VARIANT ACTIVIN RECEPTOR POLYPEPTIDES AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of United States provisional application serial number 61/065,474, filed February 11, 2008, and United States provisional application serial number 60/905,459, filed March 6, 2007, the disclosures of which are relied upon and incorporated by reference herein.

TECHNICAL FIELD OF THE INVENTION

The technical field of this invention relates to transforming growth factor-β (TGF-β) family members and soluble TGF-β receptors, as well as methods of modulating the activities of TGF-β family members for the treatment of various disorders.

BACKGROUND OF THE INVENTION

The transforming growth factor β (TGF-β) family of proteins includes the transforming growth factors-β (TGF-β), activins, bone morphogenic proteins (BMP), nerve growth factors (NGFs), brain-derived neurotrophic factor (BDNF), and growth/differentiation factors (GDFs). These family members are involved in the regulation of a wide range of biological processes including cell proliferation, differentiation, and other functions.

Growth/differentiation factor 8 (GDF-8), also referred to as myostatin, is a TGF-ß family member expressed for the most part in the cells of developing and adult skeletal muscle tissue. Myostatin appears to play an essential role in negatively controlling skeletal muscle growth (McPherron et al., Nature (London) 387, 83-90 (1997)). Antagonizing myostatin has been shown to increase lean muscle mass in animals (McFerron et al., supra, Zimmers et al., Science 296:1486 (2002)).

Another member of the TGF-β family of proteins is a related growth/differentiation factor, GDF-11. GDF-11 has approximately 90% identity of the amino acid sequence of myostatin. GDF-11 has a role in the axial patterning in developing animals (Oh et al, Genes Dev 11:1812-26 (1997)), and also appears to play a role in skeletal muscle development and growth.

Activins A, B and AB are the homodimers and heterdimer respectively of two polypeptide chains, ßA and ßB (Vale et al. Nature 321, 776-779 (1986), Ling et al., Nature

321, 779-782 (1986)). Activins were originally discovered as gonadal peptides involved in the regulation of follicle stimulating hormone synthesis, and are now believed to be involved in the regulation of a number of biological activities. Activin A is a predominant form of activin.

Activin, myostatin, GDF-11 and other members of the TGF- β superfamily bind and signal through a combination of activin type II and activin type IIB receptors, both of which are transmembrane serine/threonine kinases (Harrison et al., J. Biol. Chem. 279, 28036-28044 (2004)). Cross-linking studies have determined that myostatin is capable of binding the activin type II receptors ActRIIA and ActRIIB *in vitro* (Lee et al., PNAS USA 98:9306-11 (2001)). There is also evidence that GDF-11 binds to both ActRIIA and ActRIIB (Oh et al., Genes Dev 16:2749-54 (2002)).

TGF-β protein expression is known to be associated with a variety of diseases and disorders. Therefore, therapeutic molecules capable of antagonizing several TGF-β proteins simultaneously may be particularly effective for these diseases and disorders.

In addition, the production of protein therapeutics can be complicated by problems occuring during the expression and purification of the protein. One problem is the aggregation of proteins during expression or purification. The accumulation of high levels of protein during cell culture conditions may lead to aggregation. Purification processes may expose to the protein to additional factors promoting further aggregation (Cromwell, M.E.M. *et al.*, The AAPS Journal 8:E572-E579, 2006). Attempts can be made to mitigate the factors that cause aggregation, however, a need exists for proteins designed to have a decreased tendency to form aggregates. The present invention fulfills the need for therapeutic molecules that bind to multiple ligands, and have reduced aggregation and thus improved manufacturability, in order to efficiently produce proteins useful for treating TGF-β related disease states.

SUMMARY OF THE INVENTION

In a first aspect the present invention is directed to an isolated protein comprising a variant activin IIB receptor polypeptide (vActRIIB) wherein said polypeptide is selected from the group consisting of:

(a) a polypeptide having the polypeptide sequence set forth in SEQ ID NO: 18, except for a single amino acid substitution at position 28, wherein the substitution is selected from any one of A, F, Q, V, I, L, M, K, H, W and Y for E;

(b) a polypeptide having the polypeptide sequence set forth in amino acids 19 through 134 of SEQ ID NO: 18, except for a single amino acid substitution at position 28, wherein the substitution is selected from any one of A, F, Q, V, I, L, M, K, H, W and Y for E;

(c) a polypeptide having the polypeptide sequence set forth in amino acids 23 through 134 of SEQ ID NO: 18, except for a single amino acid substitution at position 28, wherein the substitution is selected from any one of A, F, Q, V, I, L, M, K, H, W and Y for E;

(d) a polypeptide having the polypeptide sequence set forth in amino acids 25 through 134 of SEQ ID NO: 18, except for a single amino acid substitution at position 28, wherein the substitution is selected from any one of A, F, Q, V, I, L, M, K, H, W and Y for E;

(e) a polypeptide having at least 90% identity to any one of (a) through (d), wherein the substitution at position 28 is selected from any one of A, F, Q, V, I, L, M, K, H, W and Y for E, and wherein the polypeptide is capable of binding myostatin, activin A, or GDF-11.

