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(54) **DETECTION OF COMPOUNDS THAT AFFECT THERAPEUTIC ACTIVITY**

(75) Inventors: **Shuqian Jing**, Palo Alto, CA (US); **Francesca Civoli**, Newbury Park, CA (US); **Shalini Gupta**, Newbury Park, CA (US); **Daniel Steven Halperin**, Calabasas, CA (US); **Jason Joseph Pennucci**, Santa Monica, CA (US); **Steven Swanson**, Moorpark, CA (US); **Yan Bin Yu**, Thousand Oaks, CA (US)

Correspondence Address:
AMGEN INC.
1120 VETERANS BOULEVARD
SOUTH SAN FRANCISCO, CA 94080 (US)

(73) Assignee: **Amgen Inc.**, Thousand Oaks, CA

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(57) **ABSTRACT**

The present invention relates to methods of detecting compounds that affect the activity of a therapeutic substance or composition administered to a subject, and to reagents for use in such methods.

FIG. 1A

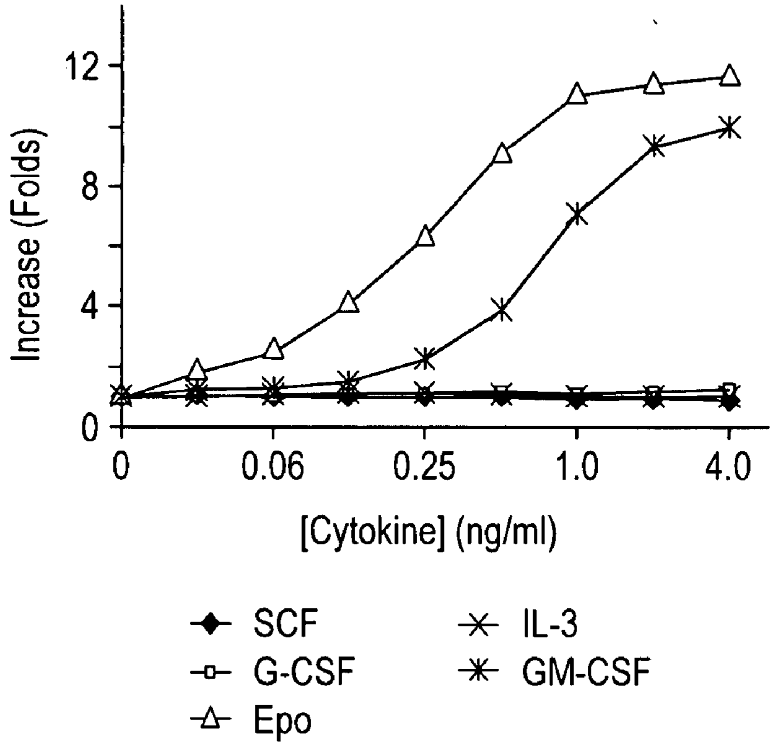

12
8
4
0
Increase (Folds)
0
0.06
0.25
1.0
4.0
[Cytokine] (ng/ml)
SCF
G-CSF
Epo
IL-3
GM-CSF

FIG. 1B

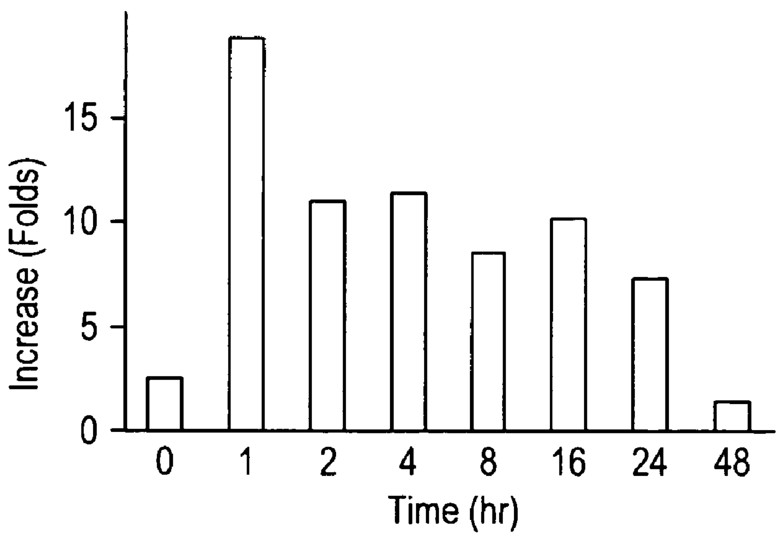

15
10
5
0
Increase (Folds)
0
1
2
4
8
16
24
48
Time (hr)

FIG. 2A

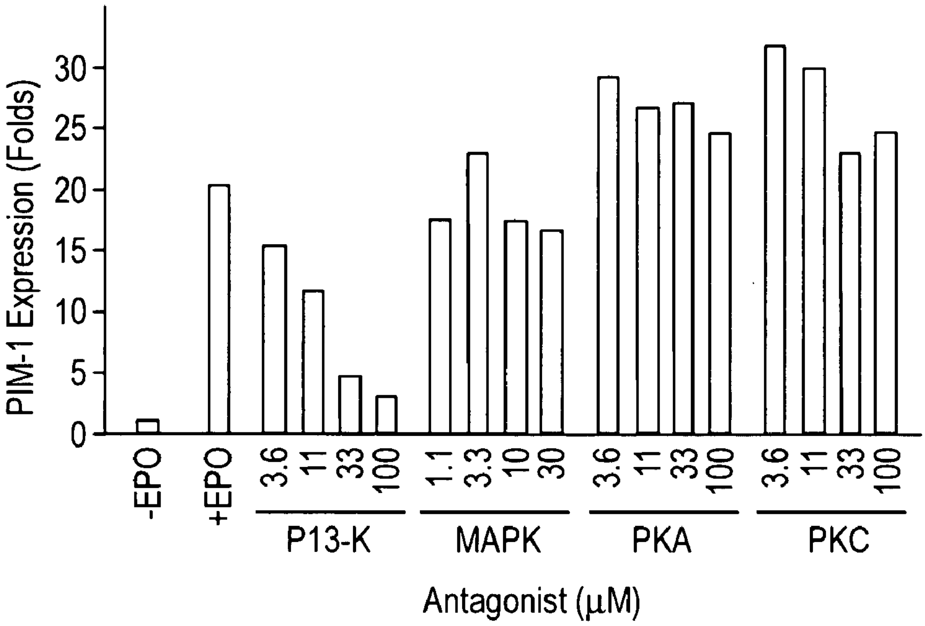

PIM-1 Expression (Folds)
0
5
10
15
20
25
30
-EPO
+EPO
3.6
11
33
100
1.1
3.3
10
30
3.6
11
33
100
3.6
11
33
100
P13-K
MAPK
PKA
PKC
Antagonist (μM)

FIG. 2B

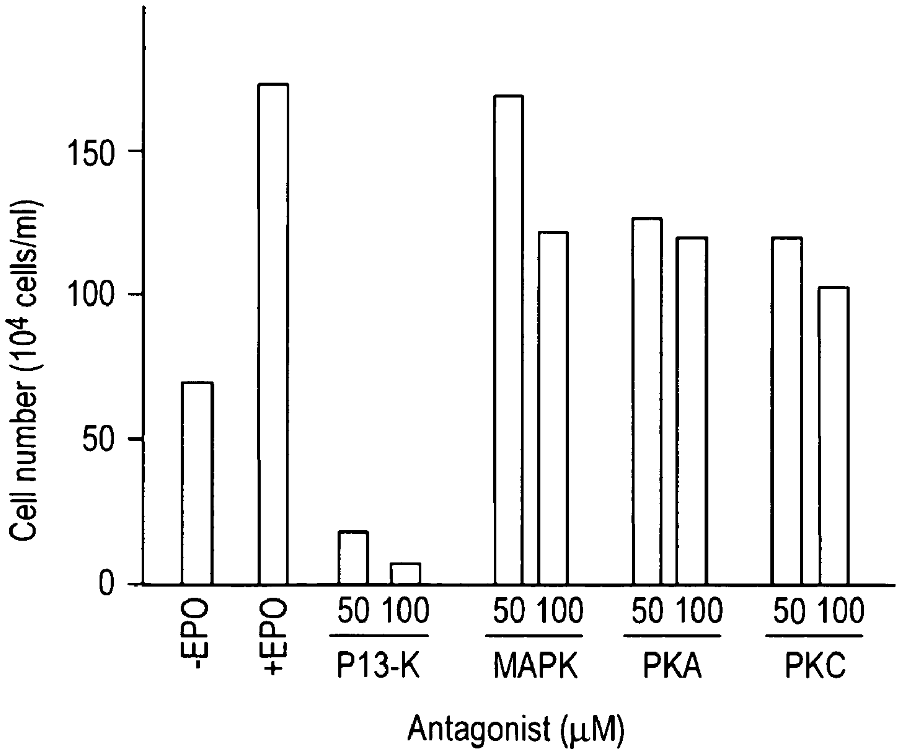

Cell number (10⁴ cells/ml)
0
50
100
150
-EPO
+EPO
50 100
P13-K
50 100
MAPK
50 100
PKA
50 100
PKC
Antagonist (μM)

FIG. 3A

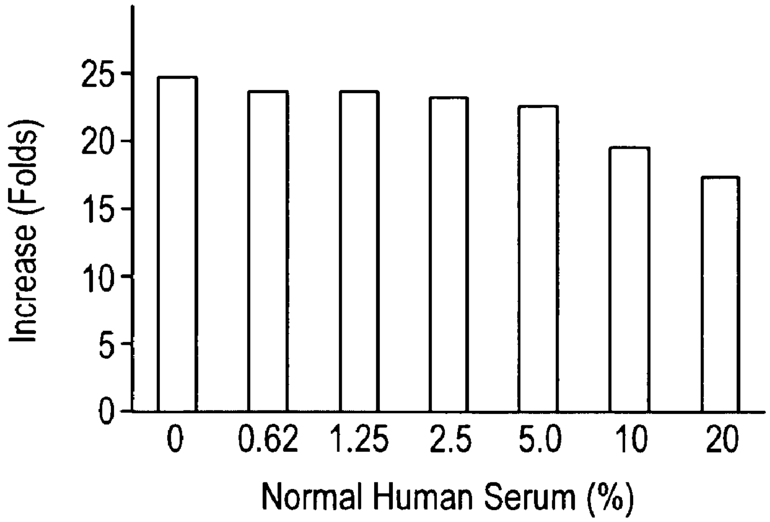

25
20
15
10
5
0
Increase (Folds)
0
0.62
1.25
2.5
5.0
10
20
Normal Human Serum (%)

FIG. 3B

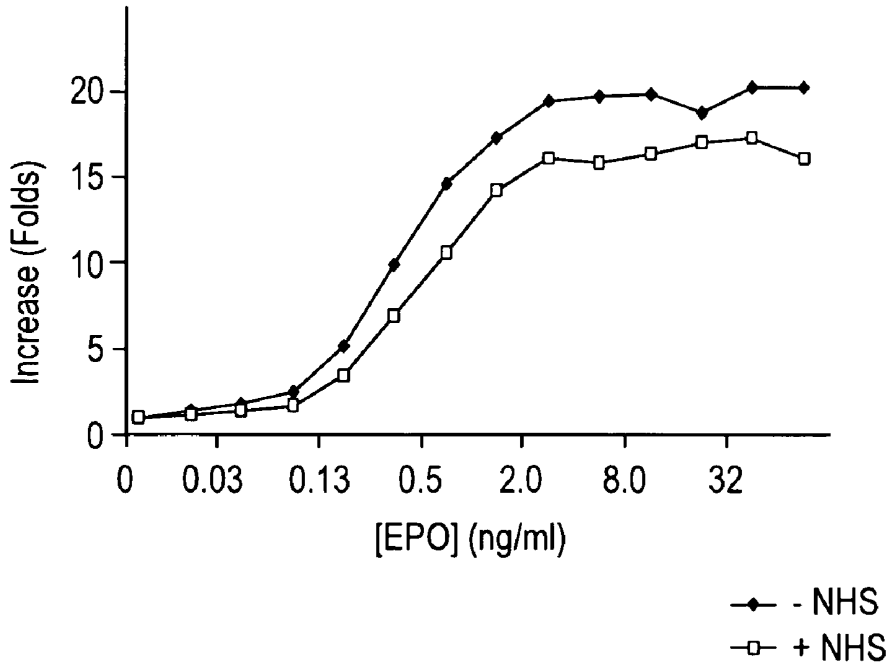

20
15
10
5
0
Increase (Folds)
0
0.03
0.13
0.5
2.0
8.0
32
[EPO] (ng/ml)
- NHS
+ NHS

FIG. 4

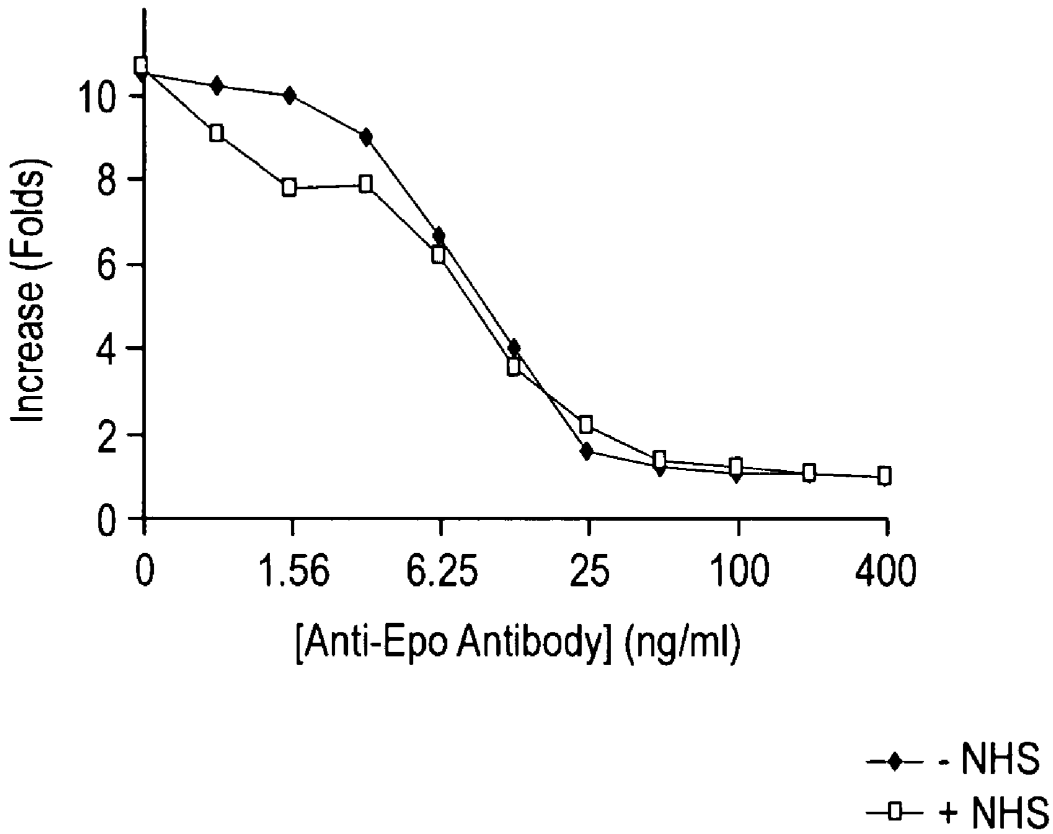

Increase (Folds)
10
8
6
4
2
0
0
1.56
6.25
25
100
400
[Anti-Epo Antibody] (ng/ml)
- NHS
+ NHS

FIG. 5

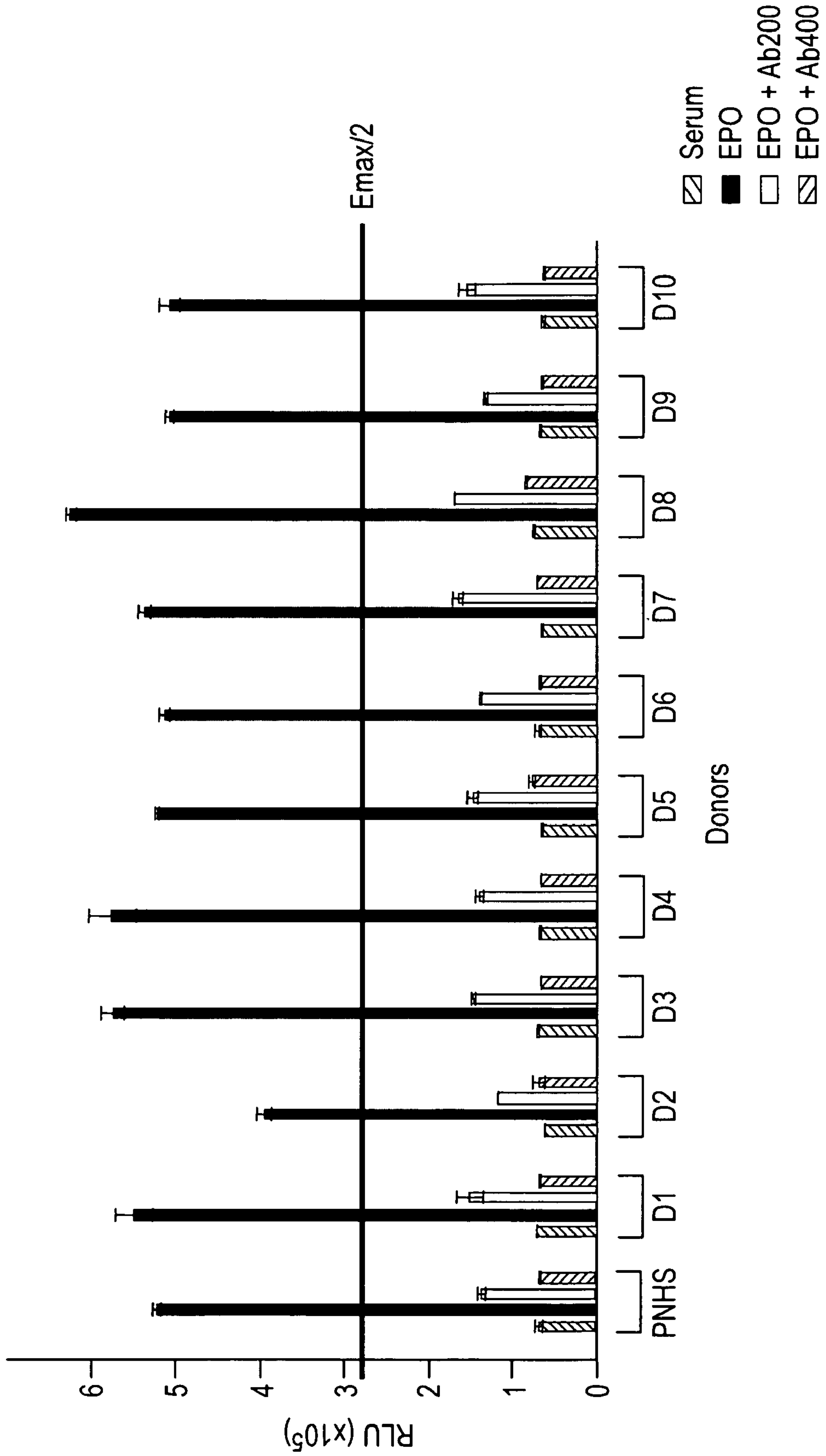
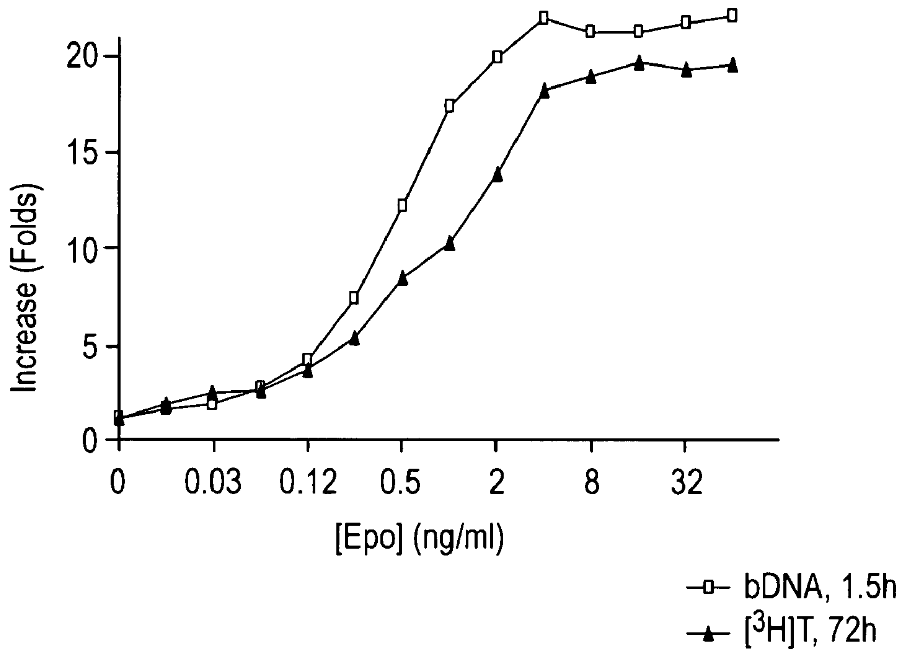
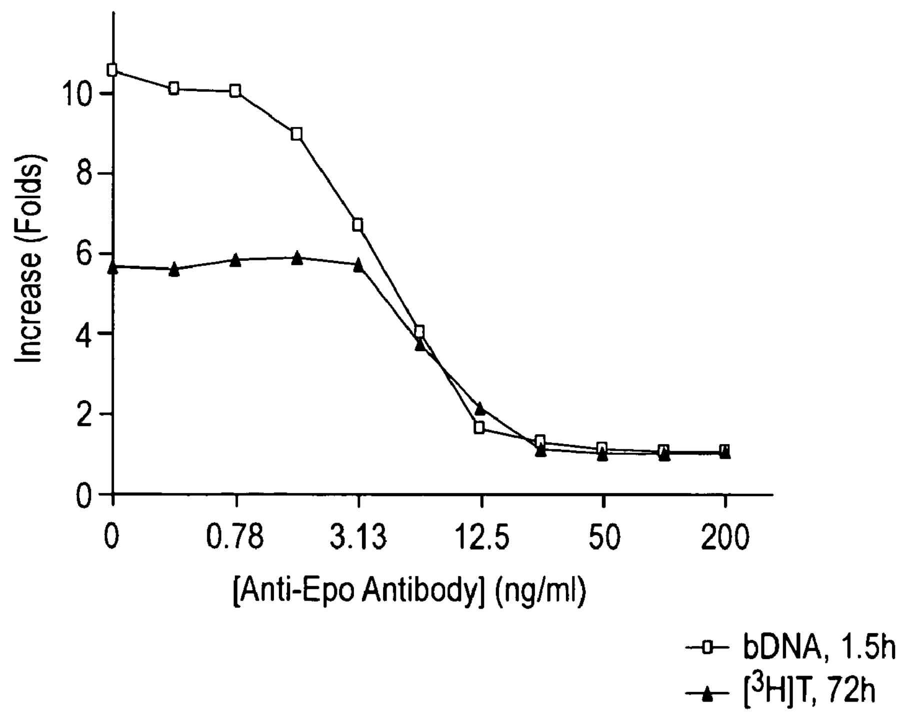

Emax/2
Serum
EPO
EPO + Ab200
EPO + Ab400
RLU (x10^5)
0
1
2
3
4
5
6
PNHS
D1
D2
D3
D4
D5
D6
D7
D8
D9
D10
Donors

FIG. 6A



20
15
10
5
0
Increase (Folds)
0
0.03
0.12
0.5
2
8
32
[Epo] (ng/ml)
bDNA, 1.5h
[3H]T, 72h

FIG. 6B



10
8
6
4
2
0
Increase (Folds)
0
0.78
3.13
12.5
50
200
[Anti-Epo Antibody] (ng/ml)
bDNA, 1.5h
[3H]T, 72h

FIG. 7

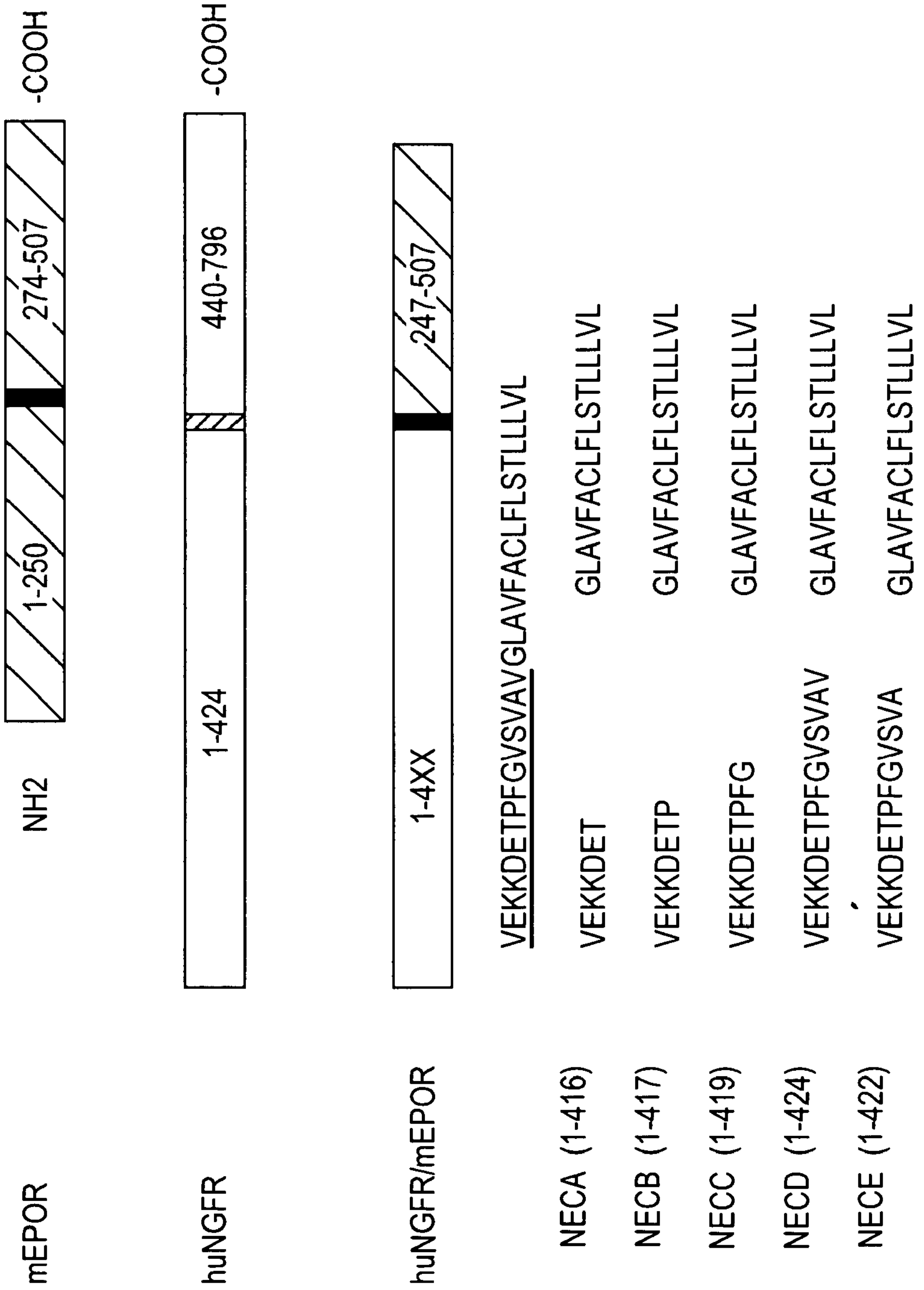

mEPOR
NH2
1-250
274-507
-COOH
huNGFR
1-424
440-796
-COOH
huNGFR/mEPOR
1-4XX
247-507
VEKKDETPFGVSVAVGLAVFACLFLSTLLLVL
NECA (1-416) VEKKDET GLAVFACLFLSTLLLVL
NECB (1-417) VEKKDETP GLAVFACLFLSTLLLVL
NECC (1-419) VEKKDETPFG GLAVFACLFLSTLLLVL
NECD (1-424) VEKKDETPFGVSVAV GLAVFACLFLSTLLLVL
NECE (1-422) VEKKDETPFGVSVA GLAVFACLFLSTLLLVL

FIG. 8

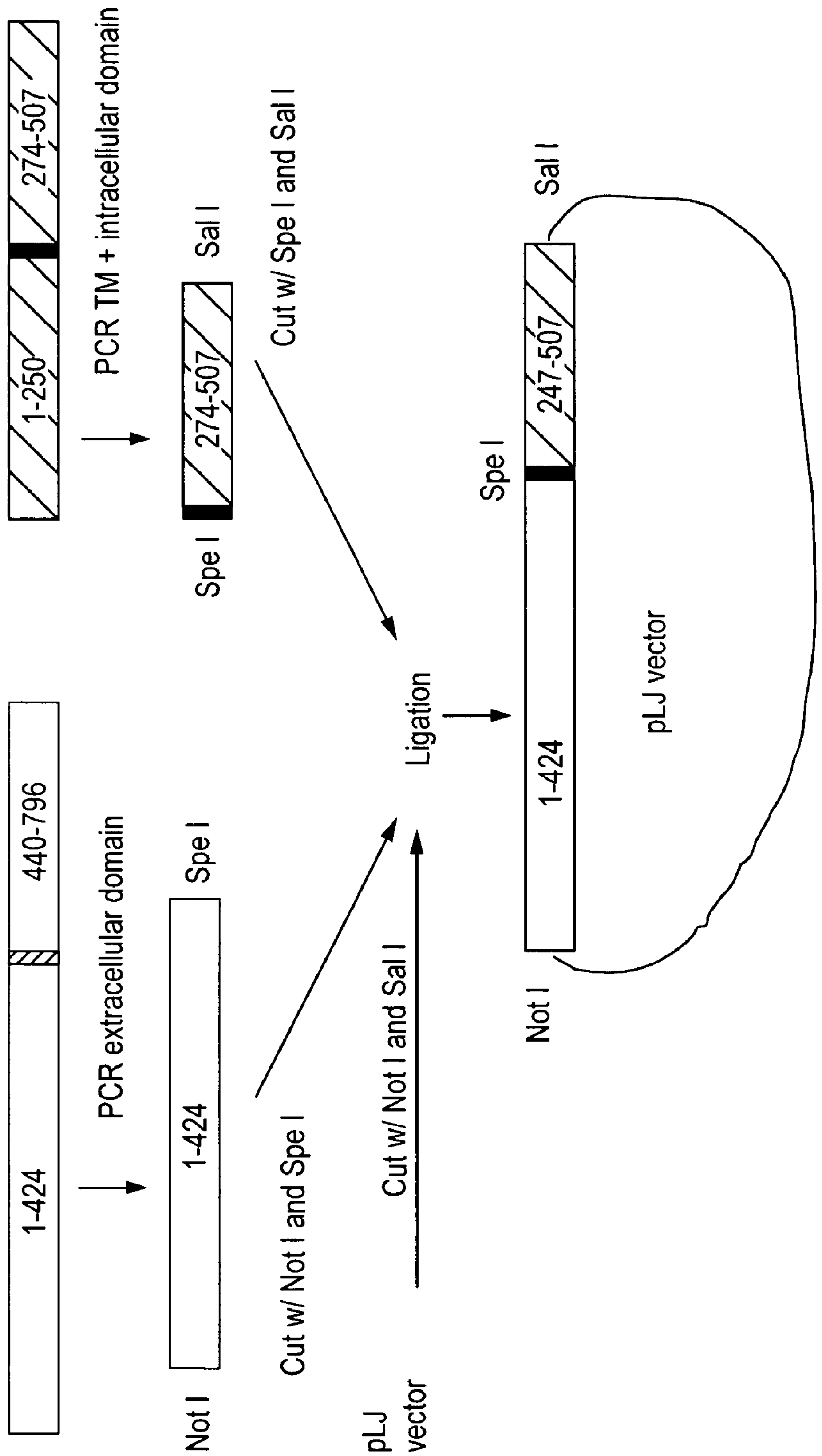

1-424
440-796
PCR extracellular domain
Not I
1-424
Spe I
Cut w/ Not I and Spe I
pLJ vector
Cut w/ Not I and Sal I
1-250
274-507
PCR TM + intracellular domain
Spe I
274-507
Sal I
Cut w/ Spe I and Sal I
Ligation
Not I
1-424
Spe I
247-507
Sal I
pLJ vector

FIG. 9

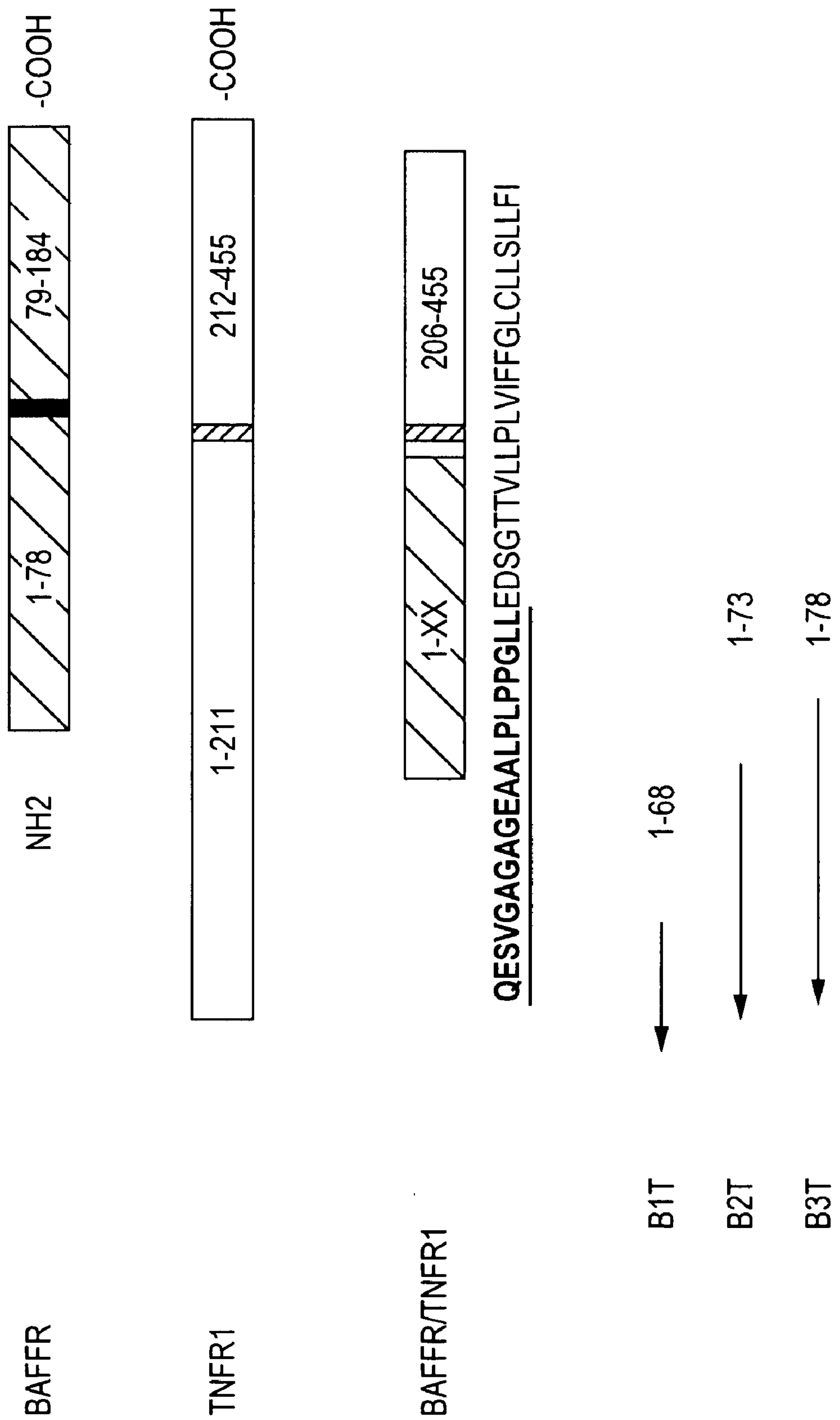

BAFFR
NH2
1-78
79-184
-COOH
TNFR1
1-211
212-455
-COOH
BAFFR/TNFR1
1-XX
206-455
QESVGAGEAALPLPPGLLEDSGTTVLLPLVIFFGLCLLSLLFI
B1T
1-68
B2T
1-73
B3T
1-78

FIG. 10

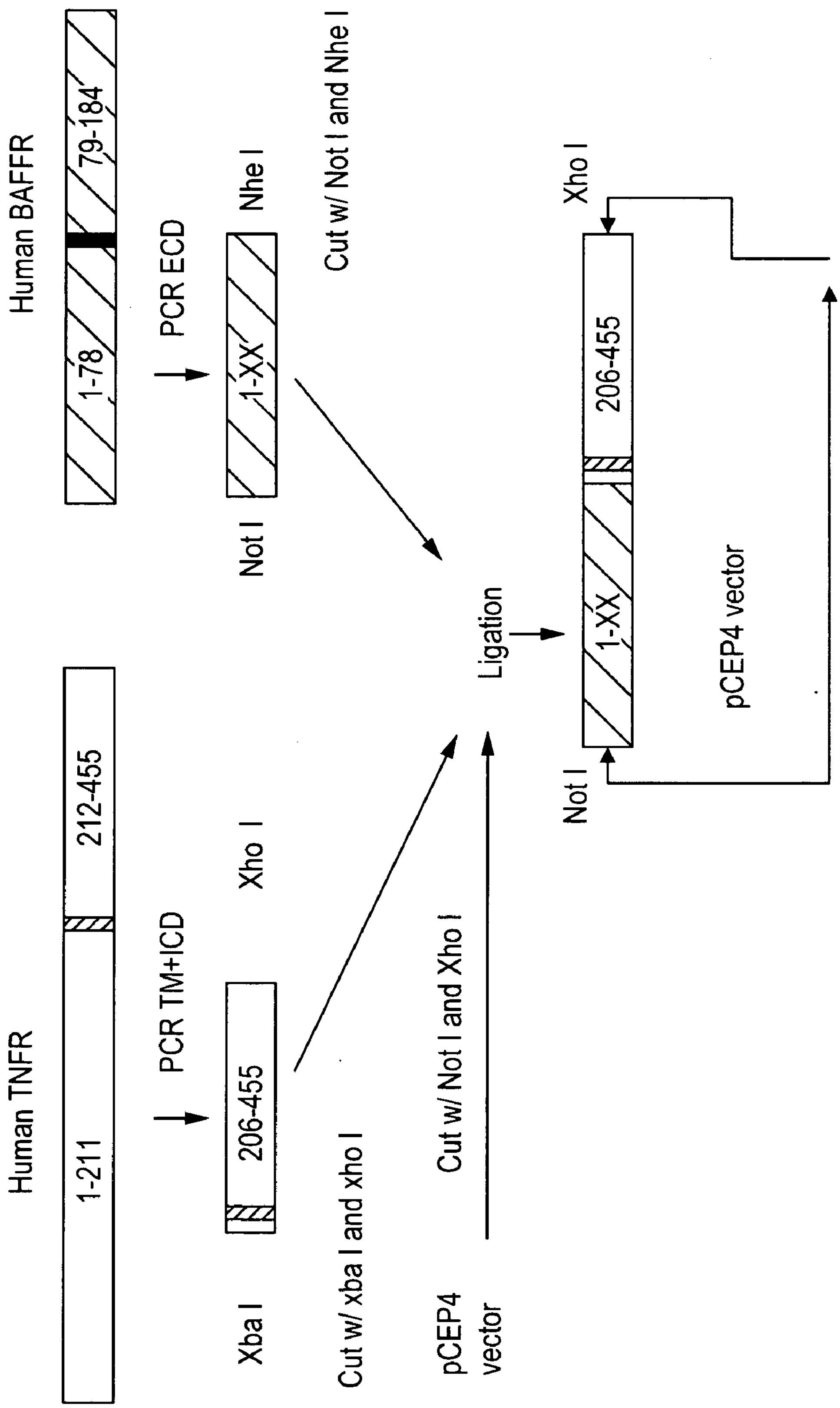

Human BAFFR
1-78
79-184
PCR ECD
Not I
1-XX
Nhe I
Cut w/ Not I and Nhe I
Human TNFR
1-211
212-455
PCR TM+ICD
Xba I
206-455
Xho I
Cut w/ xba I and xho I
pCEP4
vector
Cut w/ Not I and Xho I
Ligation
Not I
1-XX
206-455
Xho I
pCEP4 vector

FIG. 11

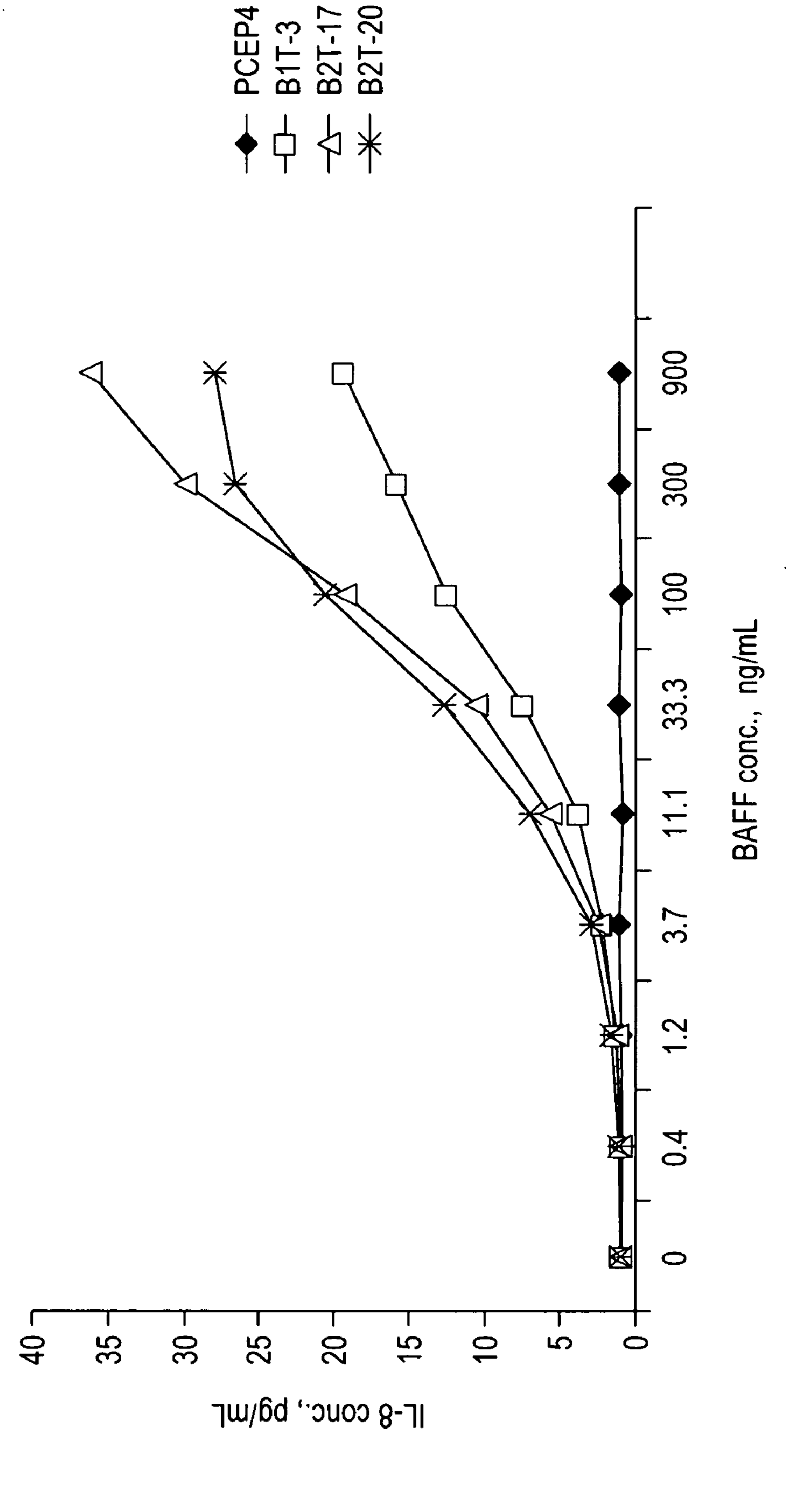

PCEP4
B1T-3
B2T-17
B2T-20
IL-8 conc., pg/mL
0
5
10
15
20
25
30
35
40
BAFF conc., ng/mL
0
0.4
1.2
3.7
11.1
33.3
100
300
900

FIG. 12

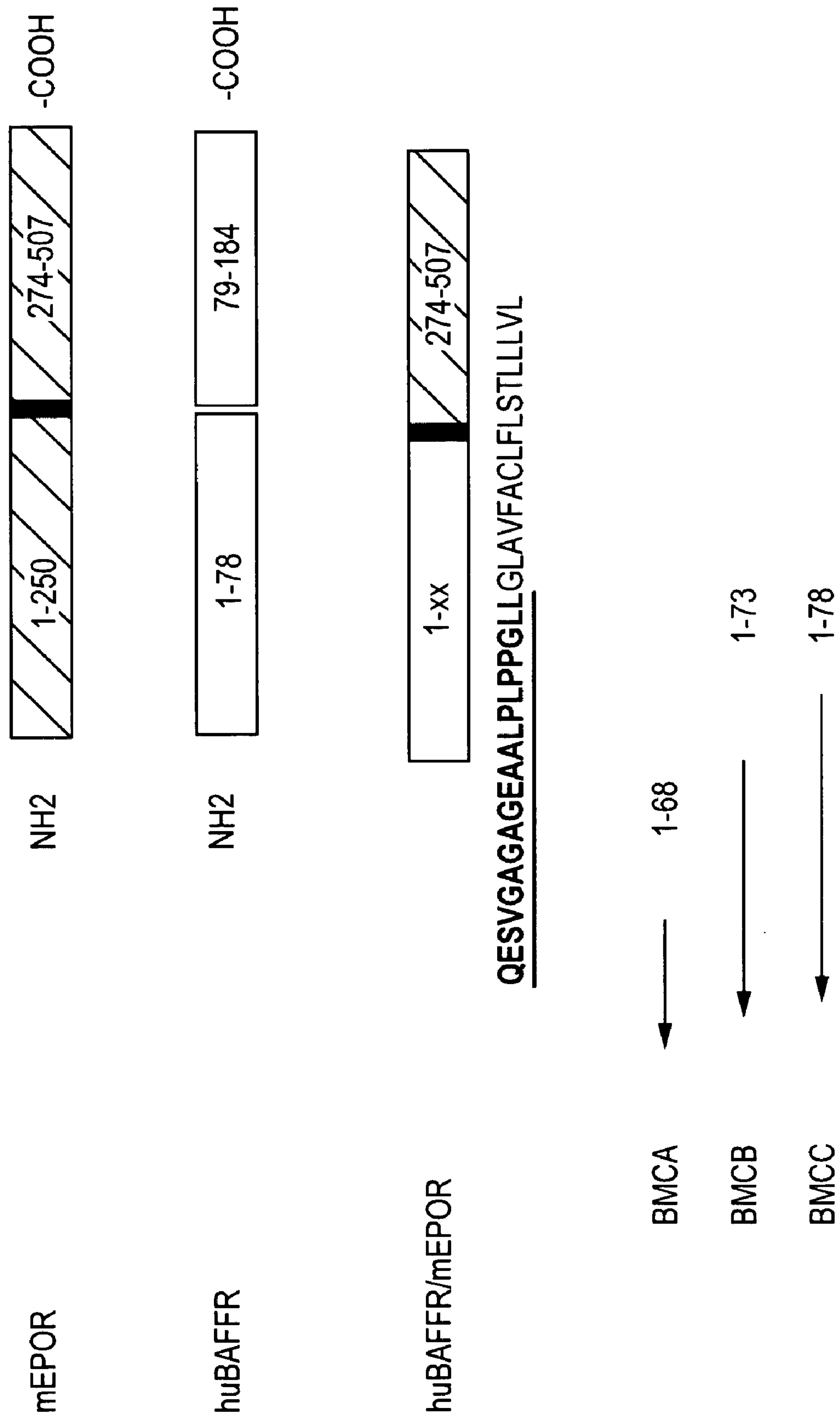
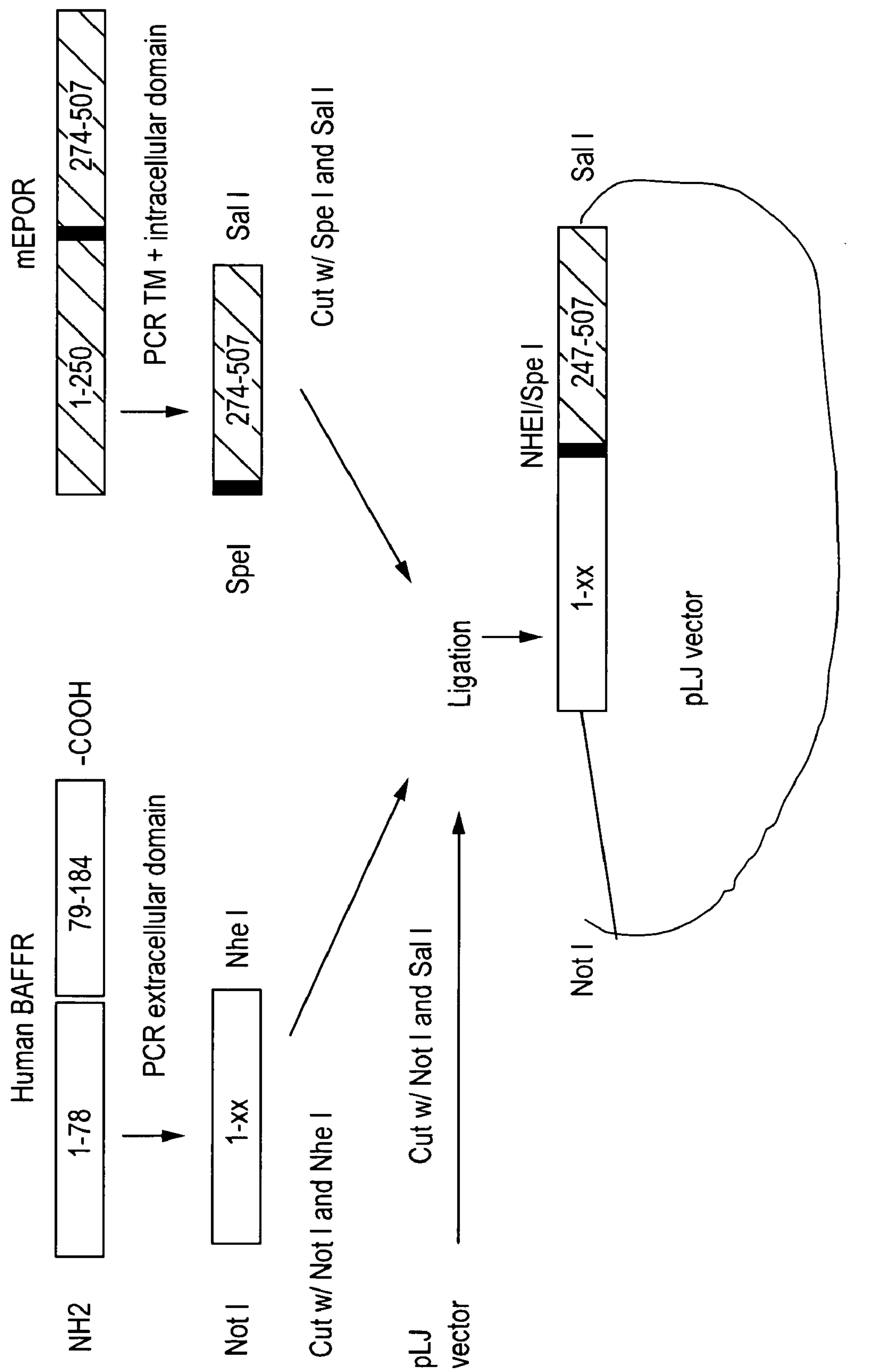

mEPOR
NH2
1-250
274-507
-COOH
huBAFFR
NH2
1-78
79-184
-COOH
huBAFFR/mEPOR
1-xx
274-507
QESVGAGEAALPLPPGLLGLAVFACLFLSTLLLVL
BMCA
1-68
BMCB
1-73
BMCC
1-78

FIG. 13



Human BAFFR
NH2
1-78
79-184
-COOH
PCR extracellular domain
Not I
1-xx
Nhe I
Cut w/ Not I and Nhe I
pLJ vector
Cut w/ Not I and Sal I
mEPOR
1-250
274-507
PCR TM + intracellular domain
SpeI
274-507
Sal I
Cut w/ Spe I and Sal I
Ligation
Not I
1-xx
NHEI/Spe I
247-507
Sal I
pLJ vector

FIG. 14

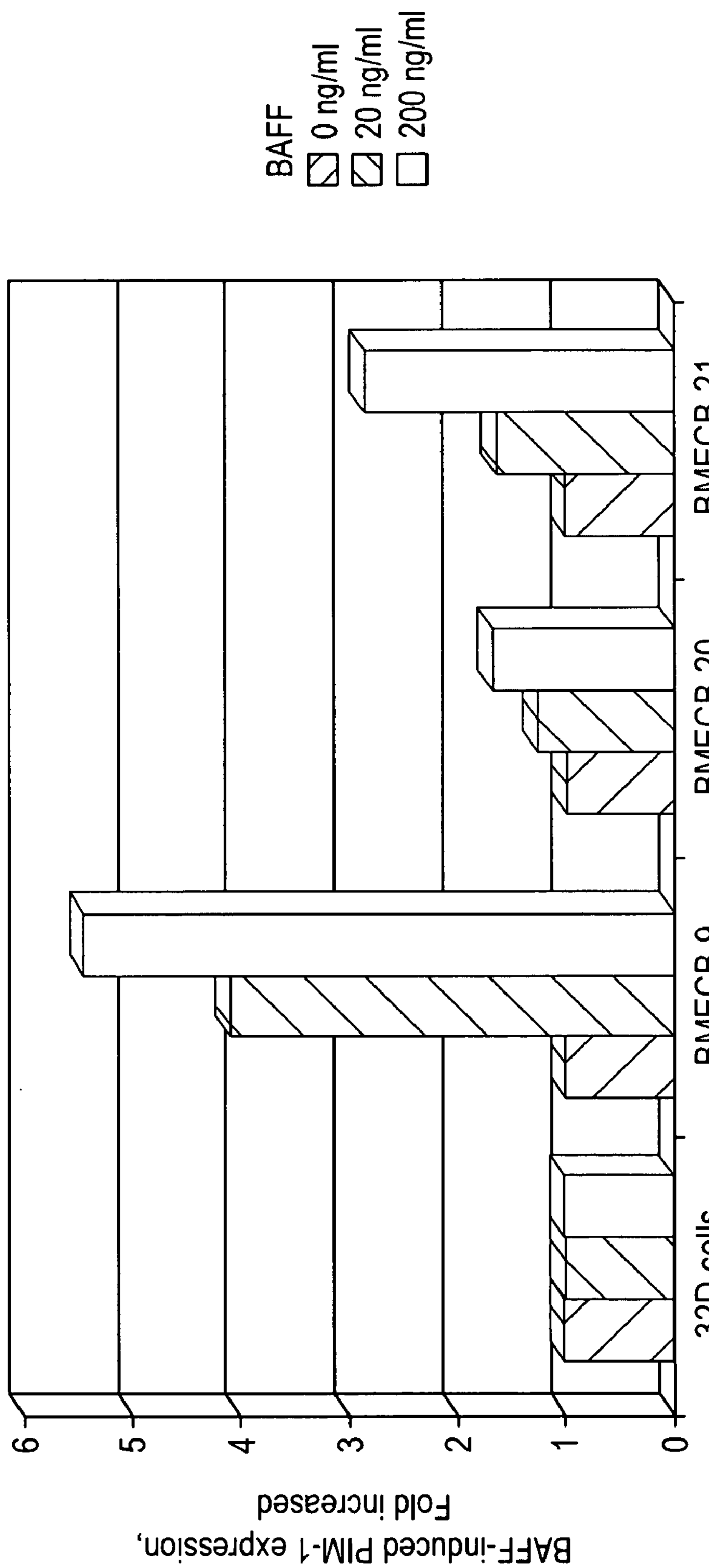

BAFF
0 ng/ml
20 ng/ml
200 ng/ml
32D cells
BMECB-9
BMECB-20
BMECB-21
0
1
2
3
4
5
6
BAFF-induced PIM-1 expression,
Fold increased

FIG. 15

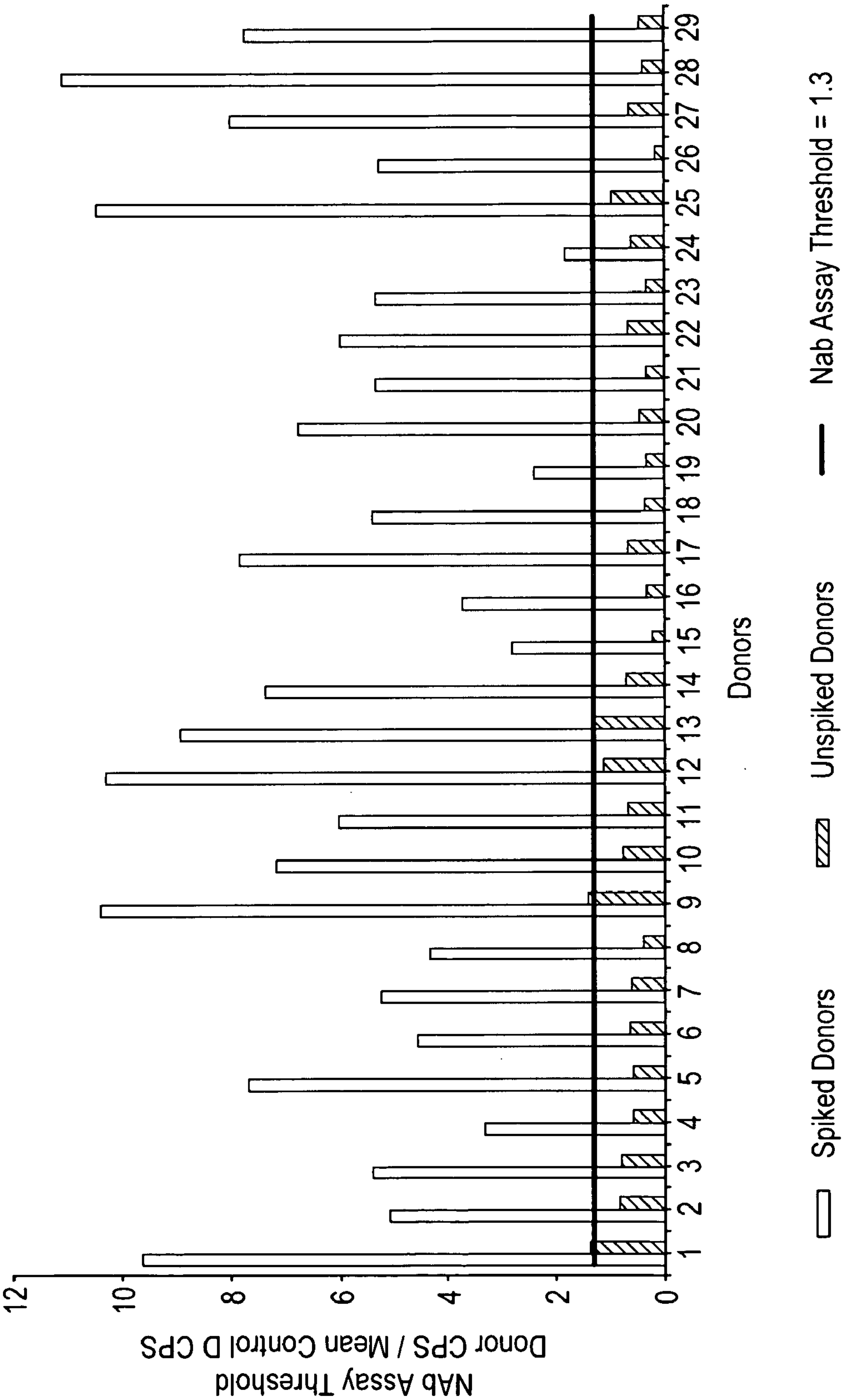
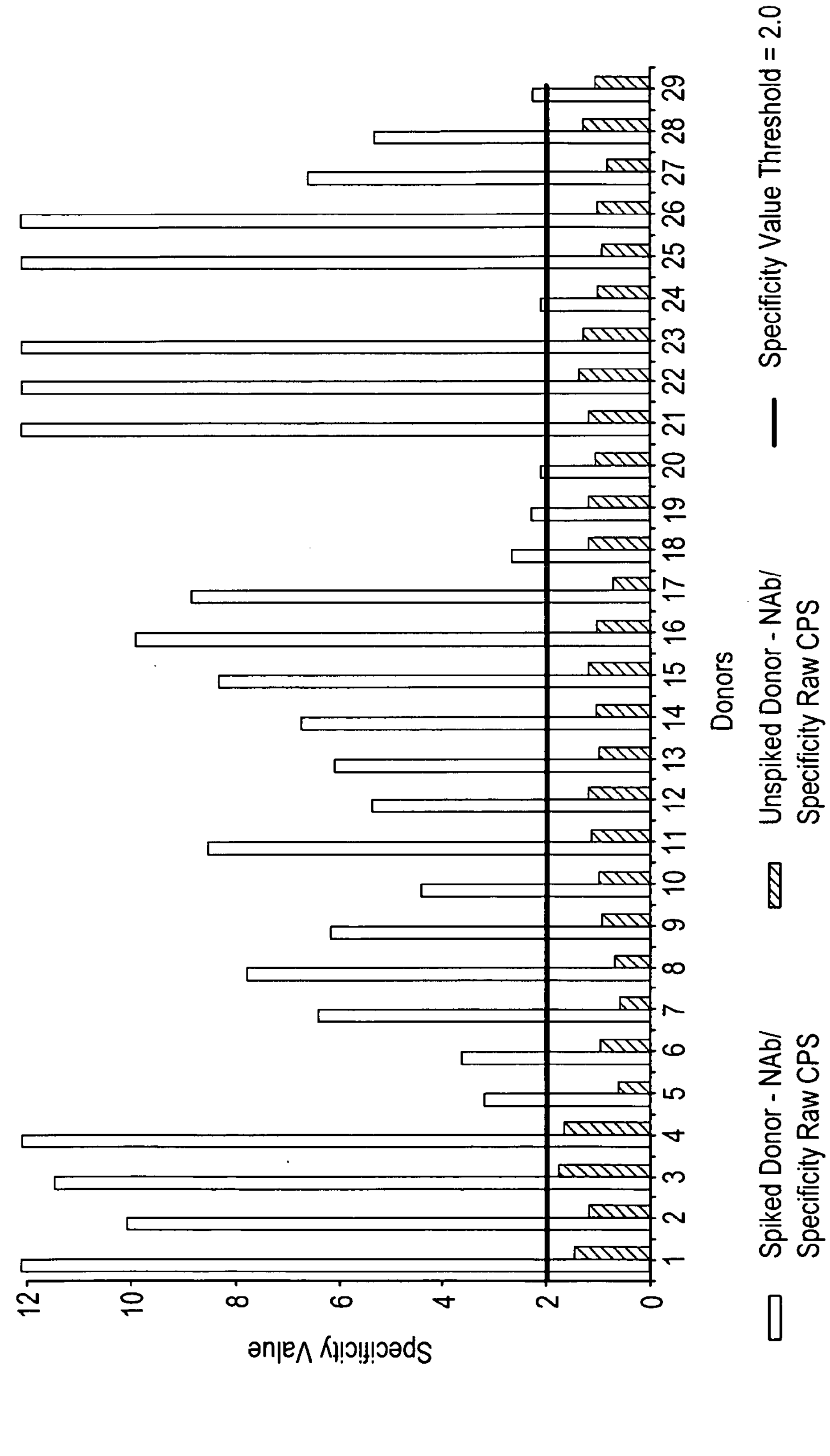

NAb Assay Threshold
Donor CPS / Mean Control D CPS
0
2
4
6
8
10
12
Donors
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29
Spiked Donors
Unspiked Donors
Nab Assay Threshold = 1.3

FIG. 16


Specificity Value
0
2
4
6
8
10
12
Donors
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
Spiked Donor - NAb/
Specificity Raw CPS
Unspiked Donor - NAb/
Specificity Raw CPS
Specificity Value Threshold = 2.0

DETECTION OF COMPOUNDS THAT AFFECT THERAPEUTIC ACTIVITY

BACKGROUND OF THE INVENTION

[0001] Subjects being treated with therapeutic substances or compositions may experience changes in the activity or the effectiveness of the therapeutic substance because of the presence of certain compounds in the subject. For example, the administration of a therapeutic substance may result in the formation of antibodies against that therapeutic substance by the subject to whom the therapeutic substance was administered. In particular, if such anti-therapeutic antibodies are neutralizing antibodies that prevent the beneficial activity of the therapeutic substance, this phenomenon can have an adverse effect on the treatment of the subject.

[0002] Cytokines or growth factors exert their biologic effects by binding to their receptors and activating various intracellular signal transduction processes (Schlessinger and Ullrich (1992) Neuron 9: 383-391; Kishimoto et al. (1994) Cell 76: 253-262; Ihle (1995) Nature 377: 591-594; Wells (1996), Proc. Natl. Acad. Sci. USA 93: 1-6; Dhanasekaran (1998), Oncogene 17: 1329-1330). The synergistic action of the activated intracellular signaling pathways causes alterations in gene expression and further leads to changes in cell survival, proliferation or apoptosis (Kishimoto et al. (1994); Ihle (1995); Appleby et al., (1996) Cell 86: 845-848; Dhanasekaran 1998). These changes reflecting the biologic effects of the growth factors or cytokines have been widely used as biomarkers in existing cell-based bioassays for determining the quantities of biologically active cytokines or growth factors (Mire-Sluis (2001) Pharm. Research 18: 1239-46; Eghbali-Fatourechi et al. (1996) Endocrinology 137(5): 1894-903). In the biomedical field, these types of assays are used to detect and characterize serum neutralizing antibodies against therapeutics, particularly protein therapeutics of which many are growth factors or cytokines.

[0003] The most widely used bioassay for serum neutralizing antibodies assesses cell proliferation by measuring the uptake of a radioisotope-labeled nucleotide, [^{3}H]-thymidine (Eghbali-Fatourechi et al. (1996); Mire-Sluis (2001)). This approach can be used as long as the cells respond to the therapeutic agent by proliferating. By monitoring the amount of [^{3}H]-Thymidine incorporated into chromosomes, either induction or inhibition of cell proliferation can be measured. When a neutralizing antibody is present, the therapeutic agent-induced proliferation is blocked. The major advantage of this method is its reliability and high sensitivity. The use of radioactive materials makes the method potentially hazardous and the disposal of radioactive waste increases the experimental costs, however. In addition, using cell proliferation as the final readouts results in a long assay duration time, typically ranging from 3 to 5 days.

[0004] Therefore, there is a need for reagents and safe, sensitive and effective methods for the detection of compounds that affect the activity of therapeutic substances and compositions.

SUMMARY OF THE INVENTION

[0005] The present invention provides methods for detecting the presence of a compound in a sample, comprising the following steps: providing, in any order: a sample suspected of comprising a compound and a control sample without the compound; a receptor and a response gene; and a ligand, wherein the ligand is capable of binding the receptor, thereby altering the expression of the response gene; combining, in any order, (i) the sample, the receptor, and the ligand; and (ii) the control sample, the receptor and the ligand; and measuring the level of the expression of the response gene; wherein the presence of the compound in the sample is detected by an alteration in the level of expression of the response gene when compared to the level of expression of the response gene when the receptor is combined with the ligand in the presence of the control sample. In one aspect, the invention provides methods for measuring the amount of a compound in a sample.

[0006] The invention further provides methods for detecting the presence of a compound in the presence or absence of a sample, comprising: providing, in any order: a compound, wherein the compound is in the presence or absence of a sample; a receptor and a response gene; and a ligand, wherein the ligand is capable of binding the receptor, thereby altering the expression of the response gene; combining, in any order, (i) the compound, the receptor, and the ligand; and (ii) the receptor and the ligand; and measuring the level of the expression of the response gene, wherein the presence of the compound is measured by an alteration in the level of expression of the response gene when the receptor is combined with the ligand and the compound compared to the level of expression of the response gene when the receptor is combined with the ligand only; and wherein when the receptor is combined with varying concentrations of the ligand and the compound, the expression of the response gene in the presence of the sample is correlated with the expression of the response gene in the absence of the sample with a correlation coefficient of at least 0.5. In one aspect, the method can be used for measuring the amount of the compound in the presence or absence of the sample.

[0007] In one aspect, the ligand can be a therapeutic substance for administration to a subject. In one aspect, the compound can be a neutralizing antibody against the therapeutic substance.

[0008] In one aspect, the receptor comprises SEQ ID NO:1. In another aspect, the receptor can comprise SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, or SEQ ID NO:5.

[0009] In one aspect, the therapeutic substance comprises SEQ ID NO:6. In another aspect, the therapeutic substance can comprise SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, or SEQ ID NO:14. In one aspect, the response gene can comprise SEQ ID NO:15. In another aspect, the response gene can comprise SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, or SEQ ID NO:21.

[0010] In one aspect, the receptor can comprise the extracellular domain of SEQ ID NO:80. In another aspect, the receptor can comprise the extracellular domain of SEQ ID NO:81, SEQ ID NO:82, or SEQ ID NO:83. In one aspect, the ligand can comprise SEQ ID NO:84. In another aspect, the ligand can comprise SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, or SEQ ID NO:91. In one aspect, the response gene can comprise SEQ ID NO:15.

[0011] In one aspect, the receptor can comprise the extracellular domain of SEQ ID NO:92. In another aspect, the receptor can comprise the extracellular domain of SEQ ID NO:93 or SEQ ID NO:94. In one aspect, the ligand can comprise SEQ ID NO:95. In another aspect, the ligand can comprise SEQ ID NO:96 or SEQ ID NO:97. In one aspect, the response gene can comprise SEQ ID NO:98. In another aspect, the response gene can comprise SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, or SEQ ID NO:103.

[0012] In one aspect, the response gene can comprise SEQ ID NO:15.

[0013] In one aspect, the ligand can comprise SEQ ID NO:105, SEQ ID NO:106, or SEQ ID NO:107. In one aspect, the receptor can comprise SEQ ID NO:108 or SEQ ID NO:109. In one aspect, the response gene is tartrate resistant acid phosphatase (TRAP).

[0014] In one aspect, the invention provides methods for detecting the presence of a compound in a sample or measuring the amount of a compound in a sample, wherein the ligand is an endogenous ligand, which is bound by a therapeutic substance for administration to a subject.

[0015] In one aspect, the level of the expression of the response gene is measured using a branched DNA (bDNA) assay.

[0016] In one aspect, the sample can be selected from the group consisting of whole blood, plasma, serum, synovial fluid, ascitic fluid, lacrimal fluid, perspiration, seminal fluid, cell extracts, and tissue extracts.

[0017] In one aspect, the invention provides methods for detecting the presence of a compound in a sample or measuring the amount of a compound in a sample, wherein the receptor is expressed by a mammalian cell.

[0018] In one aspect, the invention provides a kit comprising (a) a cell expressing a receptor, wherein the receptor comprises the intracellular domain of EPOR, and (b) one or more oligonucleotides used to detect PIM1 gene expression, the oligonucleotides selected from the group consisting of SEQ ID NOs: 22 through 79.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] **FIG. 1** illustrates the EPO-induced PIM-1 expression in UT-7 cells. The level of PIM-1 mRNA expression in UT-7 cells treated with human rSCF, rG-CSF, rEPO, rGM-CSF, and mouse rIL-3 at indicated concentrations (A), or with 2 ng/mL of rEPO for indicated periods of times (B) was determined by using bDNA technology and compared with that in the untreated cells.

[0020] **FIG. 2** schematically represents inhibition of EPO-induced PIM-1 expression by PI3-K antagonist. UT-7 cells pretreated with inhibitors for PI3-K, MAPK, PKA, and PKC and un-pretreated cells were treated with (+Epo) or without (−Epo) rEPO for 90 minutes (A) or 24 (B) hours. The levels of PIM-1 expression in cells treated with rEPO for 90 minutes were compared with that in untreated cells (A). The numbers of cells in cultures treated with or without rEPO for 24 hours were determined (B).

[0021] **FIG. 3** illustrates EPO-induced PIM-1 expression in UT-7 cells in the presence of normal human serum. UT-7 cells were treated with 3 ng/mL of rEPO for 90 minutes in the presence or absence of indicated concentrations of normal human serum (A) or with rEPO at indicated concentrations for 90 minutes in the presence or absence of 10% normal human serum (B). The level of PIM-1 mRNA in each sample was determined and compared with that in untreated cells.

[0022] **FIG. 4** is a schematic representation of inhibition of EPO-induced PIM-1 expression by Anti-EPO neutralizing antibody. UT-7 cells were treated with 0.6 ng/mL of rEPO with indicated concentrations of the anti-Epo neutralizing antibody in the presence or absence of 10% normal human serum. The expression level of PIM-1 in each sample was compared with that of untreated control cells.

[0023] **FIG. 5** illustrates the detection of anti-EPO neutralizing antibodies in serum. UT-7 cells were treated with 10% of pooled (PNHS) or individual (D1-D10) normal human donor serum spiked with 200 or 400 ng/mL anti-EPO neutralizing antibody 29123 in the presence (purple, yellow, and orange bars) or absence (blue bars) of 0.6 ng/ml of rEpo at 37oC for 1.5 hours. The expression level of PIM-1 in each sample was determined by using bDNA technology. The cutoff line for assigning the presence of an anti-EPO neutralizing antibody (Emax/2) is calculated by (PIM-1 expression in cells treated with 10% pHS only + PIM-1 expression in cells treated with 10% pHS containing 0.6 ng/mL of rEPO)/2.

[0024] **FIG. 6** schematically represents a comparison of gene expression and [3H]-Thymidine incorporation assay platforms. The levels of PIM-1 expression in UT-7 cells treated with indicated concentrations of rEPO (**FIG. 6A**), or with 0.6 ng/mL of rEPO and indicated concentrations of the anti-EPO antibody (**FIG. 6B**) for 1.5 hours were determined and compared with that in untreated control cells.

[0025] **FIG. 7** is a schematic representation of NGF and EPO hybrid receptors.

[0026] **FIG. 8** represents the generic cloning strategy for making NGFR/EPOR hybrid receptors.

[0027] **FIG. 9** is a schematic representation of BAFFR and TNFR1 hybrid receptors.

[0028] **FIG. 10** represents the generic cloning strategy for making BAFFR/TNFR1 hybrid receptors.

[0029] **FIG. 11** is a schematic representation of IL-8 production (pg/ml) induced by BAFF in COS-1 cells transfected with BAFF/TNFR constructs.

[0030] **FIG. 12** is a schematic representation of BAFFR and EPO hybrid receptors.

[0031] **FIG. 13** represents the generic cloning strategy for making BAFFR/EPOR hybrid receptors.

[0032] **FIG. 14** is a schematic representation of BAFF-induced PIM-1 expression in 32D cells expressing BMCEB constructs.

[0033] **FIG. 15** is a schematic representation of the Nab Assay for RANK/RANK ligand in 29 human donors **FIG. 16** represents the validation of the Specificity Value Threshold for RANK assay.

DETAILED DESCRIPTION OF THE INVENTION

I. Summary

[0034] The invention is directed to methods of detecting compounds that affect the activity of therapeutic substances or compositions, and to materials to be used in such methods. In one aspect, the method of the invention determines the activity of a therapeutic substance by measuring a cellular response to the binding between the therapeutic substance and a receptor for that substance, and comparing that response to the level of the response in the presence of a compound or compounds that may affect the binding between the therapeutic substance and its receptor. In other aspects, for example in cases where the therapeutic substance binds to an endogenous ligand and prevents or decreases the binding between the endogenous ligand and its receptor, the cellular response to binding of the receptor to its endogenous ligand is measured in the presence and absence of a compound that may affect the interaction of the therapeutic substance with the endogenous ligand.

[0035] II. Definitions "Polypeptide" is defined herein as natural, synthetic, and recombinant proteins or peptides generally having more than 10 amino acids. A "polypeptide linker" can be a polypeptide formed by a series of amino acids as short as one amino acid in length.

[0036] "Isolated", as used herein, refers to a polypeptide or other molecule that has been removed from the environment in which it naturally occurs.

[0037] "Substantially purified", as used herein, refers to a polypeptide that is substantially free of other polypeptides present in the environment in which it naturally occurs or in which it was produced; a preparation of a polypeptide that has been substantially purified contains at least 90% by weight (or at least 95%, at least 98%, or at least 99% by weight) of that polypeptide, wherein the weight of the polypeptide includes any carbohydrate, lipid, or other residues covalently attached to the polypeptide. A substantially purified polypeptide preparation may contain variation among polypeptide molecules within the preparation, with respect to extent and type of glycosylation or other post-translation modification, or with respect to conformation or extent of multimerization.

[0038] "Purified polypeptide", as used herein, refers to an essentially homogenous polypeptide preparation; however, an essentially homogenous polypeptide preparation may contain variation among polypeptide molecules within the preparation, with respect to extent and type of glycosylation or other post-translation modification, or with respect to conformation or extent of multimerization.

[0039] "Full-length" polypeptides are those having the complete primary amino acid sequence of the polypeptide as initially translated; for example, the full-length form of the human EPO-R is shown as SEQ ID NO:2. The "mature form" of a polypeptide refers to a polypeptide that has undergone post-translational processing steps such as cleavage of the signal sequence and/or by proteolytic cleavage to remove a prodomain. Multiple mature forms of a particular full-length polypeptide may be produced, for example by cleavage of the signal sequence at multiple sites, or by differential regulation of proteases that cleave the polypeptide. The mature form(s) of such polypeptide can be obtained by expression, in a suitable mammalian cell or other host cell, of a nucleic acid molecule that encodes the full-length polypeptide. The sequence of the mature form of the polypeptide may also be determinable from the amino acid sequence of the full-length form, through identification of signal sequences or protease cleavage sites. In certain aspects, the mature form of the human EPO-R polypeptide has amino acid positions within the corresponding SEQ ID NOs as represented in Table 6.

[0040] The "percent identity" of two amino sequences can be determined by visual inspection and mathematical calculation, and the comparison can also be done by comparing sequence information using a computer program. The first step in determining percent identity is aligning the amino acid sequences to so as to maximize overlap and identities, while minimizing gaps in the alignment. The second step in determining percent identity is calculation of the number of identities between the aligned sequences, divided by the total number of amino acids in the alignment. When determining the percent identity that an amino acid sequence has "across the length of" a target amino acid sequence, the length of the target amino acid sequence is the minimum value for the number of total bases in the alignment. For example, when determining the percent identity of a first amino acid sequence of 50 amino acids "across the length of" a second amino acid sequence of amino acids 1 through 100 of SEQ ID NO:X, if the first amino acid sequence is identical to amino acids 1 through 50 of SEQ ID NO:X, the percent identity would be 50%: 50 amino acid identities divided by the total length of the alignment (100 amino acids). An exemplary computer program for aligning amino acid sequences and computing percent identity is the BLASTP program available for use via the National Library of Medicine website ncbi.nlm.nih.gov/gorf/wblast2.cgi, or the UW-BLAST 2.0 algorithm. Standard default parameter settings for UW-BLAST 2.0 are described at the following Internet site: sapiens.wustl.edu/blast/blast/README.html. In addition, the BLAST algorithm uses the BLOSUM62 amino acid scoring matrix, and optional parameters that can be used are as follows: (A) inclusion of a filter to mask segments of the query sequence that have low compositional complexity (as determined by the SEG program of Wootton and Federhen (Computers and Chemistry, 1993); also see Wootton and Federhen, 1996, Analysis of compositionally biased regions in sequence databases, *Methods Enzymol.* 266: 554-71) or segments consisting of short-periodicity internal repeats (as determined by the XNU program of Clayerie and States (Computers and Chemistry, 1993)), and (B) a statistical significance threshold for reporting matches against database sequences, or E-score (the expected probability of matches being found merely by chance, according to the stochastic model of Karlin and Altschul (1990); if the statistical significance ascribed to a match is greater than this E-score threshold, the match will not be reported.); E-score threshold values are 0.5, 0.25, 0.1, 0.05, 0.01, 0.001, 0.0001, 1e-5, 1e-10, 1e-15, 1e-20, 1e-25, 1e-30, 1e-40, 1e-50, 1e-75, or 1e-100. Other programs used by those skilled in the art of sequence comparison can also be used to align amino acid sequences, such as, the Genetics Computer Group (GCG; Madison, Wis.) Wisconsin package version 10.0 program, 'GAP' (Devereux et al., 1984, *Nucl. Acids Res.* 12: 387). The default parameters for the 'GAP' program include: (1) The GCG implementation of a unary comparison matrix (containing a value of 1 for identities and 0 for non-identities) for nucleotides, and the weighted amino acid comparison matrix of Gribskov and Burgess, *Nucl. Acids Res.* 14:6745, 1986, as described by Schwartz and Dayhoff, eds., *Atlas of Polypeptide Sequence and Structure*, National Biomedical Research Foundation, pp. 353-358, 1979; or other comparable comparison matrices; (2) a penalty of 30 for each gap and an additional penalty of 1 for each symbol in each gap for amino acid sequences, or penalty of 50 for each gap and an additional penalty of 3 for each symbol in each gap for nucleotide sequences; (3) no penalty for end gaps; and (4) no maximum penalty for long gaps.

[0041] "Hybrid receptor" generally comprises an intracellular domain of one polypeptide joined to an extracellular domain of another polypeptide. The hybrid receptor further comprises a trans-membrane domain, which may be derived from either receptor or comprise a portion of one receptor and a portion of another one.

[0042] In one aspect, the extracellular domain includes amino acids 1-416, 1-417, 1-419, 1-422, or 1-424 of SEQ ID NO:81. In one aspect, the intracellular domain includes amino acid residues 274-507 of SEQ ID NO:3 In one aspect, the trans-membrane domain includes sequence GLAVFACLFLSTLLLVL.

[0043] In one aspect, the extracellular domain includes amino acids 1-68; 1-73 or 1-78 of SEQ ID NO:93. In one aspect, the intracellular domain includes amino acids 206-455 of SEQ ID NO:99. In one aspect, the trans-membrane domain includes sequence EDSGTTVLLPLVIFFGLCLLSLLFI.

[0044] In one aspect, the extracellular domain includes amino acids 1-68; 1-73 or 1-78 of SEQ ID NO:93. In one aspect, the intracellular domain includes amino acid residues 274-507 of SEQ ID NO:3. In one aspect, the trans-membrane domain includes sequence GLAVFACLFLSTLLLVL.

[0045] "Soluble forms" of polypeptides of the invention comprise certain fragments or domains of these polypeptides. Soluble polypeptides are polypeptides that are capable of being secreted from the cells in which they are expressed. A secreted soluble polypeptide can be identified (and distinguished from its non-soluble membrane-bound counterparts) by separating intact cells which express the desired polypeptide from the culture medium, e.g., by centrifugation, and assaying the medium (supernatant) for the presence of the desired polypeptide. The presence of the desired polypeptide in the medium indicates that the polypeptide was secreted from the cells and thus is a soluble form of the polypeptide. The use of soluble forms of cytokine polypeptides of the invention is advantageous for many applications. Purification of the polypeptides from recombinant host cells is facilitated, since the soluble polypeptides are secreted from the cells. Moreover, soluble polypeptides are generally more suitable than membrane-bound forms for parenteral administration and for many enzymatic procedures. In certain aspects of the invention, mature soluble forms of EPO-R or other polypeptides of the invention do not contain a trans-membrane or membrane-anchoring domain, or contain an insufficient portion of such a domain (e.g., 10 amino acids or fewer) to result in retention of the polypeptide in a membrane-bound form.

[0046] "An isolated polypeptide consisting essentially of an amino acid sequence" means that the polypeptide can optionally have, in addition to said amino acid sequence, additional material covalently linked to either or both ends of the polypeptide, said additional material between 1 and 10,000 additional amino acids covalently linked to either or both ends of the polypeptide; or between 1 and 1,000

[0047] additional amino acids covalently linked to either or both ends of the polypeptide; or between 1 and 100 additional amino acids covalently linked to either or both ends of the polypeptide. Covalent linkage of additional amino acids to either or both ends of the polypeptide according to the invention results in a combined amino acid sequence that is not naturally occurring.

[0048] "Correlation" and "correlation coefficient" are defined using the following formula:

$$\rho_{X,Y} = \frac{\mathrm{cov}(X, Y)}{\sigma_X \cdot \sigma_Y}$$

where

$$\sigma_X^2 = 1/n\sum (X_i - \mu_X)^2$$

and

$$\sigma_Y^2 = 1/n\sum (Y_i - \mu_Y)^2$$

[0049] This correlation formula measures the relationship between two data sets that are scaled to be independent of the unit of measurement. The population correlation calculation returns the covariance of two data sets divided by the product of their standard deviations. The correlation coefficient, symbolized in the formula above as ρx,y, will also be referred to herein using the symbol "r". The correlation formula determines whether two ranges of data move together—that is, whether large values of one set are associated with large values of the other (positive correlation or positive value of r, with a maximum value of r=1), whether small values of one set are associated with large values of the other (negative correlation or negative value of r, with a minimum value of r=−1), or whether values in both sets are unrelated (correlation near zero, or value of r equal to or near zero).

III. Receptor Polypeptides for Detection of Neutralizing Antibodies

[0050] A. Summary. Receptor polypeptides of the invention are polypeptides that comprise at least a portion of the extracellular domain of a receptor polypeptide or of a variant thereof, covalently linked to at least a portion of the intracellular domain of a receptor polypeptide or of a variant thereof. The extracellular domain and the intracellular domain portions can be derived from same or from different receptor polypeptides, including embodiments wherein the extracellular portion of the receptor is from the human receptor, for example, and the intracellular portion of the receptor is from the murine form of the receptor.

[0051] Examples of different receptors, of ligands that interact with them, and of genes that are up- or down-regulated in response to receptor-ligand interactions, are provided in Tables 7-21 below.

[0052] B. Extracellular Domains. The receptor polypeptide for crystallization comprises at least a portion of the extracellular region of the polypeptide of SEQ ID NO:1, SEQ ID NO:80, SEQ ID NO:92, or SEQ ID NO:109, or a variant thereof. In certain aspects, the entire extracellular region of the polypeptide of SEQ ID NO:1, SEQ ID NO:80, SEQ ID NO:92, or SEQ ID NO:109 is included in the receptor polypeptide. As certain examples, the receptor polypeptide can comprise amino acids 25 through 251 of SEQ ID NO:1, or amino acids 33 through 420 of SEQ ID NO:80, or amino acids 1 through 79 of SEQ ID NO:9, or a variant thereof.

[0053] C. Intracellular Domains. The receptor polypeptide for crystallization comprises at least a portion of the intracellular region of the polypeptide of SEQ ID NO:1, SEQ ID NO:80, SEQ ID NO:92, or SEQ ID NO:109, or a variant thereof. In certain aspects, the entire intracellular region of the polypeptide of SEQ ID NO:1, SEQ ID NO:80, SEQ ID NO:92, or SEQ ID NO:109 is included in the receptor polypeptide. As certain examples, the receptor polypeptide can comprise amino acids 275 through 509 of SEQ ID NO:1, or amino acids 445 through 801 of SEQ ID NO:80, or amino acids 101 through 189 of SEQ ID NO:9, or a variant thereof.

[0054] D. Variants. Another consideration that will guide those of skill in the art in making variants of receptor polypeptides is the nature of the amino acid substitutions that are made; such substitutions can be conservative, which means that the amino acid present in the variant at a certain position has the same chemical and/or size properties as the amino acid at the corresponding position in the unaltered receptor polypeptide. Table 1 summarizes groups of amino acids that are considered to have similar properties, so that the substitution of any amino acid with another from the same row of Table 1 would be a conservative substitution. In certain aspects, receptor polypeptide variants have 20% or fewer amino acid substitutions (or 15% or fewer, or 10% or fewer, or 7.5% or fewer, or 5% or fewer, or 2.5% or fewer, or 1% or fewer) across the length of polypeptides of the invention. In certain aspects, receptor polypeptide variants have 20% or fewer conservative amino acid substitutions (or 15% or fewer, or 10% or fewer, or 7.5% or fewer, or 5% or fewer, or 2.5% or fewer, or 1% or fewer) across the length of polypeptides of the invention.

[0055] In certain embodiments, the receptor polypeptides or variants thereof have EPO-binding activity, NGF-binding activity, BAFF-binding activity, or RANKL (OPG)-binding activity.

TABLE 1

Conservative Amino Acid Substitutions	
Basic:	arginine; lysine; histidine
Acidic:	glutamic acid; aspartic acid
Polar:	glutamine; asparagine
Alkyl:	leucine; isoleucine; valine; glycine; alanine
Aromatic:	phenylalanine; tryptophan; tyrosine
Small Non-Alkyl:	serine; threonine; cysteine; methionine; proline

[0056] E. Expressing Receptor Polypeptides

[0057] The receptor polypeptides of the invention can be produced by living host cells that express the polypeptide, such as host cells that have been genetically engineered to produce the polypeptide. Methods of genetically engineering cells to produce polypeptides are well known in the art. See, e.g., Ausubel et al., eds. (1990), Current Protocols in Molecular Biology (Wiley, N.Y.). Such methods include introducing nucleic acids that encode and allow expression of the polypeptide into living host cells. These host cells can be bacterial cells, fungal cells, insect cells, or animal cells grown in culture. Bacterial host cells include, but are not limited to, *Escherichia coli* cells. Examples of suitable *E. coli* strains include: HB101, DH5α, GM2929, JM109, KW251, NM538, NM539, and any *E. coli* strain that fails to cleave foreign DNA. Fungal host cells that can be used include, but are not limited to, *Saccharomyces cerevisiae, Pichia pastoris*, and *Aspergillus* cells. A few examples of animal cell lines that can be used are CHO, VERO, BHK, HeLa, Cos, MDCK, 293, 3T3, and WI38. New animal cell lines can be established using methods well known by those skilled in the art (e.g., by transformation, viral infection, and/or selection).

[0058] Purification of the expressed receptor polypeptide can be performed by any standard method. When the receptor polypeptide is produced intracellularly, the particulate debris is removed, for example, by centrifugation or ultrafiltration. When the polypeptide is secreted into the medium, supernatants from such expression systems can be first concentrated using standard polypeptide concentration filters. Protease inhibitors can also be added to inhibit proteolysis and antibiotics can be included to prevent the growth of microorganisms. Receptor polypeptides can be produced in the presence of chaperone or accessory proteins in order to obtain a desired polypeptide conformation, or can be subjected to conditions such as oxidizing and/or reducing conditions after production in order to induce refolding or changes in polypeptide conformation (see, for example, WO 02/068455).

[0059] The receptor polypeptide can be purified using, for example, hydroxyapatite chromatography, gel electrophoresis, dialysis, and affinity chromatography, and any combination of purification techniques known or yet to discovered.

[0060] F. Gene Expression Methods

[0061] The invention provides methods of detecting compounds that affect therapeutic activity by measuring gene expression of response genes.

[0062] In one aspect, the expression of PIM-1, a protein serine/threonine kinase potentially involved in EPO-dependent survival and proliferation of erythroid precursors and other types of cells (Meeker et al. (1987) *J. Cell. Biochem.* 35: 105-12.; Wang et al., (2001) *J Veterinary Sci.* 2(3): 167-79; Kumenacker et al. (2001) *J. Neuroimmunology* 133: 249-259), and regulated by EPO in EPO-dependent UT-7 cells, can be used for detecting compounds affecting therapeutic activity of EPO. Previous studies have shown that PI3-K activity is critical for EPO-supported erythroid progenitor survival and differentiation (Kumenacker et al. (2001); Myklebust et al. (2002) *Exp. Hematol.* 30:990-1000; Uddin et al. (2000) *Biochem. Biophys. Res. Comm.* 275: 16-9; Sawyer and Jacobs-Helber, (2000) *J Hematotherapy & Stem Cell Research* 9:2 1-9). Data presented in Example 1 indicate that this signal is also essential for the EPO-dependent survival and/or proliferation of the UT-7 cells. Although the exact function of PIM-1 in EPO-stimulated cell survival and proliferation remains unclear, these observations suggest that it may be a signal transducer playing roles down stream of the PI3-K. At least, the expression of PIM-1 itself in EPO-dependent UT-7 cells is clearly coregulated by PI3-K signaling. Therefore, the level of PIM-1 mRNA expressed in EPO-dependent UT-7 cells reflects the amount of EPO signal received by the cells and can be used as a quantitative measurement for EPO signaling. Thus, the same strategy can be used for determining the presence and quantitative measurement of anti-EPO neutralizing antibodies that inhibit the biological activities of EPO.

[0063] In another aspect, PIM-1 expression can be used for detection of compounds, for example, neutralizing antibodies, that affect activity of therapeutic protein or antibodies/peptibodies by generating hybrid constructs using, for example, an intracellular domain of the EPO receptor linked to an extracellular domain of the receptor of interest. In one aspect, an intracellular domain of NGF receptor can be used. In another aspect, BAFF receptor can be used.

[0064] In another aspect, different response genes can be used. In one aspect, IL-8 expression can be used as a quantitative measurement. Thus, a construct using, for example, an intracellular domain of a TNF receptor and an extracellular domain of a receptor of interest can be created. In one aspect, a hybrid construct comprising the extracellular domain of BAFFR and the intracellular domain of TNFR can be created and thereby BAFF-induced IL-8 expression can be used to detect anti-BAFF neutralizing antibody, for example.

[0065] In yet another aspect, mRNA expression of the terminal differentiation marker TRAP (tartrate-resistant acid phosphatase) can be used (Lacey et al. (1988)). The inhibition of OPG ligand/RANK by antibodies or peptibodies would inhibit TRAP production as well, however, if compounds affecting anti-RANK antibodies were present, such as neutralizing antibodies, the TRAP enzyme would continue to be produced.

[0066] The above description of the invention is exemplary, and is not meant to be limiting as to, for example, the response gene, the types of host cells used, the methods and compositions for providing for host cells having varying levels of expression of a response gene, and the like, as such can be varied and remain within scope of the present invention, and such variations will be readily appreciated by the ordinarily skilled artisan.

[0067] G. Branched DNA Technology Expression of a response gene can be detected in a variety of ways well known in the art, e.g., by use of hybridization probes, PCR primers, or antibodies specific for a response gene product.

[0068] In one aspect, branched DNA (bDNA technology) can be used to quantitatively measure expression of a response gene. This is a highly sensitive and convenient to use technique. Urdea, M. and Wuestehube, L. (2000). Branched DNA (bDNA) technology. In: C. Kessler (Ed.) Nonradioactive Analysis of Biomolecules. Srpinger-Verlag Press & Publications, Heidelberg, p. 388. It can detect the existence of as few as 1 to 50 copies of mRNA in a sample. Elbeik, T. et al. (2000) *J. Clin. Microbiol.* 38: 1113-20. The entire procedure can be fully automated, making it a good choice for high throughput operations. Murphy, D. G. et al. (2000) *J. Clin. Microbiol.* 38: 4034-41.

[0069] The above description of the invention is exemplary, and is not meant to be limiting as to, for example, the methods for detecting mRNA of the response gene, and the like, as such can be varied and remain within scope of the present invention, and such variations will be readily appreciated by the ordinarily skilled artisan.

[0070] For example, rather than detect changes in expression of a response gene by using bDNA technology, response gene expression can be detected by using methods well known in the art for detecting gene expression levels (e.g., Northern blot, microarray-based, or other solid support-based methods, tailored expression membrane assays, or Taqman assays etc.). Also it will be readily appreciated that increasing the number of response genes analyzed (e.g., two or more response genes) can provide additional information and/or increase confidence scores of the results obtained relative to detection of a single response gene. Assays with multiple response genes can be conducted simultaneously using different detectable labels for each gene (e.g., different fluorescent reporters having different excitation and/or emission wavelengths).

[0071] H. Introduction into Host Cells

[0072] Methods for introducing a construct into a host cell are well known in the art. This can be accomplished by, for example, introduction of an autonomous plasmid, which can be maintained as an episomal element and/or chromosomally integrated into the genome of the host cell. Suitable constructs, vectors, plasmids, etc. are well known in the art and will vary with the host cell, size and other characteristics of the reporter gene, etc.

[0073] The methods of the invention can be used in connection with any of a variety of host cells, including eukaryotic, prokaryotic, diploid, or haploid organisms. Host cells can be single cell organisms (e.g., bacteria) or multicellular organisms (transgenic organisms, such as insects (e.g., *Drosophila* spp), worms (e.g., *Caenorhabditis* spp, e.g., *C. elegans*) and higher animals (e.g., transgenic mammals such as mice, rats, rabbits, hamsters, humans etc. or cells isolated from such higher animals, including humans). The host cell can also be a cell infected with a virus or phage that contains a target sequence in the viral or phage genome.

[0074] The following examples are offered to more fully illustrate the invention, but are not to be construed as limiting the scope thereof.

EXAMPLE 1

[0075] This example illustrates an assay which measures the variations of target gene expression that reflect the biologic effect of a therapeutic agent and capabilities of the antibodies, if present, to neutralize the therapeutics. In particular, this method can be used for detection and measurement of anti-erythropoietin antibodies.

[0076] Cells and Proteins

[0077] UT-7, a human acute megakaryocytic leukemia cell line was maintained in growth media [RPMI/1640 (Gibco, N.Y.) containing 10% fetal calf serum (Hyclone, Logon, Utah)] supplemented with 10 ng/mL granulocyte-macrophage colony-stimulating factor (GM-CSF). Recombinant human erythropoietin (rEPO), stem cell factor (rSCF), granulocyte colony-stimulating factor (rG-CSF), rGM-CSF, mouse interleukin-3 (rIL-3), and rabbit anti-human EPO polyclonal antibody (29123) were provided by Amgen.

Protein kinase inhibitors for phosphatidylinositol 3-kinase (PI3-K) (LY294002), MAP kinase (MAPK) (UO126), protein kinase A (PKA), and protein kinase C (PKC) were all purchased from Promega (Madison, Wis.).

[0078] Microarray Analysis of Gene Expression

[0079] Microarray analysis of cell samples was performed using well-described protocols (Eisen and Brown (1999) Methods Enzymol. 303, 179-205) with minor modifications. PolyATtract (Promega) purified mRNA was reverse-transcribed using random primers in the presence of either Cy3 or Cy5 dye-labeled dCTP. Control and test fluorescent probes were hybridized to cDNA-spotted glass slides overnight in a competitive hybridization process. After washing, fluorescent images of the dried slides were obtained using a GenePix Scanner 4000 (Axon Instruments, Union City, Calif.). GenePix Pro 3.0 software (Axon Instruments, Union City, Calif.) was used for feature detection. The subsequent data were inspected using a series of internal standards that enabled determination of sensitivity, linearity, and dynamic range of response within individual experiments. Global normalized data was then exported into the Resolver (Rosetta, Kirkland, Wash.) database for storage and analysis. For each control and test pair, data was combined with a second dye-swapped hybridization to reduce potential dye incorporation biased measurements.

[0080] Oligonucleotide Probes

[0081] Human PIM-1 specific probes and human cyclophilin probes for bDNA analysis were designed by using the ProbeDesigner software from Bayer Corporation (West Haven, Conn.). Three sets of oligonucleotide probes were designed for each molecule: the capture extender (CE), label extender (LE), and blocker (BL). Thirty-one probes were generated for PIM-1, including 8 CE probes, 17 LE probes, and 6 BL probes; and 27 were made for cyclophilin, including 6 CE probes, 18 LE probes, and 3 BL probes (Table 2). All probes for each gene were pooled according to the manufacturer's instructions.

TABLE 2

Oligonucleotide probes for bDNA detection	
	Human PIM-1
CE	gctcgggcctctccaggTTTTTCTCTTGGAAAGAAAGT
	agtcgaagagatcttgcaccgTTTTTCTCTTGGAAAGAAAGT
	ggccagctcctcttgcaggTTTTTCTCTTGGAAAGAAAGT
	agctcgccgcgattgagTTTTTCTCTTGGAAAGAAAGT
	ttgagcagcgcccccgaTTTTTCTCTTGGAAAGAAAGT
	catacagcaggatccccaggTTTTTCTCTTGGAAAGAAAGT
	attctgaagagaccctctgcctgaaTTTTTCTCTTGGAAAGAAAGT
	gatttcttcgaaggttggcctTTTTTCTCTTGGAAAGAAAGT
LE	gcaggaccacttccatgggTTTTTAGGCATAGGACCCGTGTCT
	acccgagctcaccttcttcaTTTTTAGGCATAGGACCCGTGTCT
	gcctaatgacgccggagaaTTTTTAGGCATAGGACCCGTGTCT
	cctctcgaaccagtccaggaTTTTTAGGCATAGGACCCGTGTCT
	atcaggacgaaactgtcgggTTTTTAGGCATAGGACCCGTGTCT
	gctccccttttccgtgatgaTTTTTAGGCATAGGACCCGTGTCT
	gccgcacggcctccagTTTTTAGGCATAGGACCCGTGTCT
	ccccgcagttgtggcagtTTTTTAGGCATAGGACCCGTGTCT
	tgatgtcgcggtgtagcaTTTTTAGGCATAGGACCCGTGTCT
	gtcgataaggatgttttcgtcctTTTTTAGGCATAGGACCCGTGTCT
	aagtccgtgtagacggtgtccTTTTTAGGCATAGGACCCGTGTCT
	ctatacactcgggtcccatcgTTTTTAGGCATAGGACCCGTGTCT
	ctgccatggtagcgatggtaTTTTTAGGCATAGGACCCGTGTCT
	gaccagactgccgccgacTTTTTAGGCATAGGACCCGTGTCT
	aaggaatatctccacacaccatatTTTTTAGGCATAGGACCCGTGTCT
	agcaccatctaatgagatgctgacTTTTTAGGCATAGGACCCGTGTCT
	ttgcatccatggatggttctgTTTTTAGGCATAGGACCCGTGTCT
BL	cacctgccagaagaagctgcg
	cccgaagtcgatgagcttg
	gcggatccactctggaggg
	gatctcttcgtcatgctcga
	gaaaacctggcccctgat
	atctgatggtctcagggcca
	Human Cyclophilin
CE	atacaccttgacggtgactttgTTTTTCTCTTGGAAAGAAAGT
	cctttctctcctgtagctaaggcTTTTTCTCTTGGAAAGAAAGT
	ggtgtctttgcctgcgttgTTTTTCTCTTGGAAAGAAAGT
	tgaagaactgggagccgttTTTTTCTCTTGGAAAGAAAGT
	gtctgtcttggtgctctccaTTTTTCTCTTGGAAAGAAAGT
	tcaggggtttatcccggctTTTTTCTCTTGGAAAGAAAGT
LE	gccgcagaaggtcccggcTTTTTAGGCATAGGACCCGTGTCT
	ggccccttcttcttctcatcgTTTTTAGGCATAGGACCCGTGTCT
	catctccaattcgtaggtcaaaTTTTTAGGCATAGGACCCGTGTCT
	agatcacccggcctacatcttTTTTTAGGCATAGGACCCGTGTCT
	cacaaaattatccactgtttttggTTTTTAGGCATAGGACCCGTGTCT
	atttgctgtttttgtagccaaatTTTTTAGGCATAGGACCCGTGTCT
	agtctccgccctggatcatTTTTTAGGCATAGGACCCGTGTCT
	tgtgccatctcccctggtgaTTTTTAGGCATAGGACCCGTGTCT
	accgtagatgctctttcctccTTTTTAGGCATAGGACCCGTGTCT
	agttctcatcggggaagcgctTTTTTAGGCATAGGACCCGTGTCT
	aggcccgtagtgcttcagtttgaTTTTTAGGCATAGGACCCGTGTCT
	gccatgctgacccagccTTTTTAGGCATAGGACCCGTGTCT
	acatgcttgccatctagccaTTTTTAGGCATAGGACCCGTGTCT
	ccctctagaactttgccaaacaccTTTTTAGGCATAGGACCCGTGTCT
	ccttccgcaccacctccatgTTTTTAGGCATAGGACCCGTGTCT
	cagtctgcgatgatcacatcctTTTTTAGGCATAGGACCCGTGTCT
	tccacctcgatcttgccgTTTTTAGGCATAGGACCCGTGTCT
	gcgatggcaaagggcttcTTTTTAGGCATAGGACCCGTGTCT
BL	aacagtctttccgaagagaccaa
	gaagtccttgattacacgatgga
	ggctgtcttgactgtcgtga

[0082] Cell Treatment

[0083] UT-7 cells were washed 2 times with the growth media and incubated overnight in rGM-CSF-free media at 37° C. with 5% CO_2. Triplicate samples of the rGM-CSF-starved cells were seeded in 96-well tissue culture plates with 100 μL rGM-CSF-free media at a density of 1.2×10^5 cells per well and treated with various concentrations of rEPO in the absence or presence of anti-EPO antibody, or with various concentrations of other cytokines, including rGM-CSF, rG-CSF, rSCF, and rIL-3, at 37° C. for 90 minutes.

[0084] For serum tolerate experiments, GM-CSF-starved UT-7 cells were either treated with 3 ng/mL rEPO in the presence or absence of various concentrations pooled normal human serum (PNHS, Bioreclamation, Inc., East Meadow, N.Y.) or with various concentrations of rEPO in the presence or absence of 10% PNHS at 37° C. for 90 minutes.

[0085] For studies using signal transduction antagonists, the rGM-CSF-starved cells were first treated with various concentrations of LY294002, UO126, and the inhibitors for PKA and PKC separately at 37° C. for 30 minutes and then with 21 ng/mL of rEPO at 37° C. for 90 minutes or 24 hours. After all treatments, the levels of PIM-1 expression were determined using branched DNA (bDNA) technology. The number of cells in each well that had been treated with rEPO for 24 hours was counted.

[0086] Branched DNA Analysis

[0087] Branched DNA analysis was performed using the QuantiGene High Volume Kit (Bayer, West Heaven, Conn.) using a 3-step procedure provided by the manufacturer, which included specimen preparation, hybridization, and detection. Briefly, treated or untreated UT-7 cells seeded in 96-well tissue culture plates were mixed with 50 μL lysis mixture (provided by the kit) using a multiple channel pipette and incubated at 46° C. for 30 minutes to release mRNA. Aliquots of 70 μL and 30 μL of each lysate were transferred to capture plates (provided by the kit) with 30 μL pooled PIM-1-specific probes or 70 μL pooled cyclophilin probes, respectively, and incubated overnight at 53° C. The hybridization mixtures were removed and the plates were washed twice with 400 μL wash buffer (0.1 SSC, 0.03% lithium lauryl sulfate) using an Auto Plate Washer (Bio-TEK, Winooski, Vt.). After washing, 100 μL Amplifier Working Reagent (provided by the kit) was added to each well and incubated at 46° C. for 1 hour. The plates were washed twice as described above, incubated with 100 μL Labeling Working Reagent (provided by the kit) at 46° C. for 1 hour, washed again 3 times, and processed for chemiluminescent detection. The amount of the target mRNA in each sample was determined by the intensity of the luminescent emission detected using a luminometer (Wallac Victor 1420, Perkin Elmer, Finland).

[0088] [^{3}H]-Thymidine Incorporation

[0089] UT-7 cells were washed 2 times with growth media and incubated overnight in rGM-CSF-free media at 37° C., with 5% CO_2 as described above. Triplicate samples of the rGM-CSF-starved cells were seeded in 96-well tissue culture plate at a density of 1×10^5 cells per well and treated with various concentrations of rEPO in the presence or absence of anti-EPO antibody at 37° C. with 5% CO_2 for 72 hours. Then, 2 μCi [^{3}H]-thymidine (Amersham, Little Chalfont, Buckinghamshire, UK) were added to each well and the cells were further incubated for 4 hours. The cells were harvested using a cell harvester (Filtermate 196, Packard, Ill.), and the incorporated radioactivity was determined using a Matrix 9600 beta counter (Packard, Ill.).

[0090] EPO Induces PIM-1 Expression

[0091] mRNA microarray experiments determined which genes in UT-7 cells had altered expression after rEPO treatment. UT-7 cells quieted in rGM-CSF-free media were treated with 20 ng/mL rEPO at 37° C. for 2, 4, 6, or 24 hours. Messenger RNAs extracted from the rEPO-treated or untreated control cells were used to generate probes for the subsequent microarray experiments. The mRNA expression level of a number of genes has been changed in rEPO-treated cells compared with that in the untreated control cells (Table 3). In particular, the level of the PIM-1 mRNA in rEPO-treated cells was more than 20 times higher than that in the untreated control cells.

TABLE 3

Epo-Altered mRNA expression in UT-7 cells

Gene Name	Folds* 2 hr	4 hr	6 hr	24 hr
PIM 1	+8.06	+13.85	+8.49	+21
LOC64182	+2.96	+6.42	+3.98	+13.68
RTP801	+2.47	+3.75	+3.68	+9.64
NFYC	+1.48	+2.07	+2.39	+8.25
CBS	+1.43	+1.47	+1.66	+7.59
IGFBP4	+2.14	+2.91	+2.82	+5.57
ATF5	+1.12	+1.53	+1.67	+5.22
CTH	+1.32	+1.97	+2.66	+5.16
PKM2	+1.30	+1.43	+1.52	+5.15
LDHA	+1.31	+1.83	+2.24	+4.80
JTB	+1.42	+1.82	+2.53	+4.33
GPI	+1.32	+1.47	+1.50	+4.24
VEGF	+1.88	+2.05	+2.32	+3.81
ATF4	+1.85	+1.95	+2.39	+3.60
LDHC	+1.35	+1.63	+2.41	+3.31
TIMP1	+1.50	+1.50	+1.60	+3.16
POLD1	−2.45	−1.35	+1.13	−2.18
GCH1	−2.81	−1.14	+1.08	−2.21
EIF4G3	−1.25	−1.33	−1.40	−2.48
SPTA1	−1.83	−1.77	−1.74	−2.64
RYR3	−1.79	−1.91	−1.80	−2.83
MGLL	−2.77	−1.12	1.09	−284
AKR1C3	−1.01	−1.08	−1.13	−2.92

*Represent the ratio of the mRNA levels in EPO-treated cells versus that in the untreated cells

[0092] The EPO upregulated PIM-1 mRNA expression in UT-7 cells was further confirmed using bDNA technology (**FIG. 1A**). Similar to rEPO, rGM-CSF also induced expression of the PIM-1 mRNA in UT-7 cells (**FIG. 1A**), while rSCF, rG-CSF, and IL-3 showed no effect. The magnitude of the rEPO-induced PIM-1 expression in UT-7 cells was dose dependent and the maximum induction was reached after 90 minutes of rEPO treatment (**FIG. 1B**).

[0093] PIM-1 Expression is Regulated by PI3K Signaling

[0094] Chemical antagonists of the major intracellular signal transduction molecules downstream of the EPO receptor were used to determine which of the EPO signaling pathways were involved in the up-regulated PIM-1 expression. LY294002, a PI3-K inhibitor, effectively inhibited EPO-induced PIM-1 expression after 30 minutes of preincubation and the inhibition was apparently in a dose-dependent manner (**FIG. 2A**). All other antagonists showed either no or very mild effects on the regulated PIM-1 expression. When cells were treated for 24 hours, LY294002 blocked EPO-induced UT-7 cell proliferation and appeared to have activated apoptosis of the cells (**FIG. 2B**).

[0095] Effects of Serum on EPO-Induced PIM-1 Expression

[0096] To determine if PIM-1 expression could be used as a biological measurement for detecting neutralizing antibodies in serum samples, the effect of serum concentrations on EPO-induced PIM-1 expression were evaluated. As shown in **FIG. 3**, up to 20% of PNHS was well tolerated by this assay system.

[0097] Detection of Anti-EPO Neutralizing Antibodies in Serum

[0098] The rabbit polyclonal antibody 29123 is an EPO specific neutralizing antibody that has been shown to inhibit the survival and proliferation of UT-7 cells in media supplemented with rEPO. In these experiments, this antibody effectively inhibited EPO-induced elevation of PIM-1 expression (**FIG. 4**). The inhibition was dose dependent and was not affected by the presence of 10% normal human serum. Apparent inhibition could be observed at 2 ng/mL of 29123, and the maximum effect was reached at approximately 30 ng/mL.

[0099] The feasibility of using PIM-1 expression as a biological measurement for detecting anti-EPO neutralizing antibodies in serum samples was further evaluated by a more realistic spiking experiment. The levels of PIM-1 expression in cells treated with each donor serum only were compared with expression levels of the cells treated with the serum plus rEPO or rEPO and the spiked antibody. When 400 ng/mL antibody was spiked into the donor sera, EPO-induced PIM-1 expression was almost completely blocked by all of the spiked samples (**FIG. 5**). When 200 ng/mL antibody was spiked, however, effective, but weaker inhibition was observed. In either case, the levels of PIM-1 expressed in all antibody-treated samples were well below the tentative cutoff line for positive assignment. Additionally, the result indicated once again that PIM-1 expression was not influenced by the presence of at lease 10% of human serum, implying that a PIM-1 expression-based assay system could tolerate assay matrixes with high concentrations of serum for potential improvement of assay sensitivities.

[0100] Gene Expression Vs [^{3}H]-Thymidine Incorporation

[0101] As shown in **FIG. 6A**, the pattern of EPO-induced PIM-1 expression was almost superimposable to that of EPO-induced [^{3}H]-thymidine incorporation in UT-7 cells. The Pearson's correlation coefficient between the increased PIM-1 expression and [^{3}H]-thymidine incorporation was 0.974, confirming that these 2 events were highly related. The maximum induction and the EC_{50} for EPO-induced PIM-1 expression were approximately 22-fold and 0.4 ng/mL, while the same for [^{3}H]-thymidine incorporation were approximatelyl 9-fold and 1 ng/mL. The blocking of EPO-induced PIM-1 expression and that of [^{3}H]-thymidine incorporation by anti-EPO antibodies were also highly related (**FIG. 6B**). The Pearson's correlation coefficient between these 2 processes was 0.958. The maximum inhibition of PIM-1 expression and [^{3}H]-thymidine incorporation were approximately 11-fold and 6-fold; while the IC_{50} for PIM-1 expression and [^{3}H]-thymidine incorporation were approximately 3.4 ng/mL and 5.4 ng/mL, respectively (**FIG. 6**). These numbers indicated that the gene expression approach was more robust and sensitive than the [^{3}H]-Thymidine incorporation method.

EXAMPLE 2

[0102] This example illustrates the application of the method to NGFR (Nerve growth factor receptor) and EPOR hybrid receptors. Briefly, five different human NGFR and EPOR hybrid receptors (NECA-NECE, NGFR/EPOR chimera A-E) have been constructed. Different lengths of extracellular domain of human NGFR were fused with the mouse EPO receptor trans-membrane and intracellular domains (**FIG. 7**). The amino acid sequence at the bottom of **FIG. 7** represents the junction points of hybrid receptors, wherein the trans-membrane domain is italicized and the 3' end of NGFR extracellular sequence is underlined. The black bars indicate the sequence position where the 3'-end of the NGF was fused to EPOR in each chimeric construct. **FIG. 8** represents a generic cloning strategy for making NGFR/EPOR hybrid receptors. Human NGF receptor extracellular domain fragment was obtained by PCR followed by restriction enzyme digestion by Not I at 5' end and Spe I at 3' end. A fragment containing mouse EPOR trans-membrane and intracellular domains was obtained by PCR followed by digestion by Spe I at 5' end and Sal at 3' end. Two fragments were ligated and subcloned into the pLJ vector cut with Not I and Sal I. Positive clones were obtained and sequenced to confirm sequence.

[0103] These five different forms of NGFR/EPOR hybrid receptor constructs were transfected into 32Dcl3 cell via electroporation and were selected by medium containing G418 and NGF to yield 32D/NECD cells. A NGF responsive cell line NECDsc-14 was generated after two rounds of selection and single cell subcloning. These 32D/NECDsc-14 cells were maintained in either 5 ng/ml mouse interleukin-3 (mIL-3) or 25 ng/ml of NGF. NGF induced NECDsc-14 cell proliferation can be measured by [3H]-uptake. Cells were washed three times, staged overnight with growth factor-free culture medium, and treated with various amount of mIL-3 (control) or NGF (as indicated in Table 4) for 18 hours. The amounts of [^{3}H]-thymidine incorporated into the cells were measured following further incubation of the cells with [^{3}H]-thymidine for 4 hours. Results of this experiment are represented in Table 4 below.

TABLE 4

NGF Dose Response

Counts Conc (ng/ml)	NECDsc-14 mIL-3-dependent	NECDsc-14 NGF-dependent
0.00	655.3	1209.3
0.02	1724.7	1963.3
0.07	3784.0	4691.0
0.21	8645.7	8033.0
0.62	18964.0	16838.0
1.85	28205.7	22404.0
5.56	32071.3	24205.3
16.67	31791.3	22907.0
50.00	30813.7	21618.3
150.00	32221.7	20857.3

[0104] This NGF induced proliferation of NECDsc-14 cells can be used to detect anti-NGF neutralizing antibodies or peptibodies, which inhibit the NGF-induced proliferation of NECDsc-14 cells, in biological samples similar to the assay described in Example 1. Similarly, it can be used to detect neutralizing antibodies against the anti-NGF antibodies or peptibodies, which reverse the inhibitory effects mentioned above, in biological samples. Assays for detecting and measuring the concentrations of neutralizing antibodies against anti-NGF antibodies or peptibodies can be performed in 1% human serum, 5% cynomolgus monkey serum, or 2% rat serum samples (see Table 5), as no significant matrix effect from these samples was observed.

TABLE 5

NGF Dose Response in Serum Matrix

NGF conc. (ng/mL)	No serum	5% cyno serum	2% rat serum	1% human serum
0.00	462.7	1534.7	702.7	367.3
0.02	595.3	2175.7	1188.3	946.7
0.07	1389.7	5761.7	3524.0	1480.0
0.21	5423.0	15774.0	11970.7	5832.3
0.62	17073.0	32462.7	29431.7	13374.7
1.85	27445.3	43119.7	37695.3	19493.7
5.56	35224.7	52240.7	43395.7	22160.0
16.67	39675.3	51793.3	42446.0	24558.7
50.00	41018.0	56389.7	46874.3	19712.0
150.00	44119.0	62140.0	49545.3	18626.7

EXAMPLE 3

[0105] This example illustrates the application of the method to detecting the presence and measuring the concentration of neutralizing antibodies against an anti-BAFF antibody or peptibody. In particular, it is demonstrated that a BAFF-induced release of IL-8 (interleukin-8) that can be measured by ELISA can serve to identify and measure the cellular response to BAFF (B cell Activating Factor).

[0106] To measure the release of IL-8, a BAFF/TNFR hybrid receptor was constructed. As demonstrated in **FIG. 9**, three different human BAFFR and human TNFR hybrid receptors (B1T-B3T, BAFFR/TNFR hybrid receptors 1-3) were constructed. Extracellular domains of the human BAFF receptor of different length (BMCA, 68 amino acids; BMCB, 73 amino acids; BMCC, 78 amino acids) were fused with the human TNF receptor domain consisting of amino acids 206-455. The amino acid sequence in **FIG. 9** represents the junction point of the hybrid receptor, wherein the trans-membrane domain area of the TNF is italicized and the 3' end of the BAFFR extracellular domain is underlined.

[0107] **FIG. 10** outlines a generic cloning strategy for making BAFF/TNFR hybrid receptors. Briefly, a fragment of an extracellular domain of the human BAFFR was obtained by PCR followed by restriction enzyme digestion by Not I at the 5' end and Nhe I at the 3' end. A fragment including the trans-membrane and the intracellular domains of the human TNFR was obtained by PCR and restriction enzyme digestion by Xba I at 5' end and Xho I at the 3' end. Two fragments were ligated and subcloned into the pCEP4 vector cut with Not I and Xho I. Positive clones were obtained and sequenced to confirm sequence.

[0108] COS-1 cells were stably transfected with the BAFFR/TNFR chimeric constructs and selected in Hygromycin to yield clones of the hybrid receptor expressing COS-1 cells. The final clones of the cells expressing the BAFF/TNFR chimera were tested in a BAFF induced IL-8 release from COS-1 cells expressing BAFFR/TNFR hybrid. Briefly, COS-1 cells were transfected stably with the BAFFR/TNFR chimeric construct (B2T) and were selected in Hygromycin to yield COS-1/B2T cells. **FIG. 11** illustrates the IL-8 production (in pg/ml) by cell lines PCEP4, B1T-3, B2T-17, and B2T-20 **FIG. 11** illustrates the IL-8 production (in pg/ml) by cell lines PCEP4, B1T-3, B2T-17, and B2T-20. The cells were then seeded in a 12-well plate and treated with BAFF at indicated concentrations at 37°C for 18 hours. The conditioned medium was collected and the IL-8 production was measured by ELISA kit (R&D systems). Because of the highest IL-8 production, B2T-17 line was selected for the rest of the study.

[0109] This BAFF-induced IL-8 expression from B2T-17 cells can be used in biological sample to detect anti-BAFF neutralizing antibody or peptibody, which inhibits the BAFF-induced IL-8 release from B2T-17 cells. Similar to he assay described in Example 1, the same construct can be used to detect neutralizing antibodies against the anti-BAFF antibodies or peptibodies, which reverse the inhibitory effects mentioned above. Assays for detecting and measuring the amount of neutralizing antibodies against anti-BAFF antibodies or peptibodies can be performed in 1% human or 5% cynomolgus monkey serum, as no significant matrix effect from these samples was observed.

EXAMPLE 4

[0110] This example illustrates the application of the method to detecting the presence and measuring the concentration of neutralizing antibodies against an anti-BAFF antibody or peptibody by measuring an alteration in the BAFF-induced PIM-1 expression.

[0111] A mouse EPOR and human BAFFR hybrid receptor was constructed as represented in **FIG. 12**, wherein the EPOR trans-membrane domain is indicated in black. Briefly, three different human BAFFR and mEPOR hybrid receptors (BMCA-C) have been constructed. Extracellular domains of human BAFFR (of three different length: BMCA, 68 amino acids; BMCB, 73 amino acids; BMCC, 78 amino acids) were fused with the mouse EPO receptor comprising the trans-membrane and the intracellular domain. The amino acid sequence representing the junction point of the hybrid receptor is shown in **FIG. 12**, wherein the trans-membrane domain of the mouse EPOR is italicized and the 3' end of the human BAFFR extracellular sequence is underlined.

[0112] **FIG. 13** outlines a generic cloning strategy for making BAFFR/EPOR hybrid receptors. A fragment containing the extracellular domain of human BAFF receptor was obtained by PCR and restriction enzyme digestion by Not I at the 5' end and Nhe I at the 3' end. A fragment containing the mouse EPOR trans-membrane and intracellular domain was obtained by PCR and restriction enzyme digestion by Spe I at the 5' end and Sal at the 3' end. Two fragments were ligated and subcloned into pLJ vector cut with Not I and Sal I. Positive clones were obtained and sequenced to confirm sequence.

[0113] These three different forms of BAFFR/EPOR hybrid receptor construct were transfected into 32Dcl3 cell via electroporation and were selected by medium containing G418 and BAFF to yield 32D/BMC cells. A BAFF responsive cell line BMECB was generated after two rounds of selection and single cell subcloning. These 32D/BMECB cells were maintained in either 5 ng/ml mouse interleukin-3 (mIL-3) or 25 ng/ml of BAFF. BAFF induced PIM-1 expression from 32D/BMECB cells can be measured by bDNA technology. Briefly, three subclones of BMECB cells (BMECB-9, 20, 21) were washed three times, staged overnight with growth factor-free culture medium. Cells were then seeded in 96-well plate in triplicate and treated with BAFF at indicated concentrations at 37° C. for 90 minutes as represented in **FIG. 14**. Treated cells were lysed and the amount of PIM-1 expression induced by the BAFF treatment was measured by using bDNA QuantiGene kit and illustrated in **FIG. 14**.

[0114] This BAFF-induced expression of PIM-1 in 32D/BMECB cells can be used in biological samples to detect anti-BAFF neutralizing antibody or peptibody, which inhibit the BAFF-induced expression of PIM-1 in 32D/BMECB cells. Similarly, it can be used to detect neutralizing antibodies against the anti-BAFF antibodies or peptibodies, which reverse the inhibitory effects mentioned above. Assays for detecting and measuring the concentrations of neutralizing antibodies against anti-BAFF peptibodies can be performed in 1% human serum, 5% cynomolgus monkey serum, or 2% rat serum samples (Table 5), as no significant matrix effect from these samples was observed.

EXAMPLE 5

[0115] This Example illustrates the validation of a cell-based Neutralizing Antibody (NAb) bioassay for the detection of specific neutralizing activity to a therapeutic protein, such as Osteoprotegerin (OPG) or a monoclonal anti-Receptor Activator of NFκB (RANK) ligand antibody (anti-RANKL) in human serum measuring changes in TRAP (tartrate-resistant acid phosphatase) mRNA using Branched DNA (bDNA) technology (Quantigene, Genospectra, Inc. Fremont, Calif.).

[0116] For the determination of neutralizing effects of a human Fc conjugated version of OPG (OPG-Fc) or anti-RANKL, a cell-based bioassay employing a murine macrophage cell line (RAW 264.7), which expresses the receptor for RANK ligand, RANK, was developed. RAW 264.7 cells respond to RANK ligand by differentiating into osteoclast-like cells, expressing the terminal differentiation marker TRAP (tartrate-resistant acid phosphatase). Thus, the inhibition of RANK ligand by OPG-Fc or anti-RANKL would inhibit TRAP mRNA expression as well. However, if neutralizing antibodies to OPG-Fc or anti-RANKL antibodies were present, the TRAP mRNA would continue to be expressed.

[0117] Two assays were implements to determine whether there was a specific neutralizing activity to the protein therapeutic, a Screening NAb bioassay and Specificity bioassay. In the Screening NAb Bioassay patient serum was assessed for the presence of neutralizing antibodies to the protein therapeutic while the Specificity bioassay, the protein therapeutic and RANK ligand was used to eliminate false positives due to a non-specific induction of TRAP mRNA.

Example of Bioassay Format for Anti-RANK Ligand Antibody

[0118] For the Screening NAb bioassay, a sample containing 5% human patient serum, RANK Ligand and anti-RANKL antibody in cell Growth Media was used. Anti-RANK ligand antibody and RANK Ligand were sequentially added to the serum samples (NAb assay) with incubations for 30 minutes at 37°C following each addition RAW 264.7 cells (10,000 cells per well) were added to samples in Screening NAb and Specificity Assays. RAW 264.7 cells were added at 10,000 cells/well and this was incubated for 48 hours at 37° C. TRAP mRNA expression was detected using the Branched DNA Assay below.

[0119] For Specificity Bioassay, RAW 264.7 cells were added to a sample containing 5% patient serum only and incubated for 48 hours at 37° C. TRAP mRNA expression was detected using the Branched DNA Assay below.

[0120] The following samples were used for controls: Null Control (Control N), 5% pooled human serum; Maximum Control (Control M), 5% pooled human serum and RANK Ligand; Therapeutic Drug Control (Control D), 5% pooled human serum, RANK Ligand and anti-RANKL antibody or OPG; and Positive Control (Control P), 5% pooled human serum, RANK Ligand and anti-RANKL antibody and anti-anti-OPG ligand antibody (500 ng/mL in serum.

[0121] Branched DNA Assay. mRNA expression was measured using the Quantigene Screen kit commercially available from Genospectra, Inc. Briefly, RAW264.7 cells were lysed with a buffer containing Label Extender Probes, Blocking Probes and Capture Extender Probes. The cell lysate was transferred to a capture plate and was incubated overnight at 53°C. The plate was subsequently washed with a wash buffer (12.5 mL 20X SSC, 7.5 mL 0.01% Lithium Lauryl Sulfate, and 2.48 L water) followed by the addition of bDNA amplifier probe and incubated for 1 hour at 46°C. The plate was washed again with wash buffer and bDNA Label Probe was added, and incubated at 46°C for 1 hour. The plate was washed for final time with wash buffer followed by the addition of Substrate and a 30 minute incubation at 46°C. Luminescence was detected by Top-Count NXT reader and measured in Counts per Second (CPS).

TABLE 6

bDNA Probes Used for Murine TRAP mRNA
Capture Extender Probes (CE)
aggagtgggagccatatgattTTTTTctcttggaaagaaagt
tggcgatctctttggcattggTTTTTctcttggaaagaaagt
agttccagcgcttggagatcTTTTTctcttggaaagaaagt
gtccgtgctcggcgatggaTTTTTctcttggaaagaaagt
tctcgtcctgaagatactgcaTTTTTctcttggaaagaaagt
tgaagccgcccagggagtcctcaTTTTTctcttggaaagaaagt
aagagtgattttccagaggcttTTTTTctcttggaaagaaagt
Label Extender Probes (LE)
acccatgaatccatccatcctggTTTTTaggcataggacccgtgtct
tgtaggcccagcagcagcaccTTTTTaggcataggacccgtgtct
gggctgtaccgtgggtcTTTTTaggcataggacccgtgtct
gggctgtaccgtgggtcTTTTTaggcataggacccgtgtct
ccccagtcgcccacagccaTTTTTaggcataggacccgtgtct
ccatttcccgggctgtgtggaTTTTTaggcataggacccgtgtct
tcgctggcatcgtgcactcTTTTTaggcataggacccgtgtct
cggtcagagaacacgtcctcTTTTTaggcataggacccgtgtct
tggtttccagccagcacataccTTTTTaggcataggacccgtgtct

TABLE 6-continued

bDNA Probes Used for Murine TRAP mRNA
agatggccacagttatgtttgTTTTTaggcataggacccgtgtct
gcatcactgtgtccagcataaTTTTTaggcataggacccgtgtct
aagtcatctgagttgccacacaTTTTTaggcataggacccgtgtct
ctgctgccaactgctttttgaTTTTTaggcataggacccgtgtct
cttgacaaggcagcgcgtggTTTTTaggcataggacccgtgtct
tggctaacaatggtcgcaagttTTTTTaggcataggacccgtgtct
ggttgtggtcatgtccacacaTTTTTaggcataggacccgtgtct
cagcacatagcccacaccgtTTTTTaggcataggacccgtgtct
tgatgtcgcacagagggatccTTTTTaggcataggacccgtgtct

Blocking Probes (BL)
caaatctcagggtgggagtgg
atggggcattggggacccct
cagagacatgatgaagtcagc
cagtgaagtagaaattgtcccc
aaaggtctcctggaacctcttg
aggggatgttgcgaagggca
tacgtggaattttgaagcgca
cattttgggctgctgctgactggca
gccaggacagctgagtgcgg
accaaaacgtagtcctccttgg
ccagatggggtagtggccggcc
ggtaggcagtgaccccgtatg
atgaagttgccggccccact
agccgttggggacctttcgt
gatccatagtgaaaccgcaagt

TABLE 6-continued

bDNA Probes Used for Murine TRAP mRNA
tggggcttatctccacatgtg

[0122] Results were analyzed using pre-determined criteria. Three ratios were used to determine the presence of neutralizing activity. The "NAb ratio" consisting of the mean sample CPS/mean CPS of the Therapeutic Drug Control (Control D) was used to screen for a the presence of any neutralizing activity to anti-RANK ligand antibody. The "Post/Pre" ratio consisting of the mean sample CPS of the post-dose sample/mean sample CPS of the pre-dose was used to determine the development of neutralizing activity between the pre and post-doses. The "Specificity Ratio", consisting of the mean sample CPS of the Nab assay/mean sample CPS of the Specificity Assay, was used to determine if there were a factors in the serum inducing TRAP mRNA expression. In order for a sample to be considered positive for the presence of neutralizing activity as the result of a neutralizing antibody, a serum sample would be required to be found "Positive" in both the "Nab Ratio" and "Post/Pre Ratio," and be found to not have non-anti-anti-RANK ligand antibody-specific TRAP gene expression.

[0123] Serum samples from 29 healthy donor volunteers were used to determine donor to donor variability and to derive assay thresholds for both the NAb and Specificity bioassays for the determination of a "positive" and "negative" sample. Results of the cell-based NAb assay are represented in **FIG. 15**. NAb assay threshold was determined as a ratio of Sample Mean CPS to Control D Mean CPS. Donors were spiked at 500 ng/mL of anti-anti-OPG ligand antibody in neat serum. All spiked donors were found to be above Nab Assay Threshold, and two unspiked donors were found to be above Nab Assay Threshold. **FIG. 16** represents Validation of the Specificity Value Threshold. Specificity Value was determined as a ratio of Mean Raw CPS values generated in Nab Assay to Mean Raw CPS Values generated in the Specificity Assay. All spiked donors were found to be above the Specificity Value Threshold, whereas all unspiked donors were found to be below the Specificity Value Threshold, thus, no false negatives or false positives were generated.

TABLE 7

Alignment of mammalian EPO-R amino acid sequences

	SEQ ID	Alignment (numbering based on consensus sequence):
		1 50
Mouse EPOR	NO:3	MdklrvplWP rVgpLCLLLA GAaWApsPsl PDpKFESKAA LLAsRGsEEL
Rat EPOR	NO:4	MdqlrvarWP rVspLCLLLA GAaWAssPsl PDpKFESKAA LLAsRGsEEL
Human EPOR	NO:2	MdhlgaslWP qVgsLCLLLA GAaWAppPnl PDpKFESKAA LLAaRGpEEL
Pig EPOR	NO:5	MyhfgatlWP gVgSLCLLLA GAtWApsPns PDaKFESKAA LLAaRGpEEL
Consensus	NO:1	M-------WP -V--LCLLLA GA-WA--P-- PD-KFESKAA LLA-RG-EEL

TABLE 7-continued

Alignment of mammalian EPO-R amino acid sequences

	SEQ ID	Alignment (numbering based on consensus sequence):
		51 100
Mouse EPOR	NO:3	LCFTqRLEDL VCFWEEAass Gmd.fnYSFS YQLEgEsrKs CsLHQaPTvR
Rat EPOR	NO:4	LCFTqRLEDL VCFWEEAans Gmg.fnYSFS YQLEgEsrKs CrLHQaPTvR
Human EPOR	NO:2	LCFTeRLEDL VCFWEEAasa GVgpgnYSFS YQLEdEpWKl CrLHQaPTaR
Pig EPOR	NO:5	LCFTeRLEDL VCFWEEAgsa GvgpedYSFS YQLEgEpwKp ChLHQgPTaR
Consensus	NO:1	LCFT-RLEDL VCFWEEA--- G-----YSFS YQLE-E--K- C-LHQ-PT-R
		101 150
Mouse EPOR	NO:3	GsvRFWCSLP TADTSSFVPL ELqVTe.aSG sPRYHRiIHI NEVVLLDaPa
Rat EPOR	NO:4	GsmRFWCSLP TADTSSFVPL ELqVTe.aSG sPRYHRiIHI NEVVLLDaPa
Human EPOR	NO:2	GavRFWCSLP TADTSSFVPL ELrVT.aaSG aPRYHRvIHI NEVVLLDaPv
Pig EPOR	NO:5	GsvRFWCSLP TADTSSFVPL ELrVTevsSG aPRYHRiIHI NEVVLLDpPa
Consensus	NO:1	G--RFWCSLP TADTSSFVPL EL-VT---SG -PRYHR-IHI NEVVLLD-P-
		151 200
Mouse EPOR	NO:3	GLlARrAeEg sHVVLRWLPP PgaPMtthIR YEVdvSagNr AGgtQRVEvL
Rat EPOR	NO:4	GLlARrAeEg sHVVLRWLPP PgaPMtthIR YEVdvSagNr AGgtQRVEvL
Human EPOR	NO:2	GLvARlAdEs gHVVLRWLPP PetPMtshIR YEVdvSagNg AGsvQRVEiL
Pig EPOR	NO:5	GLlARrAeEs gHVVLRWLPP PgaPMaslIR YEVniSteNa AGgvQRVEiL
Consensus	NO:1	GL-AR-A-E- -HVVLRWLPP P--PM---IR YEV--S--N- AG--QRVE-L
		201 250
Mouse EPOR	NO:3	eGRTECVLSN LRGgTRYTFa VRARMAEPSF sGFWSAWSEP aSLLTaSDLD
Rat EPOR	NO:4	eGRTECVLSN LRGgTRYTFa VRARMAEPSF sGFWSAWSEP aSLLTaSDLD
Human EPOR	NO:2	eGRTECVLSN LRGrTRYTFa VRARMAEPSF gGFWSAWSEP vSLLTpSDLD
Pig EPOR	NO:5	dGRTECVLSN LRGgTRYTFm VRARMAEPSF gGFWSAWSEP aSLLTaSDLD
Consensus	NO:1	-GRTECVLSN LRG-TRYTF- VRARMAEPSF -GFWSAWSEP -SLLT-SDLD
		251 300
Mouse EPOR	NO:3	PLILTLSLIL VlIslLLtVL ALLSHRRtLq QKIWPGIPSP EsEFEGLFTT
Rat EPOR	NO:4	PLILTLSLIL VlIslLLtVL ALLSHRRaLr QKIWPGIPSP EnEFEGLFTT
Human EPOR	NO:2	PLILTLSLIL VvIlvLLtVL ALLSHRRaLk QKIWPGIPSP EsEFEGLFTT
Pig EPOR	NO:5	PLILTLSLIL VlIllLLaVL ALLSHRRtLk QKIWPGIPSP EgEFEGLFTT
Consensus	NO:1	PLILTLSLIL V-I--LL-VL ALLSHRR-L- QKIWPGIPSP E-EFEGLFTT
		301 350
Mouse EPOR	NO:3	HKGNFQLWLl QrDGCLWWSP gssFpEDPPA hLEVLSEprW avtQAgdpga
Rat EPOR	NO:4	HKGNFQLWLl QrDGCLWWSP sspFpEDPPA hLEVLSErrW gvtQAgdaga
Human EPOR	NO:2	HKGNFQLWLy QnDGCLWWSP ctpFtEDPPA sLEVLSErcW gtmQAvepgt
Pig EPOR	NO:5	HKGNFQLWLy QtDGCLWWSP ctpFaEDPPA pLEVLSErcW gvtQAvepaa
Consensus	NO:1	HKGNFQLWL- Q-DGCLWWSP ---F-EDPPA -LEVLSE--W ---QA-----
		351 400
Mouse EPOR	NO:3	dDeGpLLEPV GSEhAqDTYL VLDkWLLPRt PcSEnLsgPG gsvDpvtMDE
Rat EPOR	NO:4	eDkGpLLEPV GSErAqDTYL VLDeWLLPRc PcSEnLsgPG dsvDpatMDE

TABLE 7-continued

Alignment of mammalian EPO-R amino acid sequences

	SEQ ID	Alignment (numbering based on consensus sequence):
Human EPOR	NO:2	dDeGpLLEPV GSEhAqDTYL VLDkWLLPRn PpSEdLpgPG gsvDivaMDE
Pig EPOR	NO:5	dDeGsLLEPV GSEhArDTYL VLDkWLLPRr PaSEdLpqPG gdlDmaaMDE
Consensus	NO:1	-D-G-LLEPV GSE-A-DTYL VLD-WLLPR- P-SE-L--PG ---D---MDE
		401 450
Mouse EPOR	NO:3	aSEtSsCpSd LAsKPrPEGt SPsSFEYTIL DPSSqLLcPr aLppELPPTP
Rat EPOR	NO:4	gSEtSsCpSd LAsKPrPEGt SpsSFEYTIL DPSSkLLcPr aLppELPPTP
Human EPOR	NO:2	gSEaSsCsSa LAsKPsPEGa SaaSFEYTIL DPSSqLLrPw tLcpELPPTP
Pig EPOR	NO:5	aSEaSfCsSa LAlKPgPEGa SaaSFEYTIL DPSSqLLrPr aLpaELPPTP
Consensus	NO:1	-SE-S-C-S- LA-KP-PEG- S--SFEYTIL DPSS-LL-P- -L--ELPPTP
		451 500
Mouse EPOR	NO:3	PHLKYLYLVV SDSGISTDYS SGgSQgvhGd sSdGPYShPY ENSLvPdsEP
Rat EPOR	NO:4	PHLKYLYLVV SDSGISTDYS SCgSQgvhGd sSdGPYShPY ENSLvPdtEP
Human EPOR	NO:2	PHLKYLYLVV SDSGISTDYS SGdSQgaqGg lSdGPYSnPY ENSLiPaaEP
Pig EPOR	NO:5	PHLKYLYLVV SDSGISTDYS SGgSQetqGg sSsGPYSnPY ENSLvPapEP
Consensus	NO:1	PHLKYLYLVV SDSGISTDYS SG-SQ---G- -S-GPYS-PY ENSL-P--EP
		501 509
Mouse EPOR	NO:3	lhPgYVaCS
Rat EPOR	NO:4	lrPsYVaCS
Human EPOR	NO:2	lpPsYVaCS
Pig EPOR	NO:5	spPnYVtCS
Consensus	NO:1	--P-YV-CS

[0124]

TABLE 8

Location of domains within EPO-R amino acid sequences; numbering refers to amino acid positions within the corresponding SEQ ID NOs

Polypeptide	SEQ ID	Signal sequence	Extracellular	WSXWS	Transmembrane	Intracellular	"Mature"[A] polypeptide
Mouse EPOR	NO: 3	1–24	25–249	232–236	250–272	273–507	25–507
Rat EPOR	NO: 4	1–24	25–249	232–236	250–272	273–507	25–507
Human EPOR	NO: 2	1–24	25–250	233–237	251–273	274–508	25–508
Pig EPOR	NO: 5	1–24	25–251	234–238	252–274	275–509	25–509
Consensus	NO: 1	1–24	25–251	234–238	252–274	275–509	25–509

[A]For the purposes of the above table, the "mature" polypeptide refers to a polypeptide from which the indicated signal sequence has been cleaved; additional mature polypeptide forms may occur.

[0125]

TABLE 9

Alignment of mammalian EPO amino acid sequences

	SEQ ID	Alignment (numbering based on consensus sequence):
		1 50
Mouse EPO	NO:10	MGvpe.rptl lLlLSllliP LGlPVlcAPp RLiCDSRVLE RYiLeAkEAE
Rat EPO	NO:1	MGvpe.rptl lLlLSllliP LGlPVlcAPp RLiCDSRVLE RYiLeAkEAE
Macaque EPO	NO:9	MGvhecpawl wLlLSlvslP LGlPVpgAPp RLiCDSRVLE RYlLeAkEAE
Rhesus EPO	NO:8	MGvheCpawl wLlLSlVslP LGlPVPgAPp RLvCDSRVLE RYlLeAkEAE
Human EPO	NO:7	MGvhecpawl wLlLSllslP LGlPVlgAPp RLiCDSRVLE RYlLeAkEAE
Cow EPO	NO:12	MGardctp.. lLmLSfllfp LGfPVlgAPa RLiCDSRVLE RYiLeArEAE
Sheep EPO	NO:13	MGardctpll lLlLSfllfP LGlpVlgAPp RLiCDSRVLE RYiLeArEAE
Cat EPO	NO:14	MGscec.pal lLlLSllllP LGlPVlgAPp RLiCDSRVLE RYiLgArEAE
Consensus	NO:6	MG-------- -L-LS----P LG-PV--AP- RL-CDSRVLE RY-L-A-EAE
		51 100
Mouse EPO	NO:10	NvTmGCaEgp rlsENITVPD TKVNFYaWKR meVeeQAiEV WQGLsLLSEA
Rat EPO	NO:11	NvTmGCaEgp rlsENITVPD TKVNFYaWKR mkVeeQAvEV WQGLsLLSEA
Macaque EPO	NO:9	NvTmGCsEsc slnENITVPD TKVNFYaWKR meVgqQAvEV WQGLaLLSEA
Rhesus EPO	NO:8	NvTmGCsEsc slnENITVPD TKVNFYaWKR ieVgqQAvEV WQGLaLLSEA
Human EPO	NO:7	NiTtGCaEhc slnENITVPD TKVNFYaWKR meVgqQAvEV WQGLaLLSEA
Cow EPO	NO:12	NaTmGCaEgc sfnENITVPD TKVNFYaWKR meVqqQAlEV WQGLaLLSEA
Sheep EPO	NO:13	NaTmGCaEgc sfsENITVPD TKVNFYaWKR meVqqQAlEV WQGLaLLSEA
Cat EPO	NO:14	NvTmGCaEgc sfsENITVPD TKVNFYtWKR mdVgqQAvEV WQGLaLLSEA
Consensus	NO:6	N-T-GC-E-- ---ENITVPD TKVNFY-WKR --V--QA-EV WQGL-LLSEA
		101 150
Mouse EPO	NO:10	ilqaQAllaN sSQPpEtLqL HiDKAiSgLR SlTsLLRvLG AQkElmspPd
Rat EPO	NO:11	ilqaQAlqaN sSQPpEsLqL HiDKAiSgLR SlTsLLRvLG AQkElmspPd
Macaque EPO	NO:9	vlrgQAvlaN sSQPfEpLqL HmDKAiSgLR SiTtLLRaLG AQ.EaislPd
Rhesus EPO	NO:8	vlrgQAvlaN sSQPfEpLqL HmDKAiSgLR SiTtLLRaLG AQ.EaislPd
Human EPO	NO:7	vlrgQAllvN sSQPwEpLqL HvDKAvSgLR SlTtLLRaLG AQkEaispPd
Cow EPO	NO:12	ilrgQAllaN aSQPcEaLrL HvDKAvSgLR SlTsLLRaLG AQkEaislPd
Sheep EPO	NO:13	ifrgQAllaN aSQPcEaLrL HvDKAvSgLR SlTsLLRaLG AQkEaiplPd
Cat EPO	NO:14	ilrgQAllaN sSQPsEtLqL HvDKAvSsLR SlTsLLRaLG AQkEatslPe
Consensus	NO:6	----QA---N -SQP-E-L-L H-DKA-S-LR S-T-LLR-LG AQ-E----P-
		151 194
Mouse EPO	NO:10	ttp.pAPLRt lTvDtfcKLF RvYaNFLRGK LkLYTGEvCR rGDR
Rat EPO	NO:11	atq.aAPLRt lTaDtfcKLF RvYsNFLRGK LkLYTGEaCR rGDR
Macague EPO	NO:9	aa.saAPLRt iTaDtfcKLF RvYsNFLRGK LkLYTGEaCR rGDR
Rhesus EPO	NO:8	aa.saAPLRt iTaDtfcKLF RvYSNFLRGK LkLYTGEaCR rGDR
Human EPO	NO:7	aa.saAPLRt iTaDtfrKLF RvYsNFLRGK LkLYTGEaCR tGDR
Cow EPO	NO:12	atpsaAPLRa fTvDalsKLF RiYsNFLRGK LtLYTGEaCR rGDR

TABLE 9-continued

Alignment of mammalian EPO amino acid sequences

	SEQ ID	Alignment (numbering based on consensus sequence):
Sheep EPO	NO:13	atpsaAPLRi fTvDalsKLF RiYsNFLRGK LtLYTGEaCR rGDR
Cat EPO	NO:14	at.saAPLRt fTvDtlcKLF RiYsNFLRGK LtLYTGEaCR rGDR
Consensus	NO:6	-----APLR- -T-D---KLF R-Y-NFLRGK L-LYTGE-CR -GDR

[0126]

TABLE 10

Location of domains within EPO amino acid sequences; numbering refers to amino acid positions within the corresponding SEQ ID NOs

Polypeptide	SEQ ID	Signal sequence	"Mature"[A] polypeptide
Mouse EPO	NO: 10	1–26	27–192
Rat EPO	NO: 11	1–26	27–192
Macaque EPO	NO: 9	1–27	28–192
Rhesus EPO	NO: 8	1–27	28–192
Human EPO	NO: 7	1–27	28–193
Cow EPO	NO: 12	1–25	26–192
Sheep EPO	NO: 13	1–27	28–194
Cat EPO	NO: 14	1–26	27–192
Consensus	NO: 6	1–27	28–194

TABLE 10-continued

Location of domains within EPO amino acid sequences; numbering refers to amino acid positions within the corresponding SEQ ID NOs

Polypeptide	SEQ ID	Signal sequence	"Mature"[A] polypeptide

[A]For the purposes of the above table, the "mature" polypeptide refers to a polypeptide from which the indicated signal sequence has been cleaved; additional mature polypeptide forms may occur.

[0127]

TABLE 11

Alignment of mammalian PIM1 coding (cDNA) nucleotide sequences

	SEQ ID	Alignment (numbering based on consensus sequence):
		1 50
Mouse PIM1	NO:21	ATGCTCcTGT CCAAgATCAA CTCcCTgGCC CACCTGCGCg CcGCgCCcTG
Rat PIM1	NO:20	ATGCTCtTGT CCAAgATCAA CTCcCTgGCC CACCTGCGCg CaGCcCCtTG
Cat PIM1	NO:18	ATGCTCtTGT CCAAaATCAA CTCgCTtGCC CACCTGCGCa CcGCgCCcTG
Human PIM1	NO:16	ATGCTCtTGT CCAAaATCAA CTCgCTtGCC CACCTGCGCg CcGCgCCcTG
Cow PIM1	NO:19	ATGCTCtTGT CCAAaATCAA CTCgCTtGCC CACCTGCGCg CcGCgCCcTG
Chimp PIM1	NO:17	ATGCTCtTGT CCAAaATCAA CTCgCTtGCC CACCTGCGCg CcGCgCCcTG
Consensus[A]	NO:15	ATGCTCYTGT CCAARATCAA CTCSCTKGCC CACCTGCGCR CMGCSCCYTG
		51 100
Mouse PIM1	NO:21	CAaCGACCTG CACGCCAcCA AGCTGGCGCC gGGCAAaGAG AAGGAGCCCC
Rat PIM1	NO:20	CAaCGACCTG CACGCCAaCA AGCTGGCGCC gGGCAAaGAG AAGGAGCCCC
Cat PIM1	NO:18	CAaCGACCTG CACGCCAcCA AGCTGGCGCC cGGCAAgGAG AAGGAGCCCC
Human PIM1	NO:16	CAaCGACCTG CACGCCAcCA AGCTGGCGCC cGGCAAgGAG AAGGAGCCCC
Cow PIM1	NO:19	CAgCGACCTG CACGCCAcCA AGCTGGCGCC gGGCAAgGAG AAGGAGCCCC
Chimp PIM1	NO:17	CAaCGACCTG CACGCCAcCA AGCTGGCGCC cGGCAAgGAG AAGGAGCCCC
Consensus	NO:15	CARCGACCTG CACGCCAMCA AGCTGGCGCC SGGCAARGAG AAGGAGCCCC
		101 150

TABLE 11-continued

Alignment of mammalian PIM1 coding (cDNA) nucleotide sequences

	SEQ ID	Alignment (numbering based on consensus sequence):
Mouse PIM1	NO:21	TGGAGTCGCA GTACCAGGTG GGCCCGCTgt TGGGCAGcGG tGGCTTCGGC
Rat PIM1	NO:20	TGGAGTCGCA GTACCAGGTG GGCCCGCTgt TGGGCAGcGG tGGCTTCGGC
Cat PIM1	NO:18	TGGAGTCGCA GTACCAGGTG GGCCCGCTac TGGGCAGcGG cGGCTTCGGC
Human PIM1	NO:16	TGGAGTCGCA GTACCAGGTG GGCCCGCTac TGGGCAGcGG cGGCTTCGGC
Cow PIM1	NO:19	TGGAGTCGCA GTACCAGGTG GGCCCGCTcc TGGGCAGtGG cGGCTTCGGC
Chimp PIM1	NO:17	TGGAGTCGCA GTACCAGGTG GGCCCGCTac TGGGCAGcGG cGGCTTCGGC
Consensus	NO:15	TGGAGTCGCA GTACCAGGTG GGCCCGCTVY TGGGCAGYGG YGGCTTCGGC
		151 200
Mouse PIM1	NO:21	TCGGTcTACT CtGGCATCCG cGTCgCCGAC AACTTGCCGG TGGCCATtAA
Rat PIM1	NO:20	TCGGTcTACT CgGGCATCCG cGTCgCCGAC AACTTGCCGG TGGCCATcAA
Cat PIM1	NO:18	TCGGTcTACT CaGGCATCCG gGTCgCCGAC AACTTGCCGG TGGCCATcAA
Human PIM1	NO:16	TCGGTcTACT CaGGCATCCG cGTCtCCGAC AACTTGCCGG TGGCCATcAA
Cow PIM1	NO:19	TCGGTgTACT CaGGCATCCG tGTCgCCGAC AACTTGCCGG TGGCCATcAA
Chimp PIM1	NO:17	TCGGTcTACT CaGGCATCCG cGTCtCCGAC AACTTGCCGG TGGCCATcAA
Consensus	NO:15	TCGGTSTACT CDGGCATCCG BGTCKCCGAC AACTTGCCGG TGGCCATYAA
		201 250
Mouse PIM1	NO:21	gCACGTGGAG AAGGACCGGA TTTCCGAtTG GGGaGAaCTG CCcAAtGGCA
Rat PIM1	NO:20	gCACGTGGAG AAGGACCGGA TTTCCGAcTG GGGgGAaCTG CCcAAcGGCA
Cat PIM1	NO:18	gCACGTGGAG AAGGACCGGA TTTCCGAtTG GGGaGAgCTG CCcAAtGGCA
Human PIM1	NO:16	aCACGTGGAG AAGGACCGGA TTTCCGAcTG GGGaGAgCTG CCtAAtGGCA
Cow PIM1	NO:19	gCACGTGGAG AAGGACCGGA TTTCCGAcTG GGGaGAgCTG CCtAAtGGCA
Chimp PIM1	NO:17	aCACGTGGAG AAGGACCGGA TTTCCGAcTG GGGaGAgCTG CCtAAtGGCA
Consensus	NO:15	RCACGTGGAG AAGGACCGGA TTTCCGAYTG GGGRGARCTG CCYAAYGGCA
		251 300
Mouse PIM1	NO:21	CcCGAGTGCC CATGGAaGTG GTcCTGtTGA AGAAGGTGAG CTCGGacTTC
Rat PIM1	NO:20	CcCGAGTGCC CATGGAaGTG GTcCTGcTGA AGAAGGTGAG CTCGGgcTTC
Cat PIM1	NO:18	CcCGAGTGCC CATGGAgGTG GTcCTGcTGA AGAAGGTGAG CTCGGgcTTC
Human PIM1	NO:16	CtCGAGTGCC CATGGAaGTG GTcCTGcTGA AGAAGGTGAG CTCGGgtTTC
Cow PIM1	NO:19	CcCGAGTGCC CATGGAaGTG GTtCTGcTGA AGAAGGTGAG CTCGGgcTTC
Chimp PIM1	NO:17	CtCGAGTGCC CATGGAaGTG GTcCTGcTGA AGAAGGTGAG CTCGGgtTTC
Consensus	NO:15	CYCGAGTGCC CATGGARGTG CTYCTGYTGA AGAAGGTGAG CTCGGRYTTC
		301 350
Mouse PIM1	NO:21	TCgGGCGTCA TTaGaCTtCT GGACTGGTTc GAGAGGCCCG AtAGTTTCGT
Rat PIM1	NO:20	TCgGGCGTCA TTaGaCTtCT GGACTGGTTc GAGAGGCCCG AtAGTTTCGT
Cat PIM1	NO:18	TCcGGCGTCA TTcGgCTcCT GGACTGGTTt GAGAGGCCCG AcAGTTTCGT
Human PIM1	NO:16	TCcGGCGTCA TTaGgCTcCT GGACTGGTTc GAGAGGCCCG AcAGTTTCGT
Cow PIM1	NO:19	TCcGGCGTCA TTaGgCTcCT GGACTGGTTc GAGAGGCCCG AcAGTTTCGT

TABLE 11-continued

Alignment of mammalian PIM1 coding (cDNA) nucleotide sequences

	SEQ ID	Alignment (numbering based on consensus sequence):
Chimp PIM1	NO:17	TCcGGCGTCA TTaGgCTcCT GGACTGGTTc GAGAGGCCCG AcAGTTTCGT
Consensus	NO:15	TCSGGCGTCA TTMGRCTYCT GGACTGGTTY GAGAGGCCCG AYAGTTTCGT
		351 400
Mouse PIM1	NO:21	gcTGATCCTG GAGAGGCCcG AaCCgGTGCA AGAcCTCTTC GACTTtATCA
Rat PIM1	NO:20	gcTGATCCTG GAGAGGCCcG AaCCcGTGCA AGAcCTCTTC GACTTcATCA
Cat PIM1	NO:18	ctTGATCCTG GAGAGGCCcG AgCCgGTGCA AGAcCTCTTC GACTTtATCA
Human PIM1	NO:16	ccTGATCCTG GAGAGGCCcG AgCCgGTGCA AGAtCTCTTC GACTTcATCA
Cow PIM1	NO:19	ccTGATCCTG GAGAGGCCgG AgCCgGTGCA AGAcCTCTTC GACTTtATCA
Chimp PIM1	NO:17	ccTGATCCTG GAGAGGCCcG AgCCgGTGCA AGAtCTCTTC GACTTtATCA
Consensus	NO:15	SYTGATCCTG GAGAGGCCSG ARCCSGTGCA AGAYCTCTTC GACTTYATCA
		401 450
Mouse PIM1	NO:21	CcGAacGaGG aGCcCTaCAg GAGGAcCTgG CCCGagGaTT CTTCTGGCAG
Rat PIM1	NO:20	CcGAgcGaGG aGCcCTcCAg GAGGAgCTgG CCCGgaGcTT CTTCTGGCAG
Cat PIM1	NO:18	CgGAaaGgGG gGCtCTgCAg GAGGAgCTgG CCCGcaGcTT CTTCTGGCAG
Human PIM1	NO:16	CgGAaaGgGG aGCcCTgCAa GAGGAgCTcG CCCGcaGcTT CTTCTGGCAG
Cow PIM1	NO:19	CgGAaaGgGG gGCtCTgCAg GAGGAgCTgG CCCGcaGcTT CTTCTGGCAG
Chimp PIM1	NO:17	CgGAaaGgGG gGCcCTgCAa GAGGAgCTgG CCCGcaGcTT CTTCTGGCAG
Consensus	NO:15	CSGARMGRCG RGCYCTVCAR GAGGASCTSG CCCGVRGMTT CTTCTGGCAG
		451 500
Mouse PIM1	NO:21	GTgCTGGAGG CcGTGCGgCA tTGCCACaAC TGCGGGGTtC TcCACCGCGA
Rat PIM1	NO:20	GTgCTGGAGG CcGTGCGgCA tTGCCACaAC TGCGGGGTtC TcCACCGCGA
Cat PIM1	NO:18	GTgCTGGAGG CcGTGCGgCA cTGCCACaAC TGCGGGGTgC TcCACCGCGA
Human PIM1	NO:16	GTgCTGGAGG CcGTGCGgCA cTGCCACaAC TGCGGGGTgC TcCACCGCGA
Cow PIM1	NO:19	GTaCTGGAGG CgGTGCGaCA cTGCCACgAC TGCGGGGTgC TtCACCGCGA
Chimp PIM1	NO:17	GTgCTGGAGG CcGTGCGgCA cTGCCACaAC TGCGGGGTgC TcCACCGCGA
Consensus	NO:15	GTRCTGGAGG CSGTGCGRCA YTGCCACRAC TGCGGGGTKC TYCACCGCGA
		501 550
Mouse PIM1	NO:21	CATCAAGGAC GAgAACATCt TaATCGACCT gAgcCGCGGC GAaaTCAAaC
Rat PIM1	NO:20	CATCAAGGAC GAgAACATCt TaATCGACCT gAacCGCGGC GAacTCAAaC
Cat PIM1	NO:18	CATCAAGGAC GAgAACATCc TcATCGACCT cAatCGCGGC GAgcTCAAgC
Human PIM1	NO:16	CATCAAGGAC GAaAACATCc TtATCGACCT cAatCGCGGC GAgcTCAAgC
Cow PIM1	NO:19	CATCAAGGAC GAgAACATCc TtATCGACCT cAatCGCGGC GAgcTCAAgC
Chimp PIM1	NO:17	CATCAAGGAC GAaAACATCc TtATCGACCT cAatCGCGGC GAgcTCAAgC
Consensus	NO:15	CATCAAGGAC GARAACATCY THATCGACCT SARYCGCGGC GARMTCAARC
		551 600
Mouse PIM1	NO:21	TCATCGACTT CGGGTCGGGG GCGCTGCTCA AgGACACaGT CTACACGGAC
Rat PIM1	NO:20	TCATCGACTT CGGGTCGGGG GCGCTGCTCA AgGACACaGT CTACACGGAC
Cat PIM1	NO:18	TCATCGACTT CGGGTCGGGG GCGCTGCTCA AgGACACcGT CTACACGGAC

TABLE 11-continued

Alignment of mammalian PIM1 coding (cDNA) nucleotide sequences

	SEQ ID	Alignment (numbering based on consensus sequence):
Human PIM1	NO:16	TCATCGACTT CGGGTCGGGG GCGCTGCTCA AaGACACcGT CTACACGGAC
Cow PIM1	NO:19	TCATCGACTT CGGGTCGGGG GCGCTGCTCA AgGACACcGT CTACACGGAC
Chimp PIM1	NO:17	TCATCGACTT CGGGTCGGGG GCGCTGCTCA AgGACACcGT CTACACGGAC
Consensus	NO:15	TCATCGACTT CGGGTCGGGG GCGCTGCTCA ARGACACMGT CTACACGGAC
		601 650
Mouse PIM1	NO:21	TTtGAtGGgA CCCGAGTGTA cAGtCCtCCA GAGTGGATtC GCTAcCATCG
Rat PIM1	NO:20	TTtGAcGGaA CCCGAGTGTA cAGtCCtCCA GAGTGGATtC GCTAcCATCG
Cat PIM1	NO:18	TTcGAcGGgA CCCGAGTGTA tAGtCCcCCA GAGTGGATcC GCTAcCATCG
Human PIM1	NO:16	TTcGAtGGgA CCCGAGTGTA tAGcCCtCCA GAGTGGATcC GCTAcCATCG
Cow PIM1	NO:19	TTcGAtGGgA CCCGAGTGTA tAGtCCtCCA GAGTGGATcC GCTAtCATCG
Chimp PIM1	NO:17	TTcGAtGGgA CCCGAGTGTA tAGcCCtCCA GAGTGGATcC GCTAcCATCG
Consensus	NO:15	TTYGAYGGRA CCCGAGTGTA YAGYCCYCCA GAGTGGATYC GCTAYCATCG
		651 700
Mouse PIM1	NO:21	CTACCAcGGC AGGTCGGCaG CtGTcTGGTC cCTtGGGATC CTGCTcTATG
Rat PIM1	NO:20	CTACCAcGGC AGGTCGGCtG CtGTtTGGTC cCTgGGGATC CTGCTcTATG
Cat PIM1	NO:18	CTACCAtGGC AGGTCGGCcG CcGTcTGGTC tCTgGGGATC CTGCTgTATG
Human PIM1	NO:16	CTACCAtGGC AGGTCGGCgG CaGTcTGGTC cCTgGGGATC CTGCTgTATG
Cow PIM1	NO:19	CTACCAtGGC AGGTCGGCaG CcGTcTGGTC tCTgGGGATC CTGCTgTATG
Chimp PIM1	NO:17	CTACCAtGGC AGGTCGGCgG CaGTcTGGTC cCTgGGGATC CTGCTgTATG
Consensus	NO:15	CTACCAYGGC AGGTCGGCNG CHGTYTGGTC YCTKGGGATC CTGCTSTATG
		701 750
Mouse PIM1	NO:21	AcATGgTctg cGGaGAtaTt ccgtttgagc acgatgaaga gatcaTCaag
Rat PIM1	NO:20	AcATGgTctg cGGaGAtaTt ccatttgagc acgacgaaga gatcgTCaag
Cat PIM1	NO:18	AtATGgTctg tGGaGAtaTt ccttttgagc atgatgaaga gatcaTCagg
Human PIM1	NO:16	AtATGgTgtg tGGaGAtaTt cctttcgagc atgacgaaga gatcaTCagg
Cow PIM1	NO:19	AcATGgTgtg cGGaGAtaTt ccctttgagc acgatgagga gattgTCagg
Chimp PIM1	NO:17	AtATGtTggt aGGtGAatTg aatcatctca tcatgctcag tggtgTCtca
Consensus	NO:15	AYATGKTSKK HGGWGAWWTK MMNYWYSWSM WYRWBSWVRR KRKYRTCWVR
		751 800
Mouse PIM1	NO:21	ggccAagtgt tctTcAggca aactgtctct TCaGAgTGTC AgCAcCTtAT
Rat PIM1	NO:20	ggccAagtgt actTtAggca aagggtctct TCaGAaTGTC AaCAtCTtAT
Cat PIM1	NO:18	ggccAagttt tctTcAggca gagggtctct TCaGAgTGTC AgCAtCTcAT
Human PIM1	NO:16	ggccAggttt tctTcAggca gagggtctct TCaGAaTGTC AgCAtCTcAT
Cow PIM1	NO:19	ggccAagttt tctTcAggca gcgggtctcc TCaGAgTGTC AaCAtCTcAT
Chimp PIM1	NO:17	tcaaAatctc ttgTcAtcat ccttcctatt TCtGAaTGTC AgCAtCTcAT
Consensus	NO:15	KSMMARKYKY WYKTYAKSMW VMBKSYYWYY TCWGARTGTC ARCAYCTYAT
		801 850

TABLE 11-continued

Alignment of mammalian PIM1 coding (cDNA) nucleotide sequences

	SEQ ID	Alignment (numbering based on consensus sequence):
Mouse PIM1	NO:21	TAaATGGTGC cTGtCCcTGA GACCaTCaGA tcGGCCctCC TTtGAAGAAA
Rat PIM1	NO:20	TAgATGGTGC cTGtCCcTGA GACCaTCgGA ccGGCCctCC TTtGAAGAAA
Cat PIM1	NO:18	TAgATGGTGC tTGgCCcTGA GACCgTCaGA ccGGCCatCC TTcGAAGAAA
Human PIM1	NO:16	TAgATGGTGC tTGgCCcTGA GACCaTCaGA taGGCCaaCC TTcGAAGAAA
Cow PIM1	NO:19	TAgATGGTGC tTGgCCtTGA GACCaTCaGA tcGGCCaaCC TTcGAAGAAA
Chimp PIM1	NO:17	TAgATGGTGC tTGgCCcTGA GACCaTCaGA taGGCCaaCC TTcGAAGAAA
Consensus	NO:15	TARATGGTGC YTGKCCYTGA GACCRTCRGA YMGGCCMWCC TTYGAAGAAA
		851 900
Mouse PIM1	NO:21	TCCgGAACCA TCCaTGGATG CAgGgtGacC TCCTGCCCCA GGcagCttCt
Rat PIM1	NO:20	TCCaGAACCA TCCgTGGATG CAgGatGttC TCCTGCCCCA GGccaCcgCc
Cat PIM1	NO:18	TCCaGAACCA TCCcTGGATG CAaGatGtcC TCCTGCCCCA GGaaaCagCc
Human PIM1	NO:16	TCCaGAACCA TCCaTGGATG CAaGatGttC TCCTGCCCCA GGaaaCtgCt
Cow PIM1	NO:19	TCCaGAACCA TCCgTGGATG CAaGacGtcC TCCTGCCCCA GGaaaCtgCt
Chimp PIM1	NO:17	TCCaGAACCA TCCaTGGATG CAaGatGttC TCCTGCCCCA GGaaaCtgCt
Consensus	NO:15	TCCRGAACCA TCCVTGGATG CARGRYGWYC TCCTGCCCCA GGMMRCHKCY
		901 942
Mouse PIM1	NO:21	GAGATcCAtC TgCACAGtCT GTCaCCgggg tCCAGCAAgT AG
Rat PIM1	NO:20	GAGATtCAtC TgCACAGcCT GTCaCCatca cCCAGCAAaT AG
Cat PIM1	NO:18	GAGATCCAtC TgCACAGcCT GTCaCCaggg cCCAGCAAaT AG
Human PIM1	NO:16	GAGATcCAcC TcCACAGcCT GTCgCCgggg cCCAGCAAaT AG
Cow PIM1	NO:19	GAGATcCAtC TcCACAGcCT GTCgCCaggg cCCAGCAAaT AG
Chimp PIM1	NO:17	GAGATcCAcC TcCACAGcCT GTCgCCgggg cCCAGCAAaT AG
Consensus	NO:15	GAGATYCAYC TSCACAGYCT GTCRCCRKSR YCCAGCAART AG

[A]The symbols in the Consensus sequence conform to Annex C, Appendix 2, TABLE 1 of the Patent Cooperation Treaty Administrative Instructions.

[0128]

TABLE 12

Alignment of mammalian NGF-R amino acid sequences

	SEQ ID:	Alignment (numbering based on consensus sequence):
		1 50
Mouse NGFR	NO:82	MLRGqRlGQL GWHrpAAGlG sLmtsLmLAc AsAAsCrevC CPvGpSGLRC
Rat NGFR	NO:83	MLRGqRhGQL GWHrpAAGlG gLvtsLmLAc AcAAsCretC CPvGpSGLRC
Human NGFR	NO:81	MLRGgRrGQL GWHswAAGpG sLlawLiLAs AgAApCpdaC CPhGsSGLRC
Consensus	NO:80	MLRG-R-GQL GWH--AAG-G -L---L-LA- A-AA-C---C CP-G-SGLRC

TABLE 12-continued

	SEQ ID:	Alignment of mammalian NGF-R amino acid sequences Alignment (numbering based on consensus sequence):
		51 100
Mouse NGFR	NO:82	TRaGsLdtLr gLrGAgNLTE LYvENQqhLQ rLEfeDLqGL GELRsLTIVK
Rat NGFR	NO:83	TRaGtLntLr gLrGAgNLTE LYvENQrdLQ rLEfeDLqGL GELRsLTIVK
Human NGFR	NO:81	TRdGaLdsLh hLpGAeNLTE LYiENQqhLQ hLElrDLrGL GELRnLTIVK
Consensus	NO:80	TR-G-L--L- -L-GA-NLTE LY-ENQ--LQ -LE--DL-GL GELR-LTIVK
		101 150
Mouse NGFR	NO:82	SGLRFVAPDA FrFTPRLShL NLSsNALESL SWKTVQGLSL QdLtLSGNPL
Rat NGFR	NO:83	SGLRFVAPDA FhFTPRLShL NLSsNALESL SWKTVQGLSL QdLtLSGNPL
Human NGFR	NO:81	SGLRFVAPDA FhFTPRLSrL NLSfNALESL SWKTVQGLSL QeLvLSGNPL
Consensus	NO:80	SGLRFVAPDA F-FTPRLS-L NLS-NALESL SWKTVQGLSL Q-L-LSGNPL
		151 200
Mouse NGFR	NO:82	HCSCALfWLQ RWEqEgLcGV htQtLhdsGp GdqflPLgH. .NtSCGVPtv
Rat NGFR	NO:83	HCSCALlWLQ RWEqEdLcGV ytQkLqgsGs GdqflPLgH. .NnSCGVPsv
Human NGFR	NO:81	HCSCALrWLQ RWEeEgLgGV peQkLqchGq G....PLaHm pNaSCGVPtl
Consensus	NO:80	HCSCAL-WLQ RWE-E-L-GV --Q-L---G- G----PL-H- -N-SCGVP--
		201 250
Mouse NGFR	NO:82	KiQmPNdSVe VGDDVfLqCQ VEGlaLqQAd WILTELEgaA TvkKfGdLPS
Rat NGFR	NO:83	KiQmPNdSVe VGDDVfLgCQ VEGqaLqQAd WILTELEgtA TmkKsGdLPS
Human NGFR	NO:81	KvQvPNaSVd VGDDVlLrCQ VEGrgLeQAg WILTELEqsA TvmKsGgLPS
Consensus	NO:80	K-Q-PN-SV- VGDDV-L-CQ VEG--L-QA- WILTELE--A T--K-C-LPS
		251 300
Mouse NGFR	NO:82	LGLiLvNVTS DLNkKNvTCW AENDVGRAEV SVQVsVSFPA SVhLglAVEq
Rat NGFR	NO:83	LGLtLvNVTS DLNkKNvTCW AENDVGRAEV SVQVsVSFPA SVhLgkAVEq
Human NGFR	NO:81	LGLtLaNVTS DLNrKNlTCW AENDVGRAEV SVQVnVSFPA SVqLhtAVEm
Consensus	NO:80	LGL-L-NVTS DLN-KN-TCW AENDVGRAEV SVQV-VSFPA SV-L--AVE-
		301 350
Mouse NGFR	NO:82	HHWCIPFSVD GQPAPSLRWl FNGSVLNETS FIFTqFLEsA ltNETmRHGC
Rat NGFR	NO:83	HHWCIPFSVD GQPAPSLRWf FNGSVLNETS FIFTqFLEsA ltNETmRHGC
Human NGFR	NO:81	HHWCIPFSVD GQPAPSLRWl FNGSVLNETS FIFTeFLEpA .aNETvRHGC
Consensus	NO:80	HHWCIPFSVD GQPAPSLRW- FNGSVLNETS FIFT-FLE-A --NET-RHGC
		351 400
Mouse NGFR	NO:82	LRLNQPTHVN NGNYTLLAAN PyGQAaASvM AAFMDNPFEF NPEDPIPVSF
Rat NGFR	NO:83	LRLNQPTHVN NGNYTLLAAN PyGQAaASiM AAFMDNPFEF NPEDPIPVSF
Human NGFR	NO:81	LRLNQPTHVN NGNYTLLAAN PfGQAsASiM AAFMDNPFEF NPEDPIPVSF
Consensus	NO:80	LRLNQPTHVN NGNYTLLAAN P-GQA-AS-M AAFMDNPFEF NPEDPIPVSF
		401 450
Mouse NGFR	NO:82	SPVDgNSTSr DPVEKKDETP FGVSVAVGLA VsAaLFLSaL LLVLNKCGqR
Rat NGFR	NO:83	SPVDtNSTSr DPVEKKDETP FGVSVAVGLA VsAaLFLSaL LLVLNKCGqR
Human NGFR	NO:81	SPVDtNSTSg DPVEKKDETP FGVSVAVGLA VfAcLFLStL LLVLNKCGrR

TABLE 12-continued

Alignment of mammalian NGF-R amino acid sequences

	SEQ ID:	Alignment (numbering based on consensus sequence):
Consensus	NO:80	SPVD-NSTS- DPVEKKDETP FGVSVAVGLA V-A-LFLS-L LLVLNKCG-R
		451 500
Mouse NGFR	NO:82	sKFGINRPAV LAPEDGLAMS LHFMTLGGSS LSPTEGKGSG LQGHImENPQ
Rat NGFR	NO:83	sKFGINRPAV LAPEDGLAMS LHFMTLGGSS LSPTEGKGSG LQGHImENPQ
Human NGFR	NO:81	nKFGINRPAV LAPEDGLAMS LHFMTLGGSS LSPTEGKGSG LQGHIiENPQ
Consensus	NO:80	-KFGINRPAV LAPEDGLAMS LHFMTLGGSS LSPTEGKGSG LQGHI-ENPQ
		501 550
Mouse NGFR	NO:82	YFSDtCVHHI KRqDIiLKWE LGEGAFGKVF LAECyNLLnd QDKMLVAVKA
Rat NGFR	NO:83	YFSDtCVHHI KRqDIiLKWE LGEGAFGKVF LAECyNLLnd QDKMLVAVKA
Human NGFR	NO:81	YFSDaCVHHI KRrDIvLKWE LGEGAFGKVF LAEChNLLpe QDKMLVAVKA
Consensus	NO:80	YFSD-CVHHI KR-DI-LKWE LGEGAFGKVF LAEC-NLL-- QDKMLVAVKA
		551 600
Mouse NGFR	NO:82	LKEaSEnARQ DFqREAELLT MLQHQHIVRF FGVCTEGgPL LMVFEYMRHG
Rat NGFR	NO:83	LKEtSEnARQ DFhREAELLT MLQHQHIVRF FGVCTEGgPL LMVFEYMRHG
Human NGFR	NO:81	LKEaSEsARQ DFqREAELLT MLQHQHIVRF FGVCTEGrPL LMVFEYMRHG
Consensus	NO:80	LKE-SE-ARQ DF-REAELLT MLQHQHIVRF FGVCTEG-PL LMVFEYMRHG
		601 650
Mouse NGFR	NO:82	DLNRFLRSHG PDAKLLAGGE DVAPGPLGLG QLLAVASQVA AGMVYLAsLH
Rat NGFR	NO:83	DLNRFLRSHG PDAKLLAGGE DVAPGPLGLG QLLAVASQVA AGMVYLAsLH
Human NGFR	NO:81	DLNRFLRSHG PDAKLLAGGE DVAPGPLGLG QLLAVASQVA AGMVYLAgLH
Consensus	NO:80	DLNRFLRSHG PDAKLLAGGE DVAPGPLGLG QLLAVASQVA AGMVYLA-LH
		651 700
Mouse NGFR	NO:82	FVHRDLATRN CLVGQGLVVK IGDFGMSRDI YSTDYYRVGG RTMLPIRWMP
Rat NGFR	NO:83	FVHRDLATRN CLVGQGLVVK IGDFGMSRDI YSTDYYRVGG RTMLPIRWMP
Human NGFR	NO:81	FVHRDLATRN CLVGQGLVVK IGDFGMSRDI YSTDYYRVGG RTMLPIRWMP
Consensus	NO:80	FVHRDLATRN CLVGQGLVVK IGDFGMSRDI YSTDYYRVGG RTMLPIRWMP
		701 750
Mouse NGFR	NO:82	PESILYRKFs TESDVWSFGV VLWEIFTYGK QPWYQLSNTE AIeCITQGRE
Rat NGFR	NO:83	PESILYRKFs TESDVWSFGV VLWEIFTYGK QPWYQLSNTE AIeCITQGRE
Human NGFR	NO:81	PESILYRKFt TESDVWSFGV VLWEIFTYGK QPWYQLSNTE AIdCITQGRE
Consensus	NO:80	PESILYRKF- TESDVWSFGV VLWEIFTYGK QPWYQLSNTE AI-CITQGRE
		751 801
Mouse NGFR	NO:82	LERPRACPPd VYAIMRGCWQ REPQQRlSmK DVHARLQALA QAPPsYLDVLG
Rat NGFR	NO:83	LERPRACPPd VYAIMRGCWQ REPQQRlSmK DVHARLQALA QAPPsYLDVLG
Human NGFR	NO:81	LERPRACPPe VYAIMRGCWQ REPQQRhSiK DVHARLQALA QAPPvYLDVLG
Consensus	NO:80	LERPRACPP- VYAIMRGCWQ REPQQR-S-K DVHARLQALA QAPP-YLDVLG

[0129]

TABLE 13

Location of domains within NGF-R amino acid sequences; numbering refers to amino acid positions within the corresponding SEQ ID NOs

Polypeptide	SEQ ID	Signal sequence	Extracellular	Transmembrane	Intracellular	"Mature"[A] polypeptide
Mouse NGFR	NO: 82	1–32	33–418	419–442	443–799	33–799
Rat NGFR	NO: 83	1–32	33–418	419–442	443–799	33–799
Human NGFR	NO: 81	1–32	33–415	416–439[B]	440–796	33–796
Consensus	NO: 80	1–32	33–420	421–444	445–801	33–801

[A]For the purposes of the above table, the "mature" polypeptide refers to a polypeptide from which the indicated signal sequence has been cleaved; additional mature polypeptide forms may occur.
[B]In the table above, the location of the transmembrane domain in the human NGF-R amino acid sequence is shown as corresponding to the location of the transmembrane domain in the other mammalian NGF-R sequences.

[0130]

TABLE 14

Alignment of mammalian NGF amino acid sequences

	SEQ ID	Alignment (numbering based on consensus sequence):
		1 50
Gorilla NGF	NO:86	MSMLFYTLIT afLIGiQAEl hseSNvpaGh tiPqaHWTKL QHSLDTALRR
Orang. NGF	NO:87	MSMLFYTLIT afLIGiQAEp hseSNvpaGh tiPqaHWTKL QHSLDTALRR
Human NGF	NO:85	MSMLFYTLIT afLIGiQAEp hseSNvpaGh tiPqvHWTKL QHSLDTALRR
Mouse NGF	NO:89	MSMLFYTLIT afLIGvQAEp ytdSNvpeGd svPeaHWTKL QHSLDTALRR
Rat NGF	NO:88	MSMLFYTLIT afLIGvQAEp ytdSNvpeGd svPeaHWTKL QHSLDTALRR
Aft. rat NGF	NO:91	MSMLFYTLIT alLIGvQAEp ytdSNlpeGd svPeaHWTKL QHSLDTALRR
G. pig NGF	NO:90	MSMLFYTLIT vfLIGiQAEp ysdSNvlsGd tiPqaHWTKL QHSLDTALRR
Consensus	NO:84	MSMLFYTLIT --LIG-QAE- ---SN---G- --P--HWTKL QHSLDTALRR
		51 100
Gorilla NGF	NO:86	ArSaPaaaIA ARVaGQTrNI TVDPrLFKKR rLrSPRVLFS TQPPpeaaDt
Orang. NGF	NO:87	ArStPaaaIA ARVaGQTcNI TVDPrLFKKR rLrSPRVLFS TQPPpeaaDt
Human NGF	NO:85	ArSaPaaaIA ARVaGQTrNI TVDPrLFKKR rLrSPRVLFS TQPPreaaDt
Mouse NGF	NO:89	ArSaPtapIA ARVtGQTrNI TVDPrLFKKR rLhSPRVLFS TQPPptssDt
Rat NGF	NO:88	ArSaPaepIA ARVtGQTrNI TVDPkLFKKR rLrSPRVLFS TQPPptssDt
Afr. rat NGF	NO:91	ArSaPaapIA ARVtGQTrNI TVDPrLFKKR kLrSPRVLFS TQPPptssDt
G. pig NGF	NO:90	AhSaPaapIA ARVaGQTlNI TVDPrLFKKR rLhSPRVLFS TQPPplstDa
Consensus	NO:84	A-S-P---IA ARV-GQT-NI TVDP-LFKKR -L-SPRVLFS TQPP- - -
		101 150
Gorilla NGF	NO:86	qDLDFevgGa apfNRTHRSK RSSsHPiFhr GEFSVCDSVS VWVgDKTTAT
Orang. NGF	NO:87	qDLDFevgGa apfNRTHRSK RSSsHPiFhr GEFSVCDSVS VWVgDKTTAT
Human NGF	NO:85	qDLDFevgGa apfNRTHRSK RSSsHPiFhr GEFSVCDSVS VWVgDKTTAT
Mouse NGF	NO:89	lDLDFqahGt ipfNRTHRSK RSStHPvFhm GEFSVCDSVS VWVgDKTTAT
Rat NGF	NO:88	lDLDFqahGt isfNRTHRSK RSStHPvFhm GEFSVCDSVS VWVgDKTTAT
Afr. rat NGF	NO:91	lDLDFqahGt isfNRTHRSK RSStHPvFqm GEFSVCDSVS VWVgDKTTAT

TABLE 14-continued

Alignment of mammalian NGF amino acid sequences

	SEQ ID	Alignment (numbering based on consensus sequence):
G. pig NGF	NO:90	qDLDFevdGa asvNRTHRSK RSStHPvFhm GEFSVCDSVS VWVaDKTTAT
Consensus	NO:84	-DLDF---G- ---NRTHRSK RSS-HP-F-- GEFSVCDSVS VWV-DKTTAT
		151 200
Gorilla NGF	NO:86	DIKGkEVmVL gEVNiNNsVF kQYFFETKCR dpnPVdSGCR GIDSKHWNSY
Orang. NGF	NO:87	DIKGkEVmVL gEVNiNNsVF kQYFFETKCR dpnPVdSGCR GIDSKHWNSY
Human NGF	NO:85	DIKGkEVmVL gEVNiNNsVF kQYFFETKCR dpnPVdSGCR GIDSKHWNSY
Mouse NGF	NO:89	DIKGkEVlVL aEVNiNNsVF rQYFFETKCR asnPVeSGCR GIDSKHWNSY
Rat NGF	NO:88	DIKGkEVtVL gEVNiNNsVF kQYFFETKCR apnPVeSGCR GIDSKHWNSY
Aft. rat NGF	NO:91	DIKGnEVlVL gEVNiNNsVF kQYFFETKCR arnPVeSGCR GIDSKHWNSY
G. pig NGF	NO:90	DIKGkEVtVL aEVNvNNnVF kQYFFETKCR dpsPVdSGCR GIDSKHWNSY
Consensus	NO:84	DIKG-EV-VL -EVN-NN-VF -QYFFETKCR ---PV-SGCR GIDSKHWNSY
		201 241
Gorilla NGF	NO:86	CTTTHTFVKA LTmdgkQAAW RFIRIDTACV CVLsRKAvRR a
Orang. NGF	NO:87	CTTTHTFVKA LTmdgkQAAW RFIRIDTACV CVLsRKAvRR a
Human NGF	NO:85	CTTTHTFVKA LTmdgkQAAW RFIRIDTACV CVLsRKAvRR a
Mouse NGF	NO:89	CTTTHTFVKA LTtdekQAAW RFIRIDTACV CVLsRKAtRR g
Rat NGF	NO:88	CTTTHTFVKA LTtddkQAAW RFIRIDTACV CVLsRKAaRR g
Aft. rat NGF	NO:91	CTTTHTFVKA LTtddrQAAW RFIRIDTACV CVLtRKApRR g
G. pig NGF	NO:90	CTTTHTFVKA LTtankQAAW RFIRIDTACV CVLnRKAaRR g
Consensus	NO:84	CTTTHTFVKA LT----QAAW RFIRIDTACV CVL-RKA-RR -

[0131]

TABLE 15

Location of domains within NGF amino acid sequences; numbering refers to amino acid positions within the corresponding SEQ ID NOs

Polypeptide	SEQ ID	Signal sequence	Pro-peptide	"Mature"[A] polypeptide
Gorilla NGF[B]	NO: 86	1–18	19–121	122–241
Orang. NGF[B]	NO: 87	1–18	19–121	122–241
Human NGF	NO: 85	1–18	19–121	122–241
Mouse NGF	NO: 89	1–18	19–121	122–241
Rat NGF	NO: 88	1–18	19–121	122–241
Afr. rat NGF	NO: 91	1–18	19–121	122–241
G. pig NGF	NO: 90	1–18	19–121	122–241
Consensus	NO: 84	1–18	19–121	122–241

[A]For the purposes of the above table, the "mature" polypeptide refers to a polypeptide from which the indicated signal sequence and pro-peptide have been cleaved; additional mature polypeptide forms may occur.

[B]The location of the signal sequence, pro-peptide domain, and the mature polypeptide within the gorilla and orangutan NGF amino acid sequences was based on the location of these domains in the amino acid sequences of the other mammalian NGF amino acid sequences.

[0132]

TABLE 16

Alignment of mammalian BAFF-R amino acid sequences

	SEQ ID:	Alignment (numbering based on consensus sequence):
		1 50
Human BAFFR	NO 93	~~~mRrgpRS lRgRDapaPT pCvpaECFDl LVRhCVaCgL lrTprPkpag
Mouse BAFFR	NO:94	mgarRlrvRS qRsRDssvPT qCnqtECFDp LVRnCVsCeL fhT..Pdtgh
Consensus	NO:92	----R---RS -R-RD---PT -C---ECFD- LVR-CV-C-L --T--P---
		51 100
Human BAFFR	NO:93	aSSpaPrTAL QPQEsvgaga GeAalPlpgL LfGAPALLGL aLvLaLV.LV
Mouse BAFFR	NO:94	tSSlePgTAL QPQE...... GsAlrPdvaL LvGAPALLGL iLaLtLVgLV
Consensus	NO:92	-SS--P-TAL QPQE------ G-A--P---L L-GAPALLGL -L-L-LV-LV
		101 150
Human BAFFR	NO:93	gLVSWRrRQr rLRgASsaea PDgdkda.pE pLdkViilSp gisdAtAPaW
Mouse BAFFR	NO:94	sLVSWRwRQ. qLRtAS.... PDtsegvqqE sLenVfvpSs etphAsAPtW
Consensus	NO:92	-LVSWR-RQ- -LR-AS---- PD-------E -L--V---S- ----A-AP-W
		151 189
Human BAFFR	NO:93	PPpgEDpgtt pPgHSVPVPA TELGSTELVT TKTAGPEQq
Mouse BAFFR	NO:94	PPlkEDadsa lPrHSVPVPA TELGSTELVT TKTAGPEQ~
Consensus	NO:92	PP--ED---- -P-HSVPVPA TELGSTELVT TKTAGPEQ-

[0133]

TABLE 17

Location of domains within BAFF-R amino acid sequences; numbering refers to amino acid positions within the corresponding SEQ ID NOs

Polypeptide	SEQ ID	Extracellular	Disulfide bonds	Transmembrane	Intracellular
Human BAFFR	NO: 93	1–76	(19, 32); (24, 35)	77–96	97–184
Mouse BAFFR	NO: 94	1–71	(22, 35); (27, 38)	72–92[A]	93–175
Consensus	NO: 92	1–79	(22, 35); (27, 38)	80–100	101–189

[A]The location of the transmembrane domain in the human BAFF-R amino acid sequence is shown as corresponding to the location of the transmembrane domain in the mouse BAFF-R sequence.

[0134]

TABLE 18

Alignment of mammalian BAFF amino acid sequences

	SEQ ID:	Alignment (numbering based on consensus sequence):
		1 50
Human BAFF	NO:96	MDdSter.eq srLtsClkKr EeMKlkecvs IlPrKEsps. vrsskDGkLL
Mouse BAFF	NO:97	MDeSaktlpp pcLcfCseKg EdMKv.gydp ItPqKEegaw fgicrDGrLL
Consensus	NO:95	MD-S------ --L--C--K- E-MK------ I-P-KE---- -----DG-LL

TABLE 18-continued

Alignment of mammalian BAFF amino acid sequences

	SEQ ID:	Alignment (numbering based on consensus sequence):
		51 100
Human BAFF	NO:96	AATLLLALLS cclTvvSfYQ vAALQgDLas LRaELQghha eklPAgAGAP
Mouse BAFF	NO:97	AATLLLALLS ssfTamSlYQ lAALQaDLmn LRmELQsyrg satPAaAGAP
Consensus	NO:95	AATLLLALLS ---T--S-YQ -AALQ-DL-- LR-ELQ---- ---PA-AGAP
		101 150
Human BAFF	NO:96	Kagleeapav TAGlKifePp APgegNSSqn sRNkRAvQGP EET.......
Mouse BAFF	NO:97	e........l TAGvKlltPa APrphNSSrg hRNrRAfQGP EETeqdvdls
Consensus	NO:95	---------- TAG-K---P- AP---NSS-- -RN-RA-QGP EET-------
		151 200
Human BAFF	NO:96	....vtQDCL QLIADSeTPT IqKGsYTFVP
Mouse BAFF	NO:97	Appapclpgc rhsqhddngm nlrniiQDCL QLIADSdTPT IrKGtYPFVP
Consensus	NO:95	---------- ---------- ------QDCL QLIADS-TPT I-KG-YTFVP
		201 250
Human BAFF	NO:96	WLLSFKRGsA LEEKENKIlV keTGYFFIYg QVLYTDktyA MGHlIQRKKV
Mouse BAFF	NO:97	WLLSFKRGnA LEEKENKIvV rqTGYFFIYs QVLYTDpifA MGHvIQRKKV
Consensus	NO:95	WLLSFKRG-A LEEKENKI-V --TGYFFIY- QVLYTD---A MGH-IQRKRV
		251 300
Human BAFF	NO:96	HVFGDELSLV TLFRCIQNMP eTLPNNSCYS AGIAkLEEGD ElQLAIPREN
Mouse BAFF	NO:97	HVFGDELSLV TLFRCIQNMP kTLPNNSCYS AGIArLEEGD EiQLAIPREN
Consensus	NO:95	HVFGDELSLV TLFRCIQNMP -TLPNNSCYS AGIA-LEEGD E-QLAIPREN
		301 318
Human BAFF	NO:96	AQISldGDvT FFGALKLL
Mouse BAFF	NO:97	AQISrnGDdT FFGALKLL
Consensus	NO:95	AQIS--GD-T FFGALKLL

[0135]

TABLE 19

Location of domains within BAFF amino acid sequences; numbering refers to amino acid positions within the corresponding SEQ ID NOs

Polypeptide	SEQ ID	Intracellular	Transmembrane	Extracellular	Mature (soluble)[A]
Human BAFF	NO: 96	1–46	47–67	68–285	134–285
Mouse BAFF	NO: 97	1–47	48–68	69–309	127–309
Consensus	NO: 95	1–48	49–69	70–318	136–318

[A]For the purposes of the above table, the "mature" polypeptide refers to an extracellular domain of the polypeptide which has been cleaved from the cell surface to form a soluble polypeptide; other mature forms may occur.

[0136]

TABLE 20

Alignment of mammalian TNFR1 amino acid sequences

	SEQ ID:	Alignment (numbering based on consensus sequence):
Mouse TNFR1	NO:103	MGLptVPgLL lsLVLlaLLm gihPsgVtGL VpslgDREKR dslCPQGKYv
Rat TNFR1	NO:102	MGLpiVPgLL lsLVLlaLLm gihPsgVtGL VpslgDREKR dnlCPQGKYa
Cat TNFR1	NO:100	MGLptVPgLL qpLVLlaLLv eiyPlrVtGL VphlrDREKR aipCPQGKYi
Human TNFR1	NO:99	MGLstVPdLL lpLVLleLLv giyPsgViGL VphlgDREKR dsvCPQGKYi
Pig TNFR1	NO:101	MGLstVPgLL lpLVLraLLv dvyPagVhGL VlhpgDREKR eslCPQGKYs
Consensus	NO:98	MGL--VP-LL --LVL--LL- ---P--V-GL V----DREKR ---CPQGKY-
		51 100
Mouse TNFR1	NO:103	HsknnSICCT KCHKGTYLvs DCpsPGrdTv CreCekGtFT ASqNyl- rqCL
Rat TNFR1	NO:102	HpknnSICCT KCHKGTYLvs DCpsPGqeTv CevCdkGtFT ASqNh- vrqCL
Cat TNFR1	NO:100	HpqdnSICCT KCHKGTYLyn DCagPGldTd CreCenGtFT ASeNyl- rqCL
Human TNFR1	NO:99	HpqnnSICCT KCHKGTYLyn DCpgPGqdTd CreCesGsFT ASeNhl- rhCL
Pig TNFR1	NO:101	HpqnrSICCT KCHKGTYLhn DClgPGldTd CreCdnGtFT ASeNhltqCL
Consensus	NO:98	H----SICCT KCHKGTYL-- DC--PG--T- C--C--G-FT AS-N---- CL
		101 150
Mouse TNFR1	NO:103	SCktCRkEMs QVEISpCqad kDTVCGCkeN QfqrYlSEth FQCvdC- SpCf
Rat TNFR1	NO:102	SCktCRkEMf QVEISpCkad mDTVCGCkkN QfqrYlSEth FQCvdC- SpCf
Cat TNFR1	NO:100	SCskCRkEMy QVEISpCtvy rDTVCGCrkN QyryYwSEth FQClnCS- lCl
Human TNFR1	NO:99	SCskCRkEMg QVEISsCtvd rDTVCGCrkN QyrhYwSEnl FQCfnCS- lCl
Pig TNFR1	NO:101	SCskCRsEMs QVEISpCtvd rDTVCGCrkN QyrkYwSEtl FQClnCS- lCp
Consensus	NO:98	SC--CR-EM- QVEIS-C--- -DTVCGC--N Q---Y-SE-- FQC--CS- C-

TABLE 20-continued

Alignment of mammalian TNFR1 amino acid sequences

	SEQ ID:	Alignment (numbering based on consensus sequence):
		151 200
Mouse TNFR1	NO:103	NGTVtipCkE tQnTvCnCHa GFFLresECv pCshCkKnee CmnkLClp-ppl
Rat TNFR1	NO:102	NGTVtipCkE kQnTvCnCHa GFFLsgnECt pCshCkKnqe CmkL-Cl.ppv
Cat TNFR1	NO:100	NGTVqisCkE tQnTvCtCHa GFFLrgnECv sCvnCkKnte CtkL-Cv.piv
Human TNFR1	NO:99	NGTVhlsCqE kQnTvCtCHa GFFLrenECv sCsnCkKsle CtkL-Cl.pqi
Pig TNFR1	NO:101	NGTVqlpClE kQdTiCnCHs GFFLrdkECv sCvnC.Knad Ckn-LCp.ats
Consensus	NO:98	NGTV---C-E -Q-T-C-CH- GFFL---EC- -C--C-K--- C--LC-----
		201 250
Mouse TNFR1	NO:103	anvtnpqDsC TaVLLPLVIl lGlCllsfif isLmcRYprw rpevySIiCr
Rat TNFR1	NO:102	anvtnpqDsC TaVLLPLVIf lGlCllffic isLlcRYpqw rprvySIiCr
Cat TNFR1	NO:100	etvkdpqDpG TtVLLPLVIf fGiCvis.fs igLmcRYqrr ksklf-SIvCg
Human TNFR1	NO:99	envkgteDsG TtVLLPLVIf fGlCllsllf igLmyRYqrw kskl-ySIvCg
Pig TNFR1	NO:101	etrndfqDtG TtVLLPLVIf fGlClafflf vgLacRYqrw kpklySIiCg
Consensus	NO:98	-------D-G T-VLLPLVI- -G-C------ --L--RY--- -----SI-C-
		251 300
Mouse TNFR1	NO:103	dpvPvKE.Ek ag...kPltp apspaFSPts gfnPTlgFS. tPgf-sspvSs
Rat TNFR1	NO:102	dsapvKEvEg egivtkPltp asipaFSPnp gfnPTlgFSt tPrfsh-pvSs
Cat TNFR1	NO:100	kstPtKEgE. ....pqp.l. atgpgFSPip ..sPT..FSp sP..t-ftpSp
Human TNFR1	NO:99	kstPeKEgEl egtttkP.l. apnpsFSPtp gftPTlgFSp vPsst-ftsSs
Pig TNFR1	NO:101	kstPvKEgEp eplataPsf. gpittFSPip sfsPTttFSp vPsf-spisSp
Consensus	NO:98	---P-KE-E- ------P--- -----FSP-- ---PT--FS- -P------S-
		301 350
Mouse TNFR1	NO:103	TpispifgPs nwh.f..mpp vsEvvPt.QG AdPlLyeslc svPapts-vqK

TABLE 20-continued

Alignment of mammalian TNFR1 amino acid sequences

	SEQ ID:	Alignment (numbering based on consensus sequence):
Rat TNFR1	NO:102	TpispvfgPs nwhnf..vpp vrEvvPt.QG AdPlLygsln pvPipa- pvrK
Cat TNFR1	NO:100	T.....ftPs dwanlraasv srEmaPpyQG AgPiLsaapa ssPist- pvqK
Human TNFR1	NO:99	T.....ytPg dcpnf..aap rrEvaPpyQG AdPiLatala sdPipn- plqK
Pig TNFR1	NO:101	T.....ftPc dwsnikvtsp pkEiaPppQG AgPiLpmppa stPvpt- plpK
Consensus	NO:98	T-------P- ---------- --E--P--QG A-P-L----- --P----- -K
		351 400
Mouse TNFR1	NO:103	Wed.....sa hPqrpdnaDl AiLYAVVdgV PPaRWKEFmR fmGLSe- HEIe
Rat TNFR1	NO:102	Wed...vvaa qPgrldtaDp AmLYAVVdgV PPtRWKEFmR llGLSe- HEIe
Cat TNFR1	NO:100	Wedstht..q rPea.dpaDp AtLYAVVdgV PPsRWKEFvR rlGLSe- HEIe
Human TNFR1	NO:99	Wedsah.... kPqsldtdDp AtLYAVVenV PPlRWKEFvR rlGLSd- HEId
Pig TNFR1	NO:101	Wggsahsahs aPaqladaDp AtLYAVVdgV PPtRWKEFvR rlGLSe- HEIe
Consensus	NO:98	W--------- -P------D- A-LYAVV--V PP-RWKEF-R --GLS- HEI-
		401 450
Mouse TNFR1	NO:103	RLEmQNGRCL REAqYSMLea WRRRTpRhEd TLevVGlVLs kMnLaG- CLEn
Rat TNFR1	NO:102	RLElQNGRCL REAhYSMLea WRRRTpRhEa TLdvvGrVLc dMnLrG- CLEn
Cat TNFR1	NO:100	RLElQNGRCL REAhYSMLaa WRRRTpRrEa TLellGrVLr dMdLlGCLEd
Human TNFR1	NO:99	RLElQNGRCL REAqYSMLat WRRRTpRrEa TLellGrVLr dMdLlGCLEd
Pig TNFR1	NO:101	RLElQNGRCL REAcYSMLae WRRRTsRrEa TLellGsVLr dMdLlGCLEd
Consensus	NO:98	RLE-QNGRCL REA-YSML-- WRRRT-R-E- TL---G-VL- -M-L- GCLE-
		451 469
Mouse TNFR1	NO:103	IlEaLrnPAp .ssttrLpR
Rat	NO:102	IrEtLesPAh .sstthLpR

TABLE 20-continued

Alignment of mammalian TNFR1 amino acid sequences

	SEQ ID:	Alignment (numbering based on consensus sequence):
TNFR1		
Cat TNFR1	NO:100	IeEaLcaPAs lspaprLlR
Human TNFR1	NO:99	IeEaLcgPAa lppapsLlR
Pig TNFR1	NO:101	IeEaLrgPAr lapaphLlR
Consensus	NO:98	I-E-L--PA- ------L-R

[0137]

TABLE 21

Location of domains within TNFR1 amino acid sequences; numbering refers to amino acid positions within the corresponding SEQ ID NOs

Polypeptide	SEQ ID	Signal	ExtracellularS	Transmembrane	Intracellular	"Mature"[A] polypeptide
Mouse TNFR1	NO: 103	1–21	22–212	213–235	236–454	22–454
Rat TNFR1	NO: 102	1–21	22–211	212–234	235–461	22–461
Cat TNFR1[B]	NO: 100	1–21	22–211	212–233	234–446	22–446
Human TNFR1	NO: 99	1–21	22–211	212–234	235–455	22–455
Pig TNFR1	NO: 101	1–21	22–210	211–233	234–461	22–461
Consensus	NO: 98	1–21	22–212	213–235	236–469	22–469

[A]For the purposes of the above table, the "mature" polypeptide refers to a polypeptide from which the indicated signal sequence has been cleaved; additional mature polypeptide forms may occur.
[B]The positions of domains within the cat TNFR1 amino acid sequence have been determined by comparison with the corresponding domains of the other mammalian TNFR1 amino acid sequences.

[0138] All publications, patents and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

SEQUENCE LISTING

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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (507)..(507)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 1

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Met Xaa Xaa Xaa Xaa Xaa Xaa Xaa Trp Pro Xaa Val Xaa Xaa Leu Cys
1               5                   10                  15

Leu Leu Leu Ala Gly Ala Xaa Trp Ala Xaa Xaa Pro Xaa Xaa Pro Asp
            20                  25                  30

Xaa Lys Phe Glu Ser Lys Ala Ala Leu Leu Ala Xaa Arg Gly Xaa Glu
        35                  40                  45

Glu Leu Leu Cys Phe Thr Xaa Arg Leu Glu Asp Leu Val Cys Phe Trp
    50                  55                  60

Glu Glu Ala Xaa Xaa Xaa Gly Xaa Xaa Xaa Xaa Xaa Tyr Ser Phe Ser
65                  70                  75                  80

Tyr Gln Leu Glu Xaa Glu Xaa Xaa Lys Xaa Cys Xaa Leu His Gln Xaa
                85                  90                  95

Pro Thr Xaa Arg Gly Xaa Xaa Arg Phe Trp Cys Ser Leu Pro Thr Ala
            100                 105                 110

Asp Thr Ser Ser Phe Val Pro Leu Glu Leu Xaa Val Thr Xaa Xaa Xaa
        115                 120                 125

Ser Gly Xaa Pro Arg Tyr His Arg Xaa Ile His Ile Asn Glu Val Val
    130                 135                 140
```

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```
Leu Leu Asp Xaa Pro Xaa Gly Leu Xaa Ala Arg Xaa Ala Xaa Glu Xaa
145                 150                 155                 160

Xaa His Val Val Leu Arg Trp Leu Pro Pro Pro Xaa Xaa Pro Met Xaa
                165                 170                 175

Xaa Xaa Ile Arg Tyr Glu Val Xaa Xaa Ser Xaa Xaa Asn Xaa Ala Gly
            180                 185                 190

Xaa Xaa Gln Arg Val Glu Xaa Leu Xaa Gly Arg Thr Glu Cys Val Leu
        195                 200                 205

Ser Asn Leu Arg Gly Xaa Thr Arg Tyr Thr Phe Xaa Val Arg Ala Arg
    210                 215                 220

Met Ala Glu Pro Ser Phe Xaa Gly Phe Trp Ser Ala Trp Ser Glu Pro
225                 230                 235                 240

Xaa Ser Leu Leu Thr Xaa Ser Asp Leu Asp Pro Leu Ile Leu Thr Leu
                245                 250                 255

Ser Leu Ile Leu Val Xaa Ile Xaa Xaa Leu Leu Xaa Val Leu Ala Leu
            260                 265                 270

Leu Ser His Arg Arg Xaa Leu Xaa Gln Lys Ile Trp Pro Gly Ile Pro
        275                 280                 285

Ser Pro Glu Xaa Glu Phe Glu Gly Leu Phe Thr Thr His Lys Gly Asn
    290                 295                 300

Phe Gln Leu Trp Leu Xaa Gln Xaa Asp Gly Cys Leu Trp Trp Ser Pro
305                 310                 315                 320

Xaa Xaa Xaa Phe Xaa Glu Asp Pro Pro Ala Xaa Leu Glu Val Leu Ser
                325                 330                 335

Glu Xaa Xaa Trp Xaa Xaa Xaa Gln Ala Xaa Xaa Xaa Xaa Xaa Xaa Asp
            340                 345                 350

Xaa Gly Xaa Leu Leu Glu Pro Val Gly Ser Glu Xaa Ala Xaa Asp Thr
        355                 360                 365

Tyr Leu Val Leu Asp Xaa Trp Leu Leu Pro Arg Xaa Pro Xaa Ser Glu
    370                 375                 380

Xaa Leu Xaa Xaa Pro Gly Xaa Xaa Xaa Asp Xaa Xaa Xaa Met Asp Glu
385                 390                 395                 400

Xaa Ser Glu Xaa Ser Xaa Cys Xaa Ser Xaa Leu Ala Xaa Lys Pro Xaa
                405                 410                 415

Pro Glu Gly Xaa Ser Xaa Xaa Ser Phe Glu Tyr Thr Ile Leu Asp Pro
            420                 425                 430

Ser Ser Xaa Leu Leu Xaa Pro Xaa Xaa Leu Xaa Xaa Glu Leu Pro Pro
        435                 440                 445

Thr Pro Pro His Leu Lys Tyr Leu Tyr Leu Val Val Ser Asp Ser Gly
    450                 455                 460

Ile Ser Thr Asp Tyr Ser Ser Gly Xaa Ser Gln Xaa Xaa Xaa Gly Xaa
465                 470                 475                 480

Xaa Ser Xaa Gly Pro Tyr Ser Xaa Pro Tyr Glu Asn Ser Leu Xaa Pro
                485                 490                 495

Xaa Xaa Glu Pro Xaa Xaa Pro Xaa Tyr Val Xaa Cys Ser
            500                 505
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<210> SEQ ID NO 2
<211> LENGTH: 508
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 2

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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

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
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```
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 3
<211> LENGTH: 507
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 3

Met Asp Lys Leu Arg Val Pro Leu Trp Pro Arg Val Gly Pro Leu Cys
1               5                   10                  15

Leu Leu Leu Ala Gly Ala Ala Trp Ala Pro Ser Pro Ser Leu Pro Asp
            20                  25                  30

Pro Lys Phe Glu Ser Lys Ala Ala Leu Leu Ala Ser Arg Gly Ser Glu
        35                  40                  45

Glu Leu Leu Cys Phe Thr Gln Arg Leu Glu Asp Leu Val Cys Phe Trp
    50                  55                  60

Glu Glu Ala Ala Ser Ser Gly Met Asp Phe Asn Tyr Ser Phe Ser Tyr
65                  70                  75                  80

Gln Leu Glu Gly Glu Ser Arg Lys Ser Cys Ser Leu His Gln Ala Pro
                85                  90                  95

Thr Val Arg Gly Ser Val Arg Phe Trp Cys Ser Leu Pro Thr Ala Asp
            100                 105                 110

Thr Ser Ser Phe Val Pro Leu Glu Leu Gln Val Thr Glu Ala Ser Gly
        115                 120                 125

Ser Pro Arg Tyr His Arg Ile Ile His Ile Asn Glu Val Val Leu Leu
    130                 135                 140

Asp Ala Pro Ala Gly Leu Leu Ala Arg Arg Ala Glu Glu Gly Ser His
145                 150                 155                 160

Val Val Leu Arg Trp Leu Pro Pro Pro Gly Ala Pro Met Thr Thr His
                165                 170                 175

Ile Arg Tyr Glu Val Asp Val Ser Ala Gly Asn Arg Ala Gly Gly Thr
            180                 185                 190

Gln Arg Val Glu Val Leu Glu Gly Arg Thr Glu Cys Val Leu Ser Asn
        195                 200                 205

Leu Arg Gly Gly Thr Arg Tyr Thr Phe Ala Val Arg Ala Arg Met Ala
    210                 215                 220

Glu Pro Ser Phe Ser Gly Phe Trp Ser Ala Trp Ser Glu Pro Ala Ser
225                 230                 235                 240

Leu Leu Thr Ala Ser Asp Leu Asp Pro Leu Ile Leu Thr Leu Ser Leu
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                245                 250                 255

Ile Leu Val Leu Ile Ser Leu Leu Leu Thr Val Leu Ala Leu Leu Ser
            260                 265                 270

His Arg Arg Thr Leu Gln Gln Lys Ile Trp Pro Gly Ile Pro Ser Pro
        275                 280                 285

Glu Ser Glu Phe Glu Gly Leu Phe Thr Thr His Lys Gly Asn Phe Gln
    290                 295                 300

Leu Trp Leu Leu Gln Arg Asp Gly Cys Leu Trp Trp Ser Pro Gly Ser
305                 310                 315                 320

Ser Phe Pro Glu Asp Pro Pro Ala His Leu Glu Val Leu Ser Glu Pro
                325                 330                 335

Arg Trp Ala Val Thr Gln Ala Gly Asp Pro Gly Ala Asp Asp Glu Gly
            340                 345                 350

Pro Leu Leu Glu Pro Val Gly Ser Glu His Ala Gln Asp Thr Tyr Leu
        355                 360                 365

Val Leu Asp Lys Trp Leu Leu Pro Arg Thr Pro Cys Ser Glu Asn Leu
    370                 375                 380

Ser Gly Pro Gly Gly Ser Val Asp Pro Val Thr Met Asp Glu Ala Ser
385                 390                 395                 400

Glu Thr Ser Ser Cys Pro Ser Asp Leu Ala Ser Lys Pro Arg Pro Glu
                405                 410                 415

Gly Thr Ser Pro Ser Ser Phe Glu Tyr Thr Ile Leu Asp Pro Ser Ser
            420                 425                 430

Gln Leu Leu Cys Pro Arg Ala Leu Pro Pro Glu Leu Pro Pro Thr Pro
        435                 440                 445

Pro His Leu Lys Tyr Leu Tyr Leu Val Val Ser Asp Ser Gly Ile Ser
    450                 455                 460

Thr Asp Tyr Ser Ser Gly Gly Ser Gln Gly Val His Gly Asp Ser Ser
465                 470                 475                 480

Asp Gly Pro Tyr Ser His Pro Tyr Glu Asn Ser Leu Val Pro Asp Ser
                485                 490                 495

Glu Pro Leu His Pro Gly Tyr Val Ala Cys Ser
            500                 505


<210> SEQ ID NO 4
<211> LENGTH: 507
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 4

Met Asp Gln Leu Arg Val Ala Arg Trp Pro Arg Val Ser Pro Leu Cys
1               5                   10                  15

Leu Leu Leu Ala Gly Ala Ala Trp Ala Ser Ser Pro Ser Leu Pro Asp
            20                  25                  30

Pro Lys Phe Glu Ser Lys Ala Ala Leu Leu Ala Ser Arg Gly Ser Glu
        35                  40                  45

Glu Leu Leu Cys Phe Thr Gln Arg Leu Glu Asp Leu Val Cys Phe Trp
    50                  55                  60

Glu Glu Ala Ala Asn Ser Gly Met Gly Phe Asn Tyr Ser Phe Ser Tyr
65                  70                  75                  80

Gln Leu Glu Gly Glu Ser Arg Lys Ser Cys Arg Leu His Gln Ala Pro
                85                  90                  95
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```
Thr Val Arg Gly Ser Met Arg Phe Trp Cys Ser Leu Pro Thr Ala Asp
            100                 105                 110

Thr Ser Ser Phe Val Pro Leu Glu Leu Gln Val Thr Glu Ala Ser Gly
        115                 120                 125

Ser Pro Arg Tyr His Arg Ile Ile His Ile Asn Glu Val Val Leu Leu
    130                 135                 140

Asp Ala Pro Ala Gly Leu Leu Ala Arg Arg Ala Glu Glu Gly Ser His
145                 150                 155                 160

Val Val Leu Arg Trp Leu Pro Pro Pro Gly Ala Pro Met Thr Thr His
                165                 170                 175

Ile Arg Tyr Glu Val Asp Val Ser Ala Gly Asn Arg Ala Gly Gly Thr
            180                 185                 190

Gln Arg Val Glu Val Leu Glu Gly Arg Thr Glu Cys Val Leu Ser Asn
        195                 200                 205

Leu Arg Gly Gly Thr Arg Tyr Thr Phe Ala Val Arg Ala Arg Met Ala
    210                 215                 220

Glu Pro Ser Phe Ser Gly Phe Trp Ser Ala Trp Ser Glu Pro Ala Ser
225                 230                 235                 240

Leu Leu Thr Ala Ser Asp Leu Asp Pro Leu Ile Leu Thr Leu Ser Leu
                245                 250                 255

Ile Leu Val Leu Ile Ser Leu Leu Leu Thr Val Leu Ala Leu Leu Ser
            260                 265                 270

His Arg Arg Ala Leu Arg Gln Lys Ile Trp Pro Gly Ile Pro Ser Pro
        275                 280                 285

Glu Asn Glu Phe Glu Gly Leu Phe Thr Thr His Lys Gly Asn Phe Gln
    290                 295                 300

Leu Trp Leu Leu Gln Arg Asp Gly Cys Leu Trp Trp Ser Pro Ser Ser
305                 310                 315                 320

Pro Phe Pro Glu Asp Pro Pro Ala His Leu Glu Val Leu Ser Glu Arg
                325                 330                 335

Arg Trp Gly Val Thr Gln Ala Gly Asp Ala Gly Ala Glu Asp Lys Gly
            340                 345                 350

Pro Leu Leu Glu Pro Val Gly Ser Glu Arg Ala Gln Asp Thr Tyr Leu
        355                 360                 365

Val Leu Asp Glu Trp Leu Leu Pro Arg Cys Pro Cys Ser Glu Asn Leu
    370                 375                 380

Ser Gly Pro Gly Asp Ser Val Asp Pro Ala Thr Met Asp Glu Gly Ser
385                 390                 395                 400

Glu Thr Ser Ser Cys Pro Ser Asp Leu Ala Ser Lys Pro Arg Pro Glu
                405                 410                 415

Gly Thr Ser Pro Ser Ser Phe Glu Tyr Thr Ile Leu Asp Pro Ser Ser
            420                 425                 430

Lys Leu Leu Cys Pro Arg Ala Leu Pro Pro Glu Leu Pro Pro Thr Pro
        435                 440                 445

Pro His Leu Lys Tyr Leu Tyr Leu Val Val Ser Asp Ser Gly Ile Ser
    450                 455                 460

Thr Asp Tyr Ser Ser Gly Gly Ser Gln Gly Val His Gly Asp Ser Ser
465                 470                 475                 480

Asp Gly Pro Tyr Ser His Pro Tyr Glu Asn Ser Leu Val Pro Asp Thr
                485                 490                 495

Glu Pro Leu Arg Pro Ser Tyr Val Ala Cys Ser
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        500                 505

<210> SEQ ID NO 5
<211> LENGTH: 509
<212> TYPE: PRT
<213> ORGANISM: Sus scrofa

<400> SEQUENCE: 5

Met Tyr His Phe Gly Ala Thr Leu Trp Pro Gly Val Gly Ser Leu Cys
1               5                   10                  15

Leu Leu Leu Ala Gly Ala Thr Trp Ala Pro Ser Pro Asn Ser Pro Asp
            20                  25                  30

Ala 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 Gly Ser Ala Gly Val Gly Pro Glu Asp Tyr Ser Phe Ser
65                  70                  75                  80

Tyr Gln Leu Glu Gly Glu Pro Trp Lys Pro Cys His Leu His Gln Gly
                85                  90                  95

Pro Thr Ala Arg Gly Ser 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 Glu Val Ser
        115                 120                 125

Ser Gly Ala Pro Arg Tyr His Arg Ile Ile His Ile Asn Glu Val Val
    130                 135                 140

Leu Leu Asp Pro Pro Ala Gly Leu Leu Ala Arg Arg Ala Glu Glu Ser
145                 150                 155                 160

Gly His Val Val Leu Arg Trp Leu Pro Pro Pro Gly Ala Pro Met Ala
                165                 170                 175

Ser Leu Ile Arg Tyr Glu Val Asn Ile Ser Thr Glu Asn Ala Ala Gly
            180                 185                 190

Gly Val Gln Arg Val Glu Ile Leu Asp Gly Arg Thr Glu Cys Val Leu
        195                 200                 205

Ser Asn Leu Arg Gly Gly Thr Arg Tyr Thr Phe Met Val Arg Ala Arg
    210                 215                 220

Met Ala Glu Pro Ser Phe Gly Gly Phe Trp Ser Ala Trp Ser Glu Pro
225                 230                 235                 240

Ala Ser Leu Leu Thr Ala Ser Asp Leu Asp Pro Leu Ile Leu Thr Leu
                245                 250                 255

Ser Leu Ile Leu Val Leu Ile Leu Leu Leu Leu Ala Val Leu Ala Leu
            260                 265                 270

Leu Ser His Arg Arg Thr Leu Lys Gln Lys Ile Trp Pro Gly Ile Pro
        275                 280                 285

Ser Pro Glu Gly Glu Phe Glu Gly Leu Phe Thr Thr His Lys Gly Asn
    290                 295                 300

Phe Gln Leu Trp Leu Tyr Gln Thr Asp Gly Cys Leu Trp Trp Ser Pro
305                 310                 315                 320

Cys Thr Pro Phe Ala Glu Asp Pro Pro Ala Pro Leu Glu Val Leu Ser
                325                 330                 335

Glu Arg Cys Trp Gly Val Thr Gln Ala Val Glu Pro Ala Ala Asp Asp
            340                 345                 350
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```
Glu Gly Ser Leu Leu Glu Pro Val Gly Ser Glu His Ala Arg Asp Thr
        355                 360                 365

Tyr Leu Val Leu Asp Lys Trp Leu Leu Pro Arg Arg Pro Ala Ser Glu
    370                 375                 380

Asp Leu Pro Gln Pro Gly Gly Asp Leu Asp Met Ala Ala Met Asp Glu
385                 390                 395                 400

Ala Ser Glu Ala Ser Phe Cys Ser Ser Ala Leu Ala Leu Lys Pro Gly
                405                 410                 415

Pro Glu Gly Ala Ser Ala Ala Ser Phe Glu Tyr Thr Ile Leu Asp Pro
            420                 425                 430

Ser Ser Gln Leu Leu Arg Pro Arg Ala Leu Pro Ala Glu Leu Pro Pro
        435                 440                 445

Thr Pro Pro His Leu Lys Tyr Leu Tyr Leu Val Val Ser Asp Ser Gly
    450                 455                 460

Ile Ser Thr Asp Tyr Ser Ser Gly Gly Ser Gln Glu Thr Gln Gly Gly
465                 470                 475                 480

Ser Ser Ser Gly Pro Tyr Ser Asn Pro Tyr Glu Asn Ser Leu Val Pro
                485                 490                 495

Ala Pro Glu Pro Ser Pro Pro Asn Tyr Val Thr Cys Ser
            500                 505
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<210> SEQ ID NO 6
<211> LENGTH: 194
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: EPO mammalian
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(11)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<221> NAME/KEY: misc_feature
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<221> NAME/KEY: misc_feature
<222> LOCATION: (23)..(23)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<221> NAME/KEY: misc_feature
<222> LOCATION: (26)..(27)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<222> LOCATION: (30)..(30)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<221> NAME/KEY: misc_feature
<222> LOCATION: (47)..(47)
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<221> NAME/KEY: misc_feature
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<221> NAME/KEY: misc_feature
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<221> NAME/KEY: misc_feature
<222> LOCATION: (132)..(132)

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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<222> LOCATION: (143)..(143)
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<221> NAME/KEY: misc_feature
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<221> NAME/KEY: misc_feature
<222> LOCATION: (174)..(174)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (182)..(182)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (188)..(188)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (191)..(191)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 6

Met Gly Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Leu Xaa Leu Ser Xaa
1               5                   10                  15

Xaa Xaa Xaa Pro Leu Gly Xaa Pro Val Xaa Xaa Ala Pro Xaa Arg Leu
            20                  25                  30

Xaa Cys Asp Ser Arg Val Leu Glu Arg Tyr Xaa Leu Xaa Ala Xaa Glu
        35                  40                  45

Ala Glu Asn Xaa Thr Xaa Gly Cys Xaa Glu Xaa Xaa Xaa Xaa Xaa Glu
    50                  55                  60

Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Xaa Trp Lys Arg
65                  70                  75                  80

Xaa Xaa Val Xaa Xaa Gln Ala Xaa Glu Val Trp Gln Gly Leu Xaa Leu
                85                  90                  95

Leu Ser Glu Ala Xaa Xaa Xaa Xaa Gln Ala Xaa Xaa Xaa Asn Xaa Ser
            100                 105                 110
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```
Gln Pro Xaa Glu Xaa Leu Xaa Leu His Xaa Asp Lys Ala Xaa Ser Xaa
        115                 120                 125

Leu Arg Ser Xaa Thr Xaa Leu Leu Arg Xaa Leu Gly Ala Gln Xaa Glu
    130                 135                 140

Xaa Xaa Xaa Xaa Pro Xaa Xaa Xaa Xaa Xaa Ala Pro Leu Arg Xaa
145                 150                 155                 160

Xaa Thr Xaa Asp Xaa Xaa Xaa Lys Leu Phe Arg Xaa Tyr Xaa Asn Phe
                165                 170                 175

Leu Arg Gly Lys Leu Xaa Leu Tyr Thr Gly Glu Xaa Cys Arg Xaa Gly
            180                 185                 190

Asp Arg


<210> SEQ ID NO 7
<211> LENGTH: 193
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 7

Met Gly Val His Glu Cys Pro Ala Trp Leu Trp Leu Leu Leu Ser Leu
1               5                   10                  15

Leu Ser Leu Pro Leu Gly Leu Pro Val Leu Gly Ala Pro Pro Arg Leu
            20                  25                  30

Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu
        35                  40                  45

Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu
    50                  55                  60

Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg
65                  70                  75                  80

Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu
                85                  90                  95

Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser
            100                 105                 110

Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly
        115                 120                 125

Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu
    130                 135                 140

Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile
145                 150                 155                 160

Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu
                165                 170                 175

Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp
            180                 185                 190

Arg


<210> SEQ ID NO 8
<211> LENGTH: 192
<212> TYPE: PRT
<213> ORGANISM: Macaca mulatta

<400> SEQUENCE: 8

Met Gly Val His Glu Cys Pro Ala Trp Leu Trp Leu Leu Leu Ser Leu
1               5                   10                  15

Val Ser Leu Pro Leu Gly Leu Pro Val Pro Gly Ala Pro Pro Arg Leu
```

-continued

```
            20                  25                  30

Val Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu
        35                  40                  45

Ala Glu Asn Val Thr Met Gly Cys Ser Glu Ser Cys Ser Leu Asn Glu
    50                  55                  60

Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg
65                  70                  75                  80

Ile Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu
                85                  90                  95

Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Val Leu Ala Asn Ser Ser
            100                 105                 110

Gln Pro Phe Glu Pro Leu Gln Leu His Met Asp Lys Ala Ile Ser Gly
        115                 120                 125

Leu Arg Ser Ile Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Glu Ala
    130                 135                 140

Ile Ser Leu Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr
145                 150                 155                 160

Ala Asp Thr Phe Cys Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg
                165                 170                 175

Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Arg Gly Asp Arg
            180                 185                 190


<210> SEQ ID NO 9
<211> LENGTH: 192
<212> TYPE: PRT
<213> ORGANISM: Macaca fascicularis

<400> SEQUENCE: 9

Met Gly Val His Glu Cys Pro Ala Trp Leu Trp Leu Leu Leu Ser Leu
1               5                   10                  15

Val Ser Leu Pro Leu Gly Leu Pro Val Pro Gly Ala Pro Pro Arg Leu
            20                  25                  30

Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu
        35                  40                  45

Ala Glu Asn Val Thr Met Gly Cys Ser Glu Ser Cys Ser Leu Asn Glu
    50                  55                  60

Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg
65                  70                  75                  80

Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu
                85                  90                  95

Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Val Leu Ala Asn Ser Ser
            100                 105                 110

Gln Pro Phe Glu Pro Leu Gln Leu His Met Asp Lys Ala Ile Ser Gly
        115                 120                 125

Leu Arg Ser Ile Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Glu Ala
    130                 135                 140

Ile Ser Leu Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr
145                 150                 155                 160

Ala Asp Thr Phe Cys Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg
                165                 170                 175

Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Arg Gly Asp Arg
            180                 185                 190
```

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<210> SEQ ID NO 10
<211> LENGTH: 192
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 10

```
Met Gly Val Pro Glu Arg Pro Thr Leu Leu Leu Leu Leu Ser Leu Leu
1               5                   10                  15

Leu Ile Pro Leu Gly Leu Pro Val Leu Cys Ala Pro Pro Arg Leu Ile
            20                  25                  30

Cys Asp Ser Arg Val Leu Glu Arg Tyr Ile Leu Glu Ala Lys Glu Ala
        35                  40                  45

Glu Asn Val Thr Met Gly Cys Ala Glu Gly Pro Arg Leu Ser Glu Asn
    50                  55                  60

Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met
65                  70                  75                  80

Glu Val Glu Glu Gln Ala Ile Glu Val Trp Gln Gly Leu Ser Leu Leu
                85                  90                  95

Ser Glu Ala Ile Leu Gln Ala Gln Ala Leu Leu Ala Asn Ser Ser Gln
            100                 105                 110

Pro Pro Glu Thr Leu Gln Leu His Ile Asp Lys Ala Ile Ser Gly Leu
        115                 120                 125

Arg Ser Leu Thr Ser Leu Leu Arg Val Leu Gly Ala Gln Lys Glu Leu
    130                 135                 140

Met Ser Pro Pro Asp Thr Thr Pro Pro Ala Pro Leu Arg Thr Leu Thr
145                 150                 155                 160

Val Asp Thr Phe Cys Lys Leu Phe Arg Val Tyr Ala Asn Phe Leu Arg
                165                 170                 175

Gly Lys Leu Lys Leu Tyr Thr Gly Glu Val Cys Arg Arg Gly Asp Arg
            180                 185                 190
```

<210> SEQ ID NO 11
<211> LENGTH: 192
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 11

```
Met Gly Val Pro Glu Arg Pro Thr Leu Leu Leu Leu Leu Ser Leu Leu
1               5                   10                  15

Leu Ile Pro Leu Gly Leu Pro Val Leu Cys Ala Pro Pro Arg Leu Ile
            20                  25                  30

Cys Asp Ser Arg Val Leu Glu Arg Tyr Ile Leu Glu Ala Lys Glu Ala
        35                  40                  45

Glu Asn Val Thr Met Gly Cys Ala Glu Gly Pro Arg Leu Ser Glu Asn
    50                  55                  60

Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met
65                  70                  75                  80

Lys Val Glu Glu Gln Ala Val Glu Val Trp Gln Gly Leu Ser Leu Leu
                85                  90                  95

Ser Glu Ala Ile Leu Gln Ala Gln Ala Leu Gln Ala Asn Ser Ser Gln
            100                 105                 110

Pro Pro Glu Ser Leu Gln Leu His Ile Asp Lys Ala Ile Ser Gly Leu
        115                 120                 125
```

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```
Arg Ser Leu Thr Ser Leu Leu Arg Val Leu Gly Ala Gln Lys Glu Leu
    130                 135                 140

Met Ser Pro Pro Asp Ala Thr Gln Ala Ala Pro Leu Arg Thr Leu Thr
145                 150                 155                 160

Ala Asp Thr Phe Cys Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg
                165                 170                 175

Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Arg Gly Asp Arg
            180                 185                 190


<210> SEQ ID NO 12
<211> LENGTH: 192
<212> TYPE: PRT
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 12

Met Gly Ala Arg Asp Cys Thr Pro Leu Leu Met Leu Ser Phe Leu Leu
1               5                   10                  15

Phe Pro Leu Gly Phe Pro Val Leu Gly Ala Pro Ala Arg Leu Ile Cys
            20                  25                  30

Asp Ser Arg Val Leu Glu Arg Tyr Ile Leu Glu Ala Arg Glu Ala Glu
        35                  40                  45

Asn Ala Thr Met Gly Cys Ala Glu Gly Cys Ser Phe Asn Glu Asn Ile
    50                  55                  60

Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu
65                  70                  75                  80

Val Gln Gln Gln Ala Leu Glu Val Trp Gln Gly Leu Ala Leu Leu Ser
                85                  90                  95

Glu Ala Ile Leu Arg Gly Gln Ala Leu Leu Ala Asn Ala Ser Gln Pro
            100                 105                 110

Cys Glu Ala Leu Arg Leu His Val Asp Lys Ala Val Ser Gly Leu Arg
        115                 120                 125

Ser Leu Thr Ser Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile
    130                 135                 140

Ser Leu Pro Asp Ala Thr Pro Ser Ala Ala Pro Leu Arg Ala Phe Thr
145                 150                 155                 160

Val Asp Ala Leu Ser Lys Leu Phe Arg Ile Tyr Ser Asn Phe Leu Arg
                165                 170                 175

Gly Lys Leu Thr Leu Tyr Thr Gly Glu Ala Cys Arg Arg Gly Asp Arg
            180                 185                 190


<210> SEQ ID NO 13
<211> LENGTH: 194
<212> TYPE: PRT
<213> ORGANISM: Ovis aries

<400> SEQUENCE: 13

Met Gly Ala Arg Asp Cys Thr Pro Leu Leu Leu Leu Leu Leu Ser Phe
1               5                   10                  15

Leu Leu Phe Pro Leu Gly Leu Pro Val Leu Gly Ala Pro Pro Arg Leu
            20                  25                  30

Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Ile Leu Glu Ala Arg Glu
        35                  40                  45

Ala Glu Asn Ala Thr Met Gly Cys Ala Glu Gly Cys Ser Phe Ser Glu
    50                  55                  60
```

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```
Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg
65                  70                  75                  80

Met Glu Val Gln Gln Gln Ala Leu Glu Val Trp Gln Gly Leu Ala Leu
                85                  90                  95

Leu Ser Glu Ala Ile Phe Arg Gly Gln Ala Leu Leu Ala Asn Ala Ser
            100                 105                 110

Gln Pro Cys Glu Ala Leu Arg Leu His Val Asp Lys Ala Val Ser Gly
        115                 120                 125

Leu Arg Ser Leu Thr Ser Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu
    130                 135                 140

Ala Ile Pro Leu Pro Asp Ala Thr Pro Ser Ala Ala Pro Leu Arg Ile
145                 150                 155                 160

Phe Thr Val Asp Ala Leu Ser Lys Leu Phe Arg Ile Tyr Ser Asn Phe
                165                 170                 175

Leu Arg Gly Lys Leu Thr Leu Tyr Thr Gly Glu Ala Cys Arg Arg Gly
            180                 185                 190

Asp Arg


<210> SEQ ID NO 14
<211> LENGTH: 192
<212> TYPE: PRT
<213> ORGANISM: Felis catus

<400> SEQUENCE: 14

Met Gly Ser Cys Glu Cys Pro Ala Leu Leu Leu Leu Leu Ser Leu Leu
1               5                   10                  15

Leu Leu Pro Leu Gly Leu Pro Val Leu Gly Ala Pro Pro Arg Leu Ile
            20                  25                  30

Cys Asp Ser Arg Val Leu Glu Arg Tyr Ile Leu Gly Ala Arg Glu Ala
        35                  40                  45

Glu Asn Val Thr Met Gly Cys Ala Glu Gly Cys Ser Phe Ser Glu Asn
    50                  55                  60

Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Thr Trp Lys Arg Met
65                  70                  75                  80

Asp Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu
                85                  90                  95

Ser Glu Ala Ile Leu Arg Gly Gln Ala Leu Leu Ala Asn Ser Ser Gln
            100                 105                 110

Pro Ser Glu Thr Leu Gln Leu His Val Asp Lys Ala Val Ser Ser Leu
        115                 120                 125

Arg Ser Leu Thr Ser Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala
    130                 135                 140

Thr Ser Leu Pro Glu Ala Thr Ser Ala Ala Pro Leu Arg Thr Phe Thr
145                 150                 155                 160

Val Asp Thr Leu Cys Lys Leu Phe Arg Ile Tyr Ser Asn Phe Leu Arg
                165                 170                 175

Gly Lys Leu Thr Leu Tyr Thr Gly Glu Ala Cys Arg Arg Gly Asp Arg
            180                 185                 190


<210> SEQ ID NO 15
<211> LENGTH: 942
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<223> OTHER INFORMATION: PIM1 cDNA mammalian
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (669)..(669)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (723)..(723)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 15

```
atgctcytgt ccaaratcaa ctcsctkgcc cacctgcgcr cmgcsccytg carcgacctg     60

cacgccamca agctggcgcc sggcaargag aaggagcccc tggagtcgca gtaccaggtg    120

ggcccgctvy tgggcagygg yggcttcggc tcggtstact cdggcatccg bgtckccgac    180

aacttgccgg tggccatyaa rcacgtggag aaggaccgga tttccgaytg gggrgarctg    240

ccyaayggca cycgagtgcc catggargtg gtyctgytga agaaggtgag ctcggryttc    300

tcsggcgtca ttmgrctyct ggactggtty gagaggcccg ayagtttcgt sytgatcctg    360

gagaggccsg arccsgtgca agayctcttc gacttyatca csgarmgrgg rgcyctvcar    420

gaggasctsg cccgvrgmtt cttctggcag gtrctggagg csgtgcgrca ytgccacrac    480

tgcggggtkc tycaccgcga catcaaggac garaacatcy thatcgacct sarycgcggc    540

garmtcaarc tcatcgactt cgggtcgggg gcgctgctca argacacmgt ctacacggac    600

ttygayggra cccgagtgta yagyccycca gagtggatyc gctaycatcg ctaccayggc    660

aggtcggcng chgtytggtc yctkgggatc ctgctstatg ayatgktskk hggwgawwtk    720

mmnywysswsm wyrwbswvrr krkyrtcwvr ksmmarkyky wyktyaksmw vmbksyywyy    780

tcwgartgtc arcayctyat taratggtgc ytgkccytga gaccrtcrga ymggccmwcc    840

ttygaagaaa tccrgaacca tccvtggatg cargrygwyc tcctgcccca ggmmrchkcy    900

gagatycayc tscacagyct gtcrccrksr yccagcaart ag                       942
```

<210> SEQ ID NO 16
<211> LENGTH: 942
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 16

```
atgctcttgt ccaaaatcaa ctcgcttgcc cacctgcgcg ccgcgccctg caacgacctg     60

cacgccacca agctggcgcc cggcaaggag aaggagcccc tggagtcgca gtaccaggtg    120

ggcccgctac tgggcagcgg cggcttcggc tcggtctact caggcatccg cgtctccgac    180

aacttgccgg tggccatcaa acacgtggag aaggaccgga tttccgactg gggagagctg    240

cctaatggca ctcgagtgcc catggaagtg gtcctgctga agaaggtgag ctcgggtttc    300

tccggcgtca ttaggctcct ggactggttc gagaggcccg acagtttcgt cctgatcctg    360

gagaggcccg agccggtgca agatctcttc gacttcatca cggaaagggg agccctgcaa    420

gaggagctcg cccgcagctt cttctggcag gtgctggagg ccgtgcggca ctgccacaac    480

tgcggggtgc tccaccgcga catcaaggac gaaaacatcc ttatcgacct caatcgcggc    540

gagctcaagc tcatcgactt cgggtcgggg gcgctgctca aagacaccgt ctacacggac    600

ttcgatggga cccgagtgta tagccctcca gagtggatcc gctaccatcg ctaccatggc    660

aggtcggcgg cagtctggtc cctggggatc ctgctgtatg atatggtgtg tggagatatt    720
```

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```
cctttcgagc atgacgaaga gatcatcagg ggccaggttt tcttcaggca gagggtctct    780

tcagaatgtc agcatctcat tagatggtgc ttggccctga gaccatcaga taggccaacc    840

ttcgaagaaa tccagaacca tccatggatg caagatgttc tcctgcccca ggaaactgct    900

gagatccacc tccacagcct gtcgccgggg cccagcaaat ag                       942
```

<210> SEQ ID NO 17
<211> LENGTH: 942
<212> TYPE: DNA
<213> ORGANISM: Pan troglodytes

<400> SEQUENCE: 17

```
atgctcttgt ccaaaatcaa ctcgcttgcc cacctgcgcg ccgcgccctg caacgacctg     60

cacgccacca agctggcgcc cggcaaggag aaggagcccc tggagtcgca gtaccaggtg    120

ggcccgctac tgggcagcgg cggcttcggc tcggtctact caggcatccg cgtctccgac    180

aacttgccgg tggccatcaa acacgtggag aaggaccgga tttccgactg ggagagagctg   240

cctaatggca ctcgagtgcc catggaagtg gtcctgctga agaaggtgag ctcgggtttc    300

tccggcgtca ttaggctcct ggactggttc gagaggcccg acagtttcgt cctgatcctg    360

gagaggcccg agccggtgca agatctcttc gactttatca cggaaagggg ggccctgcaa    420

gaggagctgg cccgcagctt cttctggcag gtgctggagg ccgtgcggca ctgccacaac    480

tgcggggtgc tccaccgcga catcaaggac gaaaacatcc ttatcgacct caatcgcggc    540

gagctcaagc tcatcgactt cgggtcgggg gcgctgctca aggacaccgt ctacacggac    600

ttcgatggga cccgagtgta tagccctcca gagtggatcc gctaccatcg ctaccatggc    660

aggtcggcgg cagtctggtc cctggggatc ctgctgtatg atatgttggt aggtgaattg    720

aatcatctca tcatgctcag tggtgtctca tcaaaatctc ttgtcatcat ccttcctatt    780

tctgaatgtc agcatctcat tagatggtgc ttggccctga gaccatcaga taggccaacc    840

ttcgaagaaa tccagaacca tccatggatg caagatgttc tcctgcccca ggaaactgct    900

gagatccacc tccacagcct gtcgccgggg cccagcaaat ag                       942
```

<210> SEQ ID NO 18
<211> LENGTH: 942
<212> TYPE: DNA
<213> ORGANISM: Felis catus

<400> SEQUENCE: 18

```
atgctcttgt ccaaaatcaa ctcgcttgcc cacctgcgca ccgcgccctg caacgacctg     60

cacgccacca agctggcgcc cggcaaggag aaggagcccc tggagtcgca gtaccaggtg    120

ggcccgctac tgggcagcgg cggcttcggc tcggtctact caggcatccg ggtcgccgac    180

aacttgccgg tggccatcaa gcacgtggag aaggaccgga tttccgattg ggagagctg     240

cccaatggca cccgagtgcc catggaggtg gtcctgctga agaaggtgag ctcgggcttc    300

tccggcgtca ttcggctcct ggactggttt gagaggcccg acagtttcgt cttgatcctg    360

gagaggcccg agccggtgca agacctcttc gactttatca cggaaagggg ggctctgcag    420

gaggagctgg cccgcagctt cttctggcag gtgctggagg ccgtgcggca ctgccacaac    480

tgcggggtgc tccaccgcga catcaaggac gagaacatcc tcatcgacct caatcgcggc    540

gagctcaagc tcatcgactt cgggtcgggg gcgctgctca aggacaccgt ctacacggac    600
```

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```
ttcgacggga cccgagtgta tagtccccca gagtggatcc gctaccatcg ctaccatggc    660

aggtcggccg ccgtctggtc tctggggatc ctgctgtatg atatggtctg tggagatatt    720

ccttttgagc atgatgaaga gatcatcagg ggccaagttt tcttcaggca gagggtctct    780

tcagagtgtc agcatctcat tagatggtgc ttggccctga gaccgtcaga ccggccatcc    840

ttcgaagaaa tccagaacca tccctggatg caagatgtcc tcctgcccca ggaaacagcc    900

gagatccatc tgcacagcct gtcaccaggg cccagcaaat ag                       942
```

<210> SEQ ID NO 19
<211> LENGTH: 942
<212> TYPE: DNA
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 19

```
atgctcttgt ccaaaatcaa ctcgcttgcc cacctgcgcg ccgcgccctg cagcgacctg     60

cacgccacca agctggcgcc gggcaaggag aaggagcccc tggagtcgca gtaccaggtg    120

ggcccgctcc tgggcagtgg cggcttcggc tcggtgtact caggcatccg tgtcgccgac    180

aacttgccgg tggccatcaa gcacgtggag aaggaccgga tttccgactg ggagagagctg    240

cctaatggca cccgagtgcc catggaagtg gttctgctga agaaggtgag ctcgggcttc    300

tccggcgtca ttaggctcct ggactggttc gagaggcccg acagtttcgt cctgatcctg    360

gagaggccgg agccggtgca agacctcttc gactttatca cggaaagggg ggctctgcag    420

gaggagctgg cccgcagctt cttctggcag gtactggagg cggtgcgaca ctgccacgac    480

tgcggggtgc ttcaccgcga catcaaggac gagaacatcc ttatcgacct caatcgcggc    540

gagctcaagc tcatcgactt cgggtcgggg gcgctgctca aggacaccgt ctacacggac    600

ttcgatggga cccgagtgta tagtcctcca gagtggatcc gctatcatcg ctaccatggc    660

aggtcggcag ccgtctggtc tctggggatc ctgctgtatg acatggtgtg cggagatatt    720

ccctttgagc acgatgagga gattgtcagg ggccaagttt tcttcaggca gcgggtctcc    780

tcagagtgtc aacatctcat tagatggtgc ttggccttga gaccatcaga tcggccaacc    840

ttcgaagaaa tccagaacca tccgtggatg caagacgtcc tcctgcccca ggaaactgct    900

gagatccatc tccacagcct gtcgccaggg cccagcaaat ag                       942
```

<210> SEQ ID NO 20
<211> LENGTH: 942
<212> TYPE: DNA
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 20

```
atgctcttgt ccaagatcaa ctccctggcc cacctgcgcg cagcccctttg caacgacctg     60

cacgccaaca agctggcgcc gggcaaagag aaggagcccc tggagtcgca gtaccaggtg    120

ggcccgctgt tgggcagcgg tggcttcggc tcggtctact cgggcatccg cgtcgccgac    180

aacttgccgg tggccatcaa gcacgtggag aaggaccgga tttccgactg gggggaactg    240

cccaacggca cccgagtgcc catggaagtg gtcctgctga agaaggtgag ctcgggcttc    300

tcgggcgtca ttagacttct ggactggttc gagaggcccg atagtttcgt gctgatcctg    360

gagaggcccg aacccgtgca agacctcttc gacttcatca ccgagcgagg agccctccag    420

gaggagctgg cccggagctt cttctggcag gtgctggagg ccgtgcggca ttgccacaac    480
```

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```
tgcggggttc tccaccgcga catcaaggac gagaacatct taatcgacct gaaccgcggc    540

gaactcaaac tcatcgactt cgggtcgggg gcgctgctca aggacacagt ctacacggac    600

tttgacggaa cccgagtgta cagtcctcca gagtggattc gctaccatcg ctaccacggc    660

aggtcggctg ctgtttggtc cctggggatc ctgctctatg acatggtctg cggagatatt    720

ccatttgagc acgacgaaga gatcgtcaag ggccaagtgt actttaggca aagggtctct    780

tcagaatgtc aacatcttat tagatggtgc ctgtccctga gaccatcgga ccggccctcc    840

tttgaagaaa tccagaacca tccgtggatg caggatgttc tcctgcccca ggccaccgcc    900

gagattcatc tgcacagcct gtcaccatca cccagcaaat ag                        942
```

<210> SEQ ID NO 21
<211> LENGTH: 942
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 21

```
atgctcctgt ccaagatcaa ctccctggcc cacctgcgcg ccgcgccctg caacgacctg     60

cacgccacca agctggcgcc gggcaaagag aaggagcccc tggagtcgca gtaccaggtg    120

ggcccgctgt tgggcagcgg tggcttcggc tcggtctact ctggcatccg cgtcgccgac    180

aacttgccgg tggccattaa gcacgtggag aaggaccgga tttccgattg ggggagaactg    240

cccaatggca cccgagtgcc catggaagtg gtcctgttga agaaggtgag ctcggacttc    300

tcgggcgtca ttagacttct ggactggttc gagaggcccg atagtttcgt gctgatcctg    360

gagaggcccg aaccggtgca agacctcttc gactttatca ccgaacgagg agccctacag    420

gaggacctgg cccgaggatt cttctggcag gtgctggagg ccgtgcggca ttgccacaac    480

tgcggggttc tccaccgcga catcaaggac gagaacatct taatcgacct gagccgcggc    540

gaaatcaaac tcatcgactt cgggtcgggg gcgctgctca aggacacagt ctacacggac    600

tttgatggga cccgagtgta cagtcctcca gagtggattc gctaccatcg ctaccacggc    660

aggtcggcag ctgtctggtc ccttgggatc ctgctctatg acatggtctg cggagatatt    720

ccgtttgagc acgatgaaga gatcatcaag ggccaagtgt tcttcaggca aactgtctct    780

tcagagtgtc agcaccttat taaatggtgc ctgtccctga gaccatcaga tcggccctcc    840

tttgaagaaa tccggaacca tccatggatg cagggtgacc tcctgcccca ggcagcttct    900

gagatccatc tgcacagtct gtcaccgggg tccagcaagt ag                        942
```

<210> SEQ ID NO 22
<211> LENGTH: 38
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: hPIM1 CE oligo

<400> SEQUENCE: 22

```
gctcgggcct ctccaggttt ttctcttgga aagaaagt                             38
```

<210> SEQ ID NO 23
<211> LENGTH: 42
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: hPIM1 CE oligo

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<400> SEQUENCE: 23

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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
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<222> LOCATION: (648)..(648)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (710)..(710)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (779)..(779)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
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<221> NAME/KEY: misc_feature
<222> LOCATION: (795)..(795)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 80

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Met Leu Arg Gly Xaa Arg Xaa Gly Gln Leu Gly Trp His Xaa Xaa Ala
1               5                   10                  15

Ala Gly Xaa Gly Xaa Leu Xaa Xaa Xaa Leu Xaa Leu Ala Xaa Ala Xaa
            20                  25                  30

Ala Ala Xaa Cys Xaa Xaa Xaa Cys Cys Pro Xaa Gly Xaa Ser Gly Leu
        35                  40                  45

Arg Cys Thr Arg Xaa Gly Xaa Leu Xaa Xaa Leu Xaa Xaa Leu Xaa Gly
    50                  55                  60

Ala Xaa Asn Leu Thr Glu Leu Tyr Xaa Glu Asn Gln Xaa Xaa Leu Gln
65                  70                  75                  80

Xaa Leu Glu Xaa Xaa Asp Leu Xaa Gly Leu Gly Glu Leu Arg Xaa Leu
                85                  90                  95

Thr Ile Val Lys Ser Gly Leu Arg Phe Val Ala Pro Asp Ala Phe Xaa
            100                 105                 110

Phe Thr Pro Arg Leu Ser Xaa Leu Asn Leu Ser Xaa Asn Ala Leu Glu
        115                 120                 125

Ser Leu Ser Trp Lys Thr Val Gln Gly Leu Ser Leu Gln Xaa Leu Xaa
    130                 135                 140

Leu Ser Gly Asn Pro Leu His Cys Ser Cys Ala Leu Xaa Trp Leu Gln
145                 150                 155                 160

Arg Trp Glu Xaa Glu Xaa Leu Xaa Gly Val Xaa Xaa Gln Xaa Leu Xaa
                165                 170                 175

Xaa Xaa Gly Xaa Gly Xaa Xaa Xaa Xaa Pro Leu Xaa His Xaa Xaa Asn
            180                 185                 190

Xaa Ser Cys Gly Val Pro Xaa Xaa Lys Xaa Gln Xaa Pro Asn Xaa Ser
        195                 200                 205

Val Xaa Val Gly Asp Asp Val Xaa Leu Xaa Cys Gln Val Glu Gly Xaa
    210                 215                 220

Xaa Leu Xaa Gln Ala Xaa Trp Ile Leu Thr Glu Leu Glu Xaa Xaa Ala
225                 230                 235                 240

Thr Xaa Xaa Lys Xaa Gly Xaa Leu Pro Ser Leu Gly Leu Xaa Leu Xaa
                245                 250                 255

Asn Val Thr Ser Asp Leu Asn Xaa Lys Asn Xaa Thr Cys Trp Ala Glu
            260                 265                 270

Asn Asp Val Gly Arg Ala Glu Val Ser Val Gln Val Xaa Val Ser Phe
        275                 280                 285

Pro Ala Ser Val Xaa Leu Xaa Xaa Ala Val Glu Xaa His His Trp Cys
    290                 295                 300

Ile Pro Phe Ser Val Asp Gly Gln Pro Ala Pro Ser Leu Arg Trp Xaa
305                 310                 315                 320

Phe Asn Gly Ser Val Leu Asn Glu Thr Ser Phe Ile Phe Thr Xaa Phe
                325                 330                 335

Leu Glu Xaa Ala Xaa Xaa Asn Glu Thr Xaa Arg His Gly Cys Leu Arg
            340                 345                 350

Leu Asn Gln Pro Thr His Val Asn Asn Gly Asn Tyr Thr Leu Leu Ala
        355                 360                 365

Ala Asn Pro Xaa Gly Gln Ala Xaa Ala Ser Xaa Met Ala Ala Phe Met
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    370                 375                 380

Asp Asn Pro Phe Glu Phe Asn Pro Glu Asp Pro Ile Pro Val Ser Phe
385                 390                 395                 400

Ser Pro Val Asp Xaa Asn Ser Thr Ser Xaa Asp Pro Val Glu Lys Lys
                405                 410                 415

Asp Glu Thr Pro Phe Gly Val Ser Val Ala Val Gly Leu Ala Val Xaa
            420                 425                 430

Ala Xaa Leu Phe Leu Ser Xaa Leu Leu Leu Val Leu Asn Lys Cys Gly
        435                 440                 445

Xaa Arg Xaa Lys Phe Gly Ile Asn Arg Pro Ala Val Leu Ala Pro Glu
    450                 455                 460

Asp Gly Leu Ala Met Ser Leu His Phe Met Thr Leu Gly Gly Ser Ser
465                 470                 475                 480

Leu Ser Pro Thr Glu Gly Lys Gly Ser Gly Leu Gln Gly His Ile Xaa
                485                 490                 495

Glu Asn Pro Gln Tyr Phe Ser Asp Xaa Cys Val His His Ile Lys Arg
            500                 505                 510

Xaa Asp Ile Xaa Leu Lys Trp Glu Leu Gly Glu Gly Ala Phe Gly Lys
        515                 520                 525

Val Phe Leu Ala Glu Cys Xaa Asn Leu Leu Xaa Xaa Gln Asp Lys Met
    530                 535                 540

Leu Val Ala Val Lys Ala Leu Lys Glu Xaa Ser Glu Xaa Ala Arg Gln
545                 550                 555                 560

Asp Phe Xaa Arg Glu Ala Glu Leu Leu Thr Met Leu Gln His Gln His
                565                 570                 575

Ile Val Arg Phe Phe Gly Val Cys Thr Glu Gly Xaa Pro Leu Leu Met
            580                 585                 590

Val Phe Glu Tyr Met Arg His Gly Asp Leu Asn Arg Phe Leu Arg Ser
        595                 600                 605

His Gly Pro Asp Ala Lys Leu Leu Ala Gly Gly Glu Asp Val Ala Pro
    610                 615                 620

Gly Pro Leu Gly Leu Gly Gln Leu Leu Ala Val Ala Ser Gln Val Ala
625                 630                 635                 640

Ala Gly Met Val Tyr Leu Ala Xaa Leu His Phe Val His Arg Asp Leu
                645                 650                 655

Ala Thr Arg Asn Cys Leu Val Gly Gln Gly Leu Val Val Lys Ile Gly
            660                 665                 670

Asp Phe Gly Met Ser Arg Asp Ile Tyr Ser Thr Asp Tyr Tyr Arg Val
        675                 680                 685

Gly Gly Arg Thr Met Leu Pro Ile Arg Trp Met Pro Pro Glu Ser Ile
    690                 695                 700

Leu Tyr Arg Lys Phe Xaa Thr Glu Ser Asp Val Trp Ser Phe Gly Val
705                 710                 715                 720

Val Leu Trp Glu Ile Phe Thr Tyr Gly Lys Gln Pro Trp Tyr Gln Leu
                725                 730                 735

Ser Asn Thr Glu Ala Ile Xaa Cys Ile Thr Gln Gly Arg Glu Leu Glu
            740                 745                 750

Arg Pro Arg Ala Cys Pro Pro Xaa Val Tyr Ala Ile Met Arg Gly Cys
        755                 760                 765

Trp Gln Arg Glu Pro Gln Gln Arg Xaa Ser Xaa Lys Asp Val His Ala
    770                 775                 780
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Arg Leu Gln Ala Leu Ala Gln Ala Pro Pro Xaa Tyr Leu Asp Val Leu
785 790 795 800

Gly

<210> SEQ ID NO 81
<211> LENGTH: 796
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 81

Met Leu Arg Gly Gly Arg Arg Gly Gln Leu Gly Trp His Ser Trp Ala
1 5 10 15

Ala Gly Pro Gly Ser Leu Leu Ala Trp Leu Ile Leu Ala Ser Ala Gly
20 25 30

Ala Ala Pro Cys Pro Asp Ala Cys Cys Pro His Gly Ser Ser Gly Leu
35 40 45

Arg Cys Thr Arg Asp Gly Ala Leu Asp Ser Leu His His Leu Pro Gly
50 55 60

Ala Glu Asn Leu Thr Glu Leu Tyr Ile Glu Asn Gln Gln His Leu Gln
65 70 75 80

His Leu Glu Leu Arg Asp Leu Arg Gly Leu Gly Glu Leu Arg Asn Leu
85 90 95

Thr Ile Val Lys Ser Gly Leu Arg Phe Val Ala Pro Asp Ala Phe His
100 105 110

Phe Thr Pro Arg Leu Ser Arg Leu Asn Leu Ser Phe Asn Ala Leu Glu
115 120 125

Ser Leu Ser Trp Lys Thr Val Gln Gly Leu Ser Leu Gln Glu Leu Val
130 135 140

Leu Ser Gly Asn Pro Leu His Cys Ser Cys Ala Leu Arg Trp Leu Gln
145 150 155 160

Arg Trp Glu Glu Glu Gly Leu Gly Gly Val Pro Glu Gln Lys Leu Gln
165 170 175

Cys His Gly Gln Gly Pro Leu Ala His Met Pro Asn Ala Ser Cys Gly
180 185 190

Val Pro Thr Leu Lys Val Gln Val Pro Asn Ala Ser Val Asp Val Gly
195 200 205

Asp Asp Val Leu Leu Arg Cys Gln Val Glu Gly Arg Gly Leu Glu Gln
210 215 220

Ala Gly Trp Ile Leu Thr Glu Leu Glu Gln Ser Ala Thr Val Met Lys
225 230 235 240

Ser Gly Gly Leu Pro Ser Leu Gly Leu Thr Leu Ala Asn Val Thr Ser
245 250 255

Asp Leu Asn Arg Lys Asn Leu Thr Cys Trp Ala Glu Asn Asp Val Gly
260 265 270

Arg Ala Glu Val Ser Val Gln Val Asn Val Ser Phe Pro Ala Ser Val
275 280 285

Gln Leu His Thr Ala Val Glu Met His His Trp Cys Ile Pro Phe Ser
290 295 300

Val Asp Gly Gln Pro Ala Pro Ser Leu Arg Trp Leu Phe Asn Gly Ser
305 310 315 320

Val Leu Asn Glu Thr Ser Phe Ile Phe Thr Glu Phe Leu Glu Pro Ala
325 330 335

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Ala Asn Glu Thr Val Arg His Gly Cys Leu Arg Leu Asn Gln Pro Thr
            340                 345                 350

His Val Asn Asn Gly Asn Tyr Thr Leu Leu Ala Ala Asn Pro Phe Gly
        355                 360                 365

Gln Ala Ser Ala Ser Ile Met Ala Ala Phe Met Asp Asn Pro Phe Glu
    370                 375                 380

Phe Asn Pro Glu Asp Pro Ile Pro Val Ser Phe Ser Pro Val Asp Thr
385                 390                 395                 400

Asn Ser Thr Ser Gly Asp Pro Val Glu Lys Lys Asp Glu Thr Pro Phe
                405                 410                 415

Gly Val Ser Val Ala Val Gly Leu Ala Val Phe Ala Cys Leu Phe Leu
            420                 425                 430

Ser Thr Leu Leu Leu Val Leu Asn Lys Cys Gly Arg Arg Asn Lys Phe
        435                 440                 445

Gly Ile Asn Arg Pro Ala Val Leu Ala Pro Glu Asp Gly Leu Ala Met
    450                 455                 460

Ser Leu His Phe Met Thr Leu Gly Gly Ser Ser Leu Ser Pro Thr Glu
465                 470                 475                 480

Gly Lys Gly Ser Gly Leu Gln Gly His Ile Ile Glu Asn Pro Gln Tyr
                485                 490                 495

Phe Ser Asp Ala Cys Val His His Ile Lys Arg Arg Asp Ile Val Leu
            500                 505                 510

Lys Trp Glu Leu Gly Glu Gly Ala Phe Gly Lys Val Phe Leu Ala Glu
        515                 520                 525

Cys His Asn Leu Leu Pro Glu Gln Asp Lys Met Leu Val Ala Val Lys
    530                 535                 540

Ala Leu Lys Glu Ala Ser Glu Ser Ala Arg Gln Asp Phe Gln Arg Glu
545                 550                 555                 560

Ala Glu Leu Leu Thr Met Leu Gln His Gln His Ile Val Arg Phe Phe
                565                 570                 575

Gly Val Cys Thr Glu Gly Arg Pro Leu Leu Met Val Phe Glu Tyr Met
            580                 585                 590

Arg His Gly Asp Leu Asn Arg Phe Leu Arg Ser His Gly Pro Asp Ala
        595                 600                 605

Lys Leu Leu Ala Gly Gly Glu Asp Val Ala Pro Gly Pro Leu Gly Leu
    610                 615                 620

Gly Gln Leu Leu Ala Val Ala Ser Gln Val Ala Ala Gly Met Val Tyr
625                 630                 635                 640

Leu Ala Gly Leu His Phe Val His Arg Asp Leu Ala Thr Arg Asn Cys
                645                 650                 655

Leu Val Gly Gln Gly Leu Val Val Lys Ile Gly Asp Phe Gly Met Ser
            660                 665                 670

Arg Asp Ile Tyr Ser Thr Asp Tyr Tyr Arg Val Gly Gly Arg Thr Met
        675                 680                 685

Leu Pro Ile Arg Trp Met Pro Pro Glu Ser Ile Leu Tyr Arg Lys Phe
    690                 695                 700

Thr Thr Glu Ser Asp Val Trp Ser Phe Gly Val Val Leu Trp Glu Ile
705                 710                 715                 720

Phe Thr Tyr Gly Lys Gln Pro Trp Tyr Gln Leu Ser Asn Thr Glu Ala
                725                 730                 735
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Ile Asp Cys Ile Thr Gln Gly Arg Glu Leu Glu Arg Pro Arg Ala Cys
740 745 750

Pro Pro Glu Val Tyr Ala Ile Met Arg Gly Cys Trp Gln Arg Glu Pro
755 760 765

Gln Gln Arg His Ser Ile Lys Asp Val His Ala Arg Leu Gln Ala Leu
770 775 780

Ala Gln Ala Pro Pro Val Tyr Leu Asp Val Leu Gly
785 790 795

<210> SEQ ID NO 82
<211> LENGTH: 799
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 82

Met Leu Arg Gly Gln Arg Leu Gly Gln Leu Gly Trp His Arg Pro Ala
1 5 10 15

Ala Gly Leu Gly Ser Leu Met Thr Ser Leu Met Leu Ala Cys Ala Ser
20 25 30

Ala Ala Ser Cys Arg Glu Val Cys Cys Pro Val Gly Pro Ser Gly Leu
35 40 45

Arg Cys Thr Arg Ala Gly Ser Leu Asp Thr Leu Arg Gly Leu Arg Gly
50 55 60

Ala Gly Asn Leu Thr Glu Leu Tyr Val Glu Asn Gln Gln His Leu Gln
65 70 75 80

Arg Leu Glu Phe Glu Asp Leu Gln Gly Leu Gly Glu Leu Arg Ser Leu
85 90 95

Thr Ile Val Lys Ser Gly Leu Arg Phe Val Ala Pro Asp Ala Phe Arg
100 105 110

Phe Thr Pro Arg Leu Ser His Leu Asn Leu Ser Ser Asn Ala Leu Glu
115 120 125

Ser Leu Ser Trp Lys Thr Val Gln Gly Leu Ser Leu Gln Asp Leu Thr
130 135 140

Leu Ser Gly Asn Pro Leu His Cys Ser Cys Ala Leu Phe Trp Leu Gln
145 150 155 160

Arg Trp Glu Gln Glu Gly Leu Cys Gly Val His Thr Gln Thr Leu His
165 170 175

Asp Ser Gly Pro Gly Asp Gln Phe Leu Pro Leu Gly His Asn Thr Ser
180 185 190

Cys Gly Val Pro Thr Val Lys Ile Gln Met Pro Asn Asp Ser Val Glu
195 200 205

Val Gly Asp Asp Val Phe Leu Gln Cys Gln Val Glu Gly Leu Ala Leu
210 215 220

Gln Gln Ala Asp Trp Ile Leu Thr Glu Leu Glu Gly Ala Ala Thr Val
225 230 235 240

Lys Lys Phe Gly Asp Leu Pro Ser Leu Gly Leu Ile Leu Val Asn Val
245 250 255

Thr Ser Asp Leu Asn Lys Lys Asn Val Thr Cys Trp Ala Glu Asn Asp
260 265 270

Val Gly Arg Ala Glu Val Ser Val Gln Val Ser Val Ser Phe Pro Ala
275 280 285

Ser Val His Leu Gly Leu Ala Val Glu Gln His His Trp Cys Ile Pro
290 295 300

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Phe Ser Val Asp Gly Gln Pro Ala Pro Ser Leu Arg Trp Leu Phe Asn
305                 310                 315                 320

Gly Ser Val Leu Asn Glu Thr Ser Phe Ile Phe Thr Gln Phe Leu Glu
                325                 330                 335

Ser Ala Leu Thr Asn Glu Thr Met Arg His Gly Cys Leu Arg Leu Asn
            340                 345                 350

Gln Pro Thr His Val Asn Asn Gly Asn Tyr Thr Leu Leu Ala Ala Asn
        355                 360                 365

Pro Tyr Gly Gln Ala Ala Ala Ser Val Met Ala Ala Phe Met Asp Asn
    370                 375                 380

Pro Phe Glu Phe Asn Pro Glu Asp Pro Ile Pro Val Ser Phe Ser Pro
385                 390                 395                 400

Val Asp Gly Asn Ser Thr Ser Arg Asp Pro Val Glu Lys Lys Asp Glu
                405                 410                 415

Thr Pro Phe Gly Val Ser Val Ala Val Gly Leu Ala Val Ser Ala Ala
            420                 425                 430

Leu Phe Leu Ser Ala Leu Leu Leu Val Leu Asn Lys Cys Gly Gln Arg
        435                 440                 445

Ser Lys Phe Gly Ile Asn Arg Pro Ala Val Leu Ala Pro Glu Asp Gly
    450                 455                 460

Leu Ala Met Ser Leu His Phe Met Thr Leu Gly Gly Ser Ser Leu Ser
465                 470                 475                 480

Pro Thr Glu Gly Lys Gly Ser Gly Leu Gln Gly His Ile Met Glu Asn
                485                 490                 495

Pro Gln Tyr Phe Ser Asp Thr Cys Val His His Ile Lys Arg Gln Asp
            500                 505                 510

Ile Ile Leu Lys Trp Glu Leu Gly Glu Gly Ala Phe Gly Lys Val Phe
        515                 520                 525

Leu Ala Glu Cys Tyr Asn Leu Leu Asn Asp Gln Asp Lys Met Leu Val
    530                 535                 540

Ala Val Lys Ala Leu Lys Glu Ala Ser Glu Asn Ala Arg Gln Asp Phe
545                 550                 555                 560

Gln Arg Glu Ala Glu Leu Leu Thr Met Leu Gln His Gln His Ile Val
                565                 570                 575

Arg Phe Phe Gly Val Cys Thr Glu Gly Gly Pro Leu Leu Met Val Phe
            580                 585                 590

Glu Tyr Met Arg His Gly Asp Leu Asn Arg Phe Leu Arg Ser His Gly
        595                 600                 605

Pro Asp Ala Lys Leu Leu Ala Gly Gly Glu Asp Val Ala Pro Gly Pro
    610                 615                 620

Leu Gly Leu Gly Gln Leu Leu Ala Val Ala Ser Gln Val Ala Ala Gly
625                 630                 635                 640

Met Val Tyr Leu Ala Ser Leu His Phe Val His Arg Asp Leu Ala Thr
                645                 650                 655

Arg Asn Cys Leu Val Gly Gln Gly Leu Val Val Lys Ile Gly Asp Phe
            660                 665                 670

Gly Met Ser Arg Asp Ile Tyr Ser Thr Asp Tyr Tyr Arg Val Gly Gly
        675                 680                 685

Arg Thr Met Leu Pro Ile Arg Trp Met Pro Pro Glu Ser Ile Leu Tyr
    690                 695                 700
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Arg Lys Phe Ser Thr Glu Ser Asp Val Trp Ser Phe Gly Val Val Leu
705                 710                 715                 720

Trp Glu Ile Phe Thr Tyr Gly Lys Gln Pro Trp Tyr Gln Leu Ser Asn
                725                 730                 735

Thr Glu Ala Ile Glu Cys Ile Thr Gln Gly Arg Glu Leu Glu Arg Pro
            740                 745                 750

Arg Ala Cys Pro Pro Asp Val Tyr Ala Ile Met Arg Gly Cys Trp Gln
        755                 760                 765

Arg Glu Pro Gln Gln Arg Leu Ser Met Lys Asp Val His Ala Arg Leu
    770                 775                 780

Gln Ala Leu Ala Gln Ala Pro Pro Ser Tyr Leu Asp Val Leu Gly
785                 790                 795


<210> SEQ ID NO 83
<211> LENGTH: 799
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 83

Met Leu Arg Gly Gln Arg His Gly Gln Leu Gly Trp His Arg Pro Ala
1               5                   10                  15

Ala Gly Leu Gly Gly Leu Val Thr Ser Leu Met Leu Ala Cys Ala Cys
            20                  25                  30

Ala Ala Ser Cys Arg Glu Thr Cys Cys Pro Val Gly Pro Ser Gly Leu
        35                  40                  45

Arg Cys Thr Arg Ala Gly Thr Leu Asn Thr Leu Arg Gly Leu Arg Gly
    50                  55                  60

Ala Gly Asn Leu Thr Glu Leu Tyr Val Glu Asn Gln Arg Asp Leu Gln
65                  70                  75                  80

Arg Leu Glu Phe Glu Asp Leu Gln Gly Leu Gly Glu Leu Arg Ser Leu
                85                  90                  95

Thr Ile Val Lys Ser Gly Leu Arg Phe Val Ala Pro Asp Ala Phe His
            100                 105                 110

Phe Thr Pro Arg Leu Ser His Leu Asn Leu Ser Ser Asn Ala Leu Glu
        115                 120                 125

Ser Leu Ser Trp Lys Thr Val Gln Gly Leu Ser Leu Gln Asp Leu Thr
    130                 135                 140

Leu Ser Gly Asn Pro Leu His Cys Ser Cys Ala Leu Leu Trp Leu Gln
145                 150                 155                 160

Arg Trp Glu Gln Glu Asp Leu Cys Gly Val Tyr Thr Gln Lys Leu Gln
                165                 170                 175

Gly Ser Gly Ser Gly Asp Gln Phe Leu Pro Leu Gly His Asn Asn Ser
            180                 185                 190

Cys Gly Val Pro Ser Val Lys Ile Gln Met Pro Asn Asp Ser Val Glu
        195                 200                 205

Val Gly Asp Asp Val Phe Leu Gln Cys Gln Val Glu Gly Gln Ala Leu
    210                 215                 220

Gln Gln Ala Asp Trp Ile Leu Thr Glu Leu Glu Gly Thr Ala Thr Met
225                 230                 235                 240

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

Thr Ser Asp Leu Asn Lys Lys Asn Val Thr Cys Trp Ala Glu Asn Asp
            260                 265                 270
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Val Gly Arg Ala Glu Val Ser Val Gln Val Ser Val Ser Phe Pro Ala
        275                 280                 285

Ser Val His Leu Gly Lys Ala Val Glu Gln His His Trp Cys Ile Pro
    290                 295                 300

Phe Ser Val Asp Gly Gln Pro Ala Pro Ser Leu Arg Trp Phe Phe Asn
305                 310                 315                 320

Gly Ser Val Leu Asn Glu Thr Ser Phe Ile Phe Thr Gln Phe Leu Glu
                325                 330                 335

Ser Ala Leu Thr Asn Glu Thr Met Arg His Gly Cys Leu Arg Leu Asn
            340                 345                 350

Gln Pro Thr His Val Asn Asn Gly Asn Tyr Thr Leu Leu Ala Ala Asn
        355                 360                 365

Pro Tyr Gly Gln Ala Ala Ala Ser Ile Met Ala Ala Phe Met Asp Asn
    370                 375                 380

Pro Phe Glu Phe Asn Pro Glu Asp Pro Ile Pro Val Ser Phe Ser Pro
385                 390                 395                 400

Val Asp Thr Asn Ser Thr Ser Arg Asp Pro Val Glu Lys Lys Asp Glu
                405                 410                 415

Thr Pro Phe Gly Val Ser Val Ala Val Gly Leu Ala Val Ser Ala Ala
            420                 425                 430

Leu Phe Leu Ser Ala Leu Leu Leu Val Leu Asn Lys Cys Gly Gln Arg
        435                 440                 445

Ser Lys Phe Gly Ile Asn Arg Pro Ala Val Leu Ala Pro Glu Asp Gly
    450                 455                 460

Leu Ala Met Ser Leu His Phe Met Thr Leu Gly Gly Ser Ser Leu Ser
465                 470                 475                 480

Pro Thr Glu Gly Lys Gly Ser Gly Leu Gln Gly His Ile Met Glu Asn
                485                 490                 495

Pro Gln Tyr Phe Ser Asp Thr Cys Val His His Ile Lys Arg Gln Asp
            500                 505                 510

Ile Ile Leu Lys Trp Glu Leu Gly Glu Gly Ala Phe Gly Lys Val Phe
        515                 520                 525

Leu Ala Glu Cys Tyr Asn Leu Leu Asn Asp Gln Asp Lys Met Leu Val
    530                 535                 540

Ala Val Lys Ala Leu Lys Glu Thr Ser Glu Asn Ala Arg Gln Asp Phe
545                 550                 555                 560

His Arg Glu Ala Glu Leu Leu Thr Met Leu Gln His Gln His Ile Val
                565                 570                 575

Arg Phe Phe Gly Val Cys Thr Glu Gly Gly Pro Leu Leu Met Val Phe
            580                 585                 590

Glu Tyr Met Arg His Gly Asp Leu Asn Arg Phe Leu Arg Ser His Gly
        595                 600                 605

Pro Asp Ala Lys Leu Leu Ala Gly Gly Glu Asp Val Ala Pro Gly Pro
    610                 615                 620

Leu Gly Leu Gly Gln Leu Leu Ala Val Ala Ser Gln Val Ala Ala Gly
625                 630                 635                 640

Met Val Tyr Leu Ala Ser Leu His Phe Val His Arg Asp Leu Ala Thr
                645                 650                 655

Arg Asn Cys Leu Val Gly Gln Gly Leu Val Val Lys Ile Gly Asp Phe
            660                 665                 670
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Gly Met Ser Arg Asp Ile Tyr Ser Thr Asp Tyr Tyr Arg Val Gly Gly
        675                 680                 685

Arg Thr Met Leu Pro Ile Arg Trp Met Pro Pro Glu Ser Ile Leu Tyr
    690                 695                 700

Arg Lys Phe Ser Thr Glu Ser Asp Val Trp Ser Phe Gly Val Val Leu
705                 710                 715                 720

Trp Glu Ile Phe Thr Tyr Gly Lys Gln Pro Trp Tyr Gln Leu Ser Asn
                725                 730                 735

Thr Glu Ala Ile Glu Cys Ile Thr Gln Gly Arg Glu Leu Glu Arg Pro
            740                 745                 750

Arg Ala Cys Pro Pro Asp Val Tyr Ala Ile Met Arg Gly Cys Trp Gln
        755                 760                 765

Arg Glu Pro Gln Gln Arg Leu Ser Met Lys Asp Val His Ala Arg Leu
    770                 775                 780

Gln Ala Leu Ala Gln Ala Pro Pro Ser Tyr Leu Asp Val Leu Gly
785                 790                 795
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<210> SEQ ID NO 84
<211> LENGTH: 241
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
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<222> LOCATION: (11)..(12)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 84

Met Ser Met Leu Phe Tyr Thr Leu Ile Thr Xaa Xaa Leu Ile Gly Xaa
1               5                   10                  15

Gln Ala Glu Xaa Xaa Xaa Xaa Ser Asn Xaa Xaa Xaa Gly Xaa Xaa Xaa
            20                  25                  30

Pro Xaa Xaa His Trp Thr Lys Leu Gln His Ser Leu Asp Thr Ala Leu
        35                  40                  45

Arg Arg Ala Xaa Ser Xaa Pro Xaa Xaa Xaa Ile Ala Ala Arg Val Xaa
    50                  55                  60

Gly Gln Thr Xaa Asn Ile Thr Val Asp Pro Xaa Leu Phe Lys Lys Arg
65                  70                  75                  80

Xaa Leu Xaa Ser Pro Arg Val Leu Phe Ser Thr Gln Pro Pro Xaa Xaa
                85                  90                  95

Xaa Xaa Asp Xaa Xaa Asp Leu Asp Phe Xaa Xaa Xaa Gly Xaa Xaa Xaa
            100                 105                 110

Xaa Asn Arg Thr His Arg Ser Lys Arg Ser Ser Xaa His Pro Xaa Phe
        115                 120                 125

Xaa Xaa Gly Glu Phe Ser Val Cys Asp Ser Val Ser Val Trp Val Xaa
    130                 135                 140

Asp Lys Thr Thr Ala Thr Asp Ile Lys Gly Xaa Glu Val Xaa Val Leu
145                 150                 155                 160

Xaa Glu Val Asn Xaa Asn Asn Xaa Val Phe Xaa Gln Tyr Phe Phe Glu
                165                 170                 175

Thr Lys Cys Arg Xaa Xaa Xaa Pro Val Xaa Ser Gly Cys Arg Gly Ile
            180                 185                 190

Asp Ser Lys His Trp Asn Ser Tyr Cys Thr Thr Thr His Thr Phe Val
        195                 200                 205

Lys Ala Leu Thr Xaa Xaa Xaa Xaa Gln Ala Ala Trp Arg Phe Ile Arg
    210                 215                 220

Ile Asp Thr Ala Cys Val Cys Val Leu Xaa Arg Lys Ala Xaa Arg Arg
225                 230                 235                 240

Xaa


<210> SEQ ID NO 85
<211> LENGTH: 241
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 85

Met Ser Met Leu Phe Tyr Thr Leu Ile Thr Ala Phe Leu Ile Gly Ile
1               5                   10                  15
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Gln Ala Glu Pro His Ser Glu Ser Asn Val Pro Ala Gly His Thr Ile
            20                  25                  30

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

Arg Arg Ala Arg Ser Ala Pro Ala Ala Ala Ile Ala Ala Arg Val Ala
    50                  55                  60

Gly Gln Thr Arg Asn Ile Thr Val Asp Pro Arg Leu Phe Lys Lys Arg
65                  70                  75                  80

Arg Leu Arg Ser Pro Arg Val Leu Phe Ser Thr Gln Pro Pro Arg Glu
                85                  90                  95

Ala Ala Asp Thr Gln Asp Leu Asp Phe Glu Val Gly Gly Ala Ala Pro
            100                 105                 110

Phe Asn Arg Thr His Arg Ser Lys Arg Ser Ser Ser His Pro Ile Phe
        115                 120                 125

His Arg Gly Glu Phe Ser Val Cys Asp Ser Val Ser Val Trp Val Gly
    130                 135                 140

Asp Lys Thr Thr Ala Thr Asp Ile Lys Gly Lys Glu Val Met Val Leu
145                 150                 155                 160

Gly Glu Val Asn Ile Asn Asn Ser Val Phe Lys Gln Tyr Phe Phe Glu
                165                 170                 175

Thr Lys Cys Arg Asp Pro Asn Pro Val Asp Ser Gly Cys Arg Gly Ile
            180                 185                 190

Asp Ser Lys His Trp Asn Ser Tyr Cys Thr Thr Thr His Thr Phe Val
        195                 200                 205

Lys Ala Leu Thr Met Asp Gly Lys Gln Ala Ala Trp Arg Phe Ile Arg
    210                 215                 220

Ile Asp Thr Ala Cys Val Cys Val Leu Ser Arg Lys Ala Val Arg Arg
225                 230                 235                 240

Ala


<210> SEQ ID NO 86
<211> LENGTH: 241
<212> TYPE: PRT
<213> ORGANISM: Gorilla gorilla

<400> SEQUENCE: 86

Met Ser Met Leu Phe Tyr Thr Leu Ile Thr Ala Phe Leu Ile Gly Ile
1               5                   10                  15

Gln Ala Glu Leu His Ser Glu Ser Asn Val Pro Ala Gly His Thr Ile
            20                  25                  30

Pro Gln Ala His Trp Thr Lys Leu Gln His Ser Leu Asp Thr Ala Leu
        35                  40                  45

Arg Arg Ala Arg Ser Ala Pro Ala Ala Ala Ile Ala Ala Arg Val Ala
    50                  55                  60

Gly Gln Thr Arg Asn Ile Thr Val Asp Pro Arg Leu Phe Lys Lys Arg
65                  70                  75                  80

Arg Leu Arg Ser Pro Arg Val Leu Phe Ser Thr Gln Pro Pro Pro Glu
                85                  90                  95

Ala Ala Asp Thr Gln Asp Leu Asp Phe Glu Val Gly Gly Ala Ala Pro
            100                 105                 110

Phe Asn Arg Thr His Arg Ser Lys Arg Ser Ser Ser His Pro Ile Phe
        115                 120                 125
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His Arg Gly Glu Phe Ser Val Cys Asp Ser Val Ser Val Trp Val Gly
    130   135   140

Asp Lys Thr Thr Ala Thr Asp Ile Lys Gly Lys Glu Val Met Val Leu
145   150   155   160

Gly Glu Val Asn Ile Asn Asn Ser Val Phe Lys Gln Tyr Phe Phe Glu
                165   170   175

Thr Lys Cys Arg Asp Pro Asn Pro Val Asp Ser Gly Cys Arg Gly Ile
            180   185   190

Asp Ser Lys His Trp Asn Ser Tyr Cys Thr Thr Thr His Thr Phe Val
        195   200   205

Lys Ala Leu Thr Met Asp Gly Lys Gln Ala Ala Trp Arg Phe Ile Arg
    210   215   220

Ile Asp Thr Ala Cys Val Cys Val Leu Ser Arg Lys Ala Val Arg Arg
225   230   235   240

Ala

<210> SEQ ID NO 87
<211> LENGTH: 241
<212> TYPE: PRT
<213> ORGANISM: Pongo pygmaeus

<400> SEQUENCE: 87

Met Ser Met Leu Phe Tyr Thr Leu Ile Thr Ala Phe Leu Ile Gly Ile
1   5   10   15

Gln Ala Glu Pro His Ser Glu Ser Asn Val Pro Ala Gly His Thr Ile
            20   25   30

Pro Gln Ala His Trp Thr Lys Leu Gln His Ser Leu Asp Thr Ala Leu
        35   40   45

Arg Arg Ala Arg Ser Thr Pro Ala Ala Ala Ile Ala Ala Arg Val Ala
    50   55   60

Gly Gln Thr Cys Asn Ile Thr Val Asp Pro Arg Leu Phe Lys Lys Arg
65   70   75   80

Arg Leu Arg Ser Pro Arg Val Leu Phe Ser Thr Gln Pro Pro Pro Glu
                85   90   95

Ala Ala Asp Thr Gln Asp Leu Asp Phe Glu Val Gly Gly Ala Ala Pro
            100   105   110

Phe Asn Arg Thr His Arg Ser Lys Arg Ser Ser Ser His Pro Ile Phe
        115   120   125

His Arg Gly Glu Phe Ser Val Cys Asp Ser Val Ser Val Trp Val Gly
    130   135   140

Asp Lys Thr Thr Ala Thr Asp Ile Lys Gly Lys Glu Val Met Val Leu
145   150   155   160

Gly Glu Val Asn Ile Asn Asn Ser Val Phe Lys Gln Tyr Phe Phe Glu
                165   170   175

Thr Lys Cys Arg Asp Pro Asn Pro Val Asp Ser Gly Cys Arg Gly Ile
            180   185   190

Asp Ser Lys His Trp Asn Ser Tyr Cys Thr Thr Thr His Thr Phe Val
        195   200   205

Lys Ala Leu Thr Met Asp Gly Lys Gln Ala Ala Trp Arg Phe Ile Arg
    210   215   220

Ile Asp Thr Ala Cys Val Cys Val Leu Ser Arg Lys Ala Val Arg Arg
225   230   235   240

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Ala

<210> SEQ ID NO 88
<211> LENGTH: 241
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 88

Met Ser Met Leu Phe Tyr Thr Leu Ile Thr Ala Phe Leu Ile Gly Val
1   5   10   15

Gln Ala Glu Pro Tyr Thr Asp Ser Asn Val Pro Glu Gly Asp Ser Val
            20   25   30

Pro Glu Ala His Trp Thr Lys Leu Gln His Ser Leu Asp Thr Ala Leu
        35   40   45

Arg Arg Ala Arg Ser Ala Pro Ala Glu Pro Ile Ala Ala Arg Val Thr
    50   55   60

Gly Gln Thr Arg Asn Ile Thr Val Asp Pro Lys Leu Phe Lys Lys Arg
65   70   75   80

Arg Leu Arg Ser Pro Arg Val Leu Phe Ser Thr Gln Pro Pro Pro Thr
                85   90   95

Ser Ser Asp Thr Leu Asp Leu Asp Phe Gln Ala His Gly Thr Ile Ser
            100   105   110

Phe Asn Arg Thr His Arg Ser Lys Arg Ser Ser Thr His Pro Val Phe
        115   120   125

His Met Gly Glu Phe Ser Val Cys Asp Ser Val Ser Val Trp Val Gly
    130   135   140

Asp Lys Thr Thr Ala Thr Asp Ile Lys Gly Lys Glu Val Thr Val Leu
145   150   155   160

Gly Glu Val Asn Ile Asn Asn Ser Val Phe Lys Gln Tyr Phe Phe Glu
                165   170   175

Thr Lys Cys Arg Ala Pro Asn Pro Val Glu Ser Gly Cys Arg Gly Ile
            180   185   190

Asp Ser Lys His Trp Asn Ser Tyr Cys Thr Thr Thr His Thr Phe Val
        195   200   205

Lys Ala Leu Thr Thr Asp Asp Lys Gln Ala Ala Trp Arg Phe Ile Arg
    210   215   220

Ile Asp Thr Ala Cys Val Cys Val Leu Ser Arg Lys Ala Ala Arg Arg
225   230   235   240

Gly

<210> SEQ ID NO 89
<211> LENGTH: 241
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 89

Met Ser Met Leu Phe Tyr Thr Leu Ile Thr Ala Phe Leu Ile Gly Val
1   5   10   15

Gln Ala Glu Pro Tyr Thr Asp Ser Asn Val Pro Glu Gly Asp Ser Val
            20   25   30

Pro Glu Ala His Trp Thr Lys Leu Gln His Ser Leu Asp Thr Ala Leu
        35   40   45

Arg Arg Ala Arg Ser Ala Pro Thr Ala Pro Ile Ala Ala Arg Val Thr
    50   55   60

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Gly Gln Thr Arg Asn Ile Thr Val Asp Pro Arg Leu Phe Lys Lys Arg
65 70 75 80

Arg Leu His Ser Pro Arg Val Leu Phe Ser Thr Gln Pro Pro Pro Thr
85 90 95

Ser Ser Asp Thr Leu Asp Leu Asp Phe Gln Ala His Gly Thr Ile Pro
100 105 110

Phe Asn Arg Thr His Arg Ser Lys Arg Ser Ser Thr His Pro Val Phe
115 120 125

His Met Gly Glu Phe Ser Val Cys Asp Ser Val Ser Val Trp Val Gly
130 135 140

Asp Lys Thr Thr Ala Thr Asp Ile Lys Gly Lys Glu Val Thr Val Leu
145 150 155 160

Ala Glu Val Asn Ile Asn Asn Ser Val Phe Arg Gln Tyr Phe Phe Glu
165 170 175

Thr Lys Cys Arg Ala Ser Asn Pro Val Glu Ser Gly Cys Arg Gly Ile
180 185 190

Asp Ser Lys His Trp Asn Ser Tyr Cys Thr Thr Thr His Thr Phe Val
195 200 205

Lys Ala Leu Thr Thr Asp Glu Lys Gln Ala Ala Trp Arg Phe Ile Arg
210 215 220

Ile Asp Thr Ala Cys Val Cys Val Leu Ser Arg Lys Ala Thr Arg Arg
225 230 235 240

Gly

<210> SEQ ID NO 90
<211> LENGTH: 241
<212> TYPE: PRT
<213> ORGANISM: Cavia porcellus

<400> SEQUENCE: 90

Met Ser Met Leu Phe Tyr Thr Leu Ile Thr Val Phe Leu Ile Gly Ile
1 5 10 15

Gln Ala Glu Pro Tyr Ser Asp Ser Asn Val Leu Ser Gly Asp Thr Ile
20 25 30

Pro Gln Ala His Trp Thr Lys Leu Gln His Ser Leu Asp Thr Ala Leu
35 40 45

Arg Arg Ala His Ser Ala Pro Ala Ala Pro Ile Ala Ala Arg Val Ala
50 55 60

Gly Gln Thr Leu Asn Ile Thr Val Asp Pro Arg Leu Phe Lys Lys Arg
65 70 75 80

Arg Leu His Ser Pro Arg Val Leu Phe Ser Thr Gln Pro Pro Pro Leu
85 90 95

Ser Thr Asp Ala Gln Asp Leu Asp Phe Glu Val Asp Gly Ala Ala Ser
100 105 110

Val Asn Arg Thr His Arg Ser Lys Arg Ser Ser Thr His Pro Val Phe
115 120 125

His Met Gly Glu Phe Ser Val Cys Asp Ser Val Ser Val Trp Val Ala
130 135 140

Asp Lys Thr Thr Ala Thr Asp Ile Lys Gly Lys Glu Val Thr Val Leu
145 150 155 160

Ala Glu Val Asn Val Asn Asn Asn Val Phe Lys Gln Tyr Phe Phe Glu
165 170 175

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Thr Lys Cys Arg Asp Pro Ser Pro Val Asp Ser Gly Cys Arg Gly Ile
180 185 190

Asp Ser Lys His Trp Asn Ser Tyr Cys Thr Thr Thr His Thr Phe Val
195 200 205

Lys Ala Leu Thr Thr Ala Asn Lys Gln Ala Ala Trp Arg Phe Ile Arg
210 215 220

Ile Asp Thr Ala Cys Val Cys Val Leu Asn Arg Lys Ala Ala Arg Arg
225 230 235 240

Gly

<210> SEQ ID NO 91
<211> LENGTH: 241
<212> TYPE: PRT
<213> ORGANISM: Mastomys natalensis

<400> SEQUENCE: 91

Met Ser Met Leu Phe Tyr Thr Leu Ile Thr Ala Leu Leu Ile Gly Val
1 5 10 15

Gln Ala Glu Pro Tyr Thr Asp Ser Asn Leu Pro Glu Gly Asp Ser Val
20 25 30

Pro Glu Ala His Trp Thr Lys Leu Gln His Ser Leu Asp Thr Ala Leu
35 40 45

Arg Arg Ala Arg Ser Ala Pro Ala Ala Pro Ile Ala Ala Arg Val Thr
50 55 60

Gly Gln Thr Arg Asn Ile Thr Val Asp Pro Arg Leu Phe Lys Lys Arg
65 70 75 80

Lys Leu Arg Ser Pro Arg Val Leu Phe Ser Thr Gln Pro Pro Pro Thr
85 90 95

Ser Ser Asp Thr Leu Asp Leu Asp Phe Gln Ala His Gly Thr Ile Ser
100 105 110

Phe Asn Arg Thr His Arg Ser Lys Arg Ser Ser Thr His Pro Val Phe
115 120 125

Gln Met Gly Glu Phe Ser Val Cys Asp Ser Val Ser Val Trp Val Gly
130 135 140

Asp Lys Thr Thr Ala Thr Asp Ile Lys Gly Asn Glu Val Thr Val Leu
145 150 155 160

Gly Glu Val Asn Ile Asn Asn Ser Val Phe Lys Gln Tyr Phe Phe Glu
165 170 175

Thr Lys Cys Arg Ala Arg Asn Pro Val Glu Ser Gly Cys Arg Gly Ile
180 185 190

Asp Ser Lys His Trp Asn Ser Tyr Cys Thr Thr Thr His Thr Phe Val
195 200 205

Lys Ala Leu Thr Thr Asp Asp Arg Gln Ala Ala Trp Arg Phe Ile Arg
210 215 220

Ile Asp Thr Ala Cys Val Cys Val Leu Thr Arg Lys Ala Pro Arg Arg
225 230 235 240

Gly

<210> SEQ ID NO 92
<211> LENGTH: 189
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:

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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<222> LOCATION: (74)..(75)
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<221> NAME/KEY: misc_feature
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
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<222> LOCATION: (153)..(154)

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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (157)..(161)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (163)..(163)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (189)..(189)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 92

```
Xaa Xaa Xaa Xaa Arg Xaa Xaa Xaa Arg Ser Xaa Arg Xaa Arg Asp Xaa
1               5                   10                  15

Xaa Xaa Pro Thr Xaa Cys Xaa Xaa Xaa Glu Cys Phe Asp Xaa Leu Val
            20                  25                  30

Arg Xaa Cys Val Xaa Cys Xaa Leu Xaa Xaa Thr Xaa Xaa Pro Xaa Xaa
        35                  40                  45

Xaa Xaa Xaa Ser Ser Xaa Xaa Pro Xaa Thr Ala Leu Gln Pro Gln Glu
    50                  55                  60

Xaa Xaa Xaa Xaa Xaa Xaa Gly Xaa Ala Xaa Xaa Pro Xaa Xaa Xaa Leu
65                  70                  75                  80

Leu Xaa Gly Ala Pro Ala Leu Leu Gly Leu Xaa Leu Xaa Leu Xaa Leu
                85                  90                  95

Val Xaa Leu Val Xaa Leu Val Ser Trp Arg Xaa Arg Gln Xaa Xaa Leu
            100                 105                 110

Arg Xaa Ala Ser Xaa Xaa Xaa Xaa Pro Asp Xaa Xaa Xaa Xaa Xaa Xaa
        115                 120                 125

Xaa Glu Xaa Leu Xaa Xaa Val Xaa Xaa Xaa Ser Xaa Xaa Xaa Xaa Xaa
    130                 135                 140

Ala Xaa Ala Pro Xaa Trp Pro Pro Xaa Xaa Glu Asp Xaa Xaa Xaa Xaa
145                 150                 155                 160

Xaa Pro Xaa His Ser Val Pro Val Pro Ala Thr Glu Leu Gly Ser Thr
                165                 170                 175

Glu Leu Val Thr Thr Lys Thr Ala Gly Pro Glu Gln Xaa
            180                 185
```

<210> SEQ ID NO 93
<211> LENGTH: 184
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 93

```
Met Arg Arg Gly Pro Arg Ser Leu Arg Gly Arg Asp Ala Pro Ala Pro
1               5                   10                  15

Thr Pro Cys Val Pro Ala Glu Cys Phe Asp Leu Leu Val Arg His Cys
            20                  25                  30

Val Ala Cys Gly Leu Leu Arg Thr Pro Arg Pro Lys Pro Ala Gly Ala
        35                  40                  45

Ser Ser Pro Ala Pro Arg Thr Ala Leu Gln Pro Gln Glu Ser Val Gly
    50                  55                  60

Ala Gly Ala Gly Glu Ala Ala Leu Pro Leu Pro Gly Leu Leu Phe Gly
65                  70                  75                  80

Ala Pro Ala Leu Leu Gly Leu Ala Leu Val Leu Ala Leu Val Leu Val
```

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```
                85                  90                  95

Gly Leu Val Ser Trp Arg Arg Arg Gln Arg Arg Leu Arg Gly Ala Ser
            100                 105                 110

Ser Ala Glu Ala Pro Asp Gly Asp Lys Asp Ala Pro Glu Pro Leu Asp
        115                 120                 125

Lys Val Ile Ile Leu Ser Pro Gly Ile Ser Asp Ala Thr Ala Pro Ala
    130                 135                 140

Trp Pro Pro Pro Gly Glu Asp Pro Gly Thr Thr Pro Pro Gly His Ser
145                 150                 155                 160

Val Pro Val Pro Ala Thr Glu Leu Gly Ser Thr Glu Leu Val Thr Thr
                165                 170                 175

Lys Thr Ala Gly Pro Glu Gln Gln
            180
```

<210> SEQ ID NO 94
<211> LENGTH: 175
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 94

```
Met Gly Ala Arg Arg Leu Arg Val Arg Ser Gln Arg Ser Arg Asp Ser
1               5                   10                  15

Ser Val Pro Thr Gln Cys Asn Gln Thr Glu Cys Phe Asp Pro Leu Val
            20                  25                  30

Arg Asn Cys Val Ser Cys Glu Leu Phe His Thr Pro Asp Thr Gly His
        35                  40                  45

Thr Ser Ser Leu Glu Pro Gly Thr Ala Leu Gln Pro Gln Glu Gly Ser
    50                  55                  60

Ala Leu Arg Pro Asp Val Ala Leu Leu Val Gly Ala Pro Ala Leu Leu
65                  70                  75                  80

Gly Leu Ile Leu Ala Leu Thr Leu Val Gly Leu Val Ser Leu Val Ser
                85                  90                  95

Trp Arg Trp Arg Gln Gln Leu Arg Thr Ala Ser Pro Asp Thr Ser Glu
            100                 105                 110

Gly Val Gln Gln Glu Ser Leu Glu Asn Val Phe Val Pro Ser Ser Glu
        115                 120                 125

Thr Pro His Ala Ser Ala Pro Thr Trp Pro Pro Leu Lys Glu Asp Ala
    130                 135                 140

Asp Ser Ala Leu Pro Arg His Ser Val Pro Val Pro Ala Thr Glu Leu
145                 150                 155                 160

Gly Ser Thr Glu Leu Val Thr Thr Lys Thr Ala Gly Pro Glu Gln
                165                 170                 175
```

<210> SEQ ID NO 95
<211> LENGTH: 318
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: BAFFR mammalian
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(12)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (14)..(15)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (17)..(18)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
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<222> LOCATION: (20)..(20)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<222> LOCATION: (32)..(32)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<222> LOCATION: (34)..(34)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<222> LOCATION: (37)..(45)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<222> LOCATION: (48)..(48)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<222> LOCATION: (96)..(96)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (101)..(110)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (114)..(114)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (116)..(118)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (120)..(120)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<222> LOCATION: (123)..(125)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<222> LOCATION: (129)..(131)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<222> LOCATION: (137)..(137)
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<222> LOCATION: (209)..(209)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<222> LOCATION: (219)..(219)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<222> LOCATION: (221)..(222)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<221> NAME/KEY: misc_feature
<222> LOCATION: (230)..(230)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<222> LOCATION: (237)..(239)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<221> NAME/KEY: misc_feature
<222> LOCATION: (244)..(244)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (271)..(271)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (285)..(285)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (292)..(292)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (305)..(306)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (309)..(309)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 95

```
Met Asp Xaa Ser Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Leu Xaa Xaa Cys
1               5                   10                  15

Xaa Xaa Lys Xaa Glu Xaa Met Lys Xaa Xaa Xaa Xaa Xaa Xaa Ile Xaa
            20                  25                  30

Pro Xaa Lys Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp Gly Xaa
        35                  40                  45

Leu Leu Ala Ala Thr Leu Leu Leu Ala Leu Leu Ser Xaa Xaa Xaa Thr
    50                  55                  60

Xaa Xaa Ser Xaa Tyr Gln Xaa Ala Ala Leu Gln Xaa Asp Leu Xaa Xaa
65                  70                  75                  80

Leu Arg Xaa Glu Leu Gln Xaa Xaa Xaa Xaa Xaa Xaa Xaa Pro Ala Xaa
                85                  90                  95

Ala Gly Ala Pro Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Thr Ala
            100                 105                 110

Gly Xaa Lys Xaa Xaa Xaa Pro Xaa Ala Pro Xaa Xaa Xaa Asn Ser Ser
        115                 120                 125

Xaa Xaa Xaa Arg Asn Xaa Arg Ala Xaa Gln Gly Pro Glu Glu Thr Xaa
    130                 135                 140

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
145                 150                 155                 160

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
                165                 170                 175

Gln Asp Cys Leu Gln Leu Ile Ala Asp Ser Xaa Thr Pro Thr Ile Xaa
            180                 185                 190

Lys Gly Xaa Tyr Thr Phe Val Pro Trp Leu Leu Ser Phe Lys Arg Gly
        195                 200                 205

Xaa Ala Leu Glu Glu Lys Glu Asn Lys Ile Xaa Val Xaa Xaa Thr Gly
    210                 215                 220

Tyr Phe Phe Ile Tyr Xaa Gln Val Leu Tyr Thr Asp Xaa Xaa Xaa Ala
225                 230                 235                 240

Met Gly His Xaa Ile Gln Arg Lys Lys Val His Val Phe Gly Asp Glu
                245                 250                 255

Leu Ser Leu Val Thr Leu Phe Arg Cys Ile Gln Asn Met Pro Xaa Thr
            260                 265                 270

Leu Pro Asn Asn Ser Cys Tyr Ser Ala Gly Ile Ala Xaa Leu Glu Glu
        275                 280                 285

Gly Asp Glu Xaa Gln Leu Ala Ile Pro Arg Glu Asn Ala Gln Ile Ser
    290                 295                 300

Xaa Xaa Gly Asp Xaa Thr Phe Phe Gly Ala Leu Lys Leu Leu
305                 310                 315
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<210> SEQ ID NO 96
<211> LENGTH: 285
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 96

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Met Asp Asp Ser Thr Glu Arg Glu Gln Ser Arg Leu Thr Ser Cys Leu
1               5                   10                  15

Lys Lys Arg Glu Glu Met Lys Leu Lys Glu Cys Val Ser Ile Leu Pro
            20                  25                  30

Arg Lys Glu Ser Pro Ser Val Arg Ser Ser Lys Asp Gly Lys Leu Leu
        35                  40                  45

Ala Ala Thr Leu Leu Leu Ala Leu Leu Ser Cys Cys Leu Thr Val Val
    50                  55                  60

Ser Phe Tyr Gln Val Ala Ala Leu Gln Gly Asp Leu Ala Ser Leu Arg
65                  70                  75                  80

Ala Glu Leu Gln Gly His His Ala Glu Lys Leu Pro Ala Gly Ala Gly
                85                  90                  95

Ala Pro Lys Ala Gly Leu Glu Glu Ala Pro Ala Val Thr Ala Gly Leu
            100                 105                 110

Lys Ile Phe Glu Pro Pro Ala Pro Gly Glu Gly Asn Ser Ser Gln Asn
        115                 120                 125

Ser Arg Asn Lys Arg Ala Val Gln Gly Pro Glu Glu Thr Val Thr Gln
    130                 135                 140

Asp Cys Leu Gln Leu Ile Ala Asp Ser Glu Thr Pro Thr Ile Gln Lys
145                 150                 155                 160

Gly Ser Tyr Thr Phe Val Pro Trp Leu Leu Ser Phe Lys Arg Gly Ser
                165                 170                 175

Ala Leu Glu Glu Lys Glu Asn Lys Ile Leu Val Lys Glu Thr Gly Tyr
            180                 185                 190

Phe Phe Ile Tyr Gly Gln Val Leu Tyr Thr Asp Lys Thr Tyr Ala Met
        195                 200                 205

Gly His Leu Ile Gln Arg Lys Lys Val His Val Phe Gly Asp Glu Leu
    210                 215                 220

Ser Leu Val Thr Leu Phe Arg Cys Ile Gln Asn Met Pro Glu Thr Leu
225                 230                 235                 240

Pro Asn Asn Ser Cys Tyr Ser Ala Gly Ile Ala Lys Leu Glu Glu Gly
                245                 250                 255

Asp Glu Leu Gln Leu Ala Ile Pro Arg Glu Asn Ala Gln Ile Ser Leu
            260                 265                 270

Asp Gly Asp Val Thr Phe Phe Gly Ala Leu Lys Leu Leu
        275                 280                 285
```

<210> SEQ ID NO 97
<211> LENGTH: 309
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 97

```
Met Asp Glu Ser Ala Lys Thr Leu Pro Pro Pro Cys Leu Cys Phe Cys
1               5                   10                  15

Ser Glu Lys Gly Glu Asp Met Lys Val Gly Tyr Asp Pro Ile Thr Pro
            20                  25                  30

Gln Lys Glu Glu Gly Ala Trp Phe Gly Ile Cys Arg Asp Gly Arg Leu
```

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        35                  40                  45

Leu Ala Ala Thr Leu Leu Leu Ala Leu Leu Ser Ser Ser Phe Thr Ala
    50                  55                  60

Met Ser Leu Tyr Gln Leu Ala Ala Leu Gln Ala Asp Leu Met Asn Leu
65                  70                  75                  80

Arg Met Glu Leu Gln Ser Tyr Arg Gly Ser Ala Thr Pro Ala Ala Ala
                85                  90                  95

Gly Ala Pro Glu Leu Thr Ala Gly Val Lys Leu Leu Thr Pro Ala Ala
            100                 105                 110

Pro Arg Pro His Asn Ser Ser Arg Gly His Arg Asn Arg Arg Ala Phe
        115                 120                 125

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

Ala Pro Cys Leu Pro Gly Cys Arg His Ser Gln His Asp Asp Asn Gly
145                 150                 155                 160

Met Asn Leu Arg Asn Ile Ile Gln Asp Cys Leu Gln Leu Ile Ala Asp
                165                 170                 175

Ser Asp Thr Pro Thr Ile Arg Lys Gly Thr Tyr Thr Phe Val Pro Trp
            180                 185                 190

Leu Leu Ser Phe Lys Arg Gly Asn Ala Leu Glu Glu Lys Glu Asn Lys
        195                 200                 205

Ile Val Val Arg Gln Thr Gly Tyr Phe Phe Ile Tyr Ser Gln Val Leu
    210                 215                 220

Tyr Thr Asp Pro Ile Phe Ala Met Gly His Val Ile Gln Arg Lys Lys
225                 230                 235                 240

Val His Val Phe Gly Asp Glu Leu Ser Leu Val Thr Leu Phe Arg Cys
                245                 250                 255

Ile Gln Asn Met Pro Lys Thr Leu Pro Asn Asn Ser Cys Tyr Ser Ala
            260                 265                 270

Gly Ile Ala Arg Leu Glu Glu Gly Asp Glu Ile Gln Leu Ala Ile Pro
        275                 280                 285

Arg Glu Asn Ala Gln Ile Ser Arg Asn Gly Asp Asp Thr Phe Phe Gly
    290                 295                 300

Ala Leu Lys Leu Leu
305
```

<210> SEQ ID NO 98
<211> LENGTH: 469
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: TNFR1 mammalian
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(5)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (11)..(12)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (16)..(17)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

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<220> FEATURE:
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<222> LOCATION: (20)..(23)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<222> LOCATION: (110)..(110)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

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<220> FEATURE:
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<222> LOCATION: (116)..(116)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<222> LOCATION: (163)..(163)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<400> SEQUENCE: 98

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Met Gly Leu Xaa Xaa Val Pro Xaa Leu Leu Xaa Xaa Leu Val Leu Xaa
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Xaa Leu Leu Xaa Xaa Xaa Xaa Pro Xaa Xaa Val Xaa Gly Leu Val Xaa
            20                  25                  30

Xaa Xaa Xaa Asp Arg Glu Lys Arg Xaa Xaa Xaa Cys Pro Gln Gly Lys
        35                  40                  45

Tyr Xaa His Xaa Xaa Xaa Xaa Ser Ile Cys Cys Thr Lys Cys His Lys
    50                  55                  60

Gly Thr Tyr Leu Xaa Xaa Asp Cys Xaa Xaa Pro Gly Xaa Xaa Thr Xaa
65                  70                  75                  80

Cys Xaa Xaa Cys Xaa Xaa Gly Xaa Phe Thr Ala Ser Xaa Asn Xaa Xaa
                85                  90                  95

Xaa Xaa Cys Leu Ser Cys Xaa Xaa Cys Arg Xaa Glu Met Xaa Gln Val
            100                 105                 110

Glu Ile Ser Xaa Cys Xaa Xaa Xaa Xaa Asp Thr Val Cys Gly Cys Xaa
        115                 120                 125

Xaa Asn Gln Xaa Xaa Xaa Tyr Xaa Ser Glu Xaa Xaa Phe Gln Cys Xaa
    130                 135                 140

Xaa Cys Ser Xaa Cys Xaa Asn Gly Thr Val Xaa Xaa Xaa Cys Xaa Glu
145                 150                 155                 160

Xaa Gln Xaa Thr Xaa Cys Xaa Cys His Xaa Gly Phe Phe Leu Xaa Xaa
                165                 170                 175

Xaa Glu Cys Xaa Xaa Cys Xaa Xaa Cys Xaa Lys Xaa Xaa Xaa Cys Xaa
            180                 185                 190

Xaa Leu Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp
        195                 200                 205

Xaa Gly Thr Xaa Val Leu Leu Pro Leu Val Ile Xaa Xaa Gly Xaa Cys
    210                 215                 220

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Leu Xaa Xaa Arg Tyr Xaa Xaa Xaa
225                 230                 235                 240

Xaa Xaa Xaa Xaa Xaa Ser Ile Xaa Cys Xaa Xaa Xaa Xaa Pro Xaa Lys
                245                 250                 255

Glu Xaa Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Pro Xaa Xaa Xaa Xaa Xaa
            260                 265                 270

Xaa Xaa Xaa Phe Ser Pro Xaa Xaa Xaa Xaa Xaa Pro Thr Xaa Xaa Phe
        275                 280                 285

Ser Xaa Xaa Pro Xaa Xaa Xaa Xaa Xaa Xaa Ser Xaa Thr Xaa Xaa Xaa
    290                 295                 300

Xaa Xaa Xaa Xaa Pro Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
305                 310                 315                 320

Xaa Xaa Glu Xaa Xaa Pro Xaa Xaa Gln Gly Ala Xaa Pro Xaa Leu Xaa
                325                 330                 335

Xaa Xaa Xaa Xaa Xaa Xaa Pro Xaa Xaa Xaa Xaa Xaa Xaa Lys Trp Xaa
            340                 345                 350

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Pro Xaa Xaa Xaa Xaa Xaa Xaa
        355                 360                 365

Asp Xaa Ala Xaa Leu Tyr Ala Val Val Xaa Xaa Val Pro Pro Xaa Arg
    370                 375                 380

Trp Lys Glu Phe Xaa Arg Xaa Xaa Gly Leu Ser Xaa His Glu Ile Xaa
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385                 390                 395                 400

Arg Leu Glu Xaa Gln Asn Gly Arg Cys Leu Arg Glu Ala Xaa Tyr Ser
                405                 410                 415

Met Leu Xaa Xaa Trp Arg Arg Arg Thr Xaa Arg Xaa Glu Xaa Thr Leu
            420                 425                 430

Xaa Xaa Xaa Gly Xaa Val Leu Xaa Xaa Met Xaa Leu Xaa Gly Cys Leu
        435                 440                 445

Glu Xaa Ile Xaa Glu Xaa Leu Xaa Xaa Pro Ala Xaa Xaa Xaa Xaa Xaa
    450                 455                 460

Xaa Xaa Leu Xaa Arg
465


<210> SEQ ID NO 99
<211> LENGTH: 455
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 99

Met Gly Leu Ser Thr Val Pro Asp Leu Leu Leu Pro Leu Val Leu Leu
1               5                   10                  15

Glu Leu Leu Val Gly Ile Tyr Pro Ser Gly Val Ile Gly Leu Val Pro
            20                  25                  30

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

Tyr Ile His Pro Gln Asn Asn Ser Ile Cys Cys Thr Lys Cys His Lys
    50                  55                  60

Gly Thr Tyr Leu Tyr Asn Asp Cys Pro Gly Pro Gly Gln Asp Thr Asp
65                  70                  75                  80

Cys Arg Glu Cys Glu Ser Gly Ser Phe Thr Ala Ser Glu Asn His Leu
                85                  90                  95

Arg His Cys Leu Ser Cys Ser Lys Cys Arg Lys Glu Met Gly Gln Val
            100                 105                 110

Glu Ile Ser Ser Cys Thr Val Asp Arg Asp Thr Val Cys Gly Cys Arg
        115                 120                 125

Lys Asn Gln Tyr Arg His Tyr Trp Ser Glu Asn Leu Phe Gln Cys Phe
    130                 135                 140

Asn Cys Ser Leu Cys Leu Asn Gly Thr Val His Leu Ser Cys Gln Glu
145                 150                 155                 160

Lys Gln Asn Thr Val Cys Thr Cys His Ala Gly Phe Phe Leu Arg Glu
                165                 170                 175

Asn Glu Cys Val Ser Cys Ser Asn Cys Lys Lys Ser Leu Glu Cys Thr
            180                 185                 190

Lys Leu Cys Leu Pro Gln Ile Glu Asn Val Lys Gly Thr Glu Asp Ser
        195                 200                 205

Gly Thr Thr Val Leu Leu Pro Leu Val Ile Phe Phe Gly Leu Cys Leu
    210                 215                 220

Leu Ser Leu Leu Phe Ile Gly Leu Met Tyr Arg Tyr Gln Arg Trp Lys
225                 230                 235                 240

Ser Lys Leu Tyr Ser Ile Val Cys Gly Lys Ser Thr Pro Glu Lys Glu
                245                 250                 255

Gly Glu Leu Glu Gly Thr Thr Thr Lys Pro Leu Ala Pro Asn Pro Ser
            260                 265                 270
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Phe Ser Pro Thr Pro Gly Phe Thr Pro Thr Leu Gly Phe Ser Pro Val
275 280 285

Pro Ser Ser Thr Phe Thr Ser Ser Ser Thr Tyr Thr Pro Gly Asp Cys
290 295 300

Pro Asn Phe Ala Ala Pro Arg Arg Glu Val Ala Pro Pro Tyr Gln Gly
305 310 315 320

Ala Asp Pro Ile Leu Ala Thr Ala Leu Ala Ser Asp Pro Ile Pro Asn
325 330 335

Pro Leu Gln Lys Trp Glu Asp Ser Ala His Lys Pro Gln Ser Leu Asp
340 345 350

Thr Asp Asp Pro Ala Thr Leu Tyr Ala Val Val Glu Asn Val Pro Pro
355 360 365

Leu Arg Trp Lys Glu Phe Val Arg Arg Leu Gly Leu Ser Asp His Glu
370 375 380

Ile Asp Arg Leu Glu Leu Gln Asn Gly Arg Cys Leu Arg Glu Ala Gln
385 390 395 400

Tyr Ser Met Leu Ala Thr Trp Arg Arg Arg Thr Pro Arg Arg Glu Ala
405 410 415

Thr Leu Glu Leu Leu Gly Arg Val Leu Arg Asp Met Asp Leu Leu Gly
420 425 430

Cys Leu Glu Asp Ile Glu Glu Ala Leu Cys Gly Pro Ala Ala Leu Pro
435 440 445

Pro Ala Pro Ser Leu Leu Arg
450 455

<210> SEQ ID NO 100
<211> LENGTH: 446
<212> TYPE: PRT
<213> ORGANISM: Felis catus

<400> SEQUENCE: 100

Met Gly Leu Pro Thr Val Pro Gly Leu Leu Gln Pro Leu Val Leu Leu
1 5 10 15

Ala Leu Leu Val Glu Ile Tyr Pro Leu Arg Val Thr Gly Leu Val Pro
20 25 30

His Leu Arg Asp Arg Glu Lys Arg Ala Ile Pro Cys Pro Gln Gly Lys
35 40 45

Tyr Ile His Pro Gln Asp Asn Ser Ile Cys Cys Thr Lys Cys His Lys
50 55 60

Gly Thr Tyr Leu Tyr Asn Asp Cys Ala Gly Pro Gly Leu Asp Thr Asp
65 70 75 80

Cys Arg Glu Cys Glu Asn Gly Thr Phe Thr Ala Ser Glu Asn Tyr Leu
85 90 95

Arg Gln Cys Leu Ser Cys Ser Lys Cys Arg Lys Glu Met Tyr Gln Val
100 105 110

Glu Ile Ser Pro Cys Thr Val Tyr Arg Asp Thr Val Cys Gly Cys Arg
115 120 125

Lys Asn Gln Tyr Arg Tyr Tyr Trp Ser Glu Thr His Phe Gln Cys Leu
130 135 140

Asn Cys Ser Leu Cys Leu Asn Gly Thr Val Gln Ile Ser Cys Lys Glu
145 150 155 160

Thr Gln Asn Thr Val Cys Thr Cys His Ala Gly Phe Phe Leu Arg Gly
165 170 175

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Asn Glu Cys Val Ser Cys Val Asn Cys Lys Lys Asn Thr Glu Cys Thr
            180                 185                 190

Lys Leu Cys Val Pro Ile Val Glu Thr Val Lys Asp Pro Gln Asp Pro
        195                 200                 205

Gly Thr Thr Val Leu Leu Pro Leu Val Ile Phe Phe Gly Ile Cys Val
    210                 215                 220

Leu Ser Phe Ser Ile Gly Leu Met Cys Arg Tyr Gln Arg Arg Lys Ser
225                 230                 235                 240

Lys Leu Phe Ser Ile Val Cys Gly Lys Ser Thr Pro Thr Lys Glu Gly
                245                 250                 255

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

Pro Thr Phe Ser Pro Ser Pro Thr Phe Thr Pro Ser Pro Thr Phe Thr
        275                 280                 285

Pro Ser Asp Trp Ala Asn Leu Arg Ala Ala Ser Val Ser Arg Glu Met
    290                 295                 300

Ala Pro Pro Tyr Gln Gly Ala Gly Pro Ile Leu Ser Ala Ala Pro Ala
305                 310                 315                 320

Ser Ser Pro Ile Ser Thr Pro Val Gln Lys Trp Glu Asp Ser Thr His
                325                 330                 335

Thr Gln Arg Pro Glu Ala Asp Pro Ala Asp Pro Ala Thr Leu Tyr Ala
            340                 345                 350

Val Val Asp Gly Val Pro Pro Ser Arg Trp Lys Glu Phe Val Arg Arg
        355                 360                 365

Leu Gly Leu Ser Glu His Glu Ile Glu Arg Leu Glu Leu Gln Asn Gly
    370                 375                 380

Arg Cys Leu Arg Glu Ala His Tyr Ser Met Leu Ala Ala Trp Arg Arg
385                 390                 395                 400

Arg Thr Pro Arg Arg Glu Ala Thr Leu Glu Leu Leu Gly Arg Val Leu
                405                 410                 415

Arg Asp Met Asp Leu Leu Gly Cys Leu Glu Asp Ile Glu Glu Ala Leu
            420                 425                 430

Cys Ala Pro Ala Ser Leu Ser Pro Ala Pro Arg Leu Leu Arg
        435                 440                 445


<210> SEQ ID NO 101
<211> LENGTH: 461
<212> TYPE: PRT
<213> ORGANISM: Sus scrofa

<400> SEQUENCE: 101

Met Gly Leu Ser Thr Val Pro Gly Leu Leu Leu Pro Leu Val Leu Arg
1               5                   10                  15

Ala Leu Leu Val Asp Val Tyr Pro Ala Gly Val His Gly Leu Val Leu
            20                  25                  30

His Pro Gly Asp Arg Glu Lys Arg Glu Ser Leu Cys Pro Gln Gly Lys
        35                  40                  45

Tyr Ser His Pro Gln Asn Arg Ser Ile Cys Cys Thr Lys Cys His Lys
    50                  55                  60

Gly Thr Tyr Leu His Asn Asp Cys Leu Gly Pro Gly Leu Asp Thr Asp
65                  70                  75                  80

Cys Arg Glu Cys Asp Asn Gly Thr Phe Thr Ala Ser Glu Asn His Leu
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                85                  90                  95

Thr Gln Cys Leu Ser Cys Ser Lys Cys Arg Ser Glu Met Ser Gln Val
            100                 105                 110

Glu Ile Ser Pro Cys Thr Val Asp Arg Asp Thr Val Cys Gly Cys Arg
        115                 120                 125

Lys Asn Gln Tyr Arg Lys Tyr Trp Ser Glu Thr Leu Phe Gln Cys Leu
    130                 135                 140

Asn Cys Ser Leu Cys Pro Asn Gly Thr Val Gln Leu Pro Cys Leu Glu
145                 150                 155                 160

Lys Gln Asp Thr Ile Cys Asn Cys His Ser Gly Phe Phe Leu Arg Asp
                165                 170                 175

Lys Glu Cys Val Ser Cys Val Asn Cys Lys Asn Ala Asp Cys Lys Asn
            180                 185                 190

Leu Cys Pro Ala Thr Ser Glu Thr Arg Asn Asp Phe Gln Asp Thr Gly
        195                 200                 205

Thr Thr Val Leu Leu Pro Leu Val Ile Phe Phe Gly Leu Cys Leu Ala
    210                 215                 220

Phe Phe Leu Phe Val Gly Leu Ala Cys Arg Tyr Gln Arg Trp Lys Pro
225                 230                 235                 240

Lys Leu Tyr Ser Ile Ile Cys Gly Lys Ser Thr Pro Val Lys Glu Gly
                245                 250                 255

Glu Pro Glu Pro Leu Ala Thr Ala Pro Ser Phe Gly Pro Ile Thr Thr
            260                 265                 270

Phe Ser Pro Ile Pro Ser Phe Ser Pro Thr Thr Thr Phe Ser Pro Val
        275                 280                 285

Pro Ser Phe Ser Pro Ile Ser Ser Pro Thr Phe Thr Pro Cys Asp Trp
    290                 295                 300

Ser Asn Ile Lys Val Thr Ser Pro Pro Lys Glu Ile Ala Pro Pro Pro
305                 310                 315                 320

Gln Gly Ala Gly Pro Ile Leu Pro Met Pro Pro Ala Ser Thr Pro Val
                325                 330                 335

Pro Thr Pro Leu Pro Lys Trp Gly Gly Ser Ala His Ser Ala His Ser
            340                 345                 350

Ala Pro Ala Gln Leu Ala Asp Ala Asp Pro Ala Thr Leu Tyr Ala Val
        355                 360                 365

Val Asp Gly Val Pro Pro Thr Arg Trp Lys Glu Phe Val Arg Arg Leu
    370                 375                 380

Gly Leu Ser Glu His Glu Ile Glu Arg Leu Glu Leu Gln Asn Gly Arg
385                 390                 395                 400

Cys Leu Arg Glu Ala Gln Tyr Ser Met Leu Ala Glu Trp Arg Arg Arg
                405                 410                 415

Thr Ser Arg Arg Glu Ala Thr Leu Glu Leu Leu Gly Ser Val Leu Arg
            420                 425                 430

Asp Met Asp Leu Leu Gly Cys Leu Glu Asp Ile Glu Glu Ala Leu Arg
        435                 440                 445

Gly Pro Ala Arg Leu Ala Pro Ala Pro His Leu Leu Arg
    450                 455                 460
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<210> SEQ ID NO 102
<211> LENGTH: 461
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

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<400> SEQUENCE: 102

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Met Gly Leu Pro Ile Val Pro Gly Leu Leu Leu Ser Leu Val Leu Leu
1               5                   10                  15

Ala Leu Leu Met Gly Ile His Pro Ser Gly Val Thr Gly Leu Val Pro
            20                  25                  30

Ser Leu Gly Asp Arg Glu Lys Arg Asp Asn Leu Cys Pro Gln Gly Lys
        35                  40                  45

Tyr Ala His Pro Lys Asn Asn Ser Ile Cys Cys Thr Lys Cys His Lys
    50                  55                  60

Gly Thr Tyr Leu Val Ser Asp Cys Pro Ser Pro Gly Gln Glu Thr Val
65                  70                  75                  80

Cys Glu Val Cys Asp Lys Gly Thr Phe Thr Ala Ser Gln Asn His Val
                85                  90                  95

Arg Gln Cys Leu Ser Cys Lys Thr Cys Arg Lys Glu Met Phe Gln Val
            100                 105                 110

Glu Ile Ser Pro Cys Lys Ala Asp Met Asp Thr Val Cys Gly Cys Lys
        115                 120                 125

Lys Asn Gln Phe Gln Arg Tyr Leu Ser Glu Thr His Phe Gln Cys Val
    130                 135                 140

Asp Cys Ser Pro Cys Phe Asn Gly Thr Val Thr Ile Pro Cys Lys Glu
145                 150                 155                 160

Lys Gln Asn Thr Val Cys Asn Cys His Ala Gly Phe Phe Leu Ser Gly
                165                 170                 175

Asn Glu Cys Thr Pro Cys Ser His Cys Lys Lys Asn Gln Glu Cys Met
            180                 185                 190

Lys Leu Cys Leu Pro Pro Val Ala Asn Val Thr Asn Pro Gln Asp Ser
        195                 200                 205

Gly Thr Ala Val Leu Leu Pro Leu Val Ile Phe Leu Gly Leu Cys Leu
    210                 215                 220

Leu Phe Phe Ile Cys Ile Ser Leu Leu Cys Arg Tyr Pro Gln Trp Arg
225                 230                 235                 240

Pro Arg Val Tyr Ser Ile Ile Cys Arg Asp Ser Ala Pro Val Lys Glu
                245                 250                 255

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

Pro Ala Phe Ser Pro Asn Pro Gly Phe Asn Pro Thr Leu Gly Phe Ser
        275                 280                 285

Thr Thr Pro Arg Phe Ser His Pro Val Ser Ser Thr Pro Ile Ser Pro
    290                 295                 300

Val Phe Gly Pro Ser Asn Trp His Asn Phe Val Pro Pro Val Arg Glu
305                 310                 315                 320

Val Val Pro Thr Gln Gly Ala Asp Pro Leu Leu Tyr Gly Ser Leu Asn
                325                 330                 335

Pro Val Pro Ile Pro Ala Pro Val Arg Lys Trp Glu Asp Val Val Ala
            340                 345                 350

Ala Gln Pro Gln Arg Leu Asp Thr Ala Asp Pro Ala Met Leu Tyr Ala
        355                 360                 365

Val Val Asp Gly Val Pro Pro Thr Arg Trp Lys Glu Phe Met Arg Leu
    370                 375                 380

Leu Gly Leu Ser Glu His Glu Ile Glu Arg Leu Glu Leu Gln Asn Gly
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```
385                 390                 395                 400

Arg Cys Leu Arg Glu Ala His Tyr Ser Met Leu Glu Ala Trp Arg Arg
                405                 410                 415

Arg Thr Pro Arg His Glu Ala Thr Leu Asp Val Val Gly Arg Val Leu
            420                 425                 430

Cys Asp Met Asn Leu Arg Gly Cys Leu Glu Asn Ile Arg Glu Thr Leu
        435                 440                 445

Glu Ser Pro Ala His Ser Ser Thr Thr His Leu Pro Arg
    450                 455                 460


<210> SEQ ID NO 103
<211> LENGTH: 454
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 103

Met Gly Leu Pro Thr Val Pro Gly Leu Leu Leu Ser Leu Val Leu Leu
1               5                   10                  15

Ala Leu Leu Met Gly Ile His Pro Ser Gly Val Thr Gly Leu Val Pro
            20                  25                  30

Ser Leu Gly Asp Arg Glu Lys Arg Asp Ser Leu Cys Pro Gln Gly Lys
        35                  40                  45

Tyr Val His Ser Lys Asn Asn Ser Ile Cys Cys Thr Lys Cys His Lys
    50                  55                  60

Gly Thr Tyr Leu Val Ser Asp Cys Pro Ser Pro Gly Arg Asp Thr Val
65                  70                  75                  80

Cys Arg Glu Cys Glu Lys Gly Thr Phe Thr Ala Ser Gln Asn Tyr Leu
                85                  90                  95

Arg Gln Cys Leu Ser Cys Lys Thr Cys Arg Lys Glu Met Ser Gln Val
            100                 105                 110

Glu Ile Ser Pro Cys Gln Ala Asp Lys Asp Thr Val Cys Gly Cys Lys
        115                 120                 125

Glu Asn Gln Phe Gln Arg Tyr Leu Ser Glu Thr His Phe Gln Cys Val
    130                 135                 140

Asp Cys Ser Pro Cys Phe Asn Gly Thr Val Thr Ile Pro Cys Lys Glu
145                 150                 155                 160

Thr Gln Asn Thr Val Cys Asn Cys His Ala Gly Phe Phe Leu Arg Glu
                165                 170                 175

Ser Glu Cys Val Pro Cys Ser His Cys Lys Lys Asn Glu Glu Cys Met
            180                 185                 190

Lys Leu Cys Leu Pro Pro Pro Leu Ala Asn Val Thr Asn Pro Gln Asp
        195                 200                 205

Ser Gly Thr Ala Val Leu Leu Pro Leu Val Ile Leu Leu Gly Leu Cys
    210                 215                 220

Leu Leu Ser Phe Ile Phe Ile Ser Leu Met Cys Arg Tyr Pro Arg Trp
225                 230                 235                 240

Arg Pro Glu Val Tyr Ser Ile Ile Cys Arg Asp Pro Val Pro Val Lys
                245                 250                 255

Glu Glu Lys Ala Gly Lys Pro Leu Thr Pro Ala Pro Ser Pro Ala Phe
            260                 265                 270

Ser Pro Thr Ser Gly Phe Asn Pro Thr Leu Gly Phe Ser Thr Pro Gly
        275                 280                 285
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Phe Ser Ser Pro Val Ser Ser Thr Pro Ile Ser Pro Ile Phe Gly Pro
    290                 295                 300

Ser Asn Trp His Phe Met Pro Pro Val Ser Glu Val Val Pro Thr Gln
305                 310                 315                 320

Gly Ala Asp Pro Leu Leu Tyr Glu Ser Leu Cys Ser Val Pro Ala Pro
                325                 330                 335

Thr Ser Val Gln Lys Trp Glu Asp Ser Ala His Pro Gln Arg Pro Asp
            340                 345                 350

Asn Ala Asp Leu Ala Ile Leu Tyr Ala Val Val Asp Gly Val Pro Pro
        355                 360                 365

Ala Arg Trp Lys Glu Phe Met Arg Phe Met Gly Leu Ser Glu His Glu
    370                 375                 380

Ile Glu Arg Leu Glu Met Gln Asn Gly Arg Cys Leu Arg Glu Ala Gln
385                 390                 395                 400

Tyr Ser Met Leu Glu Ala Trp Arg Arg Arg Thr Pro Arg His Glu Asp
                405                 410                 415

Thr Leu Glu Val Val Gly Leu Val Leu Ser Lys Met Asn Leu Ala Gly
            420                 425                 430

Cys Leu Glu Asn Ile Leu Glu Ala Leu Arg Asn Pro Ala Pro Ser Ser
        435                 440                 445

Thr Thr Arg Leu Pro Arg
    450


<210> SEQ ID NO 104
<211> LENGTH: 300
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 104

atgacttcca agctggccgt ggctctcttg gcagccttcc tgatttctgc agctctgtgt     60

gaaggtgcag ttttgccaag gagtgctaaa gaacttagat gtcagtgcat aaagacatac    120

tccaaacctt tccaccccaa atttatcaaa gaactgagag tgattgagag tggaccacac    180

tgcgccaaca cagaaattat tgtaaagctt tctgatggaa gagagctctg tctggacccc    240

aaggaaaact gggtgcagag ggttgtggag aagtttttga agagggctga gaattcataa    300


<210> SEQ ID NO 105
<211> LENGTH: 317
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 105

Met Arg Arg Ala Ser Arg Asp Tyr Thr Lys Tyr Leu Arg Gly Ser Glu
1               5                   10                  15

Glu Met Gly Gly Gly Pro Gly Ala Pro His Glu Gly Pro Leu His Ala
            20                  25                  30

Pro Pro Pro Pro Ala Pro His Gln Pro Pro Ala Ala Ser Arg Ser Met
        35                  40                  45

Phe Val Ala Leu Leu Gly Leu Gly Leu Gly Gln Val Val Cys Ser Val
    50                  55                  60

Ala Leu Phe Phe Tyr Phe Arg Ala Gln Met Asp Pro Asn Arg Ile Ser
65                  70                  75                  80

Glu Asp Gly Thr His Cys Ile Tyr Arg Ile Leu Arg Leu His Glu Asn
                85                  90                  95
```

-continued

Ala Asp Phe Gln Asp Thr Thr Leu Glu Ser Gln Asp Thr Lys Leu Ile
100 105 110

Pro Asp Ser Cys Arg Arg Ile Lys Gln Ala Phe Gln Gly Ala Val Gln
115 120 125

Lys Glu Leu Gln His Ile Val Gly Ser Gln His Ile Arg Ala Glu Lys
130 135 140

Ala Met Val Asp Gly Ser Trp Leu Asp Leu Ala Lys Arg Ser Lys Leu
145 150 155 160

Glu Ala Gln Pro Phe Ala His Leu Thr Ile Asn Ala Thr Asp Ile Pro
165 170 175

Ser Gly Ser His Lys Val Ser Leu Ser Ser Trp Tyr His Asp Arg Gly
180 185 190

Trp Ala Lys Ile Ser Asn Met Thr Phe Ser Asn Gly Lys Leu Ile Val
195 200 205

Asn Gln Asp Gly Phe Tyr Tyr Leu Tyr Ala Asn Ile Cys Phe Arg His
210 215 220

His Glu Thr Ser Gly Asp Leu Ala Thr Glu Tyr Leu Gln Leu Met Val
225 230 235 240

Tyr Val Thr Lys Thr Ser Ile Lys Ile Pro Ser Ser His Thr Leu Met
245 250 255

Lys Gly Gly Ser Thr Lys Tyr Trp Ser Gly Asn Ser Glu Phe His Phe
260 265 270

Tyr Ser Ile Asn Val Gly Gly Phe Phe Lys Leu Arg Ser Gly Glu Glu
275 280 285

Ile Ser Ile Glu Val Ser Asn Pro Ser Leu Leu Asp Pro Asp Gln Asp
290 295 300

Ala Thr Tyr Phe Gly Ala Phe Lys Val Arg Asp Ile Asp
305 310 315

<210> SEQ ID NO 106
<211> LENGTH: 316
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 106

Met Arg Arg Ala Ser Arg Asp Tyr Gly Lys Tyr Leu Arg Ser Ser Glu
1 5 10 15

Glu Met Gly Ser Gly Pro Gly Val Pro His Glu Gly Pro Leu His Pro
20 25 30

Ala Pro Ser Ala Pro Ala Pro Ala Pro Pro Pro Ala Ala Ser Arg Ser
35 40 45

Met Phe Leu Ala Leu Leu Gly Leu Gly Leu Gly Gln Val Val Cys Ser
50 55 60

Ile Ala Leu Phe Leu Tyr Phe Arg Ala Gln Met Asp Pro Asn Arg Ile
65 70 75 80

Ser Glu Asp Ser Thr His Cys Phe Tyr Arg Ile Leu Arg Leu His Glu
85 90 95

Asn Ala Gly Leu Gln Asp Ser Thr Leu Glu Ser Glu Asp Thr Leu Pro
100 105 110

Asp Ser Cys Arg Arg Met Lys Gln Ala Phe Gln Gly Ala Val Gln Lys
115 120 125

Glu Leu Gln His Ile Val Gly Pro Gln Arg Phe Ser Gly Ala Pro Ala

-continued

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    130                 135                 140

Met Met Glu Gly Ser Trp Leu Asp Val Ala Gln Arg Gly Lys Pro Glu
145                 150                 155                 160

Ala Gln Pro Phe Ala His Leu Thr Ile Asn Ala Ala Ser Ile Pro Ser
                165                 170                 175

Gly Ser His Lys Val Thr Leu Ser Ser Trp Tyr His Asp Arg Gly Trp
            180                 185                 190

Ala Lys Ile Ser Asn Met Thr Leu Ser Asn Gly Lys Leu Arg Val Asn
        195                 200                 205

Gln Asp Gly Phe Tyr Tyr Leu Tyr Ala Asn Ile Cys Phe Arg His His
    210                 215                 220

Glu Thr Ser Gly Ser Val Pro Thr Asp Tyr Leu Gln Leu Met Val Tyr
225                 230                 235                 240

Val Val Lys Thr Ser Ile Lys Ile Pro Ser Ser His Asn Leu Met Lys
                245                 250                 255

Gly Gly Ser Thr Lys Asn Trp Ser Gly Asn Ser Glu Phe His Phe Tyr
            260                 265                 270

Ser Ile Asn Val Gly Gly Phe Phe Lys Leu Arg Ala Gly Glu Glu Ile
        275                 280                 285

Ser Ile Gln Val Ser Asn Pro Ser Leu Leu Asp Pro Asp Gln Asp Ala
    290                 295                 300

Thr Tyr Phe Gly Ala Phe Lys Val Gln Asp Ile Asp
305                 310                 315


<210> SEQ ID NO 107
<211> LENGTH: 318
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 107

Met Arg Arg Ala Asn Arg Asp Tyr Gly Lys Tyr Leu Arg Gly Ser Glu
1               5                   10                  15

Glu Met Gly Ser Cys Pro Gly Val Pro His Glu Gly Pro Leu His Pro
            20                  25                  30

Ala Pro Ser Ala Pro Ala Pro Ala Pro Pro Pro Ala Ala Ser Arg Phe
        35                  40                  45

Met Phe Leu Ala Leu Leu Gly Leu Gly Leu Gly Gln Val Val Cys Ser
    50                  55                  60

Ile Ala Leu Phe Leu Tyr Phe Arg Ala Gln Met Asp Pro Asn Arg Ile
65                  70                  75                  80

Ser Glu Asp Ser Thr Arg Cys Phe Tyr Arg Ile Leu Arg Leu Arg Glu
                85                  90                  95

Asn Thr Gly Leu Gln Asp Ser Thr Leu Glu Ser Glu Asp Thr Glu Ala
            100                 105                 110

Leu Pro Asp Ser Cys Arg Arg Met Lys Gln Ala Phe Gln Gly Ala Val
        115                 120                 125

Gln Arg Glu Leu Gln His Ile Val Gly Pro Gln Arg Phe Ser Gly Val
    130                 135                 140

Pro Ala Met Met Glu Gly Ser Trp Leu Asp Val Ala Arg Arg Gly Lys
145                 150                 155                 160

Pro Glu Ala Gln Pro Phe Ala His Leu Thr Ile Asn Ala Ala Asp Ile
                165                 170                 175
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Pro Ser Gly Ser His Lys Val Ser Leu Ser Ser Trp Tyr His Asp Arg
            180                 185                 190

Gly Trp Ala Lys Ile Ser Asn Met Thr Leu Ser Asn Gly Lys Leu Arg
        195                 200                 205

Val Asn Gln Asp Gly Phe Tyr Tyr Leu Tyr Ala Asn Ile Cys Phe Arg
    210                 215                 220

His His Glu Thr Ser Gly Ser Val Pro Ala Asp Tyr Leu Gln Leu Met
225                 230                 235                 240

Val Tyr Val Val Lys Thr Ser Ile Lys Ile Pro Ser Ser His Asn Leu
                245                 250                 255

Met Lys Gly Gly Ser Thr Lys Asn Trp Ser Gly Asn Ser Glu Phe His
            260                 265                 270

Phe Tyr Ser Ile Asn Val Gly Gly Phe Phe Lys Leu Arg Ala Gly Glu
        275                 280                 285

Glu Ile Ser Val Gln Val Ser Asn Pro Ser Leu Leu Asp Pro Asp Gln
    290                 295                 300

Asp Ala Thr Tyr Phe Gly Ala Phe Lys Val Gln Asp Ile Asp
305                 310                 315


<210> SEQ ID NO 108
<211> LENGTH: 616
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 108

Met Ala Pro Arg Ala Arg Arg Arg Arg Pro Leu Phe Ala Leu Leu Leu
1               5                   10                  15

Leu Cys Ala Leu Leu Ala Arg Leu Gln Val Ala Leu Gln Ile Ala Pro
            20                  25                  30

Pro Cys Thr Ser Glu Lys His Tyr Glu His Leu Gly Arg Cys Cys Asn
        35                  40                  45

Lys Cys Glu Pro Gly Lys Tyr Met Ser Ser Lys Cys Thr Thr Thr Ser
    50                  55                  60

Asp Ser Val Cys Leu Pro Cys Gly Pro Asp Glu Tyr Leu Asp Ser Trp
65                  70                  75                  80

Asn Glu Glu Asp Lys Cys Leu Leu His Lys Val Cys Asp Thr Gly Lys
                85                  90                  95

Ala Leu Val Ala Val Val Ala Gly Asn Ser Thr Thr Pro Arg Arg Cys
            100                 105                 110

Ala Cys Thr Ala Gly Tyr His Trp Ser Gln Asp Cys Glu Cys Cys Arg
        115                 120                 125

Arg Asn Thr Glu Cys Ala Pro Gly Leu Gly Ala Gln His Pro Leu Gln
    130                 135                 140

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

Asp Ala Phe Ser Ser Thr Asp Lys Cys Arg Pro Trp Thr Asn Cys Thr
                165                 170                 175

Phe Leu Gly Lys Arg Val Glu His His Gly Thr Glu Lys Ser Asp Ala
            180                 185                 190

Val Cys Ser Ser Ser Leu Pro Ala Arg Lys Pro Pro Asn Glu Pro His
        195                 200                 205

Val Tyr Leu Pro Gly Leu Ile Ile Leu Leu Leu Phe Ala Ser Val Ala
    210                 215                 220
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-continued

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Leu Val Ala Ala Ile Ile Phe Gly Val Cys Tyr Arg Lys Lys Gly Lys
225                 230                 235                 240

Ala Leu Thr Ala Asn Leu Trp His Trp Ile Asn Glu Ala Cys Gly Arg
                245                 250                 255

Leu Ser Gly Asp Lys Glu Ser Ser Gly Asp Ser Cys Val Ser Thr His
            260                 265                 270

Thr Ala Asn Phe Gly Gln Gln Gly Ala Cys Glu Gly Val Leu Leu Leu
        275                 280                 285

Thr Leu Glu Glu Lys Thr Phe Pro Glu Asp Met Cys Tyr Pro Asp Gln
    290                 295                 300

Gly Gly Val Cys Gln Gly Thr Cys Val Gly Gly Gly Pro Tyr Ala Gln
305                 310                 315                 320

Gly Glu Asp Ala Arg Met Leu Ser Leu Val Ser Lys Thr Glu Ile Glu
                325                 330                 335

Glu Asp Ser Phe Arg Gln Met Pro Thr Glu Asp Glu Tyr Met Asp Arg
            340                 345                 350

Pro Ser Gln Pro Thr Asp Gln Leu Leu Phe Leu Thr Glu Pro Gly Ser
        355                 360                 365

Lys Ser Thr Pro Pro Phe Ser Glu Pro Leu Glu Val Gly Glu Asn Asp
    370                 375                 380

Ser Leu Ser Gln Cys Phe Thr Gly Thr Gln Ser Thr Val Gly Ser Glu
385                 390                 395                 400

Ser Cys Asn Cys Thr Glu Pro Leu Cys Arg Thr Asp Trp Thr Pro Met
                405                 410                 415

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

His Trp Ala Ala Ser Pro Ser Pro Asn Trp Ala Asp Val Cys Thr Gly
        435                 440                 445

Cys Arg Asn Pro Pro Gly Glu Asp Cys Glu Pro Leu Val Gly Ser Pro
    450                 455                 460

Lys Arg Gly Pro Leu Pro Gln Cys Ala Tyr Gly Met Gly Leu Pro Pro
465                 470                 475                 480

Glu Glu Glu Ala Ser Arg Thr Glu Ala Arg Asp Gln Pro Glu Asp Gly
                485                 490                 495

Ala Asp Gly Arg Leu Pro Ser Ser Ala Arg Ala Gly Ala Gly Ser Gly
            500                 505                 510

Ser Ser Pro Gly Gly Gln Ser Pro Ala Ser Gly Asn Val Thr Gly Asn
        515                 520                 525

Ser Asn Ser Thr Phe Ile Ser Ser Gly Gln Val Met Asn Phe Lys Gly
    530                 535                 540

Asp Ile Ile Val Val Tyr Val Ser Gln Thr Ser Gln Glu Gly Ala Ala
545                 550                 555                 560

Ala Ala Ala Glu Pro Met Gly Arg Pro Val Gln Glu Glu Thr Leu Ala
                565                 570                 575

Arg Arg Asp Ser Phe Ala Gly Asn Gly Pro Arg Phe Pro Asp Pro Cys
            580                 585                 590

Gly Gly Pro Glu Gly Leu Arg Glu Pro Glu Lys Ala Ser Arg Pro Val
        595                 600                 605

Gln Glu Gln Gly Gly Ala Lys Ala
    610                 615
```

-continued

<210> SEQ ID NO 109
<211> LENGTH: 625
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 109

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Met Ala Pro Arg Ala Arg Arg Arg Arg Gln Leu Pro Ala Pro Leu Leu
1               5                   10                  15

Ala Leu Cys Val Leu Leu Val Pro Leu Gln Val Thr Leu Gln Val Thr
            20                  25                  30

Pro Pro Cys Thr Gln Glu Arg His Tyr Glu His Leu Gly Arg Cys Cys
        35                  40                  45

Ser Arg Cys Glu Pro Gly Lys Tyr Leu Ser Ser Lys Cys Thr Pro Thr
    50                  55                  60

Ser Asp Ser Val Cys Leu Pro Cys Gly Pro Asp Glu Tyr Leu Asp Thr
65                  70                  75                  80

Trp Asn Glu Glu Asp Lys Cys Leu Leu His Lys Val Cys Asp Ala Gly
                85                  90                  95

Lys Ala Leu Val Ala Val Asp Pro Gly Asn His Thr Ala Pro Arg Arg
            100                 105                 110

Cys Ala Cys Thr Ala Gly Tyr His Trp Asn Ser Asp Cys Glu Cys Cys
        115                 120                 125

Arg Arg Asn Thr Glu Cys Ala Pro Gly Phe Gly Ala Gln His Pro Leu
    130                 135                 140

Gln Leu Asn Lys Asp Thr Val Cys Thr Pro Cys Leu Leu Gly Phe Phe
145                 150                 155                 160

Ser Asp Val Phe Ser Ser Thr Asp Lys Cys Lys Pro Trp Thr Asn Cys
                165                 170                 175

Thr Leu Leu Gly Lys Leu Glu Ala His Gln Gly Thr Thr Glu Ser Asp
            180                 185                 190

Val Val Cys Ser Ser Ser Met Thr Leu Arg Arg Pro Pro Lys Glu Ala
        195                 200                 205

Gln Ala Tyr Leu Pro Ser Leu Ile Val Leu Leu Leu Phe Ile Ser Val
    210                 215                 220

Val Val Val Ala Ala Ile Ile Phe Gly Val Tyr Tyr Arg Lys Gly Gly
225                 230                 235                 240

Lys Ala Leu Thr Ala Asn Leu Trp Asn Trp Val Asn Asp Ala Cys Ser
                245                 250                 255

Ser Leu Ser Gly Asn Lys Glu Ser Ser Gly Asp Arg Cys Ala Gly Ser
            260                 265                 270

His Ser Ala Thr Ser Ser Gln Gln Glu Val Cys Glu Gly Ile Leu Leu
        275                 280                 285

Met Thr Arg Glu Glu Lys Met Val Pro Glu Asp Gly Ala Gly Val Cys
    290                 295                 300

Gly Pro Val Cys Ala Ala Gly Gly Pro Trp Ala Glu Val Arg Asp Ser
305                 310                 315                 320

Arg Thr Phe Thr Leu Val Ser Glu Val Glu Thr Gln Gly Asp Leu Ser
                325                 330                 335

Arg Lys Ile Pro Thr Glu Asp Glu Tyr Thr Asp Arg Pro Ser Gln Pro
            340                 345                 350

Ser Thr Gly Ser Leu Leu Leu Ile Gln Gln Gly Ser Lys Ser Ile Pro
        355                 360                 365
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Pro Phe Gln Glu Pro Leu Glu Val Gly Glu Asn Asp Ser Leu Ser Gln
    370                 375                 380

Cys Phe Thr Gly Thr Glu Ser Thr Val Asp Ser Glu Gly Cys Asp Phe
385                 390                 395                 400

Thr Glu Pro Pro Ser Arg Thr Asp Ser Met Pro Val Ser Pro Glu Lys
                405                 410                 415

His Leu Thr Lys Glu Ile Glu Gly Asp Ser Cys Leu Pro Trp Val Val
            420                 425                 430

Ser Ser Asn Ser Thr Asp Gly Tyr Thr Gly Ser Gly Asn Thr Pro Gly
        435                 440                 445

Glu Asp His Glu Pro Phe Pro Gly Ser Leu Lys Cys Gly Pro Leu Pro
    450                 455                 460

Gln Cys Ala Tyr Ser Met Gly Phe Pro Ser Glu Ala Ala Ala Ser Met
465                 470                 475                 480

Ala Glu Ala Gly Val Arg Pro Gln Asp Arg Ala Asp Glu Arg Gly Ala
                485                 490                 495

Ser Gly Ser Gly Ser Ser Pro Ser Asp Gln Pro Pro Ala Ser Gly Asn
            500                 505                 510

Val Thr Gly Asn Ser Asn Ser Thr Phe Ile Ser Ser Gly Gln Val Met
        515                 520                 525

Asn Phe Lys Gly Asp Ile Ile Val Val Tyr Val Ser Gln Thr Ser Gln
    530                 535                 540

Glu Gly Pro Gly Ser Ala Glu Pro Glu Ser Glu Pro Val Gly Arg Pro
545                 550                 555                 560

Val Gln Glu Glu Thr Leu Ala His Arg Asp Ser Phe Ala Gly Thr Ala
                565                 570                 575

Pro Arg Phe Pro Asp Val Cys Ala Thr Gly Ala Gly Leu Gln Glu Gln
            580                 585                 590

Gly Ala Pro Arg Gln Lys Asp Gly Thr Ser Arg Pro Val Gln Glu Gln
        595                 600                 605

Gly Gly Ala Gln Thr Ser Leu His Thr Gln Gly Ser Gly Gln Cys Ala
    610                 615                 620

Glu
625
```

What is claimed is:

1. A method for detecting the presence of a compound in a sample, comprising:

(a) providing, in any order:

(i) a sample suspected of comprising a compound and a control sample without the compound;

(ii) a receptor and a response gene; and

(iii) a ligand, wherein the ligand is capable of binding the receptor, thereby altering the expression of the response gene;

(b) combining, in any order, (i) the sample, the receptor, and the ligand;

and (ii) the control sample, the receptor and the ligand; and

(c) measuring the level of the expression of the response gene;

wherein the presence of the compound in the sample is detected by an alteration in the level of expression of the response gene when compared to the level of expression of the response gene when the receptor is combined with the ligand in the presence of the control sample.

2. A method for detecting the presence of a compound in the presence or absence of a sample, comprising:

(a) providing, in any order:

(i) a compound, wherein the compound is in the presence or absence of a sample;

(ii) a receptor and a response gene; and

(iii) a ligand, wherein the ligand is capable of binding the receptor, thereby altering the expression of the response gene;

(b) combining, in any order, (i) the compound, the receptor, and the ligand; and (ii) the receptor and the ligand; and

(c) measuring the level of the expression of the response gene, wherein the presence of the compound is measured by an alteration in the level of expression of the response gene when the receptor is combined with the ligand and the compound compared to the level of expression of the response gene when the receptor is combined with the ligand only; and wherein when the receptor is combined with varying concentrations of the ligand and the compound, the expression of the response gene in the presence of the sample is correlated with the expression of the response gene in the absence of the sample with a correlation coefficient of at least 0.5.

3. The method of claim 1, wherein the ligand is a therapeutic substance for administration to a subject.

4. The method of claim 3, wherein the compound is a neutralizing antibody against the therapeutic substance.

5. The method of any one of claims **1-4**, wherein the receptor comprises SEQ ID NO:1.

6. The method of any one of claims **1-4**, wherein the receptor comprises SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, or SEQ ID NO:5.

7. The method of claim 5, wherein the therapeutic substance comprises SEQ ID NO:6.

8. The method of claim 6, wherein the therapeutic substance comprises SEQ ID NO:6.

9. The method of claim 5, wherein the therapeutic substance comprises SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, or SEQ ID NO:14.

10. The method of claim 6, wherein the therapeutic substance comprises SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, or SEQ ID NO:14.

11. The method of claim 5, wherein the response gene comprises SEQ ID NO:15.

12. The method of claim 6, wherein the response gene comprises SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, or SEQ ID NO:21.

13. The method of any one of claims **1-4**, wherein the receptor comprises the extracellular domain of SEQ ID NO:80.

14. The method of any one of claims **1-4**, wherein the receptor comprises the extracellular domain of SEQ ID NO:81, SEQ ID NO:82, or SEQ ID NO:83.

15. The method of claim 13, wherein the ligand comprises SEQ ID NO:84.

16. The method of claim 14, wherein the ligand comprises SEQ ID NO:84.

17. The method of claim 13, wherein the ligand comprises SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, or SEQ ID NO:91.

18. The method of claim 14, wherein the ligand comprises SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, or SEQ ID NO:91.

19. The method of claim 13, wherein the response gene comprises SEQ ID NO:15.

20. The method of claim 14, wherein the response gene comprises SEQ ID NO:15.

21. The method of any one of claims **1-4**, wherein the receptor comprises the extracellular domain of SEQ ID NO:92.

22. The method of any one of claims **1-4**, wherein the receptor comprises the extracellular domain of SEQ ID NO:93 or SEQ ID NO:94.

23. The method of claim 21, wherein the ligand comprises SEQ ID NO:95.

24. The method of claim 22, wherein the ligand comprises SEQ ID NO:95.

25. The method of claim 21, wherein the ligand comprises SEQ ID NO:96 or SEQ ID NO:97.

26. The method of claim 22, wherein the ligand comprises SEQ ID NO:96 or SEQ ID NO:97.

27. The method of claim 21, wherein the response gene comprises SEQ ID NO:98.

28. The method of claim 22, wherein the response gene comprises SEQ ID NO:98.

28. The method of claim 21, wherein the response gene comprises SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, or SEQ ID NO:103.

29. The method of claim 23, wherein the response gene comprises SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, or SEQ ID NO:103.

30. The method of claim 21, wherein the response gene comprises SEQ ID NO:15.

31. The method of claim 22, wherein the response gene comprises SEQ ID NO:15.

32. The method of claim 23, wherein the response gene comprises SEQ ID NO:15.

33. The method of claim 24, wherein the response gene comprises SEQ ID NO:15.

34. The method of any one of claims **1-4**, wherein the ligand comprises SEQ ID NO:105, SEQ ID NO:106, or SEQ ID NO:107.

35. The method of claim 34, wherein the receptor comprises SEQ ID NO:108 or SEQ ID NO:109.

36. The method of claim 34, wherein the response gene is tartrate resistant acid phosphatase (TRAP).

37. The method of any one of claims **1-4**, wherein the ligand is an endogenous ligand, which is bound by a therapeutic substance for administration to a subject.

38. The method of any one of claims **1-4**, wherein the level of the expression of the response gene is measured using a bDNA assay.

39. The method of any of the claims **1-4**, wherein the sample is selected from the group consisting of whole blood, plasma, serum, synovial fluid, ascitic fluid, lacrimal fluid, perspiration, seminal fluid, cell extracts, and tissue extracts.

40. The method any one of claims **1-4**, wherein the receptor is expressed by a mammalian cell.

41. A kit comprising (a) a cell expressing a receptor, wherein the receptor comprises the intracellular domain of EPOR, and (b) one or more oligonucleotides used to detect PIM 1 gene expression, the oligonucleotides selected from the group consisting of SEQ ID NOs:22 through 79.

* * * * *

patsnap

专利名称(译)	检测影响治疗活性的化合物
公开(公告)号	US20060211022A1
公开(公告)日	2006-09-21
申请号	US11/361415
申请日	2006-02-23
[标]申请(专利权)人(译)	安姆根有限公司
申请(专利权)人(译)	安进公司.
当前申请(专利权)人(译)	安进公司.
[标]发明人	JING SHUQIAN CIVOLI FRANCESCA GUPTA SHALINI HALPERIN DANIEL STEVEN PENNUCCI JASON JOSEPH SWANSON STEVEN YU YAN BIN
发明人	JING, SHUQIAN CIVOLI, FRANCESCA GUPTA, SHALINI HALPERIN, DANIEL STEVEN PENNUCCI, JASON JOSEPH SWANSON, STEVEN YU, YAN BIN
IPC分类号	C12Q1/68 G01N33/53
CPC分类号	G01N33/5008 G01N33/5011 G01N33/5023 G01N33/5308 G01N33/564 G01N33/566 G01N33/6854
优先权	60/656696 2005-02-24 US
外部链接	Espacenet USPTO

摘要(译)

本发明涉及检测影响施用于受试者的治疗物质或组合物的活性的化合物的方法，以及用于这些方法的试剂。

FIG. 1A

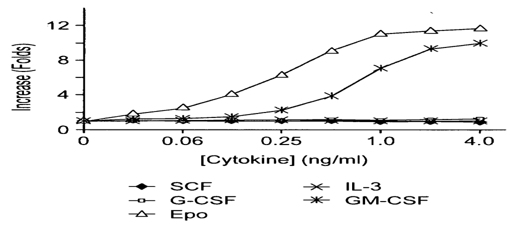

FIG. 1B