US 20080124340A1

(19) **United States**

(12) **Patent Application Publication**

(10) **Pub. No.: US 2008/0124340 A1**

(43) **Pub. Date: May 29, 2008**

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(54) **ERYTHROPOIETIN RECEPTOR AGONISTS**

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(21) Appl. No.: **11/786,879**

(22) Filed: **Apr. 13, 2007**

Related U.S. Application Data

(60) Provisional application No. 60/792,174, filed on Apr. 14, 2006.

Publication Classification

(51) **Int. Cl.**

A61K 39/395	(2006.01)
C07H 21/04	(2006.01)
C12P 21/06	(2006.01)
C12N 5/06	(2006.01)
C07K 16/28	(2006.01)

(52) **U.S. Cl.** **424/144.1**; 530/388.22; 435/326; 536/23.5; 435/320.1; 435/69.1

(57) **ABSTRACT**

Antibodies that bind erythropoietin receptor are provided. Methods of making and using such antibodies are also provided. Kits containing such antibodies are also provided.

FIGURE 1

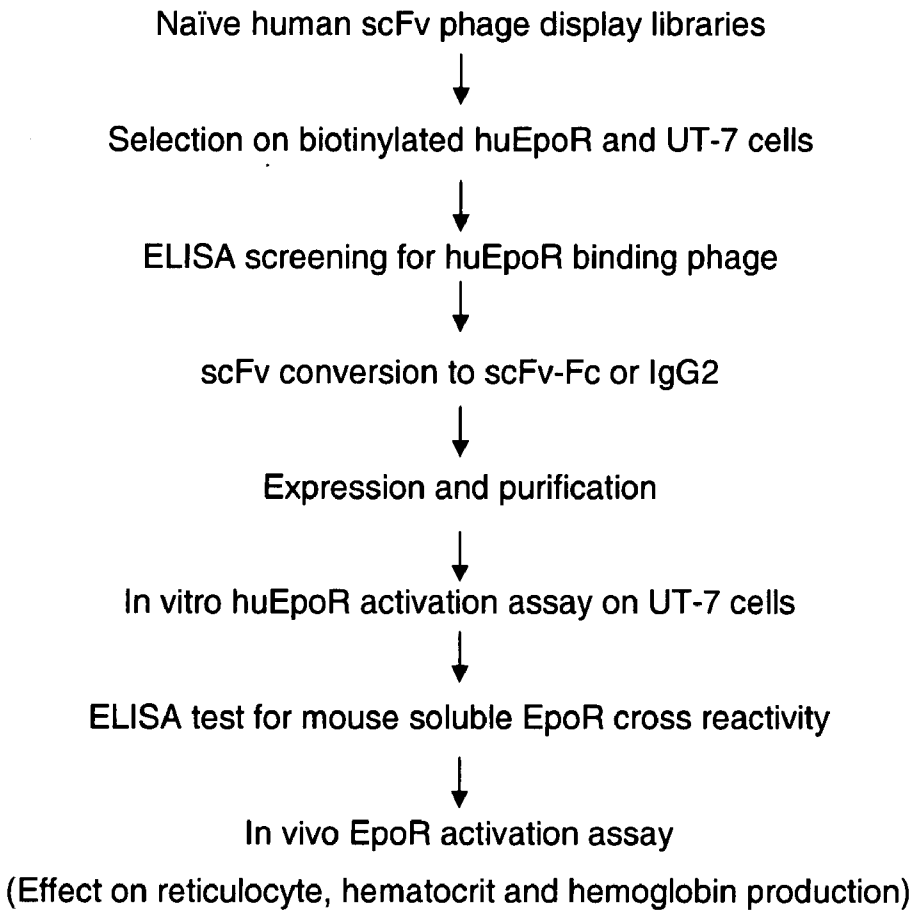

Naïve human scFv phage display libraries
Selection on biotinylated huEpoR and UT-7 cells
ELISA screening for huEpoR binding phage
scFv conversion to scFv-Fc or IgG2
Expression and purification
In vitro huEpoR activation assay on UT-7 cells
ELISA test for mouse soluble EpoR cross reactivity
In vivo EpoR activation assay
(Effect on reticulocyte, hematocrit and hemoglobin production)

FIGURE 2

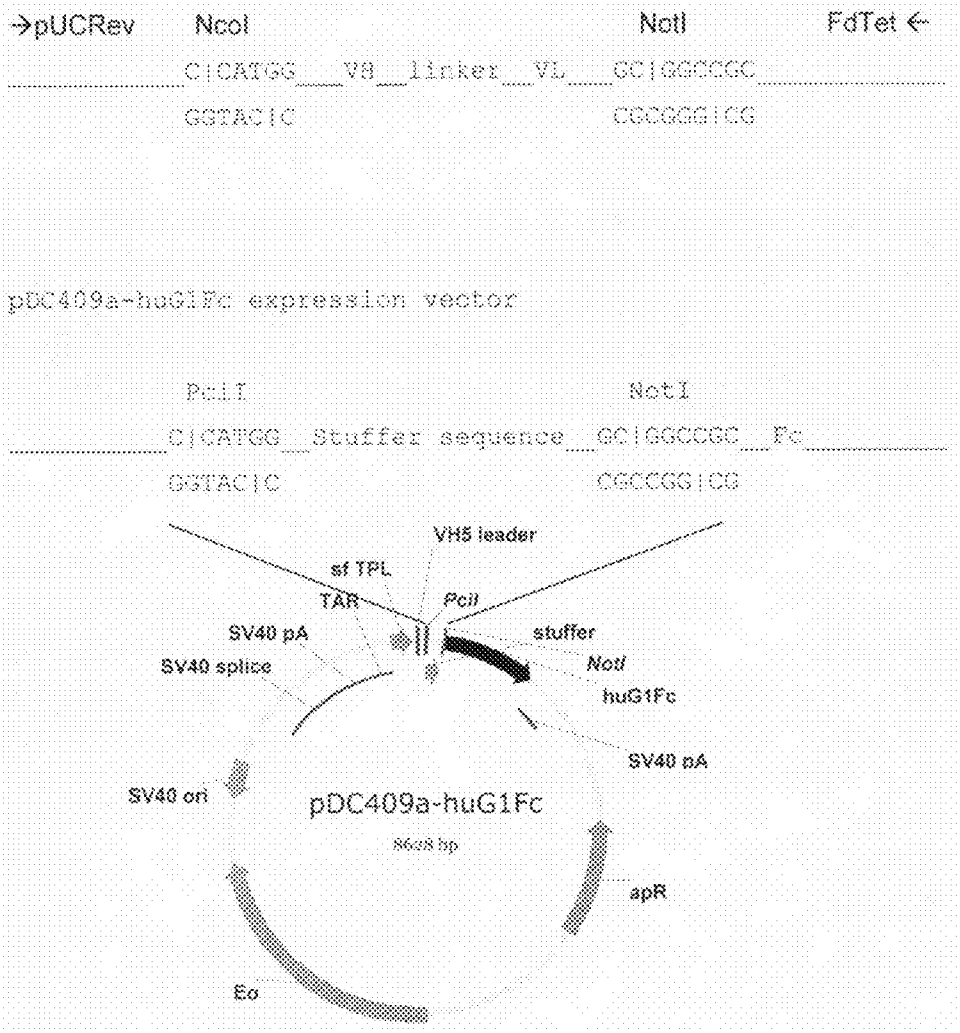

→pUCRev
NcoI
NotI
FdTet ←
C|CATGG
VH
linker
VL
GC|GGCCGC
GGTAC|C
CGCCGG|CG
pDC409a-huG1Fc expression vector
PciI
NotI
C|CATGG
Stuffer sequence
GC|GGCCGC
Fc
GGTAC|C
CGCCGG|CG
VH5 leader
sf TPL
TAR
PciI
SV40 pA
stuffer
SV40 splice
NotI
huG1Fc
SV40 pA
SV40 ori
pDC409a-huG1Fc
8628 bp
apR
Eo

FIGURE 3

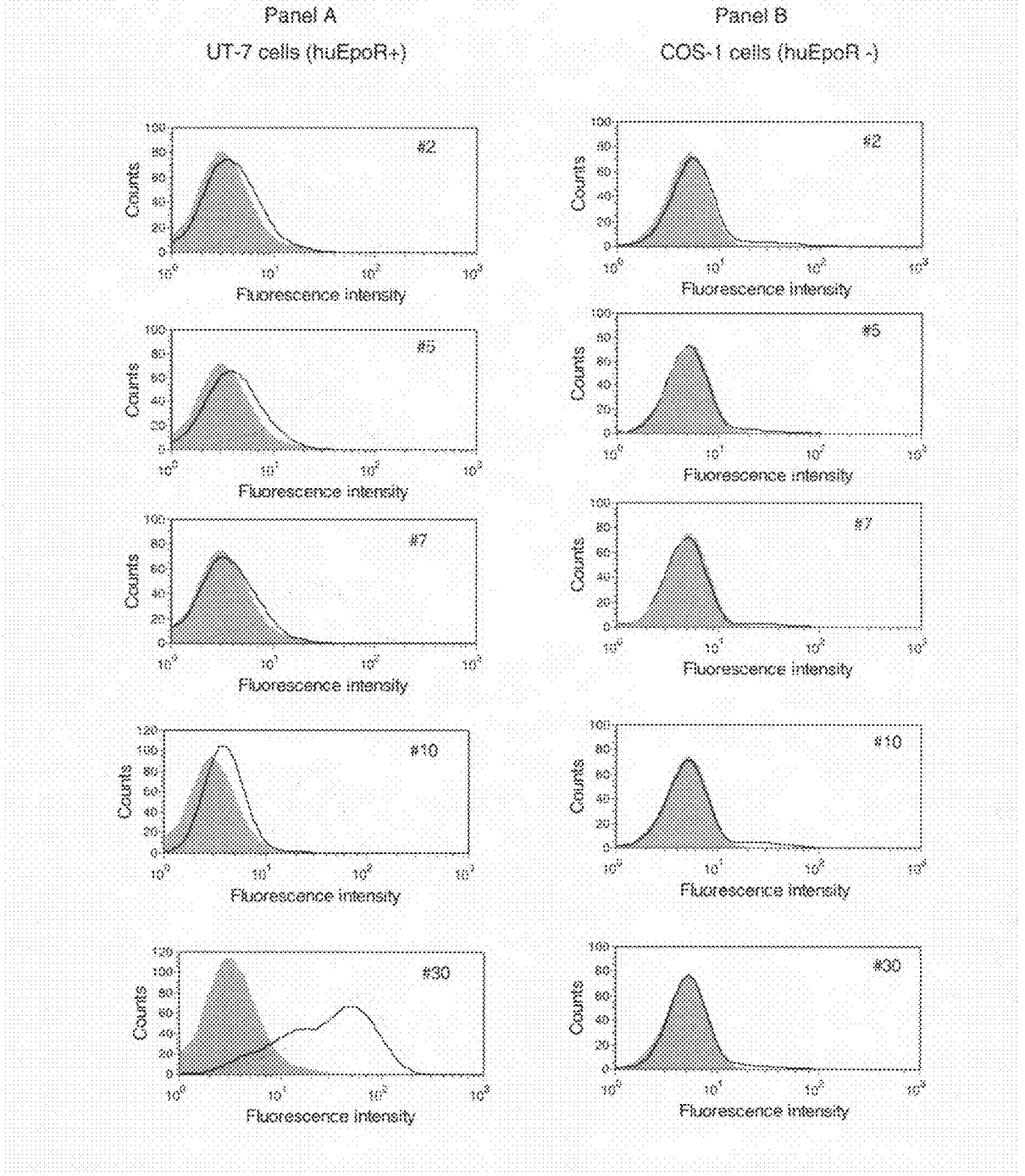
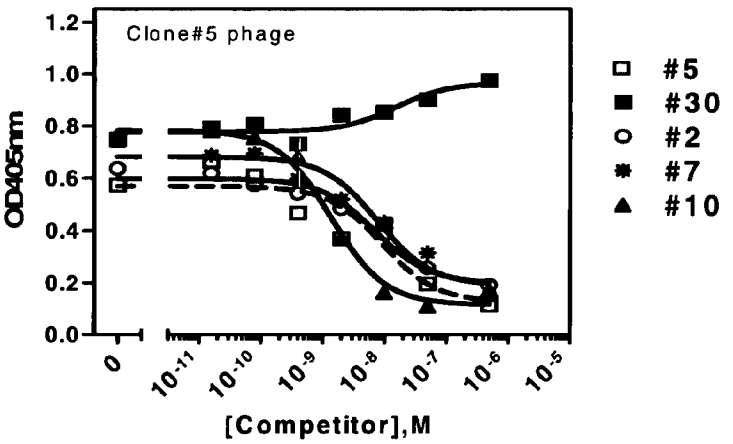

Panel A
UT-7 cells (huEpoR+)
Panel B
COS-1 cells (huEpoR -)
#2
#5
#7
#10
#30
Counts
Fluorescence intensity

FIGURE 4

A)


Clone#5 phage
OD405nm
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
10-11
10-10
10-9
10-8
10-7
10-6
10-5
[Competitor],M
#5
#30
#2
#7
#10

B)

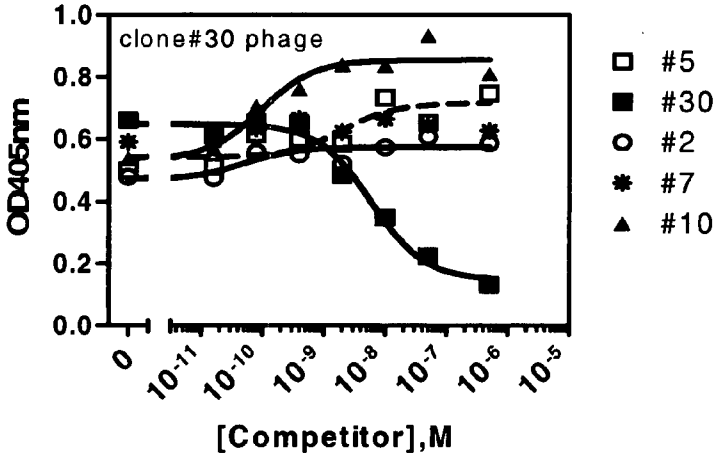

clone#30 phage
OD405nm
1.0
0.8
0.6
0.4
0.2
0.0
0
10-11
10-10
10-9
10-8
10-7
10-6
10-5
[Competitor],M
#5
#30
#2
#7
#10

FIGURE 5

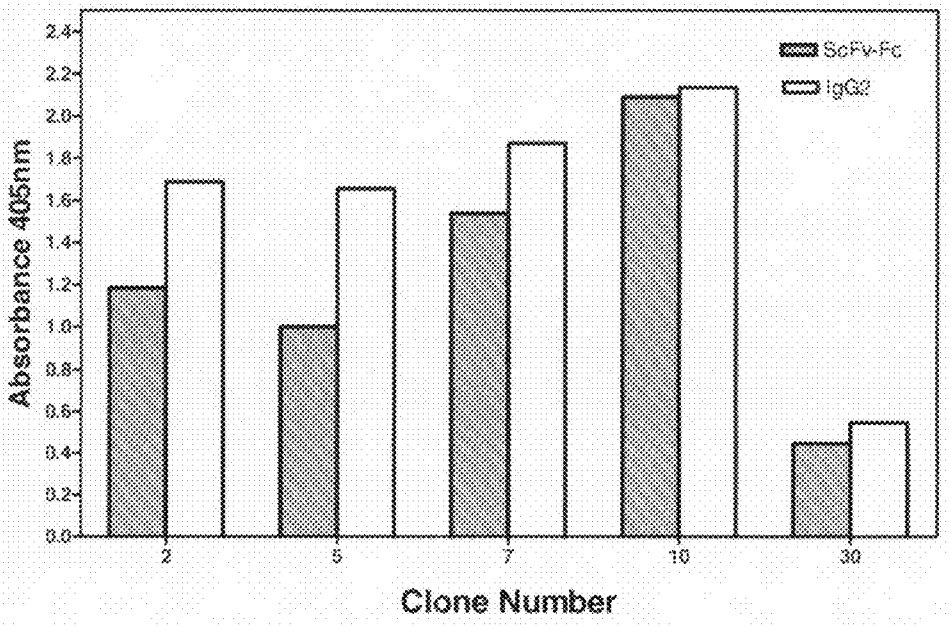

ScFv-Fc
IgG2
Absorbance 405nm
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
2
5
7
10
30
Clone Number

FIGURE 6

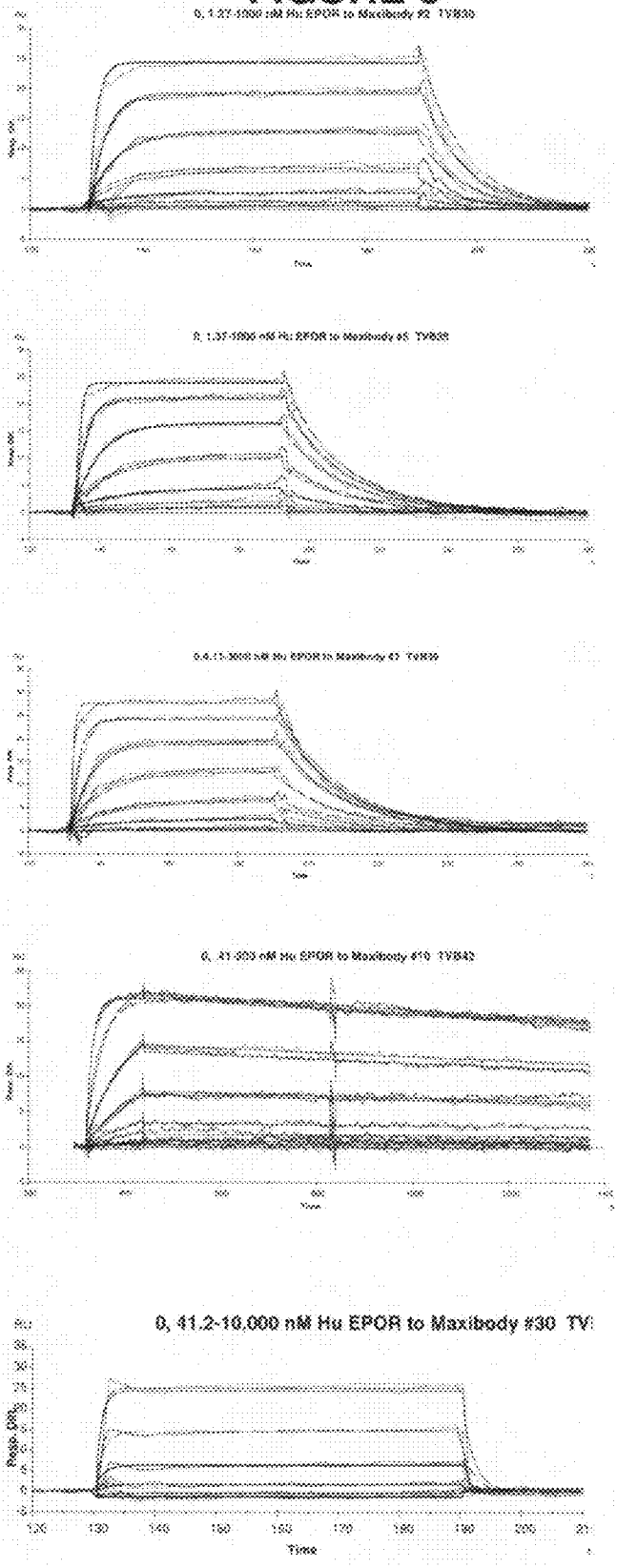


FIGURE 7

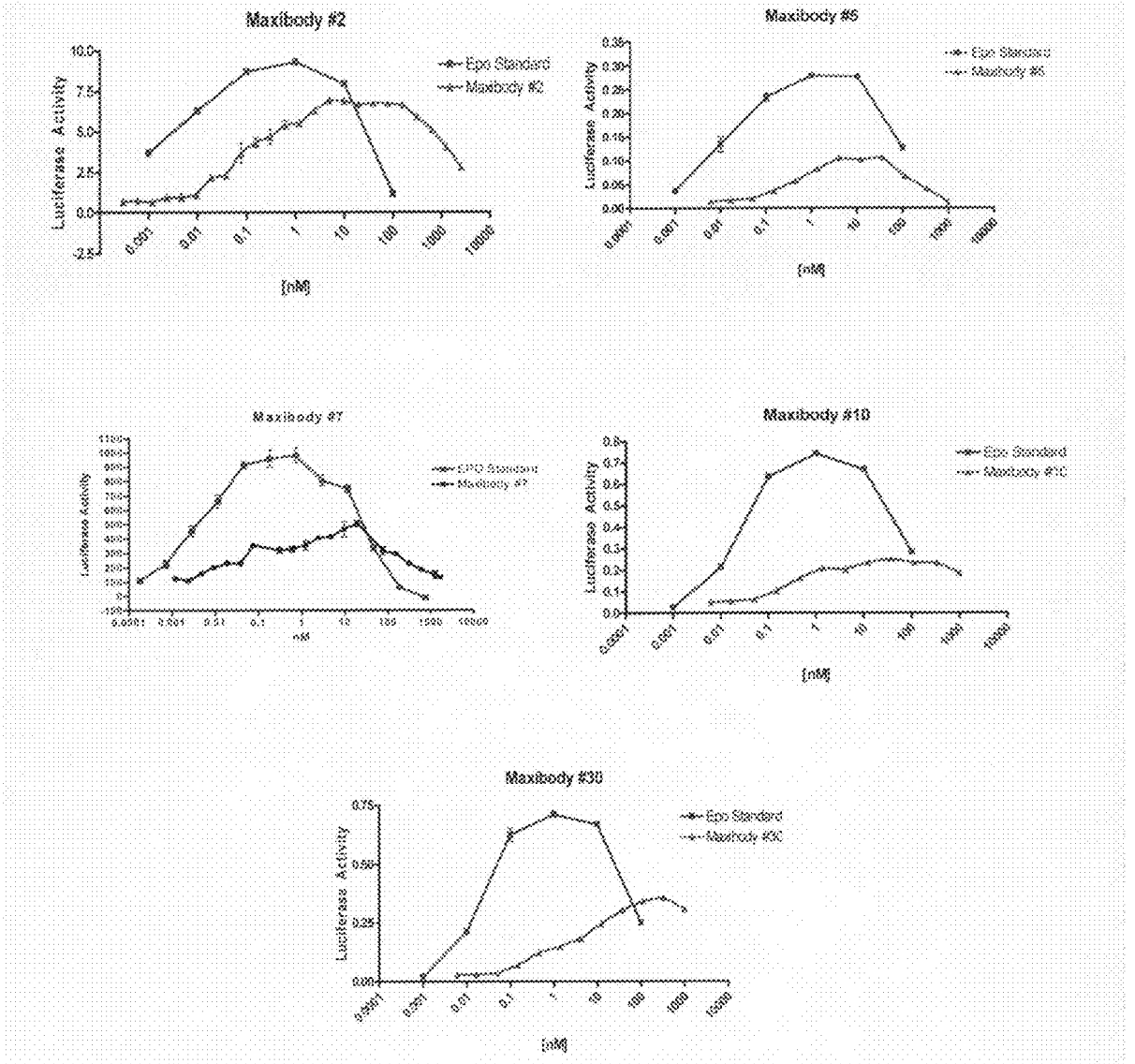

Maxibody #2
Luciferase Activity
Epo Standard
Maxibody #2
[nM]
Maxibody #6
Luciferase Activity
Epo Standard
Maxibody #6
[nM]
Maxibody #7
Luciferase Activity
EPO Standard
Maxibody #7
nM
Maxibody #10
Luciferase Activity
Epo Standard
Maxibody #10
[nM]
Maxibody #30
Luciferase Activity
Epo Standard
Maxibody #30
[nM]

FIGURE 8

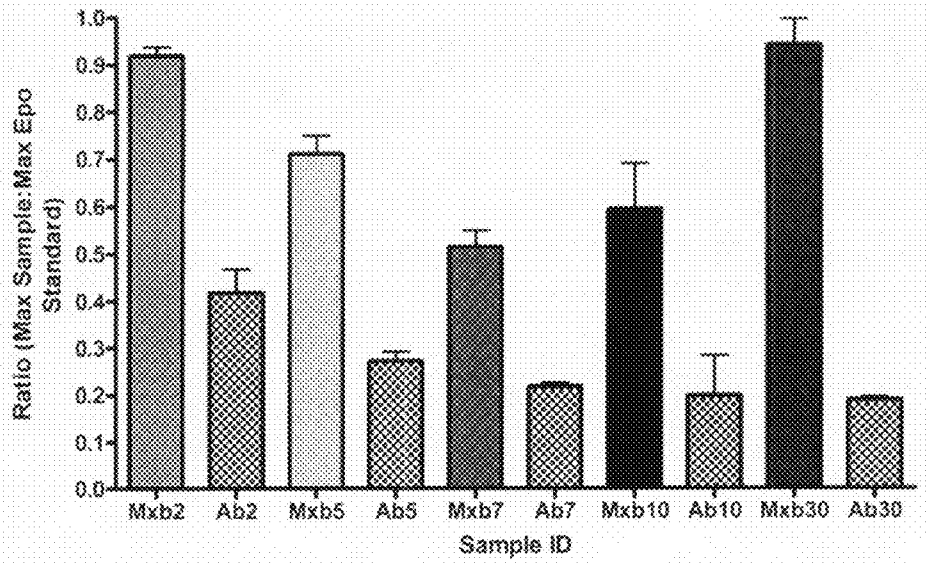

Ratio (Max Sample:Max Epo Standard)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Mxb2
Ab2
Mxb5
Ab5
Mxb7
Ab7
Mxb10
Ab10
Mxb30
Ab30
Sample ID

FIGURE 9

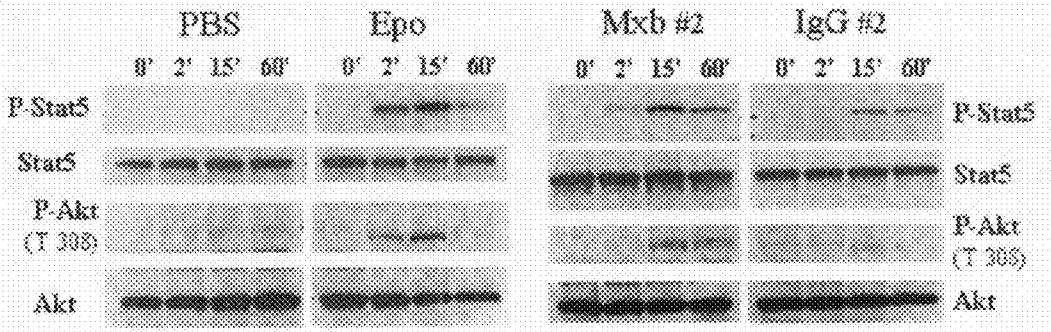

PBS
Epo
Mxb #2
IgG #2
0' 2' 15' 60'
0' 2' 15' 60'
0' 2' 15' 60'
0' 2' 15' 60'
P-Stat5
Stat5
P-Akt (T 308)
Akt
P-Stat5
Stat5
P-Akt (T 308)
Akt

FIGURE 10

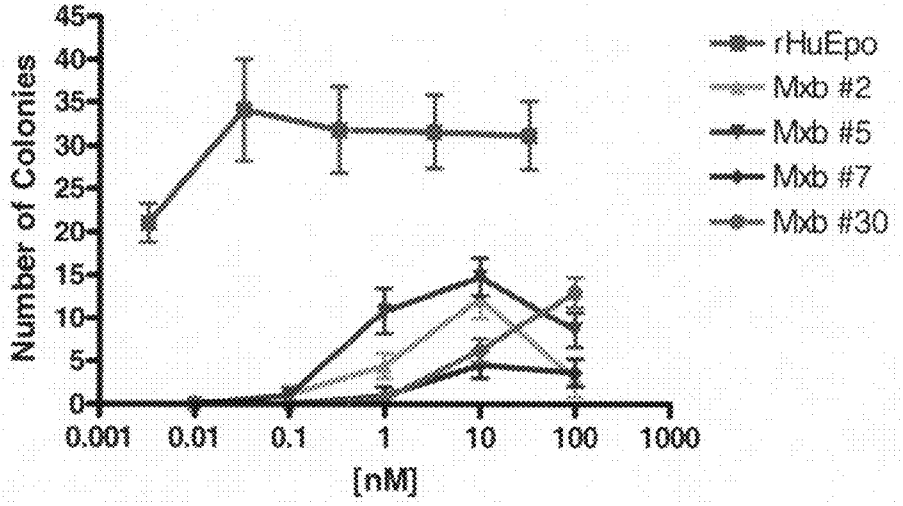

Number of Colonies
45
40
35
30
25
20
15
10
5
0
0.001
0.01
0.1
1
10
100
1000
[nM]
rHuEpo
Mxb #2
Mxb #5
Mxb #7
Mxb #30

FIGURE 11

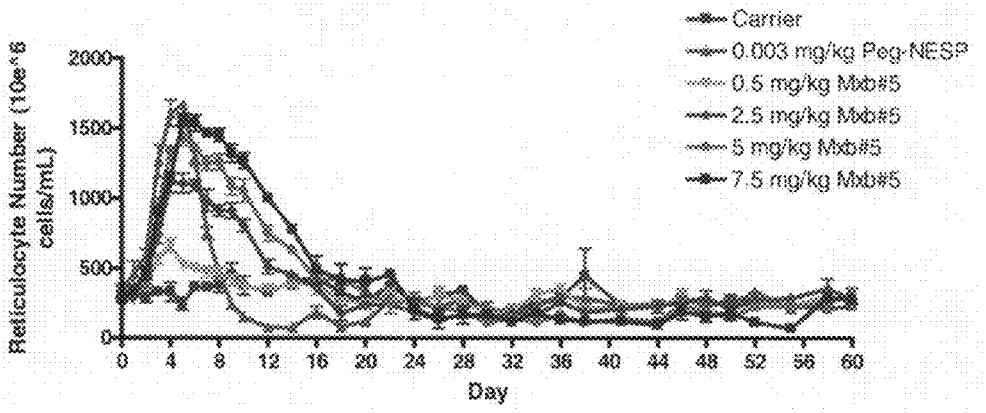


FIGURE 12

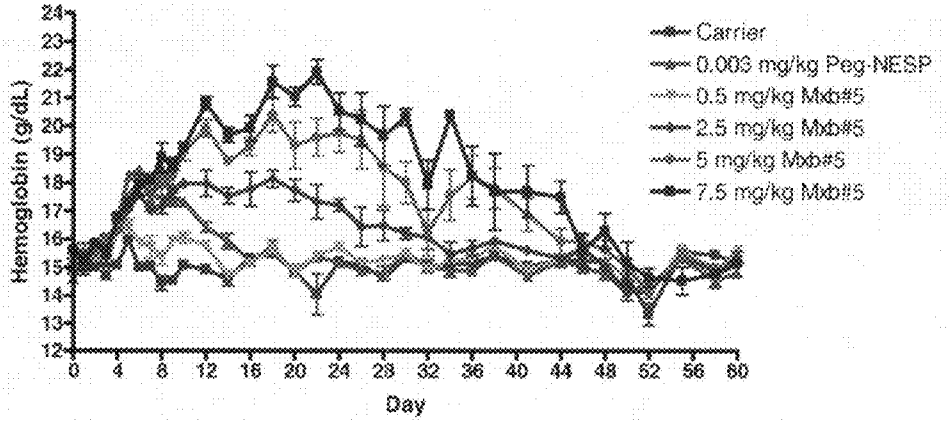


FIGURE 13

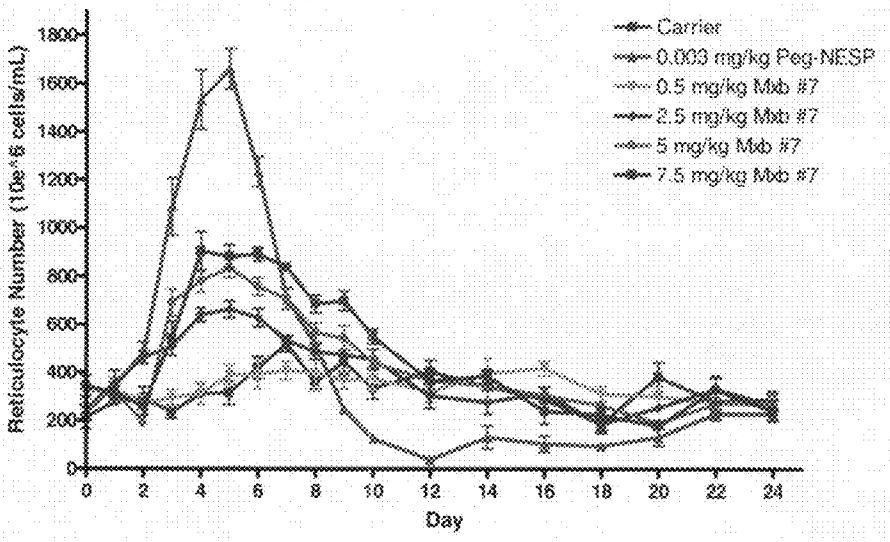


FIGURE 14

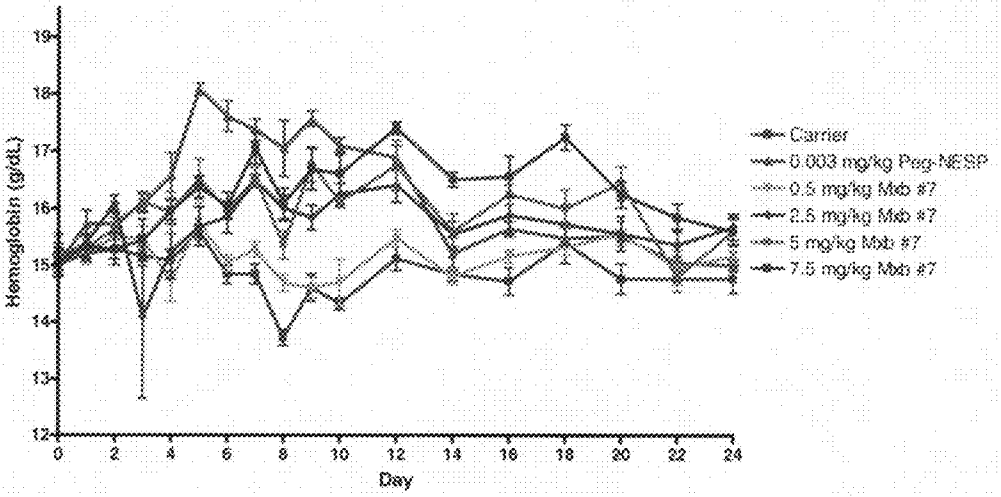


FIGURE 15

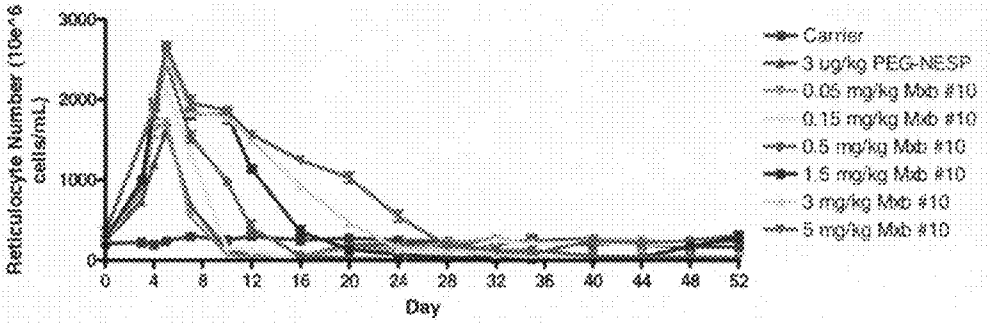


FIGURE 16

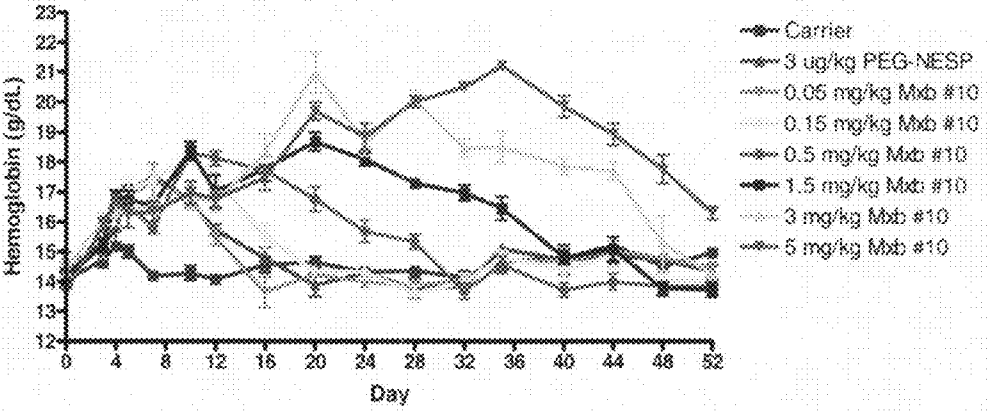


FIGURE 17

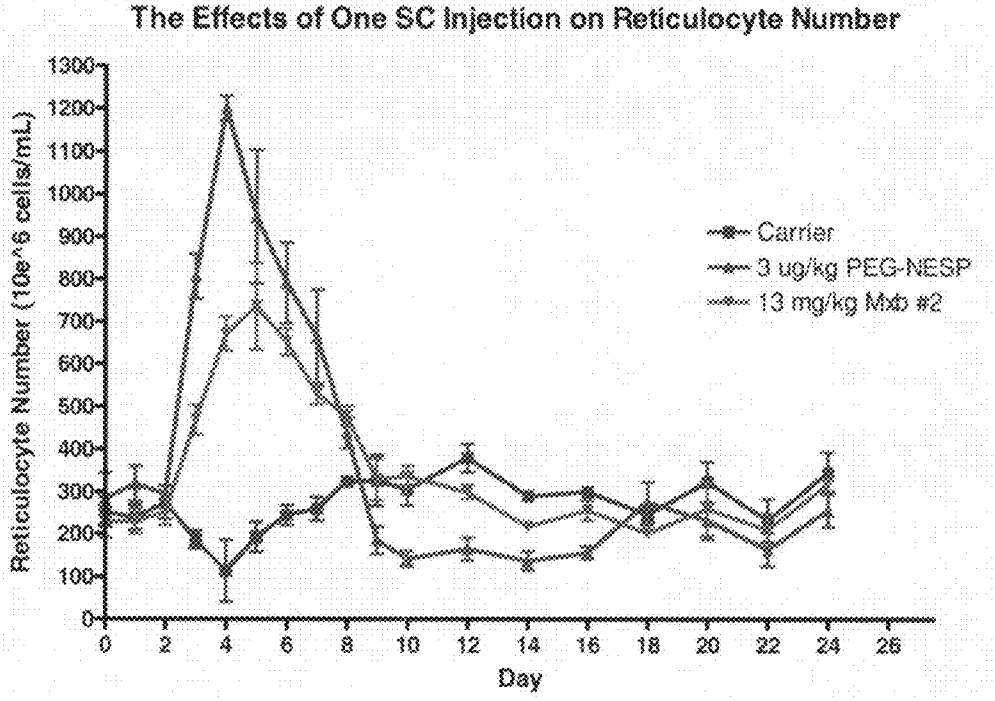


FIGURE 18

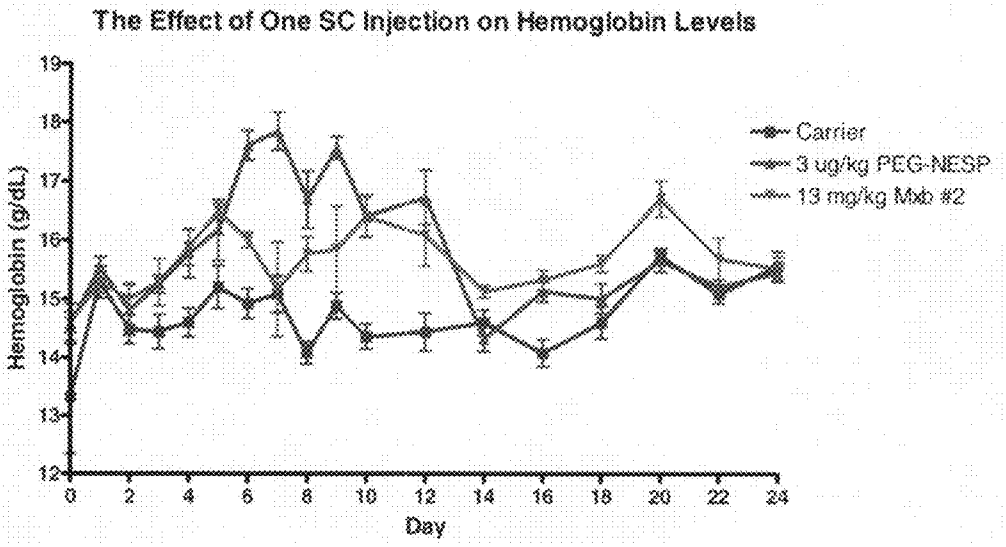


FIGURE 19

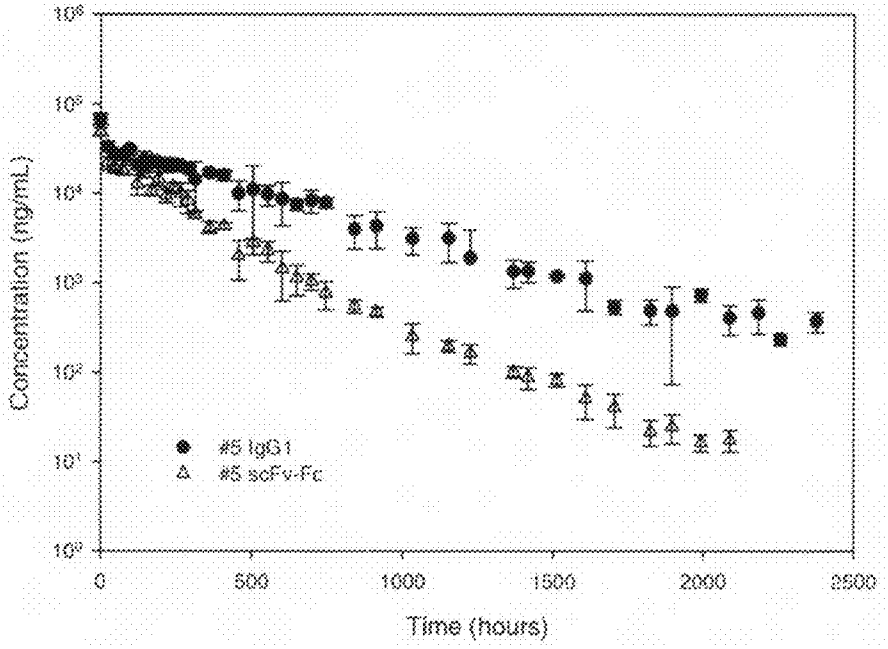

Concentration (ng/mL)
Time (hours)
#5 IgG1
#5 scFv-Fc
0
500
1000
1500
2000
2500

FIGURE 20

Parameter (units)	IgG #5 (SE%)	Mxb #5 (SE%)
Cl (mL/hr)	0.0071 (3.3)	0.012 (6.7)
V (mL)	3.26 (4.9)	2.74 (10.35)
Half Life (hours)	320.1 (4.1)	158.3
AUC (μg/mL·hr)	1572.6	6171.2

FIGURE 21

antibody	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3
Mxb 2	SYWMS	NIKPDGSEKYYVDSVKG	VSRGGSYSD	TGTSSDVGGYNYVS	EVSKRPS	SSYAGRNWV
Mxb 5	SYWMS	NIKPDGSEKYYVDSVKG	VSRGGSYSD	TGTSSDVGGYIYVS	DVSRRPS	NSYTTLSTWL
Mxb 7	SYWMS	NIKPDGSEKYYVDSVKG	VSRGGSYSD	TGTRSDIGGYNYVS	FDVNNRPS	NSFTDSRTWL
Mxb 10	SYAMS	AISGSGGSTYYADSVKG	DRVAVAGKGSYYFDS	SGSSSNIGNNAVS	YDNLLPSG	AAWDDSLNDWV
Mxb 30	SNSAAWN	RTYYRSKWYNDYAVSKS	DEGPLDY	TGSSSNLGTGYDVH	GNSNRPS	QSYDFSLSAMV

FIGURE 22

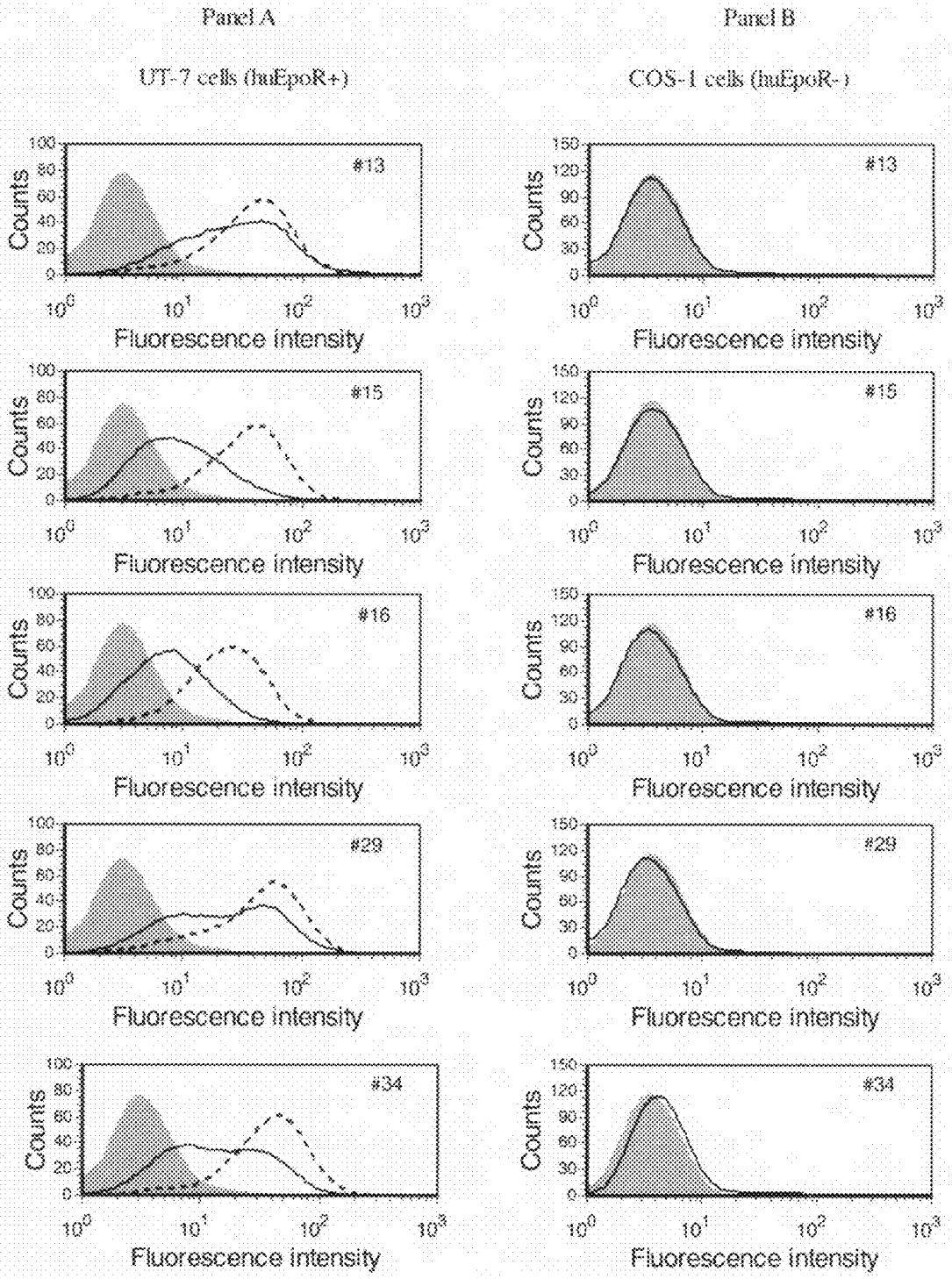

Panel A
Panel B
UT-7 cells (huEpoR+)
COS-1 cells (huEpoR-)
#13
#15
#16
#29
#34
Counts
Fluorescence intensity

FIGURE 23

Anti-EpoR maxibodies

Clone ID	EpoR Binding			Competition		
	hu	mu	cyno	Epo	#5	#30
#2	+	+	+	+	+	-
#5	+	+	+	+	+	-
#7	+	+	+	+	+	-
#10	+	+	+	+	+	-
#13	+	-	+	-	-	+
#15	+	-	+	partial	+	+
#16	+	-	+	partial	-	+
#29	+	-	+	-	-	+
#30	+	-	+	-	-	+
#34	+	-	+	partial	+	-
#201	+	-	+	+		
#276	+	+	+	+		
#295	+	-	+	+		
#307	+	-	+	+		
#318	+	-	+	+		
#319	+	-	+	+		
#323	+	+	+	+		
#330	+	-	+	+		
#352	+	+	+	+		
#378	+	+	+	+		

FIGURE 24

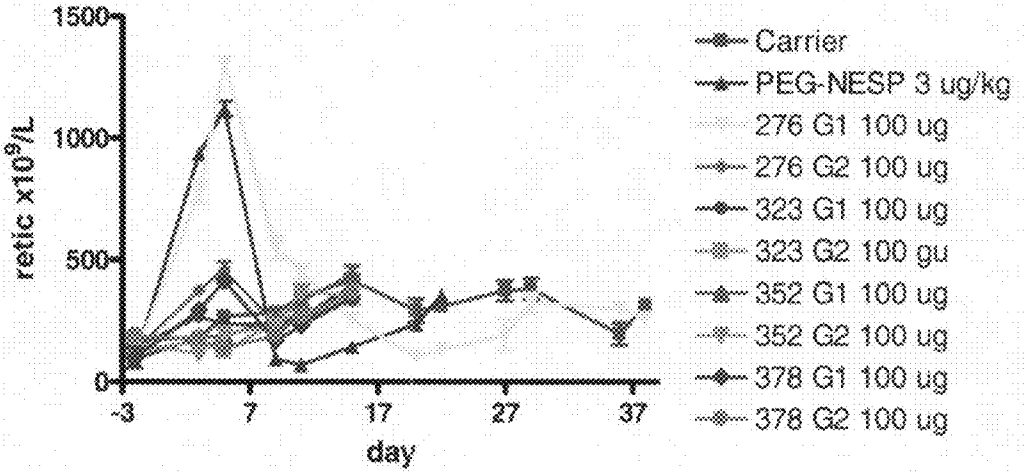

1500
1000
500
0
retic x10^9/L
-3
7
17
27
37
day
Carrier
PEG-NESP 3 ug/kg
276 G1 100 ug
276 G2 100 ug
323 G1 100 ug
323 G2 100 gu
352 G1 100 ug
352 G2 100 ug
378 G1 100 ug
378 G2 100 ug

FIGURE 25

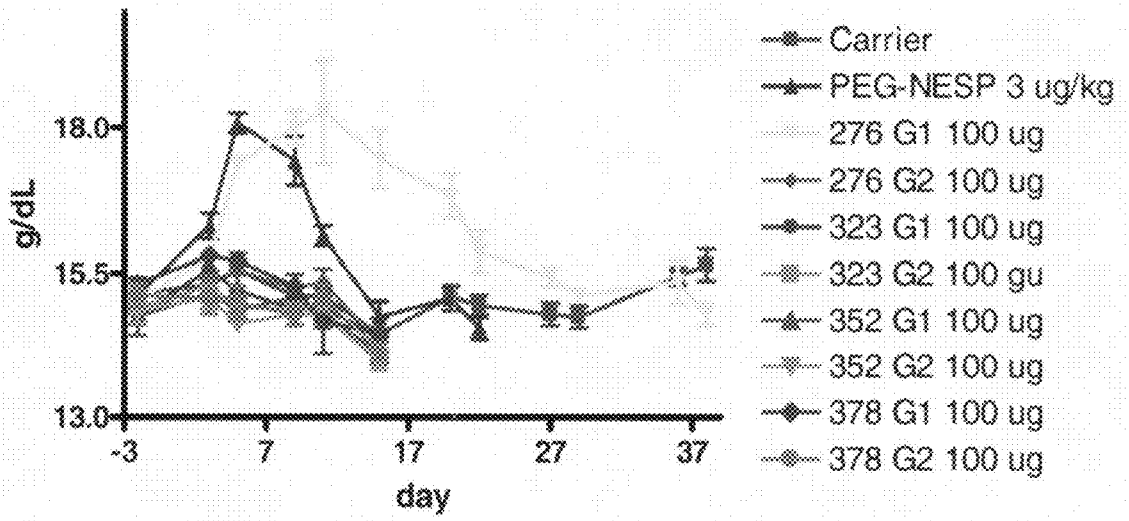

g/dL
18.0
15.5
13.0
-3
7
17
27
37
day
Carrier
PEG-NESP 3 ug/kg
276 G1 100 ug
276 G2 100 ug
323 G1 100 ug
323 G2 100 gu
352 G1 100 ug
352 G2 100 ug
378 G1 100 ug
378 G2 100 ug

FIGURE 26A

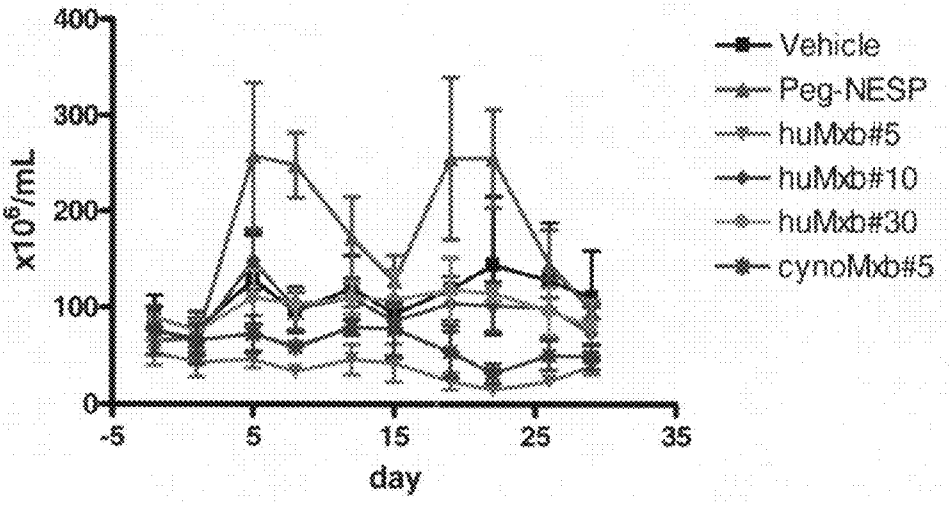


FIGURE 26B

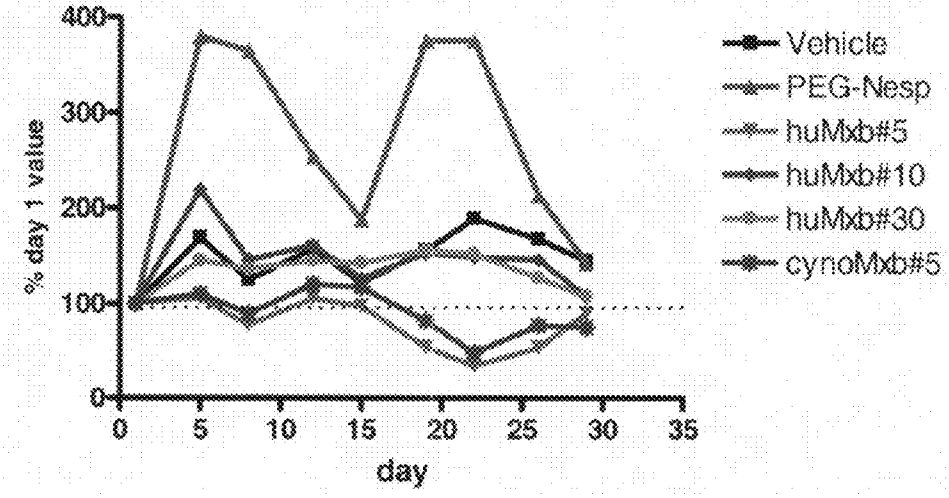


FIGURE 27

- Standard PCR Conditions
  - 94°C 3 min
  - 94°C 30 sec
  - 56°C 30 sec
  - 72°C 1 min/Kb
  - 72°C 5 min
  - 4°C hold

20X

- Standard PCR SOE-ing Conditions
  - 94°C 3 min
  - 94°C 30 sec
  - 42°C 30 sec
  - 72°C 1 min/Kb
  - 94°C 30 sec
  - 56°C 30 sec
  - 72°C 1 min/Kb
  - 72°C 5 min
  - 4°C hold

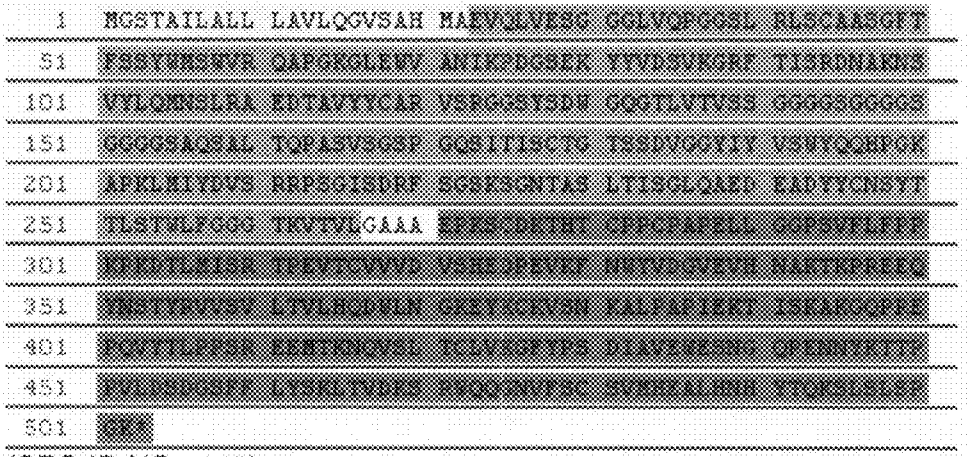
3X

22X

- PCR 50 µl total volume
  - 1 µl (10 pmol) 5' primer
  - 1 µl (10 pmol) 3' primer
  - 1 µl PCR nucleotide mix
  - 5 µl 10X PCR buffer with $MgCl_2$
  - 1 µl template DNA (20 ng)
  - 1 µl Expand High Fidelity Polymerase
  - 40 µl dH_20

FIGURE 28A

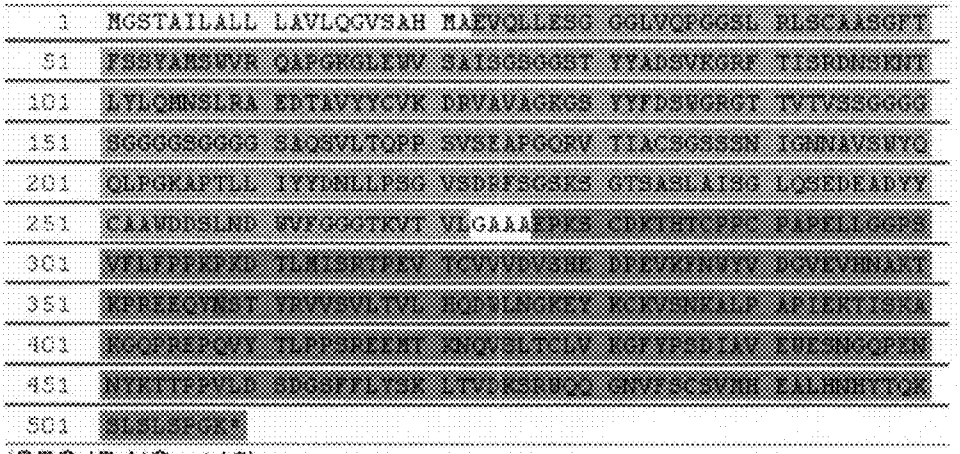
409-VH5-hu-Anti-huEpoR-PE_12204784_v1-scFv-huG1MB (Mxb#5)
GEAR ID 1037



(SEQ ID NO.: 115)

FIGURE 28B

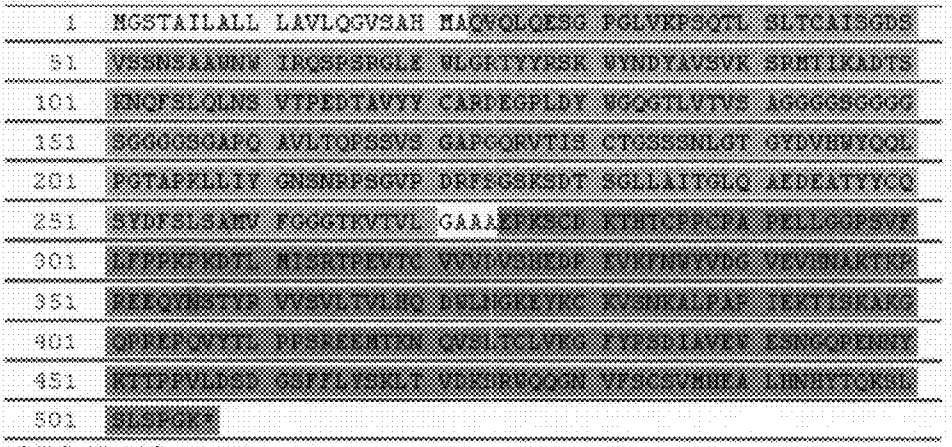
409-VH5-hu-Anti-huEpoR-PE_12204799_v1-scFv-huG1MB (Mxb#10)
GEAR ID 1036



(SEQ ID NO.: 116)

FIGURE 28C

409-VH5-hu-Anti-huEpoR-PE_12208441_v1-scFv-huG1MB (Mxb#30)
GEAR ID 1158



(SEQ ID NO.: 117)

FIGURE 28D

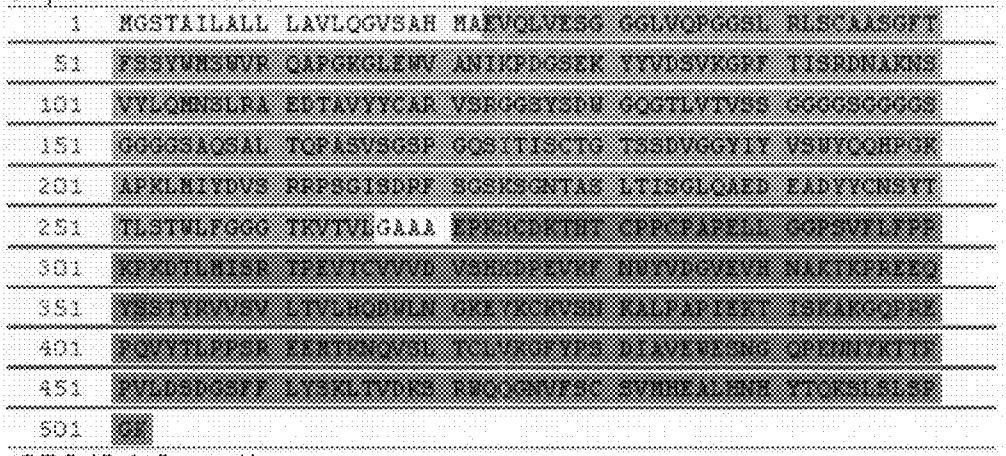
pGemT-Cyno-Fc

1	EFTPPCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSQED
51	PEVQFNWYVD GVEVHNAQTK PREPQFSSTY RVVSVLTVTH QDWLNGKEYT
101	CKVSNKGLPA PIEKTISEAK GQPREPQVYI LPPPQEELTK NQVSLTCLVT
151	GFYPSDIAVE WESNGQPENT YKTTPPVLDS DGSYFLYSKL IVDKSRWQQG
201	NTFSCSVMHE ALHNHYTQKS LSVSPGK*

(SEQ ID NO.: 118)

FIGURE 29A

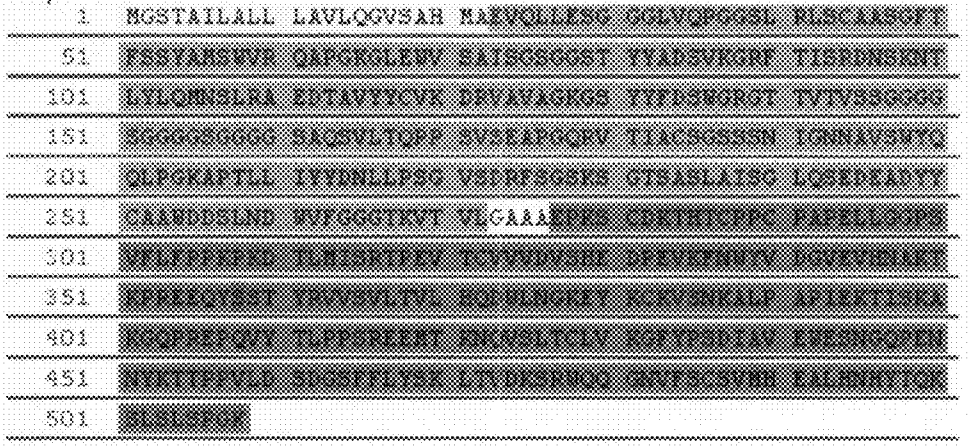
pTT5-VH5-hu-Anti-huEpoR-PE_12204784_v1-scFv-huG1MB N297S(Mxb#5)
GEAR ID 3091
Sequence20060409300



(SEQ ID NO.: 119)

FIGURE 29B

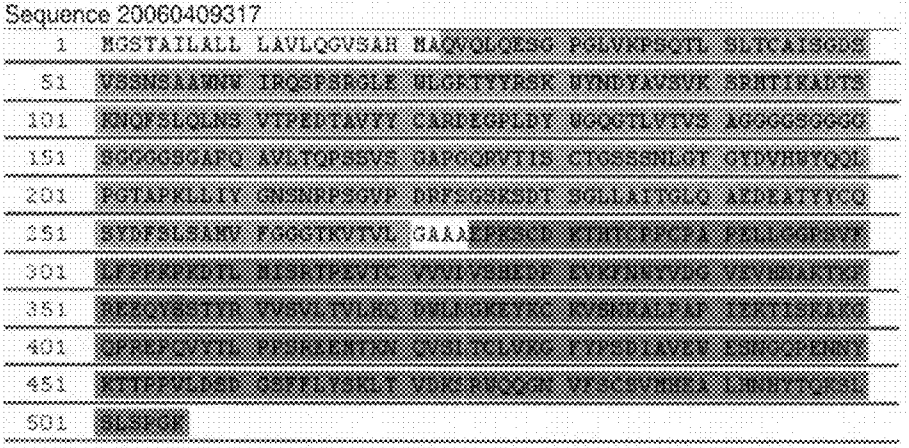
pTT5-VH5-hu-Anti-huEpoR-PE_12204799_v1-scFv-huG1MB N297S(Mxb#10)
GEAR ID 3093
Sequence 20060409308



(SEQ ID NO.: 120)

FIGURE 29C

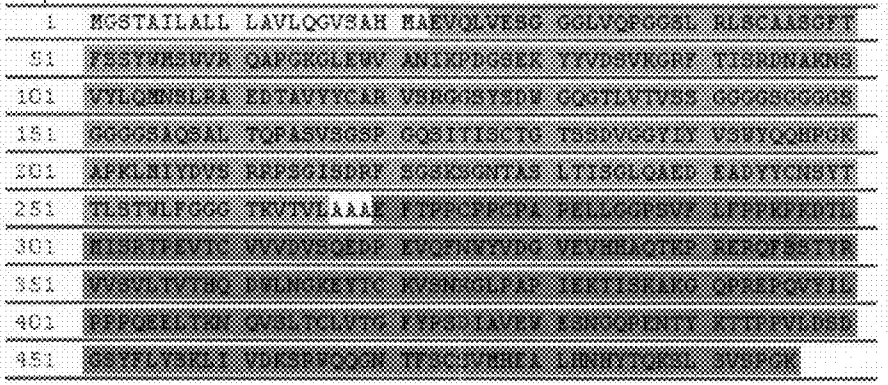
pTT5-VH5-hu-Anti-huEpoR-PE_12208441_v1-scFv-huG1MB N297S(Mxb#30-)
GEAR ID 3094
Sequence 20060409317



(SEQ ID NO.: 121)

FIGURE 29D

pTT5-VH5-hu-Anti-huEpoR-PE_12204784_v1-scFv-cynoG1MB N297S (Mxb#5-cyno-Fc N297S)
GEAR ID 3092
Sequence 20060409293



(SEQ ID NO.: 122)

FIGURE 30

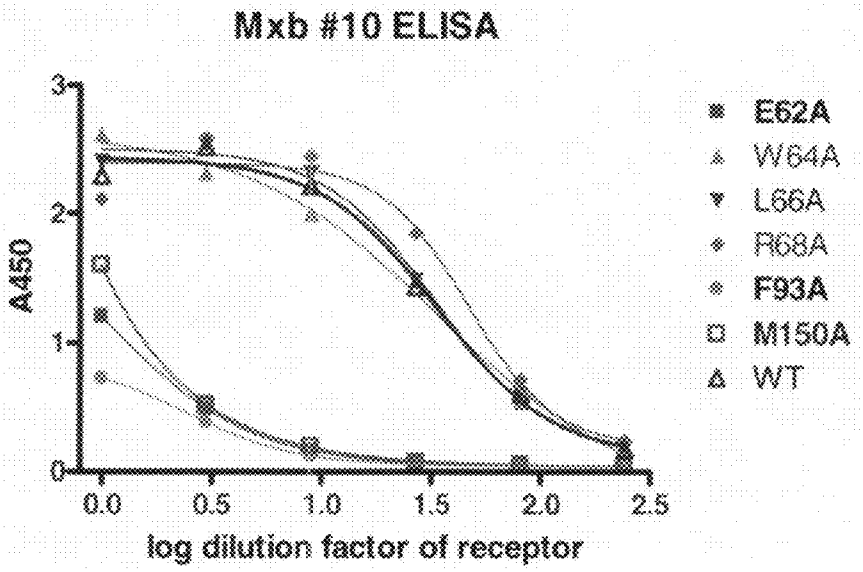

Mxb #10 ELISA
A450
0
1
2
3
0.0
0.5
1.0
1.5
2.0
2.5
log dilution factor of receptor
E62A
W64A
L66A
R68A
F93A
M150A
WT

FIGURE 31

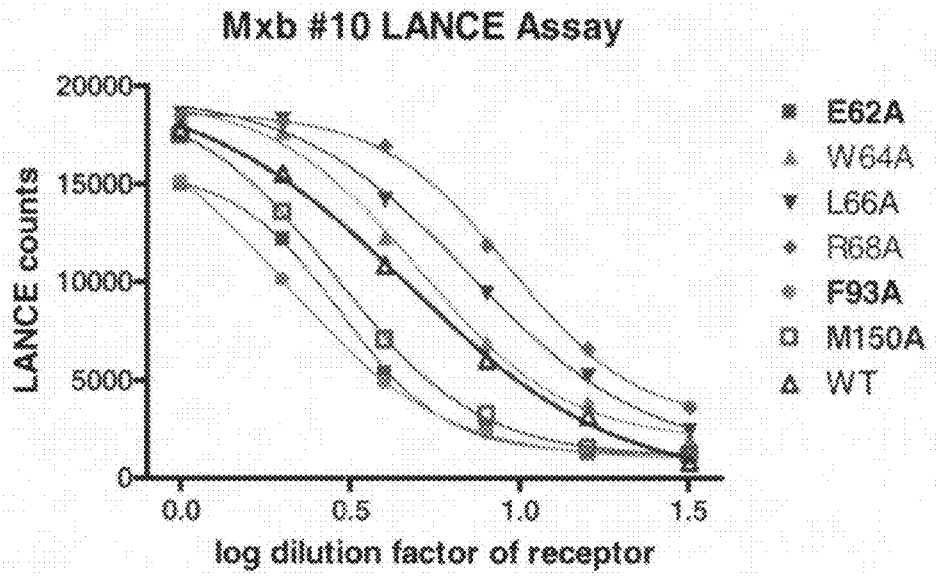

Mxb #10 LANCE Assay
LANCE counts
20000
15000
10000
5000
0
0.0
0.5
1.0
1.5
log dilution factor of receptor
E62A
W64A
L66A
R68A
F93A
M150A
WT

FIGURE 32A

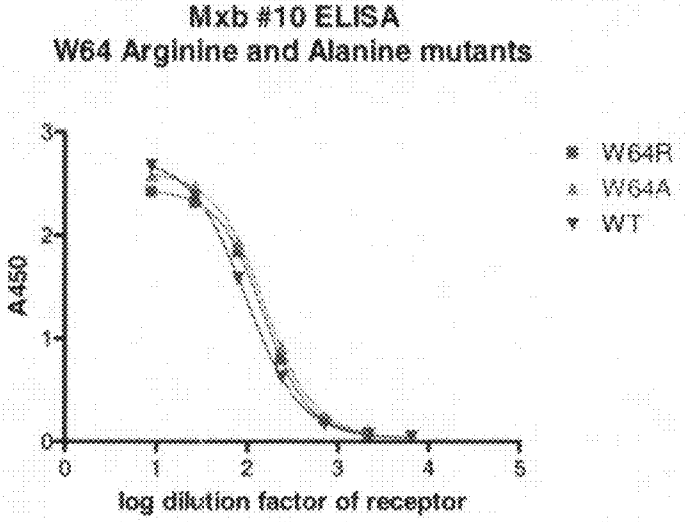


FIGURE 32B

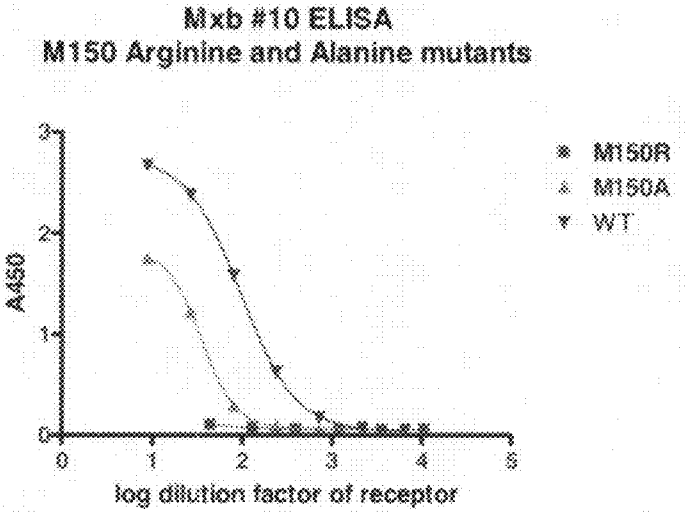


FIGURE 33A

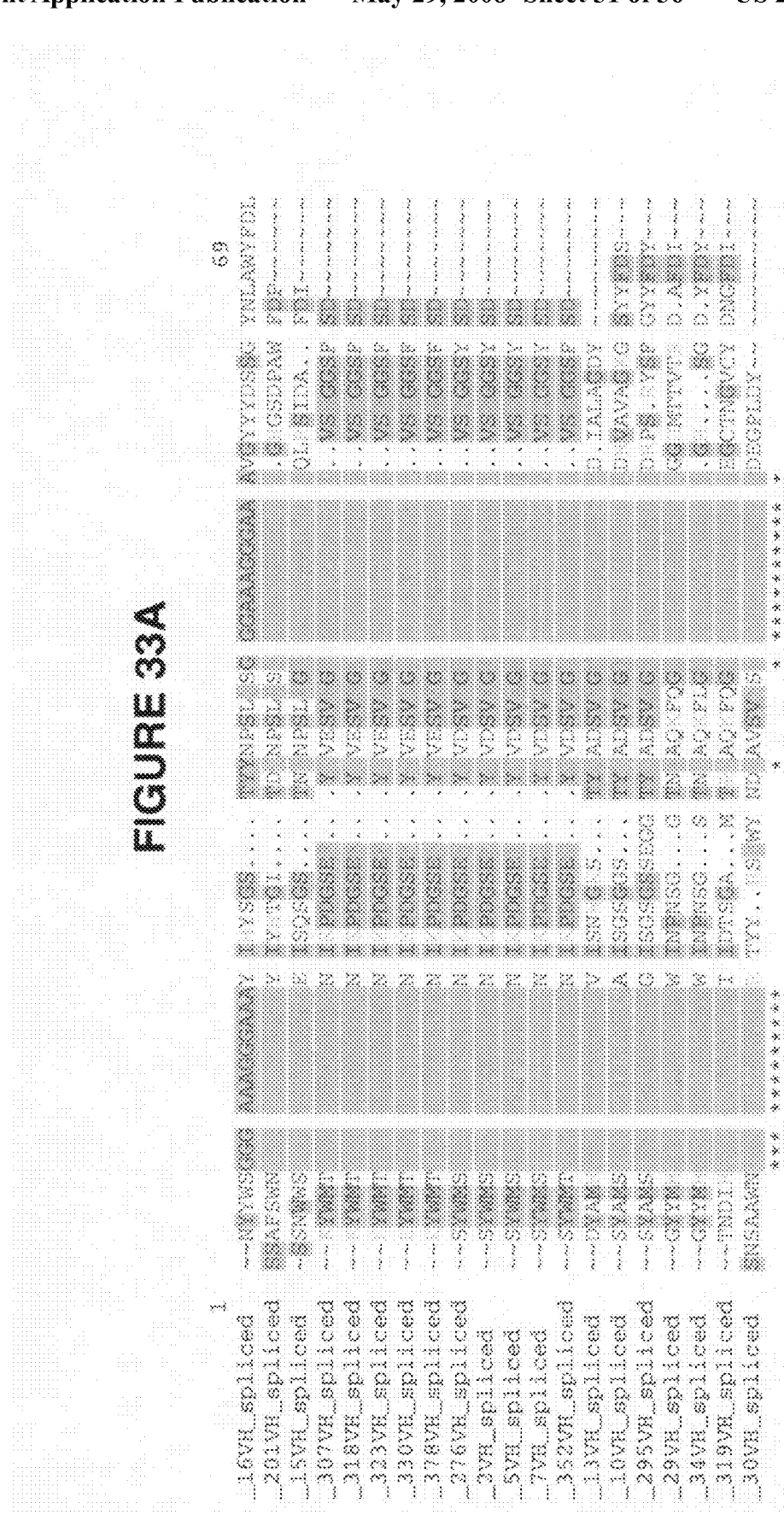
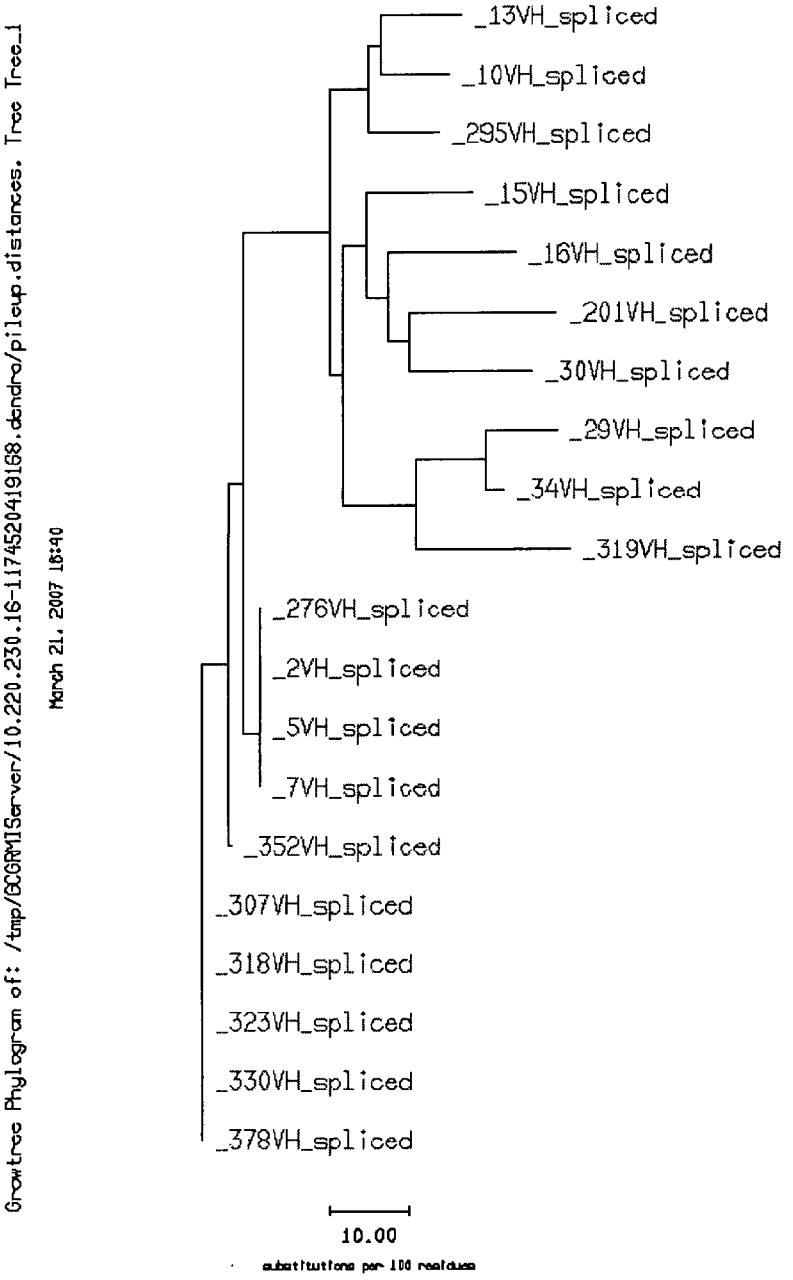


FIGURE 33B

FIGURE 34A


Growtree Phylogram of: /tmp/GCGRMIServer/10.220.230.16-1174520419168.dendro/pileup.distances. Tree Tree_1
March 21, 2007 16:40
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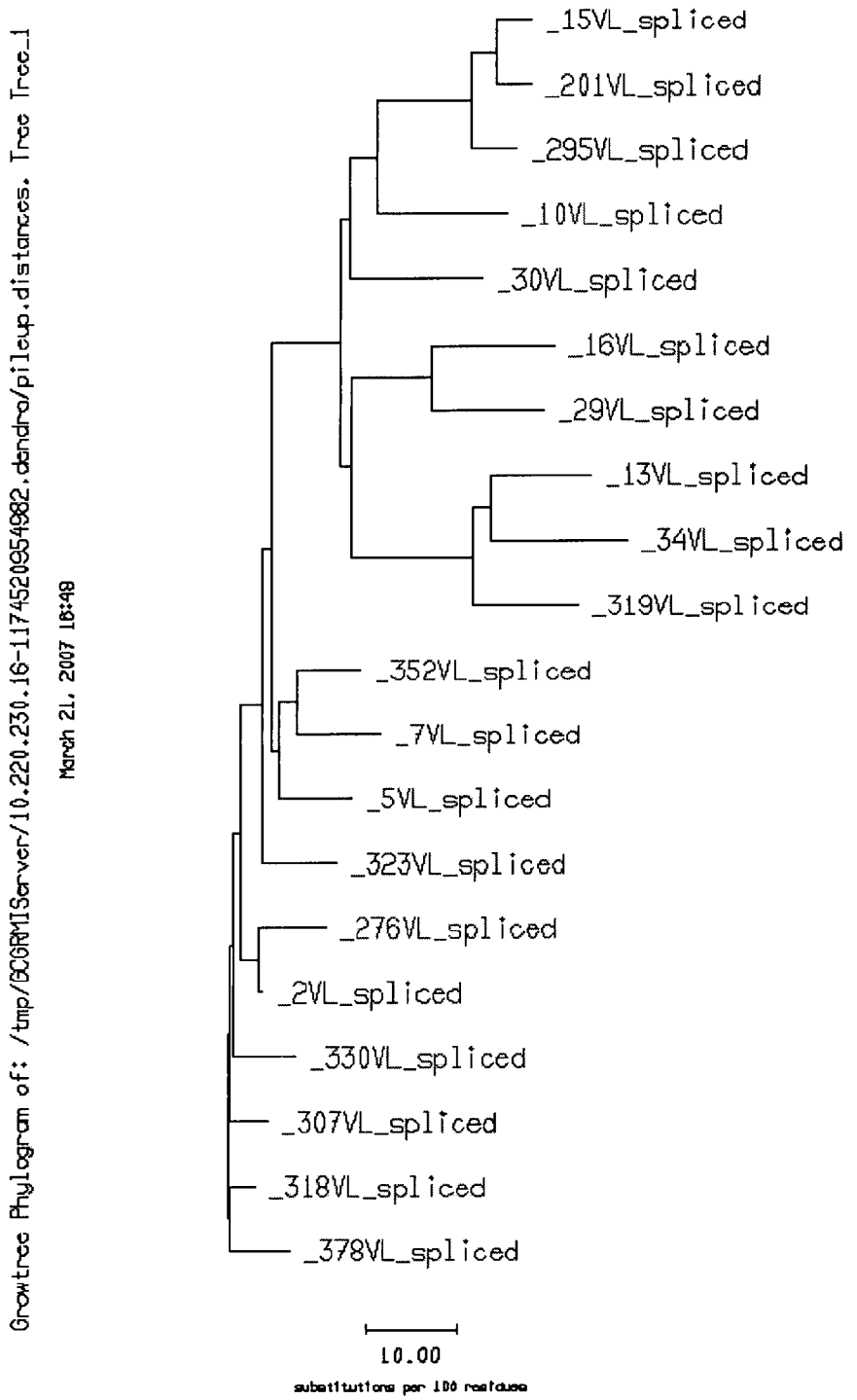
_10VH_spliced
_295VH_spliced
_15VH_spliced
_16VH_spliced
_201VH_spliced
_30VH_spliced
_29VH_spliced
_34VH_spliced
_319VH_spliced
_276VH_spliced
_2VH_spliced
_5VH_spliced
_7VH_spliced
_352VH_spliced
_307VH_spliced
_318VH_spliced
_323VH_spliced
_330VH_spliced
_378VH_spliced
10.00
substitutions per 100 residues

FIGURE 34B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March 21, 2007 18:48
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_201VL_spliced
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_319VL_spliced
_352VL_spliced
_7VL_spliced
_5VL_spliced
_323VL_spliced
_276VL_spliced
_2VL_spliced
_330VL_spliced
_307VL_spliced
_318VL_spliced
_378VL_spliced
10.00
substitutions per 100 residues

FIGURE 35

Vh consensus sequences

CDR1

X_1 YWM X_5	where X_1 can be K or S and X_5 can be T or S

CDR2

NIKPDGSEKYV X_{12} SVKG	where X_{12} can be D or E

CDR3

VSRGGS X_7 SD	where X_7 can be F or Y

Vl consensus sequences

CDR1

TGTSSD X_7 G X_9 Y X_{11} YVS	where X_7 can be V or I, and X_9 can be G, A, T or S, and X_{11} can be N, D, or I

CDR2

X_1 V X_3 X_4 RPS	where X_1 can be D or E, and X_3 can be N, S, A, or T, and X_4 can be K, N, or R

FIGURE 36

A)
Human EpoR (full length Amino Acid Sequence)

```
MDHLGASLWP QVGSLCLLLA GAAWAPPPNL PDPKFESKAA LLAARGPEEL  50
LCFTERLEDL VCFWEEAASA GVGPGNYSFS YQLEDEPWKL CRLHQAPTAR 100
GAVRFWCSLP TADTSSFVPL ELRVTAASGA PRYHRVIHIN EVVLLDAPVG 150
LVARLADESG HVVLRWLPPP ETPMTSHIRY EVDVSAGNGA GSVQRVEILE 200
GRTECVLSNL RGRTRYTFAV RARMAEPSFG GFWSAWSEPV SLLTPSDLDP 250
LILTLSLILV VILVLLTVLA LLSHRRALKQ KIWPGIPSPE SEFEGLFTTH 300
KGNFQLWLYQ NDGCLWWSPC TPFTEDPPAS LEVLSERCWG TMQAVEPGTD 350
DEGPLLEPVG SEHAQDTYLV LDKWLLPRNP PSEDLPGPGG SVDIVAMDEG 400
SEASSCSSAL ASKPSPEGAS AASFEYTILD PSSQLLRPWT LCPELPPTPH 450
HLKYLYLVVS DSGISTDYSS GDSQGAQGGL SDGPYSNPYE NSLIPAAEPL 500
PPSYVACS                                              508
```

(SEQ ID NO.: 213)

B)
Extracellular domain amino acid sequence (25-250)

```
1   apppnlpdpk feskaallaa rgpeellcft erledlvcfw eeaasagvgp gnysfsyqle
61  depwklcrlh qaptargavr fwcslptadt ssfvplelrv taasgapryh rvihinevvl
121 ldapvglvar ladesghvvl rwlpppetpm tshiryevdv sagngagsvq rvellegrte
181 cvlsnlrgrt rytfavrarm aepsfggfws awsepvslit psdldp
```

(SEQ ID NO.: 214)

ERYTHROPOIETIN RECEPTOR AGONISTS

[0001] This application claims priority benefit of U.S. Provisional Application No. 60/792,174, filed Apr. 14, 2006. The entire contents of U.S. Provisional Application No. 60/792,174 is specifically incorporated herein by reference in its entirety.

FIELD

[0002] The present teachings generally relate to erythropoietin receptor agonists, kits comprising erythropoietin receptor agonists, and methods of using erythropoietin receptor agonists.

BACKGROUND

[0003] Erythropoietin (Epo) is a glycoprotein hormone involved in the growth and maturation of erythroid progenitor cells into erythrocytes. EPO is produced by the liver during fetal life and by the kidney of adults and stimulates the production of red blood cells from erythroid precursors. Decreased production of EPO, which commonly occurs in adults as a result of renal failure, leads to anemia. EPO has been produced by genetic engineering techniques involving expression and secretion of the protein from a host cell transfected with the gene encoding erythropoietin. Administration of recombinant EPO has been effective in the treatment of anemia. For example, Eschbach et al. (N. Engl J Med 316, 73 (1987)) describe the use of EPO to correct anemia resulting from chronic renal failure.

[0004] The purification of human urinary EPO was described by Miyake et al. (J. Biol. Chem. 252, 5558 (1977)). The identification, cloning, and expression of genes encoding erythropoietin is described in U.S. Pat. No. 4,703,008 to Lin. A description of a method for purification of recombinant EPO from cell medium is included in U.S. Pat. No. 4,667,016 to Lai et al. The erythropoietin receptor (EPO-R) is thought to exist as a multimeric complex. Sedimentation studies suggested its molecular weight is 330+/−48 kDa (Mayeux et al. Eur. J. Biochem. 194, 271 (1990)). Crosslinking studies indicated that the receptor complex includes multiple distinct polypeptides, a 66-72 kDa species, and 85 and 100 kDa species (Mayeux et al. J. Biol. Chem. 266, 23380 (1991)); McCaffery et al. J. Biol. Chem. 264, 10507 (1991)). A distinct 95 kDa protein was also detected by immunoprecipitation of EPO receptor (Miura & Ihle Blood 81, 1739 (1993)). Another crosslinking study revealed three EPO containing complexes of 110, 130 and 145 kDa. The 110 and 145 kDa complexes contained EPO receptor since they could be immunoprecipitated with antibodies raised against the receptor (Miura & Ihle, supra). Expression of a carboxy-terminal truncated EPO receptor resulted in detection of the 110 kDa complex but not the 145 kDa complex. This suggests that the higher molecular weight complex contains polypeptides present in the 110 kDa complex and an additional 35 kDa protein.

[0005] Further insight into the structure and function of the EPO receptor complex was obtained upon cloning and expression of the mouse and human EPO receptors (D'Andrea et al. Cell 57, 277 (1989); Jones et al. Blood 76, 31 (1990); Winkelmann et al. Blood 76, 24 (1990); PCT Application No. WO90/08822; U.S. Pat. No. 5,278,065 to D'Andrea et al.) The full-length human EPO receptor is a 483 amino acid transmembrane protein with an approximately 224 amino acid extracellular domain and a 25 amino acid signal peptide. The human receptor shows about an 82% amino acid sequence homology with the mouse receptor. The cloned full-length EPO receptor expressed in mammalian cells (66-72 KDa) has been shown to bind EPO with an affinity similar to that of the native receptor on erythroid progenitor cells. Thus, this form is thought to contain the main EPO binding determinant. The 85 and 100 KDa proteins observed as part of a cross-linked complex are distinct from the EPO receptor but are probably in close proximity to EPO because EPO can be crosslinked to them. The 85 and 100 KDa proteins are related to each other and the 85 KDa protein may be a proteolytic cleavage product of the 100 KDa species (Sawyer J. Biol. Chem. 264, 13343 (1989)).

[0006] A soluble (truncated) form of the EPO receptor containing only the extracellular domain has been produced and found to bind EPO with an affinity of about 1 nM, or about 3 to 10-fold lower than the full-length receptor (Harris et al. J. Biol. Chem. 267, 15205 (1992); Yang & Jones Blood 82, 1713 (1993)).

[0007] Activation of the EPO receptor results in several biological effects. Three of the activities include stimulation of proliferation in immature erythroblasts, stimulation of differentiation in immature erythroblasts, and inhibition of apoptosis in erythroid progenitor cells (Liboi et al. Proc. Natl. Acad. Sci. USA 90, 11351 (1993); Koury Science 248, 378 (1990)). The signal transduction pathways resulting in stimulation of proliferation and stimulation of differentiation appear to be separable (Noguchi et al. Mol. Cell. Biol. 8, 2604 (1988); Patel et al. J. Biol. Chem. 267, 21300 (1992); Liboi et al. ibid).

SUMMARY

[0008] In certain embodiments, a single chain variable fragment is provided. In certain embodiments, the single chain variable fragment comprises: a) an amino acid sequence comprising SEQ ID NO. 1 and SEQ ID NO. 2; b) an amino acid sequence comprising SEQ ID NO. 3 and SEQ ID NO. 4; c) an amino acid sequence comprising SEQ ID NO. 5 and SEQ ID NO. 6; d) an amino acid sequence comprising SEQ ID NO. 7 and SEQ ID NO. 8; e) an amino acid sequence comprising SEQ ID NO. 9 and SEQ ID NO. 10; f) an amino acid sequence comprising SEQ ID NO. 56 and SEQ ID NO. 58; g) an amino acid sequence comprising SEQ ID NO. 60 and SEQ ID NO. 62; h) an amino acid sequence comprising SEQ ID NO. 64 and SEQ ID NO. 66; i) an amino acid sequence comprising SEQ ID NO. 68 and SEQ ID NO. 70; j) an amino acid sequence comprising SEQ, ID NO. 72 and SEQ ID NO. 74; k) an amino acid sequence comprising SEQ ID. NO. 76 and SEQ ID NO. 78; l) an amino acid sequence comprising SEQ ID NO. 80 and SEQ ID NO. 82; m) an amino acid sequence comprising SEQ ID NO. 84 and SEQ ID NO. 86; n) an amino acid sequence comprising SEQ ID NO. 88 and SEQ ID NO. 90; o) an amino acid sequence comprising SEQ ID NO. 92 and SEQ ID NO. 94; p) an amino acid sequence comprising SEQ ID NO. 96 and SEQ ID NO. 98; q) an amino acid sequence comprising SEQ ID NO. 100 and SEQ ID NO. 102; r) an amino acid sequence comprising SEQ ID NO. 104 and SEQ ID NO. 106; s) an amino acid sequence comprising SEQ ID NO. 108 and SEQ ID NO. 110; or t) an amino acid sequence comprising SEQ ID NO. 112 and SEQ ID NO. 114.

[0009] In certain embodiments, a single chain variable fragment fused to an Fc is provided. In certain embodiments,

the single chain variable fragment comprises: a) an amino acid sequence comprising SEQ ID NO. 1 and SEQ ID NO. 2; b) an amino acid sequence comprising SEQ ID NO. 3 and SEQ ID NO. 4; c) an amino acid sequence comprising SEQ ID NO. 5 and SEQ ID NO. 6; d) an amino acid sequence comprising SEQ ID NO. 7 and SEQ ID NO. 8; e) an amino acid sequence comprising SEQ ID NO. 9 and SEQ ID NO. 10; f) an amino acid sequence comprising SEQ ID NO. 56 and SEQ ID NO. 58; g) an amino acid sequence comprising SEQ ID NO. 60 and SEQ ID NO. 62; h) an amino acid sequence comprising SEQ ID NO. 64 and SEQ ID NO. 66; i) an amino acid sequence comprising SEQ ID NO. 68 and SEQ ID NO. 70; j) an amino acid sequence comprising SEQ ID NO. 72 and SEQ ID NO. 74; k) an amino acid sequence comprising SEQ ID NO. 76 and SEQ ID NO. 78; l) an amino acid sequence comprising SEQ ID NO. 80 and SEQ ID NO. 82; m) an amino acid sequence comprising SEQ ID NO. 84 and SEQ ID NO. 86; n) an amino acid sequence comprising SEQ ID NO. 88 and SEQ ID NO. 90; o) an amino acid sequence comprising SEQ ID NO. 92 and SEQ ID NO. 94; p) an amino acid sequence comprising SEQ ID NO. 96 and SEQ ID NO. 98; q) an amino acid sequence comprising SEQ ID NO. 100 and SEQ ID NO. 102; r) an amino acid sequence comprising SEQ ID NO. 104 and SEQ ID NO. 106; s) an amino acid sequence comprising SEQ ID NO. 108 and SEQ ID NO. 110; or t) an amino acid sequence comprising SEQ ID NO. 112 and SEQ ID NO. 114.

[0010] In certain embodiments, a method of treating anemia in a patient is provided. In certain embodiments, the method of treating anemia in a patient comprises administering to the patient a single chain variable fragment wherein the single chain variable fragment comprises: a) an amino acid sequence comprising SEQ ID NO. 1 and SEQ ID NO. 2; b) an amino acid sequence comprising SEQ ID NO. 3 and SEQ ID NO. 4; c) an amino acid sequence comprising SEQ ID NO. 5 and SEQ ID NO. 6; d) an amino acid sequence comprising SEQ ID NO. 7 and SEQ ID NO. 8; e) an amino acid sequence comprising SEQ ID NO. 9 and SEQ ID NO. 10; f) an amino acid sequence comprising SEQ ID NO. 56 and SEQ ID NO. 58; g) an amino acid sequence comprising SEQ ID NO. 60 and SEQ ID NO. 62; h) an amino acid sequence comprising SEQ ID NO. 64 and SEQ ID NO. 66; i) an amino acid sequence comprising SEQ ID NO. 68 and SEQ ID NO. 70; j) an amino acid sequence comprising SEQ ID NO. 72 and SEQ ID NO. 74; k) an amino acid sequence comprising SEQ ID NO. 76 and SEQ ID NO. 78; l) an amino acid sequence comprising SEQ ID NO. 80 and SEQ ID NO. 82; m) an amino acid sequence comprising SEQ ID NO. 84 and SEQ ID NO. 86; n) an amino acid sequence comprising SEQ ID NO. 88 and SEQ ID NO. 90; o) an amino acid sequence comprising SEQ ID NO. 92 and SEQ ID NO. 94; p) an amino acid sequence comprising SEQ ID NO. 96 and SEQ ID NO. 98; q) an amino acid sequence comprising SEQ ID NO. 100 and SEQ ID NO. 102; r) an amino acid sequence comprising SEQ ID NO. 104 and SEQ ID NO. 106; s) an amino acid sequence comprising SEQ ID NO. 108 and SEQ ID NO. 110; ort) an amino acid sequence comprising SEQ ID NO. 112 and SEQ ID NO. 114.

[0011] In certain embodiments, a method of promoting tissue protection in a patient is provided. In certain embodiments, the method of promoting tissue protection in a patient comprises administering to the patient a single chain variable fragment wherein the single chain variable fragment comprises: a) an amino acid sequence comprising SEQ ID NO. 1 and SEQ ID NO. 2; b) an amino acid sequence comprising SEQ ID NO. 3 and SEQ ID NO. 4; c) an amino acid sequence comprising SEQ ID NO. 5 and SEQ ID NO. 6; d) an amino acid sequence comprising SEQ ID NO. 7 and SEQ ID NO. 8; e) an amino acid sequence comprising SEQ ID NO. 9 and SEQ ID NO. 10; f) an amino acid sequence comprising SEQ ID NO. 56 and SEQ ID NO. 58; g) an amino acid sequence comprising SEQ ID NO. 60 and SEQ ID NO. 62; h) an amino acid sequence comprising SEQ ID NO. 64 and SEQ ID NO. 66; i) an amino acid sequence comprising SEQ ID NO. 68 and SEQ ID NO. 70; j) an amino acid sequence comprising SEQ ID NO. 72 and SEQ ID NO. 74; k) an amino acid sequence comprising SEQ ID NO. 76 and SEQ ID NO. 78; l) an amino acid sequence comprising SEQ ID NO. 80 and SEQ ID NO. 82; m) an amino acid sequence comprising SEQ ID NO. 84 and SEQ ID NO. 86; n) an amino acid sequence comprising SEQ ID NO. 88 and SEQ ID NO. 90; o) an amino acid sequence comprising SEQ ID NO. 92 and SEQ ID NO. 94; p) an amino acid sequence comprising SEQ ID NO. 96 and SEQ ID NO. 98; q) an amino acid sequence comprising SEQ ID NO. 100 and SEQ ID NO. 102; r) an amino acid sequence comprising SEQ ID NO. 104 and SEQ ID NO. 106; s) an amino acid sequence comprising SEQ ID NO. 108 and SEQ ID NO. 110; ort) an amino acid sequence comprising SEQ ID NO. 112 and SEQ ID NO. 114.

[0012] In certain embodiments, a method of activating an endogenous activity of an erythropoietin receptor in a mammal is provided. In certain embodiments, the method of activating an endogenous activity of an erythropoietin receptor in a mammal comprises administering to the mammal an amount of a single chain variable fragment wherein the single chain variable fragment comprises: a) an amino acid sequence comprising SEQ ID NO. 1 and SEQ ID NO. 2; b) an amino acid sequence comprising SEQ ID NO. 3 and SEQ ID NO. 4; c) an amino acid sequence comprising SEQ ID NO. 5 and SEQ ID NO. 6; d) an amino acid sequence comprising SEQ ID NO. 7 and SEQ ID NO. 8; e) an amino acid sequence comprising SEQ ID NO. 9 and SEQ ID NO. 10; f) an amino acid sequence comprising SEQ ID NO. 56 and SEQ ID NO. 58; g) an amino acid sequence comprising SEQ ID NO. 60 and SEQ ID NO. 62; h) an amino acid sequence comprising SEQ ID NO. 64 and SEQ ID NO. 66; i) an amino acid sequence comprising SEQ ID NO. 68 and SEQ ID NO. 70; j) an amino acid sequence comprising SEQ ID NO. 72 and SEQ ID NO. 74; k) an amino acid sequence comprising SEQ ID NO. 76 and SEQ ID NO. 78; l) an amino acid sequence comprising SEQ ID NO. 80 and SEQ ID NO. 82; m) an amino acid sequence comprising SEQ ID NO. 84 and SEQ ID NO. 86; n) an amino acid sequence comprising SEQ ID NO. 88 and SEQ ID NO. 90; o) an amino acid sequence comprising SEQ ID NO. 92 and SEQ ID NO. 94; p) an amino acid sequence comprising SEQ ID NO. 96 and SEQ ID NO. 98; q) an amino acid sequence comprising SEQ ID NO. 100 and SEQ ID NO. 102; r) an amino acid sequence comprising SEQ ID NO. 104 and SEQ ID NO. 106; s) an amino acid sequence comprising SEQ ID NO. 108 and SEQ ID NO. 110; or t) an amino acid sequence comprising SEQ ID NO. 112 and SEQ ID NO. 114.

[0013] In certain embodiments, an antibody is provided. In certain embodiments, the antibody comprises: a) an amino acid sequence comprising SEQ ID NO. 1 and SEQ ID NO. 2; b) an amino acid sequence comprising SEQ ID NO. 3 and SEQ ID NO. 4; c) an amino acid sequence comprising SEQ ID NO. 5 and SEQ ID NO. 6; d) an amino acid sequence

comprising SEQ ID NO. 7 and SEQ ID NO. 8; e) an amino acid sequence comprising SEQ ID NO. 9 and SEQ ID NO. 10; f) an amino acid sequence comprising SEQ ID NO. 56 and SEQ ID NO. 58; g) an amino acid sequence comprising SEQ ID NO. 60 and SEQ ID NO. 62; h) an amino acid sequence comprising SEQ ID NO. 64 and SEQ ID NO. 66; i) an amino acid sequence comprising SEQ ID NO. 68 and SEQ ID NO. 70; j) an amino acid sequence comprising SEQ ID NO. 72 and SEQ ID NO. 74; k) an amino acid sequence comprising SEQ ID NO. 76 and SEQ ID NO. 78; l) an amino acid sequence comprising SEQ ID NO. 80 and SEQ ID NO. 82; m) an amino acid sequence comprising SEQ ID NO. 84 and SEQ ID NO. 86; n) an amino acid sequence comprising SEQ ID NO. 88 and SEQ ID NO. 90; o) an amino acid sequence comprising SEQ ID NO. 92 and SEQ ID NO. 94; p) an amino acid sequence comprising SEQ ID NO. 96 and SEQ ID NO. 98; q) an amino acid sequence comprising SEQ ID NO. 100 and SEQ ID NO. 102; r) an amino acid sequence comprising SEQ ID NO. 104 and SEQ ID NO. 106; s) an amino acid sequence comprising SEQ ID NO. 108 and SEQ ID NO. 110; ort) an amino acid sequence comprising SEQ ID NO. 112 and SEQ ID NO. 114.

[0014] In certain embodiments, a method of treating anemia in a patient is provided. In certain embodiments, the method of treating anemia in a patient comprises administering to the patient an antibody wherein the antibody comprises: a) an amino acid sequence comprising SEQ ID NO. 1 and SEQ ID NO. 2; b) an amino acid sequence comprising SEQ ID NO. 3 and SEQ ID NO. 4; c) an amino acid sequence comprising SEQ ID NO. 5 and SEQ ID NO. 6; d) an amino acid sequence comprising SEQ ID NO. 7 and SEQ ID NO. 8; e) an amino acid sequence comprising SEQ ID NO. 9 and SEQ ID NO. 10; f) an amino acid sequence comprising SEQ ID NO. 56 and SEQ ID NO. 58; g) an amino acid sequence comprising SEQ ID NO. 60 and SEQ ID NO. 62; h) an amino acid sequence comprising SEQ ID NO. 64 and SEQ ID NO. 66; i) an amino acid sequence comprising SEQ ID NO. 68 and SEQ ID NO. 70; j) an amino acid sequence comprising SEQ ID NO. 72 and SEQ ID NO. 74; k) an amino acid sequence comprising SEQ ID NO. 76 and SEQ ID NO. 78; l) an amino acid sequence comprising SEQ ID NO. 80 and SEQ ID NO. 82; m) an amino acid sequence comprising SEQ ID NO. 84 and SEQ ID NO. 86; n) an amino acid sequence comprising SEQ ID NO. 88 and SEQ ID NO. 90; o) an amino acid sequence comprising SEQ ID NO. 92 and SEQ ID NO. 94; p) an amino acid sequence comprising SEQ ID NO. 96 and SEQ ID NO. 98; q) an amino acid sequence comprising SEQ ID NO. 100 and SEQ ID NO. 102; r) an amino acid sequence comprising SEQ ID NO. 104 and SEQ ID NO. 106; s) an amino acid sequence comprising SEQ ID NO. 108 and SEQ ID NO. 110; or t) an amino acid sequence comprising SEQ ID NO. 112 and SEQ ID NO. 114.

[0015] In certain embodiments, a method of promoting tissue protection in a patient is provided. In certain embodiments, a method of promoting tissue protection in a patient comprises administering to the patient an antibody wherein the antibody comprises: a) an amino acid sequence comprising SEQ ID NO. 1 and SEQ ID NO. 2; b) an amino acid sequence comprising SEQ ID NO. 3 and SEQ ID NO. 4; c) an amino acid sequence comprising SEQ ID NO. 5 and SEQ ID NO. 6; d) an amino acid sequence comprising SEQ ID NO. 7 and SEQ ID NO. 8; e) an amino acid sequence comprising SEQ ID NO. 9 and SEQ ID NO. 10; f) an amino acid sequence comprising SEQ ID NO. 56 and SEQ ID NO. 58; g) an amino acid sequence comprising SEQ ID NO. 60 and SEQ ID NO. 62; h) an amino acid sequence comprising SEQ ID NO. 64 and SEQ ID NO. 66; i) an amino acid sequence comprising SEQ ID NO. 68 and SEQ ID NO. 70; j) an amino acid sequence comprising SEQ ID NO. 72 and SEQ ID NO. 74; k) an amino acid sequence comprising SEQ ID NO. 76 and SEQ ID NO. 78; l) an amino acid sequence comprising SEQ ID NO. 80 and SEQ ID NO. 82; m) an amino acid sequence comprising SEQ ID NO. 84 and SEQ ID NO. 86; n) an amino acid sequence comprising SEQ ID NO. 88 and SEQ ID NO. 90; o) an amino acid sequence comprising SEQ ID NO. 92 and SEQ ID NO. 94; p) an amino acid sequence comprising SEQ ID NO. 96 and SEQ ID NO. 98; q) an amino acid sequence comprising SEQ ID NO. 100 and SEQ ID NO. 102; r) an amino acid sequence comprising SEQ ID NO. 104 and SEQ ID NO. 106; s) an amino acid sequence comprising SEQ ID NO. 108 and SEQ ID NO. 110; or t) an amino acid sequence comprising SEQ ID NO. 112 and SEQ ID NO. 114.

[0016] In certain embodiments, a method of activating an endogenous activity of an erythropoietin receptor in a mammal is provided. In certain embodiments, the method of activating an endogenous activity of an erythropoietin receptor in a mammal comprises administering to the mammal an amount of an antibody wherein the antibody comprises: a) an amino acid sequence comprising SEQ ID NO. 1 and SEQ ID NO. 2; b) an amino acid sequence comprising SEQ ID NO. 3 and SEQ ID NO. 4; c) an amino acid sequence comprising SEQ ID NO. 5 and SEQ ID NO. 6; d) an amino acid sequence comprising SEQ ID NO. 7 and SEQ ID NO. 8; e) an amino acid sequence comprising SEQ ID NO. 9 and SEQ ID NO. 10; f) an amino acid sequence comprising SEQ ID NO. 56 and SEQ ID NO. 58; g) an amino acid sequence comprising SEQ ID NO. 60 and SEQ ID NO. 62; h) an amino acid sequence comprising SEQ ID NO. 64 and SEQ ID NO. 66; i) an amino acid sequence comprising SEQ ID NO. 68 and SEQ ID NO. 70; j) an amino acid sequence comprising SEQ ID NO. 72 and SEQ ID NO. 74; k) an amino acid sequence comprising SEQ ID NO. 76 and SEQ ID NO. 78; l) an amino acid sequence comprising SEQ ID NO. 80 and SEQ ID NO. 82; m) an amino acid sequence comprising SEQ ID NO. 84 and SEQ ID NO. 86; n) an amino acid sequence comprising SEQ ID NO. 88 and SEQ ID NO. 90; o) an amino acid sequence comprising SEQ ID NO. 92 and SEQ ID NO. 94; p) an amino acid sequence comprising SEQ ID NO. 96 and SEQ ID NO. 98; q) an amino acid sequence comprising SEQ ID NO. 100 and SEQ ID NO. 102; r) an amino acid sequence comprising SEQ ID NO. 104 and SEQ ID NO. 106; s) an amino acid sequence comprising SEQ ID NO. 108 and SEQ ID NO. 110; or t) an amino acid sequence comprising SEQ ID NO. 112 and SEQ ID NO. 114.

[0017] In certain embodiments, a single chain variable fragment is provided. In certain embodiments, the single chain variable fragment comprises: a) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15 and SEQ ID NO. 16; b) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 17, SEQ ID NO. 18, and SEQ ID NO. 19; c) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 20, SEQ ID NO. 21, and SEQ ID NO. 22; d) an amino acid sequence comprising SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 26, SEQ ID NO. 27, and SEQ ID NO. 28; e) an amino acid sequence comprising SEQ ID NO. 29, SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID

NO. 32, SEQ ID NO. 33, and SEQ ID NO. 34; f) an amino acid sequence comprising SEQ ID NO.: 123, SEQ ID NO.: 124, SEQ ID NO.: 125, SEQ ID NO.: 126, SEQ ID NO.: 127, and SEQ ID NO.: 128; g) an amino acid sequence comprising SEQ ID NO.: 129, SEQ ID NO.: 130, SEQ ID NO.: 131, SEQ ID NO.: 132, SEQ ID NO.: 133, and SEQ ID NO.: 134; h) f) an amino acid sequence comprising SEQ ID NO.: 135, SEQ ID NO.: 136, SEQ ID NO.: 212; SEQ ID NO.: 137, SEQ ID NO.: 138, and SEQ ID NO.: 139; i) an amino acid sequence comprising SEQ ID NO.: 140, SEQ ID NO.: 141, SEQ ID NO.: 142, SEQ ID NO.: 143, SEQ ID NO.: 144, and SEQ ID NO.: 145; j) an amino acid sequence comprising SEQ ID NO.: 146, SEQ ID NO.: 147, SEQ ID NO.: 148, SEQ ID NO.: 149, SEQ ID NO.: 150, and SEQ ID NO.: 151; k) an amino acid sequence comprising SEQ ID NO.: 152, SEQ ID NO.: 153, SEQ ID NO.: 154, SEQ ID NO.: 155, SEQ ID NO.: 156, and SEQ ID NO.: 157; l) an amino acid sequence comprising SEQ ID NO.: 158, SEQ ID NO.: 159, SEQ ID NO.: 160, SEQ ID NO.: 161, SEQ ID NO.: 162, and SEQ ID NO.: 163; m) an amino acid sequence comprising SEQ ID NO.: 164, SEQ ID NO.: 165, SEQ ID NO.: 166, SEQ ID NO.: 167, SEQ ID NO.: 168, and SEQ ID NO.: 169; n) an amino acid sequence comprising SEQ ID NO.: 170, SEQ ID NO.: 171, SEQ ID NO.: 172, SEQ ID NO.: 173, SEQ ID NO.: 174, and SEQ ID NO.: 175; o) an amino acid sequence comprising SEQ ID NO.: 176, SEQ ID NO.: 177, SEQ ID NO.: 178, SEQ ID NO.: 179, SEQ ID NO.: 180, and SEQ ID NO.: 181; p) an amino acid sequence comprising SEQ ID NO.: 182, SEQ ID NO.: 183, SEQ ID NO.: 184, SEQ ID NO.: 185, SEQ ID NO.: 186, and SEQ ID NO.: 187; q) an amino acid sequence comprising SEQ ID NO.: 188, SEQ ID NO.: 189, SEQ ID NO.: 190, SEQ ID NO.: 191, SEQ ID NO.: 192, and SEQ ID NO.: 193; r) an amino acid sequence comprising SEQ ID NO.: 194, SEQ ID NO.: 195, SEQ ID NO.: 196, SEQ ID NO.: 197, SEQ ID NO.: 198, and SEQ ID NO.: 199; s) an amino acid sequence comprising SEQ ID NO.: 200, SEQ ID NO.: 201, SEQ ID NO.: 202, SEQ ID NO.: 203, SEQ ID NO.: 204, and SEQ ID NO.: 205; or t) an amino acid sequence comprising SEQ ID NO.: 206, SEQ ID NO.: 207, SEQ ID NO.: 208, SEQ ID NO.: 209, SEQ ID NO.: 210, and SEQ ID NO.: 211.

[0018] In certain embodiments, a single chain variable fragment fused to an Fc is provided. In certain embodiments, the single chain variable fragment comprises: a) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15 and SEQ ID NO. 16; b) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 17, SEQ ID NO. 18, and SEQ ID NO. 19; c) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 20, SEQ ID NO. 21, and SEQ ID NO. 22; d) an amino acid sequence comprising SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 26, SEQ ID NO. 27, and SEQ ID NO. 28; e) an amino acid sequence comprising SEQ ID NO. 29, SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, and SEQ ID NO. 34; f) an amino acid sequence comprising SEQ ID NO.: 123, SEQ ID NO.: 124, SEQ ID NO.: 125, SEQ ID NO.: 126, SEQ ID NO.: 127, and SEQ ID NO.: 128; g) an amino acid sequence comprising SEQ ID NO.: 129, SEQ ID NO.: 130, SEQ ID NO.: 131, SEQ ID NO.: 132, SEQ ID NO.: 133, and SEQ ID NO.: 134; h) f) an amino acid sequence comprising SEQ ID NO.: 135, SEQ ID NO.: 136, SEQ ID NO.: 212; SEQ ID NO.: 137, SEQ ID NO.: 138, and SEQ ID NO.: 139; i) an amino acid sequence comprising SEQ ID NO.: 140, SEQ ID NO.: 141, SEQ ID NO.: 142, SEQ ID NO.: 143, SEQ ID NO.: 144, and SEQ ID NO.: 145; j) an amino acid sequence comprising SEQ ID NO.: 146, SEQ ID NO.: 147, SEQ ID NO.: 148, SEQ ID NO.: 149, SEQ ID NO.: 150, and SEQ ID NO.: 151; k) an amino acid sequence comprising SEQ ID NO.: 152, SEQ ID NO.: 153, SEQ ID NO.: 154, SEQ ID NO.: 155, SEQ ID NO.: 156, and SEQ ID NO.: 157; l) an amino acid sequence comprising SEQ ID NO.: 158, SEQ ID NO.: 159, SEQ ID NO.: 160, SEQ ID NO.: 161, SEQ ID NO.: 162, and SEQ ID NO.: 163; m) an amino acid sequence comprising SEQ ID NO.: 164, SEQ ID NO.: 165, SEQ ID NO.: 166, SEQ ID NO.: 167, SEQ ID NO.: 168, and SEQ ID NO.: 169; n) an amino acid sequence comprising SEQ ID NO.: 170, SEQ ID NO.: 171, SEQ ID NO.: 172, SEQ ID NO.: 173, SEQ ID NO.: 174, and SEQ ID NO.: 175; o) an amino acid sequence comprising SEQ ID NO.: 176, SEQ ID NO.: 177, SEQ ID NO.: 178, SEQ ID NO.: 179, SEQ ID NO.: 180, and SEQ ID NO.: 181; p) an amino acid sequence comprising SEQ ID NO.: 182, SEQ ID NO.: 183, SEQ ID NO.: 184, SEQ ID NO.: 185, SEQ ID NO.: 186, and SEQ ID NO.: 187; q) an amino acid sequence comprising SEQ ID NO.: 188, SEQ ID NO.: 189, SEQ ID NO.: 190, SEQ ID NO.: 191, SEQ ID NO.: 192, and SEQ ID NO.: 193; r) an amino acid sequence comprising SEQ ID NO.: 194, SEQ ID NO.: 195, SEQ ID NO.: 196, SEQ ID NO.: 197, SEQ ID NO.: 198, and SEQ ID NO.: 199; s) an amino acid sequence comprising SEQ ID NO.: 200, SEQ ID NO.: 201, SEQ ID NO.: 202, SEQ ID NO.: 203, SEQ ID NO.: 204, and SEQ ID NO.: 205; or t) an amino acid sequence comprising SEQ ID NO.: 206, SEQ ID NO.: 207, SEQ ID NO.: 208, SEQ ID NO.: 209, SEQ ID NO.: 210, and SEQ ID NO.: 211.

[0019] In certain embodiments, a method of treating anemia in a patient is provided. In certain embodiments, the method of treating anemia in a patient comprises administering to the patient a single chain variable fragment wherein the single chain variable fragment comprises: a) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15 and SEQ ID NO. 16; b) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 17, SEQ ID NO. 18, and SEQ ID NO. 19; c) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 20, SEQ ID NO. 21, and SEQ ID NO. 22; d) an amino acid sequence comprising SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 26, SEQ ID NO. 27, and SEQ ID NO. 28; or e) an amino acid sequence comprising SEQ ID NO. 29, SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, and SEQ ID NO. 34; f) an amino acid sequence comprising SEQ ID NO.: 123, SEQ ID NO.: 124, SEQ ID NO.: 125, SEQ ID NO.: 126, SEQ ID NO.: 127, and SEQ ID NO.: 128; g) an amino acid sequence comprising SEQ ID NO.: 129, SEQ ID NO.: 130, SEQ ID NO.: 131, SEQ ID NO.: 132, SEQ ID NO.: 133, and SEQ ID NO.: 134; h) f) an amino acid sequence comprising SEQ ID NO.: 135, SEQ ID NO.: 136, SEQ ID NO.: 212; SEQ ID NO.: 137, SEQ ID NO.: 138, and SEQ ID NO.: 139; i) an amino acid sequence comprising SEQ ID NO.: 140, SEQ ID NO.: 141, SEQ ID NO.: 142, SEQ ID NO.: 143, SEQ ID NO.: 144, and SEQ ID NO.: 145; j) an amino acid sequence comprising SEQ ID NO.: 146, SEQ ID NO.: 147, SEQ ID NO.: 148, SEQ ID NO.: 149, SEQ ID NO.: 150, and SEQ ID NO.: 151; k) an amino acid sequence comprising SEQ ID NO.: 152, SEQ ID NO.: 153, SEQ ID NO.: 154, SEQ ID NO.: 155, SEQ ID NO.: 156, and SEQ ID NO.: 157; l) an amino acid sequence comprising SEQ ID NO.: 158, SEQ ID NO.: 159, SEQ ID NO.: 160, SEQ

ID NO.: 161, SEQ ID NO.: 162, and SEQ ID NO.: 163; m) an amino acid sequence comprising SEQ ID NO.: 164, SEQ ID NO.: 165, SEQ ID NO.: 166, SEQ ID NO.: 167, SEQ ID NO.: 168, and SEQ ID NO.: 169; n) an amino acid sequence comprising SEQ ID NO.: 170, SEQ ID NO.: 171, SEQ ID NO.: 172, SEQ ID NO.: 173, SEQ ID NO.: 174, and SEQ ID NO.: 175; o) an amino acid sequence comprising SEQ ID NO.: 176, SEQ ID NO.: 177, SEQ ID NO.: 178, SEQ ID NO.: 179, SEQ ID NO.: 180, and SEQ ID NO.: 181; p) an amino acid sequence comprising SEQ ID NO.: 182, SEQ ID NO.: 183, SEQ ID NO.: 184, SEQ ID NO.: 185, SEQ ID NO.: 186, and SEQ ID NO.: 187; q) an amino acid sequence comprising SEQ ID NO.: 188, SEQ ID NO.: 189, SEQ ID NO.: 190, SEQ ID NO.: 191, SEQ ID NO.: 192, and SEQ ID NO.: 193; r) an amino acid sequence comprising SEQ ID NO.: 194, SEQ ID NO.: 195, SEQ ID NO.: 196, SEQ ID NO.: 197, SEQ ID NO.: 198, and SEQ ID NO.: 199; s) an amino acid sequence comprising SEQ ID NO.: 200, SEQ ID NO.: 201, SEQ ID NO.: 202, SEQ ID NO.: 203, SEQ ID NO.: 204, and SEQ ID NO.: 205; or t) an amino acid sequence comprising SEQ ID NO.: 206, SEQ ID NO.: 207, SEQ ID NO.: 208, SEQ ID NO.: 209, SEQ ID NO.: 210, and SEQ ID NO.: 211.

[0020] In certain embodiments, a method of promoting tissue protection in a patient is provided. In certain embodiments, the method of promoting tissue protection in a patient comprises administering to the patient a single chain variable fragment wherein the single chain variable fragment comprises: a) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15 and SEQ ID NO. 16; b) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 17, SEQ ID NO. 18, and SEQ ID NO. 19; c) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 20, SEQ ID NO. 21, and SEQ ID NO. 22; d) an amino acid sequence comprising SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 26, SEQ ID NO. 27, and SEQ ID NO. 28; or e) an amino acid sequence comprising SEQ ID NO. 29, SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, and SEQ ID NO. 34; f) an amino acid sequence comprising SEQ ID NO.: 123, SEQ ID NO.: 124, SEQ ID NO.: 125, SEQ ID NO.: 126, SEQ ID NO.: 127, and SEQ ID NO.: 128; g) an amino acid sequence comprising SEQ ID NO.: 129, SEQ ID NO.: 130, SEQ ID NO.: 131, SEQ ID NO.: 132, SEQ ID NO.: 133, and SEQ ID NO.: 134; h) f) an amino acid sequence comprising SEQ ID NO.: 135, SEQ ID NO.: 136, SEQ ID NO.: 212; SEQ ID NO.: 137, SEQ ID NO.: 138, and SEQ ID NO.: 139; i) an amino acid sequence comprising SEQ ID NO.: 140, SEQ ID NO.: 141, SEQ ID NO.: 142, SEQ ID NO.: 143, SEQ ID NO.: 144, and SEQ ID NO.: 145; j) an amino acid sequence comprising SEQ ID NO.: 146, SEQ ID NO.: 147, SEQ ID NO.: 148, SEQ ID NO.: 149, SEQ ID NO.: 150, and SEQ ID NO.: 151; k) an amino acid sequence comprising SEQ ID NO.: 152, SEQ ID NO.: 153, SEQ ID NO.: 154, SEQ ID NO.: 155, SEQ ID NO.: 156, and SEQ ID NO.: 157; l) an amino acid sequence comprising SEQ ID NO.: 158, SEQ ID NO.: 159, SEQ ID NO.: 160, SEQ ID NO.: 161, SEQ ID NO.: 162, and SEQ ID NO.: 163; m) an amino acid sequence comprising SEQ ID NO.: 164, SEQ ID NO.: 165, SEQ ID NO.: 166, SEQ ID NO.: 167, SEQ ID NO.: 168, and SEQ ID NO.: 169; n) an amino acid sequence comprising SEQ ID NO.: 170, SEQ ID NO.: 171, SEQ ID NO.: 172, SEQ ID NO.: 173, SEQ ID NO.: 174, and SEQ ID NO.: 175; o) an amino acid sequence comprising SEQ ID NO.: 176, SEQ ID NO.: 177, SEQ ID NO.: 178, SEQ ID NO.: 179, SEQ ID NO.: 180, and SEQ ID NO.: 181; p) an amino acid sequence comprising SEQ ID NO.: 182, SEQ ID NO.: 183, SEQ ID NO.: 184, SEQ ID NO.: 185, SEQ ID NO.: 186, and SEQ ID NO.: 187; q) an amino acid sequence comprising SEQ ID NO.: 188, SEQ ID NO.: 189, SEQ ID NO.: 190, SEQ ID NO.: 191, SEQ ID NO.: 192, and SEQ ID NO.: 193; r) an amino acid sequence comprising SEQ ID NO.: 194, SEQ ID NO.: 195, SEQ ID NO.: 196, SEQ ID NO.: 197, SEQ ID NO.: 198, and SEQ ID NO.: 199; s) an amino acid sequence comprising SEQ ID NO.: 200, SEQ ID NO.: 201, SEQ ID NO.: 202, SEQ ID NO.: 203, SEQ ID NO.: 204, and SEQ ID NO.: 205; or t) an amino acid sequence comprising SEQ ID NO.: 206, SEQ ID NO.: 207, SEQ ID NO.: 208, SEQ ID NO.: 209, SEQ ID NO.: 210, and SEQ ID NO.: 211.

[0021] In certain embodiments, a method of activating an endogenous activity of an erythropoietin receptor in a mammal is provided. In certain embodiments, the method of activating an endogenous activity of an erythropoietin receptor in a mammal comprises administering to the mammal an amount of a single chain variable fragment wherein the single chain variable fragment comprises: a) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15 and SEQ ID NO. 16; b) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 17, SEQ ID NO. 18, and SEQ ID NO. 19; c) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 20, SEQ ID NO. 21, and SEQ ID NO. 22; d) an amino acid sequence comprising SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 26, SEQ ID NO. 27, and SEQ ID NO. 28; or e) an amino acid sequence comprising SEQ ID NO. 29, SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, and SEQ ID NO. 34; f) an amino acid sequence comprising SEQ ID NO.: 123, SEQ ID NO.: 124, SEQ ID NO.: 125, SEQ ID NO.: 126, SEQ ID NO.: 127, and SEQ ID NO.: 128; g) an amino acid sequence comprising SEQ ID NO.: 129, SEQ ID NO.: 130, SEQ ID NO.: 131, SEQ ID NO.: 132, SEQ ID NO.: 133, and SEQ ID NO.: 134; h) f) an amino acid sequence comprising SEQ ID NO.: 135, SEQ ID NO.: 136, SEQ ID NO.: 212; SEQ ID NO.: 137, SEQ ID NO.: 138, and SEQ ID NO.: 139; i) an amino acid sequence comprising SEQ ID NO.: 140, SEQ ID NO.: 141, SEQ ID NO.: 142, SEQ ID NO.: 143, SEQ ID NO.: 144, and SEQ ID NO.: 145; j) an amino acid sequence comprising SEQ ID NO.: 146, SEQ ID NO.: 147, SEQ ID NO.: 148, SEQ ID NO.: 149, SEQ ID NO.: 150, and SEQ ID NO.: 151; k) an amino acid sequence comprising SEQ ID NO.: 152, SEQ ID NO.: 153, SEQ ID NO.: 154, SEQ ID NO.: 155, SEQ ID NO.: 156, and SEQ ID NO.: 157; l) an amino acid sequence comprising SEQ ID NO.: 158, SEQ ID NO.: 159, SEQ ID NO.: 160, SEQ ID NO.: 161, SEQ ID NO.: 162, and SEQ ID NO.: 163; m) an amino acid sequence comprising SEQ ID NO.: 164, SEQ ID NO.: 165, SEQ ID NO.: 166, SEQ ID NO.: 167, SEQ ID NO.: 168, and SEQ ID NO.: 169; n) an amino acid sequence comprising SEQ ID NO.: 170, SEQ ID NO.: 171, SEQ ID NO.: 172, SEQ ID NO.: 173, SEQ ID NO.: 174, and SEQ ID NO.: 175; o) an amino acid sequence comprising SEQ ID NO.: 176, SEQ ID NO.: 177, SEQ ID NO.: 178, SEQ ID NO.: 179, SEQ ID NO.: 180, and SEQ ID NO.: 181; p) an amino acid sequence comprising SEQ ID NO.: 182, SEQ ID NO.: 183, SEQ ID NO.: 184, SEQ ID NO.: 185, SEQ ID NO.: 186, and SEQ ID NO.: 187; q) an amino acid sequence comprising SEQ ID NO.: 188, SEQ ID NO.: 189, SEQ ID NO.: 190, SEQ

ID NO.: 191, SEQ ID NO.: 192, and SEQ ID NO.: 193; r) an amino acid sequence comprising SEQ ID NO.: 194, SEQ ID NO.: 195, SEQ ID NO.: 196, SEQ ID NO.: 197, SEQ ID NO.: 198, and SEQ ID NO.: 199; s) an amino acid sequence comprising SEQ ID NO.: 200, SEQ ID NO.: 201, SEQ ID NO.: 202, SEQ ID NO.: 203, SEQ ID NO.: 204, and SEQ ID NO.: 205; or t) an amino acid sequence comprising SEQ ID NO.: 206, SEQ ID NO.: 207, SEQ ID NO.: 208, SEQ ID NO.: 209, SEQ ID NO.: 210, and SEQ ID NO.: 211.

[0022] In certain embodiments, an antibody is provided. In certain embodiments, the antibody comprises: a) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15 and SEQ ID NO. 16; b) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 17, SEQ ID NO. 18, and SEQ ID NO. 19; c) an amino acid sequence comprising SEQ ID NO. 1.1, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 20, SEQ ID NO. 21, and SEQ ID NO. 22; d) an amino acid sequence comprising SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 26, SEQ ID NO. 27, and SEQ ID NO. 28; or e) an amino acid sequence comprising SEQ ID NO. 29, SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, and SEQ ID NO. 34; f) an amino acid sequence comprising SEQ ID NO.: 123, SEQ ID NO.: 124, SEQ ID NO.: 125, SEQ ID NO.: 126, SEQ ID NO.: 127, and SEQ ID NO.: 128; g) an amino acid sequence comprising SEQ ID NO.: 129, SEQ ID NO.: 130, SEQ ID NO.: 131, SEQ ID NO.: 132, SEQ ID NO.: 133, and SEQ ID NO.: 134; h) f) an amino acid sequence comprising SEQ ID NO.: 135, SEQ ID NO.: 136, SEQ ID NO.: 212; SEQ ID NO.: 137, SEQ ID NO.: 138, and SEQ ID NO.: 139; i) an amino acid sequence comprising SEQ ID NO.: 140, SEQ ID NO.: 141, SEQ ID NO.: 142, SEQ ID NO.: 143, SEQ ID NO.: 144, and SEQ ID NO.: 145; j) an amino acid sequence comprising SEQ ID NO.: 146, SEQ ID NO.: 147, SEQ ID NO.: 148, SEQ ID NO.: 149, SEQ ID NO.: 150, and SEQ ID NO.: 151; k) an amino acid sequence comprising SEQ ID NO.: 152, SEQ ID NO.: 153, SEQ ID NO.: 154, SEQ ID NO.: 155, SEQ ID NO.: 156, and SEQ ID NO.: 157; l) an amino acid sequence comprising SEQ ID NO.: 158, SEQ ID NO.: 159, SEQ ID NO.: 160, SEQ ID NO.: 161, SEQ ID NO.: 162, and SEQ ID NO.: 163; m) an amino acid sequence comprising SEQ ID NO.: 164, SEQ ID NO.: 165, SEQ ID NO.: 166, SEQ ID NO.: 167, SEQ ID NO.: 168, and SEQ ID NO.: 169; n) an amino acid sequence comprising SEQ ID NO.: 170, SEQ ID NO.: 171, SEQ ID NO.: 172, SEQ ID NO.: 173, SEQ ID NO.: 174, and SEQ ID NO.: 175; o) an amino acid sequence comprising SEQ ID NO.: 176, SEQ ID NO.: 177, SEQ ID NO.: 178, SEQ ID NO.: 179, SEQ ID NO.: 180, and SEQ ID NO.: 181; p) an amino acid sequence comprising SEQ ID NO.: 182, SEQ ID NO.: 183, SEQ ID NO.: 184, SEQ ID NO.: 185, SEQ ID NO.: 186, and SEQ ID NO.: 187; q) an amino acid sequence comprising SEQ ID NO.: 188, SEQ ID NO.: 189, SEQ ID NO.: 190, SEQ ID NO.: 191, SEQ ID NO.: 192, and SEQ ID NO.: 193; r) an amino acid sequence comprising SEQ ID NO.: 194, SEQ ID NO.: 195, SEQ ID NO.: 196, SEQ ID NO.: 197, SEQ ID NO.: 198, and SEQ ID NO.: 199; s) an amino acid sequence comprising SEQ ID NO.: 200, SEQ ID NO.: 201, SEQ ID NO.: 202, SEQ ID NO.: 203, SEQ ID NO.: 204, and SEQ ID NO.: 205; or t) an amino acid sequence comprising SEQ ID NO.: 206, SEQ ID NO.: 207, SEQ ID NO. 208, SEQ ID NO.: 209, SEQ ID NO.: 210, and SEQ ID NO.: 211.

[0023] In certain embodiments, a method of treating anemia in a patient is provided. In certain embodiments, the method of treating anemia in a patient comprises administering to the patient an antibody wherein the antibody comprises: a) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15 and SEQ ID NO. 16; b) an amino acid sequence comprising SEQ ID, NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 17, SEQ ID NO. 18, and SEQ ID NO. 19; c) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 20, SEQ ID NO. 21, and SEQ ID NO. 22; d) an amino acid sequence comprising SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID, NO. 25, SEQ ID NO. 26, SEQ ID NO. 27, and SEQ ID NO. 28; or e) an amino acid sequence comprising SEQ ID NO. 29, SEQ ID NO. 30, SEQ ID. NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, and SEQ ID NO. 34; f) an amino acid sequence comprising SEQ ID NO.: 123, SEQ ID NO.: 124, SEQ ID NO.: 125, SEQ ID NO.: 126, SEQ ID NO.: 127, and SEQ ID NO.: 128; g) an amino acid sequence comprising SEQ ID NO.: 129, SEQ ID NO.: 130, SEQ ID NO.: 131, SEQ ID NO.: 132, SEQ ID NO.: 133, and SEQ ID NO.: 134; h) f) an amino acid sequence comprising SEQ ID NO.: 135, SEQ ID NO.: 136, SEQ ID NO.: 212; SEQ ID NO.: 137, SEQ ID NO.: 138, and SEQ ID NO.: 139; i) an amino acid sequence comprising SEQ ID NO.: 140, SEQ ID NO.: 141, SEQ ID NO.: 142, SEQ ID NO.: 143, SEQ ID NO.: 144, and SEQ ID NO.: 145; j) an amino acid sequence comprising SEQ ID NO.: 146, SEQ ID NO.: 147, SEQ ID NO.: 148, SEQ ID NO.: 149, SEQ ID NO.: 150, and SEQ ID NO.: 151; k) an amino acid sequence comprising SEQ ID NO.: 152, SEQ ID NO.: 153, SEQ ID NO.: 154, SEQ ID NO.: 155, SEQ ID NO.: 156, and SEQ ID NO.: 157; l) an amino acid sequence comprising SEQ ID NO.: 158, SEQ ID NO.: 159, SEQ ID NO.: 160, SEQ ID NO.: 161, SEQ ID NO.: 162, and SEQ ID NO.: 163; m) an amino acid sequence comprising SEQ ID NO.: 164, SEQ ID NO.: 165, SEQ ID NO.: 166, SEQ ID NO.: 167, SEQ ID NO.: 168, and SEQ ID NO.: 169; n) an amino acid sequence comprising SEQ ID NO.: 170, SEQ ID NO.: 171, SEQ ID NO.: 172, SEQ ID NO.: 173, SEQ ID NO.: 174, and SEQ ID NO.: 175; o) an amino acid sequence comprising SEQ ID NO.: 176, SEQ ID NO.: 177, SEQ ID NO.: 178, SEQ ID NO.: 179, SEQ ID NO.: 180, and SEQ ID NO.: 181; p) an amino acid sequence comprising SEQ ID NO.: 182, SEQ ID NO.: 183, SEQ ID NO.: 184, SEQ ID NO.: 185, SEQ ID NO.: 186, and SEQ ID NO.: 187; q) an amino acid sequence comprising SEQ ID NO.: 188, SEQ ID NO.: 189, SEQ ID NO.: 190, SEQ ID NO.: 191, SEQ ID NO.: 192, and SEQ ID NO.: 193; r) an amino acid sequence comprising SEQ ID NO.: 194, SEQ ID NO.: 195, SEQ ID NO.: 196, SEQ ID NO.: 197, SEQ ID NO.: 198, and SEQ ID NO.: 199; s) an amino acid sequence comprising SEQ ID NO.: 200, SEQ ID NO.: 201, SEQ ID NO.: 202, SEQ ID NO.: 203, SEQ ID NO.: 204, and SEQ ID NO.: 205; or t) an amino acid sequence comprising SEQ ID NO.: 206, SEQ ID NO.: 207, SEQ ID NO.: 208, SEQ ID NO.: 209, SEQ ID NO.: 210, and SEQ ID NO.: 211.

[0024] In certain embodiments, a method of promoting tissue protection in a patient is provided. In certain embodiments, the method of promoting tissue protection in a patient comprises administering to the patient an antibody wherein the antibody comprises: a) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15 and SEQ ID NO. 16; b) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 17, SEQ ID NO. 18, and SEQ ID NO. 19; c) an amino acid sequence comprising SEQ ID

NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 20, SEQ ID NO. 21, and SEQ ID NO. 22; d) an amino acid sequence comprising SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 26, SEQ ID NO. 27, and SEQ ID NO. 28; or e) an amino acid sequence comprising SEQ ID NO. 29, SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, and SEQ ID NO. 34; f) an amino acid sequence comprising SEQ ID NO.: 123, SEQ ID NO.: 124, SEQ ID NO.: 125, SEQ ID NO.: 126, SEQ ID NO.: 127, and SEQ ID NO.: 128; g) an amino acid sequence comprising SEQ ID NO.: 129, SEQ ID NO.: 130, SEQ ID NO.: 131, SEQ ID NO.: 132, SEQ ID NO.: 133, and SEQ ID NO.: 134; h) f) an amino acid sequence comprising SEQ ID NO.: 135, SEQ ID NO.: 136, SEQ ID NO.: 212; SEQ ID NO.: 137, SEQ ID NO.: 138, and SEQ ID NO.: 139; i) an amino acid sequence comprising SEQ ID NO.: 140, SEQ ID NO.: 141, SEQ ID NO.: 142, SEQ ID NO.: 143, SEQ ID NO.: 144, and SEQ ID NO.: 145; j) an amino acid sequence comprising SEQ ID NO.: 146, SEQ ID NO.: 147, SEQ ID NO.: 148, SEQ ID NO.: 149, SEQ ID NO.: 150, and SEQ ID NO.: 151; k) an amino acid sequence comprising SEQ ID NO.: 152, SEQ ID NO.: 153, SEQ ID NO.: 154, SEQ ID NO.: 155, SEQ ID NO.: 156, and SEQ ID NO.: 157; l) an amino acid sequence comprising SEQ ID NO.: 158, SEQ ID NO.: 159, SEQ ID NO.: 160, SEQ ID NO.: 161, SEQ ID NO.: 162, and SEQ ID NO.: 163; m) an amino acid sequence comprising SEQ ID NO.: 164, SEQ ID NO.: 165, SEQ ID NO.: 166, SEQ ID NO.: 167, SEQ ID NO.: 168, and SEQ ID NO.: 169; n) an amino acid sequence comprising SEQ ID NO.: 170, SEQ ID NO.: 171, SEQ ID NO.: 172, SEQ ID NO.: 173, SEQ ID NO.: 174, and SEQ ID NO.: 175; o) an amino acid sequence comprising SEQ ID NO.: 176, SEQ ID NO.: 177, SEQ ID NO.: 178, SEQ ID NO.: 179, SEQ ID NO.: 180, and SEQ ID NO.: 181; p) an amino acid sequence comprising SEQ ID NO.: 182, SEQ ID NO.: 183, SEQ ID NO.: 184, SEQ ID NO.: 185, SEQ ID NO.: 186, and SEQ ID NO.: 187; q) an amino acid sequence comprising SEQ ID NO.: 188, SEQ ID NO.: 189, SEQ ID NO.: 190, SEQ ID NO.: 191, SEQ ID NO.: 192, and SEQ ID NO.: 193; r) an amino acid sequence comprising SEQ ID NO.: 194, SEQ ID NO.: 195, SEQ ID NO.: 196, SEQ ID NO.: 197, SEQ ID NO.: 198, and SEQ ID NO.: 199; s) an amino acid sequence comprising SEQ ID NO.: 200, SEQ ID NO.: 201, SEQ ID NO.: 202, SEQ ID NO.: 203, SEQ ID NO.: 204, and SEQ ID NO.: 205; or t) an amino acid sequence comprising SEQ ID NO.: 206, SEQ ID NO.: 207, SEQ ID NO.: 208, SEQ ID NO.: 209, SEQ ID NO.: 210, and SEQ ID NO.: 211.

[0025] In certain embodiments, a method of activating an endogenous activity of an erythropoietin receptor in a mammal is provided. In certain embodiments, the method of activating an endogenous activity of an erythropoietin receptor in a mammal comprises administering to the mammal an amount of an antibody wherein the antibody comprises: a) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15 and SEQ ID NO. 16; b) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 17, SEQ ID NO. 18, and SEQ ID NO. 19; c) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 20, SEQ ID NO. 21, and SEQ ID NO. 22; d) an amino acid sequence comprising SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 26, SEQ ID NO. 27, and SEQ ID NO. 28; or e) an amino acid sequence comprising SEQ ID NO. 29, SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, and SEQ ID NO. 34; f) an amino acid sequence comprising SEQ ID NO.: 123, SEQ ID NO.: 124, SEQ ID NO.: 125, SEQ ID NO.: 126, SEQ ID NO.: 127, and SEQ ID NO.: 128; g) an amino acid sequence comprising SEQ ID NO.: 129, SEQ ID NO.: 130, SEQ ID NO.: 131, SEQ ID NO.: 132, SEQ ID NO.: 133, and SEQ ID NO.: 134; h) f) an amino acid sequence comprising SEQ ID NO.: 135, SEQ ID NO.: 136, SEQ ID NO.: 212; SEQ ID NO.: 137, SEQ ID NO.: 138, and SEQ ID NO.: 139; i) an amino acid sequence comprising SEQ ID NO.: 140, SEQ ID NO.: 141, SEQ ID NO.: 142, SEQ ID NO.: 143, SEQ ID NO.: 144, and SEQ ID NO.: 145; j) an amino acid sequence comprising SEQ ID NO.: 146, SEQ ID NO.: 147, SEQ ID NO.: 148, SEQ ID NO.: 149, SEQ ID NO.: 150, and SEQ ID NO.: 151; k) an amino acid sequence comprising SEQ ID NO.: 152, SEQ ID NO.: 153, SEQ ID NO.: 154, SEQ ID NO.: 155, SEQ ID NO.: 156, and SEQ ID NO.: 157; l) an amino acid sequence comprising SEQ ID NO.: 158, SEQ ID NO.: 159, SEQ ID NO.: 160, SEQ ID NO.: 161, SEQ ID NO.: 162, and SEQ ID NO.: 163; m) an amino acid sequence comprising SEQ ID NO.: 164, SEQ ID NO.: 165, SEQ ID NO.: 166, SEQ ID NO.: 167, SEQ ID NO.: 168, and SEQ ID NO.: 169; n) an amino acid sequence comprising SEQ ID NO.: 170, SEQ ID NO.: 171, SEQ ID NO.: 172, SEQ ID NO.: 173, SEQ ID NO.: 174, and SEQ ID NO.: 175; o) an amino acid sequence comprising SEQ ID NO.: 176, SEQ ID NO.: 177, SEQ ID NO.: 178, SEQ ID NO.: 179, SEQ ID NO.: 180, and SEQ ID NO.: 181; p) an amino acid sequence comprising SEQ ID NO.: 182, SEQ ID NO.: 183, SEQ ID NO.: 184, SEQ ID NO.: 185, SEQ ID NO.: 186, and SEQ ID NO.: 187; q) an amino acid sequence comprising SEQ ID NO.: 188, SEQ ID NO.: 189, SEQ ID NO.: 190, SEQ ID NO.: 191, SEQ ID NO.: 192, and SEQ ID NO.: 193; r) an amino acid sequence comprising SEQ ID NO.: 194, SEQ ID NO.: 195, SEQ ID NO.: 196, SEQ ID NO.: 197, SEQ ID NO.: 198, and SEQ ID NO.: 199; s) an amino acid sequence comprising SEQ ID NO.: 200, SEQ ID NO.: 201, SEQ ID NO.: 202, SEQ ID NO.: 203, SEQ ID NO.: 204, and SEQ ID NO.: 205; or t) an amino acid sequence comprising SEQ ID NO.: 206, SEQ ID NO.: 207, SEQ ID NO.: 208, SEQ ID NO.: 209, SEQ ID NO.: 210, and SEQ ID NO.: 211.

[0026] In certain embodiments, an antibody is provided. In certain embodiments, the antibody comprises: a) an amino acid sequence comprising SEQ ID NO. 45; b) an amino acid sequence comprising SEQ ID NO. 46; c) an amino acid sequence comprising SEQ ID NO. 47; d) an amino acid sequence comprising SEQ ID NO. 48; or e) an amino acid sequence comprising SEQ ID NO. 49.

[0027] In certain embodiments, a method of treating anemia in a patient is provided. In certain embodiments, the method of treating anemia in a patient comprises administering to the patient an antibody wherein the antibody comprises: a) an amino acid sequence comprising SEQ ID NO. 45; b) an amino acid sequence comprising SEQ ID NO. 46; c) an amino acid sequence comprising SEQ ID NO. 47; d) an amino acid sequence comprising SEQ ID NO. 48; or e) an amino acid sequence comprising SEQ ID NO. 49.

[0028] In certain embodiments, a method of promoting tissue protection in a patient is provided. In certain embodiments, the method of promoting tissue protection in a patient comprises administering to the patient an antibody wherein the antibody comprises: a) an amino acid sequence comprising SEQ ID NO. 45; b) an amino acid sequence comprising SEQ ID NO. 46; c) an amino acid sequence comprising SEQ

ID NO. 47; d) an amino acid sequence comprising SEQ ID NO. 48; or e) an amino acid sequence comprising SEQ ID NO. 49.

[0029] In certain embodiments, a method of activating an endogenous activity of an erythropoietin receptor in a mammal is provided. In certain embodiments, the method of activating an endogenous activity of an erythropoietin receptor in a mammal comprises administering to the mammal an amount of an antibody wherein the antibody comprises: a) an amino acid sequence comprising SEQ ID NO. 45; b) an amino acid sequence comprising SEQ ID NO. 46; c) an amino acid sequence comprising SEQ ID NO. 47; d) an amino acid sequence comprising SEQ ID NO. 48; or e) an amino acid sequence comprising SEQ ID NO. 49.

[0030] In certain embodiments, a method of making a single chain variable fragment is provided. In certain embodiments, In certain embodiments, a method of making a single chain variable fragment comprises expressing the single chain variable fragment in a host cell, wherein the single chain variable fragment comprises: a) an amino acid sequence comprising SEQ ID NO. 1 and SEQ ID NO. 2; b) an amino acid sequence comprising SEQ ID NO. 3 and SEQ ID NO. 4; c) an amino acid sequence comprising SEQ ID NO. 5 and SEQ ID NO. 6; d) an amino acid sequence comprising SEQ ID NO. 7 and SEQ ID NO. 8; or e) an amino acid sequence comprising SEQ ID NO. 9 and SEQ ID NO. 10; f) an amino acid sequence comprising SEQ ID NO. 56 and SEQ ID NO. 58; g) an amino'acid sequence comprising SEQ ID NO. 60 and SEQ ID NO. 62; h) an amino acid sequence comprising SEQ ID NO. 64 and SEQ ID NO. 66; i) an amino acid sequence comprising SEQ ID NO. 68 and SEQ ID NO. 70; j) an amino acid sequence comprising SEQ ID NO. 72 and SEQ ID NO. 74; k) an amino acid sequence comprising SEQ ID NO. 76 and SEQ ID NO. 78; l) an amino acid sequence comprising SEQ ID NO. 80 and SEQ ID NO. 82; m) an amino acid sequence comprising SEQ ID NO. 84 and SEQ ID NO. 86; n) an amino acid sequence comprising SEQ ID NO. 88 and SEQ ID NO. 90; o) an amino acid sequence comprising SEQ ID NO. 92 and SEQ ID NO. 94; p) an amino acid sequence comprising SEQ ID NO. 96 and SEQ ID NO. 98; q) an amino acid sequence comprising SEQ ID NO. 100 and SEQ ID NO. 102; r) an amino acid sequence comprising SEQ ID NO. 104 and SEQ ID NO. 106; s) an amino acid sequence comprising SEQ ID NO. 108 and SEQ ID NO. 110; or t) an amino acid sequence comprising SEQ ID NO. 112 and SEQ ID NO. 114.

[0031] In certain embodiments, a method of making a single chain variable fragment fused to an Fc is provided. In certain embodiments, a method of making a single chain variable fragment fused to an Fc comprises expressing the single chain variable fragment fused to an Fc in a host cell, wherein the single chain variable fragment comprises: a) an amino acid sequence comprising SEQ ID NO. 1 and SEQ ID NO. 2; b) an amino acid sequence comprising SEQ ID NO. 3 and SEQ ID NO. 4; c) an amino acid sequence comprising SEQ ID NO. 5 and SEQ ID NO. 6; d) an amino acid sequence comprising SEQ ID NO. 7 and SEQ ID NO. 8; or e) an amino acid sequence comprising SEQ ID NO. 9 and SEQ ID NO. 10; f) an amino acid sequence comprising SEQ ID NO. 56 and SEQ ID NO. 58; g) an amino acid sequence comprising SEQ ID NO. 60 and SEQ ID NO. 62; h) an amino acid sequence comprising SEQ ID NO. 64 and SEQ ID NO. 66; i) an amino acid sequence comprising SEQ ID NO. 68 and SEQ ID NO. 70; j) an amino acid sequence comprising SEQ ID NO. 72 and SEQ ID NO. 74; k) an amino acid sequence comprising SEQ ID NO. 76 and SEQ ID NO. 78; l) an amino acid sequence comprising SEQ ID NO. 80 and SEQ ID NO. 82; m) an amino acid sequence comprising SEQ ID NO. 84 and SEQ ID NO. 86; n) an amino acid sequence comprising SEQ ID NO. 88 and SEQ ID NO. 90; o) an amino acid sequence comprising SEQ ID NO. 92 and SEQ ID NO. 94; p) an amino acid sequence comprising SEQ ID NO. 96 and SEQ ID NO. 98; q) an amino acid sequence comprising SEQ ID NO. 100 and SEQ ID NO. 102; r) an amino acid sequence comprising SEQ ID NO. 104 and SEQ ID NO. 106; s) an amino acid sequence comprising SEQ ID NO. 108 and SEQ ID NO. 110; or t) an amino acid sequence comprising SEQ ID NO. 112 and SEQ ID NO. 114.

[0032] In certain embodiments, a method of making a single chain variable fragment is provided. In certain embodiments, a method of making a single chain variable fragment comprises expressing the single chain variable fragment in a host cell, wherein the single chain variable fragment comprises: a) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15 and SEQ ID NO. 16; b) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 17, SEQ ID NO. 18, and SEQ ID NO. 19; c) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 20, SEQ ID NO. 21, and SEQ ID NO. 22; d) an amino acid sequence comprising SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 26, SEQ ID NO. 27, and SEQ ID NO. 28; or e) an amino acid sequence comprising SEQ ID NO. 29, SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, and SEQ ID NO. 34; f) an amino acid sequence comprising SEQ ID NO.: 123, SEQ ID NO.: 124, SEQ ID NO.: 125, SEQ ID NO.: 126, SEQ ID NO.: 127, and SEQ ID NO.: 128; g) an amino acid sequence comprising SEQ ID NO.: 129, SEQ ID NO.: 130, SEQ ID NO.: 131, SEQ ID NO.: 132, SEQ ID NO.: 133, and SEQ ID NO.: 134; h) f) an amino acid sequence comprising SEQ ID NO.: 135, SEQ ID NO.: 136, SEQ ID NO.: 212; SEQ ID NO.: 137, SEQ ID NO.: 138, and SEQ ID NO.: 139; i) an amino acid sequence comprising SEQ ID NO.: 140, SEQ ID NO.: 141, SEQ ID NO.: 142, SEQ ID NO.: 143, SEQ ID NO.: 144, and SEQ ID NO.: 145; j) an amino acid sequence comprising SEQ ID NO.: 146, SEQ ID NO.: 147, SEQ ID NO.: 148, SEQ ID NO.: 149, SEQ ID NO.: 150, and SEQ ID NO.: 151; k) an amino acid sequence comprising SEQ ID NO.: 152, SEQ ID NO.: 153, SEQ ID NO.: 154, SEQ ID NO.: 155, SEQ ID NO.: 156, and SEQ ID NO.: 157; l) an amino acid sequence comprising SEQ ID NO.: 158, SEQ ID NO.: 159, SEQ ID NO.: 160, SEQ ID NO.: 161, SEQ ID NO.: 162, and SEQ ID NO.: 163; m) an amino acid sequence comprising SEQ ID NO.: 164, SEQ ID NO.: 165, SEQ ID NO.: 166, SEQ ID NO.: 167, SEQ ID NO.: 168, and SEQ ID NO.: 169; n) an amino acid sequence comprising SEQ ID NO.: 170, SEQ ID NO.: 171, SEQ ID NO.: 172, SEQ ID NO.: 173, SEQ ID NO.: 174, and SEQ ID NO.: 175; o) an amino acid sequence comprising SEQ ID NO.: 176, SEQ ID NO.: 177, SEQ ID NO.: 178, SEQ ID NO.: 179, SEQ ID NO.: 180, and SEQ ID NO.: 181; p) an amino acid sequence comprising SEQ ID NO.: 182, SEQ ID NO.: 183, SEQ ID NO.: 184, SEQ ID NO.: 185, SEQ ID NO.: 186, and SEQ ID NO.: 187; q) an amino acid sequence comprising SEQ ID NO.: 188, SEQ ID NO.: 189, SEQ ID NO.: 190, SEQ ID NO.: 191, SEQ ID NO.: 192, and SEQ ID NO.: 193; r) an amino acid sequence comprising SEQ ID NO.: 194, SEQ ID NO.: 195, SEQ ID NO.:

196, SEQ ID NO.: 197, SEQ ID NO.: 198, and SEQ ID NO.: 199; s) an amino acid sequence comprising SEQ ID NO.: 200, SEQ ID NO.: 201, SEQ ID NO.: 202, SEQ ID NO.: 203, SEQ ID NO.: 204, and SEQ ID NO.: 205; or t) an amino acid sequence comprising SEQ ID NO.: 206, SEQ ID NO.: 207, SEQ ID NO.: 208, SEQ ID NO.: 209, SEQ ID NO.: 210, and SEQ ID NO.: 211.

[0033] In certain embodiments, a method of making a single chain variable fragment fused to an Fc is provided. In certain embodiments, a method of making a single chain variable fragment fused to an Fc comprises expressing the single chain variable fragment fused to an Fc in a host cell, wherein the single chain variable fragment comprises: a) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15 and SEQ ID NO. 16; b) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 17, SEQ ID NO. 18, and SEQ ID NO. 19; c) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 20, SEQ ID NO. 21, and SEQ ID NO. 22; d) an amino acid sequence comprising SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 26, SEQ ID NO. 27, and SEQ ID NO. 28; or e) an amino acid sequence comprising SEQ ID NO. 29, SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, and SEQ ID NO. 34; f) an amino acid sequence comprising SEQ ID NO.: 123, SEQ ID NO.: 124, SEQ ID NO.: 125, SEQ ID NO.: 126, SEQ ID NO.: 127, and SEQ ID NO.: 128; g) an amino acid sequence comprising SEQ ID NO.: 129, SEQ ID NO.: 130, SEQ ID NO.: 131, SEQ ID NO.: 132, SEQ ID NO.: 133, and SEQ ID NO.: 134; h) f) an amino acid sequence comprising SEQ ID NO.: 135, SEQ ID NO.: 136, SEQ ID NO.: 212; SEQ ID NO.: 137, SEQ ID NO.: 138, and SEQ ID NO.: 139; i) an amino acid sequence comprising SEQ ID NO.: 140, SEQ ID NO.: 141, SEQ ID NO.: 142, SEQ ID NO.: 143, SEQ ID NO.: 144, and SEQ ID NO.: 145; j) an amino acid sequence comprising SEQ ID NO.: 146, SEQ ID NO.: 147, SEQ ID NO.: 148, SEQ ID NO.: 149, SEQ ID NO.: 150, and SEQ ID NO.: 151; k) an amino acid sequence comprising SEQ ID NO.: 152, SEQ ID NO.: 153, SEQ ID NO.: 154, SEQ ID NO.: 155, SEQ ID NO.: 156, and SEQ ID NO.: 157; l) an amino acid sequence comprising SEQ ID NO.: 158, SEQ ID NO.: 159, SEQ ID NO.: 160, SEQ ID NO.: 161, SEQ ID NO.: 162, and SEQ ID NO.: 163; m) an amino acid sequence comprising SEQ ID NO.: 164, SEQ ID NO.: 165, SEQ ID NO.: 166, SEQ ID NO.: 167, SEQ ID NO.: 168, and SEQ ID NO.: 169; n) an amino acid sequence comprising SEQ ID NO.: 170, SEQ ID NO.: 171, SEQ ID NO.: 172, SEQ ID NO.: 173, SEQ ID NO.: 174, and SEQ ID NO.: 175; o) an amino acid sequence comprising SEQ ID NO.: 176, SEQ ID NO.: 177, SEQ ID NO.: 178, SEQ ID NO.: 179, SEQ ID NO.: 180, and SEQ ID NO.: 181; p) an amino acid sequence comprising SEQ ID NO.: 182, SEQ ID NO.: 183, SEQ ID NO.: 184, SEQ ID NO.: 185, SEQ ID NO.: 186, and SEQ ID NO.: 187; q) an amino acid sequence comprising SEQ ID NO.: 188, SEQ ID NO.: 189, SEQ ID NO.: 190, SEQ ID NO.: 191, SEQ ID NO.: 192, and SEQ ID NO.: 193; r) an amino acid sequence comprising SEQ ID NO.: 194, SEQ ID NO.: 195, SEQ ID NO.: 196, SEQ ID NO.: 197, SEQ ID NO.: 198, and SEQ ID NO.: 199; s) an amino acid sequence comprising SEQ ID NO.: 200, SEQ ID NO.: 201, SEQ ID NO.: 202, SEQ ID NO.: 203, SEQ ID NO.: 204, and SEQ ID NO.: 205; or t) an amino acid sequence comprising SEQ ID NO.: 206, SEQ ID NO.: 207, SEQ ID NO.: 208, SEQ ID NO.: 209, SEQ ID NO.: 210, and SEQ ID NO.: 211.

[0034] In certain embodiments, a method of making a single chain variable fragment fused to an Fc is provided. In certain embodiments, a method of making a single chain variable fragment fused to an Fc comprises expressing the single chain variable fragment fused to an Fc in a host cell, wherein the single chain variable fragment comprises: a) an amino acid sequence comprising SEQ ID NO. 45; b) an amino acid sequence comprising SEQ ID NO. 46; c) an amino acid sequence comprising SEQ ID NO. 47; d) an amino acid sequence comprising SEQ ID NO. 48; or e) an amino acid sequence comprising SEQ ID NO. 49.

[0035] In certain embodiments, a single chain variable fragment is provided. In certain embodiments, the single chain variable fragment specifically binds to: a) at least amino acids F93 and H114 of the extracellular domain of the human Epo Receptor; b) at least amino acids S91, F93, and H114 of the extracellular domain of the human Epo Receptor; c) at least amino acid F93 of the extracellular domain of the human Epo Receptor; d) at least amino acids E62, F93, and M150 of the extracellular domain of the human Epo Receptor; e) at least amino acids V48, E62, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; f) at least amino acids V48, W64, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; g) at least amino acids A44, V48, P63, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; or h) at least amino acids L66 and R99 of the extracellular domain of the human Epo Receptor.

[0036] In certain embodiments, a single chain variable fragment fused to an Fc is provided. In certain embodiments, the single chain variable fragment specifically binds to: a) at least amino acids F93 and H114 of the extracellular domain of the human Epo Receptor; b) at least amino acids S91, F93, and H114 of the extracellular domain of the human Epo Receptor; c) at least amino acid F93 of the extracellular domain of the human Epo Receptor; d) at least amino acids E62, F93, and M150 of the extracellular domain of the human Epo Receptor; e) at least amino acids V48, E62, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; f) at least amino acids V48, W64, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; g) at least amino acids A44, V48, P63, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; or h) at least amino acids L66 and R99 of the extracellular domain of the human Epo Receptor.

[0037] In certain embodiments, a method of treating anemia in a patient is provided. In certain embodiments, the method of treating anemia in a patient comprising administering to the patient a single chain variable fragment wherein the single chain variable fragment specifically binds to: a) at least amino acids F93 and H114 of the extracellular domain of the human Epo Receptor; b) at least amino acids S91, F93, and H114 of the extracellular domain of the human Epo Receptor; c) at least amino acid F93 of the extracellular domain of the human Epo Receptor; d) at least amino acids E62, F93, and M150 of the extracellular domain of the human Epo Receptor; e) at least amino acids V48, E62, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; f) at least amino acids V48, W64, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; g) at least amino acids A44, V48, P63, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; or h) at least amino acids L66 and R99 of the extracellular domain of the human Epo Receptor.

[0038] In certain embodiments, a method of promoting tissue protection in a patient is provided. In certain embodiments, the method of promoting tissue protection in a patient comprises administering to the patient a single chain variable fragment wherein the single chain variable fragment specifically binds to: a) at least amino acids F93 and H114 of the extracellular domain of the human Epo Receptor; b) at least amino acids S91, F93, and H114 of the extracellular domain of the human Epo Receptor; c) at least amino acid F93 of the extracellular domain of the human Epo Receptor; d) at least amino acids E62, F93, and M150 of the extracellular domain of the human Epo Receptor; e) at least amino acids V48, E62, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; f) at least amino acids V48, W64, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; g) at least amino acids A44, V48, P63, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; or h) at least amino acids L66 and R99 of the extracellular domain of the human Epo Receptor.

[0039] In certain embodiments, a method of activating an endogenous activity of an erythropoietin receptor in a mammal is provided. In certain embodiments, the method of activating an endogenous activity of an erythropoietin receptor in a mammal comprises administering to the mammal an amount of a single chain variable fragment wherein the single chain variable fragment specifically binds to: a) at least amino acids F93 and H114 of the extracellular domain of the human Epo Receptor; b) at least amino acids S91, F93, and H114 of the extracellular domain of the human Epo Receptor; c) at least amino acid F93 of the extracellular domain of the human Epo Receptor; d) at least amino acids E62, F93, and M150 of the extracellular domain of the human Epo Receptor; e) at least amino acids V48, E62, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; f) at least amino acids V48, W64, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; g) at least amino acids A44, V48, P63, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; or h) at least amino acids L66 and R99 of the extracellular domain of the human Epo Receptor.

[0040] In certain embodiments, an antibody is provided. In certain embodiments, the antibody specifically binds to: a) at least amino acids F93 and H114 of the extracellular domain of the human Epo Receptor; b) at least amino acids S91, F93, and H114 of the extracellular domain of the human Epo Receptor; c) at least amino acid F93 of the extracellular domain of the human Epo Receptor; d) at least amino acids E62, F93, and M150 of the extracellular domain of the human Epo Receptor; e) at least amino acids V48, E62, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; f) at least amino acids V48, W64, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; g) at least amino acids A44, V48, P63, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; or h) at least amino acids L66 and R99 of the extracellular domain of the human Epo Receptor.

[0041] In certain embodiments, a method of treating anemia in a patient is provided. In certain embodiments, the method of treating anemia in a patient comprises administering to the patient an antibody wherein the antibody specifically binds to: a) at least amino acids F93 and H114 of the extracellular domain of the human Epo Receptor; b) at least amino acids S91, F93, and H114 of the extracellular domain of the human Epo Receptor; c) at least amino acid F93 of the extracellular domain of the human Epo Receptor; d) at least amino acids E62, F93, and M150 of the extracellular domain of the human Epo Receptor; e) at least amino acids V48, E62, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; f) at least amino acids V48, W64, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; g) at least amino acids A44, V48, P63, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; or h) at least amino acids L66 and R99 of the extracellular domain of the human Epo Receptor.

[0042] In certain embodiments, a method of promoting tissue protection in a patient is provided. In certain embodiments, the method of promoting tissue protection in a patient comprises administering to the patient an antibody wherein the antibody specifically binds to: a) at least amino acids F93 and H114 of the extracellular domain of the human Epo Receptor; b) at least amino acids S91, F93, and H114 of the extracellular domain of the human Epo Receptor; c) at least amino acid F93 of the extracellular domain of the human Epo Receptor; d) at least amino acids E62, F93, and M150 of the extracellular domain of the human Epo Receptor; e) at least amino acids V48, E62, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; f) at least amino acids V48, W64, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; g) at least amino acids A44, V48, P63, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; or h) at least amino acids L66 and R99 of the extracellular domain of the human Epo Receptor.

[0043] In certain embodiments, a method of activating an endogenous activity of an erythropoietin receptor in a mammal is provided. In certain embodiments, the method of activating an endogenous activity of an erythropoietin receptor in a mammal comprises administering to the mammal an amount of an antibody wherein the antibody specifically binds to: a) at least amino acids F93 and H114 of the extracellular domain of the human Epo Receptor; b) at least amino acids S91, F93, and H114 of the extracellular domain of the human Epo Receptor; c) at least amino acid F93 of the extracellular domain of the human Epo Receptor; d) at least amino acids E62, F93, and M150 of the extracellular domain of the human Epo Receptor; e) at least amino acids V48, E62, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; f) at least amino acids V48, W64, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; g) at least amino acids A44, V48, P63, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; or h) at least amino acids L66 and R99 of the extracellular domain of the human Epo Receptor.

[0044] In certain embodiments, a method of making a single chain variable fragment is provided. In certain embodiments, the method of making a single chain variable fragment comprises expressing the single chain variable fragment in a host cell. In certain embodiments, the single chain variable fragment specifically binds to: a) at least amino acids F93 and H114 of the extracellular domain of the human Epo Receptor; b) at least amino acids S91, F93, and H114 of the extracellular domain of the human Epo Receptor; c) at least amino acid F93 of the extracellular domain of the human Epo Receptor; d) at least amino acids E62, F93, and M150 of the extracellular domain of the human Epo Receptor; e) at least amino acids V48, E62, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; f) at least amino acids V48, W64, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; g) at least amino acids A44, V48, P63, L66,

R68, and H70 of the extracellular domain of the human Epo Receptor; or h) at least amino acids L66 and R99 of the extracellular domain of the human Epo Receptor.

[0045] In certain embodiments, a method of making a single chain variable fragment fused to an Fc is provided. In certain embodiments, the method of making a single chain variable fragment fused to an Fc comprises expressing the single chain variable fragment fused to an Fc in a host cell. In certain embodiments, the single chain variable fragment specifically binds to: a) at least amino acids F93 and H114 of the extracellular domain of the human Epo Receptor; b) at least amino acids S91, F93, and H114 of the extracellular domain of the human Epo Receptor; c) at least amino acid F93 of the extracellular domain of the human Epo Receptor; d) at least amino acids E62, F93, and M150 of the extracellular domain of the human Epo Receptor; e) at least amino acids V48, E62, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; f) at least amino acids V48, W64, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; g) at least amino acids A44, V48, P63, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; or h) at least amino acids L66 and R99 of the extracellular domain of the human Epo Receptor.

[0046] In certain embodiments, an antibody that binds to human Epo Receptor is provided. In certain embodiments, said antibody comprises one or more sequences selected from: A) a first amino acid sequence comprising: i) a CDR1 having the formula: X_1 YWM X_5, where X_1 is any amino acid and X_5 is any amino acid; ii) a CDR2 having the formula: NIKPDGSEKYV X_{12} SVKG where X_{12} is any amino acid; and iii) a CDR 3 having the formula: VSRGGS X_7 SD where X_7 is any amino acid; and B) a second amino acid sequence comprising: i) a CDR1 having the formula: TGTSSD X_7 G X_9 Y X_{11} YVS where X_7 is any amino acid, and X_9 is any amino acid, and X_{11} is any amino acid; and ii) a CDR2 having the formula: X_1 V X_3 X_4 RPS where X_1 is any amino acid, and X_3 is any amino acid, and X_4 is any amino acid.

[0047] In certain embodiments, a single chain variable fragment that binds to human Epo Receptor is provided. In certain embodiments, the single chain variable fragment comprises one or more sequences selected from: A) a first amino acid sequence comprising: i) a CDR1 having the formula: X_1 YWM X_5, where X_1 is any amino acid and X_5 is any amino acid; ii) a CDR2 having the formula: NIKPDGSEKYV X_{12} SVKG where X_{12} is any amino acid; and iii) a CDR 3 having the formula: VSRGGS X_7 SD where X_7 is any amino acid; and B) a second amino acid sequence comprising: i) a CDR1 having the formula: TGTSSD X_7 G X_9 Y X_{11} YVS where X_7 is any amino acid, and X_9 is any amino acid, and X_{11} is any amino acid; and ii) a CDR2 having the formula: X_1 V X_3 X_4RPS where X_1 is any amino acid, and X_3 is any amino acid, and X is any amino acid.

[0048] In certain embodiments, an antibody is provided that binds to the wild-type human Epo Receptor but fails to bind to a mutant Epo Receptor wherein the amino acid at position 34 of the extracellular domain of the mutant Epo Receptor is Arginine.

[0049] In certain embodiments, an antibody is provided that binds to the wild-type human Epo Receptor but fails to bind to a mutant Epo Receptor wherein the amino acid at position 60 of the extracellular domain of the mutant Epo Receptor is Arginine.

[0050] In certain embodiments, an antibody is provided that binds to the wild-type human Epo Receptor but fails to bind to a mutant Epo Receptor wherein the amino acid at position 88 of the extracellular domain of the mutant Epo Receptor is Arginine.

[0051] In certain embodiments, an antibody is provided that binds to the wild-type human Epo Receptor but fails to bind to a mutant Epo Receptor wherein the amino acid at position 150 of the extracellular domain of the mutant Epo Receptor is Arginine.

[0052] In certain embodiments, an antibody is provided that binds to the wild-type human Epo Receptor but fails to bind to a mutant Epo Receptor wherein the amino acid at position 87 of the extracellular domain of the mutant Epo Receptor is Arginine.

[0053] In certain embodiments, an antibody is provided that binds to the wild-type human Epo Receptor but fails to bind to a mutant Epo Receptor wherein the amino acid at position 63 of the extracellular domain of the mutant Epo Receptor is Arginine.

[0054] In certain embodiments, an antibody is provided that binds to the wild-type human Epo Receptor but fails to bind to a mutant Epo Receptor wherein the amino acid at position 64 of the extracellular domain of the mutant Epo Receptor is Arginine.

[0055] In certain embodiments, an antibody is provided that binds to the wild-type human Epo Receptor but fails to bind to a mutant Epo Receptor wherein the amino acid at position 99 of the extracellular domain of the mutant Epo Receptor is Arginine.

[0056] In certain embodiments, a single chain variable fragment is provided that binds to the wild-type human Epo Receptor but fails to bind to a mutant Epo Receptor wherein the amino acid at position 34 of the extracellular domain of the mutant Epo Receptor is Arginine.

[0057] In certain embodiments, a single chain variable fragment is provided that binds to the wild-type human Epo Receptor but fails to bind to a mutant Epo Receptor wherein the amino acid at position 60 of the extracellular domain of the mutant Epo Receptor is Arginine.

[0058] In certain embodiments, a single chain variable fragment is provided that binds to the wild-type human Epo Receptor but fails to bind to a mutant Epo Receptor wherein the amino acid at position 88 of the extracellular domain of the mutant Epo Receptor is Arginine.

[0059] In certain embodiments, a single chain variable fragment is provided that binds to the wild-type human Epo Receptor but fails to bind to a mutant Epo Receptor wherein the amino acid at position 150 of the extracellular domain of the mutant Epo Receptor is Arginine.

[0060] In certain embodiments, a single chain variable fragment is provided that binds to the wild-type human Epo Receptor but fails to bind to a mutant Epo Receptor wherein the amino acid at position 87 of the extracellular domain of the mutant Epo Receptor is Arginine.

[0061] In certain embodiments, a single chain variable fragment is provided that binds to the wild-type human Epo Receptor but fails to bind to a mutant Epo Receptor wherein the amino acid at position 63 of the extracellular domain of the mutant Epo Receptor is Arginine.

[0062] In certain embodiments, a single chain variable fragment is provided that binds to the wild-type human Epo Receptor but fails to bind to a mutant Epo Receptor wherein the amino acid at position 64 of the extracellular domain of the mutant Epo Receptor is Arginine.

[0063] In certain embodiments, a single chain variable fragment is provided fragment that binds to the wild-type human Epo Receptor but fails to bind to a mutant Epo Receptor wherein the amino acid at position 99 of the extracellular domain of the mutant Epo Receptor is Arginine.

BRIEF DESCRIPTION OF THE DRAWINGS

[0064] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0065] FIG. **1** shows a flow chart of steps for screening EpoR agonistic antibodies from human scFv phage display libraries according to work discussed in Example 1.

[0066] FIG. **2** shows a schematic diagram describing the streamline conversion of phage scFv clones from phage display libraries to an scFv-Fc format in a mammalian expression construct, pDC409a-huG1Fc according to work discussed in Example 2. NcoI and PciI create a cohesive end for ligation. The process of batchwise conversion of scFv NcoI/NotI restriction fragments to PciI/NotI restricted pDC409a-huG1Fc vector is highly efficient.

[0067] FIG. **3** shows FACS analysis of antibodies binding to cells according to work discussed in Example 3. Antibody and Epo concentration used for staining are 5 μg/ml. Panel A shows fluorescence intensity of UT-7 cells upon binding of clone 2, clone 5, clone 7, clone 10 or clone 30 in scFv-Fc in the presence (solid line) and absence (dashed line) of human Epo during staining. Antibody and Epo concentration used are both at 5 μg/ml. The shaded curves are from staining only with phycoerythrin-conjugated goat anti human F(ab')2 without any primary antibody. Panel B shows fluorescence intensity of COS-1 cells upon binding of clone 2, clone 5, clone 7, clone 10 or clone 30 in scFv-Fc (solid lines). The shaded curves are from staining only with phycoerythrin-conjugated goat anti human F(ab')2 without any primary antibody.

[0068] FIG. **4** shows competition binding of clone numbers 2, 5, 7, 10 and 30 to soluble huEpoR by ELISA according to work discussed in Example 5. Panel A shows competitive binding between clone 5 phage and clone 2, clone 5, clone 7, clone 10, or clone 30 in scFv-Fc format. Panel B shows competitive binding between clone 30 phage and clone 2, clone 5, clone 7, clone 10, and clone 30 in scFv-Fc format.

[0069] FIG. **5** shows clone 2, clone 5, clone 7, clone 10, or clone 30 antibodies binding to mouse EpoR (muEpoR) protein by ELISA according to work discussed in Example 6. Hatched bars show binding in scFv-Fc format. Open bars show binding in IgG2 format.

[0070] FIG. **6** shows BIAcore sensograms of huEpoR protein to clone 2, clone 5, clone 7, clone 10 and clone 30 scFv-Fc proteins captured on a CM4 chip according to work discussed in Example 7.

[0071] FIG. **7** shows dose-titration curves of huEpoR activation for maxibodies Mxb 2, Mxb 5, Mxb 7, Mxb 10, and Mxb 30 according to work discussed in Example 8. UT-7-Luc cells (UT-7 cells containing the luciferase reporter gene) were treated for six hours with serially diluted maxibodies in 96-well plates, in triplicate, for a final concentrations of 1000, 333, 111, 37.04, 12.35, 4.115, 1.372, 0.457, 0.152, 0.051, 0.017, and 0.006 nM for Mxb 5, Mxb 10, and Mxb 30, and 2500, 1250, 625, 312.5, 156.25, 78.125, 39.0625, 19.53125, 9.765625, 4.882813, 2.441406, 1.220703, 0.610352, 0.3051758, 0.1525879, 0.76294, 0.038147, 0.019073, 0.009537, 0.004768, 0.002384, 0.001192, 0.000596, 0.000298 nM for Mxb 2 and Mxb 7. Recombinant human Epo was used as a reference standard and was serially diluted in the same plate used to test each maxibody. Each Epo dilution was run in triplicate at the following concentrations for Mxb 2, Mxb 5, Mxb 10, and Mxb 30: 100, 10, 1, 0.1, 0.01, and 0.001 nM, and at the following concentrations for Mxb 7: 1488, 744, 372, 186, 93, 46.5, 23.2, 11.6, 5.8, 2.9, 1.5, 0.71, 0.36, 0.18, 0.09, 0.045, 0.023, 0.011, 0.006, 0.003, 0.0015, 0.0007, 0.0004, 0.0002 nM. Following the addition of the luciferase substrate, luciferase activity was read on a 96-well plate luminometer. Raw data was processed by subtracting the background luminescence (values from wells containing media only) and presented as the average of three values the standard deviation.

[0072] FIG. **8** shows a comparison of the maximal activity levels for the IgG_2 proteins (Ab) and scFv-Fc proteins (Mxb) in the induction of the huEpoR according to work discussed in Example 9. The maximal luciferase activity for each test reagent was the highest value taken from the dose titration curve of each scFv-Fc protein and IgG_2 protein divided by the maximal luciferase activity for the rHuEpo standard taken from the dose titration curve of rHuEpo on each individual plate. This ratio is represented above and is the average of three values ±the standard deviation.

[0073] FIG. **9** shows the activation of UT-7 cells by rHuEpo, Mxb 2, and IgG_2 2 as indicated by phosphorylation of the signaling molecules Stat5 and Akt according to work discussed in Example 10.

[0074] FIG. **10** shows scFv-Fc proteins Mxb 2, Mxb 5, Mxb 7, and Mxb 30 activate CD34+ human peripheral blood progenitor cells (CD34+PBPC) and stimulate the production of BFU-E derived colonies according to work discussed in Example 11.

[0075] FIG. **11** shows a single injection of Mxb 5 produces an increase in reticulocyte numbers that is dose-dependent and sustained over a period of time significantly longer than in the animals treated with PEG-NESP according to work discussed in Example 12A.

[0076] FIG. **12** shows a single injection of Mxb 5 produces an increase in hemoglobin levels that is dose-dependent and sustained over a period of time significantly longer than in the animals treated with PEG-NESP according to work discussed in Example 12A.

[0077] FIG. **13** shows a single injection of Mxb 7 produces an increase in reticulocyte numbers that is dose-dependent and sustained over a period of time significantly longer than in the animals treated with PEG-NESP according to work discussed in Example 12B.

[0078] FIG. **14** shows a single injection of Mxb 7 produces an increase in hemoglobin levels that is dose-dependent and sustained over a period of time significantly longer than in the animals treated with PEG-NESP according to work discussed in Example 12B.

[0079] FIG. **15** shows a single injection of Mxb 10 produces an increase in reticulocyte numbers that is dose-dependent and sustained over a period of time significantly longer than in the animals treated with PEG-NESP according to work discussed in Example 12C.

[0080] FIG. **16** shows a single injection of Mxb 10 produces an increase in hemoglobin levels that is dose-dependent and sustained over a period of time significantly longer than in the animals treated with PEG-NESP according to work discussed in Example 12C.

[0081] FIG. **17** shows a single injection of Mxb 2 produces an increase in reticulocytes number that is sustained over a period of time similar to that measured in the animals treated with PEG-NESP according to work discussed in Example 12D.

[0082] FIG. **18** shows a single injection of Mxb 2 produces an increase in hemoglobin levels that is sustained over a period of time significantly longer than in the animals treated with PEG-NESP according to work discussed in Example 12D.

[0083] FIG. **19** shows the change in serum concentration of Mxb 5 ("#5 Scfv-Fc") and IgG_1 5 ("#5 IgG_1") over time according to work discussed in Example 13.

[0084] FIG. **20** shows the pharmacokinetic parameters of IgG_1 5 and Mxb 5 in mice according to the work discussed in Example 13.

[0085] FIG. **21** shows CDRs from Mxb 2, Mxb 5, Mxb 7, Mxb 10, and Mxb 30.

[0086] FIG. **22** shows a FACS analysis of certain scFv-Fc proteins binding to cells according to work discussed in Example 15. Antibody and Epo concentrations used for staining are 5 μg/ml. The shaded curves are from staining only with phycoerythrin-conjugated goat anti-human F(ab')2 without any primary antibody. Panel A: Fluorescence intensity of UT-7 cells upon binding of Mxb 13, Mxb 15, Mxb 16, Mxb 29, or Mxb 34 in the presence (solid line) and absence (dashed line) of human Epo during staining. Panel B. Fluorescence intensity of COS-1 cells upon binding of Mxb 13, Mxb 15, Mxb 16, Mxb 29, or Mxb 34 (solid line).

[0087] FIG. **23** shows EpoR binding and competition binding of scFv-Fc proteins according to work discussed in Examples 15, 16, and 17. EpoR binding to human (hu), mouse (mu) and cynomolgus monkey (cyno) was tested by ELISA and FACS. The ability of Epo to compete with clone 2, clone 5, clone 7, clone 10, clone 13, clone 15, clone 16, clone 29, clone 30, or clone 34 for binding to the EpoR was tested by FACS in UT-7 cells. The ability of Epo to compete with clone 201, clone 276, clone 295, clone 307, clone 318, clone 319, clone 323, clone 330, clone 352, or clone 378 for binding to the EpoR was tested by competition ELISA. The ability of clone 5 to compete with clone 2, clone 5, clone 7, clone 10, clone 13, clone 15, clone 16, clone 29, clone 30, or clone 34 for binding to the EpoR was tested by plate-based ELISA. The ability of clone 30 to compete with clone 2, clone 5, clone 7, clone 10, clone 13, clone 15, clone 16, clone 29, clone 30, or clone 34 for binding to the EpoR was tested by plate-based ELISA.

[0088] FIG. **24** shows that a single injection of Mxb 276_G1MB produced an increase in reticulocyte numbers that is sustained over a period of time according to work discussed in Example 20. The increase is sustained significantly longer than in animals treated with PEG-NESP.

[0089] FIG. **25** shows that a single injection of Mxb 276_G1MB produced an increase in hemoglobin that is sustained over a period of time according to work discussed in Example 20. The increase in hemoglobin is sustained significantly longer than in animals treated with PEG-NESP.

[0090] FIG. **26**A shows absolute reticulocyte numbers in cynomolgus monkeys after administration of Mxb 5 human point mutant Fc (un-glycosylated Fc) ("huMxb#5" in the Figure), a Mxb 5 cynomolgus point mutant Fc (un-glycosylated Fc) ("cynoMxb#5" in the Figure), a Mxb 10 human point mutant Fc (un-glycosylated Fc) ("huMxb#10" in the Figure), and a Mxb 30 human point mutant Fc (un-glycosylated Fc) ("huMxb#30" in the Figure), or control injections ("Peg-NESP" and "Vehicle" in the Figure) according to work discussed in Example 22. Each monkey was dosed twice by IV injection, the first administration of injections occurred on day 1 and the second one on day 15. The scFv-Fc proteins were dosed at 0.5 mg/kg for the first administration on day 1 and at 5 mg/kg for the second administration on day 15. Peg-Nesp was dosed at 0.03 mg/kg for both injections. The vehicle control ("Vehicle" in the figure) (10 mM potassium phosphate, 161 mM L-Arginine, pH 7.5) was dosed at 1 ml/kg for both injections. FIG. **26**B shows reticulocyte numbers graphed as a percentage of baseline reticulocyte levels for each group after administration of huMxb#5, cynoMxb#5, huMxb#10, and huMxb#30 or control injections according to work discussed in Example 22. The baseline reticulocyte levels were obtained from the analysis of blood collected on day 1 prior to the first administration. Each monkey was dosed twice by IV injection, the first administration of test articles occurred on day 1 and the second one on day 15. The scFv-Fc proteins were dosed at 0.5 mg/kg for the first administration on day 1 and at 5 mg/kg for the second administration on day 15. Peg-Nesp was dosed at 0.03 mg/kg for both injections. The vehicle control was dosed at 1 ml/kg for both injections.

[0091] FIG. **27** shows certain PCR reaction conditions used to make constructs according to work discussed in Example 21.

[0092] FIGS. **28**A, B, C, and D show amino acid sequences that were used as templates for the N 297 S glycosylation site mutagenesis in human and cynomolgus Fc's according to work discussed in Example 21. The amino acid highlighted in red shows where the N 297 S mutation takes place. The yellow portion is the VH5 leader sequence, the green is the scFv and the blue is the Fc region. The portion in white in FIGS. **28**A, **28**B and **28**C includes a G from the original scFv library and amino acids from the introduction of a restriction site to facilitate cloning.

[0093] FIGS. **29**A, B, C, and D shows the final clones and sequences of the mutated, scFv-Fc proteins Mxb#5 human point mutant Fc, Mxb#10 human point mutant Fc, Mxb#30 human point mutant Fc, Mxb#5 cynomolgus point mutant Fc) according to work discussed in Example 21. The amino acid highlighted in red shows the N 297 S mutation. The yellow portion is the VH5 leader sequence, the green is the scFv and the blue is the Fc region. The portion in white includes a G, from the original scFv library and amino acids from the introduction of a restriction site to facilitate cloning.

[0094] FIG. **30** shows an ELISA binding assay for mutant EpoR protein binding to Mxb 10 according to work discussed in Example 23. E62A, F93A and M150A diminish binding relative to WT and appear to be part of the Mxb 10 binding epitope.

[0095] FIG. **31** shows a LANCE assay for Mxb 10 binding to mutant EpoR proteins according to work discussed in Example 23. E62A, F93A and M150A diminish binding relative to WT and appear to be part of the Mxb 10 binding epitope.

[0096] FIG. **32** shows a comparison of Mxb 10 binding to arginine and alanine EpoR mutants according to work discussed in Example 23. FIG. **32**A shows that a mutation of W64 to arginine or alanine did not diminish the binding relative to WT. W64A appears not to be part of the Mxb 10

epitope. FIG. **32**B shows a mutation of M150 to alanine diminished binding of Mxb 10. Mutation of M150 to arginine greatly diminished binding.

[0097] FIG. **33** shows sequence alignments of the A) variable heavy chain CDR regions and B) variable light chain CDR regions according to work discussed in Example 24. Sequence alignments were based on the MiniPileup program using electronically spliced CDR regions. Alignments are color coded to indicate polar (blue), apolar (red), acidic (green) and basic (yellow) amino acids. The symbol "*" represents a linker region separating the CDR1, CDR2 and CDR3.

[0098] FIG. **34** shows a phylogenetic analysis of A) variable heavy chain CDR regions and B) variable light chain CDR regions according to work discussed in Example 24. Trees are based on neighbor joining analysis of the amino acid sequences of the CDR regions.

[0099] FIG. **35** shows consensus sequences in the CDRs of the variable heavy chains and the variable light chains in the sequence alignment of FIG. **33**, according to work discussed in Example 24. The symbol "X" represents an amino acid that may vary in the consensus sequence. The subscript next to the "X" represents the position of amino acid in the sequence, e.g., "X_1" represents the first amino acid in a consensus sequence.

[0100] FIG. **36**A shows the full length amino acid sequence of the Epo Receptor. FIG. **36**B shows the amino acid sequence of the extracellular domain of the Epo Receptor. The amino acid sequence of the extracellular domain was used to identify amino acids in the epitope mapping experiments described in Example 23 and FIGS. **30** to **32**. The extracellular domain lacks the first 24 amino acids present in the amino acid sequence of the full length Epo Receptor. The extracellular domain also lacks amino acids 251 to 508 of the full length Epo Receptor.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

[0101] All documents or portions of documents cited in this application, including but not limited to patents, patent applications, articles, books, and treatises, are expressly incorporated by reference herein in their entirety for any purpose. In the event that one or more of the documents incorporated by reference defines a term that contradicts that term's definition in this application, this application controls.

[0102] Unless specific definitions are provided, the nomenclatures utilized in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques may be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, delivery, and treatment of patients.

[0103] In this application, the use of the singular includes the plural unless specifically stated otherwise. In this application, the use of "or" means "and/or" unless stated otherwise. In the context of a multiple dependent claim, the use of "or" refers back to more than one preceding independent or dependent claim in the alternative only. Furthermore, the use of the term "including", as well as other forms, such as "includes" and "included", is not limiting. Also, terms such as "element" or "component" encompass both elements and components comprising one unit and elements and components that comprise more than one subunit unless specifically stated otherwise.

[0104] As utilized in accordance with the present disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

[0105] The term "isolated polynucleotide" as used herein shall mean a polynucleotide of genomic, cDNA, or synthetic origin or some combination thereof, which by virtue of its origin the "isolated polynucleotide" (1) is not associated with all or a portion of a polynucleotide in which the "isolated polynucleotide" is found in nature, (2) is linked to a polynucleotide which it is not linked to in nature, or (3) does not occur in nature as part of a larger sequence.

[0106] The terms "polynucleotide" and "oligonucleotide" are used interchangeably, and as referred to herein mean a polymeric form of nucleotides of at least 2 bases in length. In certain embodiments, the bases may comprise at least one of ribonucleotides, deoxyribonucleotides, and a modified form of either type of nucleotide. The term includes single and double stranded forms of DNA. In certain embodiments, polynucleotides complementary to specific polynucleotides that encode certain polypeptides described herein are provided.

[0107] The term "naturally occurring nucleotides" includes deoxyribonucleotides and ribonucleotides. Deoxyribonucleotides include, but are not limited to, adenosine, guanine, cytosine, and thymidine. Ribonucleotides include, but are not limited to, adenosine, cytosine, thymidine, and uracil. The term "modified nucleotides" includes, but is not limited to, nucleotides with modified or substituted sugar groups and the like. The term "polynucleotide linkages" includes, but is not limited to, polynucleotide linkages such as phosphorothioate, phosphorodithioate, phosphoroselenoate, phosphorodiselenoate, phosphoroanilothioate, phoshoraniladate, phosphoroamidate, and the like. See, e.g., LaPlanche et al. *Nucl. Acids Res.* 14:9081 (1986); Stec et al. *J. Am. Chem. Soc.* 106:6077 (1984); Stein et al. *Nucl. Acids Res.* 16:3209 (1988); Zon et al. *Anti-Cancer Drug Design* 6:539 (1991); Zon et al. Oligonucleotides and Analogues: A Practical Approach, pp. 87-108 (F. Eckstein, Ed., Oxford University Press, Oxford England (1991)); Stec et al. U.S. Pat. No. 5,151,510; Uhlmann and Peyman *Chemical Reviews* 90:543 (1990). In certain embodiments, a polynucleotide can include a label for detection.

[0108] The term "isolated polypeptide" refers to any polypeptide that (1) is free of at least some proteins with which it would normally be found, (2) is essentially free of other proteins from the same source, e.g., from the same species, (3) is expressed by a cell from a different species, or (4) does not occur in nature.

[0109] The terms "polypeptide," "peptide," and "protein" are used interchangeably herein and refer to a polymer of two or more amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres. The terms apply to amino acid polymers containing naturally occurring amino acids as well as amino acid polymers in which one or more amino acid residues is a non-naturally occurring amino acid or a chemical analogue of a naturally occurring amino acid. An amino acid polymer may contain one or more amino acid residues that has been modified by one or more natural processes, such as post-translational processing, and/or one or more amino acid residues that has been modified by one or more chemical modification techniques known in the art.

[0110] A "fragment" of a reference polypeptide refers to a contiguous stretch of amino acids from any portion of the reference polypeptide. A fragment may be of any length that is less than the length of the reference polypeptide.

[0111] A "variant" of a reference polypeptide refers to a polypeptide having one or more amino acid substitutions, deletions, or insertions relative to the reference polypeptide. In certain embodiments, a variant of a reference polypeptide has an altered post-translational modification site (i.e., a glycosylation site). In certain embodiments, both a reference polypeptide and a variant of a reference polypeptide are specific binding agents. In certain embodiments, both a reference polypeptide and a variant of a reference polypeptide are antibodies.

[0112] Variants of a reference polypeptide include, but are not limited to, glycosylation variants. Glycosylation variants include variants in which the number and/or type of glycosylation sites have been altered as compared to the reference polypeptide. In certain embodiments, glycosylation variants of a reference polypeptide comprise a greater or a lesser number of N-linked glycosylation sites than the reference polypeptide. In certain embodiments, an N-linked glycosylation site is characterized by the sequence Asn-X-Ser or Asn-X-Thr, wherein the amino acid residue designated as X may be any amino acid residue except proline. In certain embodiments, glycosylation variants of a reference polypeptide comprise a rearrangement of N-linked carbohydrate chains wherein one or more N-linked glycosylation sites (typically those that are naturally occurring) are eliminated and one or more new N-linked sites are created.

[0113] Variants of a reference polypeptide include, but are not limited to, cysteine variants. In certain embodiments, cysteine variants include variants in which one or more cysteine residues of the reference polypeptide are replaced by one or more non-cysteine residues; and/or one or more non-cysteine residues of the reference polypeptide are replaced by one or more cysteine residues. Cysteine variants may be useful, in certain embodiments, when a particular polypeptide must be refolded into a biologically active conformation, e.g., after the isolation of insoluble inclusion bodies. In certain embodiments, cysteine variants of a reference polypeptide have fewer cysteine residues than the reference polypeptide. In certain embodiments, cysteine variants of a reference polypeptide have an even number of cysteines to minimize interactions resulting from unpaired cysteines. In certain embodiments, cysteine variants have more cysteine residues than the native protein.

[0114] A "derivative" of a reference polypeptide refers to: a polypeptide: (1) having one or more modifications of one or more amino acid residues of the reference polypeptide; and/or (2) in which one or more peptidyl linkages has been replaced with one or more non-peptidyl linkages; and/or (3) in which the N-terminus and/or the C-terminus has been modified. Certain exemplary modifications include, but are not limited to, acetylation, acylation, ADP-ribosylation, amidation, biotinylation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cystine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. In certain embodiments, both a reference polypeptide and a derivative of a reference polypeptide are specific binding agents. In certain embodiments, both a reference polypeptide and a derivative of a reference polypeptide are antibodies.

[0115] Polypeptides include, but are not limited to, amino acid sequences modified either by natural processes, such as post-translational processing, or by chemical modification techniques that are well known in the art. In certain embodiments, modifications may occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. In certain such embodiments, the modifications may be present to the same or varying degrees at several sites in a given polypeptide. In certain embodiments, a given polypeptide contains many types of modifications such as deletions, additions, and/or substitutions of one or more amino acids of a native sequence. In certain embodiments, polypeptides may be branched and/or cyclic. Cyclic, branched and branched cyclic polypeptides may result from post-translational natural processes (including, but not limited to, ubiquitination) or may be made by synthetic methods. In certain embodiments, certain polypeptide sequences comprise at least one complementarity determining region (CDR).

[0116] The term "naturally-occurring" as applied to an object means that an object can be found in nature. For example, a polypeptide or polynucleotide that is present in an organism (including viruses) that can be isolated from a source in nature and which has not been intentionally modified by man in the laboratory or otherwise is naturally-occurring.

[0117] The term "operably linked" as used herein refers to components that are in a relationship permitting them to function in their intended manner. For example, in the context of a polynucleotide sequence, a control sequence may be "operably linked" to a coding sequence when the control sequence and coding sequence are in association with each other in such a way that expression of the coding sequence is achieved under conditions compatible with the functioning of the control sequence.

[0118] The term "control sequence" refers to polynucleotide sequences which may effect the expression and processing of coding sequences with which they are in association. The nature of such control sequences may differ depending upon the host organism. Certain exemplary control sequences for prokaryotes include, but are not limited to, promoters, ribosomal binding sites, and transcription termination sequences. Certain exemplary control sequences for eukaryotes include, but are not limited to, promoters, enhancers, and transcription termination sequences. In certain embodiments, "control sequences" can include leader sequences and/or fusion partner sequences.

[0119] In certain embodiments, a first polynucleotide coding sequence is operably linked to a second polynucleotide coding sequence when the first and second polynucleotide coding sequences are transcribed into a single contiguous mRNA that can be translated into a single contiguous polypeptide.

[0120] In the context of polypeptides, two or more polypeptides are "operably linked" if each linked polypeptide is able to function in its intended manner. A polypeptide that is able

to function in its intended manner when operably linked to another polypeptide may or may not be able to function in its intended manner when not operably linked to another polypeptide. For example, in certain embodiments, a first polypeptide may be unable to function in its intended manner when unlinked, but may be stabilized by being linked to a second polypeptide such that it becomes able to function in its intended manner. Alternatively, in certain embodiments, a first polypeptide may be able to function in its intended manner when unlinked, and may retain that ability when operably linked to a second polypeptide.

[0121] As used herein, two or more polypeptides are "fused" when the two or more polypeptides are linked to form a single contiguous molecule. In certain embodiments, two or more polypeptides are fused by translating them as a single contiguous polypeptide sequence or by synthesizing them as a single contiguous polypeptide sequence. In certain embodiments, two or more fused polypeptides may have been translated in vivo from two or more operably linked polynucleotide coding sequences. In certain embodiments, two or more fused polypeptides may have been translated in vitro from two or more operably liinked polynucleotide coding sequences. In certain embodiments, two or more polypeptides are fused if the two polypeptides are linked by a polypeptide or non-polypeptide linker.

[0122] As used herein, two or more polypeptides are "operably fused" if each linked polypeptide is able to function in its intended manner.

[0123] In certain embodiments, a first polypeptide that contains two or more distinct polypeptide units is considered to be linked to a second polypeptide so long as at least one of the distinct polypeptide units of the first polypeptide is linked to the second polypeptide. As a non-limiting example, in certain embodiments, an antibody is considered linked to a second polypeptide in all of the following instances: (a) the second polypeptide is linked to one of the heavy chain polypeptides of the antibody; (b) the second polypeptide is linked to one of the light chain polypeptides of the antibody; (c) a first molecule of the second polypeptide is linked to one of the heavy chain polypeptides of the antibody and a second molecule of the second polypeptide is linked to one of the light chain polypeptides of the antibody; and (d) first and second molecules of the second polypeptide are linked to the first and second heavy chain polypeptides of the antibody and third and fourth molecules of the second polypeptide are linked to first and second light chain polypeptides of the antibody.

[0124] In certain embodiments, the language "a first polypeptide linked to a second polypeptide" encompasses situations where: (a) only one molecule of a first polypeptide is linked to only one molecule of a second polypeptide; (b) only one molecule of a first polypeptide is linked to more than one molecule of a second polypeptide; (c) more than one molecule of a first polypeptide is linked to only one molecule of a second polypeptide; and (d) more than one molecule of a first polypeptide is linked to more than one molecule of a second polypeptide. In certain embodiments, when a linked molecule comprises more than one molecule of a first polypeptide and only one molecule of a second polypeptide, all or fewer than all of the molecules of the first polypeptide may be covalently or noncovalently linked to the second polypeptide. In certain embodiments, when a linked molecule comprises more than one molecule of a first polypeptide, one or more molecules of the first polypeptide may be covalently or noncovalently linked to other molecules of the first polypeptide.

[0125] As used herein, a "flexible linker" refers to any linker that is not predicted, according to its chemical structure, to be fixed in three-dimensional space. One skilled in the art can predict whether a particular linker is flexible in its intended context. In certain embodiments, a peptide linker comprising 3 or more amino acids is a flexible linker.

[0126] As used herein, the twenty conventional amino acids and their abbreviations follow conventional usage. See Immunology—A Synthesis (2nd Edition, E. S. Golub and D. R. Gren, Eds., Sinauer Associates, Sunderland, Mass. (1991)). In certain embodiments, one or more unconventional amino acids may be incorporated into a polypeptide. The term "unconventional amino acid" refers to any amino acid that is not one of the twenty conventional amino acids. The term "non-naturally occurring amino acids" refers to amino acids that are not found in nature. Non-naturally occurring amino acids are a subset of unconventional amino acids. Unconventional amino acids include, but are not limited to, stereoisomers (e.g., D-amino acids) of the twenty conventional amino acids, unnatural amino acids such as α-, α-disubstituted amino acids, N-alkyl amino acids, lactic acid, homoserine, homocysteine, 4-hydroxyproline, γ-carboxyglutamate, ε-N, N,N-trimethyllysine, ε-N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, σ-N-methylarginine, and other similar amino acids and imino acids (e.g., 4-hydroxyproline) known in the art. In the polypeptide notation used herein, the left-hand direction is the amino terminal direction and the right-hand direction is the carboxy-terminal direction, in accordance with standard usage and convention.

[0127] In certain embodiments, conservative amino acid substitutions include substitution with one or more unconventional amino acid residues. In certain embodiments, unconventional amino acid residues are incorporated by chemical peptide synthesis rather than by synthesis in biological systems.

[0128] The term "acidic residue" refers to an amino acid residue in D- or L-form that comprises at least one acidic group when incorporated into a polypeptide between two other amino acid residues that are the same or different. In certain embodiments, an acidic residue comprises a sidechain that comprises at least one acidic group. Exemplary acidic residues include, but are not limited to, aspartic acid (D) and glutamic acid (E). In certain embodiments, an acidic residue may be an unconventional amino acid.

[0129] The term "aromatic residue" refers to an amino acid residue in D- or L-form that comprises at least one aromatic group. In certain embodiments, an aromatic residue comprises a sidechain that comprises at least one aromatic group. Exemplary aromatic residues include, but are not limited to, phenylalanine (F), tyrosine (Y), and tryptophan (W). In certain embodiments, an aromatic residue may be an unconventional amino acid.

[0130] The term "basic residue" refers to an amino acid residue in D- or L-form that may comprise at least one basic group when incorporated into a polypeptide next to one or more amino acid residues that are the same or different. In certain embodiments, a basic residue comprises a sidechain that comprises at least one basic group. Exemplary basic residues include, but are not limited to, histidine (H), lysine

(K), and arginine (R). In certain embodiments, a basic residue may be an unconventional amino acid.

[0131] The term "neutral hydrophilic residue" refers to an amino acid residue in D- or L-form that comprises at least one hydrophilic and/or polar group, but does not comprise an acidic or basic group when incorporated into a polypeptide next to one or more amino acid residues that are the same or different. Exemplary neutral hydrophilic residues include, but are not limited to, alanine (A), cysteine (C), serine (S), threonine (T), asparagine (N), and glutamine (Q). In certain embodiments, a neutral hydrophilic residue may be an unconventional amino acid.

[0132] The terms "lipophilic residue" and "Laa" refer to an amino acid residue in D- or L-form having at least one uncharged, aliphatic and/or aromatic group. In certain embodiments, a lipophilic residue comprises a side chain that comprises at least one uncharged, aliphatic, and/or aromatic group. Exemplary lipophilic sidechains include, but are not limited to, alanine (A), phenylalanine (F), isoleucine (I), leucine (L), norleucine (Nle), methionine (M), valine (V), tryptophan (W), and tyrosine (Y). In certain embodiments, a lipophilic residue may be an unconventional amino acid.

[0133] The term "amphiphilic residue" refers to an amino acid residue in D- or L-form that is capable of being either a hydrophilic or lipophilic residue. An exemplary amphiphilic residue includes, but is not limited to, alanine (A). In certain embodiments, an amphiphilic residue may be an unconventional amino acid.

[0134] The term "nonfunctional residue" refers to an amino acid residue in D- or L-form that lacks acidic, basic, and aromatic groups when incorporated into a polypeptide next to one or more amino acid residues that are the same or different. Exemplary nonfunctional amino acid residues include, but are not limited to, methionine (M), glycine (G), alanine (A), valine (V), isoleucine (I), leucine (L), and norleucine (Nie). In certain embodiments, a nonfunctional residue may be an unconventional amino acid.

[0135] In certain embodiments, glycine (G) and proline (P) are considered amino acid residues that can influence polypeptide chain orientation.

[0136] In certain embodiments, a conservative substitution may involve replacing a member of one residue type with a member of the same residue type. As a non-limiting example, in certain embodiments, a conservative substitution may involve replacing an acidic residue, such as D, with a different acidic residue, such as E. In certain embodiments, a non-conservative substitution may involve replacing a member of one residue type with a member of a different residue type. As a non-limiting example, in certain embodiments, a non-conservative substitution may involve replacing an acidic residue, such as D, with a basic residue, such as K. In certain embodiments, a cysteine residue is substituted with another amino acid residue to prevent disulfide bond formation with that position in the polypeptide.

[0137] In making conservative or non-conservative substitutions, according to certain embodiments, the hydropathic index of amino acids may be considered. Each amino acid has been assigned a hydropathic index on the basis of its hydrophobicity and charge characteristics. The hydropathic indices of the 20 naturally-occurring amino acids are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (−0.4); threonine (−0.7); serine (−0.8); tryptophan (−0.9); tyrosine (−1.3); proline (−1.6); histidine (−3.2); glutamate (−3.5); glutamine (−3.5); aspartate (−3.5); asparagine (−3.5); lysine (−3.9); and arginine (−4.5).

[0138] The importance of the hydropathic amino acid index in conferring interactive biological function on a protein is understood in the art. Kyte et al., *J. Mol. Biol.*, 157:105-131 (1982). It is known in certain instances that certain amino acids may be substituted for other amino acids having a similar hydropathic index or score and still retain a similar biological activity. In making changes based upon the hydropathic index, in certain embodiments, the substitution of amino acids whose hydropathic indices are within ±2 is included. In certain embodiments, those which are within ±1 are included, and in certain embodiments, those within ±0.5 are included.

[0139] It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity, particularly where the biologically functional protein or peptide thereby created is intended for use in immunological embodiments, as in the present case. In certain embodiments, the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with its immunogenicity and antigenicity, i.e., with a biological property of the polypeptide.

[0140] The following hydrophilicity values have been assigned to these amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0±1); glutamate (+3.0±1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (−0.4); proline (−0.5±1); alanine (−0.5); histidine (−0.5); cysteine (−1.0); methionine (−1.3); valine (−1.5); leucine (−1.8); isoleucine (−1.8); tyrosine (−2.3); phenylalanine (−2.5) and tryptophan (−3.4). In making changes based upon similar hydrophilicity values, in certain embodiments, the substitution of amino acids whose hydrophilicity values are within ±2 is included, in certain embodiments, those which are within ±1 are included, and in certain embodiments, those within ±0.5 are included. In certain instances, one may also identify epitopes from primary amino acid sequences on the basis of hydrophilicity. These regions are also referred to as "epitopic core regions."

[0141] Exemplary amino acid substitutions are set forth in Table 1.

TABLE 1

	Amino Acid Substitutions	
Original Residues	Exemplary Substitutions	More specific exemplary Substitutions
Ala	Val, Leu, Ile	Val
Arg	Lys, Gln, Asn	Lys
Asn	Gln	Gln
Asp	Glu	Glu
Cys	Ser, Ala	Ser
Gln	Asn	Asn
Glu	Asp	Asp
Gly	Pro, Ala	Ala
His	Asn, Gln, Lys, Arg	Arg
Ile	Leu, Val, Met, Ala, Phe, Norleucine	Leu
Leu	Norleucine, Ile, Val, Met, Ala, Phe	Ile
Lys	Arg, 1,4 Diamino-butyric Acid, Gln, Asn	Arg
Met	Leu, Phe, Ile	Leu
Phe	Leu, Val, Ile, Ala, Tyr	Leu

TABLE 1-continued

Amino Acid Substitutions		
Original Residues	Exemplary Substitutions	More specific exemplary Substitutions
Pro	Ala	Gly
Ser	Thr, Ala, Cys	Thr
Thr	Ser	Ser
Trp	Tyr, Phe	Tyr
Tyr	Trp, Phe, Thr, Ser	Phe
Val	Ile, Met, Leu, Phe, Ala, Norleucine	Leu

[0142] Similarly, as used herein, unless specified otherwise, the left-hand end of single-stranded polynucleotide sequences is the 5' end; the left-hand direction of double-stranded polynucleotide sequences is referred to as the 5' direction. The direction of 5' to 3' addition of nascent RNA transcripts is referred to herein as the transcription direction; sequence regions on the DNA strand having the same sequence as the RNA and which are 5' to the 5' end of the RNA transcript are referred to herein as "upstream sequences"; sequence regions on the DNA strand having the same sequence as the RNA and which are 3' to the 3' end of the RNA transcript are referred to herein as "downstream sequences."

[0143] In certain embodiments, conservative amino acid substitutions encompass non-naturally occurring amino acid residues, which are typically incorporated by chemical peptide synthesis or by synthesis in biological systems. Those non-naturally occurring amino acid residues include, but are not limited to, peptidomimetics and other reversed or inverted forms of amino acid moieties.

[0144] A skilled artisan will be able to determine suitable substitution variants of a reference polypeptide as set forth herein using well-known techniques. In certain embodiments, one skilled in the art may identify suitable areas of the molecule that may be changed without destroying activity by targeting regions not believed to be important for activity. In certain embodiments, one can identify residues and portions of the molecules that are conserved among similar polypeptides. In certain embodiments, even areas that may be important for biological activity, including, but not limited to, the CDRs of an antibody, or that may be important for structure may be subject to conservative amino acid substitutions without destroying the biological activity or without adversely affecting the polypeptide structure.

[0145] Additionally, in certain embodiments, one skilled in the art can review structure-function studies identifying residues in similar polypeptides that are important for activity and/or structure. In view of such a comparison, in certain embodiments, one can predict the importance of amino acid residues in a polypeptide that correspond to amino acid residues which are important for activity or structure in similar polypeptides. In certain embodiments, one skilled in the art may opt for chemically similar amino acid substitutions for such predicted important amino acid residues.

[0146] In certain embodiments, one skilled in the art can also analyze the three-dimensional structure and amino acid sequence in relation to that structure in similar polypeptides. In view of such information, one skilled in the art may predict the alignment of amino acid residues of an antibody with respect to its three dimensional structure. In certain embodiments, one skilled in the art may choose not to make radical changes to amino acid residues predicted to be on the surface of the protein, since such residues may be involved in important interactions with other molecules. Moreover, in certain embodiments, one skilled in the art may generate test variants containing a single amino acid substitution at each desired amino acid residue. In certain embodiments, the variants can then be screened using activity assays known to those skilled in the art. For example, in certain embodiments, the variants can be screened for their ability to bind an antibody. In certain embodiments, such variants could be used to gather information about suitable variants. For example, in certain embodiments, if one discovered that a change to a particular amino acid residue resulted in destroyed, undesirably reduced, or unsuitable activity, variants with such a change may be avoided. In other words, based on information gathered from such routine experiments, one skilled in the art can readily determine the amino acids where further substitutions should be avoided, either alone or in combination with other mutations.

[0147] A number of scientific publications have been devoted to the prediction of secondary structure. See Moult J., *Curr. Op. in Biotech.,* 7(4):422-427 (1996), Chou et al., *Biochemistry,* 13(2):222-245 (1974); Chou et al., *Biochemistry,* 113(2):211-222 (1974); Chou et al., *Adv. Enzymol. Relat. Areas Mol. Biol.,* 47:45-148 (1978); Chou et al., *Ann. Rev. Biochem.,* 47:251-276 and Chou et al., *Biophys. J.,* 26:367-384 (1979). Moreover, computer programs are currently available to assist with predicting secondary structure. One method of predicting secondary structure is based upon homology modeling. For example, two polypeptides or proteins which have a sequence identity of greater than 30%, or similarity greater than 40% often have similar structural topologies. The recent growth of the protein structural database (PDB) has provided enhanced predictability of secondary structure, including the potential number of folds within a polypeptide's or protein's structure. See Holm et al., *Nucl. Acid. Res.,* 27(1):244-247 (1999). It has been suggested that there are a limited number of folds in a given polypeptide or protein and that once a critical number of structures have been resolved, structural prediction will become dramatically more accurate. See, e.g., Brenner et al., *Curr. Op. Struct. Biol.,* 7(3):369-376 (1997).

[0148] Additional exemplary methods of predicting secondary structure include, but are not limited to, "threading" (Jones, D., *Curr. Opin. Struct. Biol.,* 7(3):377-87 (1997); Sippl et al., *Structure,* 4(1):15-19 (1996)), "profile analysis" (Bowie et al., *Science,* 253:164-170 (1991); Gribskov et al., *Meth. Enzym.,* 183:146-159 (1990); Gribskov et al., *Proc. Nat. Acad. Sci.,* 84(13):4355-4358 (1987)), and "evolutionary linkage" (See Holm, supra (1999), and Brenner, supra (1997)).

[0149] In certain embodiments, the identity and similarity of related polypeptides can be readily calculated by known methods. Such methods include, but are not limited to, those described in Computational Molecular Biology, Lesk, A. M., ed., Oxford University Press, New York (1988); Biocomputing: Informatics and Genome Projects, Smith, D. W., ed., Academic Press, New York (1993); Computer Analysis of Sequence Data, Part 1, Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey (1994); Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press (1987); Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M. Stockton Press, New York (1991); and Carillo et al., *SIAM J. Applied Math.,* 48:1073 (1988). In certain embodi-

ments, a substantially identical polypeptide has an amino acid sequence that is about 90 percent, or about 95 percent, or about 96 percent, or about 97 percent, or about 98 percent, or about 99 percent identical to a reference amino acid sequence.

[0150] In certain embodiments, methods to determine identity are designed to give the largest match between the sequences tested. In certain embodiments, certain methods to determine identity are described in publicly available computer programs. Certain computer program methods to determine identity between two sequences include, but are not limited to, the GCG program package, including GAP (Devereux et al., *Nucl. Acid. Res.,* 12:387 (1984); Genetics Computer Group, University of Wisconsin, Madison, Wis., BLASTP, BLASTN, and FASTA (Altschul et al., *J. Mol. Biol.,* 215:403-410 (1990)). The BLASTX program is publicly available from the National Center for Biotechnology Information (NCBI) and other sources (*BLAST Manual*, Altschul et al. NCB/NLM/NIH Bethesda, Md. 20894; Altschul et al., supra (1990)). In certain embodiments, the Smith Waterman algorithm, which is known in the art, may also be used to determine identity.

[0151] Certain alignment schemes for aligning two amino acid sequences may result in the matching of only a short region of the two sequences, and this small aligned region may have very high sequence identity even though there is no significant relationship between the two full-length sequences. Accordingly, in certain embodiments, the selected alignment method (GAP program) will result in an alignment that spans at least 50 contiguous amino acids of the target polypeptide.

[0152] For example, using the computer algorithm GAP (Genetics Computer Group, University of Wisconsin, Madison, Wis.), two polypeptides for which the percent sequence identity is to be determined are aligned for optimal matching of their respective amino acids (the "matched span", as determined by the algorithm). In certain embodiments, a gap opening penalty (which is calculated as 3× the average diagonal; the "average diagonal" is the average of the diagonal of the comparison matrix being used; the "diagonal" is the score or number assigned to each perfect amino acid match by the particular comparison matrix) and a gap extension penalty (which is usually 1/10 times the gap opening penalty), as well as a comparison matrix such as PAM 250 or BLOSUM 62 are used in conjunction with the algorithm. In certain embodiments, a standard comparison matrix is also used by the algorithm. See, e.g., Dayhoff et al., *Atlas of Protein Sequence and Structure,* 5(3)(1978) for the PAM 250 comparison matrix; Henikoff et al., *Proc. Natl. Acad. Sci. USA,* 89:10915-10919 (1992) for the BLOSUM 62 comparison matrix.

[0153] In certain embodiments, the parameters for a polypeptide sequence comparison include the following:

[0154] Algorithm: Needleman et al., *J. Mol. Biol.,* 48:443-453 (1970);

[0155] Comparison matrix: BLOSUM 62 from Henikoff et al., supra (1992);

[0156] Gap Penalty: 12

[0157] Gap Length Penalty: 4

[0158] Threshold of Similarity: 0

[0159] In certain embodiments, the GAP program may be useful with the above parameters. In certain embodiments, the aforementioned parameters are the default parameters for polypeptide comparisons (along with no penalty for end gaps) using the GAP algorithm.

[0160] According to certain embodiments, amino acid substitutions are those which: (1) reduce susceptibility to proteolysis, (2) reduce susceptibility to oxidation, (3) alter binding affinity for forming protein complexes, (4) alter binding affinities, and/or (4) confer or modify other physicochemical or functional properties on such polypeptides. According to certain embodiments, single or multiple amino acid substitutions (in certain embodiments, conservative amino acid substitutions) may be made in the naturally-occurring sequence (in certain embodiments, in the portion of the polypeptide outside the domain(s) forming intermolecular contacts).

[0161] In certain embodiments, a conservative amino acid substitution typically may not substantially change the structural characteristics of the parent sequence (e.g., a replacement amino acid should not tend to break a helix that occurs in the parent sequence, or disrupt other types of secondary structure that characterizes the parent sequence). Examples of art-recognized polypeptide secondary and tertiary structures are described, e.g., in Proteins, Structures and Molecular Principles (Creighton, Ed., W.H. Freeman and Company, New York (1984)); Introduction to Protein Structure (C. Branden and J. Tooze, eds., Garland Publishing, New York, N.Y. (1991)); and Thornton et al. Nature 354:105 (1991).

[0162] The term "polypeptide fragment" as used herein refers to a polypeptide that has an amino-terminal and/or carboxy-terminal deletion. In certain embodiments, fragments are at least 2 to 1,000 amino acids long. It will be appreciated that in certain embodiments, fragments are at least 5, 6, 8, 10, 14, 20, 50, 70, 100, 150, 200, 250, 300, 350, 400, 450, 500, or 1,000 amino acids long.

[0163] Peptide analogs are commonly used in the pharmaceutical industry as non-peptide drugs with properties analogous to those of the template peptide. These types of non-peptide compound are termed "peptide mimetics" or "peptidomimetics." Fauchere, *J. Adv. Drug Res.* 15:29 (1986); Veber and Freidinger TINS p. 392 (1985); and Evans et al. *J. Med. Chem.* 30:1229 (1987). Such compounds are often developed with the aid of computerized molecular modeling. Peptide mimetics that are structurally similar to therapeutically useful peptides may be used to produce a similar therapeutic or prophylactic effect. Generally, peptidomimetics are structurally similar to a paradigm polypeptide (i.e., a polypeptide that has a biochemical property or pharmacological activity), such as a human antibody, but have one or more peptide linkages optionally replaced by a linkage selected from: —CH_2 NH—, —CH_2 S—, —CH_2—CH_2—, —CH=CH-(cis and trans), —$COCH_2$—, —CH(OH) CH_2—, and —CH_2 SO—, by methods well known in the art. Systematic substitution of one or more amino acids of a consensus sequence with a D-amino acid of the same type (e.g., D-lysine in place of L-lysine) may be used in certain embodiments to generate more stable peptides. In addition, constrained peptides comprising a consensus sequence or a substantially identical consensus sequence variation may be generated by methods known in the art (Rizo and Gierasch Ann. Rev. Biochem. 61.387 (1992)); for example, and not limitation, by adding internal cysteine residues capable of forming intramolecular disulfide bridges which cyclize the peptide.

[0164] The term "specifically binds" refers to the ability of an antibody to bind to a target with greater affinity than it binds to a non-target. In certain embodiments, specific binding refers to binding to a target with an affinity that is at least 10, 50, 100, 250, 500, or 1000 times greater than the affinity

for a non-target. In certain embodiments, affinity is determined by an affinity ELISA assay. In certain embodiments, affinity is determined by a BIAcore assay. In certain embodiments, affinity is determined by a kinetic method. In certain embodiments, affinity is determined by an equilibrium/solution method.

[0165] "Antibody" or "antibody peptide(s)" both refer to an intact antibody, or a fragment thereof. In certain embodiments, the fragment includes contiguous portions of an intact antibody. In certain embodiments, the fragment includes non-contiguous portions of an intact antibody. In certain embodiments, an antibody comprises a scFv. In certain embodiments, an antibody comprises a polypeptide comprising at least one CDR. In certain embodiments, the antibody fragment may be a binding fragment that competes with the intact antibody for specific binding. The term "antibody" also encompasses polyclonal antibodies and monoclonal antibodies. In certain embodiments, binding fragments are produced by recombinant DNA techniques. In certain embodiments, binding fragments are produced by enzymatic or chemical cleavage of intact antibodies. In certain embodiments, binding fragments are produced by recombinant DNA techniques. Binding fragments include, but are not limited to, Fab, Fab', F(ab')2, Fv, scFv, scFv-Fc (maxibodies), and single-chain antibodies. Non-antigen binding fragments include, but are not limited to, Fc fragments. The term "antibody" also encompasses anti-idiotypic antibodies that specifically bind to the variable region of another antibody. In certain embodiments, anti-idiotypic antibodies may be used to detect the presence of a particular antibody in a sample or to block the activity of an antibody.

[0166] Certain assays for determining the specificity of an antibody are well known to the skilled artisan and include, but are not limited to, ELISA, ELISPOT, western blots, BIAcore assays, and solution affinity binding assays.

[0167] The term "isolated antibody" as used herein means an antibody which (1) is free of at least some proteins with which it would normally be found, (2) is essentially free of other proteins from the same source, e.g., from the same species, (3) is expressed by a cell from a different species, or (4) does not occur in nature.

[0168] The term "polyclonal antibody" refers to a heterogeneous mixture of antibodies that bind to different epitopes of the same antigen.

[0169] The term "monoclonal antibodies" refers to a collection of antibodies encoded by the same nucleic acid molecule. In certain embodiments, monoclonal antibodies are produced by a single hybridoma or other cell line, or by a transgenic mammal. Monoclonal antibodies typically recognize the same epitope. The term "monoclonal" is not limited to any particular method for making an antibody.

[0170] The term "CDR grafted antibody" refers to an antibody in which the CDR from one antibody is inserted into the framework of another antibody. In certain embodiments, the antibody from which the CDR is derived and the antibody from which the framework is derived are of different species. In certain embodiments, the antibody from which the CDR is derived and the antibody from which the framework is derived are of different isotypes.

[0171] The term "multi-specific antibody" refers to an antibody wherein two or more variable regions bind to different epitopes. The epitopes may be on the same or different targets. In certain embodiments, a multi-specific antibody is a "bi-specific antibody," which recognizes two different epitopes on the same or different antigens.

[0172] The term "catalytic antibody" refers to an antibody in which one or more catalytic moieties is attached. In certain embodiments, a catalytic antibody is a cytotoxic antibody, which comprises a cytotoxic moiety.

[0173] The term "humanized antibody" refers to an antibody in which all or part of an antibody framework region is derived from a human, but all or part of one or more CDR regions is derived from another species, for example a mouse. In certain embodiments, humanization can be performed following methods known in the art (See, e.g., Jones et al., *Nature* 321, 522-525 (1986); Riechmann et al., *Nature,* 332, 323-327 (1988); Verhoeyen et al., *Science* 239, 1534-1536 (1988)), by substituting rodent complementarily-determining regions (CDRs) for the corresponding regions of a human antibody.

[0174] The terms "human antibody" and "fully human antibody" are used interchangeably and refer to an antibody in which both the CDR and the framework comprise substantially human sequences. In certain embodiments, fully human antibodies are produced in non-human mammals, including, but not limited to, mice, rats, and lagomorphs. In certain embodiments, fully human antibodies are produced in hybridoma cells. In certain embodiments, fully human antibodies are produced recombinantly.

[0175] "Chimeric antibody" refers to an antibody that has an antibody variable region of a first species fused to another molecule, for example, an antibody constant region of another second species. See, e.g., U.S. Pat. No. 4,816,567 and Morrison et al., *Proc Natl Acad Sci* (*USA*), 81:6851-6855 (1985). In certain embodiments, the first species may be different from the second species. In certain embodiments, the first species may be the same as the second species. In certain embodiments, chimeric antibodies may be made through mutagenesis or CDR grafting. CDR grafting typically involves grafting the CDRs from an antibody with desired specificity onto the framework regions (FRs) of another antibody.

[0176] A bivalent antibody other than a "multispecific" or "multifunctional" antibody, in certain embodiments, typically is understood to have each of its binding sites be identical.

[0177] An antibody substantially inhibits adhesion of a ligand to a receptor when an excess of antibody reduces the quantity of receptor bound to the ligand by at least about 20%, 40%, 60%, 80%, 85%, or more (as measured in an in vitro competitive binding assay).

[0178] The term "epitope" refers to a portion of a molecule capable of being bound by a specific binding agent. Exemplary epitopes may comprise any polypeptide determinant capable of specific binding to a target. Exemplary epitope determinants include, but are not limited to, chemically active surface groupings of molecules, for example, but not limited to, amino acids, sugar side chains, phosphoryl groups, and sulfonyl groups. In certain embodiments, epitope determinants may have specific three dimensional structural characteristics, and/or specific charge characteristics. In certain embodiments, an epitope is a region of an antigen that is bound by an antibody. Epitopes may be contiguous or non-contiguous. In certain embodiments, epitopes may be mimetic in that they comprise a three dimensional structure that is similar to an epitope used to generate the antibody, yet

comprise none or only some of the amino acid residues found in that epitope used to generate the antibody.

[0179] The term "inhibiting and/or neutralizing epitope" refers to an epitope, which when bound by a specific binding agent results in a decrease in a biological activity in vivo, in vitro, and/or in situ. In certain embodiments, a neutralizing epitope is located on or is associated with a biologically active region of a target.

[0180] The term "activating epitope" refers to an epitope, which when bound by a specific binding agent results in activation or maintenance of a biological activity in vivo, in vitro, and/or in situ. In certain embodiments, an activating epitope is located on or is associated with a biologically active region of a target.

[0181] The term "agent" is used herein to denote a chemical compound, a mixture of chemical compounds, a biological macromolecule, or an extract made from biological materials.

[0182] The term "pharmaceutical agent or drug" as used herein refers to a chemical compound or composition capable of inducing a desired therapeutic effect when properly administered to a patient.

[0183] The term "modulator," as used herein, is a compound that changes or alters the activity or function of a molecule. For example, a modulator may cause an increase or decrease in the magnitude of a certain activity or function of a molecule compared to the magnitude of the activity or function observed in the absence of the modulator. In certain embodiments, a modulator is an inhibitor or antagonist, which decreases the magnitude of at least one activity or function of a molecule. In certain embodiments, a modulator is an agonist, which increases the magnitude of at least one activity or function of a molecule. Certain exemplary activities and functions of a molecule include, but are not limited to, binding affinity, enzymatic activity, and signal transduction. Certain exemplary inhibitors include, but are not limited to, proteins, peptides, antibodies, peptibodies, carbohydrates, and small organic molecules. Exemplary peptibodies are described, e.g., in WO 01/83525.

[0184] As used herein, "substantially pure" means an object species is the predominant species present (i.e., on a molar basis it is more abundant than any other individual species in the composition). In certain embodiments, a substantially purified fraction is a composition wherein the object species comprises at least about 50 percent (on a molar basis) of all macromolecular species present. In certain embodiments, a substantially pure composition will comprise more than about 80%, 85%, 90%, 95%, or 99% of all macromolar species present in the composition. In certain embodiments, the object species is purified to essential homogeneity (contaminant species cannot be detected in the composition by conventional detection methods) wherein the composition consists essentially of a single macromolecular species.

[0185] The term "patient" includes human and animal subjects.

[0186] "Aggregation" refers to the formation of multimers of individual protein molecules through non-covalent or covalent interactions. Aggregation can be reversible or irreversible. In certain instances, when the loss of tertiary structure or partial unfolding occurs, hydrophobic amino acid residues which are typically hidden within the folded protein structure are exposed to the solution. In certain instances, this promotes hydrophobic-hydrophobic interactions between individual protein molecules, resulting in aggregation. Srisialam et al J Am Chem Soc 124 (9):1884-8 (2002), for example, has determined that certain conformational changes of a protein accompany aggregation, and that certain regions of specific proteins can be identified as particularly responsible for the formation of aggregates. In certain instances, protein aggregation can be induced by heat (Sun et al. J Agric Food Chem 50(6): 1636-42 (2002)), organic solvents (Srisailam et al., supra), and reagents such as SDS and lysophospholipids (Hagihara et al., Biochem 41(3): 1020-6 (2002)). Aggregation can be a significant problem in in vitro protein purification and formulation. In certain instances, after formation of aggregates, solubilization with strong denaturating solutions followed by renaturation and proper refolding may be needed before biological activity is restored.

[0187] Antibody structural units typically comprise a tetramer. Each such tetramer typically is composed of two identical pairs of polypeptide chains, each pair having one full-length "light" chain (in certain embodiments, about 25 kDa) and one full-length "heavy" chain (in certain embodiments, about 50-70 kDa). The term "heavy chain" includes any polypeptide having sufficient variable region sequence to confer specificity for a particular antigen. A full-length heavy chain includes a variable region domain, V_H, and three constant region domains, C_H1, C_H2, and C_H3. The V_H domain is at the amino-terminus of the polypeptide, and the C_H3 domain is at the carboxy-terminus. The term "heavy chain", as used herein, encompasses a full-length antibody heavy chain and fragments thereof.

[0188] The term "light chain" includes any polypeptide having sufficient variable region sequence to confer specificity for a particular antigen. A full-length light chain includes a variable region domain, V_L, and a constant region domain, C_L. Like the heavy chain, the variable region domain of the light chain is at the amino-terminus of the polypeptide. The term "light chain", as used herein, encompasses a full-length light chain and fragments thereof.

[0189] The amino-terminal portion of each chain typically includes a variable region (V_H in the heavy chain and V_L in the light chain) of about 100 to 110 or more amino acids that typically is responsible for antigen recognition. The carboxy-terminal portion of each chain typically defines a constant region (C_H domains in the heavy chain and C_L in the light chain) that may be responsible for effector function. Antibody effector functions include activation of complement and stimulation of opsonophagocytosis. Human light chains are typically classified as kappa and lambda light chains. Heavy chains are typically classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. IgG has several subclasses, including, but not limited to, IgG1, IgG2, IgG3, and IgG4. IgM has subclasses including, but not limited to, IgM1 and IgM2. IgA is similarly subdivided into subclasses including, but not limited to, IgA1 and IgA2. Within full-length light and heavy chains, typically, the variable and constant regions are joined by a "J" region of about 12 or more amino acids, with the heavy chain also including a "D" region of about 10 more amino acids. See, e.g., Fundamental Immunology Ch. 7 (Paul, W., ed., 2nd ed. Raven Press, N.Y. (1989)). The variable regions of each light/heavy chain pair typically form the antigen binding site.

[0190] The variable regions typically exhibit the same general structure of relatively conserved framework regions (FR) joined by three hypervariable regions, also called complementarity determining regions or CDRs. The CDRs from the

heavy and light chains of each pair typically are aligned by the framework regions, which may enable binding to a specific epitope. From N-terminal to C-terminal, both light and heavy chain variable regions typically comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4. The assignment of amino acids to each domain is typically in accordance with the definitions of Kabat Sequences of Proteins of Immunological Interest (National Institutes of Health, Bethesda, Md. (1987 and 1991)), or Chothia & Lesk J. Mol. Biol. 196:901-917 (1987); Chothia et al. Nature 342:878-883 (1989).

[0191] As discussed above, there are several types of antibody fragments. A Fab fragment is comprised of one light chain and the C_H1 and variable regions of one heavy chain. The heavy chain of a Fab molecule cannot form a disulfide bond with another heavy chain molecule. A Fab' fragment contains one light chain and one heavy chain that contains more of the constant region, between the C_H1 and C_H2 domains, such that an interchain disulfide bond can be formed between two heavy chains to form a F(ab')2 molecule. A Fab fragment is similar to a F(ab')2 molecule, except the constant region in the heavy chains of the molecule extends to the end of the C_H2 domain. The Fv region comprises the variable regions from both the heavy and light chains, but lacks the constant regions. A single chain variable fragment (scFv) comprises variable regions from both a heavy and a light chain wherein the heavy and light chain variable regions are fused to form a single molecule which forms an antigen-binding region. In certain embodiments, a scFv comprises a single polypeptide chain. A single-chain antibody comprises a scFv. In certain embodiments, a single-chain antibody comprises additional polypeptides fused to the scFv, such as, for example and not limitation, one or more constant regions. Exemplary single chain antibodies are discussed, e.g., in WO 88/01649 and U.S. Pat. Nos. 4,946,778, 5,260,203, and 5,869,620. A Fc fragment contains the C_H2 and C_H3 domains of a heavy chain and contains all or part of the constant region between the C_H1 and C_H2 domains. In certain embodiments, the all or part of the constant region between the C_H1 and C_H2 domains comprises one or more cysteines which allows for formation of one or more interchain disulfide bonds between Fc fragments.

[0192] In certain embodiments, a single chain antibody is a maxibody. The term "maxibody" includes a scFv fused (may be by a linker or direct attachment) to an Fc or an Fc fragment. In certain embodiments, a single chain antibody is a maxibody that binds huEpoR ("a huEpoR maxibody"). In certain embodiments, a single chain antibody is a maxibody that binds to and activates huEpoR. Exemplary Ig-like domain-Fc fusions are disclosed in U.S. Pat. No. 6,117,655.

[0193] In certain embodiments, antibodies can be generated using alternative scaffolds. The term "alternative scaffold" refers to a framework other than the traditional antibody framework of two light chains and two heavy chains, wherein the framework can carry one or more altered amino acids and/or one or more sequence insertions (such as CDR sequences) that confer on the resulting protein the ability to specifically bind at least one target. In certain embodiments, an alternative scaffold carries one or more CDRs to generate an antibody. In certain embodiments, an alternative scaffold is based on a human protein. In certain embodiments, an alternative scaffold is based on a mammalian protein. In certain embodiments, an alternative scaffold is based on a protein from a eukaryote. In certain embodiments, an alternative scaffold is based on a prokaryotic protein.

[0194] Certain examples of antibodies with alternative scaffolds include, but are not limited to, nanobodies, affibodies, microbodies, evibodies, and domain antibodies. Certain examples of alternative scaffolds useful for creating antibodies include, but are not limited to, single domain antibodies from camelids; protease inhibitors; human serum transferrin; CTLA-4; fibronectin, including, but not limited to, the fibronectin type III domain; C-type lectin-like domains; lipocalin family proteins; ankyrin repeat proteins; the Z-domain of Protein A; γ-crystallin; Tendamistat; Neocarzinostatin; CBM4-2; the T-cell receptor; Im9; designed AR proteins; designed TPR proteins; zinc finger domains; pVIII; Avian Pancreatic Polypeptide; GCN4; WW domains; Src Homology 3 (SH3) domains; Src Homology 2 (SH2) domains; PDZ domains; TEM-1 β-lactamase; GFP; Thioredoxin; Staphylcoccal nuclease; PHD-finger domains; CI-2; BPTI; APPI; HPSTI; Ecotin; LACI-D1; LDTI; MTI-II; scorpion toxins; Insect Defensin A Peptide; EETI-II; Min-23; CBD; PBP; Cytochrome b_{562}; Transferrin; LDL Receptor Domain A; and ubiquitin. Certain examples of alternative scaffolds are discussed in Hey et al., "Artificial, non-antibody binding proteins for pharmaceutical and industrial applications" *Trends in Biotechnology,* 23:514-22 (2005) and Binz et al., "Engineering novel binding proteins from nonimmunoglobulin domains" *Nature Biotechnology,* 23:1257-68 (2005).

[0195] In certain embodiments, functional domains, C_H1, C_H2, C_H3, and intervening sequences can be shuffled to create a different antibody constant region. For example, in certain embodiments, such hybrid constant regions can be optimized for half-life in serum, for assembly and folding of the antibody tetramer, and/or for improved effector function. In certain embodiments, modified antibody constant regions may be produced by introducing single point mutations into the amino acid sequence of the constant region and testing the resulting antibody for improved qualities, e.g., one or more of those listed above.

[0196] In certain embodiments, an antibody of one isotype is converted to a different isotype by isotype switching without losing its specificity for a particular target molecule. Methods of isotype switching include, but are not limited to, direct recombinant techniques (see e.g., U.S. Pat. No. 4,816,397) and cell-cell fusion techniques (see e.g., U.S. Pat. No. 5,916,771), among others. In certain embodiments, an antibody can be converted from one subclass to another subclass using techniques described above or otherwise known in the art without losing its specificity for a particular target molecule, including, but not limited to, conversion from an IgG2 subclass to an IgG1, IgG3, or IgG4 subclass.

[0197] In certain embodiments, chimeric antibodies that comprise at least a portion of a human sequence and another species' sequence are provided. In certain embodiments, such a chimeric antibody may result in a reduced immune response in a host than an antibody without that host's antibody sequences. For example, in certain instances, an animal of interest may be used as a model for a particular human disease. To study the effect of an antibody on that disease in the animal host, one could use an antibody from a different species. But, in certain instances, such antibodies from another species, may elicit an immune response to the antibodies themselves in the host animal, thus impeding evaluation of these antibodies. In certain embodiments, replacing part of the amino acid sequence of an antibody with antibody amino acid sequence from the host animal may decrease the magnitude of the host animal's anti-antibody response.

[0198] In certain embodiments, a chimeric antibody comprises a heavy chain and a light chain, wherein the variable regions of the light chain and the heavy chain are from a first species and the constant regions of the light chain and the heavy chain are from a second species. In certain embodiments, the antibody heavy chain constant region is an antibody heavy chain constant region of a species other than human. In certain embodiments, the antibody light chain constant region is an antibody light chain constant region of a species other than human. In certain embodiments, the antibody heavy chain constant region is a human antibody heavy chain constant region, and the antibody heavy chain variable region is an antibody heavy chain variable region of a species other than human. In certain embodiments, the antibody light chain constant region is a human antibody light chain constant region, and the antibody light chain variable region is an antibody light chain variable region of a species other than human. Exemplary antibody constant regions include, but are not limited to, a human antibody constant region, a cynomolgus monkey antibody constant region, a mouse antibody constant region, and a rabbit antibody constant region. Exemplary antibody variable regions include, but are not limited to, a human antibody variable region, a mouse antibody variable region, a pig antibody variable region, a guinea pig antibody variable region, a cynomolgus monkey antibody variable region, and a rabbit antibody variable region. In certain embodiments, the framework regions of the variable region in the heavy chain and light chain may be replaced with framework regions derived from other antibody sequences.

[0199] Certain exemplary chimeric antibodies may be produced by methods well known to those of ordinary skill in the art. In certain embodiments, the polynucleotide of the first species encoding the heavy chain variable region and the polynucleotide of the second species encoding the heavy chain constant region can be fused. In certain embodiments, the polynucleotide of the first species encoding the light chain variable region and the nucleotide sequence of the second species encoding the light chain constant region can be fused. In certain embodiments, these fused nucleotide sequences can be introduced into a cell either in a single expression vector (e.g., a plasmid) or in multiple expression vectors. In certain embodiments, a cell comprising at least one expression vector may be used to make polypeptide. In certain embodiments, these fused nucleotide sequences can be introduced into a cell either in separate expression vectors or in a single expression vector. In certain embodiments, the host cell expresses both the heavy chain and the light chain, which combine to produce an antibody. In certain embodiments, a cell comprising at least one expression vector may be used to make an antibody. Exemplary methods for producing and expressing antibodies are discussed below.

[0200] In certain embodiments, conservative modifications to the heavy and light chains of an antibody (and corresponding modifications to the encoding nucleotides) will produce antibodies having functional and chemical characteristics similar to those of the original antibody. In contrast, in certain embodiments, substantial modifications in the functional and/or chemical characteristics of an antibody to may be accomplished by selecting substitutions in the amino acid sequence of the heavy and light chains that differ significantly in their effect on maintaining (a) the structure of the molecular backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain.

[0201] Certain desired amino acid substitutions (whether conservative or non-conservative) can be determined by those skilled in the art at the time such substitutions are desired. In certain embodiments, amino acid substitutions can be used to identify important residues of antibodies, such as those which may increase or decrease the affinity of the antibodies or the effector function of the antibodies.

[0202] Various antibodies specific to an antigen may be produced in a number of ways. In certain embodiments, an antigen containing an epitope of interest may be introduced into an animal host (e.g., a mouse), thus producing antibodies specific to that epitope. In certain instances, antibodies specific to an epitope of interest may be obtained from biological samples taken from hosts that were naturally exposed to the epitope. In certain instances, introduction of human immunoglobulin (Ig) loci into mice in which the endogenous Ig genes have been inactivated offers the opportunity to obtain human monoclonal antibodies (MAbs). In certain embodiments, antibodies specific to an epitope of interest may be obtained by in vitro screening with light and heavy chain libraries, e.g., phage display.

[0203] A bispecific or bifunctional antibody comprises two different heavy/light chain pairs and two different binding sites. Bispecific antibodies may be produced by a variety of methods including, but not limited to, fusion of hybridomas or linking of Fab' fragments. See, e.g., Songsivilai & Lachmann *Clin. Exp. Immunol* 79: 315-321 (1990), Kostelny et al. *J. Immunol.* 148:1547-1553 (1992).

[0204] In certain embodiments, antibodies can be expressed in cell lines other than hybridoma cell lines. In certain embodiments, sequences encoding particular antibodies, including chimeric antibodies, can be used for transformation of a suitable mammalian host cell. According to certain embodiments, transformation can be by any known method for introducing polynucleotides into a host cell, including, for example packaging the polynucleotide in a virus (or into a viral vector) and transducing a host cell with the virus or by transfecting a vector using procedures known in the art, as exemplified by U.S. Pat. Nos. 4,399,216; 4,912,040; 4,740,461; and 4,959,455.

[0205] In certain embodiments, an expression vector comprises a polynucleotide sequence encoding an antibody. In certain embodiments, a method of making a polypeptide comprising producing the polypeptide in a cell comprising an expression vector in conditions suitable to express the polynucleotide contained therein to produce the polypeptide is provided.

[0206] In certain embodiments, a method of making an antibody comprising producing the antibody in a cell comprising at least one of expression vectors in conditions suitable to express the polynucleotides contained therein to produce the antibody is provided.

[0207] In certain embodiments, a scFv-Fc protein is expressed from a host cell. In certain embodiments, at least some of the scFv-Fc proteins expressed in a host cell form multimers, including, but not limited to, dimers. In certain embodiments, scFV-Fc proteins expressed in a host cell include monomers and multimers.

[0208] In certain embodiments, a vector is transfected into a cell. In certain embodiments, the transfection procedure used may depend upon the host to be transformed. Certain

methods for introduction of heterologous polynucleotides into mammalian cells are known in the art and include, but are not limited to, dextran-mediated transfection, calcium phosphate precipitation, polybrene mediated transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) in liposomes, and direct microinjection of the DNA into nuclei.

[0209] Certain mammalian cell lines available as hosts for expression are known in the art and include, but are not limited to, many immortalized cell lines available from the American Type Culture Collection (ATCC), including but not limited to Chinese hamster ovary (CHO) cells, E5 cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (e.g., Hep G2), NSO cells, SP20 cells, Per C6 cells, 293 cells, and a number of other cell lines. In certain embodiments, cell lines may be selected through determining which cell lines have high expression levels and produce antibodies with constitutive antigen binding properties.

[0210] In certain embodiments, the vectors that may be transfected into a host cell comprising-control sequences that are operably linked to a polynucleotide encoding an antibody. In certain embodiments, control sequences facilitate expression of the linked polynucleotide, thus resulting in the production of the polypeptide encoded by the linked polynucleotide. In certain embodiments, the vector also comprises polynucleotide sequences that allow chromosome-independent replication in the host cell. Exemplary vectors include, but are not limited to, plasmids (e.g., BlueScript, puc, etc.), cosmids, and YACS.

[0211] In certain embodiments, an antibody is provided which comprises the sequences:

(SEQ ID. NO.: 1)
EVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVAN

IKPDGSEKYYVDSVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCARVS

RGGSYSDWGQGTLVTVSS.,
and

(SEQ ID. NO.: 2)
QSVLTQPPSASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMI

YEVSKRPSGVPDRFSGSKSGNTASLTVSGLQPEDEADYYCSSYAGRNWVF

GGGTQLTVL.

[0212] In certain embodiments, an antibody is provided which comprises the sequences:

(SEQ ID. NO.: 3)
EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVAN

IKPDGSEKYYVDSVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCARVS

RGGSYSDWGQGTLVTVSS,
and

(SEQ ID. NO.: 4)
QSALTQPASVSGSPGQSITISCTGTSSDVGGYIYVSWYQQHPGKAPKLMI

YDVSRRPSGISDRFSGSKSGNTASLTISGLQAEDEADYYCNSYTTLSTWL

FGGGTKVTVL.

[0213] In certain embodiments, an antibody is provided which comprises the sequences:

(SEQ ID. NO.: 5)
EVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVAN

IKPDGSEKYYVDSVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCARVS

RGGSYSDWGKGTLVTVSS,
and

(SEQ ID. NO.: 6)
QSALTQPASVSGSPGQSIIISCTGTRSDIGGYNYVSWYQHHPGRAPKLII

FDVNNRPSGVSHRFSGSKSGNTASLTISGLQAEDEADYYCNSFTDSRTWL

FGGGTKLTVL.

[0214] In certain embodiments, an antibody is provided which comprises the sequences:

(SEQ ID. NO.: 7)
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSA

ISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVKDR

VAVAGKGSYYFDSWGRGTTVTVSS,
and

(SEQ ID. NO.: 8)
QSVLTQPPSVSEAPGQRVTIACSGSSSNIGNNAVSWYQQLPGKAPTLLIY

YDNLLPSGVSDRFSGSKSGTSASLAISGLQSEDEADYYCAAWDDSLNDWV

FGGGTKVTVL.

[0215] In certain embodiments, an antibody is provided which comprises the sequences:

(SEQ ID. NO.: 9)
QVQLQESGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSPSRGLEWL

GRTYYRSKWYNDYAVSVKSRMTIKADTSKNQFSLQLNSVTPEDTAVYYCA

RDEGPLDYWGQGTLVTVSA,
and

(SEQ ID. NO.: 10)
QAVLTQPSSVSGAPGQRVTISCTGSSSNLGTGYDVHWYQQLPGTAPKLLI

YGNSNRPSGVPDRFSGSKSDTSGLLAITGLQAEDEATYYCQSYDFSLSAM

VFGGGTKVTVL.

[0216] In certain embodiments, an antibody is provided which comprises the sequences:

(SEQ ID NO.: 56)
QVQLQQSGGGVVQPGRSLRLSCAASGFTFSDYAMHWVRQAPGKGLEWVAV

ISNHGKSTYYADSVKGRFTISRDNSKHMLYLQMNSLRADDTALYYCARDI

ALAGDYWGQGTLVTVSA,
and

(SEQ ID NO.: 58)
DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQLPGKVPKLLIYG

ASKLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCLQDYNYPLTFGP

GTRLEIK.

[0217] In certain embodiments, an antibody is provided which comprises the sequences:

(SEQ ID NO.: 60)
QVQLQESGPGLVRPSGTLSLTCAVSGGSIGSSNWWSWVRQAPGKGLEWIG

EISQSGSTNYNPSLKGRVTISLDRSRNQLSLKLSSVTAADTAVYYCARQL

RSIDAFDIWGPGTTVTVSA,
and

(SEQ ID NO.: 62)
SYVLTQPPSVSVSPGLTATITCSGDKLGDKYASWYQQKPGQSPVLVIYQD

RKRPSGIPERFSGSNSGNTATLTISGTQAVDEADYYCQAWDSDTSYVFGT

GTQLTVL.

[0218] In certain embodiments, an antibody is provided which comprises the sequences:

(SEQ ID NO.: 64)
QVQLQESGPGLVKPSETLSLTCTVSGGYINNYYWSWIRQPPGKGLEWIGY

IHYSGSTYYNPSLKSRVTISEDTSKNQFSLKLSSATAADTAVYYCARVGY

YYDSSGYNLAWYFDLWGRGTLVTVSA,
and

(SEQ ID NO.: 66)
SSELTQDPAVSVALGQTVRITCQGDNLRSYSATWYQQKPGQAPVLVLFGE

NNRPSGIPDRFSGSKSGDTAVLTITGTQTQDEADYYCTSRVNSGNHLGVF

GPGTQLTVL.

[0219] In certain embodiments, an antibody is provided which comprises the sequences:

(SEQ ID NO.: 68)
EVQLVESGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGW

INPNSGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDTAVYYCARGG

HMTTVTRDAFDIWGQGTMVTVSA,
and

(SEQ ID NO.: 70)
SSELTQDPAVSVALGQTIRITCQGDSLRYYYATWYQQKPGQAPILVIYGQ

NNRPSGVPDRFSGSSSGNTASLTITGAQAEDEADYYCGTWDSSVSASWVF

GGGTKVTVL.

[0220] In certain embodiments, an antibody is provided which comprises the sequences:

(SEQ ID NO.: 72)
QVQLQQSGAEVKKPGASVKVSCKASGYTFSGYYMHWVRQAPGQGLEWMGW

INPNSGSTNYAQKFLGRVTMTRDTSISTAYMELSSLRSDDTAVYYCARGH

SGDYFDYWGQGTLVTVSA,
and

(SEQ ID NO.: 74)
EIVLTQSPSSLSASVGDRVTITCRASQSVSSWLAWYQQRPGQAPKLLIYA

ARLRGGGPSRFSGSGSGTEFTLTISSLQPEDFATYFCQQSYSTPISFGGG

TKLEIK.

[0221] In certain embodiments, an antibody is provided which comprises the sequences:

(SEQ ID NO.: 76)
QVQLQESGSGLARPSQTLSLTCAVSGGSISSSAFSWNWIRQPPGKGLEWI

GYIYHTGITDYNPSLKSRVTISVDRSKNQFSLNVNSVTAADTAVYYCARG

HGSDPAWFDPWGKGTLVTVSS,
and

(SEQ ID NO.: 78)
QSVLTQPPSVSVSPGQTASITCSGDKLGDKYASWYQQRPGQSPVLVIYRD

TKRPSGIPERFSGSNSGNTATLTISGTQAVDEADYYCQAWDSTTSLVFGG

GTKLTVL.

[0222] In certain embodiments, an antibody is provided which comprises the sequences:

(SEQ ID NO.: 80)
EVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVAN

IKPDGSEKYYVDSVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCARVS

RGGSYSDWGRGTMVTVSS,
and

(SEQ ID NO.: 82)
QSVLTQPPSASGSPGQSVTISCTGTSSDVGGFNYVSWYQKYPGKAPKLVI

YEVSKRPSGVPDRFSGSKSGNTASLTVSGLQAEDEADYYCSSWAPGKNLF

GGGTKLTVL.

[0223] In certain embodiments, an antibody is provided which comprises the sequences:

(SEQ ID NO.: 84)
EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSG

ISGSGSSEGGTYYADSVKGRFTLSRDNSKNTLYLQMNSLRAEDTALYYCV

KDRPSRYSFGYYFDYWGRGTLVTVSS,
and

(SEQ ID NO.: 86)
LPVLTQPPSVSVSPGQTASIACSGNKLGDKYVSWYQQKPGQSPLLVIYQD

TKRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCQAWDSSTDVVFGG

GTKLTVL.

[0224] In certain embodiments, an antibody is provided which comprises the sequences:

(SEQ ID NO.: 88)
EVQLVESGGGLVQPGGSLRLSCAVSGFTFSKYWMTWVRQAPGKGLEWVAN

IKPDGSEKYYVESVKGRFTISRDNAKNSVYLQMNSVRAEDTAVYYCARV

SRGGSFSDWGQGTMVTVSS,
and

(SEQ ID NO.: 90)
QSVLTQPPSASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPDKAPRLMI

YDVNKRPSGVPDRFSGSKSGNTASLTVSGLQAEDEAHYYCNSYAGSNNWV

FGGGTQLTVL.

[0225] In certain embodiments, an antibody is provided which comprises the sequences:

(SEQ ID NO.: 92)
QVQLVESGGGLVQPGGSLRLSCAVSGFTFSKYWMTWVRQAPGKGLEWVAN

IKPDGSEKYYVESVKGRFTISRDNAKNSVYLQMNSVRAEDTAVYYCARV

SRGGSFSDWGQGTLVTVSS,
and

(SEQ ID NO.: 94)
QSVLTQPPSASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGRAPKLII

YEVSKRPSGVPDRFSGSKSGNTASLTVSGLQADDEADYYCNSYAGSIYVF

GSGTKVTVL.

[0226] In certain embodiments, an antibody is provided which comprises the sequences:

(SEQ ID NO.: 96)
QVQLVQSGAEIKKPGASVKVSCKTFGSPFSTNDIHWVRQAPGQGLEWMGI

IDTSGAMTRYAQKFQGRVTVTRETSTSTVYMELSSLKSEDTAVYYCAREG

CTNGVCYDNGFDIWGQGTLVTVSS,
and

(SEQ ID NO.: 98)
DIQMTQSPSTLSASIGDRVTITCRASEGIYHWLAWYQQKPGKAPKLLIYK

ASSLASGAPSRFSGSGSGTDFTLTISSLQPDDFATYYCQQYSNYPLTFGG

GTKLEIK.

[0227] In certain embodiments, an antibody is provided which comprises the sequences:

(SEQ ID NO.: 100)
QVQLVESGGGLVQPGGSLRLSCAVSGFTFSKYWMTWVRQAPGKGLEWVAN

IKPDGSEKYYVESVKGRFTISRDNAKNSVYLQMNSVRAEDTAVYYCARVS

RGGSFSDWGRGTMVTVSS,
and

(SEQ ID NO.: 102)
QSALTQPASVSGSPGQSITISCTGTSSDVGSYNLVSWYQQHPGKVPKLII

YEVSNRPSGVSHRFSGSKSGNTASLTISGLQAEDEADYYCSSLTSSGTWV

FGGGTKVTVL.

[0228] In certain embodiments, an antibody is provided which comprises the sequences:

(SEQ ID NO.: 104)
EVQLVESGGGLVQPGGSLRLSCAVSGFTFSKYWMTWVRQAPGKGLEWVAN

IKPDGSEKYYVESVKGRFTISRDNAKNSVYLQMNSVRAEDTAVYYCARVS

RGGSFSDWGQGTLVTVSS,
and

(SEQ ID NO.: 106)
QSALTQPPSASGSPGQSVTISCTGTSSDVGAYNYVSWYQQHPGKAPKLMI

YEVARRPSGVPDRFSGSKSGNTASLTVSGLQAEDEADYYCSSYAGSNNFA

VFGRGTKLTVL.

[0229] In certain embodiments, an antibody is provided which comprises the sequences:

(SEQ ID NO.: 108)
EVQLVQSGGGLVQPGGSLRLSCAASGFRFSSYWMTWVRQAPGKGLEWVAN

IKPDGSEKYYVDSVKGRFTMSRDNAKNSVYLQMNSLRAEDTAVYYCARVS

RGGSFSDWGQGTLVTVSS,
and

(SEQ ID NO.: 110)
QSALTQPASVSGSPGQSITIPCTGTSSDIGTYDYVSWYQQHPGKVPKVII

YEVTNRPSGVSNRFSGSKSGNTASLTISGLQADDEADYYCNSFTKNNTWV

FGGGTKLTVL.

[0230] In certain embodiments, an antibody is provided which comprises the sequences:

(SEQ ID NO.: 112)
QVQLVESGGGLVQPGRSLILSCAVSGFTFSKYWMTWVRQAPGKGLEWVAN

IKPDGSEKYYVESVKGRFTISRDNAKNSVYLQMNSVRAEDTAVYYCARVS

RGGSFSDWSQGTLVTVSS,
and

(SEQ ID NO.: 114)
QSALTQPPSASGSPGQSVTISCTGTSGDVGAYNYVSWYQQYPGKAPKLMI

YEVSKRPSGVPDRFSGSKSGNTASLTVSGLQAEDEADYYCNSYRGSNGPW

VFGGGTKVTVL.

[0231] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

(SEQ ID. NO.: 1)
EVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVAN

IKPDGSEKYYVDSVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCARVS

RGGSYSDWGQGTLVTVSS.,
and

(SEQ ID. NO.: 2)
QSVLTQPPSASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMI

YEVSKRPSGVPDRFSGSKSGNTASLTVSGLQPEDEADYYCSSYAGRNWVF

GGGTQLTVL.

[0232] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

(SEQ ID. NO.: 3)
EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVAN

IKPDGSEKYYVDSVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCARVS

RGGSYSDWGQGTLVTVSS,
and

(SEQ ID. NO.: 4)
QSALTQPASVSGSPGQSITISCTGTSSDVGGYIYVSWYQQHPGKAPKLMI

YDVSRRPSGISDRFSGSKSGNTASLTISGLQAEDEADYYCNSYTTLSTWL

FGGGTKVTVL.

[0233] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

(SEQ ID. NO.: 5)
EVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVAN

IKPDGSEKYYVDSVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCARVS

RGGSYSDWGKGTLVTVSS,
and

(SEQ ID. NO.: 6)
QSALTQPASVSGSPGQSIIISCTGTRSDIGGYNYVSWYQHHPGRAPKLII

FDVNNRPSGVSHRFSGSKSGNTASLTISGLQAEDEADYYCNSFTDSRTWL

FGGGTKLTVL.

[0234] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

(SEQ ID. NO.: 7)
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSA

ISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVKDR

VAVAGKGSYYFDSWGRGTTVTVSS,
and

(SEQ ID. NO.: 8)
QSVLTQPPSVSEAPGQRVTIACSGSSSNIGNNAVSWYQQLPGKAPTLLIY

YDNLLPSGVSDRFSGSKSGTSASLAISGLQSEDEADYYCAAWDDSLNDWV

FGGGTKVTVL,

[0235] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

(SEQ ID. NO.: 9)
QVQLQESGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSPSRGLEWL

GRTYYRSKWYNDYAVSVKSRMTIKADTSKNQFSLQLNSVTPEDTAVYYCA

RDEGPLDYWGQGTLVTVSA,
and

(SEQ ID. NO.: 10)
QAVLTQPSSVSGAPGQRVTISCTGSSSNLGTGYDVHWYQQLPGTAPKLLI

YGNSNRPSGVPDRFSGSKSDTSGLLAITGLQAEDEATYYCQSYDFSLSAM

VFGGGTKVTVL.

[0236] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

(SEQ ID NO.: 56)
QVQLQQSGGGVVQPGRSLRLSCAASGFTFSDYAMHWVRQAPGKGLEWVAV

ISNHGKSTYYADSVKGRFTISRDNSKHMLYLQMNSLRADDTALYYCARDI

ALAGDYWGQGTLVTVSA,

-continued
and

(SEQ ID NO.: 58)
DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQLPGKVPKLLIYG

ASKLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCLQDYNYPLTFGP

GTRLEIK.

[0237] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

(SEQ ID NO.: 60)
QVQLQESGPGLVRPSGTLSLTCAVSGGSIGSSNWWSWVRQAPGKGLEWIG

EISQSGSTNYNPSLKGRVTISLDRSRNQLSLKLSSVTAADTAVYYCARQL

RSIDAFDIWGPGTTVTVSA,
and

(SEQ ID NO.: 62)
SYVLTQPPSVSVSPGLTATITCSGDKLGDKYASWYQQKPGQSPVLVIYQD

RKRPSGIPERFSGSNSGNTATLTISGTQAVDEADYYCQAWDSDTSYVFGT

GTQLTVL.

[0238] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

(SEQ ID NO.: 64)
QVQLQESGPGLVKPSETLSLTCTVSGGYINNYYWSWIRQPPGKGLEWIGY

IHYSGSTYYNPSLKSRVTISEDTSKNQFSLKLSSATAADTAVYYCARVGY

YYDSSGYNLAWYFDLWGRGTLVTVSA,
and

(SEQ ID NO.: 66)
SSELTQDPAVSVALGQTVRITCQGDNLRSYSATWYQQKPGQAPVLVLFGE

NNRPSGIPDRFSGSKSGDTAVLTITGTQTQDEADYYCTSRVNSGNHLGVF

GPGTQLTVL.

[0239] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

(SEQ ID NO.: 68)
EVQLVESGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGW

INPNSGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDTAVYYCARGG

HMTTVTRDAFDIWGQGTMVTVSA,
and

(SEQ ID NO.: 70)
SSELTQDPAVSVALGQTIRITCQGDSLRYYYATWYQQKPGQAPILVIYGQ

NNRPSGVPDRFSGSSSGNTASLTITGAQAEDEADYYCGTWDSSVSASWVF

GGGTKVTVL.

[0240] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

(SEQ ID NO.: 72)
QVQLQQSGAEVKKPGASVKVSCKASGYTFSGYYMHWVRQAPGQGLEWMGW

INPNSGSTNYAQKFLGRVTMTRDTSISTAYMELSSLRSDDTAVYYCARGH

SGDYFDYWGQGTLVTVSA,
and

(SEQ ID NO.: 74)
EIVLTQSPSSLSASVGDRVTITCRASQSVSSWLAWYQQRPGQAPKLLIYA

ARLRGGGPSRFSGSGSGTEFTLTISSLQPEDFATYFCQQSYSTPISFGGG

TKLEIK.

[0241] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

(SEQ ID NO.: 76)
QVQLQESGSGLARPSQTLSLTCAVSGGSISSSAFSWNWIRQPPGKGLEWI

GYIYHTGITDYNPSLKSRVTISVDRSKNQFSLNVNSVTAADTAVYYCARG

HGSDPAWFDPWGKGTLVTVSS,
and

(SEQ ID NO.: 78)
QSVLTQPPSVSVSPGQTASITCSGDKLGDKYASWYQQRPGQSPVLVIYRD

TKRPSGIPERFSGSNSGNTATLTISGTQAVDEADYYCQAWDSTTSLVFGG

GTKLTVL.

[0242] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

(SEQ ID NO.: 80)
EVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVAN

IKPDGSEKYYVDSVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCARVS

RGGSYSDWGRGTMVTVSS,
and

(SEQ ID NO.: 82)
QSVLTQPPSASGSPGQSVTISCTGTSSDVGGFNYVSWYQKYPGKAPKLVI

YEVSKRPSGVPDRFSGSKSGNTASLTVSGLQAEDEADYYCSSWAPGKNLF

GGGTKLTVL.

[0243] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

(SEQ ID NO.: 84)
EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSG

ISGSGSSEGGTYYADSVKGRFTLSRDNSKNTLYLQMNSLRAEDTALYYCV

KDRPSRYSFGYYFDYWGRGTLVTVSS,
and

(SEQ ID NO.: 86)
LPVLTQPPSVSVSPGQTASIACSGNKLGDKYVSWYQQKPGQSPLLVIYQD

TKRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCQAWDSSTDVVFGG

GTKLTVL.

[0244] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

(SEQ ID NO.: 88)
EVQLVESGGGLVQPGGSLRLSCAVSGFTFSKYWMTWVRQAPGKGLEWVAN

IKPDGSEKYYVESVKGRFTISRDNAKNSVYLQMNSVRAEDTAVYYCARVS

RGGSFSDWGQGTMVTVSS,
and

(SEQ ID NO.: 90)
QSVLTQPPSASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPDKAPRLMI

YDVNKRPSGVPDRFSGSKSGNTASLTVSGLQAEDEAHYYCNSYAGSNNWV

FGGGTQLTVL.

[0245] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

(SEQ ID NO.: 92)
QVQLVESGGGLVQPGGSLRLSCAVSGFTFSKYWMTWVRQAPGKGLEWVAN

IKPDGSEKYYVESVKGRFTISRDNAKNSVYLQMNSVRAEDTAVYYCARVS

RGGSFSDWGQGTLVTVSS,
and

(SEQ ID NO.: 94)
QSVLTQPPSASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGRAPKLII

YEVSKRPSGVPDRFSGSKSGNTASLTVSGLQADDEADYYCNSYAGSIYVF

GSGTKVTVL.

[0246] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

(SEQ ID NO.: 96)
QVQLVQSGAEIKKPGASVKVSCKTFGSPFSTNDIHWVRQAPGQGLEWMGI

IDTSGAMTRYAQKFQGRVTVTRETSTSTVYMELSSLKSEDTAVYYCAREG

CTNGVCYDNGFDIWGQGTLVTVSS,
and

(SEQ ID NO.: 98)
DIQMTQSPSTLSASIGDRVTITCRASEGIYHWLAWYQQKPGKAPKLLIYK

ASSLASGAPSRFSGSGSGTDFTLTISSLQPDDFATYYCQQYSNYPLTFGG

GTKLEIK.

[0247] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

(SEQ ID NO.: 100)
QVQLVESGGGLVQPGGSLRLSCAVSGFTFSKYWMTWVRQAPGKGLEWVAN

IKPDGSEKYYVESVKGRFTISRDNAKNSVYLQMNSVRAEDTAVYYCARVS

RGGSFSDWGRGTMVTVSS,
and

(SEQ ID NO.: 102)
QSALTQPASVSGSPGQSITISCTGTSSDVGSYNLVSWYQQHPGKVPKLII

YEVSNRPSGVSHRFSGSKSGNTASLTISGLQAEDEADYYCSSLTSSGTWV

FGGGTKVTVL.

[0248] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

(SEQ ID NO.: 104)
EVQLVESGGGLVQPGGSLRLSCAVSGFTFSKYWMTWVRQAPGKGLEWVAN

IKPDGSEKYYVESVKGRFTISRDNAKNSVYLQMNSVRAEDTAVYYCARVS

RGGSFSDWGQGTLVTVSS,
and

(SEQ ID NO.: 106)
QSALTQPPSASGSPGQSVTISCTGTSSDVGAYNYVSWYQQHPGKAPKLMI

YEVARRPSGVPDRFSGSKSGNTASLTVSGLQAEDEADYYCSSYAGSNNFA

VFGRGTKLTVL.

[0249] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

(SEQ ID NO.: 108)
EVQLVQSGGGLVQPGGSLRLSCAASGFRFSSYWMTWVRQAPGKGLEWVAN

IKPDGSEKYYVDSVKGRFTMSRDNAKNSVYLQMNSLRAEDTAVYYCARVS

RGGSFSDWGQGTLVTVSS,
and

(SEQ ID NO.: 110)
QSALTQPASVSGSPGQSITIPCTGTSSDIGTYDYVSWYQQHPGKVPKVII

YEVTNRPSGVSNRFSGSKSGNTASLTISGLQADDEADYYCNSFTKNNTWV

FGGGTKLTVL.

[0250] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

(SEQ ID NO.: 112)
QVQLVESGGGLVQPGRSLILSCAVSGFTFSKYWMTWVRQAPGKGLEWVAN

IKPDGSEKYYVESVKGRFTISRDNAKNSVYLQMNSVRAEDTAVYYCARVS

RGGSFSDWSQGTLVTVSS,
and

(SEQ ID NO.: 114)
QSALTQPPSASGSPGQSVTISCTGTSGDVGAYNYVSWYQQYPGKAPKLMI

YEVSKRPSGVPDRFSGSKSGNTASLTVSGLQAEDEADYYCNSYRGSNGPW

VFGGGTKVTVL.

[0251] In certain embodiments, an antibody is provided which comprises the sequences:

SYWMS; (SEQ ID NO.: 11)

NIKPDGSEKYYVDSVKG; (SEQ ID NO.: 12)
and

VSRGGSYSD. (SEQ ID NO.: 13)

[0252] In certain embodiments, an antibody is provided which comprises the sequences:

TGTSSDVGGYNYVS; (SEQ ID NO.: 14)

EVSKRPS; (SEQ ID NO.: 15)
and

SSYAGRNWV. (SEQ ID NO.: 16)

[0253] In certain embodiments, an antibody is provided which comprises the sequences:

SYWMS; (SEQ ID NO.: 11)

NIKPDGSEKYYVDSVKG; (SEQ ID NO.: 12)

VSRGGSYSD; (SEQ ID NO.: 13)

TGTSSDVGGYNYVS; (SEQ ID NO.: 14)

EVSKRPS; (SEQ ID NO.: 15)
and

SSYAGRNWV. (SEQ ID NO.: 16)

[0254] In certain embodiments, an antibody is provided which comprises the sequences:

TGTSSDVGGYIYVS; (SEQ ID NO.: 17)

DVSRRPS; (SEQ ID NO.: 18)
and

NSYTTLSTWL. (SEQ ID NO.: 19)

[0255] In certain embodiments, an antibody is provided which comprises the sequences:

SYWMS; (SEQ ID NO.: 11)

NIKPDGSEKYYVDSVKG; (SEQ ID NO.: 12)

VSRGGSYSD; (SEQ ID NO.: 13)

TGTSSDVGGYIYVS; (SEQ ID NO.: 17)

DVSRRPS; (SEQ ID NO.: 18)
and

NSYTTLSTWL. (SEQ ID NO.: 19)

[0256] In certain embodiments, an antibody is provided which comprises the sequences:

TGTRSDIGGYNYVS; (SEQ ID NO.: 20)

FDVNNRPS; (SEQ ID NO.: 21)
and

NSFTDSRTWL. (SEQ ID NO.: 22)

[0257] In certain embodiments, an antibody is provided which comprises the sequences:

SYWMS; (SEQ ID NO.: 11)

NIKPDGSEKYYVDSVKG; (SEQ ID NO.: 12)

-continued

VSRGGSYSD; (SEQ ID NO.: 13)

TGTRSDIGGYNYVS; (SEQ ID NO.: 20)

FDVNNRPS; (SEQ ID NO.: 21)
and

NSFTDSRTWL. (SEQ ID NO.: 22)

[0258] In certain embodiments, an antibody is provided which comprises the sequences:

SYAMS; (SEQ ID NO.: 23)

AISGSGGSTYYADSVKG; (SEQ ID NO.: 24)
and

DRVAVAGKGSYYFDS. (SEQ ID NO.: 25)

[0259] In certain embodiments, an antibody is provided which comprises the sequences:

SGSSSNIGNNAVS; (SEQ ID NO.: 26)

YDNLLPSG; (SEQ ID NO.: 27)
and

AAWDDSLNDWV. (SEQ ID NO.: 28)

[0260] In certain embodiments, an antibody is provided which comprises the sequences:

SYAMS; (SEQ ID NO.: 23)

AISGSGGSTYYADSVKG; (SEQ ID NO.: 24)

DRVAVAGKGSYYFDS; (SEQ ID NO.: 25)

SGSSSNIGNNAVS; (SEQ ID NO.: 26)

YDNLLPSG; (SEQ ID NO.: 27)
and

AAWDDSLNDWV. (SEQ ID NO.: 28)

[0261] In certain embodiments, an antibody is provided which comprises the sequences:

SNSAAWN; (SEQ ID NO.: 29)

RTYYRSKWYNDYAVSKS; (SEQ ID NO.: 30)
and

DEGPLDY. (SEQ ID NO.: 31)

[0262] In certain embodiments, an antibody is provided which comprises the sequences:

TGSSSNLGTGYDVH; (SEQ ID NO.: 32)

GNSNRPS; (SEQ ID NO.: 33)
and

QSYDFSLSAMV. (SEQ ID NO.: 34)

[0263] In certain embodiments, an antibody is provided which comprises the sequences:

SNSAAWN; (SEQ ID NO.: 29)

RTYYRSKWYNDYAVSKS; (SEQ ID NO.: 30)

DEGPLDY; (SEQ ID NO.: 31)

TGSSSNLGTGYDVH; (SEQ ID NO.: 32)

GNSNRPS; (SEQ ID NO.: 33)
and

QSYDFSLSAMV. (SEQ ID NO.: 34)

[0264] In certain embodiments, an antibody is provided which comprises the sequences:

DYAMH; (SEQ ID NO.: 123)

VISNHGKSTYYADSVKG; (SEQ ID NO.: 124)
and

DIALAGDY. (SEQ ID NO .: 125)

[0265] In certain embodiments, an antibody is provided which comprises the sequences: RASQSISSYLN (SEQ ID NO.: 126); GASKLQS (SEQ ID NO.: 127); and LQDYNYPLT (SEQ ID NO.: 128).

[0266] In certain embodiments, an antibody is provided which comprises the sequences:

DYAMH; (SEQ ID NO.: 123)

VISNHGKSTYYADSVKG; (SEQ ID NO.: 124)

DIALAGDY; (SEQ ID NO.: 125)

RASQSISSYLN; (SEQ ID NO.: 126)

GASKLQS; (SEQ ID NO.: 127)
and

LQDYNYPLT. (SEQ ID NO.: 128)

[0267] In certain embodiments, an antibody is provided which comprises the sequences:

SSNWWS; (SEQ ID NO.: 129)

EISQSGSTNYNPSLKG; (SEQ ID NO.: 130)
and

QLRSIDAFDI. (SEQ ID NO.: 131)

[0268] In certain embodiments, an antibody is provided which comprises the sequences:

DKYAS; (SEQ ID NO.: 132)

YQDRKRPSGI; (SEQ ID NO.: 133)
and

WDSDSTYV; (SEQ ID NO.: 134)

[0269] In certain embodiments, an antibody is provided which comprises the sequences:

SSNWWS; (SEQ ID NO.: 129)

EISQSGSTNYNPSLKG; (SEQ ID NO.: 130)

QLRSIDAFDI; (SEQ ID NO.: 131)

DKYAS; (SEQ ID NO.: 132)

YQDRKRPSGI; (SEQ ID NO.: 133)
and

WDSDTSYV. (SEQ ID NO.: 134)

[0270] In certain embodiments, an antibody is provided which comprises the sequences:

NYYWS; (SEQ ID NO.: 135)

YIHYSGSTYYNPSLKSR; (SEQ ID NO.: 136)
and

VGYYYDSSGYNLAWYFDL. (SEQ ID NO.: 212)

[0271] In certain embodiments, an antibody is provided which comprises the sequences:

QGDNLRSYSAT; (SEQ ID NO.: 137)

GENNRPS; (SEQ ID NO.: 138)
and

TSRVNSGNHLGV. (SEQ ID NO.: 139)

[0272] In certain embodiments, an antibody is provided which comprises the sequences:

NYYWS; (SEQ ID NO.: 135)

YIHYSGSTYYNPSKLSR; (SEQ ID NO.: 136)

VGYYYDSSGYNLAWYFDL; (SEQ ID NO.: 212)

QGDNLRSYSAT; (SEQ ID NO.: 137)

GENNRPS; (SEQ ID NO.: 138)
and

TSRVNSGNHLGV. (SEQ ID NO.: 139)

[0273] In certain embodiments, an antibody is provided which comprises the sequences:

GYYMH; (SEQ ID NO.: 140)

WINPNSGGTNYAQKFQGR; (SEQ ID NO.: 141)
and

GGHMTTVTRDAFDI. (SEQ ID NO.: 142)

[0274] In certain embodiments, an antibody is provided which comprises the sequences:

QGDSLRYYYAT; (SEQ ID NO.: 143)

GQNNRPS; (SEQ ID NO.: 144)

-continued

and

GTWDSSVSASWV. (SEQ ID NO.: 145)

[0275] In certain embodiments, an antibody is provided which comprises the sequences:

GYYMH; (SEQ ID NO.: 140)

WINPNSGGTNYAQFQGR; (SEQ IN NO.: 141)

GGHMTTVTRDAFDI; (SEQ ID NO.: 142)

QGDSLRYYYAT; (SEQ ID NO.: 143)

GQNNRPS; (SEQ ID NO.: 144)
and

GTWDSSVSASWV. (SEQ ID NO.: 145)

[0276] In certain embodiments, an antibody is provided which comprises the sequences:

GYYMH; (SEQ ID NO.: 146)

WINPNSGSTNYAQKFLG; (SEQ ID NO.: 147)
and

GHSGDYFDY. (SEQ ID NO.: 148)

[0277] In certain embodiments, an antibody is provided which comprises the sequences:

RASQSVSSWLA; (SEQ ID NO.: 149)

AARLRG; (SEQ ID NO.: 150)
and

QQSYSTPIS. (SEQ ID NO.: 151)

[0278] In certain embodiments, an antibody is provided which comprises the sequences:

GYYMH; (SEQ ID NO.: 146)

WINPNSGSTNYAQKFLG; (SEQ IN NO.: 147)

GHSGDYFDY; (SEQ ID NO.: 148)

RASQSVSSWLA; (SEQ ID NO.: 149)

AARLRG; (SEQ ID NO.: 150)
and

QQSYSTPIS. (SEQ ID NO.: 151)

[0279] In certain embodiments, an antibody is provided which comprises the sequences:

SSAFSWN; (SEQ ID NO.: 152)

YIYHTGITDYNPSLKS; (SEQ ID NO.: 153)
and

GHGSDPAWFDP. (SEQ ID NO.: 154)

[0280] In certain embodiments, an antibody is provided which comprises the sequences:

SGDKLGDKYAS; (SEQ ID NO.: 155)

RDTKRPS; (SEQ ID NO.: 156)
and

QAWDSTTSLV. (SEQ ID NO.: 157)

[0281] In certain embodiments, an antibody is provided which comprises the sequences:

SSAFSWN; (SEQ ID NO.: 152)

YIYHTGITDYNPSLKS; (SEQ ID NO.: 153)

GHGSDPAWFDP; (SEQ ID NO.: 154)

SGDKLGDKYAS; (SEQ ID NO.: 155)

RDTKRPS; (SEQ ID NO.: 156)
and

QAWDSTTSLV. (SEQ ID NO.: 157)

[0282] In certain embodiments, an antibody is provided which comprises the sequences:

SYWMS; (SEQ ID NO.: 158)

NIKPDGSEKYYVDSVKG; (SEQ ID NO.: 159)
and

VSRGGSYSD. (SEQ ID NO.: 160)

[0283] In certain embodiments, an antibody is provided which comprises the sequences:

TGTSSDVGGFNYVS; (SEQ ID NO.: 161)

EVSKRPS; (SEQ ID NO.: 162)
and

SSWAPGKNL. (SEQ IN NO.: 163)

[0284] In certain embodiments, an antibody is provided which comprises the sequences:

SYWMS; (SEQ IN NO.: 158)

NIKPDGSEKYYVDSVKG; (SEQ IN NO.: 159)

VSRGGSYSD; (SEQ ID NO.: 160)

TGTSSDVGGFNYVS; (SEQ ID NO.: 161)

EVSKRPS; (SEQ ID NO.: 162)
and

SSWAPGKNL. (SEQ ID NO.: 163)

[0285] In certain embodiments, an antibody is provided which comprises the sequences:

SYAMS; (SEQ ID NO.: 164)

GISGSGSSEGGTYYADSVKG; (SEQ ID NO.: 165)

-continued

and

DRPSRYSFGYYFDY. (SEQ IN NO.: 166)

[0286] In certain embodiments, an antibody is provided which comprises the sequences:

SGNKLGDKYVS; (SEQ ID NO.: 167)

QDTKRPS; (SEQ ID NO.: 168)
and

QAWDSSTDVV. (SEQ IN NO.: 169)

[0287] In certain embodiments, an antibody is provided which comprises the sequences:

SYAMS; (SEQ IN NO.: 164)

GISGSGSSEGGTYYADSVKG; (SEQ IN NO.: 165)

DRPSRYSFGYYFDY; (SEQ ID NO.: 166)

SGNKLGDKYVS; (SEQ ID NO.: 167)

QDTKRPS; (SEQ ID NO.: 168)
and

QAWDSSTDVV. (SEQ ID NO.: 169)

[0288] In certain embodiments, an antibody is provided which comprises the sequences:

KYWMT; (SEQ ID NO.: 170)

NIKPDGSEKYYVESVKG; (SEQ ID NO.: 171)
and

VSRGGSFSD. (SEQ ID NO.: 172)

[0289] In certain embodiments, an antibody is provided which comprises the sequences:

TGTSSDVGGYNYVS; (SEQ ID NO.: 173)

DVNKRPS; (SEQ ID NO.: 174)
and

NSYAGSNNWV. (SEQ IN NO.: 175)

[0290] In certain embodiments, an antibody is provided which comprises the sequences:

KYWMT; (SEQ IN NO.: 170)

NIKPDGSEKYYVESVKG; (SEQ IN NO.: 171)

VSRGGSFSD; (SEQ ID NO.: 172)

TGTSSDVGGYNYVS; (SEQ ID NO.: 173)

DVNKRPS; (SEQ ID NO.: 174)
and

NSYAGSNNWV. (SEQ ID NO.: 175)

[0291] In certain embodiments, an antibody is provided which comprises the sequences:

KYWMT; (SEQ ID NO.: 176)

NIKPDGSEKYYVESVKG; (SEQ ID NO.: 177)
and

VSRGGSFSD. (SEQ IN NO.: 178)

[0292] In certain embodiments, an antibody is provided which comprises the sequences:

TGTSSDVGGYNYVS; (SEQ ID NO.: 179)

EVSKRPS; (SEQ ID NO.: 180)
and

NSYAGSIYV. (SEQ ID NO.: 181)

[0293] In certain embodiments, an antibody is provided which comprises the sequences:

KYWMT; (SEQ ID NO.: 176)

NIKPDGSEKYYVESVKG; (SEQ ID NO.: 177)

VSRGGSFSD; (SEQ ID NO.: 178)

TGTSSDVGGYNYVS; (SEQ ID NO.: 179)

EVSKRPS; (SEQ ID NO.: 180)
and

NSYAGSIYV. (SEQ ID NO.: 181)

[0294] In certain embodiments, an antibody is provided which comprises the sequences:

TNDIH; (SEQ ID NO.: 182)

IIDTSGAMTRYAQKFQG; (SEQ ID NO.: 183)
and

EGCTNGVCYDNGFDI. (SEQ ID NO.: 184)

[0295] In certain embodiments, an antibody is provided which comprises the sequences:

RASEGIYHWLA; (SEQ ID NO.: 185)

KASSLAS; (SEQ ID NO.: 186)
and

QQYSNYPLT. (SEQ ID NO.: 187)

[0296] In certain embodiments, an antibody is provided which comprises the sequences:

TNDIH; (SEQ ID NO.: 182)

IIDTSGAMTRYAQKFQG; (SEQ ID NO.: 183)

EGCTNGVCYDNGFDI; (SEQ ID NO.: 184)

RASEGIYHWLA; (SEQ ID NO.: 185)

KASSLAS; (SEQ ID NO.: 186)

-continued

and

QQYSNYPLT. (SEQ ID NO.: 187)

[0297] In certain embodiments, an antibody is provided which comprises the sequences:

KYWMT; (SEQ ID NO.: 188)

NIKPDGSEKYYVESVKG; (SEQ ID NO.: 189)
and

VSRGGSFSD. (SEQ ID NO.: 190)

[0298] In certain embodiments, an antibody is provided which comprises the sequences:

TGTSSDVGSYNLVS; (SEQ ID NO.: 191)

EVSNRPS; (SEQ ID NO.: 192)

SSLTSSGTWV. (SEQ ID NO.: 193)

[0299] In certain embodiments, an antibody is provided which comprises the sequences:

KYWMT; (SEQ ID NO.: 188)

NIKPDGSEKYYVESVKG; (SEQ ID NO.: 189)

VSRGGSFSD; (SEQ ID NO.: 190)

TGTSSDVGSYNLVS; (SEQ ID NO.: 191)

EVSNRPS; (SEQ ID NO.: 192)
and

SSLTSSGTWV. (SEQ ID NO.: 193)

[0300] In certain embodiments, an antibody is provided which comprises the sequences:

KYWMT; (SEQ ID NO.: 194)

NIKPDGSEKYYVESVKG; (SEQ ID NO.: 195)
and

VSRGGSFSD. (SEQ ID NO.: 196)

[0301] In certain embodiments, an antibody is provided which comprises

TGTSSDVGAYNYVS; (SEQ ID NO.: 197)

EVARRPS; (SEQ ID NO.: 198)
and

SSYAGSNNFAV. (SEQ ID NO.: 199)

[0302] In certain embodiments, an antibody is provided which comprises the sequences:

KYWMT; (SEQ ID NO.: 194)

NIKPDGSEKYYVESVKG; (SEQ ID NO.: 195)

-continued

VSRGGSFSD;	(SEQ ID NO.: 196)
TGTSSDVGAYNYVS;	(SEQ ID NO.: 197)
EVARRPS;	(SEQ ID NO.: 198)
and	
SSYAGSNNFAV.	(SEQ ID NO.: 199)

[0303] In certain embodiments, an antibody is provided which comprises the sequences

SYWMT;	(SEQ ID NO.: 200)
NIKPDGSEKYYVDSVKG;	(SEQ ID NO.: 201)
and	
VSRGGSFSD.	(SEQ ID NO.: 202)

[0304] In certain embodiments, an antibody is provided which comprises the sequences:

TGTSSDIGTYDYVS;	(SEQ ID NO.: 203)
EVTNRPS;	(SEQ ID NO.: 204)
and	
NSFTKNNTWV.	(SEQ ID NO.: 205)

[0305] In certain embodiments, an antibody is provided which comprises the sequences:

SYWMT;	(SEQ ID NO.: 200)
NIKPDGSEKYYVDSVKG;	(SEQ ID NO.: 201)
VSRGGSFSD;	(SEQ ID NO.: 202)
TGTSSDIGTYDYVS;	(SEQ ID NO.: 203)
EVTNRPS;	(SEQ ID NO.: 204)
and	
NSFTKNNTWV.	(SEQ ID NO.: 205)

[0306] In certain embodiments, an antibody is provided which comprises the sequences:

KYWMT;	(SEQ ID NO.: 206)
NIKPDGSEKYYVESVKG;	(SEQ ID NO.: 207)
and	
VSRGGSFSD.	(SEQ ID NO.: 208)

[0307] In certain embodiments, an antibody is provided which comprises the sequences:

TGTSGDVGAYNYVS;	(SEQ ID NO.:209)
EVSKRPS;	(SEQ ID NO.:210)
and	
NSYRGSNGPWV.	(SEQ ID NO.:211)

[0308] In certain embodiments, an antibody is provided which comprises the sequences:

KYWMT;	(SEQ ID NO.:206)
NIKPDGSEKYYVESVKG;	(SEQ ID NO.:207)
VSRGGSFSD;	(SEQ ID NO.:208)
TGTSGDVGAYNYVS;	(SEQ ID NO.:209)
EVSKRPS;	(SEQ ID NO.:210)
and	
NSYRGSNGPWV.	(SEQ ID NO.:211)

[0309] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

SYWMS;	(SEQ ID NO.:11)
NIKPDGSEKYYVDSVKG;	(SEQ ID NO.:12)
and	
VSRGGSYSD.	(SEQ ID NO.:13)

[0310] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

TGTSSDVGGYNYVS;	(SEQ ID NO.:14)
EVSKRPS;	(SEQ ID NO.:15)
and	
SSYAGRNWV.	(SEQ ID NO.:16)

[0311] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

SYWMS;	(SEQ ID NO.:11)
NIKPDGSEKYYVDSVKG;	(SEQ ID NO.:12)
VSRGGSYSD;	(SEQ ID NO.:13)
TGTSSDVGGYNYVS;	(SEQ ID NO.:14)
EVSKRPS;	(SEQ ID NO.:15)
and	
SSYAGRNWV.	(SEQ ID NO.:16)

[0312] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

TGTSSDVGGYIYVS;	(SEQ ID NO.:17)
DVSRRPS;	(SEQ ID NO.:18)
and	
NSYTTLSTWL.	(SEQ ID NO.:19)

[0313] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

SYWMS; (SEQ ID NO.:11)

NIKPDGSEKYYVDSVKG; (SEQ ID NO.:12)

VSRGGSYSD; (SEQ ID NO.:13)

TGTSSDVGGYIYVS; (SEQ ID NO.:17)

DVSRRPS; (SEQ ID NO.:18)
and

NSYTTLSTWL. (SEQ ID NO.:19)

[0314] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

TGTRSDIGGYNYVS; (SEQ ID NO.:20)

FDVNNRPS; (SEQ ID NO.:21)
and

NSFTDSRTWL. (SEQ ID NO.:22)

[0315] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

SYWMS; (SEQ ID NO.:11)

NIKPDGSEKYYVDSVKG; (SEQ ID NO.:12)

VSRGGSYSD; (SEQ ID NO.:13)

TGTRSDIGGYNYVS; (SEQ ID NO.:20)

FDVNNRPS; (SEQ ID NO.:21)
and

NSFTDSRTWL. (SEQ ID NO.:22)

[0316] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

SYAMS; (SEQ ID NO.:23)

AISGSGGSTYYADSVKG; (SEQ ID NO.:24)
and

DRVAVAGKGSYYFDS. (SEQ ID NO.:25)

[0317] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

SGSSSNIGNNAVS; (SEQ ID NO.:26)

YDNLLPSG; (SEQ ID NO.:27)
and

AAWDDSLNDWV. (SEQ ID NO.:28)

[0318] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

SYAMS; (SEQ ID NO.:23)

AISGSGGSTYYADSVKG; (SEQ ID NO.:24)

DRVAVAGKGSYYFDS; (SEQ ID NO.:25)

SGSSSNIGNNAVS; (SEQ ID NO.:26)

YDNLLPSG; (SEQ ID NO.:27)
and

AAWDDSLNDWV. (SEQ ID NO.:28)

[0319] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

SNSAAWN; (SEQ ID NO.:29)

RTYYRSKWYNDYAVSKS; (SEQ ID NO.:30)
and

DEGPLDY. (SEQ ID NO.:31)

[0320] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

TGSSSNLGTGYDVH; (SEQ ID NO.:32)

GNSNRPS; (SEQ ID NO.:33)
and

QSYDFSLSAMV. (SEQ ID NO.:34)

[0321] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

SNSAAWN; (SEQ ID NO.:29)

RTYYRSKWYNDYAVSKS; (SEQ ID NO.:30)

DEGPLDY; (SEQ ID NO.:31)

TGSSSNLGTGYDVH; (SEQ ID NO.:32)

GNSNRPS; (SEQ ID NO.:33)
and

QSYDFSLSAMV. (SEQ ID NO.:34)

[0322] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

DYAMH; (SEQ ID NO.: 123)

VISNHGKSTYYADSVKG; (SEQ ID NO.: 124)
and

DIALAGDY. (SEQ ID NO.: 125)

[0323] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

RASQSISSYLN; (SEQ ID NO.: 126)

GASKLQS; (SEQ ID NO.: 127)
and

LQDYNYPLT. (SEQ ID NO.: 128)

[0324] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

DYAMH; (SEQ ID NO.: 123)

VISNHGKSTYYADSVKG; (SEQ ID NO.: 124)

DIALAGDY; (SEQ ID NO.: 125)

RASQSISSYLN; (SEQ ID NO.: 126)

GASKLQS; (SEQ ID NO.: 127)
and

LQDYNYPLT. (SEQ ID NO.: 128)

[0325] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

SSNWWS; (SEQ ID NO.: 129)

EISQSGSTNYNPSLKG; (SEQ ID NO.: 130)
and

QLRSIDAFDI. (SEQ ID NO.: 131)

[0326] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

DKYAS; (SEQ ID NO.: 132)

YQDRKRPSGI; (SEQ ID NO.: 133)
and

WDSDTSYV;. (SEQ ID NO.: 134)

[0327] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

SSNWWS; (SEQ ID NO.: 129)

EISQSGSTNYNPSLKG; (SEQ ID NO.: 130)

QLRSIDAFDI; (SEQ ID NO.: 131)

DKYAS; (SEQ ID NO.: 132)

YQDRKRPSGI; (SEQ ID NO.: 133)
and

WDSDTSYV. (SEQ ID NO.: 134)

[0328] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

NYYWS; (SEQ ID NO.: 135)

YIHYSGSTYYNPSLKSR; (SEQ ID NO.: 136)
and

VGYYYDSSGYNLAWYFDL. (SEQ ID NO.: 212)

[0329] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

QGDNLRSYSAT; (SEQ ID NO.: 137)

GENNRPS; (SEQ ID NO.: 138)
and

TSRVNSGNHLGV. (SEQ ID NO.: 139)

[0330] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

NYYWS; (SEQ ID NO.: 135)

YIHYSGSTYYNPSLKSR; (SEQ ID NO.: 136)

VGYYYDSSGYNLAWYFDL; (SEQ ID NO.: 212)

QGDNLRSYSAT; (SEQ ID NO.: 137)

GENNRPS; (SEQ ID NO.: 138)
and

TSRVNSGNHLGV. (SEQ ID NO.: 139)

[0331] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

GYYMH; (SEQ ID NO.: 140)

WINPNSGGTNYAQKFQGR; (SEQ ID NO.: 141)
and

GGHMTTVTRDAFDI. (SEQ ID NO.: 142)

[0332] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

QGDSLRYYYAT; (SEQ ID NO.: 143)

GQNNRPS; (SEQ ID NO.: 144)
and

GTWDSSVSASWV. (SEQ ID NO.: 145)

[0333] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

GYYMH; (SEQ ID NO.: 140)

WINPNSGGTNYAQKFQGR; (SEQ ID NO.: 141)

GGHMTTVTRDAFDI; (SEQ ID NO.: 142)

-continued

QGDSLRYYYAT; (SEQ ID NO.: 143)

GQNNRPS; (SEQ ID NO.: 144)
and

GTWDSSVSASWV. (SEQ ID NO.: 145)

[0334] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

GYYMH; (SEQ ID NO.: 146)

WINPNSGSTNYAQKFLG; (SEQ ID NO.: 147)
and

GHSGDYFDY. (SEQ ID NO.: 148)

[0335] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

RASQSVSSWLA; (SEQ ID NO.: 149)

AARLRG; (SEQ ID NO.: 150)
and

QQSYSTPIS. (SEQ ID NO.: 151)

[0336] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

GYYMH; (SEQ ID NO.: 146)

WINPNSGSTNYAQKFLG; (SEQ ID NO.: 147)

GHSGDYFDY; (SEQ ID NO.: 148)

RASQSVSSWLA; (SEQ ID NO.: 149)

AARLRG; (SEQ ID NO.: 150)
and

QQSYSTPIS. (SEQ ID NO.: 151)

[0337] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

SSAFSWN; (SEQ ID NO.: 152)

YIYHTGITDYNPSLKS; (SEQ ID NO.: 153)
and

GHGSDPAWFDP. (SEQ ID NO.: 154)

[0338] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

SGDKLGDKYAS; (SEQ ID NO.: 155)

RDTKRPS; (SEQ ID NO.: 156)
and

QAWDSTTSLV. (SEQ ID NO.: 157)

[0339] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

SSAFSWN; (SEQ ID NO.: 152)

YIYHTGITDYNPSLKS; (SEQ ID NO.: 153)

GHGSDPAWFDP; (SEQ ID NO.: 154)

SGDKLGDKYAS; (SEQ ID NO.: 155)

RDTKRPS; (SEQ ID NO.: 156)
and

QAWDSTTSLV. (SEQ ID NO.: 157)

[0340] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

SYWMS; (SEQ ID NO.: 158)

NIKPDGSEKYYVDSVKG; (SEQ ID NO.: 159)
and

VSRGGSYSD. (SEQ ID NO.: 160)

[0341] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

TGTSSDVGGFNYVS; (SEQ IN NO.: 161)

EVSKRPS; (SEQ ID NO.: 162)
and

SSWAPGKNL. (SEQ ID NO.: 163)

[0342] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

SYWMS; (SEQ ID NO.: 158)

NIKPDGSEKYYVDSVKG; (SEQ ID NO.: 159)

VSRGGSYSD; (SEQ ID NO.: 160)

TGTSSDVGGFNYVS; (SEQ ID NO.: 161)

EVSKRPS; (SEQ ID NO.: 162)
and

SSWAPGKNL. (SEQ ID NO.: 163)

[0343] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

SYAMS; (SEQ ID NO.: 164)

GISGSGSSEGGTYYADSVKG; (SEQ ID NO.: 165)
and

DRPSRYSFGYYFDY. (SEQ ID NO.: 166)

[0344] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

SGNKLGDKYVS; (SEQ ID NO.: 167)

QDTKRPS; (SEQ ID NO.: 168)
and

QAWDSSTDVV. (SEQ ID NO.: 169)

[0345] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

SYAMS; (SEQ ID NO.: 164)

GISGSGSSEGGTYYADSVKG; (SEQ ID NO.: 165)

DRPSRYSFGYYFDY; (SEQ ID NO.: 166)

SGNKLGDKYVS; (SEQ ID NO.: 167)

QDTKRPS; (SEQ ID NO.: 168)
and

QAWDSSTDVV. (SEQ ID NO.: 169)

[0346] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

KYWMT; (SEQ ID NO.: 179)

NIKPDGSEKYYVESVKG; (SEQ ID NO.: 171)
and

VSRGGSFSD. (SEQ ID NO.: 172)

[0347] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

TGTSSDVGGYNYVS; (SEQ ID NO.: 173)

DVNKRPS; (SEQ ID NO.: 174)
and

NSYAGSNNWV. (SEQ ID NO.: 175)

[0348] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

KYWMT; (SEQ ID NO.: 170)

NIKPDGSEKYYVESVKG; (SEQ ID NO.: 171)

VSRGGSFSD; (SEQ ID NO.: 172)

TGTSSDVGGYNYVS; (SEQ ID NO.: 173)

DVNKRPS; (SEQ ID NO.: 174)
and

NSYAGSNNWV. (SEQ ID NO.: 175)

[0349] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

KYWMT; (SEQ ID NO.: 176)

NIKPDGSEKYYVESVKG; (SEQ ID NO.: 177)
and

VSRGGSFSD. (SEQ ID NO.: 178)

[0350] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

TGTSSDVGGYNYVS; (SEQ ID NO.: 179)

EVSKRPS; (SEQ ID NO.: 180)
and

NSYAGSIYV. (SEQ ID NO.: 181)

[0351] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

KYWMT; (SEQ ID NO.: 176)

NIKPDGSEKYYVESVKG; (SEQ ID NO.: 177)

VSRGGSFSD; (SEQ ID NO.: 178)

TGTSSDVGGYNYVS; (SEQ ID NO.: 179)

EVSKRPS; (SEQ ID NO.: 180)
and

NSYAGSIYV. (SEQ ID NO.: 181)

[0352] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

TNDIH; (SEQ ID NO.:182)

IIDTSGAMTRYAQKFQG; (SEQ ID NO.:183)
and

EGCTNGVCYDNGFDI. (SEQ ID NO.:184)

[0353] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

RASEGIYHWLA; (SEQ ID NO.:185)

KASSLAS; (SEQ ID NO.:186)
and

QQYSNYPLT. (SEQ ID NO.:187)

[0354] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

TNDIH; (SEQ ID NO.:182)

IIDTSGAMTRYAQKFQG; (SEQ ID NO.:183)

EGCTNGVCYDNGFDI; (SEQ ID NO.:184)

-continued

RASEGIYHWLA; (SEQ ID NO.:185)

KASSLAS; (SEQ ID NO.:186)
and

QQYSNYPLT. (SEQ ID NO.:187)

[0355] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

KYWMT; (SEQ ID NO.:188)

NIKPDGSEKYYVESVKG; (SEQ ID NO.:189)
and

VSRGGSFSD. (SEQ ID NO.:190)

[0356] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

TGTSSDVGSYNLVS; (SEQ ID NO.:191)

EVSNRPS; (SEQ ID NO.:192)
and

SSLTSSGTWV. (SEQ ID NO.:193)

[0357] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

KYWMT; (SEQ ID NO.:188)

NIKPDGSEKYYVESVKG; (SEQ ID NO.:189)

VSRGGSFSD; (SEQ ID NO.:190)

TGTSSDVGSYNLVS; (SEQ ID NO.:191)

EVSNRPS; (SEQ ID NO.:192)
and

SSLTSSGTWV. (SEQ ID NO.:193)

[0358] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

KYWMT; (SEQ ID NO.:194)

NIKPDGSEKYYVESVKG; (SEQ ID NO.:195)
and

VSRGGSFSD. (SEQ ID NO.:196)

[0359] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

TGTSSDVGAYNYVS; (SEQ ID NO.:197)

EVARRPS; (SEQ ID NO.:198)
and

SSYAGSNNFAV. (SEQ ID NO.:199)

[0360] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

KYWMT; (SEQ ID NO.:194)

NIKPDGSEKYYVESVKG; (SEQ ID NO.:195)

VSRGGSFSD; (SEQ ID NO.:196)

TGTSSDVGAYNYVS; (SEQ ID NO.:197)

EVARRPS; (SEQ ID NO.:198)
and

SSYAGSNNFAV. (SEQ ID NO.:199)

[0361] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

SYWMT; (SEQ ID NO.:200)

NIKPDGSEKYYVDSVKG; (SEQ ID NO.:201)
and

VSRGGSFSD. (SEQ ID NO.:202)

[0362] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

TGTSSDIGTYDYVS; (SEQ ID NO.:203)

EVTNRPS; (SEQ ID NO.:204)
and

NSFTKNNTWV. (SEQ ID NO.:205)

[0363] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

SYWMT; (SEQ ID NO.:200)

NIKPDGSEKYYVDSVKG; (SEQ ID NO.:201)

VSRGGSFSD; (SEQ ID NO.:202)

TGTSSDIGTYDYVS; (SEQ ID NO.:203)

EVTNRPS; (SEQ ID NO.:204)
and

NSFTKNNTWV. (SEQ ID NO.:205)

[0364] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

KYWMT; (SEQ ID NO.:206)

NIKPDGSEKYYVESVKG; (SEQ ID NO.:207)
and

VSRGGSFSD. (SEQ ID NO.:208)

[0365] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

TGTSGDVGAYNYVS; (SEQ ID NO.:209)

EVSKRPS; (SEQ ID NO.:210)
and

NSYRGSNGPWV. (SEQ ID NO.:211)

[0366] In certain embodiments, a single chain variable fragment fused to an Fc is provided which comprises the sequences:

KYWMT; (SEQ ID NO.:206)

NIKPDGSEKYYVESVKG; (SEQ ID NO.:207)

VSRGGSFSD; (SEQ ID NO.:208)

TGTSGDVGAYNYVS; (SEQ ID NO.:209)

EVSKRPS; (SEQ ID NO.:210)
and

NSYRGSNGPWV. (SEQ ID NO.:211)

[0367] In certain embodiments, an antibody is provided which comprises the sequence:

(SEQ ID NO.: 45)
EVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVAN

IKPDGSEKYYVDSVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCARVS

RGGSYSDWGQGTLVTVSSGGGGSGGGGSGGGGSAQSVLTQPPSASGSPGQ

SVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYEVSKRPSGVPDRFSG

SKSGNTASLTVSGLQPEDEADYYCSSYAGRNWVFGGGTQLTVLGAAAEPK

SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH

EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE

YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL

VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ

QGNVFSCSVMHEALHNHYTQKSLSLSPGK.

[0368] In certain embodiments, an antibody is provided which comprises the sequence:

(SEQ ID NO.: 46)
EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVAN

IKPDGSEKYYVDSVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCARVS

RGGSYSDWGQGTLVTVSSGGGGSGGGGSGGGGSAQSALTQPASVSGSPGQ

SITISCTGTSSDVGGYIYVSWYQQHPGKAPKLMIYDVSRRPSGISDRFSG

SKSGNTASLTISGLQAEDEADYYCNSYTTLSTWLFGGGTKVTVLGAAAEP

KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS

HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK

EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC

LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW

QQGNVFSCSVMHEALHNHYTQKSLSLSPGK.

[0369] In certain embodiments, an antibody is provided which comprises the sequence:

(SEQ ID NO.: 47)
EVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVAN

IKPDGSEKYYVDSVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCARVS

RGGSYSDWGKGTLVTVSSGGGGSGGGGSGGGGSAQSALTQPASVSGSPGQ

SIIISCTGTRSDIGGYNYVSWYQHHPGRAPKLIIFDVNNRPSGVSHRFSG

SKSGNTASLTISGLQAEDEADYYCNSFTDSRTWLFGGGTKLTVLGAAAEP

KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS

HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK

EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC

LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW

QQGNVFSCSVMHEALHNHYTQKSLSLSPGK.

[0370] In certain embodiments, an antibody is provided which comprises the sequence:

(SEQ ID NO.: 48)
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSA

ISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVKDR

VAVAGKGSYYFDSWGRGTTVTVSSGGGGSGGGGSGGGGSAQSVLTQPPSV

SEAPGQRVTIACSGSSSNIGNNAVSWYQQLPGKAPTLLIYYDNLLPSGVS

DRFSGSKSGTSASLAISGLQSEDEADYYCAAWDDSLNDWVFGGGTKVTVL

GAAAEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC

VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ

DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKN

QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT

VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK.

[0371] In certain embodiments, an antibody is provided which comprises the sequence:

(SEQ ID NO.: 49)
QVQLQESGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSPSRGLEWL

GRTYYRSKWYNDYAVSVKSRMTIKADTSKNQFSLQLNSVTPEDTAVYYCA

RDEGPLDYWGQGTLVTVSAGGGGSGGGGSGGGGSGAPQAVLTQPSSVSGA

PGQRVTISCTGSSSNLGTGYDVHWYQQLPGTAPKLLIYGNSNRPSGVPDR

FSGSKSDTSGLLAITGLQAEDEATYYCQSYDFSLSAMVFGGGTKVTVLAA

AEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV

DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL

NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVS

LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK

SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK.

[0372] In certain embodiments, a single chain variable fragment fused to an Fc is provided which specifically binds to amino acids F93 and H114 of the extracellular domain of the human Epo Receptor.

[0373] In certain embodiments, a single chain variable fragment fused to an Fc is provided which specifically binds to amino acids S91, F93, and H114 of the extracellular domain of the human Epo Receptor.

[0374] In certain embodiments, a single chain variable fragment fused to an Fc is provided which specifically binds to amino acid F93 of the extracellular domain of the human Epo Receptor.

[0375] In certain embodiments, a single chain variable fragment fused to an Fc is provided which specifically binds to amino acids E62, F93, and M150 of the extracellular domain of the human Epo Receptor.

[0376] In certain embodiments, a single chain variable fragment fused to an Fc is provided which specifically binds to amino acids V48, E62, L66, R68, and H70 of the extracellular domain of the human Epo Receptor.

[0377] In certain embodiments, a single chain variable fragment fused to an Fc is provided which specifically binds to amino acids V48, W64, L66, R68, and H70 of the extracellular domain of the human Epo Receptor.

[0378] In certain embodiments, a single chain variable fragment fused to an Fc is provided which specifically binds to amino acids A44, V48, P63, L66, R68, and H70 of the extracellular domain of the human Epo Receptor.

[0379] In certain embodiments, a single chain variable fragment fused to an Fc is provided which specifically binds to amino acids L66 and R99 of the extracellular domain of the human Epo Receptor.

[0380] In certain embodiments, an antibody is provided which specifically binds to amino acids F93 and H114 of the extracellular domain of the human Epo Receptor.

[0381] In certain embodiments, an antibody is provided which specifically binds to amino acids S91, F93, and H114 of the extracellular domain of the human Epo Receptor.

[0382] In certain embodiments, an antibody is provided which specifically binds to amino acid F93 of the extracellular domain of the human Epo Receptor.

[0383] In certain embodiments, an antibody is provided which specifically binds to amino acids E62, F93, and M150 of the extracellular domain of the human Epo Receptor.

[0384] In certain embodiments, an antibody is provided which specifically binds to amino acids V48, E62, L66, R68, and H70 of the extracellular domain of the human Epo Receptor.

[0385] In certain embodiments, an antibody is provided which specifically binds to amino acids V48, W64, L66, R68, and H70 of the extracellular domain of the human Epo Receptor.

[0386] In certain embodiments, an antibody is provided which specifically binds to amino acids A44, V48, P63, L66, R68, and H70 of the extracellular domain of the human Epo Receptor.

[0387] In certain embodiments, an antibody is provided which specifically binds to amino acids L66 and R99 of the extracellular domain of the human Epo Receptor.

[0388] In certain embodiments, a single chain variable fragment fused to an Fc is provided which specifically binds to amino acids F93, E60, and H114 of the extracellular domain of the human Epo Receptor.

[0389] In certain embodiments, a single chain variable fragment fused to an Fc is provided which specifically binds to amino acid V48 of the extracellular domain of the human Epo Receptor.

[0390] In certain embodiments, a single chain variable fragment fused to an Fc is provided which specifically binds to amino acid L66 of the extracellular domain of the human Epo Receptor.

[0391] In certain embodiments, a single chain variable fragment fused to an Fc is provided which specifically binds to amino acid W64 of the extracellular domain of the human Epo Receptor.

[0392] In certain embodiments, a single chain variable fragment fused to an Fc is provided which specifically binds to amino acid H70 of the extracellular domain of the human Epo Receptor.

[0393] In certain embodiments, a single chain variable fragment fused to an Fc is provided which specifically binds to amino acids V48 and W64 of the extracellular domain of the human Epo Receptor.

[0394] In certain embodiments, a single chain variable fragment fused to an Fc is provided which specifically binds to amino acids V48 and L66 of the extracellular domain of the human Epo Receptor.

[0395] In certain embodiments, a single chain variable fragment fused to an Fc is provided which specifically binds to amino acids V48 and R68 of the extracellular domain of the human Epo Receptor.

[0396] In certain embodiments, a single chain variable fragment fused to an Fc is provided which specifically binds to amino acids V48 and H70 of the extracellular domain of the human Epo Receptor.

[0397] In certain embodiments, a single chain variable fragment fused to an Fc is provided which specifically binds to amino acids W64 and R68 of the extracellular domain of the human Epo Receptor.

[0398] In certain embodiments, a single chain variable fragment fused to an Fc is provided which specifically binds to amino acids W64 and H70 of the extracellular domain of the human Epo Receptor.

[0399] In certain embodiments, a single chain variable fragment fused to an Fc is provided which specifically binds to amino acids L66 and R68 of the extracellular domain of the human Epo Receptor.

[0400] In certain embodiments, a single chain variable fragment fused to an Fc is provided which specifically binds to amino acids L66 and H70 of the extracellular domain of the human Epo Receptor.

[0401] In certain embodiments, a single chain variable fragment fused to an Fc is provided which specifically binds to amino acids R68 and H70 of the extracellular domain of the human Epo Receptor.

[0402] In certain embodiments, a single chain variable fragment fused to an Fc is provided which specifically binds to one or more of amino acids A44, V48, E62, P63, W64, L66, R68, H70, S91, F93, R99, H114, and M150 of the extracellular domain of the human Epo Receptor.

[0403] In certain embodiments, an antibody is provided which specifically binds to amino acids F93, E60, and H114 of the extracellular domain of the human Epo Receptor.

[0404] In certain embodiments, an antibody is provided which specifically binds to amino acid V48 of the extracellular domain of the human Epo Receptor.

[0405] In certain embodiments, an antibody is provided which specifically binds to amino acid L66 of the extracellular domain of the human Epo Receptor.

[0406] In certain embodiments, an antibody is provided which specifically binds to amino acid W64 of the extracellular domain of the human Epo Receptor.

[0407] In certain embodiments, an antibody is provided which specifically binds to amino acid H70 of the extracellular domain of the human Epo Receptor.

[0408] In certain embodiments, an antibody is provided which specifically binds to amino acids V48 and W64 of the extracellular domain of the human Epo Receptor.

[0409] In certain embodiments, an antibody is provided which specifically binds to amino acids V48 and L66 of the extracellular domain of the human Epo Receptor.

[0410] In certain embodiments, an antibody is provided which specifically binds to amino acids V48 and R68 of the extracellular domain of the human Epo Receptor.

[0411] In certain embodiments, an antibody is provided which specifically binds to amino acids V48 and H70 of the extracellular domain of the human Epo Receptor.

[0412] In certain embodiments, an antibody is provided which specifically binds to amino acids W64 and R68 of the extracellular domain of the human Epo Receptor.

[0413] In certain embodiments, an antibody is provided which specifically binds to amino acids W64 and H70 of the extracellular domain of the human Epo Receptor.

[0414] In certain embodiments, an antibody is provided which specifically binds to amino acids L66 and R68 of the extracellular domain of the human Epo Receptor.

[0415] In certain embodiments, an antibody is provided which specifically binds to amino acids L66 and H70 of the extracellular domain of the human-Epo Receptor.

[0416] In certain embodiments, an antibody is provided which specifically binds to amino acids R68 and H70 of the extracellular domain of the human Epo Receptor.

[0417] In certain embodiments, an antibody is provided which specifically binds to one or more of amino acids A44, V48, E62, P63, W64, L66, R68, H70, S91, F93, R99, H114, and M150 of the extracellular domain of the human Epo Receptor.

[0418] In certain embodiments, the effects of an antibody may be evaluated by measuring a reduction in the amount of symptoms of a disease of interest. In certain embodiments, the disease of interest may be caused by a pathogen. In certain embodiments, a disease may be established in an animal host by other methods including introduction of a substance (such as a carcinogen) and genetic manipulation. In certain embodiments, effects may be evaluated by detecting one or more adverse events in the animal host. The term "adverse event" includes, but is not limited to, an adverse reaction in an animal host that receives an antibody that is not present in an animal host that does not receive the antibody. In certain embodiments, adverse events include, but are not limited to, a fever, an immune response to an antibody, inflammation, and/or death of the animal host.

[0419] In certain embodiments, the composition further comprises a maxibody and at least one sugar. As used herein, the term "sugar" refers to monosaccharides such as glucose and mannose, or polysaccharides including disaccharides such as sucrose and lactose, as well as sugar derivatives including sugar alcohols and sugar acids. Sugar alcohols include, but are not limited to, mannitol, xylitol, erythritol, threitol, sorbitol and glycerol. A non-limiting example of a sugar acid is L-gluconate. Certain exemplary sugars include, but are not limited to, trehalose, fucose, and glycine.

[0420] In certain embodiments, the composition further comprises at least one bulking/osmolarity regulating agent. Such agents may be either crystalline (for example, glycine, mannitol) or amorphous (for example, L-histidine, sucrose, polymers such as dextran, polyvinylpyrolidone, carboxymethylcellulose, and lactose). In certain embodiments, a bulking/osmolarity regulating agent is provided at a concentration between 2% and 5%. In certain embodiments, a bulking/osmolarity regulating agent is provided at a concentration between 2.5% and 4.5%.

[0421] In certain embodiments, antibodies which bind to a particular protein and block interaction with other binding compounds may have therapeutic use. In this application, when discussing the use of antibodies to treat diseases or conditions, such use may include use of compositions comprising antibodies; and/or combination therapies comprising antibodies and one or more additional active ingredients. When antibodies are used to "treat" a disease or condition, such treatment may or may not include prevention of the disease or condition.

[0422] In certain embodiments, an antibody is administered alone. In certain embodiments, an antibody is administered prior to the administration of at least one other therapeutic agent. In certain embodiments, an antibody is administered concurrent with the administration of at least one other therapeutic agent. In certain embodiments, an antibody is administered subsequent to the administration of at least one other therapeutic agent.

[0423] In certain embodiments, antibodies may be used to treat non-human animals, such as pets (dogs, cats, birds, primates, etc.), and domestic farm animals (horses cattle, sheep, pigs, birds, etc.). In certain such instances, an appropriate dose may be determined according to the animal's body weight. For example, in certain embodiments, a dose of 0.2-1 mg/kg may be used. In certain embodiments, the dose may be determined according to the animal's surface area, an exemplary dose ranging from 0.1 to 20 mg/in^2, or from 5 to 12 mg/m^2. For small animals, such as dogs or cats, in certain embodiments, a suitable dose is 0.4 mg/kg. In certain embodiments, antibodies are administered by injection or other suitable route one or more times per week until the animal's condition is improved, or it may be administered indefinitely.

[0424] It is understood that the response by individual patients to the aforementioned medications or combination therapies may vary, and an appropriate efficacious combination of drugs for each patient may be determined by his or her physician.

[0425] In certain embodiments, an antibody may be part of a conjugate molecule comprising all or part of the antibody and a prodrug. In certain embodiments, the term "prodrug" refers to a precursor or derivative form of a pharmaceutically active substance. In certain embodiments, a prodrug is less cytotoxic to cells compared to the parent drug and is capable of being enzymatically activated or converted into the more active cytotoxic parent form. Exemplary prodrugs include, but are not limited to, phosphate-containing prodrugs, thiophosphate-containing prodrugs, sulfate-containing prodrugs, peptide-containing prodrugs, D-amino acid-modified prodrugs, glycosylated prodrugs, beta-lactam-containing prodrugs, optionally substituted phenoxyacetamide-containing prodrugs and optionally substituted phenylacetamide-containing prodrugs, 5-fluorocytosine and other 5-fluorouridine

prodrugs which can be converted into a more active cytotoxic free drug. Examples of cytotoxic drugs that can be derivatized into a prodrug form include, but are not limited to, those cytotoxic agents described above. See, e.g., U.S. Pat. No. 6,702,705.

[0426] In certain embodiments, antibody conjugates function by having the antibody portion of the molecule target the cytotoxic portion or prodrug portion of the molecule to a specific population of cells in the patient.

[0427] In certain embodiments, methods of treating a patient comprising administering a therapeutically effective amount of an antibody are provided. In certain embodiments, methods of treating a patient comprising administering a therapeutically effective amount of an antibody conjugate are provided. In certain embodiments, an antibody is used in conjunction with a therapeutically effective amount of at least one additional therapeutic agent, as discussed above.

[0428] As discussed above, in certain embodiments, antibodies may be administered concurrently with one or more other drugs that are administered to the same patient, each drug being administered according to a regimen suitable for that medicament. Such treatment encompasses pre-treatment, simultaneous treatment, sequential treatment, and alternating regimens. Additional examples of such drugs include, but are not limited to, antivirals, antibiotics, analgesics, corticosteroids, antagonists of inflammatory cytokines, DMARDs, nonsteroidal anti-inflammatories, chemotherapeutics, inhibitors of angiogenesis, and stimulators of angiogenesis.

[0429] In certain embodiments, a composition comprises a therapeutically effective amount of an antibody and a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative and/or adjuvant.

[0430] In certain embodiments, pharmaceutical compositions are provided comprising a therapeutically effective amount of an antibody and a therapeutically effective amount of at least one additional therapeutic agent, together with a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative and/or adjuvant.

[0431] In certain embodiments, acceptable formulation materials preferably are nontoxic to recipients at the dosages and concentrations employed.

[0432] In certain embodiments, the pharmaceutical composition may contain formulation materials for modifying, maintaining or preserving, for example, the pH, osmolarity, viscosity, clarity, color, isotonicity, odor, sterility, stability, rate of dissolution or release, adsorption or penetration of the composition. In certain embodiments, suitable formulation materials include, but are not limited to, amino acids (such as glycine, glutamine, asparagine, arginine or lysine); antimicrobials; antioxidants (such as ascorbic acid, sodium sulfite or sodium hydrogen-sulfite); buffers (such as borate, bicarbonate, Tris-HCl, citrates, phosphates or other organic acids); bulking agents (such as mannitol or glycine); chelating agents (such as ethylenediamine tetraacetic acid (EDTA)); complexing agents (such as caffeine, polyvinylpyrrolidone, beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin); fillers; monosaccharides; disaccharides; and other carbohydrates (such as glucose, mannose or dextrins); proteins (such as serum albumin, gelatin or immunoglobulins); coloring, flavoring and diluting agents; emulsifying agents; hydrophilic polymers (such as polyvinylpyrrolidone); low molecular weight polypeptides; salt-forming counterions (such as sodium); preservatives (such as benzalkonium chloride, benzoic acid, salicylic acid, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid or hydrogen peroxide); solvents (such as glycerin, propylene glycol or polyethylene glycol); sugar alcohols (such as mannitol or sorbitol); suspending agents; surfactants or wetting agents (such as pluronics, PEG, sorbitan esters, polysorbates such as polysorbate 20, polysorbate 80, triton, tromethamine, lecithin, cholesterol, tyloxapal); stability enhancing agents (such as sucrose or sorbitol); tonicity enhancing agents (such as alkali metal halides, preferably sodium or potassium chloride, mannitol sorbitol); delivery vehicles; diluents; excipients and/or pharmaceutical adjuvants. (*Remington's Pharmaceutical Sciences,* 18th Edition, A. R. Gennaro, ed., Mack Publishing Company (1990).

[0433] In certain embodiments, an antibody and/or an additional therapeutic molecule is linked to a half-life extending vehicle known in the art. Such vehicles include, but are not limited to, the Fc domain, polyethylene glycol, and dextran. Such vehicles are described, e.g., in U.S. Pat. No. 6,660,843 and published PCT Application No. WO 99/25044.

[0434] In certain embodiments, the optimal pharmaceutical composition will be determined by one skilled in the art depending upon, for example, the intended route of administration, delivery format and desired dosage. See, for example, *Remington's Pharmaceutical Sciences*, supra. In certain embodiments, such compositions may influence the physical state, stability, rate of in vivo release and rate of in vivo clearance of the antibodies.

[0435] In certain embodiments, the primary vehicle or carrier in a pharmaceutical composition may be either aqueous or non-aqueous in nature. For example, in certain embodiments, a suitable vehicle or carrier may be water for injection, physiological saline solution or artificial cerebrospinal fluid, possibly supplemented with other materials common in compositions for parenteral administration. In certain embodiments, neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. In certain embodiments, pharmaceutical compositions comprise Tris buffer of about pH 7.0-8.5, or acetate buffer of about pH 4.0-5.5, which may further include sorbitol or a suitable substitute therefor. In certain embodiments, a pharmaceutical composition is an aqueous or liquid formulation comprising an acetate buffer of about pH 4.0-5.5, a polyol (polyalcohol), and optionally, a surfactant, wherein the composition does not comprise a salt, e.g., sodium chloride, and wherein the composition is isotonic for the patient. Exemplary polyols include, but are not limited to, sucrose, glucose, sorbitol, and mannitol. An exemplary surfactant includes, but is not limited to, polysorbate. In certain embodiments, a pharmaceutical composition is an aqueous or liquid formulation comprising an acetate buffer of about pH 5.0, sorbitol, and a polysorbate, wherein the composition does not comprise a salt, e.g., sodium chloride, and wherein the composition is isotonic for the patient. Certain exemplary compositions are found, for example, in U.S. Pat. No. 6,171,586. Additional pharmaceutical carriers include, but are not limited to, oils, including petroleum oil, animal oil, vegetable oil, peanut oil, soybean oil, mineral oil, sesame oil, and the like. In certain embodiments, aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. In certain embodiments, a composition comprising an antibody, with or without at least one additional therapeutic agent, may be prepared for storage by mixing the selected composition having the desired degree of purity with optional formulation agents

(*Remington's Pharmaceutical Sciences*, supra) in the form of a lyophilized cake or an aqueous solution. Further, in certain embodiments, a composition comprising an antibody, with or without at least one additional therapeutic agent, may be formulated as a lyophilizate using appropriate excipient solutions (e.g., sucrose) as diluents.

[0436] In certain embodiments, antibodies are administered in the form of a physiologically acceptable composition comprising purified recombinant protein in conjunction with physiologically acceptable carriers, excipients or diluents. In certain embodiments, such carriers are nontoxic to recipients at the dosages and concentrations employed. In certain embodiments, preparing such compositions may involve combining the antibodies with buffers, antioxidants such as ascorbic acid, low molecular weight polypeptides (such as those having fewer than 10 amino acids), proteins, amino acids, carbohydrates such as glucose, sucrose or dextrins, chelating agents such as EDTA, glutathione and/or other stabilizers, and excipients. In certain embodiments, appropriate dosages are determined in standard dosing trials, and may vary according to the chosen route of administration. In certain embodiments, in accordance with appropriate industry standards, preservatives may also be added, which include, but are not limited to, benzyl alcohol. In certain embodiments, the amount and frequency of administration may be determined based on such factors as the nature and severity of the disease being treated, the desired response, the age and condition of the patient, and so forth.

[0437] In certain embodiments, pharmaceutical compositions can be selected for parenteral delivery. The preparation of certain such pharmaceutically acceptable compositions is within the skill of the art.

[0438] In certain embodiments, the formulation components are present in concentrations that are acceptable to the site of administration. In certain embodiments, buffers are used to maintain the composition at physiological pH or at a slightly lower pH, typically within a pH range of from about 5 to about 8.

[0439] In certain embodiments, when parenteral administration is contemplated, a therapeutic composition may be in the form of a pyrogen-free, parenterally acceptable aqueous solution comprising the desired antibody, with or without additional therapeutic agents, in a pharmaceutically acceptable vehicle. In certain embodiments, a vehicle for parenteral injection is sterile distilled water in which the antibody, with or without at least one additional therapeutic agent, is formulated as a sterile, isotonic solution, properly preserved. In certain embodiments, the preparation can involve the formulation of the desired molecule with an agent, such as injectable microspheres, bio-erodible particles, polymeric compounds (such as polylactic acid or polyglycolic acid), beads, or liposomes, that may provide for the controlled or sustained release of the product which may then be delivered via a depot injection. In certain embodiments, hyaluronic acid may also be used, and may have the effect of promoting sustained duration in the circulation. In certain embodiments, implantable drug delivery devices may be used to introduce the desired molecule.

[0440] In certain embodiments, a pharmaceutical composition may be formulated for inhalation. In certain embodiments, administration by inhalation is beneficial when treating diseases associated with pulmonary disorders. In certain embodiments, an antibody, with or without at least one additional therapeutic agent, may be formulated as a dry powder for inhalation. In certain embodiments, an inhalation solution comprising an antibody, with or without at least one additional therapeutic agent, may be formulated with a propellant for aerosol delivery. In certain embodiments, solutions may be nebulized. Pulmonary administration is further described in PCT publication no. WO94/20069, which describes pulmonary delivery of chemically modified proteins.

[0441] In certain embodiments, it is contemplated that formulations may be administered orally. In certain embodiments, an antibody, with or without at least one additional therapeutic agent, that is administered in this fashion may be formulated with or without those carriers customarily used in the compounding of solid dosage forms such as tablets and capsules. In certain embodiments, a capsule may be designed to release the active portion of the formulation at the point in the gastrointestinal tract when bioavailability is maximized and pre-systemic degradation is minimized. In certain embodiments, at least one additional agent can be included to facilitate absorption of the antibody and/or any additional therapeutic agents. In certain embodiments, diluents, flavorings, low melting point waxes, vegetable oils, lubricants, suspending agents, tablet disintegrating agents, and/or binders may also be employed.

[0442] In certain embodiments, a pharmaceutical composition may involve an effective quantity of antibodies, with or without at least one additional therapeutic agent, in a mixture with non-toxic excipients which are suitable for the manufacture of tablets. In certain embodiments, by dissolving the tablets in sterile water, or another appropriate vehicle, solutions may be prepared in unit-dose form. Suitable excipients include, but are not limited to, inert diluents, such as calcium carbonate, sodium carbonate or bicarbonate, lactose, or calcium phosphate; and binding agents, such as starch, gelatin, and acacia; and lubricating agents such as magnesium stearate, stearic acid, and talc.

[0443] Additional pharmaceutical compositions will be evident to those skilled in the art, including formulations involving antibodies, with or without at least one additional therapeutic agent, in sustained- or controlled-delivery formulations. In certain exemplary sustained- or controlled-delivery formulations include, but are not limited to, liposome carriers, bio-erodible microparticles, porous beads, and depot injections. Certain exemplary techniques for preparing certain formulations are known to those skilled in the art. See for example, PCT publication no. WO93/15722, which describes the controlled release of porous polymeric microparticles for the delivery of pharmaceutical compositions. In certain embodiments, sustained-release preparations may include semipermeable polymer matrices in the form of shaped articles, e.g. films, or microcapsules. Sustained release matrices include, but are not limited to, polyesters, hydrogels, polylactides (U.S. Pat. No. 3,773,919 and EP 058,481), copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman et al., *Biopolymers,* 22:547-556 (1983)), poly (2-hydroxyethyl-methacrylate) (Langer et al., *J. Biomed. Mater. Res.,* 15:167-277 (1981) and Langer, *Chem. Tech.,* 12:98-105 (1982)), ethylene vinyl acetate (Langer et al., supra), and poly-D(−)-3-hydroxybutyric acid (EP 133, 988). In certain embodiments, sustained release compositions may also include liposomes, which can be prepared, in certain embodiments, by any of several methods known in the art. See e.g., Eppstein et al., *Proc. Natl. Acad. Sci. USA,* 82:3688-3692 (1985); EP 036,676; EP 088,046 and EP 143, 949.

[0444] In certain embodiments, the pharmaceutical composition to be used for in vivo administration is sterile. In certain embodiments, the pharmaceutical composition to be used for in vivo administration is made sterile by filtration through sterile filtration membranes. In certain embodiments, where the composition is lyophilized, sterilization using sterile filtration membranes may be conducted either prior to or following lyophilization and reconstitution. In certain embodiments, the composition for parenteral administration may be stored in lyophilized form or in a solution. In certain embodiments, parenteral compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

[0445] In certain embodiments, after the pharmaceutical composition has been formulated, it may be stored in sterile vials as a solution, suspension, gel, emulsion, solid, or as a dehydrated or lyophilized powder. In certain embodiments, such formulations may be stored either in a ready-to-use form or in a form (e.g., a lyophilized form) that is reconstituted prior to administration.

[0446] In certain embodiments, kits for producing a single-dose administration unit are provided. In certain embodiments, the kits may each contain both a first container having a dried protein and a second container having an aqueous formulation. In certain embodiments, kits containing single and/or multi-chambered pre-filled syringes (e.g., liquid syringes and lyosyringes) are included.

[0447] In certain embodiments, the effective amount of a pharmaceutical composition comprising an antibody, with or without at least one additional therapeutic agent, to be employed therapeutically will depend, for example, upon the therapeutic context and objectives. One skilled in the art will appreciate that the appropriate dosage levels for treatment, according to certain embodiments, will thus vary depending, in part, upon the molecule delivered, the indication for which the antibody, with or without at least one additional therapeutic agent, is being used, the route of administration, and the size (body weight, body surface or organ size) and/or condition (the age and general health) of the patient. In certain embodiments, the clinician may titer the dosage and modify the route of administration to obtain the optimal therapeutic effect. In certain embodiments, a typical dosage may range from about 0.1 μg/kg to up to about 100 mg/kg or more, depending on the factors mentioned above. In certain embodiments, the dosage may range from 0.1 μg/kg up to about 100 mg/kg; or 1 μg/kg up to about 100 mg/kg; or 5 μg/kg up to about 100 mg/kg; or 0.1 mg/kg up to about 100 mg/kg.

[0448] In certain embodiments, the frequency of dosing will take into account the pharmacokinetic parameters of the antibody and/or any additional therapeutic agents in the formulation used. In certain embodiments, a clinician will administer the composition until a dosage is reached that achieves the desired effect. In certain embodiments, the composition may therefore be administered as a single dose, or as two or more doses (which may or may not contain the same amount of the desired molecule) over time, or as a continuous infusion via an implantation device or catheter. Certain methods of further refining the appropriate dosage are within the skill in the art. In certain embodiments, appropriate dosages may be ascertained through use of appropriate dose-response data.

[0449] In certain embodiments, the route of administration of the pharmaceutical composition is in accord with known methods, e.g. orally, through injection by intravenous, intraperitoneal, intracerebral (intra-parenchymal), intracerebroventricular, intramuscular, intra-ocular, intraarterial, intraportal, or intralesional routes; by sustained release systems or by implantation devices. In certain embodiments, the compositions may be administered by bolus injection or continuously by infusion, or by implantation device.

[0450] As discussed above, in various embodiments, any efficacious route of administration may be used to administer antibodies. If injected, in certain embodiments, antibodies may be administered, for example, via intra-articular, intravenous, intramuscular, intralesional, intraperitoneal, intracranial, intranasal, inhalation or subcutaneous routes by bolus injection or by continuous infusion. Exemplary methods of administration include, but are not limited to, sustained release from implants, aerosol inhalation, eyedrops, oral preparations, and topical preparations such as lotions, gels, sprays, ointments, and other suitable techniques.

[0451] When antibodies are administered in combination with one or more other biologically active compounds, in certain embodiments, these may be administered by the same or by different routes, and may be administered together, separately, or sequentially.

[0452] In certain embodiments, the composition may be administered locally via implantation of a membrane, sponge or another appropriate material onto which the desired molecule has been absorbed or encapsulated. In certain embodiments, where an implantation device is used, the device may be implanted into any suitable tissue or organ, and delivery of the desired molecule may be via diffusion, timed-release bolus, or continuous administration.

[0453] In certain embodiments, it may be desirable to use a pharmaceutical composition comprising an antibody, with or without at least one additional therapeutic agent, in an ex vivo manner. In such embodiments, cells, tissues and/or organs that have been removed from the patient are exposed to a pharmaceutical composition comprising an antibody, with or without at least one additional therapeutic agent, after which the cells, tissues and/or organs are subsequently implanted back into the patient.

[0454] In certain embodiments, a first antibody binds to a first epitope on a molecule and a second antibody binds to a second epitope on the same molecule. In certain such embodiments, the first epitope overlaps with the second epitope such that binding of either the first antibody or second antibody to the molecule inhibits binding of the other antibody to the molecule. In certain embodiments, the first epitope does not overlap with the second epitope such that binding of the first antibody or the second antibody to the molecule does not inhibit binding of the other antibody.

[0455] In certain embodiments, an epitope on a receptor overlaps with a ligand binding site on the receptor. In certain such embodiments, binding of an antibody to the receptor inhibits binding of the ligand to the receptor. In certain embodiments, binding of an antibody to the receptor blocks binding of the ligand to the receptor. In certain embodiments, binding of an antibody partially inhibits binding of the ligand to the receptor.

[0456] In certain embodiments, an epitope on a receptor molecule does not overlap with a ligand binding site on the receptor. In certain such embodiments, binding of an antibody to the epitope at least partially activates the receptor. In

certain other embodiments, binding of an antibody to the epitope does not activate the receptor.

[0457] In certain embodiments, an epitope on a receptor molecule overlaps with a ligand binding site on the receptor. In certain such embodiments, binding of an antibody to the epitope at least partially activates the receptor. In certain other embodiments, binding of an antibody to the epitope does not activate the receptor. In certain embodiments, binding of an antibody to the epitope on the receptor inhibits activation of the receptor by the receptor ligand. In certain embodiments, binding of an antibody to the epitope on the receptor blocks activation of the receptor by the receptor ligand.

[0458] In certain embodiments, dimerization of a receptor increases its activation. In certain embodiments, receptors must dimerize to activate. In certain embodiments, a bivalent antibody facilitates receptor dimerization. In certain embodiments, a monovalent antibody is crosslinked with another monovalent antibody to create a bivalent molecule.

[0459] In certain embodiments, an EpoR agonist is an antibody which activates huEpoR. In certain embodiments, an antibody that activates huEpoR (a huEpoR antibody) is a maxibody. In certain embodiments, a huEpoR antibody is administered less frequently than an erythropoiesis stimulating protein (ESP). Examples of ESPs include epoietin alfa, epoietin beta and darbepoietin alfa. In certain embodiments, a huEpoR antibody is administered about once per month, or about once every two months, or about once every three months, or about once every four months, or about once every five months, or about once every six months.

[0460] In certain embodiments, antibodies against a huEpoR antibody are unable to cross-react with native erythropoietin (Epo) and thus are unable to induce Pure Red Cell Aplasia (PRCA). As a consequence, administration of a huEpoR antibody carries a reduced risk of inducing PRCA when compared with administration of other erythropoiesis stimulating proteins. In certain embodiments, a huEpoR antibody with a reduced risk of inducing PRCA is used to treat a disease or condition using a method of administration to allow for controlled release over an extended period of time. For example, and not limitation, a huEpoR antibody could be administered orally or with non-invasive delivery devices without increasing the risk of PRCA.

[0461] In certain embodiments, at least one antibody is used to treat a disease or condition. In certain embodiments, an antibody comprising an amino acid sequence comprising SEQ ID NO.: 1 and SEQ ID NO.: 2 is used to treat a disease or condition. In certain embodiments, an antibody comprising an amino acid sequence comprising SEQ ID NO.: 3 and SEQ ID NO.: 4 is used to treat a disease or condition. In certain embodiments, an antibody comprising an amino acid sequence comprising SEQ ID NO.: 5 and SEQ ID NO.: 6 is used to treat a disease or condition. In certain embodiments, an antibody comprising an amino acid sequence comprising SEQ ID NO.: 7 and SEQ ID NO.: 8 is used to treat a disease or condition. In certain embodiments, an antibody comprising an amino acid sequence comprising SEQ ID NO.: 9 and SEQ ID NO.: 10 is used to treat a disease or condition. In certain embodiments, an antibody comprising an amino acid sequence comprising SEQ ID NO. 56 and SEQ ID NO. 58 is used to treat a disease or condition. In certain embodiments, an antibody comprising an amino acid sequence comprising SEQ ID NO. 60 and SEQ ID NO. 62 is used to treat a disease or condition. In certain embodiments, an antibody comprising an amino acid sequence comprising SEQ ID NO. 64 and SEQ ID NO. 66 is used to treat a disease or condition. In certain embodiments, an antibody comprising an amino acid sequence comprising SEQ ID NO. 68 and SEQ ID NO. 70 is used to treat a disease or condition. In certain embodiments, an antibody comprising an amino acid sequence comprising SEQ ID NO. 72 and SEQ ID NO. 74 is used to treat a disease or condition. In certain embodiments, an antibody comprising an amino acid sequence comprising SEQ ID NO. 76 and SEQ ID NO. 78 is used to treat a disease or condition. In certain embodiments, an antibody comprising an amino acid sequence comprising SEQ ID NO. 80 and SEQ ID NO. 82 is used to treat a disease or condition. In certain embodiments, an antibody comprising an amino acid sequence comprising SEQ ID NO. 84 and SEQ ID NO. 86 is used to treat a disease or condition. In certain embodiments, an antibody comprising an amino acid sequence comprising SEQ ID NO. 88 and SEQ ID NO. 90 is used to treat a disease or condition. In certain embodiments, an antibody comprising an amino acid sequence comprising SEQ ID NO. 92 and SEQ ID NO. 94 is used to treat a disease or condition. In certain embodiments, an antibody comprising an amino acid sequence comprising SEQ ID NO. 96 and SEQ ID NO. 98 is used to treat a disease or condition. In certain embodiments, an antibody comprising an amino acid sequence comprising SEQ ID NO. 100 and SEQ ID NO. 102 is used to treat a disease or condition. In certain embodiments, an antibody comprising an amino acid sequence comprising SEQ ID NO. 104 and SEQ ID NO. 106 is used to treat a disease or condition. In certain embodiments, an antibody comprising an amino acid sequence comprising SEQ ID NO. 108 and SEQ ID NO. 110 is used to treat a disease or condition. In certain embodiments, an antibody comprising an amino acid sequence comprising SEQ ID NO. 112 and SEQ ID NO. 114 is used to treat a disease or condition.

[0462] In certain embodiments, an antibody that specifically binds to amino acids F93 and H114 of the extracellular domain of the human Epo Receptor is used to treat a disease or condition. In certain embodiments, an antibody that specifically binds to amino acids S91, F93, and H114 of the extracellular domain of the human Epo Receptor is used to treat a disease or condition. In certain embodiments, an antibody that specifically binds to amino acid F93 of the extracellular domain of the human Epo Receptor is used to treat a disease or condition. In certain embodiments, an antibody that specifically binds to amino acids E62, F93, and M150 of the extracellular domain of the human Epo Receptor is used to treat a disease or condition. In certain embodiments, an antibody that specifically binds to amino acids V48, E62, L66, R68, and H70 of the extracellular domain of the human Epo Receptor is used to treat a disease or condition. In certain embodiments, an antibody that specifically binds to amino acids V48, W64, L66, R68, and H70 of the extracellular domain of the human Epo Receptor is used to treat a disease or condition. In certain embodiments, an antibody that specifically binds to amino acids A44, V48, P63, L66, R68, and H70 of the extracellular domain of the human Epo Receptor is used to treat a disease or condition. In certain embodiments, an antibody that specifically binds to amino acids L66 and R99 of the extracellular domain of the human Epo Receptor is used to treat a disease or condition.

[0463] In certain embodiments, the disease or condition treated is associated with decreased red blood cell and/or hemoglobin levels. In certain embodiments, the disease or condition treated is anemia. In certain embodiments, treat-

ment of anemia with a huEpoR antibody is characterized by a longer-duration erythropoietic response than is observed with other ESPs.

[0464] In certain embodiments, a huEpoR antibody is used to treat anemia of chronic diseases or conditions. Chronic means persistent or lasting. In certain embodiments, a chronic disease or condition may worsen over time. In certain embodiments, a chronic disease or condition may not worsen over time. Exemplary chronic diseases include, but are not limited to, chronic kidney disease, congestive heart failure, and myelodysplastic syndromes.

[0465] In certain embodiments, a huEpoR antibody possesses a pharmacokinetic profile appropriate for treating a chronic disease or condition. In certain such embodiments, a huEpoR antibody possesses a pharmacokinetic profile that comprises an erythropoietic response extending over a longer duration than the erythropoietic response that is observed with other ESPs.

[0466] In certain embodiments, a huEpoR antibody is used to treat anemia of cancer, chemotherapy-induced anemia, anemia of the elderly, or other anemias, including, but not limited to, anemia due to infection, inflammation, iron deficiency, blood loss, hemolysis, secondary hyperparathyroidism, inadequate dialysis, protein energy malnutrition, vitamin deficiencies, or metal toxicity (e.g., aluminum). In certain embodiments, a huEpoR antibody is used to treat PRCA in patients that develop this condition as a result of disease or in response to the administration of erythropoietic drugs.

[0467] In certain embodiments, a huEpoR antibody is used to promote tissue protection in erythropoietin-responsive cells, tissues, and organs. For example, and without limitation, in certain embodiments, a huEpoR antibody is used to promote tissue protection during or after a myocardial infarction or a stroke. In certain embodiments, a huEpoR antibody is used to promote tissue protection in tissues that can be protected by administration of erythropoietin. Certain examples of cells, tissues, and organs that can be protected by administration of erythropoietin are described in PCT Publications WO 02/053580 and WO 00/61164.

[0468] In certain embodiments, a huEpoR antibody is used to increase hematocrit in a patient in need thereof. In certain embodiments, a huEpoR antibody is administered once to increase hematocrit for a period of about 30 days, or about 60 days, or about 90 days, or about 120 days, or about 150 days, or about 180 days.

EXAMPLES

Example 1

Identification of Anti-huEpoR Antibodies from Naïve Human scFv Phage Display Libraries

Selection Strategy 1

[0469] In a first round of selection, approximately 10^{12} human scFv phage from naïve phage libraries were incubated with 200 nM biotinylated huEpoR in 1 ml 2% non fat dry milk in PBS/0.1% tween 20 (PBSrT) for 1 hour at room temperature followed by 5 washes using PBS/T. The scFv phage that bound to huEpoR were captured using streptavidin coated magnetic beads. Bound phage were released from magnetic beads by incubation with 1 ml trypsinization solution (50 μg/ml porcine trypsin in 50 mM Tris HCl/1 mM CaCl2 at pH 8.0) at 37° C. for 10 minutes.

[0470] To re-introduce the released phage to *E. coli* cells, 10 ml of log phase TG1 cells were used for incubation with the entire population of phage released from the magnetic beads at 37° C. for 30 minutes without shaking and another 30 minutes with slow shaking. Gently pelleted TG1 cells were re-suspended into approximately 1.5 ml of 2xYT media, spread on 2 Nunc plates (25 cm×25 cm) with 2xYT media supplemented with 100 μg/ml carbenicillin and 4% glucose and amplified overnight at 30° C. Amplified cells were then scraped from the plates and pooled. Approximately 10-100 μl of the pooled cells, covering greater than 10 fold of the released phage particles, were used to inoculate 25 ml of 2xYT media/100 μg/ml carbenicillin and 2% glucose and grown at 37° C. with shaking to an OD_{600} of 0.5. This log phase culture was then super-infected with approximately 10^{11} M13KO7 helper phage at 37° C. for 30 minutes and another 30 minutes with gentle shaking. Cells were pelleted and resuspended into 25 ml of 2xYT media supplemented with 100 μg/ml carbenicillin and 25 μg/ml of kanamycin. Cells were shaken at 250 rpm at 25° C. overnight. The supernatant of the culture was harvested by centrifugation at 10,000 rpm for 10 minutes. The phage in the supernatant were precipitated by adding ⅕ volume of 20% PEG8000/2.5 M NaCl incubated on ice for greater than 30 minutes. The phage were then pelleted by centrifugation at 10,000 rpm for 10 minutes and resuspended into TE buffer (10 mM Tris and 1 mM EDTA, pH7.5).

[0471] In a second round of selection, the resuspended scFv phage were incubated with 50 nM biotinylated huEpoR for 1 hour at room temperature followed by 10 washes using PBS/0.1% tween 20. huEpoR binding scFv phage were captured using streptavidin coated magnetic beads. Bound phage were released from magnetic beads by incubation with 1 ml trypsinization solution at 37° C. for 10 minutes. Half of the released phage were used in the Selection Strategy 2 described below.

[0472] A small fraction of the released phage from the second round of selection were reintroduced into TG1 by incubating properly diluted phage with mid log phase *E. coli* cells. The TG1 cells were then plated on 2xYT 100 μg/ml carbenicillin petridish plates to generate single colonies. 384 randomly selected single colonies were individually picked off the petridish plates and placed into separate wells of 96-well plates containing 100 μl of 2xYT media supplemented with 100 μg/ml carbenicillin and 2% glucose to create 96-well experimental plates. The 96-well experimental plates were incubated at 37° C. with shaking until TG1 cells reached an OD_{600} of approximately 0.5 (mid log phase).

[0473] As a separate step, a new set of 96-well culture plates containing the same culture media described above were inoculated with a small fraction of the growing cultures in the 96-well experimental plates to create duplicate plates. These duplicate plates were grown at 37° C. overnight. 20 μl of a 50% glycerol solution was then added to each well of the plates and the plates were frozen on dry ice and stored at −70° C. as master plates.

[0474] The mid log phase cultures in the 96-well experimental plates were then super-infected with approximately 10^{9} M13KO7 helper phage at 37° C. for 30 minutes and another 30 minutes with gentle shaking. The 96-well plates were then centrifuged at 3000 rpm for 5 minutes and the supernatants in the wells were removed by flipping the plates. 200 μl of 2xYT media supplemented with 100 μg/ml carbenicillin and 25 μg/ml of Kanamycin were then added to each

well and the plates were incubated with shaking at 250 rpm at 30° C. overnight. The overnight phage culture was centrifuged at 3,000 rpm for 5 minutes and the resultant supernatant samples were used for ELISA experiments.

[0475] A new set of Nunc-Immuno Polysorp 96-well ELISA plates (Nalge Nunc International) were prepared by adding huEpoR at 1 μg/ml to the wells of the plates and incubating the plates overnight at 4° C. A 1/20 dilution of culture supernatant containing one of the 384 different monoclonal phage in 2% non-fat dry milk solution in PBS/T was added to each separate well of the 96-well plates containing the huEpoR coated on the surface. The plates were incubated for 1 hour followed by 3 washes in PBS/T. Detection of the bound phage was performed using anti-M13 mAb/HRP conjugate (Amersham Biosciences) followed by 3 washes in PBS/T. ABTS was used as the substrate and absorption at 405 nm detected. A total of 96 phage that bind to huEpoR were identified from the ELISA screening of the 384 randomly picked phage clones.

Selection Strategy 2

[0476] Half of the eluted phage from the round 2 selection in Selection Strategy 1 described in paragraph 464 were reintroduced to TG1 cells and a phage preparation was made using the same procedure as described in paragraph 463 of Selection Strategy 1. Approximately 10^{12} amplified scFv phage were used for cell panning by incubating the scFv phage with huEpoR expressing UT-7 cells (2×10^6 cells in 1 ml PBS/2% BSA) at 4° C. for 2 hours followed by 10 washes with PBS/T.

[0477] UT-7 binding phage were eluted from the cell surface by incubation with 1 ml glycine/HCl buffer (100 mM glycine/HCl at pH2.5) for 10 minutes followed by centrifugation at 3,000 rpm for 5 minutes. The acidic supernatant containing the eluted phage was neutralized with 50 μl of 1M Tris base solution.

[0478] A small aliquot of the eluted phage from the UT-7 cell panning was introduced into TG1 cells through phage infection. The phage infected TG1 cells were then plated on 2xYT 100 μg/ml carbenicillin petridish plates to generate single colonies. 192 randomly selected single colonies were picked off the petridish plates and individually placed into separate wells of two 96-deep well plates containing 1 ml of 2xYT media supplemented with 100 μg/ml carbenicillin and 2% glucose. The two 96-deep well plates were incubated at 37° C. with shaking until the culture reached an OD_{600} of approximately 0.5

[0479] As a separate step, a new set of 96-well culture plates containing the same culture media described above were inoculated with a small fraction of the growing cultures in the 96-deep well plates to create duplicate plates. These duplicate plates were grown at 37° C. overnight. 20 μl of a 50% glycerol solution was then added to each well of the plates and the plates were frozen on dry ice and stored at −70° C. as master plates.

[0480] After inoculating the master plates, the two 96-deep well plates with cultures at an OD_{600} of approximately 0.5 were used in a FACS experiment as described below.

Screening of UT-7 Cell Binding Phage by FACS

[0481] 1 ml of 2xYT/2xYT media supplemented with 100 μg/ml carbenicillin and 2% glucose was placed in each well of a 96-deep well plate. New phage samples of the 96 positive clones identified by ELISA in Selection Strategy 1 were prepared by inoculating the media in each well of the 96-deep well plate with cells from the corresponding wells on the master plates. The 96-deep well plate was incubated at 37° C. with shaking until the culture reached an OD_{600} of approximately 0.5.

[0482] As discussed in Selection Strategy 2, cultures containing 192 different phage from Selection Strategy 2 were incubated in two 96-deep well plates at 37° C. with shaking until the cultures reached an OD_{600} of approximately 0.5.

[0483] The three 96-deep well plates containing log phase cultures (described in the two preceeding paragraphs) were then super-infected with approximately 10^9 M13KO7 helper phage at 37° C. for 30 minutes and another 30 minutes with gentle shaking. The plates were then centrifuged at 3000 rpm for 5 minutes and the supernatants were removed by flipping the plates. 1 ml of 2xYT media supplemented with 100 μg/ml carbenicillin and 25 μg/ml of kanamycin were then added to each well and the plates were incubated by shaking at 250 rpm at 30° C. overnight. The supernatants containing phage were prepared by centrifugation of the overnight culture at 3000 rpm for 5 minutes. The phage were purified from the supernatant by adding 1/5 vol of 20% PEG8000/2.5 M NaCl solution. The precipitated phage were pelleted by centrifugation and the resultant phage pellets in each well of the 96-deep well plates were resuspended into 100 μl of TE buffer (10 mM tris HCl, 1 mM EDTA, pH7.5) for use in FACS experiments.

[0484] In each well of a new set of three 96-well plates, UT-7 cells were incubated with a 10 μl aliquot of a single phage and 90 μl of 2% BSA PBS/T for 1 hour at 4° C. After 2 quick washes using cold PBS, cells were then incubated with 100 μl of 1 μg/ml anti-M13 mouse monoclonal antibody (Amersham Biosciences) in 2% BSA PBS/T at 4° C. for 1 hour Following 2 quick washes with cold PBS, 100 μl of 1 μg/ml phycoerythrin-conjugated goat F(ab')2 anti-mouse IgG Fc (Jackson Immuno Research Laboratories) was added to each well on the plates. The plates were then incubated for 1 hour at 4° C. The cells were washed twice again using cold PBS and were resuspended in 1 ml of fixation buffer (2% paraformaldehyde PBS pH 7.4). FACS was done using a Multiwell Caliber flow cytometer.

[0485] 14 phage clones from Selection Strategy 1 and 38 from Selection Strategy 2 were identified as binders of UT-7 cells expressing EpoR. DNA sequencing analysis of those scFv phage samples resulted in a total of 29 unique scFv sequences.

Example 2

Conversion of Phage scFv to scFv-Fc, IgG_2, and IgG_1 Protein Expression and Purification

[0486] All 29 phage scFv clones were converted to scFv-Fc fusion proteins using a streamlined subcloning procedure (FIG. **2**). DNA encoding the scFv was amplified the phagemid encoding the clones by PCR using a pair of vector-specific primers (pUCRev/FdTet). Ligation of the NcoI and NotI restriction fragments of scFv into a PciI (creates a cohesive end with NcoI) and NotI digested mammalian expression vector, pDC409a-G1Fc, resulted in fusion of the scFv to the human IgG_1 Fc. pDC409a-huG1Fc contains a human IgG, Fc after the NotI site. NcoI and PciI restriction fragments have the same cohesive end. The secretion of scFv-Fc protein is mediated by a VH5α signal sequence. Maxibodies derived

from individual phage clones are referred to by the designation "Mxb x" where x represents the clone number.

[0487] For converting scFv clones to IgG_2 expression constructs, DNA fragments encoding a VH or VL region were PCR amplified from phagemids encoding the clones using primers specific for each variable domain. Ligation of the VH (Nhe/AscI) fragment to a similarly restriction digested IgG2 heavy chain expression vector, pVE414NhuIgG2 resulted in an antibody heavy chain expression construct. Ligation of the Vλ NheI/NarI fragment to a similarly restriction digested light chain expression vector pVE414NhuλLC resulted in an antibody lambda light chain expression construct. Ligation of the Vκ NheI/Bsi WI fragment to a similarly restriction digested light chain expression vector pVE414NhuκLC resulted in antibody kappa light chain expression constructs. The choice of light chain constant type matches the variable light chain isotypes.

[0488] For generation of the IgG_1 expression constructs, the same VH Nhe/AscI fragment used for the IgG_2 expression construct was ligated into a similarly restriction digested pVE414NhuIgG1 vector. The light chain expression constructs described in the preceeding paragraph were used to express the IgG_1 light chains as well as the IgG_2 light chains.

[0489] scFv-Fc proteins were expressed transiently in mammalian COS-1 PKB E5 cells by cotransfection of antibody heavy and light chain expression constructs. IgG_1 proteins were also expressed transiently in mammalian COS-1 PKB E5 cells by cotransfection of antibody heavy and light chain expression constructs. IgG_2 proteins were also expressed transiently in mammalian COS-1 PKB E5 cells by cotransfection of antibody heavy and light chain expression constructs. The expressed antibodies were purified to greater than 95% purity from the conditioned media using protein A affinity chromatography. Protein identities were verified by N-terminal amino acid sequencing and concentrations were determined by absorption at 280 nm.

Example 3

Antibody Binding to Cell Surface huEpoR Analysis by FACS

[0490] The binding of the scFv-Fc protein to a cell surface expressed huEpoR was analyzed using FACS. UT-7 cells were incubated with either 5 nM scFv-Fc protein alone or with 5 nM scFv-Fc protein plus 0.5 μg/ml of rHuEpo for 1 hour at 4° C. After 2 quick washes using cold PBS, UT-7 cells were then incubated with 1 μg/ml phycoerythrin-conjugated goat F(ab')2 anti-human IgG Fc (Jackson Immuno Research Laboratories) for 1 hour at 4° C. The cells were washed twice using cold PBS and resuspended into 1 ml of fixation buffer (2% paraformaldehyde PBS pH 7.4). FACS was done using a FACSCaliber flow cytometer (Becton-Dickinson)

[0491] The FACS traces of the proteins expressed from the scFv-Fc expression vectors are shown in FIG. **3**. Clone 2, clone 5, clone 7, clone 10, and clone 30 all bind to huEpoR expressing UT-7 cells (FIG. **3**A) but not to the negative control cells (FIG. **3**B). UT-7 cell surface binding of clone 2, clone 5, clone 7, and clone 10 was blocked by an excess amount of rHuEpo (FIG. **3**A). rHuEpo did not block the binding of clone 30 (FIG. **3**A).

Example 4

Sequences of Clones 2, 5, 7, 10, and 30

[0492] Clone 2, clone 5, clone 7, clone 10, and clone 30 were sequenced using standard techniques. Nucleic acid and amino acid sequences for the variable heavy chains and variable light chains of clone 2, clone 5, clone 7, clone 10 and clone 30 appear below. Heavy chain and light chain CDR1, CDR2, and CDR3 are underlined in order within each amino acid sequence.

>Clone #2VH nucleic acid sequence (SEQ ID. NO.: 35)

GAGGTCCAGCTGGTGCAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTC

CCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGTAGCTATTGGA

TGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAAC

ATAAAGCCAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCG

ATTCACCATCTCCAGAGACAACGCCAAGAATTCAGTGTATCTGCAAATGA

ACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGTTTCG

AGGGGTGGGAGCTACTCGGACTGGGGCCAAGGCACCCTGGTCACCGTCTC

GAGT

>Clone #2VH amino acid sequence (SEQ ID. NO.: 1)

EVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVAN

IKPDGSEKYYVDSVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCARVS

RGGSYSDWGQGTLVTVSS

>Clone #2VL nucleic acid sequence (SEQ ID. NO.: 36)

CAGTCTGTGCTGACTCAGCCACCCTCCGCGTCCGGGTCTCCTGGACAGTC

AGTCACCATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGGTTATAACT

ATGTCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAACTCATGATT

TATGAGGTCAGTAAGCGGCCCTCAGGGGTCCCTGATCGCTTCTCTGGCTC

CAAGTCTGGCAACACGGCCTCCCTGACCGTCTCTGGGCTCCAGCCTGAGG

ATGAGGCTGATTATTACTGCAGCTCATATGCAGGCAGGAACTGGGTGTTC

GGCGGAGGGACCCAGCTCACCGTTTTA

>Clone #2VL amino acid sequence (SEQ ID. NO.: 2)

QSVLTQPPSASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMI

YEVSKRPSGVPDRFSGSKSGNTASLTVSGLQPEDEADYYCSSYAGRNWVF

GGGTQLTVL

>Clone #5VH nucleic acid sequence (SEQ ID. NO.: 37)

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTC

CCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGTAGCTATTGGA

TGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAAC

ATAAAGCCAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCG

-continued

ATTCACCATCTCCAGAGACAACGCCAAGAATTCAGTGTATCTGCAAATGA

ACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCAAGAGTTTCG

AGGGGTGGGAGCTACTCGGACTGGGGCCAGGGAACCCTGGTCACCGTCTC

GAGT

>Clone #5VH amino acid sequence

(SEQ ID. NO.: 3)

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVAN

IKPDGSEKYYVDSVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCARVS

RGGSYSDWGQGTLVTVSS

>Clone #5VL nucleic acid sequence

(SEQ ID. NO.: 38)

CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTC

GATCACCATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGGCTATATTT

ATGTCTCCTGGTACCAACAACACCCAGGCAAAGCCCCCAAACTCATGATT

TATGATGTCAGTCGTCGGCCCTCAGGGATTTCTGATCGCTTCTCTGGCTC

CAAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGG

ACGAGGCTGATTATTACTGCAACTCATATACAACCCTCAGCACCTGGCTC

TTCGGCGGAGGGACCAAGGTCACCGTCCTA

>Clone #5VL amino acid sequence

(SEQ ID. NO.: 4)

QSALTQPASVSGSPGQSITISCTGTSSDVGGYIYVSWYQQHPGKAPKLMI

YDVSRRPSGISDRFSGSKSGNTASLTISGLQAEDEADYYCNSYTTLSTWL

FGGGTKVTVL

>Clone #7VH nucleic acid sequence

(SEQ ID. NO.: 39)

GAGGTGCAGCTGGTGCAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTC

CCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGTAGCTATTGGA

TGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAAC

ATAAAGCCAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCG

ATTCACCATCTCCAGAGACAACGCCAAGAATTCAGTGTATCTGCAAATGA

ACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGTTTCG

AGGGGTGGGAGCTACTCGGACTGGGGCAAAGGAACCCTGGTCACCGTCTC

GAGT

>Clone #7VH amino acid sequence

(SEQ ID. NO.: 5)

EVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVAN

IKPDGSEKYYVDSVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCARVS

RGGSYSDWGKGTLVTVSS

>Clone #7VL nucleic acid sequence

(SEQ ID. NO.: 40)

CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTC

GATCATCATCTCCTGCACTGGAACCCGCAGTGACATTGGTGGTTACAACT

ATGTCTCCTGGTACCAACACCACCCAGGCAGAGCCCCCAAACTCATCATT

TTTGATGTCAATAATCGGCCCTCAGGAGTCTCTCACCGCTTCTCTGGCTC

CAAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGG

-continued

ACGAGGCTGATTATTACTGCAATTCATTTACAGACAGCCGGACTTGGCTG

TTCGGCGGAGGGACCAAGCTGACCGTCCTA

>Clone #7VL amino acid sequence

(SEQ ID. NO.: 6)

QSALTQPASVSGSPGQSIIISCTGTRSDIGGYNYVSWYQHHPGRAPKLII

FDVNNRPSGVSHRFSGSKSGNTASLTISGLQAEDEADYYCNSFTDSRTWL

FGGGTKLTVL

>Clone #10VH nucleic acid sequence

(SEQ ID. NO.: 41)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTC

CCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGCAGCTATGCCA

TGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGCT

ATTAGTGGTAGTGGTGGTAGCACATACTACGCAGACTCCGTGAAGGGCCG

GTTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGA

ACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGTAAAAGATAGG

GTTGCTGTAGCTGGTAAGGGTTCGTATTACTTTGACTCTTGGGGGAGGGG

GACCACGGTCACCGTCTCGAGT

>Clone #10VH amino acid sequence

(SEQ ID. NO.: 7)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSA

ISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVKDR

VAVAGKGSYYFDSWGRGTTVTVSS

>Clone #10VL nucleic acid sequence

(SEQ ID. NO.: 42)

CAGTCTGTGCTGACGCAGCCGCCCTCGGTGTCTGAAGCCCCCGGGCAGAG

GGTCACCATCGCCTGTTCTGGAAGCAGCTCCAACATCGGAAATAATGCTG

TAAGTTGGTACCAGCAACTCCCAGGAAAGGCTCCCACACTCCTCATCTAT

TATGATAATCTGCTGCCCTCAGGGGTCTCTGACCGATTCTCTGGCTCCAA

GTCTGGCACCTCAGCCTCCCTGGCCATCAGTGGGCTCCAGTCTGAGGATG

AGGCTGATTATTACTGTGCTGCATGGGATGACAGCCTGAATGATTGGGTG

TTCGGCGGTGGGACCAAGGTCACCGTCCTA

>Clone #10VL amino acid sequence

(SEQ ID. NO.: 8)

QSVLTQPPSVSEAPGQRVTIACSGSSSNIGNNAVSWYQQLPGKAPTLLIY

YDNLLPSGVSDRFSGSKSGTSASLAISGLQSEDEADYYCAAWDDSLNDWV

FGGGTKVTVL

>Clone #30VH nucleic acid sequence

(SEQ ID. NO.: 43)

CAGGTGCAGCTGCAGGAGTCGGGTCCAGGACTGGTGAAGCCCTCGCAGAC

CCTCTCACTCACCTGTGCCATCTCCGGGGACAGTGTCTCTAGCAACAGTG

CTGCTTGGAACTGGATCAGGCAGTCCCCATCGAGAGGCCTTGAGTGGCTG

GGAAGGACATACTACAGGTCCAAGTGGTATAATGATTATGCAGTATCTGT

GAAAAGTCGAATGACCATAAAAGCAGACACATCCAAGAACCAGTTCTCCC

TGCAACTGAACTCTGTGACTCCCGAAGACACGGCTGTGTATTACTGTGCA

-continued

AGAGATGAGGGACCGCTTGACTACTGGGGCCAGGGAACCCTGGTCACCGT

CTCGGCC

>Clone #30VH amino acid sequence

(SEQ ID. NO.: 9)

QVQLQESGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSPSRGLEWL

GRTYYRSKWYNDYAVSVKSRMTIKADTSKNQFSLQLNSVTPEDTAVYYCA

RDEGPLDYWGQGTLVTVSA

>Clone #30VL nucleic acid sequence

(SEQ ID. NO.: 44)

CAGGCTGTGCTCACTCAGCCGTCCTCAGTGTCTGGGGCCCCAGGGCAGAG

GGTCACCATCTCCTGCACTGGGAGCAGCTCCAACCTCGGGACAGGTTATG

ATGTACACTGGTACCAGCAGCTTCCAGGAACAGCCCCCAAACTCCTCATC

TATGGTAACAGCAATCGGCCCTCAGGGGTCCCTGACCGATTCTCGGGCTC

CAAGTCTGACACCTCAGGTTTGCTGGCCATCACTGGGCTCCAGGCTGAGG

ATGAGGCTACTTATTACTGCCAGTCCTATGACTTCAGCCTGAGTGCTATG

GTATTCGGCGGAGGGACCAAGGTCACCGTCCTA

>Clone #30VL amino acid sequence

(SEQ ID. NO.: 10)

QAVLTQPSSVSGAPGQRVTISCTGSSSNLGTGYDVHWYQQLPGTAPKLLI

YGNSNRPSGVPDRFSGSKSDTSGLLAITGLQAEDEATYYCQSYDFSLSAM

VFGGGTKVTVL

[0493] Clones 2, 5, 7, 10, and 30 were used to make scFv-Fc proteins. The nucleic acid sequences and the amino acid sequences of the scFv-Fc proteins that they encode are shown below:

>Mxb #2 scFv-Fc nucleic acid sequence:

(SEQ ID NO.: 50)

GAGGTCCAGCTGGTGCAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTC

CCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGTAGCTATTGGA

TGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAAC

ATAAAGCCAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCG

ATTCACCATCTCCAGAGACAACGCCAAGAATTCAGTGTATCTGCAAATGA

ACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGTTTCG

AGGGGTGGGAGCTACTCGGACTGGGGCCAAGGCACCCTGGTCACCGTCTC

GAGTGGAGGCGGCGGTTCAGGCGGAGGTGGCTCTGGCGGTGGCGGAAGTG

CACAGTCTGTGCTGACTCAGCCACCCTCCGCGTCCGGGTCTCCTGGACAG

TCAGTCACCATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGGTTATAA

CTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAACTCATGA

TTTATGAGGTCAGTAAGCGGCCCTCAGGGGTCCCTGATCGCTTCTCTGGC

TCCAAGTCTGGCAACACGGCCTCCCTGACCGTCTCTGGGCTCCAGCCTGA

GGATGAGGCTGATTATTACTGCAGCTCATATGCAGGCAGGAACTGGGTGT

TCGGCGGAGGGACCCAGCTCACCGTTTTAGGTGCGGCCGCAGAGCCCAAA

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TCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCT

GGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCA

TGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCAC

GAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCA

TAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTG

TGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAG

TACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAAC

CATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGC

CCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTG

GTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGG

GCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACG

GCTCCTTCTTCCTCTATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAG

CAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCA

CTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

>Mxb #2 scFv-Fc amino acid sequence:

(SEQ ID NO.: 45)

EVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVAN

IKPDGSEKYYVDSVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCARVS

RGGSYSDWGQGTLVTVSSGGGGSGGGGSGGGGSAQSVLTQPPSASGSPGQ

SVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYEVSKRPSGVPDRFSG

SKSGNTASLTVSGLQPEDEADYYCSSYAGRNWVFGGGTQLTVLGAAAEPK

SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH

EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE

YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL

VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ

QGNVFSCSVMHEALHNHYTQKSLSLSPGK

>Mxb #5 scFv-Fc nucleic acid sequence

(SEQ ID NO.: 51)

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTC

CCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGTAGCTATTGGA

TGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAAC

ATAAAGCCAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCG

ATTCACCATCTCCAGAGACAACGCCAAGAATTCAGTGTATCTGCAAATGA

ACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCAAGAGTTTCG

AGGGGTGGGAGCTACTCGGACTGGGGCCAGGGAACCCTGGTCACCGTCTC

GAGTGGAGGCGGCGGTTCAGGCGGAGGTGGCTCTGGCGGTGGCGGAAGTG

CACAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAG

TCGATCACCATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGGCTATAT

TTATGTCTCCTGGTACCAACAACACCCAGGCAAAGCCCCCAAACTCATGA

TTTATGATGTCAGTCGTCGGCCCTCAGGGATTTCTGATCGCTTCTCTGGC

TCCAAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCTCCAGGCTGA

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GGACGAGGCTGATTATTACTGCAACTCATATACAACCCTCAGCACCTGGC

TCTTCGGCGGAGGGACCAAGGTCACCGTCCTAGGTGCGGCCGCAGAGCCC

AAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACT

CCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCC

TCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGC

CACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGT

GCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACC

GTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAG

GAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAA

AACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCC

TGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGC

CTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAA

TGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCG

ACGGCTCCTTCTTCCTCTATAGCAAGCTCACCGTGGACAAGAGCAGGTGG

CAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAA

CCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

>Mxb #5 scFv-Fc amino acid sequence:

(SEQ ID NO.: 46)

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVAN

IKPDGSEKYYVDSVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCARVS

RGGSYSDWGQGTLVTVSSGGGGSGGGGSGGGGSAQSALTQPASVSGSPGQ

SITISCTGTSSDVGGYIYVSWYQQHPGKAPKLMIYDVSRRPSGISDRFSG

SKSGNTASLTISGLQAEDEADYYCNSYTTLSTWLFGGGTKVTVLGAAAEP

KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS

HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK

EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC

LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW

QQGNVFSCSVMHEALHNHYTQKSLSLSPGK

>Mxb #7 scFv-Fc nucleic acid sequence

(SEQ ID NO.: 52)

GAGGTGCAGCTGGTGCAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTC

CCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGTAGCTATTGGA

TGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAAC

ATAAAGCCAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCG

ATTCACCATCTCCAGAGACAACGCCAAGAATTCAGTGTATCTGCAAATGA

ACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGTTTCG

AGGGGTGGGAGCTACTCGGACTGGGGCAAAGGAACCCTGGTCACCGTCTC

GAGTGGAGGCGGCGGTTCAGGCGGAGGTGGCTCTGGCGGTGGCGGAAGTG

CACAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAG

TCGATCATCATGTCCTGCACTGGAACCCGCAGTGACATTGGTGGTTACAA

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CTATGTCTCCTGGTACCAACACCACCCAGGCAGAGCCCCCAAACTCATCA

TTTTTGATGTCAATAATCGGCCCTCAGGAGTCTCTCACCGGTTCTCTGGC

TCCAAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCTCCAGGCTGA

GGACGAGGCTGATTATTACTGCAATTCATTTACAGACAGCCGGACTTGGC

TGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTGCGGCCGCAGAGCCC

AAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACT

GCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCC

TCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGC

CACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGT

GCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACC

GTGTGGTCAGCGTCCTCACCGTCCTGCAGCAGGACTGGCTGAATGGCAAG

GAGTACAAGTGCAAGGTCTCCAACAAAGCGCTCCCAGCCCCCATCGAGAA

AACCATCTCCAAAGCCAAAGGGCAGCGCCGAGAACCACAGGTGTACACCC

TGCCCCCATCCCGGGAGGAGATGACCAAGAACGAGGTCAGCCTGACCTGC

CTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAA

TGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCG

ACGGCTCCTTCTTCCTCTATAGCAAGCTCACCGTGGACAAGAGCAGGTGG

CAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAA

CCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

>Mxb #7 scFv-Fc amino acid sequence:

(SEQ ID NO.: 47)

EVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVAN

IKPDGSEKYYVDSVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCARVS

RGGSYSDWGKGTLVTVSSGGGGSGGGGSGGGGSAQSALTQPASVSGSPGQ

SIIISCTGTRSDIGGYNYVSWYQHHPGRAPKLIIFDVNNRPSGVSHRFSG

SKSGNTASLTISGLQAEDEADYYCNSFTDSRTWLFGGGTKLTVLGAAAEP

KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS

HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK

EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC

LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW

QQGNVFSCSVMHEALHNHYTQKSLSLSPGK

>Mxb #10 scFv-Fc nucleic acid sequence

(SEQ ID NO.: 53)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTC

CCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGCAGCTATGCCA

TGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGCT

ATTAGTGGTAGTGGTGGTAGCACATACTACGCAGACTCCGTGAAGGGCCG

GTTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGA

ACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGTAAAAGATAGG

GTTGCTGTAGCTGGTAAGGGTTCGTATTACTTTGACTCTTGGGGGAGGGG

GACCACGGTCACCGTCTCGAGTGGAGGCGGCGGTTCAGGCGGAGGTGGCT

-continued

CTGGCGGTGGCGGAAGTGCACAGTCTGTGCTGACGCAGCCGCCCTCGGTG

TCTGAAGCCCCCGGGCAGAGGGTCACCATCGCCTGTTCTGGAAGCAGCTC

CAACATCGGAAATAATGCTGTAAGTTGGTACCAGCAACTCCCAGGAAAGG

CTCCCACACTCCTCATCTATTATGATAATCTGCTGCCCTCAGGGGTCTCT

GACCGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCATCAG

TGGGCTCCAGTCTGAGGATGAGGCTGATTATTACTGTGCTGCATGGGATG

ACAGCCTGAATGATTGGGTGTTCGGCGGTGGGACCAAGGTCACCGTCCTA

GGTGCGGCCGCAGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACC

GTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCC

CAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGC

GTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTA

CGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGC

AGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAG

GACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCT

CCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAG

AACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAAC

CAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGC

CGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGC

CTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTATAGCAAGCTCACC

GTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGAT

GCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTC

CGGGTAAA

>Mxb #10 scFv-Fc amino acid sequence:

(SEQ ID NO.: 48)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSA

ISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVKDR

VAVAGKGSYYFDSWGRGTTVTVSSGGGGSGGGGSGGGGSAQSVLTQPPSV

SEAPGQRVTIACSGSSSNIGNNAVSWYQQLPGKAPTLLIYYDNLLPSGVS

DRFSGSKSGTSASLAISGLQSEDEADYYCAAWDDSLNDWVFGGGTKVTVL

GAAAEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC

VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ

DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKN

QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT

VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

>Mxb #30 scFv-Fc nucleic acid sequence

(SEQ ID NO.: 54)

CAGGTGCAGCTGCAGGAGTCGGGTCCAGGACTGGTGAAGCCCTCGCAGAC

CCTCTCACTCACCTGTGCCATCTCCGGGGACAGTGTCTCTAGCAACAGTG

CTGCTTGGAACTGGATCAGGCAGTCCCCATCGAGAGGCCTTGAGTGGCTG

GGAAGGACATACTACAGGTCCAAGTGGTATAATGATTATGCAGTATCTGT

-continued

GAAAAGTCGAATGACCATAAAAGCAGACACATCCAAGAACCAGTTCTCCC

TGCAACTGAACTCTGTGACTCCCGAAGACACGGCTGTGTATTACTGTGCA

AGAGATGAGGGACCGCTTGACTACTGGGGCCAGGGAACCCTGGTCACCGT

CTCGGCCGGTGGCGGTGGCAGCGGCGGTGGTGGGTCCGGTGGCGGCGGAT

CTGGCGCGCCACAGGCTGTGCTCACTCAGCCGTCCTCAGTGTCTGGGGCC

CCAGGGCAGAGGGTCACCATCTCCTGCACTGGGAGCAGCTCCAACCTCGG

GACAGGTTATGATGTACACTGGTACCAGCAGCTTCCAGGAACAGCCCCCA

AACTCCTCATCTATGGTAACAGCAATCGGCCCTCAGGGGTCCCTGACCGA

TTCTCGGGCTCCAAGTCTGACACCTCCAGGTTTGCTGGCCATCACTGGGC

TCCAGGCTGAGGATGAGGCTACTTATTACTGCCAGTCCTATGACTTCAGC

CTGAGTGCTATGGTATTCGGCGGAGGGACCAAGGTCACCGTCCTAGCGGC

CGCAGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAG

CACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCC

AAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGT

GGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACG

GCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAAC

AGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCT

GAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCC

CCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAG

GTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAG

CCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGT

GGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTG

CTGGACTCCGACGGCTCCTTCTTCCTCTATAGCAAGCTCACCGTGGACAA

GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGG

CTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

>Mxb #30 scFv-Fc amino acid sequence:

(SEQ ID NO.: 49)

QVQLQESGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSPSRGLEWL

GRTYYRSKWYNDYAVSVKSRMTIKADTSKNQFSLQLNSVTPEDTAVYYCA

RDEGPLDYWGQGTLVTVSAGGGGSGGGGSGGGGSGAPQAVLTQPSSVSGA

PGQRVTISCTGSSSNLGTGYDVHWYQQLPGTAPKLLIYGNSNRPSGVPDR

FSGSKSDTSGLLAITGLQAEDEATYYCQSYDFSLSAMVFGGGTKVTVLAA

AEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV

DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL

NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVS

LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK

SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Example 5

Competitive Binding to huEpoR

[0494] Clone 2, clone 5, clone 7, clone 10, and clone 30 scFv-Fc proteins were tested for their ability to compete with

clone 5 and clone 30 scFv phage for binding to huEpoR using a plate-based ELISA. Biotinylated huEpoR was immobilized on a streptavidin plate. A scFv-Fc protein and a scFv phage were added to the plate. Binding of the scFv phage was then detected using an anti-M13 mouse monoclonal antibody followed by a phycoerythrin-conjugated goat F(ab')2 anti-mouse IgG Fc (Jackson Immuno Research Laboratories). The inhibition of phage binding by clone 2, clone 5, clone 7, clone 10 and clone 30 scFv-Fc protein was tested by using a series of 8 concentrations for each scFv-Fc protein (0, 0.032, 0.16, 0.8, 4, 20, 100, and 500 nM). Clone 2, clone 5, clone 7, and clone 10 scFv-Fc proteins demonstrated a dose dependent inhibition of binding of clone 5 scFv phage to huEpoR (FIG. **4**A). However, clone 30 scFv-Fc protein did not inhibit binding of clone 5 scFv phage to huEpoR at concentrations up to 500 nM (FIG. **4**A). Binding of clone 30 scFv phage to huEpoR was inhibited by clone 30 scFv-Fc protein in a dose dependent fashion, but not by clone 2, clone 5, clone 7, or clone 10 scFv-Fc proteins at concentrations up to 500 nM (FIG. **4**B). Those results suggest that the epitopes for clone 2, clone, 7, and clone 10 scFv-Fc proteins overlap with the epitope of clone 5 scFv-Fc protein, but that clone 30 scFv-Fc protein binds to an epitope that does not overlap with the epitopes of clone 2, clone 5, clone 7, and clone 10 scFv-Fc proteins.

Example 6

Antibody Binding to Mouse EpoR-Fc Protein (muEpoR-Fc)

[0495] The cross reactivity of clone 2, clone 5, clone 7, clone 10, and clone 30 scFv-Fc proteins and clone 2, clone 5, clone 7, clone 10, and clone 30 IgG_2 proteins with mouse EpoR (muEpoR) was determined using an ELISA assay. Individual scFv-Fc proteins or IgG_2 proteins (100 μl of a 1 μg/ml antibody stock in 50 mM $NaHCO_3$, pH8.5) were added to each well on a Nunc-Immuno Polysorp ELISA plate (Nalge Nunc International) such that each well comprised only a single clone. The plate was incubated at 4° C. overnight. After blocking the wells with 4% milk/PBS/0.1% tween 20 for 1 hour at room temperature, plates were washed three times with PBS/0.1% tween 20. 100 μl of 5 μg/ml biotinylated muEpoR-Fc protein was added to each well and incubated for 1 hour at 25° C. The bound muEpoR-Fc was detected using streptavidin-HRP conjugate (1:1000 dilution in 4% milk PBS/0.1% tween 20). 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid) (ABTS) was used as a substrate and the absorption was measured at 405 nm on a plate reader. All of the antibodies (clone 2, clone 5, clone 7, clone 10, and clone 30 scFv-Fc proteins and clone 2, clone 5, clone 7, clone 10, and clone 30 IgG_2 proteins) showed significant levels of cross reactivity to muEpoR-Fc (FIG. **5**).

Example 7

Measurement of Binding Kinetics to huEpoR Using BIAcore

[0496] The affinities for clone 2, clone 5, clone 7, clone 10, and clone 30 scFv-Fc proteins were determined on a BIAcore 3000 instrument (BIAcore International AB). Goat anti-human Fc antibody (Jackson Immuno Research Laboratories) was immobilized on a CM4 chip (BIAcore International AB) activated through N-hydroxyl succinamide chemistry. An scFv-Fc protein solution was flowed over the chip and the scFv-Fc protein in the solution was captured on the chip through Fc binding to the immobilized goat anti human Fc antibody. Each kinetics run used a 50 μl/min flow rate at 25° C. Each run used huEpoR protein at concentrations up to 1000 nM as analyte. An association phase of 1 minute and dissociation phase of 5 minutes were used for data analysis by 1:1 Langmuir with mass transfer+local Rmax fit using BIAevaluation software version 3 provided by BIAcore. Flowing low pH glycine buffer (50 mM glycine HCl, pH 1.5) over the chip to remove the captured scFv-Fc protein regenerated the goat anti-human Fc antibody CM4 chip surface. This same chip surface was used for separately capturing each of the five scFv-Fc proteins.

[0497] BIAcore kinetic binding sensograms are shown in FIG. **6** and the binding parameters are summarized in Table 2 below. The affinities for the five different scFv-Fc proteins varied from 1.1 nM to 14,900 nM. The association and dissociation rate (k_{on} and k_{off}, respectively) for all five scFv-Fc proteins were within typical ranges for antibodies. The highest affinity scFv-Fc protein, the clone 10 scFv-Fc protein, had the slowest k_{off} (2.2×10^{-4} s^{-1}). The lowest affinity scFv-Fc protein, the clone 30 scFv-Fc protein, had the slowest k_{on} (1.8×10^{4} $M^{-1}s^{-1}$) and fastest k_{off} ($2{,}740\times10^{-4}$ s^{-1}).

TABLE 2

Summary of scFv-Fc BIAcore binding kinetics to huEpoR

ScFv-Fc clone	k_{on} (10^5, 1/Ms)	k_{off} (10^{-4}, 1/s)	K_D (10^{-9}, M)
#2	4.1	1,360	334
#5	2.8	612	217
#7	2.0	541	271
#10	2.0	2.2	1.1
#30	.18	2,740	14,900

Example 8

Screening of scFv-Fc Proteins In Vitro for the Activation of the Human Erythropoietin Receptor

[0498] The twenty-nine scFv sequences identified in Example 1 were screened as either scFv-Fc proteins or as IgG proteins for the activation of the huEpoR. The in vitro screening of the scFv-Fc proteins and IgG proteins was done by a luciferase-based reporter assay (luciferase assay) in UT-7 cells (human megakaryoblasts) transfected with a construct containing nine STAT5 binding sites in front of a luciferase reporter (UT-7-LUC cells). All cells were maintained and all cellular assays were conducted at 37° C. in a humidified incubator at 5% CO_2/95% atmospheric air, unless otherwise noted. All fetal bovine serum (FBS) was heat inactivated at 55° C. for 45 minutes prior to usage. All Dulbecco's Phosphate-Buffered Saline (PBS) used for cell manipulation was without calcium chloride and magnesium chloride. UT-7-LUC cells (Amgen, Inc.; Thousand Oaks, Calif.) were maintained in growth media comprising IMDM (Invitrogen; Carlsbad, Calif.) containing 10% FBS (HyClone; Logan, Utah), 500 μg/mL hygromycin (Roche; Penzberg, Germany), 100 U/mL penicillin, 100 μg/mL streptomycin, 292 μg/mL L-glutamine (1×PSG; Invitrogen) and 1 U/mL recombinant human erythropoietin (Epoetin Alpha, rHuEpo; Amgen, Inc.). The cells were washed two times in PBS (Invitrogen) and resuspended at 400,000 cells per mL in assay media (RPMI Medium 1640 with 1% FBS, 1×PSG, and 12.5 mM HEPES (Invitrogen)). Following an overnight incubation,

cell number and viability were determined, and the cells were resuspended at 200,000 cells per mL in assay media.

[0499] Each scFv-Fc protein was serially diluted in a 96-well opaque plate (Corning; Corning, N.Y.). Each dilution was run in triplicate and the following concentrations of scFv-Fc protein were used: Mxb 5, Mxb 10, and Mxb 30: 1000, 333, 111, 37.04, 12.35, 4.115, 1.372, 0.457, 0.152, 0.051, 0.017, and 0.006 nM. For Mxb 2 and Mxb 7: 2500, 1250, 625, 312.5, 156.25, 78.125, 39.0625, 19.53125, 9.765625, 4.882813, 2.441406, 1.220703, 0.610352, 0.3051758, 0.1525879, 0.76294, 0.038147, 0.019073, 0.009537, 0.004768, 0.002384, 0.001192, 0.000596, 0.000298 nM. To serve as a control standard, rHuEpo was serially diluted in the same plate used to test each scFv-Fc protein. Each Epo dilution was run in triplicate and the following concentrations of Epo were used: for the plates with Mxb 2, Mxb 5, Mxb 10, and Mxb 30: 100, 10, 1, 0.1, 0.01, and 0.001 nM. For the plate testing Mxb 7: 1.488, 744, 372, 186, 93, 46.5, 23.2, 11.6, 5.8, 2.9, 1.5, 0.71, 0.36, 0.18, 0.09, 0.045, 0.023, 0.011, 0.006, 0.003, 0.0015, 0.0007, 0.0004, 0.0002 nM. Approximately 10,000 cells were added to each well. The cells were then cultured for six hours, and the assay was performed according to the manufacturer's protocol for the Steady-Glo Luciferase Assay. (Promega Corporation).

[0500] Twenty-two of the twenty-nine maxibodies identified in Example 1 were shown to bind the huEpoR and induce a response in the UT-7-Luc cells of varying degrees. The results for Mxb2, Mxb5, Mxb7, Mxb10, and Mxb30 are represented graphically in FIG. **7**.

Example 9

Screening of Antibodies In Vitro for the Activation of the huEpoR

[0501] The twenty-nine scFv-Fc proteins described in Example 2 and the twenty-nine IgG_2 proteins also described in Example 2 were individually used to activate the huEpoR using a luciferase-based reporter assay as reported above for the scFv-Fc proteins in Example 8. The resulting dose-titrations were converted to ratios of the maximal luciferase signal of the antibody (scFv-Fc protein or IgG_2 protein) to the maximal luciferase signal of the recombinant human erythropoietin (rHuEpo) standard. The results for clone 2, clone 5, clone 7, clone 10, and clone 30 scFv-Fc proteins and clone 2, clone 5, clone 7, clone 10, and clone 30 IgG_2 proteins are represented graphically in FIG. **8**. The clone 2, clone 5, clone 7, clone 10, and clone 30 scFv-Fc proteins were more potent agonists of the huEpoR than the corresponding clone 2, clone 5, clone 7, clone 10, and clone 30 IgG_2 proteins.

Example 10

In Vitro Signaling Experiments

[0502] UT-7 cells were maintained in growth media consisting of IMDM (Invitrogen) containing 10% FBS (HyClone), 100 U/mL penicillin, 100 μg/mL streptomycin, 292 μg/mL L-glutamine (1×PSG; Invitrogen) and 1 U/mL rHuEpo (Epoetin Alpha, rHuEpo; Amgen Inc.). The cells were washed two times in PBS (Invitrogen) and resuspended in starvation media consisting of IMDM and 0.5% FBS. Following an overnight incubation, cell number and viability were determined, and the cells were resuspended at 3,000,000 cells per mL in IMDM containing either 50 ng/mL rHuEpo, 1 μg/mL Mxb2, 1 μg/mL Mxb5, 1.54 μg/mL clone 2 IgG_2 protein ($IgG_2$2), 1.54 μg/mL clone 5 IgG_2 protein ($IgG_2$5), or PBS. Cells were stimulated for 0, 2, 15, or 60 minutes in a 37° C. heat block. Activation of these cells by rHuEpo engages the huEpoR and induces phosphorylation of the signaling molecules Stat5 and Akt. The cell suspensions were then centrifuged for 1 minute, 7000 rpm, at 4° C. and the supernatant was removed. The cell pellet was washed with ice-cold PBS and centrifuged for 1 minute, 7000 rpm, at 4° C. The supernatant was removed and cell lysates were generated using M-PER mammalian protein extraction reagent (Pierce Biotechnology, Inc.; Rockford, Ill.) supplemented with Complete (EDTA-free) protease inhibitor cocktail tablets (Roche Diagnostics). All of the samples were then vortexed for 10 seconds, and the lysates were incubated at room temperature for 5 minutes with occasional vortexing. The lysates were then centrifuged at 2000 rpm for 5 minutes, and the supernatants were transferred into aliquots and snap frozen in a dry ice/ethanol bath and stored at −80° C. until used.

[0503] Western Blotting: All protein samples were combined with 1× NuPAGE Sample Reducing Agent (Invitrogen) and 1× NuPAGE LDS sample buffer (Invitrogen), incubated at 10° C. for 5 minutes, and run on pre-cast 4-20% Tris-Glycine gels (Invitrogen). All gels were loaded with the See-Blue Plus2 protein ladder (Invitrogen). Proteins were then transferred to a nitrocellulose membrane filter paper sandwich with 0.45 μm pore size (Invitrogen). Following the protein transfer, the membranes were blocked in 5% blotting grade blocker non-fat dry milk (milk; Bio-Rad Laboratories; Hercules, Calif.) in tris-buffered saline with tween 20, pH 8.0 (TBS-T; SIGMA) for at least one hour at room temperature. The membranes were first blotted with an anti-phosphorylated Stat5 A/B antibody (Upstate; Charlottesville, Va.) at 1 μg/mL in 2.5% bovine serum albumin (BSA; SIGMA) in TBS-T. Incubations with the anti-phosphorylated Stat5 A/B antibody were conducted for one hour at room temperature on a shaking platform, followed by three rinses and three washes for 15 minutes in TBS-T. The membranes were then blotted with a goat anti-mouse-horseradish peroxidase (HRP) conjugated antibody (Pierce Biotechnology, Inc.) diluted to 1:2000 in 1.25% BSA in TBS-T. All of the incubations with the goat anti-mouse-HRP conjugated antibody were performed for one hour at room temperature on a shaking platform, followed by three rinses and three washes for 15 minutes in TBS-T. Enhanced chemiluminescence (ECL) western blotting detection system (Amersham Bioscience) was used to detect the proteins on the nitrocellulose membranes. The membranes were then exposed to Kodak BIOMAX Light Film for chemiluminescence (Kodak; Rochester, N.Y.). Following detection, the membranes were stripped in Restore Western Blot Stripping Buffer (PIERCE) for 20 minutes.

[0504] Blotting was repeated using the same process described above for the following antibodies: Total Stat5: primary antibody—anti-Stat5 (Cell Signaling Technology; Danvers, Mass.) at 1:1000, secondary antibody—goat anti-rabbit-HRP (Pierce Biotechnology, Inc.) at 1:2000 dilution. Phosphorylated Akt: primary antibody—anti-phosphorylated Akt (Thr308) (Cell Signaling Technology) 1:1000 dilution, secondary antibody—goat anti-rabbit-HRP 1:2000 dilution. Total Akt: primary antibody—anti-Akt (Cell Signaling Technology) at 1:1000 dilution, secondary antibody—goat anti-rabbit HRP 1:2000.

[0505] The results of this experiment demonstrated that Mxb 2, Mxb 5, $IgG_2$2, and $IgG_2$5 activated the huEpoR and induced phosphorylation of both Stat5 and Akt. The kinetics

of phosphorylation by Mxb 2, Mxb 5, $IgG_2$2, and $IgG_2$5 were slightly delayed in relation to rHuEpo. The results for Mxb 2 and $IgG_2$2 are shown in FIG. **9**. FIG. **9** shows that after rHuEpo stimulation of UT-7 cells, strong phosphorylation of Stat5 was detected within 2 minutes and reached a maximum at 15 minutes, whereas, in the case of Mxb 2 and $IgG_2$2, the level of Stat5 phosphorylation was low at 2 minutes after stimulation. The same was true for Akt phosphorylation. The level of Stat5 and Akt phosphorylation was lower in cells stimulated by $IgG_2$2 compared to cells stimulated by Mxb 2. This signaling experiment indicated that Mxb 2 and $IgG_2$2 were weaker agonists of the huEpoR than rHuEpo.

Example 11

BFU-E Assays

[0506] The activity of a subset of Mxbs including Mxb 2, Mxb 5, Mxb 7, and Mxb 30 was evaluated on CD34+ human peripheral blood progenitor cells (CD34+PBPC) using a Burst Forming Unit-Erythroid (BFU-E) assay. The BFU-E assay is described in Elliott et al., Activation of the Erythropoietin (EPO) receptor by bivalent anti-EPO receptor antibodies, J. Biol. Chem. 271(40), 24691-24697. In this case, the BFU-E assay tested the ability of scFv-Fc proteins to stimulate the production of erythroid colonies from human primary cells isolated from the blood of healthy volunteers. Certain agents that promote erythroid colony formation also promote proliferation of erythroid progenitor cells, prevent apoptosis, and induce cellular differentiation.

[0507] For this assay, CD34+PBPC were purified from apheresis products obtained from rhG-CSF mobilized hematologically normal donors. One thousand CD34+PBPC per mL were cultured in 35 mm petri dishes in a methylcellulose-based medium (METHOCULT™ H4230, StemCell Technologies, Vancouver, BC, Canada) containing 100 ng/mL each of rhSCF, rhIL-3, and rhIL-6 with log escalating doses from 0.1 to 1,000 ng/mL of rHuEpo or 1 to 10,000 ng/mL of either Mxb 2, Mxb 5, Mxb 7, or Mxb 30, all in triplicate. Cultures were incubated at 37° C. in 5% CO_2/95% atmospheric air in a humidified chamber, and 14 days later, the number of BFU-E derived colonies was counted. Each culture was observed and enumerated with a dissecting microscope at 20×. BFU-E derived colonies were defined as uni- or multifocal hemoglobinized cellular clusters containing greater than 50 cells.

[0508] Mxb 2, Mxb 5, Mxb 7, and Mxb30 induced the formation of hemoglobin-containing erythroid colonies, but all maxibodies were significantly less potent than rHuEpo in inducing BFU-E-derived colonies. The maximal number of colonies induced by any of the maxibodies was significantly lower than the number induced by rHuEpo, and this maximal number was induced at significantly higher concentrations than in the case of rHuEpo as seen in FIG. **10**. These data suggest that the scFv-Fc proteins are low potency agonists of the huEpoR compared to rHuEpo.

Example 12

In Vivo Experiments

[0509] The effect of a single injection of Mxb 2, Mxb 5, Mxb 7, or Mxb 10 was tested in several experiments in mice.

Example 12A

Mxb 5 Dose Titration Experiment in Mice

[0510] 2-month-old female BDF-1 mice were injected subcutaneously with carrier (PBS with 0.1% BSA), 3 μg/kg PEG-NESP (PEG-NESP and methods of preparing PEG-NESP are generally described in PCT publication no. WO01/76640), or 0.5, 2.5, 5, or 7.5 mg/kg Mxb 5 in a final volume of 200 μl. Blood was collected from the retro-orbital sinus at numerous time-points for up to 60 days and evaluated for CBC parameters using an ADVIA blood analyzer. Data are presented in FIGS. **12** and **13** with n=5 at each time point.

[0511] There was a clear dose effect of Mxb 5 with very limited activity at 0.5 mg/kg, but significant erythropoietic activity was observed in mice injected with doses of Mxb 5 between 2.5 and 7.5 mg/kg. The activity profile of Mxb 5 was different from that of PEG-NESP; the peak reticulocyte number was achieved on day 4 after an injection of either PEG-NESP or Mxb 5, but the duration of the reticulocyte response was significantly increased in the mice that received doses of Mxb 5 between 2.5 and 7.5 mg/kg. The reticulocyte numbers returned to baseline on day 8 in the PEG-NESP-treated mice, but it took 14 to 18 days for the reticulocytes to return to baseline in the Mxb 5-treated mice. In mice injected with Mxb 5 at doses between 5 and 7.5 mg/kg, the hemoglobin levels stayed above baseline for 46 to 52 days. In contrast, the hemoglobin level in the PEG-NESP-treated mice returned to baseline at day 16, thus showing a very significant difference in the duration and magnitude of the hemoglobin response in the mice treated with Mxb 5 or PEG-NESP. This experiment demonstrates that a single injection of Mxb 5 increases hemoglobin levels above baseline for a period of time that is longer than the total life span of the red blood cells in mice (40 days). Since the rate of hemoglobin decline after the administration of an erythropoietic agent is related to the life span of erythrocytes (120 days in humans), a single administration of Mxb 5 in humans could potentially be enough to correct anemia over a period of 2-4 months.

Example 12B

Mxb 7 Dose Titration Experiment in Mice

[0512] 2-month-old female BDF-1 mice were injected subcutaneously with carrier (PBS with 0.1% BSA), 3 μg/kg PEG-NESP (Amgen, Inc.), or 0.5, 2.5, 5, or 7.5 mg/kg Mxb 7 (Amgen, Inc.) in a final volume of 200 μl. Blood was collected from the retro-orbital sinus at numerous time-points for up to 24 days and evaluated for CBC parameters using an ADVIA blood analyzer. Data are presented in FIGS. **14** and **15** with n=5 at each time point.

[0513] A single injection of Mxb 7 produced an increase in reticulocyte numbers and hemoglobin levels that were dose-dependent and sustained over a long period of time. After a single subcutaneous (SC) injection of Mxb 7 at 7.5 mg/kg, the reticulocyte numbers stayed above baseline for 12 days while in the mice injected with PEG-NESP, the reticulocyte numbers stayed above baseline for 8 days. In this experiment, hemoglobin levels were measured for 24 days, and during this time, the increase in hemoglobin was sustained at higher levels and for a longer period of time in the mice that received Mxb 7 at 7.5 mg/kg compared to the PEG-NESP-treated mice. After a single PEG-NESP injection, the hemoglobin peak was reached on day 5, and hemoglobin was back to baseline on day 14. In contrast, after a single injection of Mxb 7 (7.5 mg/kg), the hemoglobin peak was reached on day 12, and hemoglobin returned to baseline on day 24. This experiment indicates that Mxb 7 had very different properties from PEG-NESP. After a single administration, the mice treated with Mxb 7 had a longer-duration erythropoietic response

than PEG-NESP-treated mice as demonstrated by the increase in reticulocyte numbers and hemoglobin levels.

Example 12C

Mxb 10 Dose Titration Experiment in Mice

[0514] 2-month-old female BDF-1 mice were injected subcutaneously with carrier (PBS with 0.1% BSA), 3 μg/kg PEG-NESP (Amgen, Inc.), or 0.05, 0.15, 0.5, 1.5, 3, or 5 mg/kg Mxb 10 (Amgen, Inc.) in a final volume of 200 μl. Blood was collected from the retro-orbital sinus at numerous time-points for up to 52 days and evaluated for CBC parameters using an ADVIA blood analyzer. Data are presented in FIGS. **16** and **17** with n=5 at each time point.

[0515] There was a very clear dose-dependent effect of Mxb 10. Changes in reticulocyte numbers and hemoglobin levels were evident even at the lowest dose (0.05 mg/kg) of Mxb 10, which had an activity very similar to 3 μg/kg of PEG-NESP. Mxb 10 was a more potent agent than Mxb 2, Mxb 7, and Mxb 5. In the mice that were treated with 0.15 mg/kg of Mxb 2, the reticulocyte numbers stayed above baseline for 10 days and hemoglobin levels were above baseline for 19 days. At the dose of 0.5 mg/kg of Mxb 10, the reticulocyte numbers stayed above baseline for 13 days and hemoglobin levels were above baseline for 31 days. At the dose of 1.5 mg/kg of Mxb 10, the reticulocyte numbers stayed above baseline for 18 days and hemoglobin levels were above baseline for 40 days. At the dose of 3 mg/kg of Mxb 10, the reticulocyte numbers stayed above baseline for 23 days and hemoglobin levels were above baseline for 50 days. Finally, at the dose of 5 mg/kg of Mxb 10, the reticulocyte numbers stayed above baseline for 28 days and hemoglobin levels were still above baseline at day 52 when the experiment was terminated. In another experiment with mice dosed at 5 mg/kg of Mxb 10, the hemoglobin level returned to baseline at day 56 after a single subcutanious injection of Mxb 10.

Example 12D

Mxb 2 Single Dose Experiment in Mice

[0516] 3-month-old female BDF-1 mice were injected subcutaneously with carrier (PBS with 0.1% BSA), 3 μg/kg PEG-NESP (Amgen, Inc.), or 13 mg/kg Mxb 2 (Amgen, Inc.) in a final volume of 200 μl. Blood was collected from the retro-orbital sinus at numerous time-points for up to 24 days and evaluated for CBC parameters using an ADVIA blood analyzer (Bayer; Germany). Data are presented in FIGS. **18** and **19** with n=5 at each time point.

[0517] In this experiment, the erythropoietic effects of a single dose of Mxb 2 were compared to those induced by the control agent PEG-NESP. Reticulocyte numbers stayed above baseline for an additional day in the animals that received Mxb 2 (8 days in the PEG-NESP-treated animals versus 9 days in the Mxb 2-treated mice), but the magnitude of the differences in the erythropoietic responses were significantly accentuated when considering the hemoglobin response. Hemoglobin levels returned to baseline 14 days after PEG-NESP treatment, whereas it took 24 days for the hemoglobin to drop to baseline in the mice treated with Mxb 2. These data further demonstrated that the erythropoietic response induced by Mxb 2 was significantly longer than that induced by PEG-NESP.

Example 13

Phamacokinetics Study of Mxb 5 and IgG_1 5

[0518] The pharmacokinetic (PK) profiles of Mxb 5 and IgG, 5 were characterized in female BDF-1 mice. The animals were injected intravenously with either 3.75 mg/kg Mxb 5 or 5.7 mg/kg IgG_1 5 (equimolar amounts). Blood was collected from either the retro-orbital sinus or by cardiac puncture at numerous time points for 100 days with n=4 at each time point. The blood samples were transferred to Costar microcentrifuge tubes and allowed to clot. The samples were then centrifuged at 11,500 rpm for 10 minutes at 4° C. The resulting serum samples were then transferred into individual tubes and stored at −70° C. prior to analysis. Mxb 5 and IgG_1 5 concentrations in the samples were measured by ELISA using immobilized huEpoR protein and an anti-human Fc/HRP conjugate. Pharmacokinetic analysis was carried out using serum concentration values over time.

[0519] The average and standard deviation of the serum concentration for each protein at each time-point (mean composite) used for this analysis is depicted in FIG. **19**. Some pharmacokinetic parameters of IgG_1 5 and Mxb 5 are shown in FIGS. **21**A, **21**B, and **22**. IgG, 5 showed a longer half-life than Mxb 5 (320.1 vs. 158.3 hours, respectively). Consistently, the clearance is slower for IgG_1 5 than for the Mxb 5 (0.0071 vs. 0.012 mL/hour, respectively) and the Mean Residence Time is greater for IgG, 5 than the Mxb 5 (482.27 vs. 217.51 hours, respectively) This analysis suggests significant differences in the pharmacokinetic profile of these two proteins, with a longer residence time for IgG_1 5 versus the Mxb 5 due to its slower elimination.

Example 14

Screening and Identification of Additional Clones

[0520] scFv phage from naïve phage libraries were put through two rounds of selection on soluble huEpoR using the selection strategies described in Example 1. 2,000 scFv phage were randomly picked from the phage pool after the two rounds of selection. The 2,000 phage were used in an ELISA screen, which identified 960 scFv phage that appeared to specifically bind to huEpoR.

[0521] Plasmid DNA minipreps from the 960 scFv phage clones were made and pooled. The DNA pool from the 960 scFv phage clones was digested with NcoI and NotI. The resulting 0.75 kb fragments were ligated to a PciI and NotI digested mammalian expression vector, pDC409a-G1 Fc. pDC409a-G1Fc is described in Example 2. Ligation products were transformed into TG1 cells. After ligation, 1,920 single colonies were picked and plasmid DNA minipreps from each of the 1,920 colonies were made in 96-well plates using a Qiagen BioRobot 3000. These 96-well plates served as stock plates. The DNA concentration of each well in the stock plates was between 50 and 200 ng/ul.

[0522] Aliquots of DNA from the stock plates were combined with Lipofectamine 2000 (Invitrogen) in a new set of 96-well plates (first set of test plates). Lipid/DNA complexes were formed by incubation at room temperature for 30 minutes in the wells of the first set of test plates. Lipid/DNA complexes were then added to a second set of 96-well plates

(second set of test plates) containing Cos PKB cells. Lipid DNA complexes were transfected into the Cos PKB cells.

[0523] 5 days after transfection, cultured supernatant containing expressed protein was collected from the second set of test plates. The cultured supernatants were tested for the ability to bind EpoR using an in vitro EpoR activation assay. Two in vitro EpoR activation assays were performed for each protein being tested. The first assay used culture supernatant at a final dilution of 1:2. The second assay used a culture supernatant at a final dilution of 1:20.

[0524] The supernatants from the second set of test plates were also tested for protein titer by Fc ELISA. The concentration ranges from the Fc ELISA were between 5-20 μg/ml.

[0525] These screens identified a second set of clones: clone 201, clone 276, clone 295, clone 307, clone 318, clone 319, clone 323, clone 330, clone 352, and clone 378.

[0526] Clone 13, clone 15, clone 16, clone 29, and clone 34 were isolated as generally described in Example 1.

[0527] IgG2 and Fab expression constructs containing the second set of clones were constructed using the cloning strategy described in Example 2.

[0528] Protein identities were verified by N-terminal amino acid sequencing and concentrations determined on a Spectrophotometer by absorption at 280 nm.

[0529] The second set of clones were sequenced. DNA and amino acid sequences for the variable heavy chains and variable light chains for clone 13, clone 15, clone 16, clone 29, clone 34, clone 201, clone 276, clone 295, clone 307, clone 318, clone 319, clone 323, clone 330, clone 352, and clone 378 are shown below. Heavy chain and light chain CDR1, CDR2 and CDR3 are underlined in order within each sequence.

>#13VH nucleic acid sequence (SEQ ID NO.: 55)

CAGGTACAGCTGCAGCAGTCAGGGGGAGGCGTGGTCCAGCCTGGGAGGTC

CCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTGACTATGCTA

TGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTAGAGTGGGTGGCAGTT

ATATCAAATCATGGAAAGAGCACATACTACGCAGACTCCGTGAAGGGCCG

ATTCACCATCTCCAGAGACAATTCCAAGCACATGCTGTATCTGCAAATGA

ACAGCCTGAGAGCTGACGACACGGCTCTATATTACTGTGCGAGAGATATA

GCATTGGCTGGGGACTACTGGGGCCAGGGCACCCTGGTCACCGTCTCTGCC

>#13VH amino acid sequence (SEQ ID NO.: 56)

QVQLQQSGGGVVQPGRSLRLSCAASGFTFSDYAMHWVRQAPGKGLEWVAV

ISNHGKSTYYADSVKGRFTISRDNSKHMLYLQMNSLRADDTALYYCARDI

ALAGDYWGQGTLVTVSA

>#13VL nucleic acid sequence (SEQ ID NO.: 57)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGA

CAGAGTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATCTTA

ATTGGTATCAGCAACTACCAGGGAAAGTCCCTAAACTCCTGATCTATGGT

GCATCGAAGTTGCAAAGTGGGGTCCCCTCCAGGTTCAGTGGCAGTGGATC

TGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATTTTG

-continued

CAACTTATTACTGTCTCCAAGATTACAATTATCCTCTCACTTTCGGCCCT

GGGACACGACTGGAGATCAAA

>#13VL amino acid sequence (SEQ ID NO.: 58)

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQLPGKVPKLLIYG

ASKLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCLQDYNYPLTFGP

GTRLEIK

>#15VH nucleic acid sequence (SEQ ID NO.: 59)

CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAGGCCTTCGGGGAC

CCTGTCCCTCACCTGCGCTGTCTCTGGTGGCTCCATCGGCAGTAGTAACT

GGTGGAGTTGGGTCCGCCAGGCCCCAGGGAAGGGGCTGGAGTGGATTGGG

GAAATCTCTCAGAGTGGGAGCACCAACTACAACCCGTCCCTCAAGGGTCG

AGTCACCATATCACTAGACAGGTCCAGGAACCAGTTGTCCCTGAAGTTGA

GTTCTGTGACCGCCGCGGACACGGCCGTGTATTACTGTGCGAGACAGCTG

CGGTCGATTGATGCTTTTGATATCTGGGGCCCAGGGACCACGGTCACCGT

CTCGGCC

>#15VH amino acid sequence (SEQ ID NO.: 60)

QVQLQESGPGLVRPSGTLSLTCAVSGGSIGSSNWWSWVRQAPGKGLEWIG

EISQSGSTNYNPSLKGRVTISLDRSRNQLSLKLSSVTAADTAVYYCARQL

RSIDAFDIWGPGTTVTVSA

>#15VL nucleic acid sequence (SEQ ID NO.: 61)

TCCTATGTGCTGACTCAGCCACCCTCAGTGTCCGTGTCCCCAGGACTGAC

AGCCACCATCACCTGCTCTGGAGATAAATTGGGGGACAAATATGCTTCCT

GGTATCAGCAGAAGCCAGGCCAGTCCCCTGTGTTGGTCATCTATCAAGAT

AGGAAGCGACCCTCAGGGATCCCTGAGCGATTCTCTGGGTCCAATTCTGG

GAACACAGCCACTCTGACCATCAGCGGGACCCAGGCTGTGGATGAGGCTG

ACTATTACTGTCAGGCGTGGGACAGCGACACTTCTTATGTCTTCGGAACT

GGGACCCAGCTCACCGTTTTA

>#15VL amino acid sequence (SEQ ID NO.: 62)

SYVLTQPPSVSVSPGLTATITCSGDKLGDKYASWYQQKPGQSPVLVIYQD

RKRPSGIPERFSGSNSGNTATLTISGTQAVDEADYYCQAWDSDTSYVFGT

GTQLTVL

>#16VH nucleic acid sequence (SEQ ID NO.: 63)

CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGAC

CCTGTCCCTCACCTGCACTGTCTCTGGTGGCTACATCAATAATTACTACT

GGAGCTGGATCCGGCAGCCCCCAGGGAAGGGCCTGGAGTGGATTGGGTAC

ATCCATTACAGTGGGAGCACCTACTACAACCCGTCCCTCAAGAGTCGAGT

CACCATATCAGAAGACACGTCCAAGAACCAGTTCTCCCTGAAGCTGAGCT

CTGCGACCGCTGCGGACACGGCCGTGTATTACTGTGCGAGAGTTGGGTAT

-continued

TACTATGATAGTAGTGGTTATAATCTTGCCTGGTACTTCGATCTCTGGGG

CCGTGGAACCCTGGTCACCGTCTCGGCC

>#16VH amino acid sequence

(SEQ ID NO.: 64)

QVQLQESGPGLVKPSETLSLTCTVSGGYINNYYWSWIRQPPGKGLEWIGY

IHYSGSTYYNPSLKSRVTISEDTSKNQFSLKLSSATAADTAVYYCARVGY

YYDSSGYNLAWYFDLWGRGTLVTVSA

>#16VL nucleic acid sequence

(SEQ ID NO.: 65)

TCTTCTGAGCTGACTCAGGACCCTGCTGTGTCTGTGGCCTTGGGACAGAC

GGTCAGGATCACATGCCAGGGAGACAACCTCAGAAGTTATTCTGCAACTT

GGTACCAACAGAAGCCAGGACAGGCCCCTGTCCTTGTCCTCTTTGGTGAA

AACAACCGGCCCTCAGGGATCCCAGACCGATTCTCTGGCTCCAAGTCAGG

GGACACAGCTGTCTTGACCATCACTGGGACTCAGACCCAAGATGAGGCTG

ACTATTATTGCACTTCCAGGGTCAATAGCGGGAACCATCTGGGGGTGTTC

GGCCCAGGGACCCAGCTCACCGTTTTA

>#16VL amino acid sequence

(SEQ ID NO.: 66)

SSELTQDPAVSVALGQTVRITCQGDNLRSYSATWYQQKPGQAPVLVLFGE

NNRPSGIPDRFSGSKSGDTAVLTITGTQTQDEADYYCTSRVNSGNHLGVF

GPGTQLTVL

>#29VH nucleic acid sequence

(SEQ ID NO.: 67)

GAGGTGCAGCTGGTGGAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTC

AGTGAAGGTCTCCTGCAAGGCTTCTGGATACACCTTCACCGGCTACTATA

TGCACTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGG

ATCAACCCTAACAGTGGTGGCACAAACTATGCACAGAAGTTTCAGGGCAG

GGTCACCATGACCAGGGACACGTCCATCAGCACAGCCTACATGGAGCTGA

GCAGGCTGAGATCTGACGACACGGCCGTGTATTACTGTGCGAGAGGGGGG

CACATGACTACGGTGACCCGTGATGCTTTTGATATCTGGGGCCAAGGGAC

AATGGTCACCGTCTCTGCC

>#29VH amino acid sequence

(SEQ ID NO.: 68)

EVQLVESGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGW

INPNSGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDTAVYYCARGG

HMTTVTRDAFDIWGQGTMVTVSA

>#29VL nucleic acid sequence

(SEQ ID NO.: 69)

TCTTCTGAGCTGACTCAGGACCCTGCTGTGTCTGTGGCCTTGGGACAGAC

AATCAGGATCACATGCCAAGGAGACAGCCTCAGATACTATTATGCAACCT

GGTATCAGCAGAAGCCAGGACAGGCCCCTATACTTGTCATCTATGGTCAG

AATAATCGGCCCTCAGGGGTCCCAGACCGATTCTCTGGCTCCAGCTCAGG

AAACACAGCTTCCTTGACCATCACTGGGGCTCAGGCGGAAGATGAGGCTG

ACTATTACTGCGGAACATGGGATAGCAGTGTGAGTGCCTCTTGGGTGTTC

GGCGGAGGGACCAAGGTCACCGTCCTA

-continued

>#29VL amino acid sequence

(SEQ ID NO.: 70)

SSELTQDPAVSVALGQTIRITCQGDSLRYYYATWYQQKPGQAPILVIYGQ

NNRPSGVPDRFSGSSSGNTASLTITGAQAEDEADYYCGTWDSSVSASWVF

GGGTKVTVL

>#34VH nucleic acid sequence

(SEQ ID NO.: 71)

CAGGTACAGCTGCAGCAGTCAGGGGCTGAGGTGAAGAAGCCTGGGGCCTC

AGTGAAGGTCTCCTGCAAGGCTTCTGGATACACCTTCAGCGGCTATTATA

TGCACTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGG

ATCAACCCTAACAGTGGCAGCACAAATTATGCACAGAAGTTTCTGGGCAG

GGTCACCATGACCAGGGACACGTCCATCAGCACAGCCTACATGGAACTGA

GCAGCCTGAGATCTGACGACACGGCCGTGTATTACTGTGCGAGGGGACAC

TCCGGTGACTATTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTC

GGCC

>#34VH amino acid sequence

(SEQ ID NO.: 72)

QVQLQQSGAEVKKPGASVKVSCKASGYTFSGYYMHWVRQAPGQGLEWMGW

INPNSGSTNYAQKFLGRVTMTRDTSISTAYMELSSLRSDDTAVYYCARGH

SGDYFDYWGQGTLVTVSA

>#34VL nucleic acid sequence

(SEQ ID NO.: 73)

GAAATTGTGTTGACGCAGTCTCCATCCTCCCTGTCTGCATCTGTTGGAGA

CAGAGTCACCATCACTTGCCGGGCCAGTCAGAGTGTTAGCAGCTGGTTGG

CCTGGTATCAACAGAGACCAGGGCAAGCCCCTAAACTGCTGATCTATGCT

GCACGTTTGCGAGGTGGAGGCCCTTCAAGGTTCAGTGGCAGCGGCTCTGG

GACAGAATTCACTCTCACCATCAGCAGTCTGCAACCTGAAGACTTTGCGA

CTTACTTCTGTCAACAGAGTTACAGTACCCCGATCAGTTTCGGCGGAGGG

ACCAAGCTGGAGATCAAA

>#34VL amino acid sequence

(SEQ ID NO.: 74)

EIVLTQSPSSLSASVGDRVTITCRASQSVSSWLAWYQQRPGQAPKLLIYA

ARLRGGGPSRFSGSGSGTEFTLTISSLQPEDFATYFCQQSYSTPISFGGG

TKLEIK

>#201VH nucleic acid sequence

(SEQ ID NO.: 75)

CAGGTGCAGCTGCAGGAGTCGGGCTCAGGACTGGCGAGGCCTTCACAGAC

CCTGTCCCTCACCTGCGCTGTCTCTGGTGGCTCCATCAGCAGTAGTGCTT

TCTCCTGGAATTGGATCCGGCAGCCACCAGGGAAGGGCCTGGAGTGGATT

GGATACATCTATCATACTGGGATCACCGATTATAACCCGTCCCTCAAGAG

TCGAGTCACCATATCAGTGGACAGGTCCAAGAACCAGTTCTCCCTGAACG

TGAACTCTGTGACCGCCGCGGACACGGCCGTGTATTATTGTGCCAGAGGA

CACGGTTCGGACCCCGCCTGGTTCGACCCCTGGGGCAAGGGCACCCTGGT

CACCGTCTCGAGT

-continued

>#201VH amino acid sequence

(SEQ ID NO.: 76)

QVQLQESGSGLARPSQTLSLTCAVSGGSISSSAFSWNWIRQPPGKGLEWI

GYIYHTGITDYNPSLKSRVTISVDRSKNQFSLNVNSVTAADTAVYYCARG

HGSDPAWFDPWGKGTLVTVSS

>#201VL nucleic acid sequence

(SEQ ID NO.: 77)

CAATCTGTGCTGACTCAGCCACCCTCAGTGTCGGTGTCCCCAGGACAGAC

AGCCAGCATCACCTGCTCTGGAGATAAATTGGGGGATAAATATGCTTCCT

GGTATCAGCAGAGGCCAGGCCAGTCCCCTGTTCTGGTCATCTATCGAGAC

ACCAAGCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCTCCAACTCTGG

GAACACAGCCACTCTGACCATCAGCGGGACCCAGGCTGTGGATGAGGCTG

ACTATTACTGTCAGGCGTGGGACAGCACCACCTCCCTGGTTTTCGGCGGA

GGGACCAAGCTGACCGTCCTA

>#201VL amino acid sequence

(SEQ ID NO.: 78)

QSVLTQPPSVSVSPGQTASITCSGDKLGDKYASWYQQRPGQSPVLVIYRD

TKRPSGIPERFSGSNSGNTATLTISGTQAVDEADYYCQAWDSTTSLVFGG

GTKLTVL

>#276VH nucleic acid sequence

(SEQ ID NO.: 79)

GAGGTCCAGCTGGTACAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTC

CCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGTAGCTATTGGA

TGAGCTGGGTCCGCCAGGCTCCTGGGAAGGGGCTGGAGTGGGTGGCCAAC

ATAAAGCCAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCG

ATTCACCATCTCCAGAGACAACGCCAAGAATTCAGTGTATCTGCAAATGA

ACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGTTTCG

AGGGGTGGGAGCTACTCGGACTGGGGCCGAGGGACAATGGTCACCGTCTC

GAGT

>#276VH amino acid sequence

(SEQ ID NO.: 80)

EVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVAN

IKPDGSEKYYVDSVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCARVS

RGGSYSDWGRGTMVTVSS

>#276VL nucleic acid sequence

(SEQ ID NO.: 81)

CAGTCTGTGCTGACTCAGCCACCCTCCGCGTCCGGGTCTCCTGGACAGTC

AGTCACCATCTCCTGCACTGGAACCAGCAGTGACGTTGGCGGTTTTAACT

ATGTCTCCTGGTACCAAAAGTACCCAGGCAAAGCCCCCAAACTCGTCATT

TATGAGGTCAGTAAGCGGCCCTCAGGGGTCCCTGATCGCTTCTCTGGCTC

CAAGTCCGGCAACACGGCCTCCCTGACCGTCTCTGGGCTCCAGGCTGAGG

ATGAGGCTGATTATTACTGCAGCTCATGGGCACCTGGTAAAAACTTATTC

GGCGGAGGGACCAAGCTGACCGTCCTA

-continued

>#276VL amino acid sequence

(SEQ ID NO.: 82)

QSVLTQPPSASGSPGQSVTISCTGTSSDVGGFNYVSWYQKYPGKAPKLVI

YEVSKRPSGVPDRFSGSKSGNTASLTVSGLQAEDEADYYCSSWAPGKNLF

GGGTKLTVL

>#295VH nucleic acid sequence

(SEQ ID NO.: 83)

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTC

CCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGCAGCTATGCCA

TGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGGT

ATTAGTGGTAGTGGTAGTAGTGAAGGTGGCACATACTACGCAGACTCCGT

GAAGGGCCGGTTCACCCTCTCCAGAGACAATTCCAAGAATACCCTGTATC

TGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCTTATATTACTGTGTG

AAAGATCGCCCTAGTCGATACAGCTTTGGTTATTACTTTGACTACTGGGG

CCGGGGAACCCTGGTCACCGTCTCGAGT

>#295VH amino acid sequence

(SEQ ID NO.: 84)

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSG

ISGSGSSEGGTYYADSVKGRFTLSRDNSKNTLYLQMNSLRAEDTALYYCV

KDRPSRYSFGYYFDYWGRGTLVTVSS

>#295VL nucleic acid sequence

(SEQ ID NO.: 85)

CTGCCTGTGCTGACTCAGCCACCCTCAGTGTCCGTGTCCCCAGGACAGAC

AGCCAGCATCGCCTGCTCTGGAAATAAATTGGGGGATAAATATGTTTCCT

GGTATCAGCAGAAGCCAGGCCAGTCCCCTCTGCTGGTCATCTATCAAGAT

ACCAAGCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCTCCAACTCAGG

GAACACAGCCACTCTGACCATCAGCGGGACCCAGGCTATGGATGAGGCTG

ACTATTACTGTCAGGCGTGGGACAGCAGCACTGATGTGGTATTCGGCGGA

GGGACCAAGCTGACCGTCCTA

>#295VL amino acid sequence

(SEQ ID NO.: 86)

LPVLTQPPSVSVSPGQTASIACSGNKLGDKYVSWYQQKPGQSPLLVIYQD

TKRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCQAWDSSTDVVFGG

GTKLTVL

>#307VH nucleic acid sequence

(SEQ ID NO.: 87)

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTC

CCTGAGACTCTCCTGTGCGGTCTCTGGGTTCACCTTTAGTAAGTATTGGA

TGACCTGGGTCCGCCAGGCTCCAGGGAAGGGACTGGAGTGGGTGGCCAAC

ATAAAGCCAGATGGAAGTGAGAAATACTATGTGGAGTCTGTGAAGGGCCG

ATTCACCATCTCCAGAGACAACGCCAAGAATTCAGTGTATCTGCAAATGA

ACAGTGTGAGAGCCGAAGACACGGCCGTGTATTACTGTGCGAGAGTTTCG

AGGGGTGGGAGCTTCTCGGACTGGGGCCAGGGGACAATGGTCACCGTCTC

GAGT

-continued

>#307VH amino acid sequence

(SEQ ID NO.: 88)

EVQLVESGGGLVQPGGSLRLSCAVSGFTFSKYWMTWVRQAPGKGLEWVAN

IKPDGSEKYYVESVKGRFTISRDNAKNSVYLQMNSVRAEDTAVYYCARVS

RGGSFSDWGQGTMVTVSS

>#307VL nucleic acid sequence

(SEQ ID NO.: 89)

CAGTCTGTGCTGACTCAGCCACCCTCCGCGTCCGGGTCTCCTGGACAGTC

AGTCACCATCTCCTGCACTGGAACCAGCAGCGACGTTGGTGGTTATAACT

ATGTCTCCTGGTACCAACAACACCCAGACAAAGCCCCCAGACTCATGATT

TATGACGTCAATAAGCGGCCCTCAGGGGTCCCTGATCGCTTCTCTGGCTC

CAAGTCTGGCAACACGGCCTCCCTGACCGTCTCTGGGCTCCAGGCTGAGG

ATGAGGCTCATTATTACTGCAACTCATATGCAGGCAGCAACAATTGGGTG

TTCGGCGGAGGGACCCAGCTCACCGTTTTA

>#307VL amino acid sequence

(SEQ ID NO.: 90)

QSVLTQPPSASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPDKAPRLMI

YDVNKRPSGVPDRFSGSKSGNTASLTVSGLQAEDEAHYYCNSYAGSNNWV

FGGGTQLTVL

>#318VH nucleic acid sequence

(SEQ ID NO.: 91)

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTC

CCTGAGACTCTCCTGTGCGGTCTCTGGGTTCACCTTTAGTAAGTATTGGA

TGACCTGGGTCCGCCAGGCTCCAGGGAAGGGACTGGAGTGGGTGGCCAAC

ATAAAGCCAGATGGAAGTGAGAAATACTATGTGGAGTCTGTGAAGGGCCG

ATTCACCATCTCCAGAGACAACGCCAAGAATTCAGTGTATCTGCAAATGA

ACAGTGTGAGAGCCGAAGACACGGCCGTGTATTACTGTGCGAGAGTTTCG

AGGGGTGGGAGCTTCTCGGACTGGGGCCAAGGAACCCTGGTCACCGTCTC

GAGT

>#318VH amino acid sequence

(SEQ ID NO.: 92)

QVQLVESGGGLVQPGGSLRLSCAVSGFTFSKYWMTWVRQAPGKGLEWVAN

IKPDGSEKYYVESVKGRFTISRDNAKNSVYLQMNSVRAEDTAVYYCARVS

RGGSFSDWGQGTLVTVSS

>#318VL nucleic acid sequence

(SEQ ID NO.: 93)

CAGTCTGTGCTGACTCAGCCACCCTCCGCGTCCGGGTCTCCTGGACAGTC

AGTCACCATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGGTTATAATT

ATGTCTCCTGGTACCAACAACACCCAGGCAGAGCCCCCAAACTCATCATT

TATGAGGTCAGTAAGCGGCCCTCAGGGGTCCCTGATCGCTTCTCTGGCTC

CAAGTCTGGCAACACGGCCTCCCTGACCGTCTCTGGGCTCCAGGCTGACG

ATGAGGCTGATTATTACTGCAACTCATATGCAGGCAGCATTTATGTCTTC

GGGAGTGGGACCAAGGTCACCGTCCTA

-continued

>#31 8VL amino acid sequence

(SEQ ID NO.: 94)

QSVLTQPPSASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGRAPKLII

YEVSKRPSGVPDRFSGSKSGNTASLTVSGLQADDEADYYCNSYAGSIYVF

GSGTKVTVL

>#319VH nucleic acid sequence

(SEQ ID NO.: 95)

CAGGTGCAGCTGGTGCAATCTGGGGCTGAAATTAAGAAGCCTGGGGCCTC

AGTGAAGGTTTCCTGCAAGACATTTGGATCCCCCTTCAGCACGAATGACA

TACACTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAATA

ATCGACACTAGTGGCGCCATGACAAGGTACGCACAGAAGTTCCAGGGCAG

AGTCACCGTGACCAGGGAAACGTCCACGAGCACAGTCTACATGGAGCTGA

GCAGCCTGAAATCTGAAGACACGGCTGTGTACTACTGTGCGAGAGAGGGT

TGTACTAATGGTGTATGCTATGATAATGGTTTTGATATCTGGGGCCAAGG

CACCCTGGTCACCGTCTCGAGT

>#319VH amino acid sequence

(SEQ ID NO.: 96)

QVQLVQSGAEIKKPGASVKVSCKTFGSPFSTNDIHWVRQAPGQGLEWMGI

IDTSGAMTRYAQKFQGRVTVTRETSTSTVYMELSSLKSEDTAVYYCAREG

CTNGVCYDNGFDIWGQGTLVTVSS

>#319VL nucleic acid sequence

(SEQ ID NO.: 97)

GATATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTATTGGAGA

CAGAGTCACCATCACCTGCCGGGCCAGTGAGGGTATTTATCATTGGTTGG

CCTGGTATCAGCAGAAGCCAGGGAAAGCCCCTAAACTCCTGATCTATAAG

GCCTCTAGTTTAGCCAGTGGGGCCCCATCAAGGTTCAGCGGCAGTGGATC

TGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGATGATTTTG

CAACTTATTACTGCCAACAATATAGTAATTATCCGCTCACTTTCGGCGGA

GGGACCAAGCTGGAGATCAAA

>#319VL amino acid sequence

(SEQ ID NO.: 98)

DIQMTQSPSTLSASIGDRVTITCRASEGIYHWLAWYQQKPGKAPKLLIYK

ASSLASGAPSRFSGSGSGTDFTLTISSLQPDDFATYYCQQYSNYPLTFGG

GTKLEIK

>#323VH nucleic acid sequence

(SEQ ID NO.: 99)

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTC

CCTGAGACTCTCCTGTGCGGTCTCTGGGTTCACCTTTAGTAAGTATTGGA

TGACCTGGGTCCGCCAGGCTCCAGGGAAGGGACTGGAGTGGGTGGCCAAC

ATAAAGCCAGATGGAAGTGAGAAATACTATGTGGAGTCTGTGAAGGGCCG

ATTCACCATCTCCAGAGACAACGCCAAGAATTCAGTGTATCTGCAAATGA

ACAGTGTGAGAGCCGAAGACACGGCCGTGTATTACTGTGCGAGAGTTTCG

AGGGGTGGGAGCTTCTCGGACTGGGGCCGGGGGACAATGGTCACCGTCTC

GAGT

-continued

>#323VH amino acid sequence

(SEQ ID NO.: 100)

QVQLVESGGGLVQPGGSLRLSCAVSGFTFSKYWMTWVRQAPGKGLEWVAN

IKPDGSEKYYVESVKGRFTISRDNAKNSVYLQMNSVRAEDTAVYYCARVS

RGGSFSDWGRGTMVTVSS

>#323VL nucleic acid sequence

(SEQ ID NO.: 101)

CAATCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTC

GATCACCATCTCCTGCACTGGAACCAGCAGTGATGTTGGGAGTTATAACC

TTGTCTCCTGGTACCAACAACACCCAGGCAAAGTCCCCAAACTCATCATT

TATGAGGTCAGTAATCGGCCCTCAGGGGTTTCTCATCGCTTCTCTGGCTC

CAAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGACTCCAGGCTGAGG

ACGAGGCTGATTATTACTGCAGCTCATTGACAAGCAGCGGCACTTGGGTG

TTCGGCGGAGGGACCAAGGTCACCGTCCTA

>#323VL amino acid sequence

(SEQ ID NO.: 102)

QSALTQPASVSGSPGQSITISCTGTSSDVGSYNLVSWYQQHPGKVPKLII

YEVSNRPSGVSHRFSGSKSGNTASLTISGLQAEDEADYYCSSLTSSGTWV

FGGGTKVTVL

>#330VH nucleic acid sequence

(SEQ ID NO.: 103)

GAGGTGCAGCTGGTGGAGTCCGGGGGAGGCTTGGTCCAGCCCGGGGGGTC

CCTGAGACTCTCCTGTGCGGTCTCTGGGTTCACCTTTAGTAAGTATTGGA

TGACCTGGGTCCGCCAGGCTCCAGGGAAGGGACTGGAGTGGGTGGCCAAC

ATAAAGCCAGATGGAAGTGAGAAATACTATGTGGAGTCTGTGAAGGGCCG

ATTCACCATCTCCAGAGACAACGCCAAGAATTCAGTGTATCTGCAAATGA

ACAGTGTGAGAGCCGAAGACACGGCCGTGTATTACTGTGCGAGAGTTTCG

AGGGGTGGGAGCTTCTCGGACTGGGGCCAGGGCACCCTGGTCACCGTCTC

GAGT

>#330VH amino acid sequence

(SEQ ID NO.: 104)

EVQLVESGGGLVQPGGSLRLSCAVSGFTFSKYWMTWVRQAPGKGLEWVAN

IKPDGSEKYYVESVKGRFTISRDNAKNSVYLQMNSVRAEDTAVYYCARVS

RGGSFSDWGQGTLVTVSS

>#330VL nucleic acid sequence

(SEQ ID NO.: 105)

CAGTCTGCCCTGACTCAGCCTCCCTCCGCGTCCGGGTCTCCTGGGCAGTC

AGTCACCATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGCTTATAACT

ATGTCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAACTCATGATT

TATGAGGTCGCTAGGCGGCCCTCAGGGGTCCCTGATCGCTTCTCTGGCTC

TAAGTCTGGCAACACGGCCTCCCTGACCGTCTCTGGGCTCCAGGCTGAGG

ATGAGGCTGATTATTATTGCAGCTCATATGCAGGCAGCAACAATTTCGCG

GTCTTCGGCAGAGGGACCAAGCTGACCGTCCTA

-continued

>#330VL amino acid sequence

(SEQ ID NO.: 106)

QSALTQPPSASGSPGQSVTISCTGTSSDVGAYNYVSWYQQHPGKAPKLMI

YEVARRPSGVPDRFSGSKSGNTASLTVSGLQAEDEADYYCSSYAGSNNFA

VFGRGTKLTVL

>#352VH nucleic acid sequence

(SEQ ID NO.: 107)

GAGGTGCAGCTGGTGCAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTC

CCTGAGACTCTCCTGTGCAGCCTCTGGATTCAGGTTTAGTAGCTATTGGA

TGACCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAAC

ATAAAGCCAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCG

ATTCACCATGTCCAGAGACAACGCCAAGAATTCAGTGTATCTGCAAATGA

ACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGTTTCG

AGGGGTGGGAGCTTCTCGGACTGGGGCCAAGGAACCCTGGTCACCGTCTC

GAGT

>#352VH amino acid sequence

(SEQ ID NO.: 108)

EVQLVQSGGGLVQPGGSLRLSCAASGFRFSSYWMTWVRQAPGKGLEWVAN

IKPDGSEKYYVDSVKGRFTMSRDNAKNSVYLQMNSLRAEDTAVYYCARVS

RGGSFSDWGQGTLVTVSS

>#352VL nucleic acid sequence

(SEQ ID NO.: 109)

CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTC

GATCACCATCCCCTGCACTGGAACCAGCAGTGACATTGGTACTTATGACT

ATGTCTCCTGGTACCAACAACACCCAGGCAAAGTCCCCAAAGTCATTATT

TATGAGGTCACCAATCGGCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTC

CAAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCTCCAGGCTGACG

ACGAGGCTGATTATTACTGCAACTCATTTACAAAGAACAACACTTGGGTG

TTCGGCGGAGGGACCAAGCTGACCGTCCTA

>#352VL amino acid sequence

(SEQ ID NO.: 110)

QSALTQPASVSGSPGQSITIPCTGTSSDIGTYDYVSWYQQHPGKVPKVII

YEVTNRPSGVSNRFSGSKSGNTASLTISGLQADDEADYYCNSFTKNNTWV

FGGGTKLTVL

>#378VH nucleic acid sequence

(SEQ ID NO.: 111)

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGAGGTC

CCTGATACTCTCCTGTGCGGTCTCTGGGTTCACCTTTAGTAAGTATTGGA

TGACCTGGGTCCGCCAGGCTCCAGGGAAGGGACTGGAGTGGGTGGCCAAC

ATAAAGCCAGATGGAAGTGAGAAATACTATGTGGAGTCTGTGAAGGGCCG

ATTCACCATCTCCAGAGACAACGCCAAGAATTCAGTGTATCTGCAAATGA

ACAGTGTGAGAGCCGAAGACACGGCCGTGTATTACTGTGCGAGAGTTTCG

AGGGGTGGGAGCTTCTCGGACTGGAGCCAAGGAACCTTGGTCACCGTCTC

GAGT

-continued

>#378VH amino acid sequence

(SEQ ID NO.: 112)

QVQLVESGGGLVQPGRSLILSCAVSGFTFSKYWMTWVRQAPGKGLEWVAN

IKPDGSEKYYVESVKGRFTISRDNAKNSVYLQMNSVRAEDTAVYYCARVS

RGGSFSDWSQGTLVTVSS

>#378VL nucleic acid sequence

(SEQ ID NO.: 113)

CAGTCTGCCCTGACTCAGCCTCCCTCCGCGTCCGGGTCTCCTGGGCAGTC

AGTCACCATCTCCTGCACTGGAACCAGCGGTGACGTTGGTGCTTATAACT

ATGTCTCCTGGTACCAACAGTACCCAGGCAAAGCCCCCAAACTCATGATT

TATGAGGTCAGTAAGAGGCCCTCCGGGGTCCCTGATCGCTTCTCTGGCTC

CAAGTCTGGCAACACGGCCTCCCTGACCGTCTCTGGGCTCCAGGCTGAGG

ATGAGGCTGATTATTACTGCAACTCATATAGGGGCAGCAACGGTCCTTGG

GTGTTCGGCGGAGGGACCAAGGTCACCGTCCTA

>#378VL amino acid sequence

(SEQ ID NO.: 114)

QSALTQPPSASGSPGQSVTISCTGTSGDVGAYNYVSWYQQYPGKAPKLMI

YEVSKRPSGVPDRFSGSKSGNTASLTVSGLQAEDEADYYCNSYRGSNGPW

VFGGGTKVTVL

Example 15

Antibody Binding to Cell Surface huEpoR Analysis by FACS

[0530] The binding of scFv-Fc protein to a cell surface expressed huEpoR was analyzed using FACS. All scFv-Fc proteins used had an Fc derived from IgG1. UT-7 cells were incubated with either 5 nM scFv-Fc protein alone or with 5 nM scFv-Fc protein plus 0.5 μg/ml of rHuEpo for 1 hour at 4° C. After 2 quick washes using cold PBS, UT-7 cells were then incubated with 1 μg/ml phycoerythrin-conjugated goat F(ab')2 anti-human IgG Fc (Jackson Immuno Research Laboratories) for 1 hour at 4° C. The cells were washed twice using cold PBS and resuspended into 1 ml of fixation buffer (2% paraformaldehyde PBS pH 7.4). FACS was done using a FACSCaliber flow cytometer (Becton-Dickinson)

[0531] The FACS traces of the proteins expressed from the scFv-Fc expression vectors are shown in FIG. **22**. Clone 13, clone 15, clone 16, clone 29, and clone 34 all bound to huEpoR expressing UT-7 cells (FIG. **22**A) but not to the negative control cells (FIG. **22**B). UT-7 cell surface binding of clone 15, clone 16, and clone 34, was blocked by an excess amount of rHuEpo (FIG. **22**A). rHuEpo did not block the binding of clone 13 or clone 29 (FIG. **22**A).

Example 16

Competitive Binding of Clone 201, Clone 276, Clone 295, Clone 307, Clone 318, Clone 319, Clone 323, Clone 330, Clone 352, and Clone 378 to huEpoR

[0532] Clone 201, clone 276, clone 295, clone 307, clone 318, clone 319, clone 323, clone 330, clone 352, and clone 378 were tested for their ability to compete with Epo for binding to huEpoR.Fc using a plate-based ELISA. All scFv-Fc proteins used had an Fc derived from IgG1. Biotinylated Epo, which binds to huEpoR.Fc, was used as the competitor. huEpoR.Fc was immobilized on the polysorp ELISA plate. Inhibition of Epo binding by clone 201, clone 276, clone 295, clone 307, clone 318, clone 319, clone 323, clone 330, clone 352 and clone 378 in scFv-Fc was tested by concentration titration with each protein at 0 to 50 μg/ml, using streptavidin-HRP conjugate. All of the clones except clone 13, clone 15, clone 16, clone 29, clone 30, and clone 34 substantially blocked the Epo binding at high concentrations (FIG. **23**). Clone 2, clone 5, clone 7, clone 10, clone 13, clone 15, clone 16, clone 29, clone 30 and clone 34 in phage format were tested for their ability to compete with clone 5 and clone 30 in maxibody format for binding to EpoR as generally described in Example 5.

Example 17

Antibody Binding to Mouse EpoR (muEpoR) and Cynomolgus Monkey EpoR (cynoEpoR)

[0533] The cross reactivity of certain clones in scFv-Fc format was tested using an ELISA Assay. All scFv-Fc proteins used had an Fc derived from IgG1. The clones tested Were: clone 13, clone 15, clone 16, clone 29, clone 34, clone 201, clone 276, clone 295, clone 307, clone 318, clone 319, clone 323, clone 330, clone 352 and clone 378. 100 μl of 1 μg/ml (in 50 mM $NaHCO_3$, pH8.5) cynoEpoR or muEpoR was added to each well on a polysorp ELISA plate and incubated at 4° C. overnight. After blocking the wells with 4% milk/PBS/0.1% Tween20 for 1 hour at room temperature, plates were washed three times with PBS/0.1% Tween20. 100 μl of 5 μg/ml scFv-Fc was added to each well and incubated for 1 hour at 25° C. The bound cynoEpoR or muEpoR was detected using anti-human IgG Fc-HRP conjugate (1:1000 dilution in 4% milk PBS/0.1% Tween20). ABTS (2,2'-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid)) was used as a substrate and the absorption was measured at 405 nm on a plate reader. All clones showed a significant level of cross reactivity to cynoEpoR (FIG. **23**). Clone 276, clone 323, clone 352, and clone 378 showed a substantial level of cross reactivity to muEpoR (FIG. **23**).

Example 18

Measurement of Rate and Affinity Constants for Human and Cyno EpoR Using Biacore

[0534] Surface plasmon resonance experiments were conducted at 25° C. using a Biacore T100 instrument (Biacore AB, Uppsala, Sweden) equipped with a CM5 sensor chip. Each flow cell on the CM5 chips was activated with a 1:1 (v/v) mixture of 0.1 M N-hydroxysuccinimide (NHS) and 0.4 M 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC). Fcγ Fragment Specific AffiniPure Goat Anti-Human IgG antibody at 30 μg/ml in 10 mM sodium acetate, pH 5.0 was immobilized to two flow cells on the CM5 chips using standard amine coupling chemistry with a target level of 10,000 Resonance Units (RU). Residual reactive surfaces were deactivated with an injection of 1 M ethanolamine. The running buffer was then switched to HBS-EP+0.1 mg/ml BSA for all remaining steps.

[0535] For each scFv-Fc protein to be tested, the scFv-Fc protein was diluted in running buffer to 200 ng/ml and injected over the test flow cell at 10 μl/min for 2 minutes to capture the maxibody. All scFv-Fc proteins used had an Fc derived from IgG1. No scFv-Fc protein was captured on the

control flow cell surface. Either human or cyno EpoR was then flown over the two flow cells at concentrations ranging from 24.7-6000 nM along with buffer blanks. A flow rate of 50 μl/min was used and a 1 minute association phase followed by a 5 minute (for cyno EpoR) or 10 minute (for hu EpoR) dissociation phase. After each cycle the surfaces were regenerated with a 30 second injection of 10 mM glycine pH 1.5. Fresh scFv-Fc protein was then captured on the test flow cell to prepare for the next cycle.

[0536] Data was double referenced by subtracting the control surface responses to remove bulk refractive index changes, and then the averaged buffer blank response was subtracted to remove systematic artifacts from the experimental flow cells. The EpoR data were processed and globally fit to a 1:1 interaction model with mass transfer and a local Rmax in Biacore T100 Evaluation Software v 1.1. (Biacore AB, Uppsala, Sweden). The measured interactions between clone 30 and human EpoR; clone 34 and cyno EpoR; and clone 318 and cyno EpoR had off-rates that were too rapid to measure accurately so the data was instead fit to a steady state model. The steady state model results in only an affinity determination and not kinetic values.

[0537] The rate and affinity constants are summarized in Table 3. The calculated affinities for hu EpoR to the scFv-Fc proteins varied from 1.1 nM for clone #10 (previous data shown in Table 2) to 4030 nM for clone # 201. For the Cyno EpoR the range was from 6.83 nM for clone #10 to 18,600 for clone #201. Clone #10 had the slowest k_{off}, while clone #201 had the slowest k_{on}. In general, the calculated affinities were quite similar for the human and cynomolgus monkey EpoR with only two scFv-Fc proteins (clones #34 and #307) showing greater than a 10× variation between the species.

TABLE 3

Summary of Human and Cyno EpoR Binding Kinetics to scFv-Fc Proteins

scFv-Fc protein clone	EpoR Used	k_{on} (10^5, 1/Ms)	k_{off} (10^{-4}, 1/s)	K_D (nM)
#5	Human	Not repeated, see previous data		
	Cynomolgus	4.37	611	140
#10	Human	Not repeated, see previous data		
	Cynomolgus	1.56	10.7	6.83
#13	Human	0.55	568	1,040
	Cynomolgus	0.65	597	920
#15	Human	0.61	1,190	1,950
	Cynomolgus	0.37	1,150	3,130
#16	Human	0.65	1,420	2,190
	Cynomolgus	0.65	2,830	4,360
#29	Human	1.29	629	487
	Cynomolgus	1.90	504	265
#30	Human	Fit to steady-state model		3,690
	Cynomolgus	2.11	4,850	2,310
#34	Human	5.36	2,030	378
	Cynomolgus	Fit to steady-state model		5,810
#201	Human	0.046	187	4,030
	Cynomolgus	0.027	508	18,600
#295	Human	0.18	29.6	163
	Cynomolgus	0.41	221	539
#307	Human	22.8	2,460	108
	Cynomolgus	2.99	3,610	1,210
#318	Human	6.59	5,580	847
	Cynomolgus	Fit to steady-state model		4890
#319	Human	1.58	335	212
	Cynomolgus	2.13	258	121
#330	Human	8.22	373	45.4
	Cynomolgus	1.08	965	890

Example 19

Screening of scFv-Fc Proteins In Vitro for the Activation of the Human Erythropoietin Receptor

[0538] scFv-Fc proteins were screened for the activation of the huEpoR. The in vitro screening of the scFv-Fc proteins was done by a luciferase-based reporter assay (luciferase assay) in UT-7 cells (human megakaryoblasts) transfected with a construct containing 9 STAT5 binding sites in front of a luciferase reporter gene (UT-7-LUC cells). All scFv-Fc proteins used had an Fc derived from IgG1. All cells were maintained and all cellular assays were conducted at 37° C. in a humidified incubator at 5% CO_2/95% atmospheric air, unless otherwise noted. All fetal bovine serum (FBS) was heat inactivated at 55° C. for 45 minutes prior to usage. All Dulbecco's Phosphate-Buffered Saline (PBS) used for cell manipulation was without calcium chloride and magnesium chloride. UT-7-LUC cells (Amgen, Inc.; Thousand Oaks, Calif.) were maintained in growth media comprising IMDM (Invitrogen; Carlsbad, Calif.) containing 10% FBS (HyClone; Logan, Utah), 500 μg/mL hygromycin (Roche; Penzberg, Germany), 100 U/mL penicillin, 100 μg/mL streptomycin, 292 μg/mL L-glutamine (1×PSG; Invitrogen) and 0.5 U/mL recombinant human erythropoietin (Epoetin Alpha, rHuEpo; Amgen, Inc.). The cells were washed two times in assay media (RPMI Medium 1640 with 1% FBS, 1×PSG, and 12.5 mM HEPES (Invitrogen)) and resuspended at 400,000 cells per mL in assay media. Following an overnight incubation, cell number and viability were determined, and the cells were resuspended at 200,000 cells per mL in assay media.

[0539] Each scFv-Fc protein was serially diluted in a 96-well opaque plate (Corning; Corning, N.Y.). The concentration range, fold dilution, number of dilutions and number of replicates varied with each experiment and are indicated in Table 4. To serve as a control standard, recombinant human EPO was serially diluted in 7 wells of every 96-well plate, in duplicate, for a final concentration of 0.82 nM to 5.25E-05 nM. Approximately 10,000 cells were added to each well. The cells were then cultured for 18 to 24 hours, and the assay was performed according to the manufacturer's protocol for the Steady-Glo Luciferase Assay. (Promega Corporation). Luciferase activity was read on a 96-well plate luminometer. The data were plotted to generate binding curves and EC_{50} values using GraphPad Prism® software. The data is presented in Table 5 as average EC_{50}±the standard deviation.

TABLE 4

Summary of Mxb concentrations used in UT-7-luciferase assays.

	Concentration range				
maxibody	highest conc (nM)	lowest conc (nM)	fold dilution	# replicates	# of assays
Mxb#2	2,500	0.032	5	1	1
Mxb#5	5,000	6.86	3	1	1
"	5,000	0.028	3	3	1
"	2,500	0.16	5	1	1
"	2,500	0.16	5	3	1
"	2,500	0.16	5	2	1
"	2,500	0.032	5	1	1
"	2,500	1.143	3	1	1
"	1,000	0.457	3	2	1
Mxb#7	2,500	0.032	5	1	1
Mxb#10	5,000	6.859	3	1	1
"	5,000	0.0282	3	3	1
"	2,500	0.032	5	1	1

TABLE 4-continued

Summary of Mxb concentrations used in UT-7-luciferase assays.

maxibody	Concentration range: highest conc (nM)	lowest conc (nM)	fold dilution	# replicates	# of assays
Mxb#13	5,000	6.859	3	1	1
Mxb#15	5,000	6.859	3	1	1
Mxb#29	5,000	6.859	3	1	1
Mxb#30	2,500	1.143	3	1	1
Mxb#34	5,000	6.859	3	1	1
"	25	0.034	3	3	1
Mxb#201	5,000	6.859	3	1	1
Mxb#276	5,000	0.028	3	3	1
"	5,000	6.859	3	2	1
"	2,500	0.032	5	1	1
"	2,500	1.143	3	1	1
Mxb#295	5,000	6.859	3	1	1
Mxb#307	5,000	6.859	3	1	1
Mxb#318	25	0.034	3	3	1
Mxb#319	5,000	6.859	3	1	1
Mxb#323	5,000	6.859	3	2	1
"	2,500	0.032	5	1	1
"	2,500	1.143	3	1	1
Mxb#330	25	0.034	3	3	1
Mxb#352	5,000	0.028	3	3	1
"	5,000	6.859	3	2	1
"	2,500	0.032	5	1	1
"	2,500	1.143	3	1	1
Mxb#378	2,500	0.032	5	1	1
"	2,500	1.143	3	1	1

TABLE 5

in Vitro activity (UT-7-luciferase assay)

clone	Average EC50 (nM)	Std Dev
#2	0.6035	N/A
#5	0.7911	0.4156
#7	0.4683	N/A
#10	0.2955	0.2416
#13	4.0250	N/A
#15	2.8025	N/A
#16	N/A	N/A
#29	1.5215	N/A
#30	0.6705	N/A
#34	0.1095	0.0916
#201	8.2755	N/A
#276	0.3215	0.4016
#295	0.6065	N/A
#307	0.3810	N/A
#318	0.0154	N/A
#319	5.8655	N/A
#323	0.6133	0.5003
#330	0.0075	N/A
#352	2.1560	1.2868
#378	0.0550	0.0210

[0540] Table 5 shows EC_{50} values of huEpoR activation and EpoR activity levels for Mxb 2, Mxb 5, Mxb 7, Mxb 10, Mxb 13, Mxb 15, Mxb 16, Mxb 29, Mxb 30, Mxb 34, Mxb 201, Mxb 276, Mxb 295, Mxb 307, Mxb 318, Mxb 319, Mxb 323, Mxb 330, Mxb 352, and Mxb 378. The results are presented as average EC_{50} values calculated using GraphPad Prism software (without any background subtraction) ±the standard deviation. When only one experiment was done, standard deviation is presented as N/A.

Example 20

In Vivo Experiments with Mxb 276, Mxb 323, Mxb 352, and Mxb 378

[0541] The effect of a single injection of scFv-Fc proteins Mxb 276, Mxb 323, Mxb 352, or Mxb 378 was tested in mice. The scFv-Fc proteins were tested with either a IgG1fc or a IgG2fc. scFv-Fc proteins with an IgG1fc were abbreviated Mxb X_G1MB or X_G1MB, where "X" is the clone number. scFv-Fc proteins with an IgG2fc were abbreviated Mxb X_G2MB or X_G2MB, where "X" is the clone number. PEG-NESP was used as a positive control in this experiment. Carrier (10 mM Potassium Phosphate, 161 mM L-Arginine, pH 7.5) was used as a negative control.

[0542] 2-month-old female BDF-1 mice were injected subcutaneously with carrier (PBS with 0.1% BSA), 3 μg/kg PEG-NESP (Amgen, Inc.), or 100 μg of a scFv-Fc protein in a final volume of 200 μl. The following scFv-Fc proteins were tested at a single bolus dose of 100 μg/mouse: Mxb 276_G1MB, Mxb 323_G1MB, Mxb 352_G1MB, Mxb 378_G1MB, Mxb 276_G2MB, Mxb 323_G2MB, Mxb 352_G2MB, and Mxb 378_G2MB. Blood was collected from the retro-orbital sinus at numerous time-points and evaluated for CBC (Compete Blood Count) parameters using an ADVIA blood analyzer. For the first experiment, blood was collected on days −2, 3, 5, 9, 11, 15, 20, 22, 27, 29, 36, and 38 for the carrier and 276_Mxb groups. For the group of mice treated with PEG-NESP, blood was collected on days −2, 3, 5, 9, 11, 15, 20 and 22. For all other groups, blood was collected on days −2, 3, 5, 9, 11 and 16. In the second experiment, blood was collected on days −2, 3, 5, 9, 11 and 16 for all groups. As seen in FIGS. **24** and **25**, not all mice were monitored for the full 38 days. Collections were stopped when the CBC parameter returned to a baseline level. Collections were made from five mice at each time point. Data are presented in FIGS. **24** and **25**.

[0543] Mxb 276_G1MB had an erythropoietic stimulatory effect as observed by the increase in hemoglobin and reticulocyte numbers at 100 μg/mouse dose. There was no significant effect observed at this dose for any of the other Mxbs tested in this experiment. PEG-NESP acted as a positive control and performed as predicted. The activity profile of Mxb 276_G1MB was different from that of PEG-NESP; the peak reticulocyte number was achieved on day 5 after an injection of either PEG-NESP or Mxb 276_G1MB, but the duration of the reticulocyte response was significantly increased in the mice that received a dose of Mxb 276_G1MB. The reticulocyte numbers returned to baseline on day 9 in the PEG-NESP-treated mice, but it took 19 to 20 days for the reticulocytes to return to baseline in the Mxb 276_G1MB-treated mice. In mice injected with Mxb 276_G1MB at this dose, the hemoglobin levels stayed above baseline for 22 to 29 days. In contrast, the hemoglobin level in the PEG-NESP-treated mice returned to baseline at day 15, thus showing a very significant difference in the duration and magnitude of the hemoglobin response in the mice treated with Mxb 276_G1MB versus mice treated with PEG-NESP. This experiment demonstrates that a single injection of Mxb 276_G1MB increases hemoglobin levels above baseline for a significant period of time that is close to the total life span of the red blood cells in mice (approximately 40 days). Since the rate of hemoglobin decline after the administration of an erythropoietic agent is related to the life span of erythrocytes (approximately 120 days in humans), it is possible that a single admin-

istration of Mxb 276_G1MB in humans could potentially be enough to correct anemia over a period of 2-3 months.

Example 21

Generation of Mxb Human Point Mutant Fc and Mxb Cynomolgus Point Mutant Fc

[0544] Mxb 5, Mxb 10, and Mxb 30 (with human Fc) and Mxb 5 (with cynomolgus Fc) were mutated at asparagine 297 of the Fc portion of the proteins. The mutated asparagine is in the position equivalent to asparagine 297 of the CH2 domain of human IgG. The asparagine at position 297 was replaced by a serine residue in all of the mutants (N2975) using Stratagene's QuikChange II Site-Directed Mutagenesis Kit. For the human Fc mutagenesis, primers 4606-78 (CGG GAG GAG CAG TAC AGC AGC ACG TAC CGT GTG) and 4606-79 (CAC ACG GTA CGT GCT GCT GTA CTG CTC CTC CCG) were used in the reaction. For the cynomolgus Fc mutagenesis, primers 4606-76 (GGG AGA GGC AGT TCA GCA GCA CGT ACC GCG) and 4606-77 (CGC GGT ACG TGC TGC TGA ACT GCC TCT CCC) were used. Mutagenesis was carried out according to the manufacturer's instructions. The template DNAs are shown in FIG. **28**.

[0545] The mutation to asparagine 297 was made to inhibit binding of the Mxb to the Fc Gamma Receptor III ("FcgRIII") on effector cells present in vivo. The goal was to minimize any killing of the hematopoietic progenitor cells in the bone marrow by immune effector cells expressing FcgR111. Engagement of this receptor in effector cells triggers ADCC (antibody dependent cell-mediated cytotoxicity). See, e.g., Radaev et al., *J Biol. Chem.* 2001 May 11; 276(19):16478-83 and Radaev et al., *J Biol. Chem.* 2001 May 11; 276(19): 16469-77.

[0546] After the mutagenesis, colonies were picked and the correct DNA sequence was confirmed via sequence analysis.

[0547] DNA maxipreps of clones Mxb#5-huFc-N297S (21457), Mxb#10-huFc-N297S (21480), Mxb#30-huFc-N297S (21481) and cyno-Fc N297S (21456) were prepared using the Qiagen Compact Prep Kit according to the manufacturers instructions. A 5' Hind III site and 3' Bam HI site were added to each of the clones via polymerase chain reaction (PCR). The maxipreps mentioned above were used as the template DNA for the PCR reactions.

[0548] Primers 4611-63 (GAC TGC AAG CTT GAC ACC ATG GGG TCA ACC GCC) and 4611-64 (GCA TAC GGA TCC TCA UT ACC CGG AGA CAG) were used in the PCR's for Mxb#5-huFc-N297S, Mxb#10-huFc-N297S, and Mxb#30-huFc-N297S (FIG. **27**).

[0549] For the Mxb 5 (with cynomolgus Fc), primers 4611-63 and 4606-84 (CAT GGG GGT GTG AAC TCT GCG GCC GCT AGG ACG G) were used to amplify clone 5 scFv and add the 5' Hind III site in a PCR reaction. Primers 4606-83 (CCG TCC TAG CGG CCG CAG AGT TCA CAC CCC CAT G) and 4611-65 (GCA TCA GGA TCC TCA UTl ACC CGG AGA CAC) were used to amplify the cyno-Fc N297S and add a 3' Bam HI site in a PCR reaction. The clone 5 scFv amplified product and cyno-Fc N297S amplified product were then used as templates in a Gene Splicing by Overlap Extension "SOE-ing" PCR reaction (FIG. **27**). Primers 4611-63 and 4611-65 were used in that reaction.

[0550] All PCR reactions were run in a MJ Research Peltier Thermal Cycler (PTC, Waltham, Mass.) using an Expand High Fidelity PCR System (Roche, Indianapolis, Ind., cat. no. 11732650001). The reaction and conditions for the PCR are shown in FIG. **27**.

[0551] After PCR amplification, all of the amplification products were column purified using a Qiagen's Qiaquik Gel Extraction Kit following the manufacturer's instructions. The amplification products were then cut with Hind III for 90 minutes. The amplification products were column purified using a Qiagen Qiaquik Gel Extraction Kit according to the manufacturer's instructions. The amplification products were then cut with Bam HI for 90 minutes. The cut products were gel purified using a Qiagen Qiaquik Gel Extraction Kit according to the manufacturer's instructions and then ligated into pTT5 BamHI/HindIII using New England Biolab's T4 ligase overnight.

[0552] The ligation products were column purified the next day and transformed via electroporation into DH10B cells. Colonies were then picked for sequencing and were sequenced. The four scFv-Fc protein sequences are presented in FIG. **29**.

Example 22

Dose Escalation Study of Mxb 5, Mxb 10, and Mxb 30 in Cynomolgus Monkeys

[0553] Each of the four scFv-Fc proteins described in Example 21 was intravenously administered to cynomolgus monkeys, and the pharmacodynamics (hematological effects) and pharmacokinetics (PK) effects after intravenous administration were measured. As noted in Example 21, the Fc regions of the scFv-Fc proteins tested lacked the ability to bind to FcgRIII. The human point mutant Fc used in the scFv-Fc proteins was a human IgG1 point mutant Fc that lacks a glycosylation site required for FcgRIII binding. The cynomolgus point mutant Fc used in the scFv-Fc proteins was a cyno IgG1 Fc that also lacks a glycosylation site required for FcgRIII binding. The scFv-Fc proteins tested were a Mxb 5 human point mutant Fc (un-glycosylated Fc), a Mxb 5 cynomolgus point mutant Fc (un-glycosylated Fc), a Mxb 10 human point mutant Fc (un-glycosylated Fc), and a Mxb 30 human point mutant Fc (un-glycosylated Fc).

[0554] A total of 18 female cynomolgus monkeys weighing between 2 and 4 kg were used in the study. The monkeys were divided into the following 6 experimental groups:

[0555] 1. Vehicle control (10 mM potassium phosphate, 161 mM L-Arginine, pH 7.5)

[0556] 2. Positive control group (Peg-NESP)

[0557] 3. Mxb#5 human point mutant Fc

[0558] 4. Mxb#10 human point mutant Fc

[0559] 5. Mxb#30 human point mutant Fc

[0560] 6. Mxb#5 cynomolgus point mutant Fc

[0561] The study had a duration of 31 days and scFv-Fc proteins or control samples were administered to each animal twice by IV injection. The administration of the scFv-Fc proteins, vehicle control, and positive control (Peg-NESP) occurred on day 1 and day 15 of the study. Each scFv-Fc protein injection was dosed at 0.5 mg/kg in 10 mM potassium phosphate, 161 mM L-Arginine, pH 7.5 for the first administration on day 1 and at 5 mg/kg in 10 mM potassium phosphate, 161 mM L-Arginine, pH 7.5 for the second administration on day 15. Peg-Nesp was dosed at 0.03 mg/kg for both injections. The vehicle control (10 mM potassium phosphate, 161 mM L-Arginine, pH 7.5) was dosed at 1 ml/kg for both injections.

[0562] Following intravenous administration, blood (approximately 1 mL) was collected from each animal for PK and hematological analysis at predose (Day −2), predose (Day 1) and 120, 192, 288, 360, 456, 528, 624, and 696 hours after the first dose was administered.

[0563] Preliminary analysis of the data showed differences among Mxb 5, Mxb 10, and Mxb 30. See FIGS. **26**A and **26**B. The 2 variants of Mxb 5 induced a drop in reticulocyte and hemoglobin levels when dosed at 5 mg/kg, but Mxb 30 and Mxb 10 did not induce any drop in reticulocytes or hemoglobin. In addition, at day 5 after administration of the first dose, the increase in reticulocyte levels in monkeys administered Mxb 10 was statistically significant when compared to the pre-dose baseline reticulocyte level (p=0.029, F-test).

Example 23

Epitope Mapping of Anti-EpoR scFv-Fc proteins Alanine Scanning of EpoR

[0564] A crystal structure of the extracellular ligand-binding domain of EpoR complexed to the ligand has been determined (Syed et al., *Nature* 395, 511-6 (1998)). This information was used to create a panel of mutants which could be used to map individual surface residues involved in antibody binding. An alanine-scanning strategy was pursued for EpoR. The method used to choose residues to mutate involved both computational mechanisms and interactive structure analysis. All residues were colored red. Next, the solvent exposures of all residues in the dimer were calculated. Residues with ≧60 $Å^2$ surface area or with solvent exposure ratios ≧50% were colored green. Next, glycines with positive (D angles were colored magenta, as were Asp8 and Pro9 since they cap the N-terminal helix. Residues (colored blue) were then chosen to fill in the surface gaps. Further residues were then chosen by viewing the structure for residues that point toward the surface but were excluded in the solvent exposure calculations. These were colored cyan. To bring the number of mutations down to 95, prolines in turns, specifically residues 23, 50 and 203, were colored magenta. The cyan residues were then sorted by solvent exposure and solvent exposure ratio. The top six of each measure were kept while the rest were colored magenta. Non-alanine residues were mutated to alanine, and alanine mutated to serine.

[0565] The binding of an antibody to an antigen covers the antigen surface area in the region of antibody binding. This covered patch of antigen residues includes both residues that are directly involved in antibody binding and those that are in the region of antibody binding but may not directly contribute to binding. The covered patch of antigen residues-defines a structural epitope on the antigen. Residues within this covered patch that are not seen as directly involved in binding the antibody by alanine scanning may-be contributing to overall antibody binding through other interactions.

[0566] Alanine scanning is a method that tests whether the mutated residue is part of a functional epitope. The functional epitope describes those residues in the antigen which are directly involved in antibody binding. Single site alanine mutants were used to determine those residues in the antigen with side chains that are directly involved in antibody binding; alanine has a smaller side chain than all other residues except glycine and would therefore cause the loss of a side chain binding site and affect antibody binding.

[0567] A different type of epitope map is the structural epitope, or those residues in the antigen which are contacting or buried by the antibody. Introducing arginine mutants into the antigen is a method that tests whether a residue is part of the structural epitope. The arginine sidechain is large and bulky, effectively blocking antibody binding regardless of whether the wild type residue is directly involved in antibody binding. Accordingly, single site arginine mutants were used to determine those residues in the antigen that are in the covered patch. If an antigen residue mutated to arginine modulates the binding of the antibody, it suggest that the residue is part of the structural epitope. If the antigen wild type residue is arginine, it is mutated to glutamate.

Construction, Expression and Characterization of Alanine Mutants

[0568] 95 individual alanine or serine mutants were produced according to standard techniques. Sense and anti-sense oligonucleotides containing the mutated residues were synthesized in a 96 well format. Mutagenesis of the wild-type (WT) huEpoR was performed using a Quickchange II kit (Stratagene) following the manufacturer's instructions. All mutants were constructed in a pTT5 vector, and were tagged with 6×His-Avitag (Avidity, LLC, Denver, Colo.) on the C-terminus. Mutagenesis reactions and transformations were performed in a 96 well format. 2936-E suspension cells (NRCC) were transiently transfected. The expression levels and integrity of the recombinant proteins in conditioned media were checked by Western analysis. The average expression level was estimated to be ~5 μg/mL; 6 mutants did not express, while another 8 mutants expressed poorly.

[0569] All amino acid residues were identified by their position in the extracellular domain of the human Epo Receptor. The following mutants were not able to be epitope mapped due to non-expression or poor expression: R32A, S54A, K65A, Q71A, W82A, R108A, W209A and W212A. Finally, mutated residues F208A and P86A affected binding of all of the scFv-Fc proteins, and are likely to be incorrectly folded. Thus even though they diminish antibody binding, they were not considered to be part of the epitope. Where possible, mutants were checked for the ability to bind to Epo in order to confirm that they were correctly folded.

Assay Methodology

[0570] 1. ELISA Binding Assay.

[0571] An ELISA binding assay was used to measure binding of the anti-EpoR antibodies to conditioned supernatants containing the mutant protein of interest. 100 μl of purified scFv-Fc protein at 1 μg/mL in 1×PBS was coated upon a Nunc Maxisorp plate, and incubated at 4 degrees overnight. All scFv-Fc proteins used had an Fc derived from IgG1. After blocking the wells with 2% BSA/PBS/0.1% Tween20 for 1 hour at room temperature, plates were washed three times with PBS/0.1% Tween20. EpoR mutant protein concentrations were normalized based on gel densitometry relative to

the WT protein. The EpoR mutant proteins were serially diluted 3-fold in 0.1% BSA/PBS/0.1% Tween20, which also contained a constant 1:5000 dilution of anti-6×His mAb-HRP (R&DSystems). The EpoR mutant/anti-6×His mAb-HRP mixture was captured for 2 hours at room temperature. TMB (3,3',5,5'-Tetramethylbenzidine) was used as a substrate and the absorption was measured at 450 nm on a plate reader. Binding data were analyzed by non-linear regression analysis (sigmoidal dose-response, variable slope) to generate EC_{50} values using GraphPad Prism® software. It was suggested that mutations which abolished binding, or decreased binding by 50% relative to wild type were part of the epitope. Representative data is shown in FIG. **30**.

[0572] 2. EpoR LANCE Binding Assay

[0573] A homogeneous LANCE FRET (Fluorescence Resonance Energy Transfer) assay for EpoR-Ab binding was also used, using an Eu-chelate-conjugated anti-IgG mAb and an APC-conjugated anti-pHis mAb. EpoR mutant concentrations were normalized based on gel densitometry relative to the wild type protein. Mutant EpoR proteins were serially diluted 2-fold in a mixture of purified anti-EpoR scFv-Fc protein (1.5 nM), 0.75 nM Eu chelate labeled-anti-IgG mAb (Perkin Elmer) and 35 nM APC-anti-His mAb Ab (Perkin Elmer). The samples were incubated for 2 hours at room temperature before excitation at 535 nm and detection at 655 nm in a fluorescent plate reader. EpoR mutants which were suggested to be part of the epitope diminish or abolish the FRET signal. The binding data were plotted to generate binding curves and EC_{50} values using GraphPad Prism® software. It was suggested that mutations which abolished binding, or decreased binding by 50% relative to wild type were part of the epitope. Representative data is shown in FIG. **31**.

Arginine Scanning

[0574] As noted above, all amino acid residues were identified by their position in the extracellular domain of the human Epo Receptor. The following mutants: E34R, E60R, P63R, W64R, T87R, A88R, R99E, A103R, V112R, M150R H153R and A166R were also made by the same method as the alanine mutants. The arginine mutants were expected to introduce a greater structural perturbation than the alanine mutants, thus confirming our assignments for these residues (FIG. **32**).

[0575] Eight candidate agonistic scFv-Fc proteins, Mxb #2, #5, #7, #10, #13, #15, #29 and #30, were mapped. A summary of alanine mutations which diminish binding by >50% relative to WT or abolish binding by both the LANCE and ELISA assays is shown in Table 6 Also shown in Table 6 is a summary of arginine mutations which diminish binding by >50% relative to WT or abolish binding by the ELISA assay. That table does not exclude other residues not listed in the table from being part of the epitope; those residues may not have been mutated, or the assays may not have been sensitive enough to identify them as being part of the epitope.

TABLE 6

Summary of residues that are affected part of the human EpoR epitope of 8 anti-EpoR agonistic scFv-Fc proteins.

scFv-Fc protein	Residues in the Extracellular Domain of EpoR Changed to Alanine	Residues in the Extracellular Domain of EpoR Changed to Arginine
Mxb #2	F93, H114	E34, E60
Mxb #5	S91, F93, H114	E60
Mxb #7	F93	E60
Mxb #10	E62, F93, M150	A88, M150
Mxb #13	V48, E62, L66, R68, H70	
Mxb #15	V48, W64, L66, R68, H70	T87
Mxb #29	A44, V48, P63, L66, R68, H70	P63, W64, R99
Mxb #30	L66, R99	R99

[0576] The epitopes for these antibodies fall into two distinct classes. The first class is the Epo competitive scFv-Fc proteins (Mxb 2, Mxb 5, Mxb 7 and Mxb 10). The second class are those scFv-Fc proteins that do not compete with Epo (Mxb 30, Mxb 13, Mxb 15, and Mxb 29). Those data are consistent with the hypothesis that the non-Epo competitive scFv-Fc proteins agonise the EpoR receptor by binding to regions which are distal to the ligand-binding pocket of the dimer.

Example 24

Sequence Alignments and Phylogenetic Analysis of scFv-Fc Proteins Variable Heavy Chain and Variable Light Chain CDR Regions

[0577] To determine the diversity among the scFv-Fc proteins' CDRs, electronic splicing of the CDRs was used. First the CDR regions were identified. Then the framework regions were removed from the sequences and small peptide sequences were used as linkers between the CDRs. A multiple alignment of the electronically spliced sequences was used to create phylogenetic trees. The process was used for both the variable heavy and variable light chain sequences. The MiniPileup program (CGC software) was used to produce the multiple alignments and phylogenetic trees (FIGS. **33** and **34**). The results are summarized in the phylogenetic neighbor joining analysis (FIG. **34**). Clone 307, clone 2, clone 318, clone 378, clone 330, clone 276, clone 352, clone 7, clone 5, and clone 323 share a relatively high level of identity in the variable heavy CDR regions. Among these clones, the diversity in amino acid sequence of the variable light chain is seen mainly in the CDR3 region. Clone 16, clone 201, clone 15, clone 13, clone 10, clone 295, clone 29, clone 34, clone 319 and clone 30 show higher level of sequence variation in both the variable heavy and variable light CDRs.

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1 5 10 15

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

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

Ala Asn Ile Lys Pro Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
50 55 60

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

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

Ala Arg Val Ser Arg Gly Gly Ser Tyr Ser Asp Trp Gly Gln Gly Thr
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Leu Val Thr Val Ser Ser
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1 5 10 15

Ser Val Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Glu Val Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Val Ser Gly Leu
65 70 75 80

Gln Pro Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Ala Gly Arg
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Asn Trp Val Phe Gly Gly Gly Thr Gln Leu Thr Val Leu
100 105

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

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

Ala Asn Ile Lys Pro Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
50                  55                  60

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

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

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

Leu Val Thr Val Ser Ser
115


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1               5                   10                  15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20                  25                  30

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

Met Ile Tyr Asp Val Ser Arg Arg Pro Ser Gly Ile Ser Asp Arg Phe
50                  55                  60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80

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

Ser Thr Trp Leu Phe Gly Gly Gly Thr Lys Val Thr Val Leu
100                 105                 110


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1               5                   10                  15

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

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

Ala Asn Ile Lys Pro Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
50                  55                  60
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Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Val Tyr
65                  70                  75                  80

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

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

Leu Val Thr Val Ser Ser
115


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1               5                   10                  15

Ser Ile Ile Ile Ser Cys Thr Gly Thr Arg Ser Asp Ile Gly Gly Tyr
20                  25                  30

Asn Tyr Val Ser Trp Tyr Gln His His Pro Gly Arg Ala Pro Lys Leu
35                  40                  45

Ile Ile Phe Asp Val Asn Asn Arg Pro Ser Gly Val Ser His Arg Phe
50                  55                  60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Phe Thr Asp Ser
85                  90                  95

Arg Thr Trp Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100                 105                 110


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1               5                   10                  15

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

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

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50                  55                  60

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

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

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

Arg Val Thr Ile Ala Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn
20 25 30

Ala Val Ser Trp Tyr Gln Gln Leu Pro Gly Lys Ala Pro Thr Leu Leu
35 40 45

Ile Tyr Tyr Asp Asn Leu Leu Pro Ser Gly Val Ser Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Gln
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu
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Asn Asp Trp Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu
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1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
20 25 30

Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Met Thr Ile Lys Ala Asp Thr Ser Lys Asn
65 70 75 80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95

Tyr Tyr Cys Ala Arg Asp Glu Gly Pro Leu Asp Tyr Trp Gly Gln Gly
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Thr Leu Val Thr Val Ser Ala
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1 5 10 15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Leu Gly Thr Gly
20 25 30

Tyr Asp Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Gly Asn Ser Asn Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

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

Gln Ala Glu Asp Glu Ala Thr Tyr Tyr Cys Gln Ser Tyr Asp Phe Ser
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Leu Ser Ala Met Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu
100 105 110

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1 5

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Gly

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<400> SEQUENCE: 13

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1 5

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1 5

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1 5 10

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1 5

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Gly

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Ala Ala Trp Asp Asp Ser Leu Asn Asp Trp Val
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<210> SEQ ID NO 29
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<210> SEQ ID NO 30
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Ser

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<210> SEQ ID NO 33
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1 5

<210> SEQ ID NO 34
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ccagggaagg ggctggagtg ggtggccaac ataaagccag atggaagtga gaaatactat 180

gtggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ttcagtgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc gagagtttcg 300

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cacccaggca aagcccccaa actcatgatt tatgaggtca gtaagcggcc ctcaggggtc 180

cctgatcgct tctctggctc caagtctggc aacacggcct ccctgaccgt ctctgggctc 240

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ccagggaagg ggctggagtg ggtggccaac ataaagccag atggaagtga gaaatactat 180

gtggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ttcagtgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc aagagtttcg 300

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 38

cagtctgccc tgactcagcc tgcctccgtg tctgggtctc ctggacagtc gatcaccatc 60

tcctgcactg gaaccagcag tgacgttggt ggctatattt atgtctcctg gtaccaacaa 120

cacccaggca aagcccccaa actcatgatt tatgatgtca gtcgtcggcc ctcagggatt 180

tctgatcgct tctctggctc caagtctggc aacacggcct ccctgaccat ctctgggctc 240

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caggctgagg acgaggctga ttattactgc aactcatata caaccctcag cacctggctc 300

ttcggcggag ggaccaaggt caccgtccta 330

<210> SEQ ID NO 39
<211> LENGTH: 354
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 39

gaggtgcagc tggtgcagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttagt agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaagccag atggaagtga gaaatactat 180

gtggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ttcagtgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc gagagtttcg 300

aggggtggga gctactcgga ctggggcaaa ggaaccctgg tcaccgtctc gagt 354

<210> SEQ ID NO 40
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 40

cagtctgccc tgactcagcc tgcctccgtg tctgggtctc ctggacagtc gatcatcatc 60

tcctgcactg gaacccgcag tgacattggt ggttacaact atgtctcctg gtaccaacac 120

cacccaggca gagcccccaa actcatcatt tttgatgtca ataatcggcc ctcaggagtc 180

tctcaccgct tctctggctc caagtctggc aacacggcct ccctgaccat ctctgggctc 240

caggctgagg acgaggctga ttattactgc aattcattta cagacagccg gacttggctg 300

ttcggcggag ggaccaagct gaccgtccta 330

<210> SEQ ID NO 41
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 41

gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttagc agctatgcca tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtctcagct attagtggta gtggtggtag cacatactac 180

gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgt aaaagatagg 300

gttgctgtag ctggtaaggg ttcgtattac tttgactctt gggggagggg gaccacggtc 360

accgtctcga gt 372

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<210> SEQ ID NO 42
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 42

cagtctgtgc tgacgcagcc gccctcggtg tctgaagccc ccgggcagag ggtcaccatc 60

gcctgttctg gaagcagctc caacatcgga aataatgctg taagttggta ccagcaactc 120

ccaggaaagg ctcccacact cctcatctat tatgataatc tgctgccctc aggggtctct 180

gaccgattct ctggctccaa gtctggcacc tcagcctccc tggccatcag tgggctccag 240

tctgaggatg aggctgatta ttactgtgct gcatgggatg acagcctgaa tgattgggtg 300

ttcggcggtg ggaccaaggt caccgtccta 330

<210> SEQ ID NO 43
<211> LENGTH: 357
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 43

caggtgcagc tgcaggagtc gggtccagga ctggtgaagc cctcgcagac cctctcactc 60

acctgtgcca tctccgggga cagtgtctct agcaacagtg ctgcttggaa ctggatcagg 120

cagtccccat cgagaggcct tgagtggctg ggaaggacat actacaggtc caagtggtat 180

aatgattatg cagtatctgt gaaaagtcga atgaccataa aagcagacac atccaagaac 240

cagttctccc tgcaactgaa ctctgtgact cccgaagaca cggctgtgta ttactgtgca 300

agagatgagg gaccgcttga ctactggggc cagggaaccc tggtcaccgt ctcggcc 357

<210> SEQ ID NO 44
<211> LENGTH: 333
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 44

caggctgtgc tcactcagcc gtcctcagtg tctggggccc cagggcagag ggtcaccatc 60

tcctgcactg ggagcagctc caacctcggg acaggttatg atgtacactg gtaccagcag 120

cttccaggaa cagccccaa actcctcatc tatggtaaca gcaatcggcc ctcaggggtc 180

cctgaccgat tctcgggctc caagtctgac acctcaggtt tgctggccat cactgggctc 240

caggctgagg atgaggctac ttattactgc cagtcctatg acttcagcct gagtgctatg 300

gtattcggcg gagggaccaa ggtcaccgtc cta 333

<210> SEQ ID NO 45
<211> LENGTH: 479
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

-continued

protein sequence

<400> SEQUENCE: 45

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

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

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

Ala Asn Ile Lys Pro Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
50                  55                  60

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

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

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

Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
115                 120                 125

Gly Gly Gly Gly Ser Ala Gln Ser Val Leu Thr Gln Pro Pro Ser Ala
130                 135                 140

Ser Gly Ser Pro Gly Gln Ser Val Thr Ile Ser Cys Thr Gly Thr Ser
145                 150                 155                 160

Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln His Pro
165                 170                 175

Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Val Ser Lys Arg Pro Ser
180                 185                 190

Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser
195                 200                 205

Leu Thr Val Ser Gly Leu Gln Pro Glu Asp Glu Ala Asp Tyr Tyr Cys
210                 215                 220

Ser Ser Tyr Ala Gly Arg Asn Trp Val Phe Gly Gly Gly Thr Gln Leu
225                 230                 235                 240

Thr Val Leu Gly Ala Ala Ala Glu Pro Lys Ser Cys Asp Lys Thr His
245                 250                 255

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
260                 265                 270

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
275                 280                 285

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
290                 295                 300

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
305                 310                 315                 320

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
325                 330                 335

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
340                 345                 350

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
355                 360                 365

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
370                 375                 380
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Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
385                 390                 395                 400

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
405                 410                 415

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
420                 425                 430

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
435                 440                 445

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
450                 455                 460

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
465                 470                 475


<210> SEQ ID NO 46
<211> LENGTH: 480
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      protein sequence

<400> SEQUENCE: 46

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 Thr Phe Ser Ser Tyr
20                  25                  30

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

Ala Asn Ile Lys Pro Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
50                  55                  60

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

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

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

Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
115                 120                 125

Gly Gly Gly Gly Ser Ala Gln Ser Ala Leu Thr Gln Pro Ala Ser Val
130                 135                 140

Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser
145                 150                 155                 160

Ser Asp Val Gly Gly Tyr Ile Tyr Val Ser Trp Tyr Gln Gln His Pro
165                 170                 175

Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp Val Ser Arg Arg Pro Ser
180                 185                 190

Gly Ile Ser Asp Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser
195                 200                 205

Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys
210                 215                 220

Asn Ser Tyr Thr Thr Leu Ser Thr Trp Leu Phe Gly Gly Gly Thr Lys
225                 230                 235                 240

Val Thr Val Leu Gly Ala Ala Ala Glu Pro Lys Ser Cys Asp Lys Thr
245                 250                 255
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His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
260                 265                 270

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
275                 280                 285

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
290                 295                 300

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
305                 310                 315                 320

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
325                 330                 335

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

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
355                 360                 365

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
370                 375                 380

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
385                 390                 395                 400

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
405                 410                 415

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
420                 425                 430

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
435                 440                 445

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
450                 455                 460

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
465                 470                 475                 480


<210> SEQ ID NO 47
<211> LENGTH: 480
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      protein sequence

<400> SEQUENCE: 47

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

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

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

Ala Asn Ile Lys Pro Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
50                  55                  60

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

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

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

Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
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115                 120                 125

Gly Gly Gly Gly Ser Ala Gln Ser Ala Leu Thr Gln Pro Ala Ser Val
130                 135                 140

Ser Gly Ser Pro Gly Gln Ser Ile Ile Ile Ser Cys Thr Gly Thr Arg
145                 150                 155                 160

Ser Asp Ile Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln His His Pro
165                 170                 175

Gly Arg Ala Pro Lys Leu Ile Ile Phe Asp Val Asn Asn Arg Pro Ser
180                 185                 190

Gly Val Ser His Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser
195                 200                 205

Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys
210                 215                 220

Asn Ser Phe Thr Asp Ser Arg Thr Trp Leu Phe Gly Gly Gly Thr Lys
225                 230                 235                 240

Leu Thr Val Leu Gly Ala Ala Ala Glu Pro Lys Ser Cys Asp Lys Thr
245                 250                 255

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
260                 265                 270

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
275                 280                 285

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
290                 295                 300

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
305                 310                 315                 320

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
325                 330                 335

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

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
355                 360                 365

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
370                 375                 380

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
385                 390                 395                 400

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
405                 410                 415

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
420                 425                 430

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
435                 440                 445

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
450                 455                 460

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
465                 470                 475                 480


<210> SEQ ID NO 48
<211> LENGTH: 486
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      protein sequence
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<400> SEQUENCE: 48

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

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

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

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

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

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

Val Lys Asp Arg Val Ala Val Ala Gly Lys Gly Ser Tyr Tyr Phe Asp
100 105 110

Ser Trp Gly Arg Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly
115 120 125

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Ser Val Leu
130 135 140

Thr Gln Pro Pro Ser Val Ser Glu Ala Pro Gly Gln Arg Val Thr Ile
145 150 155 160

Ala Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn Ala Val Ser Trp
165 170 175

Tyr Gln Gln Leu Pro Gly Lys Ala Pro Thr Leu Leu Ile Tyr Tyr Asp
180 185 190

Asn Leu Leu Pro Ser Gly Val Ser Asp Arg Phe Ser Gly Ser Lys Ser
195 200 205

Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Gln Ser Glu Asp Glu
210 215 220

Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu Asn Asp Trp Val
225 230 235 240

Phe Gly Gly Gly Thr Lys Val Thr Val Leu Gly Ala Ala Ala Glu Pro
245 250 255

Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
260 265 270

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
275 280 285

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
290 295 300

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
305 310 315 320

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
325 330 335

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
340 345 350

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
355 360 365

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
370 375 380

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn

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385 390 395 400

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
405 410 415

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
420 425 430

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
435 440 445

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
450 455 460

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
465 470 475 480

Ser Leu Ser Pro Gly Lys
485

<210> SEQ ID NO 49
<211> LENGTH: 483
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic protein sequence

<400> SEQUENCE: 49

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

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
20 25 30

Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Met Thr Ile Lys Ala Asp Thr Ser Lys Asn
65 70 75 80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95

Tyr Tyr Cys Ala Arg Asp Glu Gly Pro Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly
115 120 125

Ser Gly Gly Gly Gly Ser Gly Ala Pro Gln Ala Val Leu Thr Gln Pro
130 135 140

Ser Ser Val Ser Gly Ala Pro Gly Gln Arg Val Thr Ile Ser Cys Thr
145 150 155 160

Gly Ser Ser Ser Asn Leu Gly Thr Gly Tyr Asp Val His Trp Tyr Gln
165 170 175

Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu Ile Tyr Gly Asn Ser Asn
180 185 190

Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Asp Thr
195 200 205

Ser Gly Leu Leu Ala Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Thr
210 215 220

Tyr Tyr Cys Gln Ser Tyr Asp Phe Ser Leu Ser Ala Met Val Phe Gly
225 230 235 240

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Gly Gly Thr Lys Val Thr Val Leu Ala Ala Ala Glu Pro Lys Ser Cys
245                 250                 255

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
260                 265                 270

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
275                 280                 285

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
290                 295                 300

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
305                 310                 315                 320

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
325                 330                 335

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

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
355                 360                 365

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
370                 375                 380

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
385                 390                 395                 400

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
405                 410                 415

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
420                 425                 430

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
435                 440                 445

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
450                 455                 460

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
465                 470                 475                 480

Pro Gly Lys


<210> SEQ ID NO 50
<211> LENGTH: 1437
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide sequence

<400> SEQUENCE: 50

gaggtccagc tggtgcagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc     60

tcctgtgcag cctctggatt cacctttagt agctattgga tgagctgggt ccgccaggct    120

ccagggaagg ggctggagtg ggtggccaac ataaagccag atggaagtga gaaatactat    180

gtggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ttcagtgtat    240

ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc gagagtttcg    300

aggggtggga gctactcgga ctggggccaa ggcaccctgg tcaccgtctc gagtggaggc    360

ggcggttcag gcggaggtgg ctctggcggt ggcggaagtg cacagtctgt gctgactcag    420

ccaccctccg cgtccgggtc tcctggacag tcagtcacca tctcctgcac tggaaccagc    480

agtgacgttg gtggttataa ctatgtctcc tggtaccaac agcacccagg caaagccccc    540
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aaactcatga tttatgaggt cagtaagcgg ccctcagggg tccctgatcg cttctctggc 600

tccaagtctg gcaacacggc ctccctgacc gtctctgggc tccagcctga ggatgaggct 660

gattattact gcagctcata tgcaggcagg aactgggtgt tcggcggagg gacccagctc 720

accgttttag gtgcggccgc agagcccaaa tcttgtgaca aaactcacac atgcccaccg 780

tgcccagcac ctgaactcct gggggggaccg tcagtcttcc tcttcccccc aaaacccaag 840

gacaccctca tgatctcccg gacccctgag gtcacatgcg tggtggtgga cgtgagccac 900

gaagaccctg aggtcaagtt caactggtac gtggacggcg tggaggtgca taatgccaag 960

acaaagccgc gggaggagca gtacaacagc acgtaccgtg tggtcagcgt cctcaccgtc 1020

ctgcaccagg actggctgaa tggcaaggag tacaagtgca aggtctccaa caaagccctc 1080

ccagccccca tcgagaaaac catctccaaa gccaaagggc agccccgaga accacaggtg 1140

tacaccctgc ccccatcccg ggaggagatg accaagaacc aggtcagcct gacctgcctg 1200

gtcaaaggct tctatcccag cgacatcgcc gtggagtggg agagcaatgg gcagccggag 1260

aacaactaca agaccacgcc tcccgtgctg gactccgacg gctccttctt cctctatagc 1320

aagctcaccg tggacaagag caggtggcag caggggaacg tcttctcatg ctccgtgatg 1380

catgaggctc tgcacaacca ctacacgcag aagagcctct ccctgtctcc gggtaaa 1437

<210> SEQ ID NO 51
<211> LENGTH: 1440
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 51

gaggtgcagc tggtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttagt agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaagccag atggaagtga gaaatactat 180

gtggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ttcagtgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc aagagtttcg 300

aggggtggga gctactcgga ctggggccag ggaaccctgg tcaccgtctc gagtggaggc 360

ggcggttcag gcggaggtgg ctctggcggt ggcggaagtg cacagtctgc cctgactcag 420

cctgcctccg tgtctgggtc tcctggacag tcgatcacca tctcctgcac tggaaccagc 480

agtgacgttg gtggctatat ttatgtctcc tggtaccaac aacacccagg caaagccccc 540

aaactcatga tttatgatgt cagtcgtcgg ccctcaggga tttctgatcg cttctctggc 600

tccaagtctg gcaacacggc ctccctgacc atctctgggc tccaggctga ggacgaggct 660

gattattact gcaactcata tacaaccctc agcacctggc tcttcggcgg agggaccaag 720

gtcaccgtcc taggtgcggc cgcagagccc aaatcttgtg acaaaactca cacatgccca 780

ccgtgcccag cacctgaact cctgggggga ccgtcagtct tcctcttccc cccaaaaccc 840

aaggacaccc tcatgatctc ccggaccccct gaggtcacat gcgtggtggt ggacgtgagc 900

cacgaagacc ctgaggtcaa gttcaactgg tacgtggacg gcgtggaggt gcataatgcc 960

aagacaaagc cgcgggagga gcagtacaac agcacgtacc gtgtggtcag cgtcctcacc 1020

gtcctgcacc aggactggct gaatggcaag gagtacaagt gcaaggtctc caacaaagcc 1080

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ctcccagccc ccatcgagaa aaccatctcc aaagccaaag ggcagccccg agaaccacag 1140

gtgtacaccc tgcccccatc ccgggaggag atgaccaaga accaggtcag cctgacctgc 1200

ctggtcaaag gcttctatcc cagcgacatc gccgtggagt gggagagcaa tgggcagccg 1260

gagaacaact acaagaccac gcctcccgtg ctggactccg acggctcctt cttcctctat 1320

agcaagctca ccgtggacaa gagcaggtgg cagcagggga acgtcttctc atgctccgtg 1380

atgcatgagg ctctgcacaa ccactacacg cagaagagcc tctccctgtc tccgggtaaa 1440

<210> SEQ ID NO 52
<211> LENGTH: 1440
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 52

gaggtgcagc tggtgcagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttagt agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaagccag atggaagtga gaaatactat 180

gtggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ttcagtgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc gagagtttcg 300

aggggtggga gctactcgga ctggggcaaa ggaaccctgg tcaccgtctc gagtggaggc 360

ggcggttcag gcggaggtgg ctctggcggt ggcggaagtg cacagtctgc cctgactcag 420

cctgcctccg tgtctgggtc tcctggacag tcgatcatca tctcctgcac tggaacccgc 480

agtgacattg gtggttacaa ctatgtctcc tggtaccaac accacccagg cagagccccc 540

aaactcatca tttttgatgt caataatcgg ccctcaggag tctctcaccg cttctctggc 600

tccaagtctg gcaacacggc ctccctgacc atctctgggc tccaggctga ggacgaggct 660

gattattact gcaattcatt tacagacagc cggacttggc tgttcggcgg agggaccaag 720

ctgaccgtcc taggtgcggc cgcagagccc aaatcttgtg acaaaactca cacatgccca 780

ccgtgcccag cacctgaact cctgggggga ccgtcagtct tcctcttccc cccaaaaccc 840

aaggacaccc tcatgatctc ccggacccct gaggtcacat gcgtggtggt ggacgtgagc 900

cacgaagacc ctgaggtcaa gttcaactgg tacgtggacg gcgtggaggt gcataatgcc 960

aagacaaagc cgcgggagga gcagtacaac agcacgtacc gtgtggtcag cgtcctcacc 1020

gtcctgcacc aggactggct gaatggcaag gagtacaagt gcaaggtctc caacaaagcc 1080

ctcccagccc ccatcgagaa aaccatctcc aaagccaaag ggcagccccg agaaccacag 1140

gtgtacaccc tgcccccatc ccgggaggag atgaccaaga accaggtcag cctgacctgc 1200

ctggtcaaag gcttctatcc cagcgacatc gccgtggagt gggagagcaa tgggcagccg 1260

gagaacaact acaagaccac gcctcccgtg ctggactccg acggctcctt cttcctctat 1320

agcaagctca ccgtggacaa gagcaggtgg cagcagggga acgtcttctc atgctccgtg 1380

atgcatgagg ctctgcacaa ccactacacg cagaagagcc tctccctgtc tccgggtaaa 1440

<210> SEQ ID NO 53
<211> LENGTH: 1458
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 53

gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttagc agctatgcca tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtctcagct attagtggta gtggtggtag cacatactac 180

gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgt aaaagatagg 300

gttgctgtag ctggtaaggg ttcgtattac tttgactctt gggggagggg gaccacggtc 360

accgtctcga gtggaggcgg cggttcaggc ggaggtggct ctggcggtgg cggaagtgca 420

cagtctgtgc tgacgcagcc gccctcggtg tctgaagccc ccgggcagag ggtcaccatc 480

gcctgttctg gaagcagctc caacatcgga aataatgctg taagttggta ccagcaactc 540

ccaggaaagg ctcccacact cctcatctat tatgataatc tgctgccctc aggggtctct 600

gaccgattct ctggctccaa gtctggcacc tcagcctccc tggccatcag tgggctccag 660

tctgaggatg aggctgatta ttactgtgct gcatgggatg acagcctgaa tgattgggtg 720

ttcggcggtg ggaccaaggt caccgtccta ggtgcggccg cagagcccaa atcttgtgac 780

aaaactcaca catgcccacc gtgcccagca cctgaactcc tgggggggacc gtcagtcttc 840

ctcttccccc caaaacccaa ggacaccctc atgatctccc ggacccctga ggtcacatgc 900

gtggtggtgg acgtgagcca cgaagaccct gaggtcaagt tcaactggta cgtggacggc 960

gtggaggtgc ataatgccaa gacaaagccg cgggaggagc agtacaacag cacgtaccgt 1020

gtggtcagcg tcctcaccgt cctgcaccag gactggctga atggcaagga gtacaagtgc 1080

aaggtctcca acaaagccct cccagccccc atcgagaaaa ccatctccaa agccaaaggg 1140

cagccccgag aaccacaggt gtacaccctg cccccatccc gggaggagat gaccaagaac 1200

caggtcagcc tgacctgcct ggtcaaaggc ttctatccca gcgacatcgc cgtggagtgg 1260

gagagcaatg ggcagccgga gaacaactac aagaccacgc ctcccgtgct ggactccgac 1320

ggctccttct tcctctatag caagctcacc gtggacaaga gcaggtggca gcaggggaac 1380

gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 1440

tccctgtctc cgggtaaa 1458

<210> SEQ ID NO 54
<211> LENGTH: 1449
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 54

caggtgcagc tgcaggagtc gggtccagga ctggtgaagc cctcgcagac cctctcactc 60

acctgtgcca tctccgggga cagtgtctct agcaacagtg ctgcttggaa ctggatcagg 120

cagtccccat cgagaggcct tgagtggctg ggaaggacat actacaggtc caagtggtat 180

aatgattatg cagtatctgt gaaaagtcga atgaccataa aagcagacac atccaagaac 240

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cagttctccc tgcaactgaa ctctgtgact cccgaagaca cggctgtgta ttactgtgca 300

agagatgagg gaccgcttga ctactggggc cagggaaccc tggtcaccgt ctcggccggt 360

ggcggtggca gcggcggtgg tgggtccggt ggcggcggat ctggcgcgcc acaggctgtg 420

ctcactcagc cgtcctcagt gtctggggcc ccagggcaga gggtcaccat ctcctgcact 480

gggagcagct ccaacctcgg gacaggttat gatgtacact ggtaccagca gcttccagga 540

acagccccca aactcctcat ctatggtaac agcaatcggc cctcaggggt ccctgaccga 600

ttctcgggct ccaagtctga cacctcaggt ttgctggcca tcactgggct ccaggctgag 660

gatgaggcta cttattactg ccagtcctat gacttcagcc tgagtgctat ggtattcggc 720

ggagggacca aggtcaccgt cctagcggcc gcagagccca aatcttgtga caaaactcac 780

acatgcccac cgtgcccagc acctgaactc ctgggggggac cgtcagtctt cctcttcccc 840

ccaaaaccca aggacaccct catgatctcc cggacccctg aggtcacatg cgtggtggtg 900

gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt acgtggacgg cgtggaggtg 960

cataatgcca agacaaagcc gcgggaggag cagtacaaca gcacgtaccg tgtggtcagc 1020

gtcctcaccg tcctgcacca ggactggctg aatggcaagg agtacaagtg caaggtctcc 1080

aacaaagccc tcccagcccc catcgagaaa accatctcca aagccaaagg gcagccccga 1140

gaaccacagg tgtacaccct gcccccatcc cgggaggaga tgaccaagaa ccaggtcagc 1200

ctgacctgcc tggtcaaagg cttctatccc agcgacatcg ccgtggagtg ggagagcaat 1260

gggcagccgg agaacaacta caagaccacg cctcccgtgc tggactccga cggctccttc 1320

ttcctctata gcaagctcac cgtggacaag agcaggtggc agcaggggaa cgtcttctca 1380

tgctccgtga tgcatgaggc tctgcacaac cactacacgc agaagagcct ctccctgtct 1440

ccgggtaaa 1449

<210> SEQ ID NO 55
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 55

caggtacagc tgcagcagtc aggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cctctggatt caccttcagt gactatgcta tgcactgggt ccgccaggct 120

ccaggcaagg ggctagagtg ggtggcagtt atatcaaatc atggaaagag cacatactac 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagca catgctgtat 240

ctgcaaatga acagcctgag agctgacgac acggctctat attactgtgc gagagatata 300

gcattggctg gggactactg gggccagggc accctggtca ccgtctctgc c 351

<210> SEQ ID NO 56
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic protein sequence

<400> SEQUENCE: 56

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Gln Val Gln Leu Gln Gln 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 Asp Tyr
20                  25                  30

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

Ala Val Ile Ser Asn His Gly Lys Ser Thr Tyr Tyr Ala Asp Ser Val
50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys His Met Leu Tyr
65                  70                  75                  80

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

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

Val Thr Val Ser Ala
115


<210> SEQ ID NO 57
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide sequence

<400> SEQUENCE: 57

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc     60

atcacttgcc gggcaagtca gagcattagc agctatctta attggtatca gcaactacca    120

gggaaagtcc ctaaactcct gatctatggt gcatcgaagt tgcaaagtgg ggtcccctcc    180

aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct    240

gaagattttg caacttatta ctgtctccaa gattacaatt atcctctcac tttcggccct    300

gggacacgac tggagatcaa a                                              321


<210> SEQ ID NO 58
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      protein sequence

<400> SEQUENCE: 58

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20                  25                  30

Leu Asn Trp Tyr Gln Gln Leu Pro Gly Lys Val Pro Lys Leu Leu Ile
35                  40                  45

Tyr Gly Ala Ser Lys Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Asp Tyr Asn Tyr Pro Leu
85                  90                  95
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Thr Phe Gly Pro Gly Thr Arg Leu Glu Ile Lys
100 105

<210> SEQ ID NO 59
<211> LENGTH: 357
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 59

caggtgcagc tgcaggagtc gggcccagga ctggtgaggc cttcggggac cctgtccctc 60

acctgcgctg tctctggtgg ctccatcggc agtagtaact ggtggagttg ggtccgccag 120

gccccaggga aggggctgga gtggattggg gaaatctctc agagtgggag caccaactac 180

aacccgtccc tcaagggtcg agtcaccata tcactagaca ggtccaggaa ccagttgtcc 240

ctgaagttga gttctgtgac cgccgcggac acggccgtgt attactgtgc gagacagctg 300

cggtcgattg atgcttttga tatctggggc ccagggacca cggtcaccgt ctcggcc 357

<210> SEQ ID NO 60
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic protein sequence

<400> SEQUENCE: 60

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

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Gly Ser Ser
20 25 30

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

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

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

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gln Leu Arg Ser Ile Asp Ala Phe Asp Ile Trp Gly Pro Gly
100 105 110

Thr Thr Val Thr Val Ser Ala
115

<210> SEQ ID NO 61
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 61

tcctatgtgc tgactcagcc accctcagtg tccgtgtccc caggactgac agccaccatc 60

acctgctctg gagataaatt gggggacaaa tatgcttcct ggtatcagca gaagccaggc 120

-continued

cagtcccctg tgttggtcat ctatcaagat aggaagcgac cctcagggat ccctgagcga 180

ttctctgggt ccaattctgg gaacacagcc actctgacca tcagcgggac ccaggctgtg 240

gatgaggctg actattactg tcaggcgtgg gacagcgaca cttcttatgt cttcggaact 300

gggacccagc tcaccgtttt a 321

<210> SEQ ID NO 62
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic protein sequence

<400> SEQUENCE: 62

Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Leu
1 5 10 15

Thr Ala Thr Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
20 25 30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45

Gln Asp Arg Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Val
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Asp Thr Ser Tyr
85 90 95

Val Phe Gly Thr Gly Thr Gln Leu Thr Val Leu
100 105

<210> SEQ ID NO 63
<211> LENGTH: 378
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 63

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60

acctgcactg tctctggtgg ctacatcaat aattactact ggagctggat ccggcagccc 120

ccagggaagg gcctggagtg gattgggtac atccattaca gtgggagcac ctactacaac 180

ccgtccctca agagtcgagt caccatatca gaagacacgt ccaagaacca gttctccctg 240

aagctgagct ctgcgaccgc tgcggacacg gccgtgtatt actgtgcgag agttgggtat 300

tactatgata gtagtggtta taatcttgcc tggtacttcg atctctgggg ccgtggaacc 360

ctggtcaccg tctcggcc 378

<210> SEQ ID NO 64
<211> LENGTH: 126
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic protein sequence

<400> SEQUENCE: 64

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Tyr Ile Asn Asn Tyr
20                  25                  30

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35                  40                  45

Gly Tyr Ile His Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser Leu Lys
50                  55                  60

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

Lys Leu Ser Ser Ala Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85                  90                  95

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

Phe Asp Leu Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ala
115                 120                 125


<210> SEQ ID NO 65
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide sequence

<400> SEQUENCE: 65

tcttctgagc tgactcagga ccctgctgtg tctgtggcct tgggacagac ggtcaggatc     60

acatgccagg gagacaacct cagaagttat tctgcaactt ggtaccaaca gaagccagga    120

caggcccctg tccttgtcct ctttggtgaa aacaaccggc cctcagggat cccagaccga    180

ttctctggct ccaagtcagg ggacacagct gtcttgacca tcactgggac tcagacccaa    240

gatgaggctg actattattg cacttccagg gtcaatagcg ggaaccatct gggggtgttc    300

ggcccaggga cccagctcac cgtttta                                        327


<210> SEQ ID NO 66
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      protein sequence

<400> SEQUENCE: 66

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

Thr Val Arg Ile Thr Cys Gln Gly Asp Asn Leu Arg Ser Tyr Ser Ala
20                  25                  30

Thr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Leu Phe
35                  40                  45

Gly Glu Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
50                  55                  60

Lys Ser Gly Asp Thr Ala Val Leu Thr Ile Thr Gly Thr Gln Thr Gln
65                  70                  75                  80

Asp Glu Ala Asp Tyr Tyr Cys Thr Ser Arg Val Asn Ser Gly Asn His
85                  90                  95
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Leu Gly Val Phe Gly Pro Gly Thr Gln Leu Thr Val Leu
100 105

<210> SEQ ID NO 67
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 67

gaggtgcagc tggtggagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggata caccttcacc ggctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggatgg atcaacccta acagtggtgg cacaaactat 180

gcacagaagt ttcagggcag ggtcaccatg accagggaca cgtccatcag cacagcctac 240

atggagctga gcaggctgag atctgacgac acggccgtgt attactgtgc gagaggggg 300

cacatgacta cggtgacccg tgatgctttt gatatctggg gccaagggac aatggtcacc 360

gtctctgcc 369

<210> SEQ ID NO 68
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic protein sequence

<400> SEQUENCE: 68

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Gly Gly His Met Thr Thr Val Thr Arg Asp Ala Phe Asp Ile
100 105 110

Trp Gly Gln Gly Thr Met Val Thr Val Ser Ala
115 120

<210> SEQ ID NO 69
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 69

tcttctgagc tgactcagga ccctgctgtg tctgtggcct tgggacagac aatcaggatc 60

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acatgccaag gagacagcct cagatactat tatgcaacct ggtatcagca gaagccagga 120

caggccccta tacttgtcat ctatggtcag aataatcggc cctcaggggt cccagaccga 180

ttctctggct ccagctcagg aaacacagct tccttgacca tcactggggc tcaggcggaa 240

gatgaggctg actattactg cggaacatgg gatagcagtg tgagtgcctc ttgggtgttc 300

ggcggaggga ccaaggtcac cgtccta 327

<210> SEQ ID NO 70
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic protein sequence

<400> SEQUENCE: 70

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

Thr Ile Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Tyr Tyr Tyr Ala
20 25 30

Thr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Ile Leu Val Ile Tyr
35 40 45

Gly Gln Asn Asn Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser
50 55 60

Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gly Thr Trp Asp Ser Ser Val Ser Ala
85 90 95

Ser Trp Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu
100 105

<210> SEQ ID NO 71
<211> LENGTH: 354
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 71

caggtacagc tgcagcagtc aggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggata caccttcagc ggctattata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggatgg atcaacccta acagtggcag cacaaattat 180

gcacagaagt ttctgggcag ggtcaccatg accagggaca cgtccatcag cacagcctac 240

atggaactga gcagcctgag atctgacgac acggccgtgt attactgtgc gaggggacac 300

tccggtgact attttgacta ctggggccag ggaaccctgg tcaccgtctc ggcc 354

<210> SEQ ID NO 72
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic protein sequence

<400> SEQUENCE: 72

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

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

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

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

Leu Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

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

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

Leu Val Thr Val Ser Ala
115


<210> SEQ ID NO 73
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide sequence

<400> SEQUENCE: 73

gaaattgtgt tgacgcagtc tccatcctcc ctgtctgcat ctgttggaga cagagtcacc     60

atcacttgcc gggccagtca gagtgttagc agctggttgg cctggtatca acagagacca    120

gggcaagccc ctaaactgct gatctatgct gcacgtttgc gaggtggagg cccttcaagg    180

ttcagtggca gcggctctgg gacagaattc actctcacca tcagcagtct gcaacctgaa    240

gactttgcga cttacttctg tcaacagagt tacagtaccc cgatcagttt cggcggaggg    300

accaagctgg agatcaaa                                                  318


<210> SEQ ID NO 74
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      protein sequence

<400> SEQUENCE: 74

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Val Ser Ser Trp
20                  25                  30

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

Tyr Ala Ala Arg Leu Arg Gly Gly Gly Pro Ser Arg Phe Ser Gly Ser
50                  55                  60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
65                  70                  75                  80

Asp Phe Ala Thr Tyr Phe Cys Gln Gln Ser Tyr Ser Thr Pro Ile Ser
85                  90                  95
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-continued

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> SEQ ID NO 75
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 75

caggtgcagc tgcaggagtc gggctcagga ctggcgaggc cttcacagac cctgtccctc 60

acctgcgctg tctctggtgg ctccatcagc agtagtgctt tctcctggaa ttggatccgg 120

cagccaccag ggaagggcct ggagtggatt ggatacatct atcatactgg gatcaccgat 180

tataacccgt ccctcaagag tcgagtcacc atatcagtgg acaggtccaa gaaccagttc 240

tccctgaacg tgaactctgt gaccgccgcg gacacggccg tgtattattg tgccagagga 300

cacggttcgg accccgcctg gttcgacccc tggggcaagg gcaccctggt caccgtctcg 360

agt 363

<210> SEQ ID NO 76
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic protein sequence

<400> SEQUENCE: 76

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

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
20 25 30

Ala Phe Ser Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
35 40 45

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

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

Ser Leu Asn Val Asn Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Arg Gly His Gly Ser Asp Pro Ala Trp Phe Asp Pro Trp Gly
100 105 110

Lys Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 77
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 77

caatctgtgc tgactcagcc accctcagtg tccgtgtccc caggacagac agccagcatc 60

-continued

acctgctctg gagataaatt gggggataaa tatgcttcct ggtatcagca gaggccaggc 120

cagtcccctg ttctggtcat ctatcgagac accaagcggc cctcagggat ccctgagcga 180

ttctctggct ccaactctgg gaacacagcc actctgacca tcagcgggac ccaggctgtg 240

gatgaggctg actattactg tcaggcgtgg gacagcacca cctccctggt tttcggcgga 300

gggaccaagc tgaccgtcct a 321

<210> SEQ ID NO 78
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic protein sequence

<400> SEQUENCE: 78

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

Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
20 25 30

Ser Trp Tyr Gln Gln Arg Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45

Arg Asp Thr Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Val
65 70 75 80

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

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> SEQ ID NO 79
<211> LENGTH: 354
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 79

gaggtccagc tggtacagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttagt agctattgga tgagctgggt ccgccaggct 120

cctgggaagg ggctggagtg ggtggccaac ataaagccag atggaagtga gaaatactat 180

gtggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ttcagtgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc gagagtttcg 300

aggggtggga gctactcgga ctggggccga gggacaatgg tcaccgtctc gagt 354

<210> SEQ ID NO 80
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic protein sequence

<400> SEQUENCE: 80

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

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

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

Ala Asn Ile Lys Pro Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
50                  55                  60

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

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

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

Met Val Thr Val Ser Ser
115


<210> SEQ ID NO 81
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide sequence

<400> SEQUENCE: 81

cagtctgtgc tgactcagcc accctccgcg tccgggtctc ctggacagtc agtcaccatc     60

tcctgcactg gaaccagcag tgacgttggc ggttttaact atgtctcctg gtaccaaaag    120

tacccaggca aagcccccaa actcgtcatt tatgaggtca gtaagcggcc ctcaggggtc    180

cctgatcgct tctctggctc caagtccggc aacacggcct ccctgaccgt ctctgggctc    240

caggctgagg atgaggctga ttattactgc agctcatggg cacctggtaa aaacttattc    300

ggcggaggga ccaagctgac cgtccta                                        327


<210> SEQ ID NO 82
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      protein sequence

<400> SEQUENCE: 82

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

Ser Val Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Phe
20                  25                  30

Asn Tyr Val Ser Trp Tyr Gln Lys Tyr Pro Gly Lys Ala Pro Lys Leu
35                  40                  45

Val Ile Tyr Glu Val Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
50                  55                  60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Val Ser Gly Leu
65                  70                  75                  80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Trp Ala Pro Gly
85                  90                  95
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Lys Asn Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> SEQ ID NO 83
<211> LENGTH: 378
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 83

gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttagc agctatgcca tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtctcaggt attagtggta gtggtagtag tgaaggtggc 180

acatactacg cagactccgt gaagggccgg ttcaccctct ccagagacaa ttccaagaat 240

accctgtatc tgcaaatgaa cagcctgaga gccgaggaca cggccttata ttactgtgtg 300

aaagatcgcc ctagtcgata cagctttggt tattactttg actactgggg ccggggaacc 360

ctggtcaccg tctcgagt 378

<210> SEQ ID NO 84
<211> LENGTH: 126
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic protein sequence

<400> SEQUENCE: 84

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 Thr Phe Ser Ser Tyr
20 25 30

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

Ser Gly Ile Ser Gly Ser Gly Ser Ser Glu Gly Gly Thr Tyr Tyr Ala
50 55 60

Asp Ser Val Lys Gly Arg Phe Thr Leu Ser Arg Asp Asn Ser Lys Asn
65 70 75 80

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

Tyr Tyr Cys Val Lys Asp Arg Pro Ser Arg Tyr Ser Phe Gly Tyr Tyr
100 105 110

Phe Asp Tyr Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 85
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 85

ctgcctgtgc tgactcagcc accctcagtg tccgtgtccc caggacagac agccagcatc 60

-continued

gcctgctctg gaaataaatt gggggataaa tatgtttcct ggtatcagca gaagccaggc 120

cagtcccctc tgctggtcat ctatcaagat accaagcggc cctcagggat ccctgagcga 180

ttctctggct ccaactcagg gaacacagcc actctgacca tcagcgggac ccaggctatg 240

gatgaggctg actattactg tcaggcgtgg gacagcagca ctgatgtggt attcggcgga 300

gggaccaagc tgaccgtcct a 321

<210> SEQ ID NO 86
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic protein sequence

<400> SEQUENCE: 86

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

Thr Ala Ser Ile Ala Cys Ser Gly Asn Lys Leu Gly Asp Lys Tyr Val
20 25 30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Leu Leu Val Ile Tyr
35 40 45

Gln Asp Thr Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

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

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> SEQ ID NO 87
<211> LENGTH: 354
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 87

gaggtgcagc tggtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc 60

tcctgtgcgg tctctgggtt cacctttagt aagtattgga tgacctgggt ccgccaggct 120

ccagggaagg gactggagtg ggtggccaac ataaagccag atggaagtga gaaatactat 180

gtggagtctg tgaagggccg attcaccatc tccagagaca acgccaagaa ttcagtgtat 240

ctgcaaatga acagtgtgag agccgaagac acggccgtgt attactgtgc gagagtttcg 300

aggggtggga gcttctcgga ctggggccag gggacaatgg tcaccgtctc gagt 354

<210> SEQ ID NO 88
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic protein sequence

<400> SEQUENCE: 88

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

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

Ala Asn Ile Lys Pro Asp Gly Ser Glu Lys Tyr Tyr Val Glu Ser Val
50                  55                  60

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

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

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

Met Val Thr Val Ser Ser
115


<210> SEQ ID NO 89
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide sequence

<400> SEQUENCE: 89

cagtctgtgc tgactcagcc accctccgcg tccgggtctc ctggacagtc agtcaccatc     60

tcctgcactg gaaccagcag cgacgttggt ggttataact atgtctcctg gtaccaacaa    120

cacccagaca aagcccccag actcatgatt tatgacgtca ataagcggcc ctcaggggtc    180

cctgatcgct tctctggctc caagtctggc aacacggcct ccctgaccgt ctctgggctc    240

caggctgagg atgaggctca ttattactgc aactcatatg caggcagcaa caattgggtg    300

ttcggcggag ggacccagct caccgtttta                                     330


<210> SEQ ID NO 90
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      protein sequence

<400> SEQUENCE: 90

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

Ser Val Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20                  25                  30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Asp Lys Ala Pro Arg Leu
35                  40                  45

Met Ile Tyr Asp Val Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
50                  55                  60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Val Ser Gly Leu
65                  70                  75                  80

Gln Ala Glu Asp Glu Ala His Tyr Tyr Cys Asn Ser Tyr Ala Gly Ser
85                  90                  95
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Asn Asn Trp Val Phe Gly Gly Gly Thr Gln Leu Thr Val Leu
100 105 110

<210> SEQ ID NO 91
<211> LENGTH: 354
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 91

caggtgcagc tggtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc 60

tcctgtgcgg tctctgggtt cacctttagt aagtattgga tgacctgggt ccgccaggct 120

ccagggaagg gactggagtg ggtggccaac ataaagccag atggaagtga gaaatactat 180

gtggagtctg tgaagggccg attcaccatc tccagagaca acgccaagaa ttcagtgtat 240

ctgcaaatga acagtgtgag agccgaagac acggccgtgt attactgtgc gagagtttcg 300

aggggtggga gcttctcgga ctggggccaa ggaaccctgg tcaccgtctc gagt 354

<210> SEQ ID NO 92
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic protein sequence

<400> SEQUENCE: 92

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

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

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

Ala Asn Ile Lys Pro Asp Gly Ser Glu Lys Tyr Tyr Val Glu Ser Val
50 55 60

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

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

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

Leu Val Thr Val Ser Ser
115

<210> SEQ ID NO 93
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 93

cagtctgtgc tgactcagcc accctccgcg tccgggtctc ctggacagtc agtcaccatc 60

tcctgcactg gaaccagcag tgacgttggt ggttataatt atgtctcctg gtaccaacaa 120

-continued

cacccaggca gagcccccaa actcatcatt tatgaggtca gtaagcggcc ctcaggggtc 180

cctgatcgct tctctggctc caagtctggc aacacggcct ccctgaccgt ctctgggctc 240

caggctgacg atgaggctga ttattactgc aactcatatg caggcagcat ttatgtcttc 300

gggagtggga ccaaggtcac cgtccta 327

<210> SEQ ID NO 94
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic protein sequence

<400> SEQUENCE: 94

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

Ser Val Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Arg Ala Pro Lys Leu
35 40 45

Ile Ile Tyr Glu Val Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Val Ser Gly Leu
65 70 75 80

Gln Ala Asp Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Tyr Ala Gly Ser
85 90 95

Ile Tyr Val Phe Gly Ser Gly Thr Lys Val Thr Val Leu
100 105

<210> SEQ ID NO 95
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 95

caggtgcagc tggtgcaatc tggggctgaa attaagaagc ctggggcctc agtgaaggtt 60

tcctgcaaga catttggatc ccccttcagc acgaatgaca tacactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcgacacta gtggcgccat gacaaggtac 180

gcacagaagt tccagggcag agtcaccgtg accagggaaa cgtccacgag cacagtctac 240

atggagctga gcagcctgaa atctgaagac acggctgtgt actactgtgc gagagagggt 300

tgtactaatg gtgtatgcta tgataatggt tttgatatct ggggccaagg caccctggtc 360

accgtctcga gt 372

<210> SEQ ID NO 96
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic protein sequence

<400> SEQUENCE: 96

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

Ser Val Lys Val Ser Cys Lys Thr Phe Gly Ser Pro Phe Ser Thr Asn
20                  25                  30

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

Gly Ile Ile Asp Thr Ser Gly Ala Met Thr Arg Tyr Ala Gln Lys Phe
50                  55                  60

Gln Gly Arg Val Thr Val Thr Arg Glu Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

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

Ala Arg Glu Gly Cys Thr Asn Gly Val Cys Tyr Asp Asn Gly Phe Asp
100                 105                 110

Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115                 120


<210> SEQ ID NO 97
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide sequence

<400> SEQUENCE: 97

gatatccaga tgacccagtc tccttccacc ctgtctgcat ctattggaga cagagtcacc     60

atcacctgcc gggccagtga gggtatttat cattggttgg cctggtatca gcagaagcca    120

gggaaagccc ctaaactcct gatctataag gcctctagtt tagccagtgg ggccccatca    180

aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct    240

gatgattttg caacttatta ctgccaacaa tatagtaatt atccgctcac tttcggcgga    300

gggaccaagc tggagatcaa a                                              321


<210> SEQ ID NO 98
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      protein sequence

<400> SEQUENCE: 98

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Ile Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Gly Ile Tyr His Trp
20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35                  40                  45

Tyr Lys Ala Ser Ser Leu Ala Ser Gly Ala 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

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Asn Tyr Pro Leu
85                  90                  95
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Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> SEQ ID NO 99
<211> LENGTH: 354
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 99

caggtgcagc tggtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc 60

tcctgtgcgg tctctgggtt cacctttagt aagtattgga tgacctgggt ccgccaggct 120

ccagggaagg gactggagtg ggtggccaac ataaagccag atggaagtga gaaatactat 180

gtggagtctg tgaagggccg attcaccatc tccagagaca acgccaagaa ttcagtgtat 240

ctgcaaatga acagtgtgag agccgaagac acggccgtgt attactgtgc gagagtttcg 300

aggggtggga gcttctcgga ctggggccgg gggacaatgg tcaccgtctc gagt 354

<210> SEQ ID NO 100
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic protein sequence

<400> SEQUENCE: 100

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

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

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

Ala Asn Ile Lys Pro Asp Gly Ser Glu Lys Tyr Tyr Val Glu Ser Val
50 55 60

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

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

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

Met Val Thr Val Ser Ser
115

<210> SEQ ID NO 101
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 101

caatctgccc tgactcagcc tgcctccgtg tctgggtctc ctggacagtc gatcaccatc 60

tcctgcactg gaaccagcag tgatgttggg agttataacc ttgtctcctg gtaccaacaa 120

-continued

cacccaggca aagtccccaa actcatcatt tatgaggtca gtaatcggcc ctcaggggtt 180

tctcatcgct tctctggctc caagtctggc aacacggcct ccctgaccat ctctggactc 240

caggctgagg acgaggctga ttattactgc agctcattga caagcagcgg cacttgggtg 300

ttcggcggag ggaccaaggt caccgtccta 330

<210> SEQ ID NO 102
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic protein sequence

<400> SEQUENCE: 102

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Ser Tyr
20 25 30

Asn Leu Val Ser Trp Tyr Gln Gln His Pro Gly Lys Val Pro Lys Leu
35 40 45

Ile Ile Tyr Glu Val Ser Asn Arg Pro Ser Gly Val Ser His Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

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

Gly Thr Trp Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu
100 105 110

<210> SEQ ID NO 103
<211> LENGTH: 354
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 103

gaggtgcagc tggtggagtc cgggggaggc ttggtccagc ccgggggtc cctgagactc 60

tcctgtgcgg tctctgggtt cacctttagt aagtattgga tgacctgggt ccgccaggct 120

ccagggaagg gactggagtg ggtggccaac ataaagccag atggaagtga gaaatactat 180

gtggagtctg tgaagggccg attcaccatc tccagagaca acgccaagaa ttcagtgtat 240

ctgcaaatga acagtgtgag agccgaagac acggccgtgt attactgtgc gagagtttcg 300

aggggtggga gcttctcgga ctggggccag ggcaccctgg tcaccgtctc gagt 354

<210> SEQ ID NO 104
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic protein sequence

<400> SEQUENCE: 104

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

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

Ala Asn Ile Lys Pro Asp Gly Ser Glu Lys Tyr Tyr Val Glu Ser Val
50 55 60

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

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

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

Leu Val Thr Val Ser Ser
115

<210> SEQ ID NO 105
<211> LENGTH: 333
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 105

cagtctgccc tgactcagcc tccctccgcg tccgggtctc ctgggcagtc agtcaccatc 60

tcctgcactg gaaccagcag tgacgttggt gcttataact atgtctcctg gtaccaacag 120

cacccaggca aagcccccaa actcatgatt tatgaggtcg ctaggcggcc ctcaggggtc 180

cctgatcgct tctctggctc taagtctggc aacacggcct ccctgaccgt ctctgggctc 240

caggctgagg atgaggctga ttattattgc agctcatatg caggcagcaa caatttcgcg 300

gtcttcggca gagggaccaa gctgaccgtc cta 333

<210> SEQ ID NO 106
<211> LENGTH: 111
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic protein sequence

<400> SEQUENCE: 106

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

Ser Val Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Ala Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Glu Val Ala Arg Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Val Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Ala Gly Ser
85 90 95

Asn Asn Phe Ala Val Phe Gly Arg Gly Thr Lys Leu Thr Val Leu
100 105 110

-continued

<210> SEQ ID NO 107
<211> LENGTH: 354
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 107

gaggtgcagc tggtgcagtc tgggggaggc ttggtccagc ggggggggtc cctgagactc 60

tcctgtgcag cctctggatt caggtttagt agctattgga tgacctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaagccag atggaagtga gaaatactat 180

gtggactctg tgaagggccg attcaccatg tccagagaca acgccaagaa ttcagtgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc gagagtttcg 300

aggggtggga gcttctcgga ctggggccaa ggaaccctgg tcaccgtctc gagt 354

<210> SEQ ID NO 108
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic protein sequence

<400> SEQUENCE: 108

Glu Val Gln Leu Val Gln 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 Arg Phe Ser Ser Tyr
20 25 30

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

Ala Asn Ile Lys Pro Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
50 55 60

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

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

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

Leu Val Thr Val Ser Ser
115

<210> SEQ ID NO 109
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 109

cagtctgccc tgactcagcc tgcctccgtg tctgggtctc ctggacagtc gatcaccatc 60

ccctgcactg gaaccagcag tgacattggt acttatgact atgtctcctg gtaccaacaa 120

cacccaggca aagtccccaa agtcattatt tatgaggtca ccaatcggcc ctcaggggtt 180

-continued

tctaatcgct tctctggctc caagtctggc aacacggcct ccctgaccat ctctgggctc 240

caggctgacg acgaggctga ttattactgc aactcattta caaagaacaa cacttgggtg 300

ttcggcggag ggaccaagct gaccgtccta 330

<210> SEQ ID NO 110
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic protein sequence

<400> SEQUENCE: 110

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

Ser Ile Thr Ile Pro Cys Thr Gly Thr Ser Ser Asp Ile Gly Thr Tyr
20 25 30

Asp Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Val Pro Lys Val
35 40 45

Ile Ile Tyr Glu Val Thr Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Asp Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Phe Thr Lys Asn
85 90 95

Asn Thr Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> SEQ ID NO 111
<211> LENGTH: 354
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 111

caggtgcagc tggtggagtc tgggggaggc ttggtccagc ctgggaggtc cctgatactc 60

tcctgtgcgg tctctgggtt cacctttagt aagtattgga tgacctgggt ccgccaggct 120

ccagggaagg gactggagtg ggtggccaac ataaagccag atggaagtga gaaatactat 180

gtggagtctg tgaagggccg attcaccatc tccagagaca acgccaagaa ttcagtgtat 240

ctgcaaatga acagtgtgag agccgaagac acggccgtgt attactgtgc gagagtttcg 300

aggggtggga gcttctcgga ctggagccaa ggaaccttgg tcaccgtctc gagt 354

<210> SEQ ID NO 112
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic protein sequence

<400> SEQUENCE: 112

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

Ser Leu Ile Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Ser Lys Tyr

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20                  25                  30

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

Ala Asn Ile Lys Pro Asp Gly Ser Glu Lys Tyr Tyr Val Glu Ser Val
50                  55                  60

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

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

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

Leu Val Thr Val Ser Ser
115
```

<210> SEQ ID NO 113
<211> LENGTH: 333
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide sequence

<400> SEQUENCE: 113

```
cagtctgccc tgactcagcc tccctccgcg tccgggtctc ctgggcagtc agtcaccatc     60

tcctgcactg gaaccagcgg tgacgttggt gcttataact atgtctcctg gtaccaacag    120

tacccaggca aagcccccaa actcatgatt tatgaggtca gtaagaggcc ctccggggtc    180

cctgatcgct tctctggctc caagtctggc aacacggcct ccctgaccgt ctctgggctc    240

caggctgagg atgaggctga ttattactgc aactcatata ggggcagcaa cggtccttgg    300

gtgttcggcg gagggaccaa ggtcaccgtc cta                                 333
```

<210> SEQ ID NO 114
<211> LENGTH: 111
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic protein sequence

<400> SEQUENCE: 114

```
Gln Ser Ala Leu Thr Gln Pro Pro Ser Ala Ser Gly Ser Pro Gly Gln
1               5                   10                  15

Ser Val Thr Ile Ser Cys Thr Gly Thr Ser Gly Asp Val Gly Ala Tyr
20                  25                  30

Asn Tyr Val Ser Trp Tyr Gln Gln Tyr Pro Gly Lys Ala Pro Lys Leu
35                  40                  45

Met Ile Tyr Glu Val Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
50                  55                  60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Val Ser Gly Leu
65                  70                  75                  80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Tyr Arg Gly Ser
85                  90                  95

Asn Gly Pro Trp Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu
100                 105                 110
```

-continued

<210> SEQ ID NO 115
<211> LENGTH: 502
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic protein sequence

<400> SEQUENCE: 115

Met Gly Ser Thr Ala Ile Leu Ala Leu Leu Leu Ala Val Leu Gln Gly
1 5 10 15

Val Ser Ala His Met Ala Glu Val Gln Leu Val Glu Ser Gly Gly Gly
20 25 30

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
35 40 45

Phe Thr Phe Ser Ser Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly
50 55 60

Lys Gly Leu Glu Trp Val Ala Asn Ile Lys Pro Asp Gly Ser Glu Lys
65 70 75 80

Tyr Tyr Val Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
85 90 95

Ala Lys Asn Ser Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
100 105 110

Thr Ala Val Tyr Tyr Cys Ala Arg Val Ser Arg Gly Gly Ser Tyr Ser
115 120 125

Asp Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly
130 135 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Ser Ala Leu
145 150 155 160

Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile
165 170 175

Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Ile Tyr Val Ser
180 185 190

Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp
195 200 205

Val Ser Arg Arg Pro Ser Gly Ile Ser Asp Arg Phe Ser Gly Ser Lys
210 215 220

Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
225 230 235 240

Glu Ala Asp Tyr Tyr Cys Asn Ser Tyr Thr Thr Leu Ser Thr Trp Leu
245 250 255

Phe Gly Gly Gly Thr Lys Val Thr Val Leu Gly Ala Ala Ala Glu Pro
260 265 270

Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
275 280 285

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
290 295 300

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
305 310 315 320

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
325 330 335

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
340 345 350

-continued

```
Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
355                 360                 365

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
370                 375                 380

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
385                 390                 395                 400

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
405                 410                 415

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
420                 425                 430

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
435                 440                 445

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
450                 455                 460

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
465                 470                 475                 480

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
485                 490                 495

Ser Leu Ser Pro Gly Lys
500


<210> SEQ ID NO 116
<211> LENGTH: 508
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      protein sequence

<400> SEQUENCE: 116

Met Gly Ser Thr Ala Ile Leu Ala Leu Leu Leu Ala Val Leu Gln Gly
1               5                   10                  15

Val Ser Ala His Met Ala Glu Val Gln Leu Leu Glu Ser Gly Gly Gly
20                  25                  30

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
35                  40                  45

Phe Thr Phe Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly
50                  55                  60

Lys Gly Leu Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr
65                  70                  75                  80

Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
85                  90                  95

Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
100                 105                 110

Thr Ala Val Tyr Tyr Cys Val Lys Asp Arg Val Ala Val Ala Gly Lys
115                 120                 125

Gly Ser Tyr Tyr Phe Asp Ser Trp Gly Arg Gly Thr Thr Val Thr Val
130                 135                 140

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145                 150                 155                 160

Ser Ala Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Glu Ala Pro
165                 170                 175

Gly Gln Arg Val Thr Ile Ala Cys Ser Gly Ser Ser Ser Asn Ile Gly
180                 185                 190
```

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Asn Asn Ala Val Ser Trp Tyr Gln Gln Leu Pro Gly Lys Ala Pro Thr
195                 200                 205

Leu Leu Ile Tyr Tyr Asp Asn Leu Leu Pro Ser Gly Val Ser Asp Arg
210                 215                 220

Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly
225                 230                 235                 240

Leu Gln Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp
245                 250                 255

Ser Leu Asn Asp Trp Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu
260                 265                 270

Gly Ala Ala Ala Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro
275                 280                 285

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
290                 295                 300

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
305                 310                 315                 320

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
325                 330                 335

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
340                 345                 350

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
355                 360                 365

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
370                 375                 380

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
385                 390                 395                 400

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
405                 410                 415

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
420                 425                 430

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
435                 440                 445

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
450                 455                 460

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
465                 470                 475                 480

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
485                 490                 495

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
500                 505


<210> SEQ ID NO 117
<211> LENGTH: 506
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      protein sequence

<400> SEQUENCE: 117

Met Gly Ser Thr Ala Ile Leu Ala Leu Leu Leu Ala Val Leu Gln Gly
1               5                   10                  15

Val Ser Ala His Met Ala Gln Val Gln Leu Gln Glu Ser Gly Pro Gly
```

-continued

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20                  25                  30

Leu Val Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly
35                  40                  45

Asp Ser Val Ser Ser Asn Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser
50                  55                  60

Pro Ser Arg Gly Leu Glu Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys
65                  70                  75                  80

Trp Tyr Asn Asp Tyr Ala Val Ser Val Lys Ser Arg Met Thr Ile Lys
85                  90                  95

Ala Asp Thr Ser Lys Asn Gln Phe Ser Leu Gln Leu Asn Ser Val Thr
100                 105                 110

Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Asp Glu Gly Pro Leu
115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Gly Gly Gly
130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Ala Pro Gln
145                 150                 155                 160

Ala Val Leu Thr Gln Pro Ser Ser Val Ser Gly Ala Pro Gly Gln Arg
165                 170                 175

Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Leu Gly Thr Gly Tyr
180                 185                 190

Asp Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
195                 200                 205

Ile Tyr Gly Asn Ser Asn Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
210                 215                 220

Gly Ser Lys Ser Asp Thr Ser Gly Leu Leu Ala Ile Thr Gly Leu Gln
225                 230                 235                 240

Ala Glu Asp Glu Ala Thr Tyr Tyr Cys Gln Ser Tyr Asp Phe Ser Leu
245                 250                 255

Ser Ala Met Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu Gly Ala
260                 265                 270

Ala Ala Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
275                 280                 285

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
290                 295                 300

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
305                 310                 315                 320

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
325                 330                 335

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
340                 345                 350

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
355                 360                 365

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
370                 375                 380

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

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
405                 410                 415

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
420                 425                 430
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-continued

```
Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
435                 440                 445

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
450                 455                 460

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
465                 470                 475                 480

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
485                 490                 495

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
500                 505


<210> SEQ ID NO 118
<211> LENGTH: 227
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      protein sequence

<400> SEQUENCE: 118

Glu Phe Thr Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1               5                   10                  15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20                  25                  30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln
35                  40                  45

Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50                  55                  60

His His Ala Gln Thr Lys Pro Arg Glu Arg Gln Phe Ser Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Thr His Gln Asp Trp Leu Asn Gly
85                  90                  95

Lys Glu Tyr Thr Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile
100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
115                 120                 125

Tyr Ile Leu Pro Pro Pro Gln Glu Glu Leu Thr Lys Asn Gln Val Ser
130                 135                 140

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

Trp Glu Ser Asn Gly Gln Pro Glu Asn Thr Tyr Lys Thr Thr Pro Pro
165                 170                 175

Val Leu Asp Ser Asp Gly Ser Tyr Phe Leu Tyr Ser Lys Leu Ile Val
180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Thr Phe Ser Cys Ser Val Met
195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Val Ser
210                 215                 220

Pro Gly Lys
225


<210> SEQ ID NO 119
<211> LENGTH: 502
<212> TYPE: PRT
```

-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic protein sequence

<400> SEQUENCE: 119

Met Gly Ser Thr Ala Ile Leu Ala Leu Leu Leu Ala Val Leu Gln Gly
1 5 10 15

Val Ser Ala His Met Ala Glu Val Gln Leu Val Glu Ser Gly Gly Gly
20 25 30

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
35 40 45

Phe Thr Phe Ser Ser Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly
50 55 60

Lys Gly Leu Glu Trp Val Ala Asn Ile Lys Pro Asp Gly Ser Glu Lys
65 70 75 80

Tyr Tyr Val Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
85 90 95

Ala Lys Asn Ser Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
100 105 110

Thr Ala Val Tyr Tyr Cys Ala Arg Val Ser Arg Gly Gly Ser Tyr Ser
115 120 125

Asp Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly
130 135 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Ser Ala Leu
145 150 155 160

Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile
165 170 175

Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Ile Tyr Val Ser
180 185 190

Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp
195 200 205

Val Ser Arg Arg Pro Ser Gly Ile Ser Asp Arg Phe Ser Gly Ser Lys
210 215 220

Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
225 230 235 240

Glu Ala Asp Tyr Tyr Cys Asn Ser Tyr Thr Thr Leu Ser Thr Trp Leu
245 250 255

Phe Gly Gly Gly Thr Lys Val Thr Val Leu Gly Ala Ala Ala Glu Pro
260 265 270

Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
275 280 285

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
290 295 300

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
305 310 315 320

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
325 330 335

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ser
340 345 350

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
355 360 365

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Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
370                 375                 380

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
385                 390                 395                 400

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
405                 410                 415

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
420                 425                 430

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
435                 440                 445

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
450                 455                 460

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
465                 470                 475                 480

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
485                 490                 495

Ser Leu Ser Pro Gly Lys
500


<210> SEQ ID NO 120
<211> LENGTH: 508
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      protein sequence

<400> SEQUENCE: 120

Met Gly Ser Thr Ala Ile Leu Ala Leu Leu Leu Ala Val Leu Gln Gly
1               5                   10                  15

Val Ser Ala His Met Ala Glu Val Gln Leu Leu Glu Ser Gly Gly Gly
20                  25                  30

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
35                  40                  45

Phe Thr Phe Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly
50                  55                  60

Lys Gly Leu Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr
65                  70                  75                  80

Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
85                  90                  95

Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
100                 105                 110

Thr Ala Val Tyr Tyr Cys Val Lys Asp Arg Val Ala Val Ala Gly Lys
115                 120                 125

Gly Ser Tyr Tyr Phe Asp Ser Trp Gly Arg Gly Thr Thr Val Thr Val
130                 135                 140

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145                 150                 155                 160

Ser Ala Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Glu Ala Pro
165                 170                 175

Gly Gln Arg Val Thr Ile Ala Cys Ser Gly Ser Ser Ser Asn Ile Gly
180                 185                 190

Asn Asn Ala Val Ser Trp Tyr Gln Gln Leu Pro Gly Lys Ala Pro Thr
195                 200                 205
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Leu Leu Ile Tyr Tyr Asp Asn Leu Leu Pro Ser Gly Val Ser Asp Arg
210                 215                 220

Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly
225                 230                 235                 240

Leu Gln Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp
245                 250                 255

Ser Leu Asn Asp Trp Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu
260                 265                 270

Gly Ala Ala Ala Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro
275                 280                 285

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
290                 295                 300

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
305                 310                 315                 320

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
325                 330                 335

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
340                 345                 350

Arg Glu Glu Gln Tyr Ser Ser Thr Tyr Arg Val Val Ser Val Leu Thr
355                 360                 365

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
370                 375                 380

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
385                 390                 395                 400

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
405                 410                 415

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
420                 425                 430

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
435                 440                 445

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
450                 455                 460

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
465                 470                 475                 480

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
485                 490                 495

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
500                 505


<210> SEQ ID NO 121
<211> LENGTH: 506
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      protein sequence

<400> SEQUENCE: 121

Met Gly Ser Thr Ala Ile Leu Ala Leu Leu Leu Ala Val Leu Gln Gly
1               5                   10                  15

Val Ser Ala His Met Ala Gln Val Gln Leu Gln Glu Ser Gly Pro Gly
20                  25                  30

Leu Val Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly
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35                  40                  45

Asp Ser Val Ser Ser Asn Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser
50                  55                  60

Pro Ser Arg Gly Leu Glu Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys
65                  70                  75                  80

Trp Tyr Asn Asp Tyr Ala Val Ser Val Lys Ser Arg Met Thr Ile Lys
85                  90                  95

Ala Asp Thr Ser Lys Asn Gln Phe Ser Leu Gln Leu Asn Ser Val Thr
100                 105                 110

Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Asp Glu Gly Pro Leu
115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Gly Gly Gly
130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Ala Pro Gln
145                 150                 155                 160

Ala Val Leu Thr Gln Pro Ser Ser Val Ser Gly Ala Pro Gly Gln Arg
165                 170                 175

Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Leu Gly Thr Gly Tyr
180                 185                 190

Asp Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
195                 200                 205

Ile Tyr Gly Asn Ser Asn Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
210                 215                 220

Gly Ser Lys Ser Asp Thr Ser Gly Leu Leu Ala Ile Thr Gly Leu Gln
225                 230                 235                 240

Ala Glu Asp Glu Ala Thr Tyr Tyr Cys Gln Ser Tyr Asp Phe Ser Leu
245                 250                 255

Ser Ala Met Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu Gly Ala
260                 265                 270

Ala Ala Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
275                 280                 285

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
290                 295                 300

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
305                 310                 315                 320

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
325                 330                 335

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
340                 345                 350

Glu Gln Tyr Ser Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
355                 360                 365

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
370                 375                 380

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

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
405                 410                 415

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
420                 425                 430

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
435                 440                 445
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Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
450                 455                 460

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
465                 470                 475                 480

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
485                 490                 495

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
500                 505


<210> SEQ ID NO 122
<211> LENGTH: 496
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      protein sequence

<400> SEQUENCE: 122

Met Gly Ser Thr Ala Ile Leu Ala Leu Leu Leu Ala Val Leu Gln Gly
1               5                   10                  15

Val Ser Ala His Met Ala Glu Val Gln Leu Val Glu Ser Gly Gly Gly
20                  25                  30

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
35                  40                  45

Phe Thr Phe Ser Ser Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly
50                  55                  60

Lys Gly Leu Glu Trp Val Ala Asn Ile Lys Pro Asp Gly Ser Glu Lys
65                  70                  75                  80

Tyr Tyr Val Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
85                  90                  95

Ala Lys Asn Ser Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
100                 105                 110

Thr Ala Val Tyr Tyr Cys Ala Arg Val Ser Arg Gly Gly Ser Tyr Ser
115                 120                 125

Asp Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly
130                 135                 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Ser Ala Leu
145                 150                 155                 160

Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile
165                 170                 175

Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Ile Tyr Val Ser
180                 185                 190

Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp
195                 200                 205

Val Ser Arg Arg Pro Ser Gly Ile Ser Asp Arg Phe Ser Gly Ser Lys
210                 215                 220

Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
225                 230                 235                 240

Glu Ala Asp Tyr Tyr Cys Asn Ser Tyr Thr Thr Leu Ser Thr Trp Leu
245                 250                 255

Phe Gly Gly Gly Thr Lys Val Thr Val Leu Ala Ala Ala Glu Phe Thr
260                 265                 270

Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
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275                 280                 285

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
290                 295                 300

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro
305                 310                 315                 320

Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His His Ala
325                 330                 335

Gln Thr Lys Pro Arg Glu Arg Gln Phe Ser Ser Thr Tyr Arg Val Val
340                 345                 350

Ser Val Leu Thr Val Thr His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
355                 360                 365

Thr Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr
370                 375                 380

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Ile Leu
385                 390                 395                 400

Pro Pro Pro Gln Glu Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
405                 410                 415

Leu Val Thr Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
420                 425                 430

Asn Gly Gln Pro Glu Asn Thr Tyr Lys Thr Thr Pro Pro Val Leu Asp
435                 440                 445

Ser Asp Gly Ser Tyr Phe Leu Tyr Ser Lys Leu Ile Val Asp Lys Ser
450                 455                 460

Arg Trp Gln Gln Gly Asn Thr Phe Ser Cys Ser Val Met His Glu Ala
465                 470                 475                 480

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Val Ser Pro Gly Lys
485                 490                 495


<210> SEQ ID NO 123
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide

<400> SEQUENCE: 123

Asp Tyr Ala Met His
1               5


<210> SEQ ID NO 124
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide

<400> SEQUENCE: 124

Val Ile Ser Asn His Gly Lys Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1               5                   10                  15

Gly


<210> SEQ ID NO 125
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
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-continued

<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 125

Asp Ile Ala Leu Ala Gly Asp Tyr
1 5

<210> SEQ ID NO 126
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 126

Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn
1 5 10

<210> SEQ ID NO 127
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 127

Gly Ala Ser Lys Leu Gln Ser
1 5

<210> SEQ ID NO 128
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 128

Leu Gln Asp Tyr Asn Tyr Pro Leu Thr
1 5

<210> SEQ ID NO 129
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 129

Ser Ser Asn Trp Trp Ser
1 5

<210> SEQ ID NO 130
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 130

-continued

Glu Ile Ser Gln Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys Gly
1 5 10 15

<210> SEQ ID NO 131
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 131

Gln Leu Arg Ser Ile Asp Ala Phe Asp Ile
1 5 10

<210> SEQ ID NO 132
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 132

Asp Lys Tyr Ala Ser
1 5

<210> SEQ ID NO 133
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 133

Tyr Gln Asp Arg Lys Arg Pro Ser Gly Ile
1 5 10

<210> SEQ ID NO 134
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 134

Trp Asp Ser Asp Thr Ser Tyr Val
1 5

<210> SEQ ID NO 135
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 135

Asn Tyr Tyr Trp Ser
1 5

<210> SEQ ID NO 136
<211> LENGTH: 17

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 136

Tyr Ile His Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

Arg

<210> SEQ ID NO 137
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 137

Gln Gly Asp Asn Leu Arg Ser Tyr Ser Ala Thr
1 5 10

<210> SEQ ID NO 138
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 138

Gly Glu Asn Asn Arg Pro Ser
1 5

<210> SEQ ID NO 139
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 139

Thr Ser Arg Val Asn Ser Gly Asn His Leu Gly Val
1 5 10

<210> SEQ ID NO 140
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 140

Gly Tyr Tyr Met His
1 5

<210> SEQ ID NO 141
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

-continued

peptide

<400> SEQUENCE: 141

Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly Arg

<210> SEQ ID NO 142
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 142

Gly Gly His Met Thr Thr Val Thr Arg Asp Ala Phe Asp Ile
1 5 10

<210> SEQ ID NO 143
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 143

Gln Gly Asp Ser Leu Arg Tyr Tyr Tyr Ala Thr
1 5 10

<210> SEQ ID NO 144
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 144

Gly Gln Asn Asn Arg Pro Ser
1 5

<210> SEQ ID NO 145
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 145

Gly Thr Trp Asp Ser Ser Val Ser Ala Ser Trp Val
1 5 10

<210> SEQ ID NO 146
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 146

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Gly Tyr Tyr Met His
1 5

<210> SEQ ID NO 147
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 147

Trp Ile Asn Pro Asn Ser Gly Ser Thr Asn Tyr Ala Gln Lys Phe Leu
1 5 10 15

Gly

<210> SEQ ID NO 148
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 148

Gly His Ser Gly Asp Tyr Phe Asp Tyr
1 5

<210> SEQ ID NO 149
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 149

Arg Ala Ser Gln Ser Val Ser Ser Trp Leu Ala
1 5 10

<210> SEQ ID NO 150
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 150

Ala Ala Arg Leu Arg Gly
1 5

<210> SEQ ID NO 151
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 151

Gln Gln Ser Tyr Ser Thr Pro Ile Ser
1 5

-continued

<210> SEQ ID NO 152
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 152

Ser Ser Ala Phe Ser Trp Asn
1 5

<210> SEQ ID NO 153
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 153

Tyr Ile Tyr His Thr Gly Ile Thr Asp Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> SEQ ID NO 154
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 154

Gly His Gly Ser Asp Pro Ala Trp Phe Asp Pro
1 5 10

<210> SEQ ID NO 155
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 155

Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala Ser
1 5 10

<210> SEQ ID NO 156
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 156

Arg Asp Thr Lys Arg Pro Ser
1 5

<210> SEQ ID NO 157
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

-continued

peptide

<400> SEQUENCE: 157

Gln Ala Trp Asp Ser Thr Thr Ser Leu Val
1 5 10

<210> SEQ ID NO 158
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 158

Ser Tyr Trp Met Ser
1 5

<210> SEQ ID NO 159
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 159

Asn Ile Lys Pro Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 160
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 160

Val Ser Arg Gly Gly Ser Tyr Ser Asp
1 5

<210> SEQ ID NO 161
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 161

Thr Gly Thr Ser Ser Asp Val Gly Gly Phe Asn Tyr Val Ser
1 5 10

<210> SEQ ID NO 162
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 162

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Glu Val Ser Lys Arg Pro Ser
1 5

<210> SEQ ID NO 163
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 163

Ser Ser Trp Ala Pro Gly Lys Asn Leu
1 5

<210> SEQ ID NO 164
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 164

Ser Tyr Ala Met Ser
1 5

<210> SEQ ID NO 165
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 165

Gly Ile Ser Gly Ser Gly Ser Ser Glu Gly Gly Thr Tyr Tyr Ala Asp
1 5 10 15

Ser Val Lys Gly
20

<210> SEQ ID NO 166
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 166

Asp Arg Pro Ser Arg Tyr Ser Phe Gly Tyr Tyr Phe Asp Tyr
1 5 10

<210> SEQ ID NO 167
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 167

Ser Gly Asn Lys Leu Gly Asp Lys Tyr Val Ser
1 5 10

-continued

<210> SEQ ID NO 168
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 168

Gln Asp Thr Lys Arg Pro Ser
1 5

<210> SEQ ID NO 169
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 169

Gln Ala Trp Asp Ser Ser Thr Asp Val Val
1 5 10

<210> SEQ ID NO 170
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 170

Lys Tyr Trp Met Thr
1 5

<210> SEQ ID NO 171
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 171

Asn Ile Lys Pro Asp Gly Ser Glu Lys Tyr Tyr Val Glu Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 172
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 172

Val Ser Arg Gly Gly Ser Phe Ser Asp
1 5

<210> SEQ ID NO 173
<211> LENGTH: 14
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 173

Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser
1 5 10

<210> SEQ ID NO 174
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 174

Asp Val Asn Lys Arg Pro Ser
1 5

<210> SEQ ID NO 175
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 175

Asn Ser Tyr Ala Gly Ser Asn Asn Trp Val
1 5 10

<210> SEQ ID NO 176
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 176

Lys Tyr Trp Met Thr
1 5

<210> SEQ ID NO 177
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 177

Asn Ile Lys Pro Asp Gly Ser Glu Lys Tyr Tyr Val Glu Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 178
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

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<400> SEQUENCE: 178

Val Ser Arg Gly Gly Ser Phe Ser Asp
1 5

<210> SEQ ID NO 179
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 179

Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser
1 5 10

<210> SEQ ID NO 180
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 180

Glu Val Ser Lys Arg Pro Ser
1 5

<210> SEQ ID NO 181
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 181

Asn Ser Tyr Ala Gly Ser Ile Tyr Val
1 5

<210> SEQ ID NO 182
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 182

Thr Asn Asp Ile His
1 5

<210> SEQ ID NO 183
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 183

Ile Ile Asp Thr Ser Gly Ala Met Thr Arg Tyr Ala Gln Lys Phe Gln
1 5 10 15

-continued

Gly

<210> SEQ ID NO 184
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 184

Glu Gly Cys Thr Asn Gly Val Cys Tyr Asp Asn Gly Phe Asp Ile
1 5 10 15

<210> SEQ ID NO 185
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 185

Arg Ala Ser Glu Gly Ile Tyr His Trp Leu Ala
1 5 10

<210> SEQ ID NO 186
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 186

Lys Ala Ser Ser Leu Ala Ser
1 5

<210> SEQ ID NO 187
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 187

Gln Gln Tyr Ser Asn Tyr Pro Leu Thr
1 5

<210> SEQ ID NO 188
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 188

Lys Tyr Trp Met Thr
1 5

<210> SEQ ID NO 189
<211> LENGTH: 17
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 189

Asn Ile Lys Pro Asp Gly Ser Glu Lys Tyr Tyr Val Glu Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 190
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 190

Val Ser Arg Gly Gly Ser Phe Ser Asp
1 5

<210> SEQ ID NO 191
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 191

Thr Gly Thr Ser Ser Asp Val Gly Ser Tyr Asn Leu Val Ser
1 5 10

<210> SEQ ID NO 192
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 192

Glu Val Ser Asn Arg Pro Ser
1 5

<210> SEQ ID NO 193
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 193

Ser Ser Leu Thr Ser Ser Gly Thr Trp Val
1 5 10

<210> SEQ ID NO 194
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

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<400> SEQUENCE: 194

Lys Tyr Trp Met Thr
1 5

<210> SEQ ID NO 195
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 195

Asn Ile Lys Pro Asp Gly Ser Glu Lys Tyr Tyr Val Glu Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 196
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 196

Val Ser Arg Gly Gly Ser Phe Ser Asp
1 5

<210> SEQ ID NO 197
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 197

Thr Gly Thr Ser Ser Asp Val Gly Ala Tyr Asn Tyr Val Ser
1 5 10

<210> SEQ ID NO 198
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 198

Glu Val Ala Arg Arg Pro Ser
1 5

<210> SEQ ID NO 199
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 199

Ser Ser Tyr Ala Gly Ser Asn Asn Phe Ala Val

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1 5 10

<210> SEQ ID NO 200
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 200

Ser Tyr Trp Met Thr
1 5

<210> SEQ ID NO 201
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 201

Asn Ile Lys Pro Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 202
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 202

Val Ser Arg Gly Gly Ser Phe Ser Asp
1 5

<210> SEQ ID NO 203
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 203

Thr Gly Thr Ser Ser Asp Ile Gly Thr Tyr Asp Tyr Val Ser
1 5 10

<210> SEQ ID NO 204
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 204

Glu Val Thr Asn Arg Pro Ser
1 5

<210> SEQ ID NO 205

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<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 205

Asn Ser Phe Thr Lys Asn Asn Thr Trp Val
1 5 10

<210> SEQ ID NO 206
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 206

Lys Tyr Trp Met Thr
1 5

<210> SEQ ID NO 207
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 207

Asn Ile Lys Pro Asp Gly Ser Glu Lys Tyr Tyr Val Glu Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 208
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 208

Val Ser Arg Gly Gly Ser Phe Ser Asp
1 5

<210> SEQ ID NO 209
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 209

Thr Gly Thr Ser Gly Asp Val Gly Ala Tyr Asn Tyr Val Ser
1 5 10

<210> SEQ ID NO 210
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 210

Glu Val Ser Lys Arg Pro Ser
1 5

<210> SEQ ID NO 211
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 211

Asn Ser Tyr Arg Gly Ser Asn Gly Pro Trp Val
1 5 10

<210> SEQ ID NO 212
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 212

Val Gly Tyr Tyr Tyr Asp Ser Ser Gly Tyr Asn Leu Ala Trp Tyr Phe
1 5 10 15

Asp Leu

<210> SEQ ID NO 213
<211> LENGTH: 508
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 213

Met Asp His Leu Gly Ala Ser Leu Trp Pro Gln Val Gly Ser Leu Cys
1 5 10 15

Leu Leu Leu Ala Gly Ala Ala Trp Ala Pro Pro Pro Asn Leu Pro Asp
20 25 30

Pro Lys Phe Glu Ser Lys Ala Ala Leu Leu Ala Ala Arg Gly Pro Glu
35 40 45

Glu Leu Leu Cys Phe Thr Glu Arg Leu Glu Asp Leu Val Cys Phe Trp
50 55 60

Glu Glu Ala Ala Ser Ala Gly Val Gly Pro Gly Asn Tyr Ser Phe Ser
65 70 75 80

Tyr Gln Leu Glu Asp Glu Pro Trp Lys Leu Cys Arg Leu His Gln Ala
85 90 95

Pro Thr Ala Arg Gly Ala Val Arg Phe Trp Cys Ser Leu Pro Thr Ala
100 105 110

Asp Thr Ser Ser Phe Val Pro Leu Glu Leu Arg Val Thr Ala Ala Ser
115 120 125

Gly Ala Pro Arg Tyr His Arg Val Ile His Ile Asn Glu Val Val Leu
130 135 140

Leu Asp Ala Pro Val Gly Leu Val Ala Arg Leu Ala Asp Glu Ser Gly
145 150 155 160

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His Val Val Leu Arg Trp Leu Pro Pro Pro Glu Thr Pro Met Thr Ser
165                 170                 175

His Ile Arg Tyr Glu Val Asp Val Ser Ala Gly Asn Gly Ala Gly Ser
180                 185                 190

Val Gln Arg Val Glu Ile Leu Glu Gly Arg Thr Glu Cys Val Leu Ser
195                 200                 205

Asn Leu Arg Gly Arg Thr Arg Tyr Thr Phe Ala Val Arg Ala Arg Met
210                 215                 220

Ala Glu Pro Ser Phe Gly Gly Phe Trp Ser Ala Trp Ser Glu Pro Val
225                 230                 235                 240

Ser Leu Leu Thr Pro Ser Asp Leu Asp Pro Leu Ile Leu Thr Leu Ser
245                 250                 255

Leu Ile Leu Val Val Ile Leu Val Leu Leu Thr Val Leu Ala Leu Leu
260                 265                 270

Ser His Arg Arg Ala Leu Lys Gln Lys Ile Trp Pro Gly Ile Pro Ser
275                 280                 285

Pro Glu Ser Glu Phe Glu Gly Leu Phe Thr Thr His Lys Gly Asn Phe
290                 295                 300

Gln Leu Trp Leu Tyr Gln Asn Asp Gly Cys Leu Trp Trp Ser Pro Cys
305                 310                 315                 320

Thr Pro Phe Thr Glu Asp Pro Pro Ala Ser Leu Glu Val Leu Ser Glu
325                 330                 335

Arg Cys Trp Gly Thr Met Gln Ala Val Glu Pro Gly Thr Asp Asp Glu
340                 345                 350

Gly Pro Leu Leu Glu Pro Val Gly Ser Glu His Ala Gln Asp Thr Tyr
355                 360                 365

Leu Val Leu Asp Lys Trp Leu Leu Pro Arg Asn Pro Pro Ser Glu Asp
370                 375                 380

Leu Pro Gly Pro Gly Gly Ser Val Asp Ile Val Ala Met Asp Glu Gly
385                 390                 395                 400

Ser Glu Ala Ser Ser Cys Ser Ser Ala Leu Ala Ser Lys Pro Ser Pro
405                 410                 415

Glu Gly Ala Ser Ala Ala Ser Phe Glu Tyr Thr Ile Leu Asp Pro Ser
420                 425                 430

Ser Gln Leu Leu Arg Pro Trp Thr Leu Cys Pro Glu Leu Pro Pro Thr
435                 440                 445

Pro Pro His Leu Lys Tyr Leu Tyr Leu Val Val Ser Asp Ser Gly Ile
450                 455                 460

Ser Thr Asp Tyr Ser Ser Gly Asp Ser Gln Gly Ala Gln Gly Gly Leu
465                 470                 475                 480

Ser Asp Gly Pro Tyr Ser Asn Pro Tyr Glu Asn Ser Leu Ile Pro Ala
485                 490                 495

Ala Glu Pro Leu Pro Pro Ser Tyr Val Ala Cys Ser
500                 505


<210> SEQ ID NO 214
<211> LENGTH: 226
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 214

Ala Pro Pro Pro Asn Leu Pro Asp Pro Lys Phe Glu Ser Lys Ala Ala
1               5                   10                  15
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Leu Leu Ala Ala Arg Gly Pro Glu Glu Leu Leu Cys Phe Thr Glu Arg
20                  25                  30

Leu Glu Asp Leu Val Cys Phe Trp Glu Glu Ala Ala Ser Ala Gly Val
35                  40                  45

Gly Pro Gly Asn Tyr Ser Phe Ser Tyr Gln Leu Glu Asp Glu Pro Trp
50                  55                  60

Lys Leu Cys Arg Leu His Gln Ala Pro Thr Ala Arg Gly Ala Val Arg
65                  70                  75                  80

Phe Trp Cys Ser Leu Pro Thr Ala Asp Thr Ser Ser Phe Val Pro Leu
85                  90                  95

Glu Leu Arg Val Thr Ala Ala Ser Gly Ala Pro Arg Tyr His Arg Val
100                 105                 110

Ile His Ile Asn Glu Val Val Leu Leu Asp Ala Pro Val Gly Leu Val
115                 120                 125

Ala Arg Leu Ala Asp Glu Ser Gly His Val Val Leu Arg Trp Leu Pro
130                 135                 140

Pro Pro Glu Thr Pro Met Thr Ser His Ile Arg Tyr Glu Val Asp Val
145                 150                 155                 160

Ser Ala Gly Asn Gly Ala Gly Ser Val Gln Arg Val Glu Ile Leu Glu
165                 170                 175

Gly Arg Thr Glu Cys Val Leu Ser Asn Leu Arg Gly Arg Thr Arg Tyr
180                 185                 190

Thr Phe Ala Val Arg Ala Arg Met Ala Glu Pro Ser Phe Gly Gly Phe
195                 200                 205

Trp Ser Ala Trp Ser Glu Pro Val Ser Leu Leu Thr Pro Ser Asp Leu
210                 215                 220

Asp Pro
225


<210> SEQ ID NO 215
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Variable amino acid

<400> SEQUENCE: 215

Asn Ile Lys Pro Asp Gly Ser Glu Lys Tyr Val Xaa Ser Val Lys Gly
1               5                   10                  15


<210> SEQ ID NO 216
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Variable amino acid

<400> SEQUENCE: 216
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Val Ser Arg Gly Gly Ser Xaa Ser Asp
1 5

<210> SEQ ID NO 217
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Variable amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Variable amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: Variable amino acid

<400> SEQUENCE: 217

Thr Gly Thr Ser Ser Asp Xaa Gly Xaa Tyr Xaa Tyr Val Ser
1 5 10

<210> SEQ ID NO 218
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Variable amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (3)..(4)
<223> OTHER INFORMATION: Variable amino acid

<400> SEQUENCE: 218

Xaa Val Xaa Xaa Arg Pro Ser
1 5

<210> SEQ ID NO 219
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 219

cgggaggagc agtacagcag cacgtaccgt gtg 33

<210> SEQ ID NO 220
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 220

cacacggtac gtgctgctgt actgctcctc ccg 33

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<210> SEQ ID NO 221
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 221

gggagaggca gttcagcagc acgtaccgcg 30

<210> SEQ ID NO 222
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 222

cgcggtacgt gctgctgaac tgcctctccc 30

<210> SEQ ID NO 223
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 223

gactgcaagc ttgacaccat ggggtcaacc gcc 33

<210> SEQ ID NO 224
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 224

gcatacggat cctcatttac ccggagacag 30

<210> SEQ ID NO 225
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 225

catgggggtg tgaactctgc ggccgctagg acgg 34

<210> SEQ ID NO 226
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 226

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ccgtcctagc ggccgcagag ttcacacccc catg 34

<210> SEQ ID NO 227
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 227

gcatcaggat cctcatttac ccggagacac 30

<210> SEQ ID NO 228
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Asp or Glu

<400> SEQUENCE: 228

Asn Ile Lys Pro Asp Gly Ser Glu Lys Tyr Val Xaa Ser Val Lys Gly
1 5 10 15

<210> SEQ ID NO 229
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Phe or Tyr

<400> SEQUENCE: 229

Val Ser Arg Gly Gly Ser Xaa Ser Asp
1 5

<210> SEQ ID NO 230
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Val or Ile
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Gly, Ala, Thr or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: Asn, Asp or Ile

<400> SEQUENCE: 230

Thr Gly Thr Ser Ser Asp Xaa Gly Xaa Tyr Xaa Tyr Val Ser

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1 5 10

<210> SEQ ID NO 231
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Asp or Glu
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Asn, Ser, Ala or Thr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Lys, Asn or Arg

<400> SEQUENCE: 231

Xaa Val Xaa Xaa Arg Pro Ser
1 5

<210> SEQ ID NO 232
<211> LENGTH: 63
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 232

Asn Tyr Tyr Trp Ser Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala
1 5 10 15

Ala Tyr Ile His Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser Leu Lys
20 25 30

Ser Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Val Gly Tyr
35 40 45

Tyr Tyr Asp Ser Ser Gly Tyr Asn Leu Ala Trp Tyr Phe Asp Leu
50 55 60

<210> SEQ ID NO 233
<211> LENGTH: 57
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 233

Ser Ser Ala Phe Ser Trp Asn Gly Gly Gly Ala Ala Ala Gly Gly Gly
1 5 10 15

Ala Ala Ala Tyr Ile Tyr His Thr Gly Ile Thr Asp Asn Pro Ser Leu
20 25 30

Lys Ser Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Gly His
35 40 45

Gly Ser Asp Pro Ala Trp Phe Asp Pro
50 55

<210> SEQ ID NO 234

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<211> LENGTH: 55
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 234

Ser Ser Asn Trp Trp Ser Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala
1 5 10 15

Ala Ala Glu Ile Ser Gln Ser Gly Ser Thr Asn Asn Pro Ser Leu Lys
20 25 30

Gly Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Gln Leu Arg
35 40 45

Ser Ile Asp Ala Phe Asp Ile
50 55

<210> SEQ ID NO 235
<211> LENGTH: 54
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 235

Lys Tyr Trp Met Thr Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala
1 5 10 15

Ala Asn Ile Lys Pro Asp Gly Ser Glu Lys Tyr Val Glu Ser Val Lys
20 25 30

Gly Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Val Ser Arg
35 40 45

Gly Gly Ser Phe Ser Asp
50

<210> SEQ ID NO 236
<211> LENGTH: 54
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 236

Lys Tyr Trp Met Thr Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala
1 5 10 15

Ala Asn Ile Lys Pro Asp Gly Ser Glu Lys Tyr Val Glu Ser Val Lys
20 25 30

Gly Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Val Ser Arg
35 40 45

Gly Gly Ser Phe Ser Asp
50

<210> SEQ ID NO 237
<211> LENGTH: 54
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

-continued

<400> SEQUENCE: 237

Lys Tyr Trp Met Thr Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala
1 5 10 15

Ala Asn Ile Lys Pro Asp Gly Ser Glu Lys Tyr Val Glu Ser Val Lys
20 25 30

Gly Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Val Ser Arg
35 40 45

Gly Gly Ser Phe Ser Asp
50

<210> SEQ ID NO 238
<211> LENGTH: 54
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 238

Lys Tyr Trp Met Thr Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala
1 5 10 15

Ala Asn Ile Lys Pro Asp Gly Ser Glu Lys Tyr Val Glu Ser Val Lys
20 25 30

Gly Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Val Ser Arg
35 40 45

Gly Gly Ser Phe Ser Asp
50

<210> SEQ ID NO 239
<211> LENGTH: 54
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 239

Lys Tyr Trp Met Thr Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala
1 5 10 15

Ala Asn Ile Lys Pro Asp Gly Ser Glu Lys Tyr Val Glu Ser Val Lys
20 25 30

Gly Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Val Ser Arg
35 40 45

Gly Gly Ser Phe Ser Asp
50

<210> SEQ ID NO 240
<211> LENGTH: 54
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 240

Ser Tyr Trp Met Ser Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala
1 5 10 15

Ala Asn Ile Lys Pro Asp Gly Ser Glu Lys Tyr Val Asp Ser Val Lys
20 25 30

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Gly Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Val Ser Arg
35 40 45

Gly Gly Ser Tyr Ser Asp
50

<210> SEQ ID NO 241
<211> LENGTH: 54
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 241

Ser Tyr Trp Met Ser Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala
1 5 10 15

Ala Asn Ile Lys Pro Asp Gly Ser Glu Lys Tyr Val Asp Ser Val Lys
20 25 30

Gly Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Val Ser Arg
35 40 45

Gly Gly Ser Tyr Ser Asp
50

<210> SEQ ID NO 242
<211> LENGTH: 54
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 242

Ser Tyr Trp Met Ser Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala
1 5 10 15

Ala Asn Ile Lys Pro Asp Gly Ser Glu Lys Tyr Val Asp Ser Val Lys
20 25 30

Gly Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Val Ser Arg
35 40 45

Gly Gly Ser Tyr Ser Asp
50

<210> SEQ ID NO 243
<211> LENGTH: 54
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 243

Ser Tyr Trp Met Ser Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala
1 5 10 15

Ala Asn Ile Lys Pro Asp Gly Ser Glu Lys Tyr Val Asp Ser Val Lys
20 25 30

Gly Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Val Ser Arg
35 40 45

Gly Gly Ser Tyr Ser Asp
50

-continued

<210> SEQ ID NO 244
<211> LENGTH: 54
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 244

Ser Tyr Trp Met Thr Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala
1 5 10 15

Ala Asn Ile Lys Pro Asp Gly Ser Glu Lys Tyr Val Asp Ser Val Lys
20 25 30

Gly Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Val Ser Arg
35 40 45

Gly Gly Ser Phe Ser Asp
50

<210> SEQ ID NO 245
<211> LENGTH: 53
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 245

Asp Tyr Ala Met His Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala
1 5 10 15

Ala Val Ile Ser Asn His Gly Lys Ser Thr Tyr Ala Asp Ser Val Lys
20 25 30

Gly Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Asp Ile Ala
35 40 45

Leu Ala Gly Asp Tyr
50

<210> SEQ ID NO 246
<211> LENGTH: 60
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 246

Ser Tyr Ala Met Ser Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala
1 5 10 15

Ala Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Ala Asp Ser Val Lys
20 25 30

Gly Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Asp Arg Val
35 40 45

Ala Val Ala Gly Lys Gly Ser Tyr Tyr Phe Asp Ser
50 55 60

<210> SEQ ID NO 247
<211> LENGTH: 62
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

-continued

polypeptide

<400> SEQUENCE: 247

Ser Tyr Ala Met Ser Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala
1 5 10 15

Ala Gly Ile Ser Gly Ser Gly Ser Ser Glu Gly Gly Thr Tyr Ala Asp
20 25 30

Ser Val Lys Gly Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala
35 40 45

Asp Arg Pro Ser Arg Tyr Ser Phe Gly Tyr Tyr Phe Asp Tyr
50 55 60

<210> SEQ ID NO 248
<211> LENGTH: 59
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 248

Gly Tyr Tyr Met His Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala
1 5 10 15

Ala Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Ala Gln Lys Phe Gln
20 25 30

Gly Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Gly Gly His
35 40 45

Met Thr Thr Val Thr Arg Asp Ala Phe Asp Ile
50 55

<210> SEQ ID NO 249
<211> LENGTH: 54
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 249

Gly Tyr Tyr Met His Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala
1 5 10 15

Ala Trp Ile Asn Pro Asn Ser Gly Ser Thr Asn Ala Gln Lys Phe Leu
20 25 30

Gly Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Gly His Ser
35 40 45

Gly Asp Tyr Phe Asp Tyr
50

<210> SEQ ID NO 250
<211> LENGTH: 60
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 250

Thr Asn Asp Ile His Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala
1 5 10 15

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Ala Ile Ile Asp Thr Ser Gly Ala Met Thr Arg Ala Gln Lys Phe Gln
20                  25                  30

Gly Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Glu Gly Cys
35                  40                  45

Thr Asn Gly Val Cys Tyr Asp Asn Gly Phe Asp Ile
50                  55                  60


<210> SEQ ID NO 251
<211> LENGTH: 55
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 251

Ser Asn Ser Ala Ala Trp Asn Gly Gly Gly Ala Ala Ala Gly Gly Gly
1               5                   10                  15

Ala Ala Ala Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Ala Val
20                  25                  30

Ser Val Lys Ser Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala
35                  40                  45

Asp Glu Gly Pro Leu Asp Tyr
50                  55


<210> SEQ ID NO 252
<211> LENGTH: 51
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 252

Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn Gly Gly Gly Ala Ala
1               5                   10                  15

Ala Gly Gly Gly Ala Ala Ala Gly Ala Ser Lys Leu Gln Ser Gly Gly
20                  25                  30

Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Leu Gln Asp Tyr Asn Tyr
35                  40                  45

Pro Leu Thr
50


<210> SEQ ID NO 253
<211> LENGTH: 50
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 253

Arg Ala Ser Gln Ser Val Ser Ser Trp Leu Ala Gly Gly Gly Ala Ala
1               5                   10                  15

Ala Gly Gly Gly Ala Ala Ala Ala Ala Arg Leu Arg Gly Gly Gly Gly
20                  25                  30

Ala Ala Ala Gly Gly Gly Ala Ala Ala Gln Gln Ser Tyr Ser Thr Pro
35                  40                  45

Ile Ser
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50

<210> SEQ ID NO 254
<211> LENGTH: 51
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 254

Arg Ala Ser Glu Gly Ile Tyr His Trp Leu Ala Gly Gly Gly Ala Ala
1 5 10 15

Ala Gly Gly Gly Ala Ala Ala Lys Ala Ser Ser Leu Ala Ser Gly Gly
20 25 30

Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Gln Gln Tyr Ser Asn Tyr
35 40 45

Pro Leu Thr
50

<210> SEQ ID NO 255
<211> LENGTH: 54
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 255

Gln Gly Asp Asn Leu Arg Ser Tyr Ser Ala Thr Gly Gly Gly Ala Ala
1 5 10 15

Ala Gly Gly Gly Ala Ala Ala Gly Glu Asn Asn Arg Pro Ser Gly Gly
20 25 30

Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Thr Ser Arg Val Asn Ser
35 40 45

Gly Asn His Leu Gly Val
50

<210> SEQ ID NO 256
<211> LENGTH: 54
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 256

Gln Gly Asp Ser Leu Arg Tyr Tyr Tyr Ala Thr Gly Gly Gly Ala Ala
1 5 10 15

Ala Gly Gly Gly Ala Ala Ala Gly Gln Asn Asn Arg Pro Ser Gly Gly
20 25 30

Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Gly Thr Trp Asp Ser Ser
35 40 45

Val Ser Ala Ser Trp Val
50

<210> SEQ ID NO 257
<211> LENGTH: 55
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 257

Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Gly Gly
1 5 10 15

Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Asp Val Asn Lys Arg Pro
20 25 30

Ser Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Asn Ser Tyr
35 40 45

Ala Gly Ser Asn Asn Trp Val
50 55

<210> SEQ ID NO 258
<211> LENGTH: 54
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 258

Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Gly Gly
1 5 10 15

Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Glu Val Ser Lys Arg Pro
20 25 30

Ser Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Ser Ser Tyr
35 40 45

Ala Gly Arg Asn Trp Val
50

<210> SEQ ID NO 259
<211> LENGTH: 54
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 259

Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Gly Gly
1 5 10 15

Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Glu Val Ser Lys Arg Pro
20 25 30

Ser Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Asn Ser Tyr
35 40 45

Ala Gly Ser Ile Tyr Val
50

<210> SEQ ID NO 260
<211> LENGTH: 56
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 260

Thr Gly Thr Ser Gly Asp Val Gly Ala Tyr Asn Tyr Val Ser Gly Gly

-continued

1 5 10 15

Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Glu Val Ser Lys Arg Pro
20 25 30

Ser Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Asn Ser Tyr
35 40 45

Arg Gly Ser Asn Gly Pro Trp Val
50 55

<210> SEQ ID NO 261
<211> LENGTH: 56
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 261

Thr Gly Thr Ser Ser Asp Val Gly Ala Tyr Asn Tyr Val Ser Gly Gly
1 5 10 15

Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Glu Val Ala Arg Arg Pro
20 25 30

Ser Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Ser Ser Tyr
35 40 45

Ala Gly Ser Asn Asn Phe Ala Val
50 55

<210> SEQ ID NO 262
<211> LENGTH: 54
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 262

Thr Gly Thr Ser Ser Asp Val Gly Gly Phe Asn Tyr Val Ser Gly Gly
1 5 10 15

Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Glu Val Ser Lys Arg Pro
20 25 30

Ser Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Ser Ser Trp
35 40 45

Ala Pro Gly Lys Asn Leu
50

<210> SEQ ID NO 263
<211> LENGTH: 55
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 263

Thr Gly Thr Ser Ser Asp Ile Gly Thr Tyr Asp Tyr Val Ser Gly Gly
1 5 10 15

Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Glu Val Thr Asn Arg Pro
20 25 30

Ser Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Asn Ser Phe
35 40 45

-continued

Thr Lys Asn Asn Thr Trp Val
50 55

<210> SEQ ID NO 264
<211> LENGTH: 55
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 264

Thr Gly Thr Arg Ser Asp Ile Gly Gly Tyr Asn Tyr Val Ser Gly Gly
1 5 10 15

Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Asp Val Asn Asn Arg Pro
20 25 30

Ser Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Asn Ser Phe
35 40 45

Thr Asp Ser Arg Thr Trp Leu
50 55

<210> SEQ ID NO 265
<211> LENGTH: 55
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 265

Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Ile Tyr Val Ser Gly Gly
1 5 10 15

Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Asp Val Ser Arg Arg Pro
20 25 30

Ser Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Asn Ser Tyr
35 40 45

Thr Thr Leu Ser Thr Trp Leu
50 55

<210> SEQ ID NO 266
<211> LENGTH: 55
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 266

Thr Gly Thr Ser Ser Asp Val Gly Ser Tyr Asn Leu Val Ser Gly Gly
1 5 10 15

Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Glu Val Ser Asn Arg Pro
20 25 30

Ser Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Ser Ser Leu
35 40 45

Thr Ser Ser Gly Thr Trp Val
50 55

<210> SEQ ID NO 267
<211> LENGTH: 52

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 267

Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala Ser Gly Gly Gly Ala Ala
1 5 10 15

Ala Gly Gly Gly Ala Ala Ala Gln Asp Arg Lys Arg Pro Ser Gly Gly
20 25 30

Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Gln Ala Trp Asp Ser Asp
35 40 45

Thr Ser Tyr Val
50

<210> SEQ ID NO 268
<211> LENGTH: 52
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 268

Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala Ser Gly Gly Gly Ala Ala
1 5 10 15

Ala Gly Gly Gly Ala Ala Ala Arg Asp Thr Lys Arg Pro Ser Gly Gly
20 25 30

Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Gln Ala Trp Asp Ser Thr
35 40 45

Thr Ser Leu Val
50

<210> SEQ ID NO 269
<211> LENGTH: 52
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 269

Ser Gly Asn Lys Leu Gly Asp Lys Tyr Val Ser Gly Gly Gly Ala Ala
1 5 10 15

Ala Gly Gly Gly Ala Ala Ala Gln Asp Thr Lys Arg Pro Ser Gly Gly
20 25 30

Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Gln Ala Trp Asp Ser Ser
35 40 45

Thr Asp Val Val
50

<210> SEQ ID NO 270
<211> LENGTH: 55
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 270

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Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn Ala Val Ser Gly Gly Gly
1               5                   10                  15

Ala Ala Ala Gly Gly Gly Ala Ala Ala Tyr Asp Asn Leu Leu Pro Ser
20                  25                  30

Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Ala Ala Trp Asp
35                  40                  45

Asp Ser Leu Asn Asp Trp Val
50                  55


<210> SEQ ID NO 271
<211> LENGTH: 56
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 271

Thr Gly Ser Ser Ser Asn Leu Gly Thr Gly Tyr Asp Val His Gly Gly
1               5                   10                  15

Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Gly Asn Ser Asn Arg Pro
20                  25                  30

Ser Gly Gly Gly Ala Ala Ala Gly Gly Gly Ala Ala Ala Gln Ser Tyr
35                  40                  45

Asp Phe Ser Leu Ser Ala Met Val
50                  55
```

1. The EpoR agonist of claim **18**, wherein the agonist is a single chain variable fragment.

2. The EpoR agonist of claim **18**, wherein the EpoR agonist is a single chain variable fragment fused to an Fc.

3. The EpoR agonist of claim **2**, wherein the single chain variable fragment further comprises a polypeptide linker.

4. The EpoR agonist of claim **2**, wherein the Fc is derived from IgG_1, IgG_2, IgG_3, or IgG_4.

5. The EpoR agonist of claim **1**, wherein the single chain variable fragment comprises:

a) a fusion of a V_H chain of SEQ ID NO. 1 to a V_L chain of SEQ ID NO. 2;

b) a fusion of a V_H chain of SEQ ID NO. 3 to a V_L chain of SEQ ID NO. 4;

c) a fusion of a V_H chain of SEQ ID NO. 5 to a V_L chain of SEQ ID NO. 6;

d) a fusion of a V_H chain of SEQ ID NO. 7 to a V_L chain of SEQ ID NO. 8;

e) a fusion of a V_H chain of SEQ ID NO. 9 to a V_L chain of SEQ ID NO. 10;

f) a fusion of a V_H chain of SEQ ID NO. 56 to a V_L chain of SEQ ID NO. 58;

g) a fusion of a V_H chain of SEQ ID NO. 60 to a V_L chain of SEQ ID NO. 62;

h) a fusion of a V_H chain of SEQ ID NO. 64 to a V_L chain of SEQ ID NO. 66;

i) a fusion of a V_H chain of SEQ ID NO. 68 to a V_L chain of SEQ ID NO. 70;

j) a fusion of a V_H chain of SEQ ID NO. 72 to a V_L chain of SEQ ID NO. 74;

k) a fusion of a V_H chain of SEQ ID NO. 76 to a V_L chain of SEQ ID NO. 78;

l) a fusion of a V_H chain of SEQ ID NO. 80 to a V_L chain of SEQ ID NO. 82;

m) a fusion of a V_H chain of SEQ ID NO. 84 to a V_L chain of SEQ ID NO. 86;

n) a fusion of a V_H chain of SEQ ID NO. 88 to a V_L chain of SEQ ID NO. 90;

o) a fusion of a V_H chain of SEQ ID NO. 92 to a V_L chain of SEQ ID NO. 94;

p) a fusion of a V_H chain of SEQ ID NO. 96 to a V_L chain of SEQ ID NO. 98;

q) a fusion of a V_H chain of SEQ ID NO. 100 to a V_L chain of SEQ ID NO. 102;

r) a fusion of a V_H chain of SEQ ID NO. 104 to a V_L chain of SEQ ID NO. 106;

s) a fusion of a V_H chain of SEQ ID NO. 108 to a V_L chain of SEQ ID NO. 110; or

t) a fusion of a V_H chain of SEQ ID NO. 112 to a V_L chain of SEQ ID NO. 114;

6. The EpoR agonist of claim **5**, wherein the carboxy terminus of the V_H chain is fused to the amino terminus of the V_L chain.

7. A nucleic acid comprising a sequence encoding the EpoR agonist of claim **1**.

8-13. (canceled)

14. The method of claim **26**, wherein the EpoR agonist is a single chain variable fragment.

15. The method of claim **27**, wherein the EpoR agonist is a single chain variable fragment.

16. The method of claim **28**, wherein the EpoR agonist is a single chain variable fragment.

17. The method of claim **16**, wherein the erythropoietin receptor is a human erythropoietin receptor.

18. An erythropoietin receptor (EpoR) agonist selected from an antibody, a single chain variable fragment and a single chain variable fragment fused to an Fc, wherein the EpoR agonist comprises:

a) an amino acid sequence comprising SEQ ID NO. 1 and SEQ ID NO. 2;

b) an amino acid sequence comprising SEQ ID NO. 3 and SEQ ID NO. 4;

c) an amino acid sequence comprising SEQ ID NO. 5 and SEQ ID NO. 6;

d) an amino acid sequence comprising SEQ ID NO. 7 and SEQ ID NO. 8;

e) an amino acid sequence comprising SEQ ID NO. 9 and SEQ ID NO. 10;

f) an amino acid sequence comprising SEQ ID NO. 56 and SEQ ID NO. 58;

g) an amino acid sequence comprising SEQ ID NO. 60 and SEQ ID NO. 62;

h) an amino acid sequence comprising SEQ ID NO. 64 and SEQ ID NO. 66

i) an amino acid sequence comprising SEQ ID NO. 68 and SEQ ID NO. 70;

j) an amino acid sequence comprising SEQ ID NO. 72 and SEQ ID NO. 74;

k) an amino acid sequence comprising SEQ ID NO. 76 and SEQ ID NO. 78;

l) an amino acid sequence comprising SEQ ID NO. 80 and SEQ ID NO. 82;

m) an amino acid sequence comprising SEQ ID NO. 84 and SEQ ID NO. 86;

n) an amino acid sequence comprising SEQ ID NO. 88 and SEQ ID NO. 90;

o) an amino acid sequence comprising SEQ ID NO. 92 and SEQ ID NO. 94;

p) an amino acid sequence comprising SEQ ID NO. 96 and SEQ ID NO. 98;

q) an amino acid sequence comprising SEQ ID NO. 100 and SEQ ID NO. 102;

r) an amino acid sequence comprising SEQ ID NO. 104 and SEQ ID NO. 106;

s) an amino acid sequence comprising SEQ ID NO. 108 and SEQ ID NO. 110; or

t) an amino acid sequence comprising SEQ ID NO. 112 and SEQ ID NO. 114.

19. A nucleic acid comprising a sequence encoding the EpoR agonist of claim **18**.

20. The nucleic acid of claim **19**, further comprising one or more control elements, wherein one or more of the one or more control elements are operably linked to the sequence encoding the antibody.

21. A vector comprising the nucleic acid of claim **19**.

22. A vector comprising the nucleic acid of claim **20**.

23. A host cell comprising the vector of claim **21**.

24. A host cell comprising the vector of claim **22**.

25. A pharmaceutical composition comprising the EpoR agonist of claim **18**.

26. A method of treating anemia in a patient comprising administering to the patient the EpoR agonist of claim **18**.

27. A method of promoting tissue protection in a patient comprising administering to the patient the EpoR agonist of claim **18**.

28. A method of activating an endogenous activity of an erythropoietin receptor in a mammal comprising administering to the mammal an amount of the EpoR agonist of claim **18**.

29. The method of claim **28**, wherein the erythropoietin receptor is a human erythropoietin receptor.

30. The EpoR agonist of claim **47**, wherein the agonist is a single chain variable fragment.

31. The EpoR agonist of claim **47**, wherein the agonist is a single chain variable fragment fused to an Fc.

32. The EpoR agonist of claim **31**, wherein the single chain variable fragment further comprises a polypeptide linker.

33. The EpoR agonist of claim **31**, wherein the Fc is derived from IgG_1, IgG_2, IgG_3, or IgG_4.

34. The EpoR agonist of claim **18**, wherein the agonist comprises a single chain variable fragment comprising:

a) a fusion of a V_H chain comprising SEQ ID NO. 11, SEQ ID NO. 12, and SEQ ID NO. 13 to a V_L chain comprising SEQ ID NO. 14, SEQ ID NO. 15 and SEQ ID NO. 16;

b) a fusion of a V_H chain comprising SEQ ID NO. 11, SEQ ID NO. 12, and SEQ ID NO. 13 to a V_L chain comprising SEQ ID NO. 17, SEQ ID NO. 18, and SEQ ID NO. 19;

c) a fusion of a V_H chain comprising SEQ ID NO. 11, SEQ ID NO. 12, and SEQ ID NO. 13 to a V_L chain comprising SEQ ID NO. 20, SEQ ID NO. 21, and SEQ ID NO. 22;

d) a fusion of a V_H chain comprising SEQ ID NO. 23, SEQ ID NO. 24, and SEQ ID NO. 25 to a V_L chain comprising SEQ ID NO. 26, SEQ ID NO. 27, and SEQ ID NO. 28;

e) a fusion of a V_H chain comprising SEQ ID NO. 29, SEQ ID NO. 30, and SEQ ID NO. 31 to a V_L chain comprising SEQ ID NO. 32, SEQ ID NO. 33, and SEQ ID NO. 34;

f) a fusion of a V_H chain comprising SEQ ID NO.: 123, SEQ ID NO.: 124, and SEQ ID NO.: 125, to a V_L chain comprising SEQ ID NO.: 126, SEQ ID NO.: 127, and SEQ ID NO.: 128;

g) a fusion of a V_H chain comprising SEQ ID NO.: 129, SEQ ID NO.: 130, and SEQ ID NO.: 131, to a V_L chain comprising SEQ ID NO.: 132, SEQ ID NO.: 133, and SEQ ID NO.: 134;

h) a fusion of a V_H chain comprising SEQ ID NO.: 135, SEQ ID NO.: 136, and SEQ ID NO.: 212, to a V_L chain comprising SEQ ID NO.: 137, SEQ ID NO.: 138, and SEQ ID NO.: 139;

i) a fusion of a V_H chain comprising SEQ ID NO.: 140, SEQ ID NO.: 141, and SEQ ID NO.: 142, to a V_L chain comprising SEQ ID NO.: 143, SEQ ID NO.: 144, and SEQ ID NO.: 145;

j) a fusion of a V_H chain comprising SEQ ID NO.: 146, SEQ ID NO.: 147, and SEQ ID NO.: 148, to a V_L chain comprising SEQ ID NO.: 149, SEQ ID NO.: 150, and SEQ ID NO.: 151;

k) a fusion of a V_H chain comprising SEQ ID NO.: 152, SEQ ID NO.: 153, and SEQ ID NO.: 154, to a V_L chain comprising SEQ ID NO.: 155, SEQ ID NO.: 156, and SEQ ID NO.: 157;

l) a fusion of a V_H chain comprising SEQ ID NO.: 158, SEQ ID NO.: 159, and SEQ ID NO.: 160, to a V_L chain comprising SEQ ID NO.: 161, SEQ ID NO.: 162, and SEQ ID NO.: 163;

m) a fusion of a V_H chain comprising SEQ ID NO.: 164, SEQ ID NO.: 165, and SEQ ID NO.: 166, to a V_L chain comprising SEQ ID NO.: 167, SEQ ID NO.: 168, and SEQ ID NO.: 169;

n) a fusion of a V_H chain comprising SEQ ID NO.: 170, SEQ ID NO.: 171, and SEQ ID NO.: 172, to a V_L chain comprising SEQ ID NO.: 173, SEQ ID NO.: 174, and SEQ ID NO.: 175;

o) a fusion of a V_H chain comprising SEQ ID NO.: 176, SEQ ID NO.: 177, and SEQ ID NO.: 178, to a V_L chain comprising SEQ ID NO.: 179, SEQ ID NO.: 180, and SEQ ID NO.: 181;

p) a fusion of a V_H chain comprising SEQ ID NO.: 182, SEQ ID NO.: 183, and SEQ ID NO.: 184, to a V_L chain comprising SEQ ID NO.: 185, SEQ ID NO.: 186, and SEQ ID NO.: 187;

q) a fusion of a V_H chain comprising SEQ ID NO.: 188, SEQ ID NO.: 189, and SEQ ID NO.: 190, to a V_L chain comprising SEQ ID NO.: 191, SEQ ID NO.: 192, and SEQ ID NO.: 193;

r) a fusion of a V_H chain comprising SEQ ID NO.: 194, SEQ ID NO.: 195, and SEQ ID NO.: 196, to a V_L chain comprising SEQ ID NO.: 197, SEQ ID NO.: 198, and SEQ ID NO.: 199;

s) a fusion of a V_H chain comprising SEQ ID NO.: 200, SEQ ID NO.: 201, and SEQ ID NO.: 202, to a V_L chain comprising SEQ ID NO.: 203, SEQ ID NO.: 204, and SEQ ID NO.: 205; or

t) a fusion of a V_H chain comprising SEQ ID NO.: 206, SEQ ID NO.: 207, and SEQ ID NO.: 208, to a V_L chain comprising SEQ ID NO.: 209, SEQ ID NO.: 210, and SEQ ID NO.: 211.

35. The EpoR agonist of claim **34**, wherein the carboxy terminus of the V_H chain is fused to the amino terminus of the V_L chain.

36-42. (canceled)

43. The method of claim **55**, wherein the EpoR agonist is a single chain variable fragment.

44. The method of claim **56**, wherein the EpoR agonist is a single chain variable fragment.

45. The method of claim **57**, wherein the EpoR agonist is a single chain variable fragment.

46. The method of claim **45**, wherein the erythropoietin receptor is a human erythropoietin receptor.

47. An EpoR agonist selected from an antibody, a single chain variable fragment, and a single chain variable fragment fused to an Fc, wherein the agonist comprises:

a) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15 and SEQ ID NO. 16;

b) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 17, SEQ ID NO. 18, and SEQ ID NO. 19;

c) an amino acid sequence comprising SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 20, SEQ ID NO. 21, and SEQ ID NO. 22;

d) an amino acid sequence comprising SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 26, SEQ ID NO. 27, and SEQ ID NO. 28;

e) an amino acid sequence comprising SEQ ID NO. 29, SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, and SEQ ID NO. 34

f) an amino acid sequence comprising SEQ ID NO.: 123, SEQ ID NO.: 124, SEQ ID NO.: 125, SEQ ID NO.: 126, SEQ ID NO.: 127, and SEQ ID NO.: 128;

g) an amino acid sequence comprising SEQ ID NO.: 129, SEQ ID NO.: 130, SEQ ID NO.: 131, SEQ ID NO.: 132, SEQ ID NO.: 133, and SEQ ID NO.: 134;

h) f an amino acid sequence comprising SEQ ID NO.: 135, SEQ ID NO.: 136, SEQ ID NO.: 212, SEQ ID NO.: 137, SEQ ID NO.: 138, and SEQ ID NO.: 139;

i) an amino acid sequence comprising SEQ ID NO.: 140, SEQ ID NO.: 141, SEQ ID NO.: 142, SEQ ID NO.: 143, SEQ ID NO.: 144, and SEQ ID NO.: 145;

j) an amino acid sequence comprising SEQ ID NO.: 146, SEQ ID NO.: 147, SEQ ID NO.: 148, SEQ ID NO.: 149, SEQ ID NO.: 150, and SEQ ID NO.: 151;

k) an amino acid sequence comprising SEQ ID NO.: 152, SEQ ID NO.: 153, SEQ ID NO.: 154, SEQ ID NO.: 155, SEQ ID NO.: 156, and SEQ ID NO.: 157;

l) an amino acid sequence comprising SEQ ID NO.: 158, SEQ ID NO.: 159, SEQ ID NO.: 160, SEQ ID NO.: 161, SEQ ID NO.: 162, and SEQ ID NO.: 163;

m) an amino acid sequence comprising SEQ ID NO.: 164, SEQ ID NO.: 165, SEQ ID NO.: 166, SEQ ID NO.: 167, SEQ ID NO.: 168, and SEQ ID NO.: 169;

n) an amino acid sequence comprising SEQ ID NO.: 170, SEQ ID NO.: 171, SEQ ID NO.: 172, SEQ ID NO.: 173, SEQ ID NO.: 174, and SEQ ID NO.: 175;

o) an amino acid sequence comprising SEQ ID NO.: 176, SEQ ID NO.: 177, SEQ ID NO.: 178, SEQ ID NO.: 179, SEQ ID NO.: 180, and SEQ ID NO.: 181;

p) an amino acid sequence comprising SEQ ID NO.: 182, SEQ ID NO.: 183, SEQ ID NO.: 184, SEQ ID NO.: 185, SEQ ID NO.: 186, and SEQ ID NO.: 187;

q) an amino acid sequence comprising SEQ ID NO.: 188, SEQ ID NO.: 189, SEQ ID NO.: 190, SEQ ID NO.: 191, SEQ ID NO.: 192, and SEQ ID NO.: 193;

r) an amino acid sequence comprising SEQ ID NO.: 194, SEQ ID NO.: 195, SEQ ID NO.: 196, SEQ ID NO.: 197, SEQ ID NO.: 198, and SEQ ID NO.: 199;

s) an amino acid sequence comprising SEQ ID NO.: 200, SEQ ID NO.: 201, SEQ ID NO.: 202, SEQ ID NO.: 203, SEQ ID NO.: 204, and SEQ ID NO.: 205; or

t) an amino acid sequence comprising SEQ ID NO.: 206, SEQ ID NO.: 207, SEQ ID NO.: 208, SEQ ID NO.: 209, SEQ ID NO.: 210, and SEQ ID NO.: 211.

48. A nucleic acid comprising a sequence encoding the EpoR agonist of claim **47**.

49. The nucleic acid of claim **48**, further comprising one or more control elements, wherein one or more of the one or more control elements are operably linked to the sequence encoding the EpoR agonist.

50. A vector comprising the nucleic acid of claim **48**.

51. A vector comprising the nucleic acid of claim **49**.

52. A host cell comprising the vector of claim **50**.

53. A host cell comprising the vector of claim **51**.

54. A pharmaceutical composition comprising the EpoR agonist of claim **47**.

55. A method of treating anemia in a patient comprising administering to the patient the EpoR agonist of claim **47**.

56. A method of promoting tissue protection in a patient comprising administering to the patient the EpoR agonist of claim **47**.

57. A method of activating an endogenous activity of an erythropoietin receptor in a mammal comprising administering to the mammal the EpoR agonist of claim **47**.

58. The method of claim **57**, wherein the erythropoietin receptor is a human erythropoietin receptor.

59. An EpoR agonist selected from an antibody, a single chain variable fragment, and a single chain variable fragment fused to an Fc, wherein the agonist comprises:

a) an amino acid sequence comprising SEQ ID NO. 45;

b) an amino acid sequence comprising SEQ ID NO. 46;

c) an amino acid sequence comprising SEQ ID NO. 47;

d) an amino acid sequence comprising SEQ ID NO. 48; or

e) an amino acid sequence comprising SEQ ID NO. 49.

60. A nucleic acid comprising a sequence encoding the EpoR agonist of claim **59**.

61. The nucleic acid of claim **60**, further comprising one or more control elements, wherein one or more of the one or more control elements are operably linked to the sequence encoding the EpoR agonist.

62. A vector comprising the nucleic acid of claim **60**.

63. A vector comprising the nucleic acid of claim **61**.

64. A host cell comprising the vector of claim **62**.

65. A host cell comprising the vector of claim **63**.

66. A pharmaceutical composition comprising the EpoR agonist of claim **59**.

67. A method of treating anemia in a patient comprising administering to the patient an EpoR agonist of claim **59**.

68. A method of promoting tissue protection in a patient comprising administering to the patient EpoR agonist of claim **59**.

69. A method of activating an endogenous activity of an erythropoietin receptor in a mammal comprising administering to the mammal an amount of EpoR agonist of claim **59**.

70. The method of claim **69**, wherein the erythropoietin receptor is a human erythropoietin receptor.

71. A method of making an EpoR agonist comprising expressing the nucleic acid of claim **19** in a host cell.

72. The method of claim **71**, wherein the EpoR agonist is a single chain variable fragment fused to an Fc.

73. A method of making an EpoR agonist comprising expressing the nucleic acid of claim **48** in a host cell.

74. The method of claim **73**, wherein the EpoR agonist is a single chain variable fragment fused to an Fc.

75. A method of making an EpoR agonist comprising expressing the nucleic acid of claim **60** in a host cell.

76. The EpoR agonist of claim **91**, wherein the EpoR agonist is a single chain variable fragment.

77. The EpoR agonist of claim **91**, wherein the EpoR agonist is a single chain variable fragment fused to an Fc.

78. The EpoR agonist of claim **77**, wherein the single chain variable fragment further comprises a polypeptide linker.

79. The EpoR agonist of claim **77**, wherein the Fc is derived from IgG_1, IgG_2, IgG_3, or IgG_4.

80-86. (canceled)

87. The method of claim **99**, wherein the EpoR agonist is a single chain variable fragment.

88. The method of claim **100**, wherein the EpoR agonist is a single chain variable fragment.

89. The method of claim **101**, wherein the EpoR agonist is a single chain variable fragment.

90. The method of claim **89**, wherein the erythropoietin receptor is a human erythropoietin receptor.

91. An EpoR agonist selected from an antibody, a single chain variable fragment, and a single chain variable fragment fused to an Fc, wherein the agonist specifically binds to:

a) at least amino acids F93 and H114 of the extracellular domain of the human Epo Receptor;

b) at least amino acids S91, F93, and H114 of the extracellular domain of the human Epo Receptor;

c) at least amino acid F93 of the extracellular domain of the human Epo Receptor;

d) at least amino acids E62, F93, and M150 of the extracellular domain of the human Epo Receptor;

e) at least amino acids V48, E62, L66, R68, and H70 of the extracellular domain of the human Epo Receptor;

f) at least amino acids V48, W64, L66, R68, and H70 of the extracellular domain of the human Epo Receptor;

g) at least amino acids A44, V48, P63, L66, R68, and H70 of the extracellular domain of the human Epo Receptor; or

h) at least amino acids L66 and R99 of the extracellular domain of the human Epo Receptor.

92. A nucleic acid comprising a sequence encoding the EpoR agonist of claim **91**.

93. The nucleic acid of claim **92**, further comprising one or more control elements, wherein one or more of the one or more control elements are operably linked to the sequence encoding the EpoR agonist.

94. A vector comprising the nucleic acid of claim **92**.

95. A vector comprising the nucleic acid of claim **93**.

96. A host cell comprising the vector of claim **94**.

97. A host cell comprising the vector of claim **95**.

98. A pharmaceutical composition comprising the EpoR agonist of claim **91**.

99. A method of treating anemia in a patient comprising administering to the patient the EpoR agonist of claim **91**.

100. A method of promoting tissue protection in a patient comprising administering to the patient the EpoR agonist of claim **91**.

101. A method of activating an endogenous activity of an erythropoietin receptor in a mammal comprising administering to the mammal an amount of the EpoR agonist of claim **91**.

102. The method of claim **101**, wherein the erythropoietin receptor is a human erythropoietin receptor.

103. A method of making an EpoR agonist comprising expressing the nucleic acid of claim **92** in a host cell.

104. The method of claim **103**, wherein the EpoR agonist is a single chain variable fragment fused to an Fc.

105. An EpoR agonist that binds to human Epo Receptor, wherein the agonist is selected from an antibody, a single chain variable fragment, and a single chain variable fragment fused to an Fc, and wherein the agonist comprises one or more sequences selected from:

A) a first amino acid sequence comprising:

i) a CDR1 having the formula: X_1 YWM X_5, where X_1 is any amino acid and X_5 is any amino acid;

ii) a CDR2 having the formula: NIKPDGSEKYV X_{12} SVKG where X_{12} is any amino acid; and

iii) a CDR 3 having the formula: VSRGGS X_7 SD where X_7 is any amino acid; and

B) a second amino acid sequence comprising:

i) a CDR1 having the formula: TGTSSD X_7 G X_9 Y X_{11} YVS where X_7 is any amino acid, and X_9 is any amino acid, and X_{11} is any amino acid; and

ii) a CDR2 having the formula: X_1 V X_3 X_4 RPS where X_1 is any amino acid, and X_3 is any amino acid, and X_4 is any amino acid.

106. The EpoR agonist of claim **105**, wherein

A) the first amino acid sequence comprises:

i) a CDR1 having the formula: X_1 YWM X_5, where X_1 is K or S and X_5 is T or S;

ii) a CDR2 having the formula: NIKPDGSEKYV X_{12} SVKG where X_{12} is D or E; and

iii) a CDR 3 having the formula: VSRGGS X_7 SD where X_7 is F or Y; and

B) the second amino acid sequence comprises:

i) a CDR1 having the formula: TGTSSD X_7 G X_9 Y X_{11} YVS where X_7 is V or I, and X_9 is G, A, T or S, and X_{11} is N, D, or I; and

ii) a CDR2 having the formula: X_1 V X_3 X_4 RPS where X_1 is D or E, and X_3 is N, S, A, or T, and X_4 is K, N, or R.

107. The EpoR agonist of claim **105**, wherein said agonist is an antibody comprising said first amino acid sequence and said second amino acid sequence.

108. The EpoR agonist of claim **107**, wherein said first amino acid sequence is covalently bonded to said second amino acid sequence.

109. The EpoR agonist of claim **105**, wherein the agonist is a single chain variable fragment that binds to human Epo Receptor.

110. The EpoR agonist of claim **109**, wherein

A) the first amino acid sequence comprises:

i) a CDR1 having the formula: X_1 YWM X_5, where X_1 is K or S and X_5 is T or S;

ii) a CDR2 having the formula: NIKPDGSEKYV X_{12} SVKG where X_{12} is D or E; and

iii) a CDR 3 having the formula: VSRGGS X_7 SD where X_7 is F or Y; and

B) the second amino acid sequence comprises:

i) a CDR1 having the formula: TGTSSD X_7 G X_9 Y X_{11} YVS where X_7 is V or I, and X_9 is G, A, T or S, and X_1 is N, D, or I; and

ii) a CDR2 having the formula: X_1 V X_3 X_4 RPS where X_1 is D or E, and X_3 is N, S, A, or T, and X_4 is K, N, or R.

111. The EpoR agonist of claim **110**, wherein said single chain variable fragment comprises said first amino acid sequence and said second amino acid sequence.

112. The EpoR agonist of claim **111**, wherein said first amino acid sequence is covalently bonded to said second amino acid sequence.

113. An antibody that binds to the wild-type human Epo Receptor but fails to bind to a mutant Epo Receptor wherein the mutant Epo Receptor is selected from:

A) a mutant Epo Receptor wherein the amino acid at position 34 of the extracellular domain of the mutant Epo Receptor is Arginine;

B) a mutant Epo Receptor wherein the amino acid at position 60 of the extracellular domain of the mutant Epo Receptor is Arginine;

C) a mutant Epo Receptor wherein the amino acid at position 88 of the extracellular domain of the mutant Epo Receptor is Arginine;

D) a mutant Epo Receptor wherein the amino acid at position 150 of the extracellular domain of the mutant Epo Receptor is Arginine;

E) a mutant Epo Receptor wherein the amino acid at position 87 of the extracellular domain of the mutant Epo Receptor is Arginine:

F) a mutant Epo Receptor wherein the amino acid at position 63 of the extracellular domain of the mutant Epo Receptor is Arginine;

G) a mutant Epo Receptor wherein the amino acid at position 64 of the extracellular domain of the mutant Epo Receptor is Arginine; or

H) a mutant Epo Receptor wherein the amino acid at position 99 of the extracellular domain of the mutant Epo Receptor is Arginine.

114-120. (canceled)

121. The antibody of claim **113**, wherein the antibody is a single chain variable fragment.

122-129. (canceled)

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