In a second aspect the present invention is directed to an isolated protein comprising a variant activin IIB receptor polypeptide (vActRIIB) wherein said polypeptide is selected from the group consisting of:

(a) a polypeptide having the polypeptide sequence set forth in SEQ ID NO: 2, except for a single amino acid substitution at position 28, wherein the substitution is selected from any one of A, F, Q, V, I, L, M, K, H, W and Y for E;

(b) a polypeptide having the polypeptide sequence set forth in amino acids 19 through 160 of SEQ ID NO: 2, except for a single amino acid substitution at position 28, wherein the substitution is selected from any one of A, F, Q, V, I, L, M, K, H, W and Y for E;

(c) a polypeptide having the polypeptide sequence set forth in amino acids 23 through 160 of SEQ ID NO: 2, except for a single amino acid substitution at position 28, wherein the substitution is selected from any one of A, F, Q, V, I, L, M, K, H, W and Y for E;

(d) a polypeptide having the polypeptide sequence set forth in amino acids 25 through 160 of SEQ ID NO: 2, except for a single amino acid substitution at position 28, wherein the substitution is selected from any one of A, F, Q, V, I, L, M, K, H, W and Y for E;

(e) a polypeptide having at least 90% identity to any one of (a) through (c), wherein the substitution at position 28 is selected from any one of A, F, Q, V, I, L, M, K, H, W and Y for E, and wherein the polypeptide is capable of binding myostatin, activin A, or GDF-11.

In a third aspect the present invention is directed to an isolated protein comprising a variant activin IIB receptor polypeptide (vActRIIB) wherein said polypeptide is selected from the group consisting of:

(a) a polypeptide having the polypeptide sequence set forth in SEQ ID NO: 2, or SEQ ID NO: 18, except for a single amino acid substitution at position 28, wherein the substitution is selected from one of A, F, Q, V, I, L, M, K, H, W and Y for E, and a single amino acid substitution at position 40, wherein the substitution is selected from A, G, Q, M, H, K and N for R;

(b) a polypeptide having the polypeptide sequence set forth in amino acids 19 through 160 of SEQ ID NO: 2, or 19 through 134 of SEQ ID NO: 18, except for a single amino acid substitution at position 28, wherein the substitution is selected from one of A, F, Q, V, I, L, M, K, H, W and Y for E, and a single amino acid substitution at position 40, wherein the substitution is selected from A, G, Q, M, H, K and N for R;

(c) a polypeptide having the polypeptide sequence set forth in amino acids 23 through 160 of SEQ ID NO: 2, or 23 through 134 of SEQ ID NO: 18, except for a single amino acid substitution at position 28, wherein the substitution is selected from one of A, F, Q, V, I, L, M, K, H, W and Y for E, and a single amino acid substitution at position 40, wherein the substitution is selected from A, G, Q, M, H, K and N for R;

(d) a polypeptide having the polypeptide sequence set forth in amino acids 25 through 160 of SEQ ID NO: 2, or 25 through 134 for SEQ ID NO: 18, except for a single amino acid substitution at position 28, wherein the substitution is selected from one of A,

F, Q, V, I, L, M, K, H, W and Y for E, and a single amino acid substitution at position 40, wherein the substitution is selected from A, G, Q, M, H, K and N for R;

(e) a polypeptide having at least 90% identity to any one of (a) through (d), wherein the substitution at position 28 is selected from any one of A, F, Q, V, I, L, M, K, H, W and Y for E, and wherein the substitution at position 40 is selected from a single amino acid substitution at position 40, wherein the substitution is selected from A, G, Q, M, H, K and N for R, and wherein the polypeptide is capable of binding myostatin, activin A, or GDF-11.

In a fourth aspect the present invention is directed to an isolated protein comprising a variant activin IIB receptor polypeptide (vActRIIB) wherein said polypeptide is selected from the group consisting of:

(a) a polypeptide having the polypeptide sequence set forth in SEQ ID NO: 2, or SEQ ID NO: 18, except for a single amino acid substitution at position 40, wherein the substitution is selected from A, G, Q, M, H, K and N for R;

(b) a polypeptide having the polypeptide sequence set forth in amino acids 19 through 160 of SEQ ID NO: 2, or 19 through 134 of SEQ ID NO: 18, except for a single amino acid substitution at position 40, wherein the substitution is selected from A, G, Q, M, H, K and N for R;

(c) a polypeptide having the polypeptide sequence set forth in amino acids 23 through 160 of SEQ ID NO: 2, or 23 through 134 for SEQ ID NO: 18, except for a single amino acid substitution at position 40, wherein the substitution is selected from A, G, Q, M, H, K and N for R;

(d) a polypeptide having the polypeptide sequence set forth in amino acids 25 through 160 of SEQ ID NO: 2, or 25 through 134 for SEQ ID NO: 18, except for a single amino acid substitution at position 40, wherein the substitution is selected from A, G, Q, M, H, K and N for R;

(e) a polypeptide having at least 90% identity to any one of (a) through (d), wherein the substitution at position 40 is selected from A, G, Q, M, H, K and N for R, and wherein the polypeptide is capable of binding myostatin, activin A, or GDF-11.

In a fifth aspect the present invention is directed to a pharmaceutical composition comprising an effective amount of the protein of the present invention in admixture with a pharmaceutically acceptable carrier.

In a sixth aspect the present invention is directed to an isolated nucleic acid molecule comprised a polynucleotide encoding the protein of the present invention.

In a seventh aspect the present invention is directed to an isolated nucleic acid molecule comprising a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the sequence selected from the group consisting of SEQ ID NO: 19, 23, 25, 27, 33, 37, 39, 41, 59, 61, 63, 92, 94, and 96, or its complement, and

(b) a polynucleotide encoding a polypeptide having the sequence selected from the group consisting of SEQ ID NO: 20, 24, 26, 28, 34, 38, 40, 42, 60, 62, 64, 87, 88, 91, 93, 95, and 97.

In an eighth aspect the present invention is directed to a recombinant expression vector comprising the nucleic acids of the present invention.

In a ninth aspect the present invention is directed to a recombinant host cell comprising the vector of the present invention.

In a tenth aspect the present invention is directed to a method of producing the protein of the present invention, comprising culturing the host cell of the present invention, thereby expressing the protein.

In an eleventh aspect the present invention is directed to the use of the protein of the present invention or the composition of the present invention in the manufacture of a medicament for treating a subject in need of myostatin inhibition.

In a twelfth aspect the present invention is directed to the use of the protein of the present invention or the composition of the present invention in the manufacture of a medicament for treating a subject in need of increasing lean muscle mass or increasing the ratio of lean muscle mass to fat mass.

In a thirteenth aspect the present invention is directed to the use of the protein of the present invention or the composition of the present invention in the manufacture of a medicament for treating a metabolic disorder in a subject in need of such treatment.

In a fourteenth aspect the present invention is directed to the use of the protein of the present invention or the composition of the present invention in the manufacture of a medicament for treating a disease in which activin is over-expressed in a subject in need of such treatment.

In a fifteenth aspect the present invention is directed to the use of the vector of the present invention in the manufacture of a medicament for treating a muscle wasting disorder or metabolic disorder in a subject in need of such a treatment, wherein the vector is capable of directing expression of vActRIIB polypeptides in the subject.

Also described herein is an isolated protein comprising a variant human activin receptor IIB (designated vActRIIB) polypeptide. As used herein the term vActRIIB polypeptide refers to both human vActRIIB polypeptides and human vActRIIB5 polypeptides. In one embodiment, the protein comprises a polypeptide having an amino acid sequence of SEQ ID NO: 2 or 18 in which amino acids at either position E28 or R40, or both position E28 and R40 are substituted with another non-native amino acid, and

wherein the polypeptide is capable of binding myostatin, activin A, or GDF-11. In one embodiment the protein comprises a polypeptide having an amino acid sequence of SEQ ID NO: 2 or 18 in which the amino acids at positions E28 or R40, or both E28 and R40 are substituted with a non-native amino acid, and wherein the signal peptide is removed, and wherein the polypeptide is capable of binding myostatin, activin A, or GDF-11. In one embodiment the protein comprises a polypeptide having an amino acid sequence of SEQ ID NO: 2 or 18 in which amino acids at positions E28 or R40, or both E28 and R40 are substituted with another amino acid, wherein the signal sequence is removed, and N-terminal of the mature polypeptide is truncated, and wherein the polypeptide is capable of binding myostatin, activin A, or GDF-11. In one embodiment the N-terminal mature truncated vActRIIB polypeptide lacks the N-terminal four amino acids or the N-terminal six amino acids of the mature sequence, wherein the polypeptide is capable of binding myostatin, activin A, or GDF-11. In one embodiment, the substitution at position E28 is selected from the group consisting of W, Y and A. In a further embodiment, the substitution at position E28 is selected from the group of amino acids consisting of A, F, Q, V, I, L, M, K, H, W and Y. In a further embodiment, the substitution at position R40 is selected from the group of amino acids consisting of G, Q, M, H, K and N. In a further embodiment the substitution at position E28 is selected from the group of amino acids consisting of A, F, Q, V, I, L, M, K, H, W and Y and the substitution at position R40 is selected from the group of amino acids consisting of A, G, Q, M, H, K and N. In a further embodiment the polypeptide further comprises a heterologous protein. In one embodiment, the heterologous protein is an Fc domain. In a further embodiment, the Fc domain is a human IgG Fc domain.

In one embodiment, the protein comprises polypeptides having an amino acid sequence set forth in SEQ ID NO: 4, 6, 8, 10, 12, 14, 16, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 52, 54, 56, 60, 62, 64, 66, 70, 72, 87, 88, 91, 93, 95, and 97.

In another embodiment, the protein comprises a polypeptide encoded by the polynucleotide having the sequence set forth in SEQ ID NO: 3, 5, 7, 9, 11, 13, 15, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 51, 53, 55, 59, 61, 63, 65, 67, 69, 71, 92, 94, 96 or its complement.

In another aspect the present invention provides an isolated nucleic acid molecule comprising a polynucleotide encoding a vActRIIB polypeptide. In one embodiment, the nucleic acid molecule comprises a polynucleotide having the nucleic acid sequence set

forth in SEQ ID NO: 3, 5, 7, 9, 11, 13, 15, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 51, 53, 55, 59, 61, 63, 65, 69, 71, 92, 94, 96 or its complement.

In another embodiment, the nucleic acid molecule comprises a polynucleotide encoding a polypeptide consisting of the amino acid sequence set forth in the group consisting of SEQ ID NO: 4, 6, 8, 10, 12, 14, 16, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 52, 54, 56, 60, 62, 64, 66, 68, 70, 72, 87, 88, 91, 93, 95, and 97. In a further embodiment, the nucleic acid molecule further comprises a transcriptional or translational regulatory sequence. In another example a recombinant vector comprising the vActRIIB nucleic acid molecule is provided. In another example, host cells comprising the recombinant vectors are provided, and methods of producing the vActRIIB polypeptides are provided.

Also described herein is a composition containing at least one vActRIIB polypeptide or protein described herein. In one embodiment, the composition is a pharmaceutical composition containing the vActRIIB polypeptide or protein in admixture with a pharmaceutically acceptable carrier.

In another example, it is described a method of treating or preventing a muscle wasting disease in a subject suffering from such a disorder by administering a therapeutic composition containing a vActRIIB polypeptide or protein to the subject. The muscle wasting disease includes or results from, but is not limited to, the following conditions: cancer cachexia, muscular dystrophy, amyotrophic lateral sclerosis, congestive obstructive pulmonary disease, chronic heart failure, chemical cachexia, cachexia from HIV/AIDS, renal failure, uremia, rheumatoid arthritis, age-related sarcopenia, age-related frailty, organ atrophy, carpal tunnel syndrome, androgen deprivation, and muscle-wasting due to inactivity from prolonged bed rest, spinal chord injury, stroke, bone fracture, and aging. The muscle wasting may also result from weightlessness due to space flight, insulin resistance, muscle wasting due to burns, androgen deprivation, and other disorders. In another aspect, the present invention provides a method of treating a disease correlated to expression of activin A. In one embodiment, the disease is cancer. In another example, it is described a method of treating a metabolic disorder comprising administering a therapeutic composition to a subject in need of such treatment, wherein the metabolic disorder is selected from bone loss, diabetes, obesity, impaired glucose tolerance, hyperglycemia, androgen deprivation, and metabolic syndrome. In another example, the use of the therapeutic composition in the preparation

of a medicament for treating the above disorders is described. In another example, it is described a method of gene therapy comprising administering a vector encoding a vActRIIB polypeptide or protein described herein to a subject in need thereof, wherein the vector is capable of expressing the vActRIIB polypeptide or protein in the subject.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1. Figure 1 shows the amino acid sequence of wild-type soluble ActRIIB-human IgG1Fc (SEQ ID NO: 98). The signal peptide sequence is in bold, followed by the mature ActRIIB extracellular domain, and the human IgG1 Fc in italics, including a partial hinge region. Amino acids E28 and R40 are underlined. The linker sequence GGGGS (SEQ ID NO: 75) is in italics and underlined.

Figure 2. Figure 2 shows the amino acid sequence of soluble ActRIIB5-human IgG1Fc (SEQ ID NO: 99). The signal peptide sequence is in bold, followed by the mature ActRIIB5 soluble domain, and the human IgG1 Fc, including a partial hinge region, is in italics. E28 and R40 are underlined. The linker sequence (GGGGS) (SEQ ID NO: 75) is in italics and underlined.

Figure 3. Figure 3 shows the effect of soluble vActRIIB-Fc E28W treatment on testicular (Figure 3A) and ovarian (Figure 3B) mass in inhibin-α knockout mice.

Figure 4. Figure 4 shows the effect of soluble vActRIIB-Fc E28W treatment on survival rates in male (Figure 4A) and female (Figure 4B) inhibin-α knockout mice.

Figure 5. Figure 5 shows the effect of soluble vActRIIB-Fc E28W treatment on body weight in colon 26 tumor-bearing mice.

Figure 6. Figure 6 shows the effect of soluble vActRIIB-Fc E28W treatment on the survival of colon 26 tumor bearing mice.

DETAILED DESCRIPTION

Proteins comprising variant human activin IIB receptor (vActRIIB) polypeptides are disclosed. These proteins and polypeptides are characterized by their ability to bind to at least one of three TGF-β proteins, myostatin (GDF-8), activin A, and GDF-11, and to inhibit the activities of these proteins. These proteins and polypeptides also exhibit a reduced tendency to aggregate compared to polypeptides not containing the modifications disclosed herein. The modifications consist of amino acid substitutions at positions 28,

40, or both 28 and 40 with reference to wild type ActRIIB of accession number NP_001097 (SEQ ID NO: 47), and the extracellular domain of ActRIIB (SEQ ID NO: 18) or ActRIIB5 (SEQ ID NO: 2).

As used herein the term "TGF-β family members" or "TGF-β proteins" refers to the structurally related growth factors of the transforming growth factor family including activins, and growth and differential factor (GDF) proteins (Kingsley et al. Genes Dev. 8: 133-146 (1994), McPherron et al. Growth factors and cytokines in health and disease, Vol. 1B, D. LeRoith and C.Bondy. ed., JAI Press Inc., Greenwich, Conn, USA: pp 357-393).

GDF-8, also referred to as myostatin, is a negative regulator of skeletal muscle tissue (McPherron et al. PNAS USA 94:12457-12461 (1997)). Myostatin is synthesized as an inactive protein complex approximately 375 amino acids in length, having GenBank Accession No: AAB86694 (SEQ ID NO: 49) for human. The precursor protein is activated by proteolytic cleavage at a tetrabasic processing site to produce an N-terminal inactive prodomain and an approximately 109 amino acid C-terminal protein which dimerizes to form a homodimer of about 25 kDa. This homodimer is the mature, biologically active protein (Zimmers et al., Science 296, 1486 (2002)).

As used herein, the term "prodomain" or "propeptide" refers to the inactive N-terminal protein which is cleaved off to release the active C-terminal protein. As used herein the term "myostatin" or "mature myostatin" refers to the mature, biologically active C-terminal polypeptide, in monomer, dimer or other form, as well as biologically active fragments or related polypeptides including allelic variants, splice variants, and fusion peptides and polypeptides. The mature myostatin has been reported to have 100% sequence identity among many species including human, mouse, chicken, porcine, turkey, and rat (Lee et al., PNAS 98, 9306 (2001)).

As used herein GDF-11 refers to the BMP (bone morphogenic protein) having Swissprot accession number O95390 (SEQ ID NO: 50), as well as variants and species homologs of that protein. GDF-11 has approximately 90% identity to myostatin at the amino acid level. GDF-11 is involved in the regulation of anterior/posterior patterning of the axial skeleton (McPherron et al, Nature Genet. 22 (93): 260-264 (1999); Gamer et al, Dev. Biol. 208 (1), 222-232 (1999)) but postnatal functions are unknown.

Activin A is the homodimer of the polypeptide chains ßA. As used herein the term "activin A" refers to the activin protein having GenBank Accession No: NM_002192 (SEQ ID NO: 48), as well as variants and species homologs of that protein.

Activin Receptors

As used herein, the term activin type II B receptors (ActRIIB) refers to human activin receptors having accession number NP_001097 (SEQ ID NO: 47). The term soluble ActRIIB encompasses the extracellular domain of ActRIIB (SEQ ID NO: 18), ActRIIB5 (SEQ ID NO: 2) and these sequences wherein the arginine at position 64 is substituted with alanine, as well as.

Variant soluble ActRIIB polypeptides

The present invention provides isolated proteins comprising human variant soluble ActIIB receptor polypeptides (referred to herein as vActRIIB polypeptides, or variant polypeptides). As used herein the term "vActRIIB protein" refers to a protein comprising a vActRIIB polypeptide. As used herein the term "isolated" refers to a protein or polypeptide molecule purified to some degree from endogenous material. These polypeptides and proteins are characterized as having the ability to bind and inhibit the activity of any one of activin A, myostatin, or GDF-11. In some embodiments, the binding affinity of the variant polypeptides for activin A, myostatin, or GDF-11 is improved compared to wild-type polypeptides.

In one embodiment, the vActRIIB polypeptide has the amino acid sequence of SEQ ID NO: 2 or 18 in which amino acids at either position E28 or R40, or both position E28 and R40 are substituted with another non-native amino acid, and wherein the polypeptide is capable of binding myostatin, activin A, or GDF-11. In another embodiment, the vActRIIB polypeptides are the mature versions, or the truncated mature versions of these sequences. As used herein the term "mature vActRIIB polypeptide" refers to the polypeptide having the amino acid signal sequence removed. In one embodiment, the mature sequences are, for example, amino acids 19 through 160 of SEQ ID NO: 2, and amino acids 19 through 134 of SEQ ID NO: 18, wherein one or both amino acids at positions 28 and 40 are substituted with another non-native amino acid and the polypeptides retain the ability to bind to activin A, myostatin, or GDF-11. As used herein the term truncated mature vActRIIB polypeptide refers to the polypeptide having the signal sequence and in addition amino acids from the N-terminal of the mature polypeptide removed. In one embodiment, the mature N-terminal 4 amino acids or the N-terminal 6 amino acids of the mature polypeptide are removed. In this embodiment, the

truncated mature sequences are, for example, amino acids 23 through 160 of SEQ ID NO: 2, or amino acids 25 through 160 of SEQ ID NO: 2; and amino acids 23 through 134 of SEQ ID NO: 18, or amino acids 25 through 134 of SEQ ID NO: 18 wherein one or both amino acids at positions 28 and 40 are substituted with non-wild type amino acids which retain the ability to bind to activin A, myostatin, or GDF-11. As used herein, the term "position 28" and "position 40" (that is, E28 and R40) refers to the amino acid position with reference to the sequences SEQ ID NO: 2 and 18 that include an 18 amino acid signal sequence. For consistency, if mature vActRIIB polypeptides have substitutions at position 10 and/or position 22, or truncated mature polypeptides have substitutions at position 6 and/or position 18, or substitutions at positions 4 and/or position 16 with respect to the mature or truncated mature sequences, these variants will still be referred to with respect to the full length SEQ ID NO: 2 and 18, or as shown in Figure 1 or 2, i.e., the amino acid substitution at position E28 and/or R40. Such mature embodiments or N-terminal truncated embodiments are exemplified below.

In one embodiment, the substitution at position E28 is selected from the group of amino acids consisting of W, Y and A. In one embodiment, the substitution at position 28 is W. In a further embodiment the substitution at position 28 is selected from the group of amino acids consisting of A, F, Q, V, I, L, M, K, H, W and Y. In a further embodiment, the substitution at position 40 is selected from the group of amino acids consisting of G, Q, M, H, K and N. In a further embodiment the substitution at position 28 is selected from the group of amino acids consisting of A, F, Q, V, I, L, M, K, H, W and Y and the substitution at position 40 is selected from the group of amino acids consisting of A, G, Q, M, H, K, and N. In one embodiment, the protein comprises polypeptides having an amino acid sequence selected from the group consisting of SEQ ID NO: 4, 6, 8, 10, 12, 14, 16, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 52, 54, 56, 60, 62, 64, 66, 68, 70, 72, 87, 88, 91, 93, 95, and 97. In another embodiment, the protein comprises a polypeptide encoded by the polynucleotide having the sequence set forth in the group consisting of SEQ ID NO: 3, 5, 7, 9, 11, 13, 15, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 51, 53, 55, 59, 61, 63, 65, 67, 69, 71, 92, 94, 96 or its complement.

In one embodiment, the signal sequences are removed from the vActRIIB polypeptide, leaving the mature variant polypeptides. Various signal peptides can be used in the preparation of the polypeptides of the instant application. The signal peptides can have the sequence shown in Figures 1 and 2 (SEQ ID NO: 73), or alternative signal

sequences such as SEQ ID NO: 74, the signal sequence for SEQ ID NO: 2 and 18. Any other signal peptides useful for expressing vActRIIB or vActRIIB5 polypeptides may be used.

In another embodiment, the vActRIIB polypeptides have sequences that are substantially similar to SEQ ID NO: 2 and 18. As used herein the term "substantially similar" refers to polypeptides having at least about 80% identity, at least about 85% identity, at least about 90% identity, at least about 95% identity, at least about 98% identity, or at least about 99% identity to the amino acid sequence set forth in SEQ ID NO: 2 and 18, and wherein one or both amino acids at positions 28 and/or 40 are substituted with non-wild type amino acids, wherein the polypeptide retains the activity of the polypeptide of SEQ ID NO: 2 and 18, that is the ability to bind and inhibit myostatin, activin A or GDF-11. In addition, the term vActRIIB polypeptide encompasses fragments of SEQ ID NO: 2 or 18 such as N and C terminal truncations containing the substitutions at position 28 and /or 40 described herein, wherein the polypeptide is capable of binding and inhibiting myostatin, activin A or GDF-11.

As used herein the term "derivative" of the vActRIIB and vActRIIB5 polypeptides refers to the attachment of at least one additional chemical moiety, or at least one additional polypeptide to form covalent or aggregate conjugates such as glycosyl groups, lipids, acetyl groups, or C-terminal or N-terminal fusion polypeptides, conjugation to PEG molecules, and other modifications which are described more fully below. Variant ActRIIB receptor polypeptides (vActRIIB) can also include additional modifications and derivatives, including modifications to the C and N termini which arise from processing due to expression in various cell types such as mammalian cells, E. coli, yeasts and other recombinant host cells. Further included are vActRIIB polypeptide fragments and polypeptides comprising inactivated N-glycosylation site(s), inactivated protease processing site(s), or conservative amino acid substitution(s), of the polypeptide sequences set forth in SEQ ID NO: 4, 6, 8, 10, 12, 14, 16, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 52, 54, 56, 60, 62, 64, 66, 68, 70, 72, 87, 88, 91, 93, 95, and 97.

As used herein, the term a "vActRIIB or vActRIIB5 polypeptide activity" or "a biological activity of a soluble ActRIIB or ActRIIB5 polypeptide" refers to one or more *in vitro* or *in vivo* activities of the vActRIIB and vActRIIB5 polypeptides including but not limited to those demonstrated in the Example below. Activities of the vActRIIB polypeptides include, but are not limited to, the ability to bind to myostatin or activin A or

GDF-11, and the ability to reduce or neutralize an activity of myostatin or activin A or GDF-11. As used herein, the term "capable of binding" to myostatin, activin A, or GDF-11 refers to binding measured by methods known in the art, such as the Biacore method described in Example 2 below. Also, in Example 2, the pMARE C2C12 cell-based assay measures activin A neutralizing activity, myostatin neutralizing activity, and GDF-11 neutralizing activity. *In vivo* activities include but are not limited to increasing body weight, increasing lean muscle mass, increasing skeletal muscle mass, decreasing fat mass as demonstrated in animal models below and as known in the art. Biological activities further include reducing or preventing cachexia caused by certain types of tumors, preventing the growth of certain types of tumors, and increasing survival of certain animal models. Further discussion of the vActRIIB polypeptide activities is provided below.

The polypeptides of the present invention further comprise heterologous polypeptides attached to the vActRIIB polypeptide either directly or through a linker sequence to form a fusion protein. As used herein the term "fusion protein" refers to a protein having a heterologous polypeptide attached via recombinant DNA techniques. Heterologous polypeptides include but are not limited to Fc polypeptides, his tags, and leucine zipper domains to promote oligomerization and stabilization of the variant ActRIIB polypeptides as described in, for example, WO 00/29581, which is herein incorporated by reference. In one embodiment, the heterologous polypeptide is an Fc polypeptide or domain. In one embodiment, the Fc domain is selected from a human IgG1, IgG2, and IgG4 Fc domain. These are provided in SEQ ID NO: 80, 82 and 84. The vActRIIB can further comprise all or a portion of the hinge sequence of the IgG1, IgG2, or IgG4 adjacent to its respective IgG Fc region. The full hinge sequence for IgG1, IgG2, and IgG4 are provided in SEQ ID NO: 76, 77, and 78 respectively.

The vActRIIB polypeptide can optionally further comprise a "linker" sequence. Linkers serve primarily as a spacer between a polypeptide and a second heterologous polypeptide or other type of fusion or between two or more variant ActRIIB polypeptides. In one embodiment, the linker is made up of amino acids linked together by peptide bonds, preferably from 1 to 20 amino acids linked by peptide bonds, wherein the amino acids are selected from the 20 naturally occurring amino acids. One or more of these amino acids may be glycosylated, as is understood by those in the art. In one embodiment, the 1 to 20 amino acids are selected from glycine, alanine, proline, asparagine, glutamine, and lysine. Preferably, a linker is made up of a majority of amino acids that are sterically unhindered,

such as glycine and alanine. Exemplary linkers are polyglycines (particularly $(Gly)_5$, $(Gly)_8$, poly(Gly-Ala), and polyalanines. One exemplary suitable linker as shown in the Examples below is $(Gly)_4Ser$ (SEQ ID NO: 75). In a further embodiment, vActRIIB can comprise a hinge linker, that is a linker sequence are provided adjacent to the hinge region, as exemplified in SEQ ID NO: 79.

The linkers are also non-peptide linkers. For example, alkyl linkers such as -NH-(CH_2)s-C(O)-, wherein s = 2-20 can be used. These alkyl linkers may further be substituted by any non-sterically hindering group such as lower alkyl (e.g., C_1-C_6) lower acyl, halogen (e.g., Cl, Br), CN, NH_2, phenyl, etc.

In one embodiment the vActRIIB polypeptides can be attached to an Fc polypeptide, directly or via a linker, or via a hinge linker. In one embodiment, the Fc is a human IgG Fc. vActRIIB attached to Fc include for example, vActRIIB-IgG1Fc, E28A (SEQ ID NO: 60); vActRIIB-IgG1Fc, E28W (SEQ ID NO: 62), vActRIIB-IgG1Fc, E28Y (SEQ ID NO: 64), vActRIIB-IgG Fc, R40G (SEQ ID NO: 66), vActRIIB5-IgG1Fc, E28A (SEQ ID NO: 70), and vActRIIB5-IgG1Fc E28W (SEQ ID NO: 72), as shown in Tables 1 and 2, and described in the Examples herein. Further embodiments include vActRIIB-IgG2 Fc, E28W(SEQ ID NO: 91), vActRIIB-IgG2 Fc, E28Y (SEQ ID NO: 93), and vActRIIB-IgG2 Fc (SEQ ID NO: 95). The variants have been demonstrated to produce less aggregation compared to the wild type ActRIIB-IgG2 IgG2, as demonstrated in the Examples below.

The vActRIIB polypeptides disclosed herein can also be attached to a non-polypeptide molecule for the purpose of conferring desired properties such as reducing degradation and/or increasing half-life, reducing toxicity, reducing immunogenicity, and/or increasing the biological activity of the ActRIIB polypeptides. Exemplary molecules include but are not limited to linear polymers such as polyethylene glycol (PEG), polylysine, a dextran; a lipid; a cholesterol group (such as a steroid); a carbohydrate, or an oligosaccharide molecule.

In another aspect, the present invention provides isolated nucleic acid molecules comprising polynucleotides encoding the vActRIIB polypeptides of the present invention. As used herein the term "isolated" refers to nucleic acid molecules purified to some degree from endogenous material. In one embodiment, the nucleic acid molecule of the present invention comprises a polynucleotide encoding the polypeptides of SEQ ID NO: 4, 6, 8, 10, 12, 14, 16, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 52, 54, 56, 60, 62, 64,

66, 68, 70, 72, 87, 88, 91, 93, 95, and 97. Due to the known degeneracy of the genetic code, wherein more than one codon can encode the same amino acid, a DNA sequence can vary from that shown in SEQ ID NO: 3, 5, 7, 9, 11, 13, 15, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 51, 53, 55, 59, 61, 63, 65, 67, 69, 71, 92, 94, and 96 or the complementary strand of SEQ ID NO: 3, 5, 7, 9, 11, 13, 15, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 51, 53, 55, 59, 61, 63, 65, 67, 69, 71, 92, 94, and 96, and still encode a polypeptide having the amino acid sequence of SEQ ID NO: 4, 6, 8, 10, 12, 14, 16, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 52, 54, 56, 60, 62, 64, 66, 68, 70, 72, 87, 88, 91, 93, 95, and 97. Such variant DNA sequences can result from silent mutations occurring during production, or can be the product of deliberate mutagenesis of these sequences.

In another embodiment the nucleic acid molecule of the present invention comprises a polynucleotide having the polynucleotide sequence set forth in SEQ ID NO: 3, 5, 7, 9, 11, 13, 15, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 51, 53, 55, 59, 61, 63, 65, 67, 69, 71, 92, 94, and 96 or the complementary strand of SEQ ID NO: 3, 5, 7, 9, 11, 13, 15, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 51, 53, 55, 59, 61, 63, 65, 67, 69, 71, 92, 94, and 96. In another embodiment, the present invention provides nucleic acid molecules which hybridize under stringent or moderate conditions with the polypeptide-encoding regions of SEQ ID NO: 3, 5, 7, 9, 11, 13, 15, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 51, 53, 55, 59, 61, 63, 65, 67, 69, 71, 92, 94, and 96 wherein the encoded polypeptide comprises an amino acid sequence as set forth in SEQ ID NO: 4, 6, 8, 10, 12, 14, 16, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 52, 54, 56, 60, 62, 64, 66, 68, 70, 72, 87, 88, 91, 93, 95, and 97 and wherein the encoded polypeptide maintains an activity of a vActRIIB polypeptide.

Nucleic acid molecules of the invention include DNA in both single-stranded and double-stranded form, as well as the RNA complement thereof. DNA includes, for example, cDNA, genomic DNA, synthetic DNA, DNA amplified by PCR, and combinations thereof. Genomic DNA may be isolated by conventional techniques, such as by using the DNA of SEQ ID NO:1 or 17, or a suitable fragment thereof, as a probe. Genomic DNA encoding ActRIIB polypeptides is obtained from genomic libraries which are available for a number of species. Synthetic DNA is available from chemical synthesis of overlapping oligonucleotide fragments followed by assembly of the fragments to reconstitute part or all of the coding regions and flanking sequences. RNA may be

obtained from procaryotic expression vectors which direct high-level synthesis of mRNA, such as vectors using T7 promoters and RNA polymerase. cDNA is obtained from libraries prepared from mRNA isolated from various tissues that express ActRIIB. The DNA molecules of the invention include full length genes as well as polynucleotides and fragments thereof. The full length gene may also include sequences encoding the N-terminal signal sequence.

In another aspect of the present invention, expression vectors containing the nucleic acid sequences are also provided, and host cells transformed with such vectors and methods of producing the vActRIIB polypeptides are also provided. The term "expression vector" refers to a plasmid, phage, virus or vector for expressing a polypeptide from a polynucleotide sequence. Vectors for the expression of the vActRIIB polypeptides contain at a minimum sequences required for vector propagation and for expression of the cloned insert. An expression vector comprises a transcriptional unit comprising an assembly of (1) a genetic element or elements having a regulatory role in gene expression, for example, promoters or enhancers, (2) a sequence that encodes vActRIIB polypeptides to be transcribed into mRNA and translated into protein, and (3) appropriate transcription initiation and termination sequences. These sequences may further include a selection marker. Vectors suitable for expression in host cells are readily available and the nucleic acid molecules are inserted into the vectors using standard recombinant DNA techniques. Such vectors can include promoters which function in specific tissues, and viral vectors for the expression of vActRIIB in targeted human or animal cells. An exemplary expression vector suitable for expression of vActRIIB is the pDSRa, (described in WO 90/14363, herein incorporated by reference) and its derivatives, containing vActRIIB polynucleotides, as well as any additional suitable vectors known in the art or described below.

The application further provides methods of making vActRIIB polypeptides. A variety of other expression/host systems may be utilized. These systems include but are not limited to microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with virus expression vectors (e.g., baculovirus); plant cell systems transfected with virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with bacterial expression vectors (e.g., Ti or pBR322 plasmid); or animal cell systems. Mammalian cells

useful in recombinant protein production include but are not limited to VERO cells, HeLa cells, Chinese hamster ovary (CHO) cell lines, or their derivatives such as Veggie CHO and related cell lines which grow in serum-free media (see Rasmussen et al., 1998, Cytotechnology 28:31) or CHO strain DX-B11, which is deficient in DHFR (see Urlaub et al., 1980, Proc. Natl. Acad. Sci. USA 77:4216-20) COS cells such as the COS-7 line of monkey kidney cells (ATCC CRL 1651) (see Gluzman et al., 1981, Cell 23:175), W138, BHK, HepG2, 3T3 (ATCC CCL 163), RIN, MDCK, A549, PC12, K562, L cells, C127 cells, BHK (ATCC CRL 10) cell lines, the CV1/EBNA cell line derived from the African green monkey kidney cell line CV1 (ATCC CCL 70) (see McMahan et al., 1991, EMBO J. 10:2821), human embryonic kidney cells such as 293, 293 EBNA or MSR 293, human epidermal A431 cells, human Colo205 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from in vitro culture of primary tissue, primary explants, HL-60, U937, HaK or Jurkat cells. Mammalian expression allows for the production of secreted or soluble polypeptides which may be recovered from the growth medium.

Using an appropriate host-vector system, vActRIIB polypeptides are produced recombinantly by culturing a host cell transformed with an expression vector containing the nucleic acid molecules of the present invention under conditions allowing for production. Transformed cells can be used for long-term, high-yield polypeptide production. Once such cells are transformed with vectors that contain selectable markers as well as the desired expression cassette, the cells can be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The selectable marker is designed to allow growth and recovery of cells that successfully express the introduced sequences. Resistant clumps of stably transformed cells can be proliferated using tissue culture techniques appropriate to the cell line employed. An overview of expression of recombinant proteins is found in Methods of Enzymology, v. 185, Goeddell, D.V., ed., Academic Press (1990).

In some cases, such as in expression using procaryotic systems, the expressed polypeptides of this invention may need to be "refolded" and oxidized into a proper tertiary structure and disulfide linkages generated in order to be biologically active. Refolding can be accomplished using a number of procedures well known in the art. Such methods include, for example, exposing the solubilized polypeptide to a pH usually above 7 in the presence of a chaotropic agent. The selection of chaotrope is similar to the choices used for inclusion body solubilization, however a chaotrope is typically used at a

lower concentration. Exemplary chaotropic agents are guanidine and urea. In most cases, the refolding/oxidation solution will also contain a reducing agent plus its oxidized form in a specific ratio to generate a particular redox potential which allows for disulfide shuffling to occur for the formation of cysteine bridges. Some commonly used redox couples include cysteine/cystamine, glutathione/dithiobisGSH, cupric chloride, dithiothreitol DTT/dithiane DTT, and 2-mercaptoethanol (bME)/dithio-bME. In many instances, a co-solvent may be used to increase the efficiency of the refolding. Commonly used cosolvents include glycerol, polyethylene glycol of various molecular weights, and arginine.

In addition, the polypeptides can be synthesized in solution or on a solid support in accordance with conventional techniques. Various automatic synthesizers are commercially available and can be used in accordance with known protocols. See, for example, