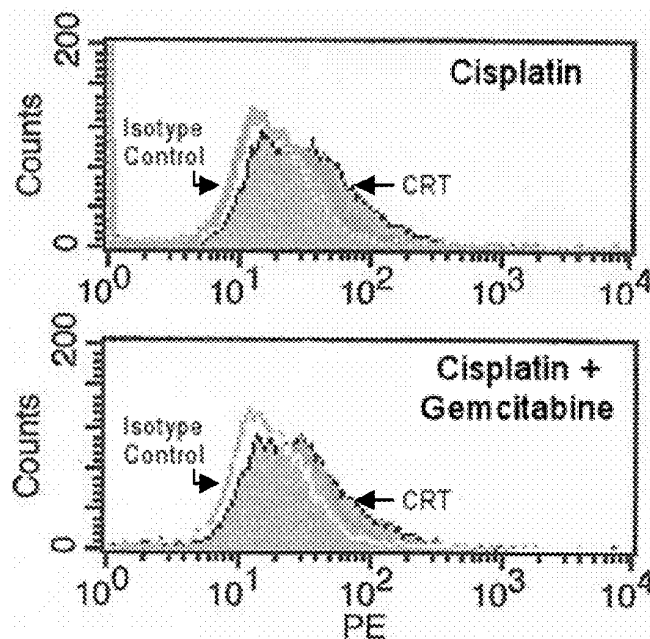


FIG. 56A

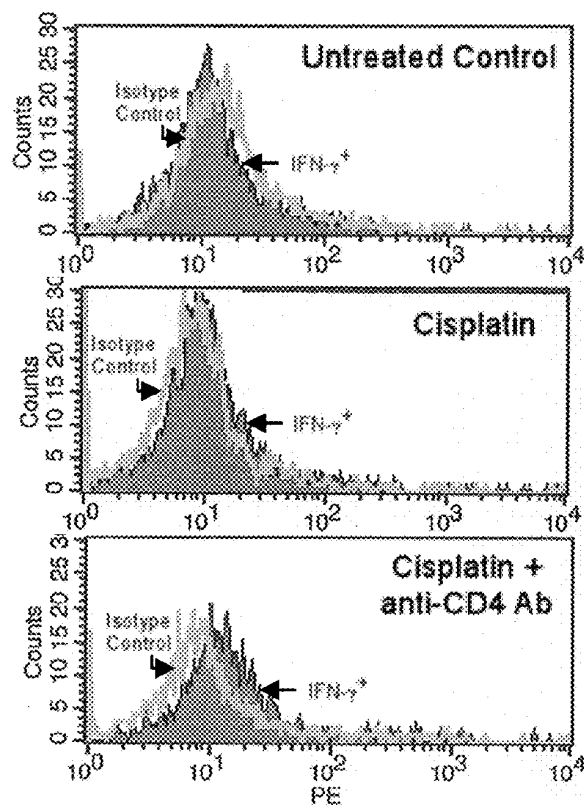


FIG. 56B

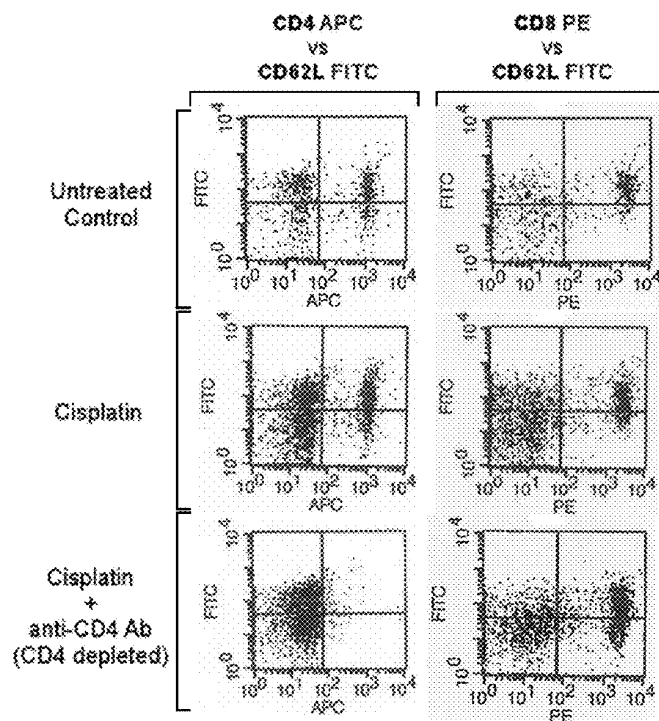


FIG. 56C

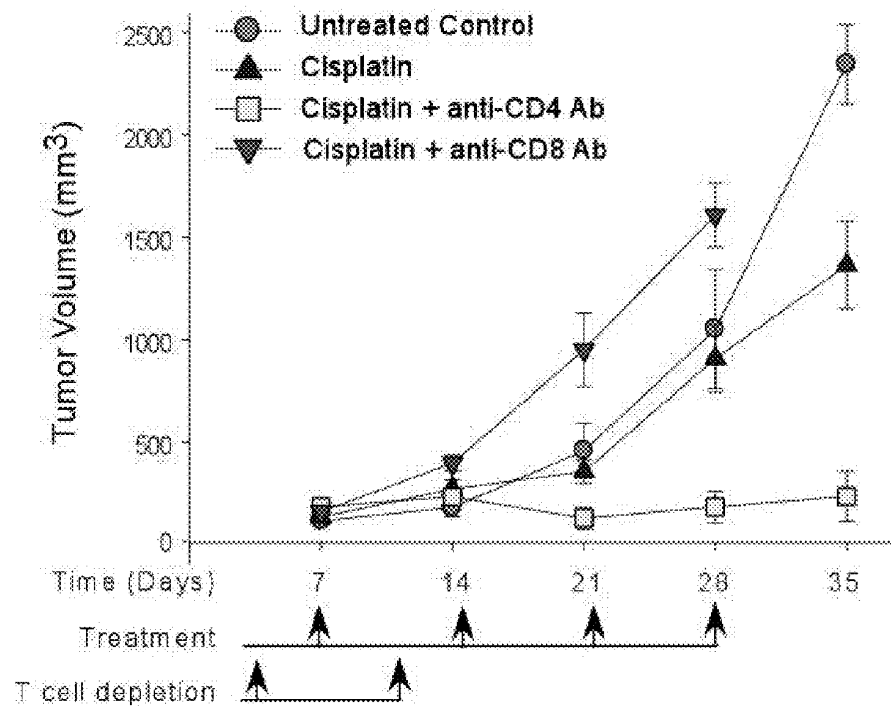


FIG. 56D

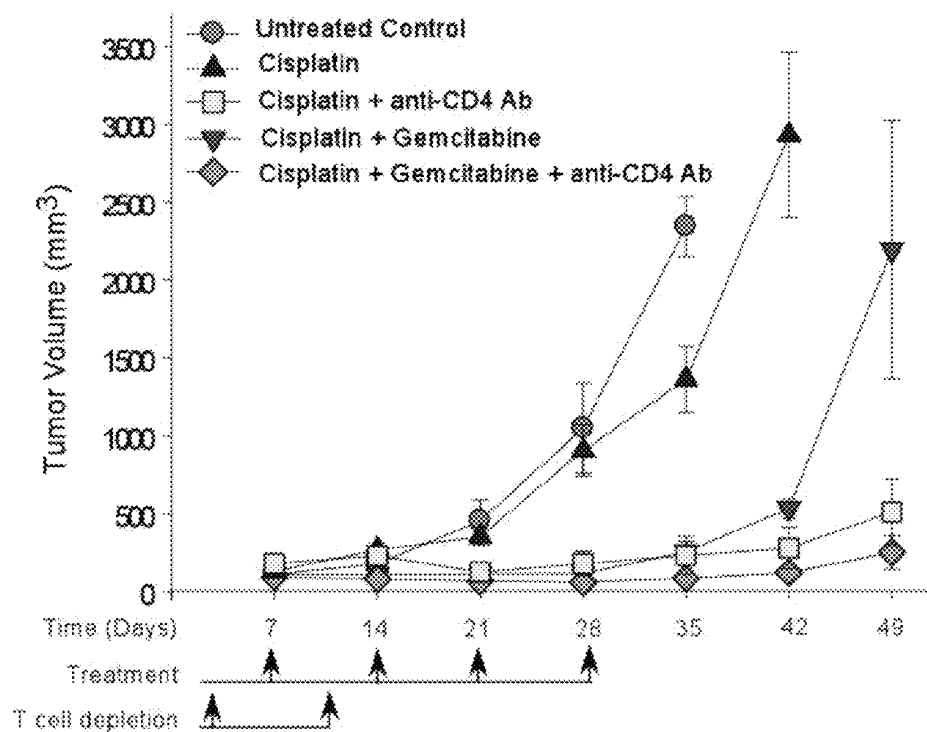


FIG. 56E

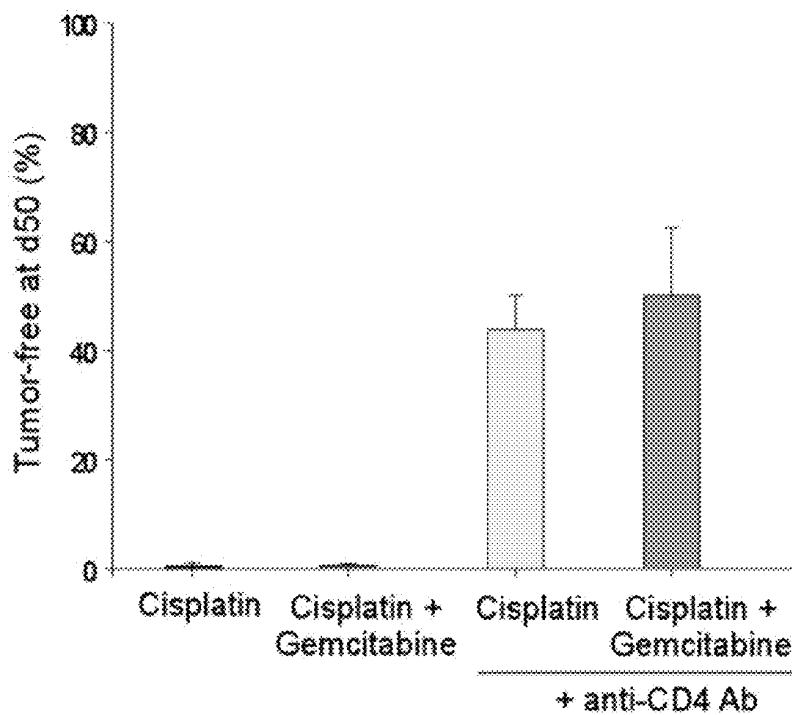


FIG. 56F

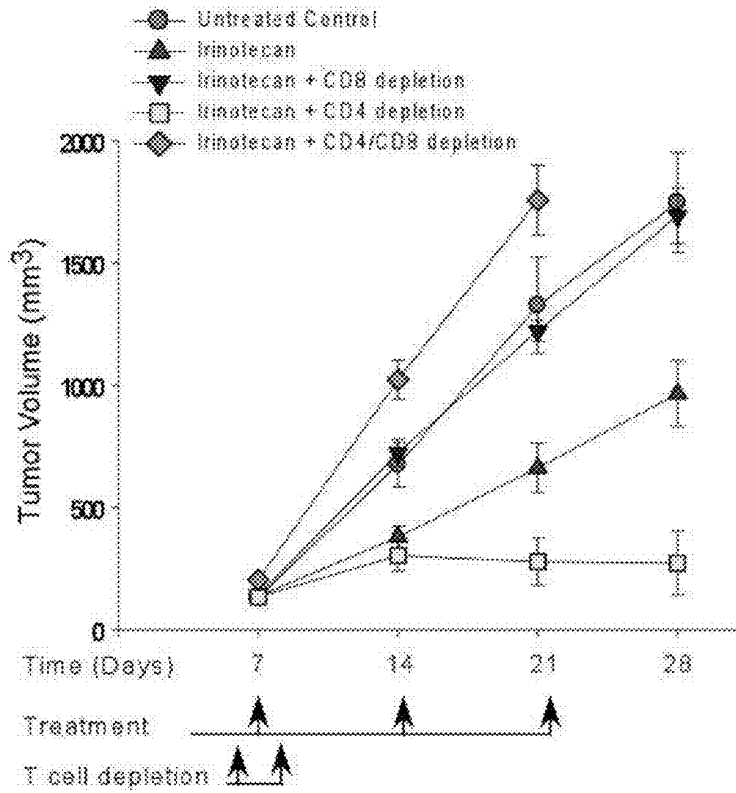


FIG. 57A

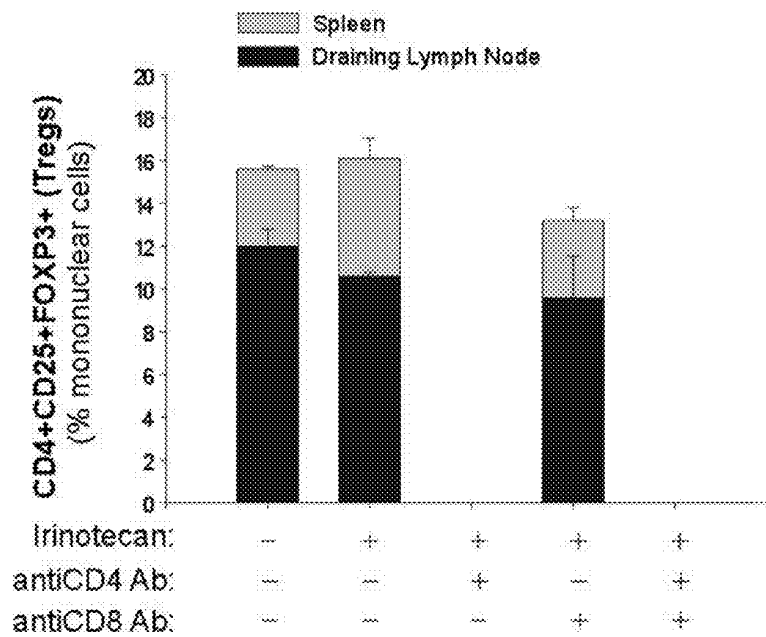


FIG. 57B

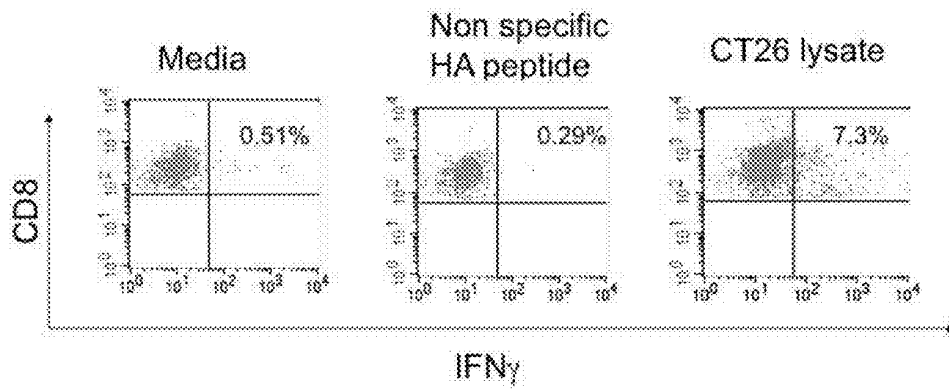


FIG. 57C

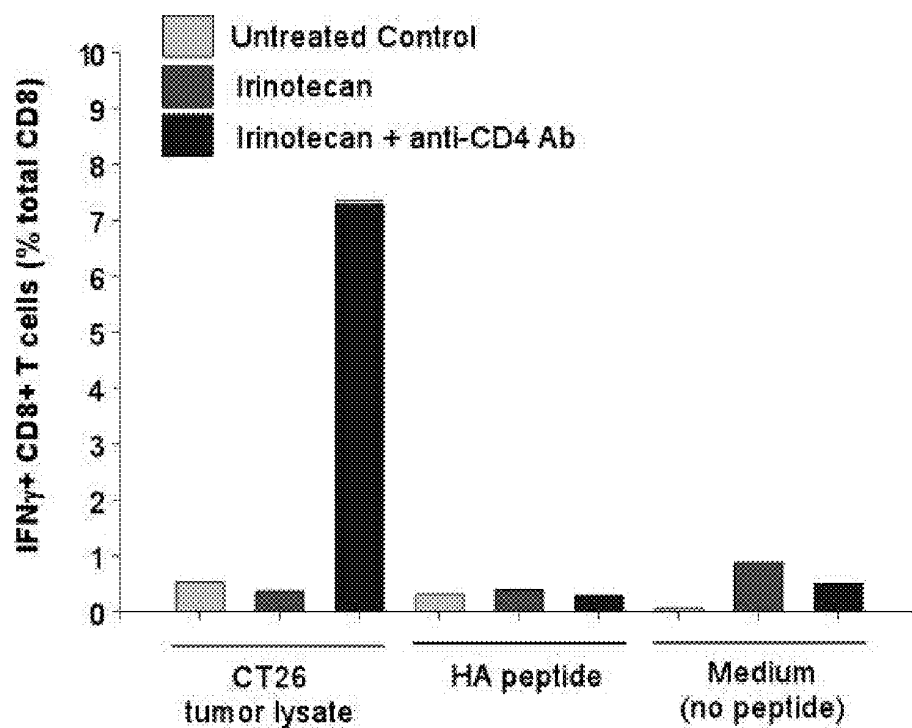


FIG. 57D

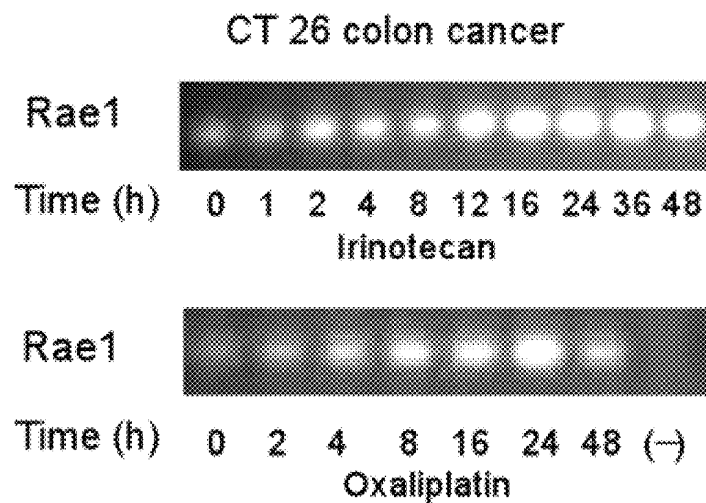


FIG. 57E

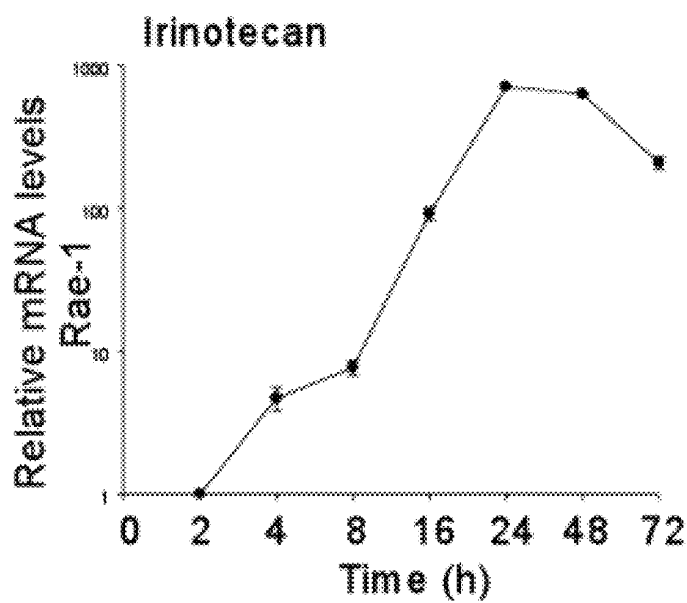


FIG. 57F

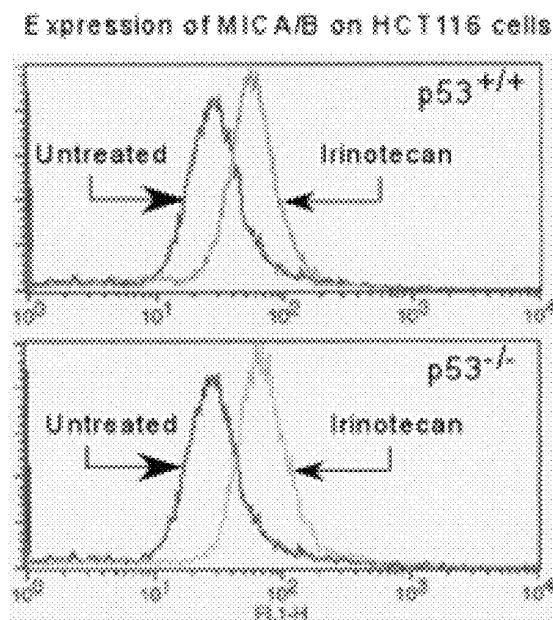


FIG. 57G

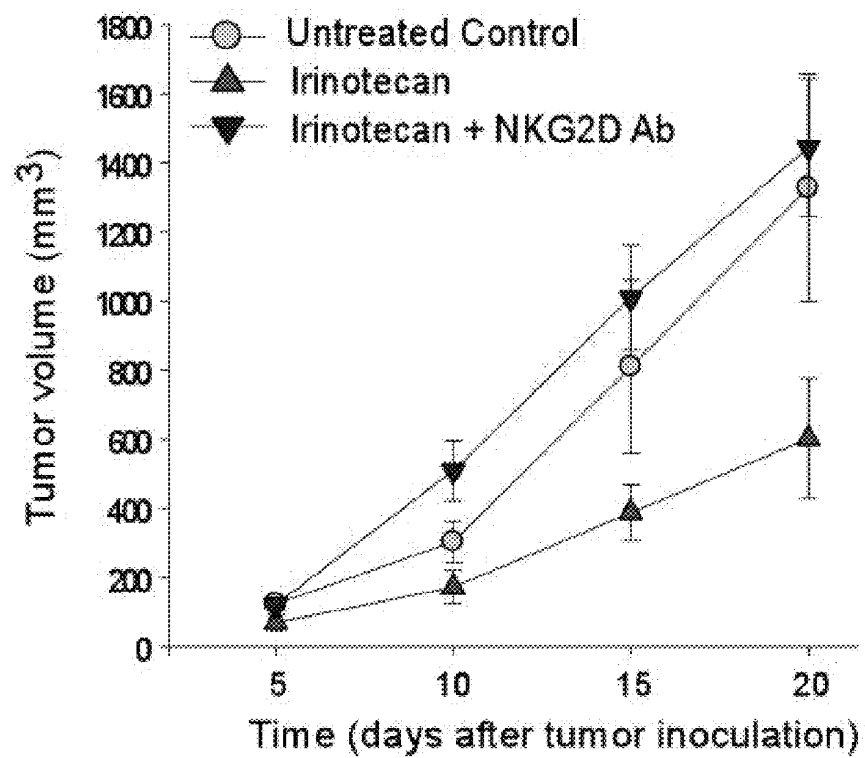


FIG. 57H

COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation application of U.S. application Ser. No. 13/582,717 filed Oct. 17, 2012, now pending; which is a 35 USC §371 National Stage application of International Application No. PCT/US2011/027317 filed Mar. 4, 2011; 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-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); 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-2 α R), 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

TGFβRII 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-κB (RANK) or Receptor activator of nuclear factor-κB ligand (RANKL). In another aspect, the targeting moiety includes an extracellular ligand-binding domain or ectodomain of Receptor activator of nuclear factor-κB (RANK). In an additional aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain of TGF-βRII. In another aspect, the molecule includes RANK ectodomain, immunoglobulin Fc region, and TGFβRII 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-2α receptor; IL-2αR), 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-κB (RANK) or Receptor activator of nuclear factor-κB ligand (RANKL). In another aspect, the targeting moiety includes an extracellular ligand-binding domain or ectodomain of Receptor activator of nuclear factor-κB (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-κB ligand (RANKL). In another aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain or ectodomain of Receptor activator of nuclear factor-κB (RANK). In an additional aspect, the immunomodulatory moiety inhibits the activity or function of Receptor activator of nuclear factor-κB 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-2α receptor; IL-2αR), or CD4. In an additional aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain or ectodomain of Receptor activator of nuclear factor-κB (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 Cy1), 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 Cy1), 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-2α receptor; IL-2αR), 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 CD4 $^{+}$ 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

FIGS. 1A-1C show exemplary amino acid sequences of transforming growth factor beta receptor type II (TGF- β -RII) 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 FIGS. 1A-1C 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 aa from the C-terminus (SEQ ID NO: 82); (ii) TGF- β R-II (Δ cyt): TGF β RII lacking the kinase domain & juxtamembrane region (SEQ ID NO: 83) and TGF- β R-IIB (Δ cyt): TGF β RIIb lacking the kinase domain & juxtamembrane region (SEQ ID NO: 84); (iii) TGF- β R-II containing the N-terminus region including the extracellular domain (SEQ ID NO: 85) and TGF- β R-IIB containing the N-terminus region including the extracellular domain (SEQ ID NO: 86); (iv) TGF- β R-II containing the extracellular domain that binds TGF- β (SEQ ID NO: 87) and TGF- β R-IIB 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, FIGS. 1A-1C also show 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.

FIGS. 8A-8B show 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-EGFR1 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).

FIGS. 18A-18B show 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 GGGGSGGGSGGGGS (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. 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).

FIGS. 28A-28B show 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 GGGGSGGGSGGGGS (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. 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 β) antibody and PD-1 ligand, including anti-TNF α heavy chain+PD-1L (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).

FIGS. 35A-35B show 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 GGGGSGGGSGGGGS (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 QEPKSCDK (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), Immu-

noglobulin 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-L1+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.

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-13 (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).

FIGS. 44A-44B show 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 (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 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 +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).

FIGS. 53A-53G show Regulatory T cells (Treg) accumulate in the tumor microenvironment and counteract the ability of chemotherapy to activate CD8 $^{+}$ T cell-mediated antitumor immunity. (FIG. 53A) 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. (FIG. 53B) Priming of tumor-reactive immune responses by MB49 tumor cells treated with doxorubicin ex vivo or in vivo. 5 $\times$ 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 $\times$ 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. (FIG. 53C) 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 $\times$ 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. (FIG. 53D) Delayed administration of chemotherapy in mice with pre-established tumors decreases its immunogenicity and antitumor efficacy. C57BL/6 mice were injected with 5 $\times$ 10 ^{5} live syngeneic

MB49 tumor cells and then administered intratumoral doxorubicin (10 μ g) at d3, d7, or d10 following tumor inoculation. (FIG. 53E) 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 $\times$ 10⁵ live MB49 tumor cells. (FIG. 53F) 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 $\times$ 10⁶ doxorubicin-killed MB49 cells with or without intravenous adoptive transfer of 5 $\times$ 10⁶ 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. (FIG. 53G) Tregs infiltrating the tumor microenvironment suppress the activation of adaptive anti-tumor immunity in response to chemotherapy-induced tumor cell death. Naïve C57BL/6 mice were vaccinated with 5 $\times$ 10⁶ doxorubicin-killed MB49 cells (left flank) with or without pre-treatment with either an anti-CD8 antibody (Clone GK2.43) (5 μ g $\times$ 2 doses, iv) to deplete CD8⁺ T cells or adoptive transfer of 5 $\times$ 10⁶ 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.

FIGS. 54A-54F show inhibition of TGF- β in the tumor microenvironment reduces 'adaptive' FoxP3⁺ regulatory T cells and enhances the antitumor efficacy chemotherapy. (FIG. 54A) 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 $\times$ 10⁵ live MB49 tumor cells were evaluated utilizing ELISA. (FIG. 54B) 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. (FIG. 54C) TGF β R2: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 R2:Fc (0-400 ng/ml) for 24 h followed by measurement of TGF- β (pg/ml/10⁶ cells) in supernatants via ELISA. (FIG. 54D) 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 R2: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. (FIGS. 54E, 54F). Sequestration of intratumoral TGF- β with TGF β R2: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 R2:Fc (1 μ g intratumoral). The percentage of CD4⁺CD25⁺FoxP3⁺ cells (Tregs) among tumor cells was assessed by flow cytometry (FIG. 54E), and tumor volume was monitored to determine the effect of counter-

acting tumor-induced TGF- β -mediated immune tolerance on the *in vivo* antitumor efficacy of doxorubicin (FIG. 54F).

FIGS. 55A-55D show 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. (FIG. 55A) *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 $\times$ 10⁵ 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. (FIG. 55B) 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 $\times$ 10⁵ 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. (FIG. 55C) Depletion of CD4⁺ regulatory T cells facilitates chemotherapy-induced activation of tumor-reactive CD8⁺ T cells. C57BL/6 mice injected s.c. with 5 $\times$ 10⁵ 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-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. (FIG. 55D) 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 $\times$ 10⁵ 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.

FIGS. 56A-56F show 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. (FIG. 56A) 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. (FIGS. 56B, 56C) 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 $\times$ 10⁵ 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 (FIG. 56B). The percentage of effector memory T_{EM} cells was determined by flow cytometric analyses of CD8 $^{+}$ CD62L $^{-}$ cells (FIG. 56C). (FIGS. 56D, 56E and 56F) 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 $\times$ 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.

FIGS. 57A-57H show 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. (FIG. 57A) 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 μ g/ml) or oxaliplatin (10 μ g/ml). Quantitative RT-PCR was carried out using Rae-1 specific primers [sense, 5'-CTAGTGCCACCTGGGAATTCA-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)]. (FIG. 57B) Genotoxic chemotherapeutic agents induce p53-independent cell surface expression of human NKG2D ligands (MHC-I-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 μ g/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). (FIG. 57C) and (FIG. 57D) Induction of NKG2D ligands contributes to the antitumor effect of chemotherapy in vivo. Immunocompetent Balb/C mice injected s.c. with 2 $\times$ 10 ^{5} syngeneic CT26 tumor cells were treated with irinotecan (50 mg/kg i.p. weekly $\times$ 3) beginning at d5 following tumor inoculation, with or without pre-treatment with an NKG2D blocking antibody (CX5, eBioscience) (200 μ g 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. (FIG. 57E) 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 $\times$ 10 ^{5} CT26 tumor cells s.c. were left untreated or treated with irinotecan (50 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. CD4 $^{+}$ CD25 $^{+}$ FoxP3 $^{+}$ T cells in spleen and drain-

ing lymph node isolated from mice at d16 following tumor challenge were detected by flow cytometry. (FIG. 57F) Depletion of CD4 $^{+}$ regulatory T cells facilitates irinotecan-induced activation of tumor-reactive IFN- γ $^{+}$ CD8 $^{+}$ T cells. Balb/C mice injected with 2 $\times$ 10 ^{5} CT26 tumor cells s.c. were left untreated or treated with irinotecan (50 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 (DLN) in response to in vitro stimulation with either CT26 cell lysates, an irrelevant peptide (Hemagglutinin-HA), or medium alone. (FIG. 57G) and (FIG. 57H) 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 $\times$ 10 ^{5} CT26 tumor cells s.c. were left untreated or treated with irinotecan (50 mg/kg i.p. weekly $\times$ 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 inven-

tion 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 reinforces 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 immunosuppres-

sive 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: (i) 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 naive 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 binds 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) Trans-

forming 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 (xii) 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 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 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 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 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 extracel-

lular 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 extracellular 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, epipodophyllotoxin, 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 reference 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.

A 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 proteins (IGFBPs), IGFR 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 13 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-al-

pha-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), MLA-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/Pmel17 (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, OAI, prostate specific antigen (PSA), prostate specific membrane antigen, TRP-1/gp75, TRP-2, adipophilin, interferon inducible protein absent in melanoma 2 (AIM-2), BING-4, CPSF, cyclin D1, epithelial cell adhesion molecule (Ep-CAM), 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, BRDT, SPANX, XAGE, ADAM2, PAGE-5, LIP1, CTAGE-1, CSAGE, MMA1, CAGE, BORIS, HOM-TES-85, AF15q14, HCA66I, 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, ErbB-1), HER2/neu (ErbB-2), CD20, Vascular endothelial growth factor (VEGF), insulin-like growth factor receptor (IGF-1R), TRAIL-receptor, epithelial cell adhe-

sion 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); Zalutumumab (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-I131 (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 (ami-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) pancreatic carcinoma 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; TNFR4); 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; TNFR4); 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 Zanolimumab (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); lerdelimumab/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-TNF); 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); T1 h (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 Fc).

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; TNFR4); 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; TNFR4); 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 fragments: 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; TNFR4); 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; TNFR4); 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; TNFR4), 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; TNFR4), 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; TNFR4), 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 nonhuman 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 immu-

nomodulatory 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 dis-

closed 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); Pitner 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 inactivate 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. 53A). 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. 53B). 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. 53C). 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. 53B). 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. 53D). 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. 53E). 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. 53F). 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. 53G). 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. 54A). 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. 54B). 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. 54B). 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. 54C). At 5d 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. 54D) and a dramatic reduction of CD4⁺CD25⁺FoxP3⁺ Tregs in tumor tissue (FIG. 54E). 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. 55A). 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 (FIGS. 55A, 55B). 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. 55C). 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. 55C). 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. 55D).

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 anthracycline, 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. 56A). Whereas tumor-reactive IFN- γ ⁺CD8⁺ T cells were evident in tumors of MB49 tumor-bearing mice treated with doxorubicin (FIG. 55C), 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. 56B). 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 (FIGS. 56B, 56C). 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. 56D). 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. 56E). 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 complete 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,

$\gamma\delta$ -TCR⁺ T cells and $\alpha\beta$ -TCR⁺ 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. 57A). 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. 57A). Flow cytometric analysis demonstrated that cell surface expression of human NKG2D ligands (MHC-I-related A and B molecules—MICA, MICB) was also upregulated on human colorectal cancer cells (HCT116) in response to treatment with irinotecan (FIG. 53B). Isogenic HCT116 cells that differ only in their p53 status demonstrated that p53 is not required for irinotecan-induced upregulation of MICA/B (FIG. 53B). 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. 57D). Antibody-mediated depletion of CD4⁺ T cells enhanced the percentage of tumor-reactive IFN- γ ⁺CD8⁺ T cells in irinotecan-treated animals (FIG. 57E). 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. 57F). 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. 57F).

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 microenvironment; 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 chemoimmunotherapy (combination of chemotherapeutic agent with immunotherapeutic agents).

Example 2

Exemplary Targeted Immunomodulatory Antibodies and 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. Cross-linkers 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 recombination 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 receptor 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 II (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 (IgG C γ 1), 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- β -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 provides 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- β (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- β 1; FIG. 47). SEQ ID NO: 60 provides a fusion protein including 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) (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

<160> NUMBER OF SEQ ID NOS: 122

<210> SEQ ID NO 1

<211> LENGTH: 602

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 1

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
 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

-continued

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 Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile
 465 470 475 480
 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
 545 550 555 560
 Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe
 565 570 575
 Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe
 580 585 590
 Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
 595 600

<210> SEQ ID NO 2
 <211> LENGTH: 601
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 2

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

-continued

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
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	530	535	540	
Asp	Pro	Lys	Leu	Pro	Tyr	His	Asp	Phe	Ile	Leu	Glu	Asp	Ala	Ala	Ser	545	550	555	560

-continued

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
580 585 590

Glu Glu Tyr Asn Thr Ser Asn Pro Asp
595 600

<210> SEQ ID NO 3

<211> LENGTH: 603

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 3

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

-continued

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 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 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

-continued

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
				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			

-continued

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

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

-continued

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

<210> SEQ ID NO 6

<211> LENGTH: 525

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

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

-continued

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	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
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				

-continued

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		
	115	120 125
Glu Glu Tyr Asn Thr Ser Asn Pro Asp Gly Gly Gly Ser Gly Gly		
	130	135 140
Gly Gly Ser 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

-continued

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 Gly Ser Ala Pro Thr Ser Ser Ser Thr Lys
 385 390 395 400
 Lys Thr Gln Leu Gln Leu Glu His 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

<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

-continued

```

<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
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
          290             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

```

-continued

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

-continued

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
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 Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met	465	470	475
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
Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr	565	570	575

-continued

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

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

-continued

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			

<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	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	

-continued

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
 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

-continued

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 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

-continued

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				
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

-continued

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
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
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

<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
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
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
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

-continued

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
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				
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										

-continued

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
          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

```

-continued

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 Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp Asn Pro
 465 470 475 480
 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
 545 550 555 560
 Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu Ala Pro
 565 570 575
 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

-continued

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
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
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
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
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	Pro	Gly	Trp	Phe	Leu	Asp	Ser	Pro	Asp	Arg	Pro	Trp	465	470	475
Asn	Pro	Pro	Thr	Phe	Ser	Pro	Ala	Leu	Leu	Val	Val	Thr	Glu	Gly	Asp	485	490	495
Asn	Ala	Thr	Phe	Thr	Cys	Ser	Phe	Ser	Asn	Thr	Ser	Glu	Ser	Phe	Val	500	505	510
Leu	Asn	Trp	Tyr	Arg	Met	Ser	Pro	Ser	Asn	Gln	Thr	Asp	Lys	Leu	Ala	515	520	525
Ala	Phe	Pro	Glu	Asp	Arg	Ser	Gln	Pro	Gly	Gln	Asp	Cys	Arg	Phe	Arg	530	535	540

-continued

Val	Thr	Gln	Leu	Pro	Asn	Gly	Arg	Asp	Phe	His	Met	Ser	Val	Val	Arg
545					550					555					560
Ala	Arg	Arg	Asn	Asp	Ser	Gly	Thr	Tyr	Leu	Cys	Gly	Ala	Ile	Ser	Leu
			565						570					575	
Ala	Pro	Lys	Ala	Gln	Ile	Lys	Glu	Ser	Leu	Arg	Ala	Glu	Leu	Arg	Val
			580					585					590		
Thr	Glu	Arg	Arg	Ala	Glu	Val	Pro	Thr	Ala	His	Pro	Ser	Pro	Ser	Pro
		595					600					605			
Arg	Pro	Ala	Gly	Gln	Phe	Gln	Thr	Leu	Val						
	610					615									

<210> SEQ ID NO 19
 <211> LENGTH: 613
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19

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
			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				

-continued

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
 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

-continued

50					55					60					
Lys 65	Asp	Lys	Ala	Thr	Ile 70	Thr	Ala	Asp	Glu	Ser 75	Thr	Asn	Thr	Ala	Tyr 80
Met	Glu	Leu	Ser 85	Leu	Arg	Ser	Glu	Asp 90	Thr	Ala	Val	Tyr 95	Tyr	Cys	
Ala	Arg	Gly 100	Gly	Val	Phe	Asp 105	Trp	Gly	Gln	Gly 110	Thr	Leu	Val		
Thr	Val	Ser 115	Ser	Ala	Ser	Thr 120	Lys	Gly	Pro	Ser 125	Val	Phe	Pro	Leu	Ala
Pro	Ser 130	Ser	Lys	Ser	Thr 135	Ser	Gly	Gly	Thr	Ala 140	Ala	Leu	Gly	Cys	Leu
Val 145	Lys	Asp	Tyr	Phe 150	Pro	Glu	Pro	Val	Thr	Val 155	Ser	Trp	Asn	Ser	Gly 160
Ala	Leu	Thr	Ser	Gly 165	Val	His	Thr	Phe 170	Pro	Ala	Val	Leu	Gln	Ser 175	Ser
Gly	Leu	Tyr 180	Ser	Leu	Ser	Ser	Val	Val 185	Thr	Val	Pro	Ser	Ser	Ser	Leu
Gly	Thr 195	Gln	Thr	Tyr	Ile	Cys	Asn 200	Val	Asn	His	Lys 205	Pro	Ser	Asn	Thr
Lys 210	Val	Asp	Lys	Lys	Val	Glu 215	Pro	Lys	Ser	Cys 220	Asp	Lys	Thr	His	Thr
Cys 225	Pro	Pro	Cys	Pro	Ala 230	Pro	Glu	Leu	Leu	Gly 235	Gly	Pro	Ser	Val	Phe 240
Leu	Phe	Pro	Pro 245	Lys	Pro	Lys	Asp	Thr 250	Leu	Met	Ile	Ser	Arg	Thr 255	Pro
Glu	Val	Thr 260	Cys	Val	Val	Val	Asp	Val 265	Ser	His	Glu	Asp	Pro	Glu	Val
Lys	Phe 275	Asn	Trp	Tyr	Val	Asp	Gly 280	Val	Glu	Val	His 285	Asn	Ala	Lys	Thr
Lys 290	Pro	Arg	Glu	Glu	Gln	Tyr 295	Asn	Ser	Thr	Tyr	Arg 300	Val	Val	Ser	Val
Leu 305	Thr	Val	Leu	His	Gln 310	Asp	Trp	Leu	Asn	Gly 315	Lys	Glu	Tyr	Lys	Cys 320
Lys	Val	Ser	Asn	Lys 325	Ala	Leu	Pro	Ala 330	Pro	Ile	Glu	Lys	Thr	Ile	Ser 335
Lys	Ala	Lys 340	Gly	Gln	Pro	Arg	Glu	Pro 345	Gln	Val	Tyr	Thr	Leu	Pro	Pro 350
Ser	Arg 355	Asp	Glu	Leu	Thr	Lys	Asn	Gln 360	Val	Ser	Leu	Thr 365	Cys	Leu	Val
Lys	Gly 370	Phe	Tyr	Pro	Ser	Asp 375	Ile	Ala	Val	Glu	Trp 380	Glu	Ser	Asn	Gly
Gln 385	Pro	Glu	Asn	Asn	Tyr 390	Lys	Thr	Thr	Pro	Pro 395	Val	Leu	Asp	Ser	Asp 400
Gly	Ser	Phe 405	Phe	Leu	Tyr	Ser	Lys	Leu	Thr 410	Val	Asp	Lys	Ser	Arg	Trp 415
Gln	Gln	Gly 420	Asn	Val	Phe	Ser	Cys	Ser	Val 425	Met	His	Glu	Ala	Leu	His
Asn	His 435	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu 440	Ser	Pro	Gly 445	Lys	Gly	Gly
Gly	Gly 450	Ser	Gly	Gly	Gly 455	Gly	Ser	Gly	Gly	Gly 460	Gly	Ser	Pro	Gly	Trp
Phe 465	Leu	Asp	Ser	Pro	Asp 470	Arg	Pro	Trp	Asn	Pro 475	Pro	Thr	Phe	Ser	Pro 480

-continued

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

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

-continued

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 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
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
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

-continued

<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
 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 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

-continued

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
			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			
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	

-continued

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
 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 Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp Asn Pro
 465 470 475 480
 Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp Asn Ala
 485 490 495

-continued

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						560
Arg	Asn	Asp	Ser	Gly	Thr	Tyr	Leu	Cys	Gly	Ala	Ile	Ser	Leu	Ala	Pro
			565						570					575	
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 25

<211> LENGTH: 590

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 25

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	

-continued

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

<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 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

-continued

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			
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	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				

-continued

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
 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

-continued

245																250						255					
Ser	Arg	Thr	Pro 260			Glu	Val	Thr	Cys	Val 265			Val	Val	Asp	Val	Ser	His	Glu								
Asp	Pro	Glu	Val 275			Lys	Phe	Asn	Trp	Tyr 280			Val	Asp	Gly	Val	Ser	His	Glu								
Asn	Ala	Lys	Thr	Lys	Pro 290			Arg	Glu	Gln 295			Tyr	Asn	Ser	Thr	Tyr	Arg									
Val	Val	Ser	Val	Leu	Thr 305			Val	Leu	His	Gln 315			Asp	Trp	Leu	Asn	Gly	Lys								
Glu	Tyr	Lys	Cys	Lys	Val 325			Ser	Asn	Lys	Ala 330			Leu	Pro	Ala	Pro	Ile	Glu								
Lys	Thr	Ile	Ser	Lys	Ala 340			Lys	Gly	Gln	Pro 345			Arg	Glu	Pro	Gln	Val	Tyr								
Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn 355			Gln	Val	Ser	Leu										
Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile 370			Ala	Val	Glu	Trp										
Glu	Ser	Asn	Gly	Gln	Pro 385			Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val										
Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp												
Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His												
Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro												
Gly	Lys	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly													
Ser	Gln	Ile	Ala	Pro	Pro 465			Cys	Thr	Ser	Glu	Lys	His	Tyr	Glu	His	Leu										
Gly	Arg	Cys	Cys	Asn	Lys	Cys	Glu	Pro	Gly	Lys	Tyr	Met	Ser	Ser	Lys												
Cys	Thr	Thr	Thr	Ser	Asp	Ser	Val	Cys	Leu	Pro	Cys	Gly	Pro	Asp	Glu												
Tyr	Leu	Asp	Ser	Trp	Asn	Glu	Glu	Asp	Lys	Cys	Leu	Leu	His	Lys	Val												
Cys	Asp	Thr	Gly	Lys	Ala	Leu	Val	Ala	Val	Val	Ala	Gly	Asn	Ser	Thr												
Thr	Pro	Arg	Arg	Cys	Ala	Cys	Thr	Ala	Gly	Tyr	His	Trp	Ser	Gln	Asp												
Cys	Glu	Cys	Cys	Arg	Arg	Asn	Thr	Glu	Cys	Ala	Pro	Gly	Leu	Gly	Ala												
Gln	His	Pro	Leu	Gln	Leu	Asn	Lys	Asp	Thr	Val	Cys	Lys	Pro	Cys	Leu												
Ala	Gly	Tyr	Phe	Ser	Asp	Ala	Phe	Ser	Ser	Thr	Asp	Lys	Cys	Arg	Pro												
Trp	Thr	Asn	Cys	Thr	Phe	Leu	Gly	Lys	Arg	Val	Glu	His	His	Gly	Thr												
Glu	Lys	Ser	Asp	Ala	Val	Cys	Ser	Ser	Ser	Leu	Pro	Ala	Arg	Lys	Pro												
Pro	Asn	Glu	Pro	His	Val	Tyr	Leu	Pro	Gly																		

<210> SEQ ID NO 28

-continued

```

<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    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

```

-continued

385	390	395	400
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	585	590
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
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	

-continued

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	
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

-continued

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 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		

-continued

```

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

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 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 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

-continued

<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
 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

-continued

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 Ser Gln
 450 455 460
 Ile Ala Pro Pro Cys Thr Ser Glu Lys His Tyr Glu His Leu Gly Arg
 465 470 475 480
 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
 545 550 555 560
 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
 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

-continued

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			
Gly	Gly	Ser	Gly	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		

-continued

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
 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

-continued

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
 305 310 315 320
 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
 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
 545 550 555 560
 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
 625 630 635 640
 Val Tyr Leu Pro Gly
 645

<210> SEQ ID NO 34
 <211> LENGTH: 573
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

-continued

<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 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
 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

-continued

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

<210> SEQ ID NO 35
 <211> LENGTH: 573
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 35

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

-continued

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 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

-continued

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		
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

-continued

435					440					445					
Pro	Gly	Lys	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 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	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

-continued

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
		450				455						460			
Gly	Ser	Arg	Ile	Phe	Ala	Val	Phe	Ile	Phe	Met	Thr	Tyr	Trp	His	Leu
				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
					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

-continued

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
										650					655
Asn	Val	Thr	Ser	Thr	Leu	Arg	Ile	Asn	Thr	Thr	Thr	Asn	Glu	Ile	Phe
															670
Tyr	Cys	Thr	Phe	Arg	Arg	Leu	Asp	Pro	Glu	Glu	Asn	His	Thr	Ala	Glu
		675						680							
Leu	Val	Ile	Pro	Glu	Leu	Pro	Leu	Ala	His	Pro	Pro	Asn	Glu	Arg	Thr
		690						695							
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
															735
Cys	Gly	Ile	Gln	Asp	Thr	Asn	Ser	Lys	Lys	Gln	Ser	Asp	Thr	His	Leu
															750
Glu	Glu	Thr													
															755

<210> SEQ ID NO 38

<211> LENGTH: 771

<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
					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
Gly	Thr	Phe	Ser	Asn	Thr	Thr	Ser	Ser	Thr	Asp	Ile	Cys	Arg	Pro	His
															160
Gln	Ile	Cys	Asn	Val	Val	Ala	Ile	Pro	Gly	Asn	Ala	Ser	Met	Asp	Ala
															175
Val	Cys	Thr	Ser	Thr	Ser	Pro	Thr	Arg	Ser	Met	Ala	Pro	Gly	Ala	Val
															190

-continued

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
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

-continued

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		
<400> SEQUENCE: 39		
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

-continued

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	
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

-continued

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
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

<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	

-continued

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
		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

-continued

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
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	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		
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		
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	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		
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		
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		
Thr	Thr	Asn	Ser	Lys	Arg	Glu	Glu	Lys	Leu	Phe	Asn	Val	Thr	Ser	Thr</	

-continued

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
	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		

-continued

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						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	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					480
Thr	Val	Pro	Lys	Asp	Leu	Tyr	Val	Val	Glu	Tyr	Gly	Ser	Asn	Met	Thr
			485						490					495	
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

-continued

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	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	

-continued

```

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 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

```

-continued

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									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	
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	Arg	Ile	Phe	Ala	Val	Phe	Ile	Phe	Met			

-continued

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
 465 470 475 480
 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
 545 550 555 560
 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
 625 630 635 640
 Ala Leu Thr Phe Ile Phe Arg Leu Arg Lys Gly Arg Met Met Asp Val
 645 650 655
 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

-continued

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			
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	

-continued

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 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

-continued

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	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		

-continued

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

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

-continued

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
 485 490 495
 Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 500 505 510
 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

-continued

```

<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
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

```

-continued

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
 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

-continued

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				

-continued

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

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

-continued

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 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

-continued

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
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				

-continued

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
 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

-continued

```

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

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	
			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			

-continued

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
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				

-continued

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
 Gly Gly Ser Gly Gly Gly Gly Ser 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

-continued

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
 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
 305 310 315 320
 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

-continued

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
 465 470 475 480

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
 545 550 555 560

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

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

-continued

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
 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

-continued

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	
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

-continued

<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
 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

-continued

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 59

<211> LENGTH: 510

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 59

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

Bicara Ex. 1013
Bicara v. JHU - PGR2026-00025

-continued

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		
Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala
		115						120					125		
Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro
	130							135				140			
Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val
145					150					155					160
Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val
				165					170					175	
Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln
		180						185					190		
Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln
		195						200					205		
Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala
	210							215				220			
Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro
225					230					235					240
Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr
				245					250					255	
Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser
		260						265					270		
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												

-continued

```

<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     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

```

-continued

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 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

-continued

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
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

-continued

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
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			

-continued

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 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	

-continued

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
			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		

-continued

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 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
 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

-continued

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
				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			

-continued

```

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

```

<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

```

-continued

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 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

-continued

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
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
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
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 Ser	290	295	300
Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro	305	310	315
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
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

-continued

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
 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

-continued

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
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
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
Phe Pro Val Glu Lys Gln Leu Asp Leu Ala Ala Leu Ile Val Tyr Trp	485	490	495

-continued

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 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
 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

-continued

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
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		

-continued

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														

<210> SEQ ID NO 73

<211> LENGTH: 214

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 73

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	

-continued

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 74

<211> LENGTH: 215

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 74

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

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

-continued

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 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

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

-continued

<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
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

```

-continued

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
 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

-continued

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	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			

-continued

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
			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

-continued

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	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	
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	

-continued

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	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
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		

-continued

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
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		

-continued

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			
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

-continued

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

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

-continued

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
						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

-continued

```

<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
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

```

-continued

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
 <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

-continued

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			

<210> SEQ ID NO 93
 <211> LENGTH: 150
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<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					
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

-continued

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
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
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
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
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

-continued

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
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 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

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

-continued

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			
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																

-continued

```

<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

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

```

-continued

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

<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

-continued

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
Thr		
<210> SEQ ID NO 102		
<211> LENGTH: 390		
<212> TYPE: PRT		
<213> ORGANISM: Homo sapiens		
<400> SEQUENCE: 102		
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		
	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		

-continued

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
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

<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

-continued

```

<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

```

```

<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

```

-continued

```

<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 tgcagctggt ggaatccggc ggaggactgg tgcagcctgg cggatccctg                60
agactgtctt gcgcgcctc cggttcaac atcaaggaca cctacatcca ctgggtgcga                120
caggccctct gcaagggaact ggaatgggtg gcccggtatc accccaccaa cggetacacc                180
agatacgccg actccgtgaa gggccgggtc accatctccg ccgacacctc caagaacacc                240
gcctacctgc agatgaactc cctgcggggc gaggacaccg ccgtgtacta ctgctccaga                300
tggggaggcg acggcttcta cgccatggac tactggggcc agggcacccct ggtgacagtg                360
tctctgcctc ccaccaaggg cccctctgtg ttccctctgg ccccttcag caagtccaca                420
tctggcgcca ccgcgcctct gggtgcctg gtgaaagact acttccccga gcccgtagcc                480
gtgtcctgga actctgggc cctgacctc ggctgcaca ctttccagc cgtgctgcag                540
tcctccggcc tgtactccct gtctccgtg gtgacctgc cctccagctc tctgggcacc                600
cagacctaca tctgcaactg gaaccacaag ccctccaaca ccaagggtga caagaagggtg                660
gaaccaagt cctgcgacaa gaccacacc tgtccccctt gccctgctcc tgaactgctg                720
ggcggaccct ccgtgttctt gtcccccca aagcccaagg acacctgat gatctcccgg                780
acccccgaag tgacctgcgt ggtggtggac gtgtccacg aggacctga agtgaagtgc                840
aattggtatg tggacggcgt ggaagtgcac aacgccaaga ccaagcccag agaggaacag                900
tacaactcca cctaccgggt ggtgtctgtg ctgacctgc tgcaccagga ctggtgaac                960
ggcaaagagt acaagtgcaa ggtgtccaac aaggccctgc ctgcccccat cgaaaagacc                1020
atctccaagg ccaagggtca gcctcgcgag cctcaggtgt acacactgcc ccctagccgg                1080
gaagagatga ccaagaacca ggtgtccctg acctgtctgg tgaaaggctt ctaccctcc                1140
gatatgcctg tggaatggga gtccaacggc cagcccgaga acaactacaa gaccaccccc                1200
cctgtgctgg actccgacgg ctcatcttc ctgtactcca agctgacctg ggacaagtcc                1260
cgggtggcagc agggcaactg gttctcctgc tccgtgatgc acgaggccct gcacaaccac                1320
tacaccaga agtccctgtc cctgagccct ggaaggggcg gaggcggctc tgggtgtgga                1380
ggctctggag gcggaggctc taccatccct ccacacgtgc agaaatccgt gaacaacgac                1440
atgatcgtga ccgacaacaa cggcgccgtg aagttcccc agctgtgcaa gttctgcgac                1500

```

-continued

```

gtgcgggttct ctacctgcga caaccagaaa tctgcatgt ccaactgtct catcacctcc 1560
atctgcgaga agccccagga agtgtgctg gccgtgtggc ggaagaacga cgagaacatc 1620
accctggaaa ccgtgtgcca cgaccccaag ctgacctacc acgacttcat 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 ccagtcctcc tccagcctgt ccgcctctgt gggcgacaga 60
gtgaccatca cctgtcgggc ctctcaggac gtgaacaccg ccgtggcctg gtatcagcag 120
aagcctggca agggcccaaa gctgctgac tactccgcct ccttctctga ctccggggtg 180
ccatcccggt tctccggtc tagatccggc accgacttca cctgaccat ctccagcctg 240
cagcccgagg acttcgcaac ctactactgc cagcagcact acaccacccc ccctaccttc 300
ggccagggca ccaagtgga aatcaagcgg accgtggccg ctccctccgt gttcatcttc 360
ccaccctccg acgagcagct gaagtctggc accgcctccg tcgtgtgcct gctgaacaac 420
ttctaccccc gcgaggccaa ggtgcagtgg aaggtggaca acgcctgca gtcggcaac 480
tcccaggaat ccgtgaccga gcaggactcc aaggacagca cctactccct gtctccacc 540
ctgacctgt ccaaggccga ctacgagaag cacaaggtgt acgcctgcga agtgaccac 600
cagggcctgt ccagcccggt 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 gtacctgtgc cggtctctcc ctgaccaact acggcgtgca ctgggtccga 120
cagtcctcag gcaagggcct ggaatggctg ggagtgattt ggagcggcgg caacaccgac 180
tacaacaccc ccttccactc ccggtgtgac atcaacaagg acaactcaa gtcccagggtg 240
ttcttcaaga tgaactccct gcagtcacac gacaccgcca tctactactg cgccagagcc 300
ctgacctact atgactacga gtctgcctac tggggacagg gcacctggt caccgtgtct 360
gccgcctcta ccaaggggcc ctccgtgttt cccctggccc cctccagcaa gtccacatct 420
ggcggcaccg ccgctctggg ctgcctggtc aaggactact tccccgagcc cgtgaccgtg 480
tcttggaact ctgggcctcc gacctccggc gtgcacacct ttccagccgt gctgcagtc 540
tccggcctgt actcctgtc ctccgtctgt accgtgccct ccagctctct gggcaccacg 600
acctacatct gcaacgtgaa ccacaagccc tccaacacca aggtggacaa gcgggtggaa 660
cccaagtct ggcacaagac ccacacctgt ccccccctgc ctgcccctga actgctggga 720
ggcccttccg tgttctctgt cccccaaaag cccaaggaca cctgatgat ctcccgacc 780
cccgaagtga cctgcgtggt ggtggacgtg tcccacgagg accctgaagt gaagttcaat 840
tggtagctgg acggcgtgga agtgcacaac gcccaagacca agcccagaga ggaacagtac 900

```

- continued

```

aactccacct accgggtggt gtccgtgctg accgtgctgc accaggactg gctgaacggc 960
aaagagtaca agtgcaaggt ctccaacaag gccctgcttg ccccatcgaa aaagaccatc 1020
tccaaggcca agggccagcc ccgcgagcct caggtgtaca ctctgcctcc cagccgggac 1080
gagctgacca agaaccaggt gtccctgacc tgtctggtca agggcttcta cccctccgat 1140
atcgccgtgg aatgggagtc caacggccag cccgagaaca actacaagac cccccccct 1200
gtgctggact ccgacggctc attcttcttg tactccaagc tgaccgtgga caagtcccg 1260
tggcagcagg gcaacgtgtt ctctgctcc gtgatgcacg agggcctgca caaccactac 1320
accagaagt cctgtctctt gagccccggc aagggcggag gcggtatctg tgggtggtggc 1380
tctggtggcg gaggtctac catccctcca cactgacaga aatccgtgaa caacgacatg 1440
atcgtagacc acaacaacgg cgcgtgaag ttccccagc tgtgcaagtt ctgcgacgtg 1500
cggttctcta cctgcgacaa ccagaaatcc tgcattgcca actgctccat cactccatc 1560
tgcgagaagc cccaggaagt gtgcgtcgcc gtctggcgga agaacgacga gaacatcacc 1620
ctggaaaccg tgtgccacga ccccaagctg cctaccacg acttcatcct ggaagatgcc 1680
gcctcccca agtgcattcat gaaggaaaag aagaagcccg gcgagacttt cttcatgtgc 1740
agctgctcct ccgacgagtg caacgacaac atcatcttct ccgaagagta caacacctcc 1800
aaccgccact gaggtacc 1818

```

```

<210> SEQ ID NO 117
<211> LENGTH: 657
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 117

```

```

gagctcgata tctctgtgac ccagtcctcc gtgatcctgt ccgtgtctcc tggcgagcgg 60
gtgtccttct cctgcccggc ctcccagtc atcggcacca acatccactg gtatcagcag 120
cggaccaacg gctcccctcg gctgctgatt aagtacgcct ccgagtctat ctccggcatc 180
ccctcccggg tctccggctc tggctccggc accgacttca cctgttccat caactccgtg 240
gaatccgagg atatgcgca ctactactgc cagcagaaca acaactggcc caccaccttc 300
ggcgctggca ccaagctgga actgaagcgg accgtggccg ctccctccgt gttcatcttc 360
ccacctccg acgagcagct gaagtccggc accgcctccg tcgtgtgcct gctgaacaac 420
ttctaccccc gcgaggccaa ggtgcagtgg aaggtggaca acgcctgca gtccggcaac 480
tcccaggaat ccgtcacga gcaggactcc aagacagca cctactcct gtctccacc 540
ctgacctgt ccaaggccga ctacgagaag cacaaggtgt acgcctgcga agtgaccac 600
cagggcctgt ccagccccgt gaccaagtcc ttaaccggg gcgagtgtg aggtacc 657

```

```

<210> SEQ ID NO 118
<211> LENGTH: 1824
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 118

```

```

gagctccagg tgcagctgca gcagcctggc gccgagctgg tcaagcctgg cgcttccgtg 60
aagatgtcct gcaaggcctc cggctacacc ttaccagct acaacatgca ctgggtcaag 120
cagacccccg gcagaggcct ggaatggatc ggcgccatct acccggcaa cgcgacacc 180
tcctacaacc agaagttaa gggaaaggcc accctgaccg ccgacaagtc ctctccacc 240

```

- continued

gectacatgc agctgtcctc cctgacctcc gaggactccg ccgtgtacta ctgcgcccg	300
tccacctact acggcggcga ctggtacttc aacgtgtggg gcgtggcac caccgtgacc	360
gtgtctgccg cctctaccaa gggccccctc gtgtttcccc tggccccctc cagcaagtcc	420
acatctggcg gcaccgccgc tctgggctgc ctggtcaagg actacttccc cgagcccgctg	480
acagtgtcct ggaactctgg cgcctgacc agcggcgtgc acacctttcc agcgtgtctg	540
cagtctcttg gcctgtactc cctgtccagc gtcgtgaccg tgccctccag ctctctgggc	600
accagacct acatctgcaa cgtgaaccac aagccctcca acaccaaggt ggacaagaag	660
gccgagccca agtctcgca caagaccac acctgtcccc cctgcctgc ccctgaactg	720
ctgggaggcc cttctgtgtt cctgttcccc ccaaagccca aggacacct gatgatctcc	780
cggacccccg aagtgacctg cgtggtggtg gacgtgtccc acgaggacct tgaagtgaag	840
ttcaattggt acgtggacgg cgtggaagtg cacaacgcca agaccaagcc cagagaggaa	900
cagtacaact ccacctaccg ggtggtgtcc gtgctgaccg tgetgcacca ggactggctg	960
aacggcaaag agtacaagtg caaggtgtcc aacaaggccc tgcctgcccc catcgaaaag	1020
accatctcca aggccaaagg ccagccccgc gagcctcagg tgtacactct gcctcccagc	1080
cgggacgagc tgaccaagaa ccagggtgcc ctgacctgtc tggtaagggt cttctacccc	1140
tccgatatcg ccgtggaatg ggagtccaac ggccagcccg agaacaacta caagaccacc	1200
ccccctgtgc tggactccga cggtcattc ttctgtact ccaagctgac cgtggacaag	1260
tcccggtggc agcagggcaa cgtgttctcc tgcctcgtga tgcacgagge cctgcacaac	1320
cactacaccc agaagtcctc gtccctgagc cccggaagg gcggaggcgg atctggtggt	1380
ggaggatcag gcggcggagg ctctaccatc cccccacag tgcagaaate cgtgaacaac	1440
gacatgatcg tgaccgacaa caacggcgcc gtgaagtccc ccagctgtg caagttctgc	1500
gacgtgcggt tctctacctg cgacaaccag aaatcctgca tgtccaactg ctccatcacc	1560
tccatctgcg agaagcccca ggaagtgtgc gtgcctgtct ggccgaagaa cgacgagaac	1620
atcacctcgt aaacgtgtg ccacgacccc aagctgcct accacgactt catcctggaa	1680
gatgccgcct cccccaagtg catcatgaag gaaaagaaga agccccgcga gactttcttc	1740
atgtgctctt gctcctccga cgagtcaac gacaacatca tcttctccga agagtacaac	1800
acctccaacc ccgactgagg tacc	1824

<210> SEQ ID NO 119

<211> LENGTH: 654

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 119

gagctccaga tcgtgtgtgc ccagtcccc gccatcctgt ctgctagccc tggcgagaaa	60
gtgacaatga cctgcggggc ctctcctccc gtgtcctaca tccactggtt ccagcagaag	120
cccggtccca gcccgaagcc ctggatctac gccacctcca acctggcctc cggcgtgcca	180
gtgcggttct ctggctccgg ctccggcacc tcctactccc tgaccatctc ccgggtggaa	240
gccgaggacg ccgccaccta ctactgccag cagtggacct ccaaccccc cactttggc	300
ggaggacca agctggaaat caagcggacc gtggcgcctc cctccgtgtt catcttccca	360
ccctccgacg agcagctgaa gtccggcacc gcctccgtcg tgtgcctgct gaacaacttc	420
tacccccgcg aggccaaagt gcagtggaag gtggacaacg ccctgcagtc cggcaactcc	480
caggaatccg tcaccgagca ggactccaag gacagcacct acagcctgtc ctccacctg	540

- continued

```

acctgtcca aggcgacta cgagaagcac aaggtgtacg cctgcgaagt gacccaccag    600
ggcctgtcca gccccgtgac caagtccttc aaccggggcg agtgctgagg tacc        654

```

```

<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 gtgcgccttc cggctacacc ttcaccaact acggcatgaa ctgggtccga    120
caggccctct gcaaggccct ggaatgggtc ggatggatca acacctacac cggcgagccc    180
acctacgccg cggacttcaa ggcgcgggtc accttctccc tggacacctc caagtcacc    240
gcctacctgc agatgaactc cctgcgggcc gaggacaccg ccgtgtacta ctgcgccaag    300
taccctccact actacggctc ctcccactgg tacttcgacg tgtggggcca gggcacctg    360
gtcacctgtg cctccgcctc taccagggc cctccctgtg tccctctggc cccctccagc    420
aagtccacat ctggcggcac cgcgcctctg ggctgctggt tcaaggacta cttccccgag    480
cccgtgaccg tgtcctggaa ctctggcgcc ctgacctccg gcgtgcacac ctttccagcc    540
gtgctgcagt cctccggcct gtactccctg tctccctgct tgacctgccc ctccagctct    600
ctgggcaccc agacctacat ctgcaacgtg aaccacaagc cctccaacac caagtgggac    660
aagaaggtgg aacccaagtc ctgcgacaag acccacacct gtccccctg cctgccccct    720
gaactgctgg gaggccttag cgtgttctct tccccccaa agcccaagga caccctgatg    780
atctcccgga cccccaagt gacctgcgtg gtggtggacg tgtcccacga ggacctgaa    840
gtgaagttca attggtacgt ggacggcgtg gaagtgcaca acgccaagac caagcccaga    900
gaggaacagt acaactccac ctaccgggtg gtgtccgtgc tgacctgctt gcaccaggac    960
tggtctgaacg gcaaagagta caagtcaag gtgtccaaca aggcctgccc tgccccatc   1020
gaaaagacca tctccaaggc caaggccag ccccgcgagc ctcaggtgta cactctgccc   1080
cctagccggg aagagatgac caagaaccag gtgtccctga cctgtctggt caaggccttc   1140
taccctcccg atatcgccgt ggaatgggag tccaacggcc agcccagaaa caactacaag   1200
accaccccc ctgtgctgga ctccgacggc tcattcttcc tgtactccaa gctgacctg   1260
gacaagtccc ggtggcagca gggcaacgtg ttctctctgt ccgtgatgca cgaggccctg   1320
cacaaccact acaccagaa gtccctgtcc ctgagcccag gcaagggcgg aggcggatct   1380
ggtggtggag gatcaggcgg cggaggtctt accatcccc caccagtgca gaaatccgtg   1440
aacaacgaca tgatcgtgac cgacaacaac ggcgcctgta agttccccca gctgtgcaag   1500
ttctgcgacg tgcggttctc tacctgcgac aaccagaaat cctgcatgtc caactgctcc   1560
atcacctcca tctgcgagaa gccccaggaa gtgtgcgtcg ccgtctggcg gaagaacgac   1620
gagaacatca ccttggaaac cgtgtgccac gaccccaagc tgccctacca cgacttcac   1680
ctggaagatg ccgcctcccc caagtgcac atgaaggaaa agaagaagcc cggcgagact   1740
ttcttcatgt gcagctgctc ctccgacgag tgcaacgaca acatcatctt ctccgaagag   1800
tacaacacct ccaaccccg ctgaggtacc                                1830

```

```

<210> SEQ ID NO 121
<211> LENGTH: 657
<212> TYPE: DNA

```

- continued

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 121

```

gagctcgata tccagatgac ccagtcctcc tccagcctgt ccgcctctgt gggecacaga      60
gtgaccatca cctgttccgc cagccaggac atctccaact acctgaactg gtatcagcag      120
aagcccgga aggccctaa ggtgctgac tacttcacct cctccctgca ctccggcgtg      180
ccctccagat tctccggctc tggtcccgcc accgacttta cctgacat ctccagcctg      240
cagcccgagg acttcgccac ctactactgc cagcagtact ccacgtgcc ctggaccttc      300
ggccaggga ccaaggtgga aatcaagcgg accgtggccg ctccctccgt gttcatcttc      360
ccaccctccg acgagcagct gaagtcgggc accgcctccg tcgtgtgcct gctgaacaac      420
ttctacccc gcgaggccaa ggtgcagtgg aaggtggaca acgcctgca gtccggcaac      480
tcccaggaat ccgtaccga gcaggactcc aaggacagca cctactccct gtccctccacc      540
ctgaccctgt ccaagggcca ctacgagaag cacaaggtgt acgcctgcga agtgaccac      600
cagggcctgt ccagcccggt gaccaagtc 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
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 Epidermal Growth Factor Receptor (EGFR); and

(b) the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain of Transforming growth factor-beta receptor II (TGF- β RII).

2. The molecule of claim 1, wherein the targeting moiety comprises an antibody, antibody fragment, scFv, or Fc-containing polypeptide that specifically binds EGFR or a fragment thereof.

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 the amino acid sequence corresponding to SEQ ID NO: 87 or a binding fragment thereof.

5. The molecule of claim 4, wherein the molecule comprises the amino acid sequence corresponding to SEQ ID NO: 2 or a binding fragment thereof.

6. The molecule of claim 5, wherein the molecule comprises the amino acid sequence corresponding to SEQ ID NO: 2 or a binding fragment thereof and the amino acid sequence corresponding to SEQ ID NO: 71 or a binding fragment thereof.

7. The isolated molecule of claim 1, further comprising a linker at the CH3 region of the Fc.

8. The isolated molecule of claim 7, wherein the linker is (GGGGS)_n (SEQ ID NO:104)_n and wherein n is 1, 2, 3, 4, 5, 6, 7 or 8.

9. The isolated molecule of claim 7, wherein the linker comprises the amino acid sequence GGGSGGGSGGGSGGGGS (SEQ ID NO:104).

10. An isolated molecule comprising a targeting moiety fused with an immunomodulatory moiety, wherein:

(a) the targeting moiety specifically binds Epidermal Growth Factor Receptor (EGFR); and

(b) the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain of Transforming growth factor-beta receptor (TGF- β R).

* * * * *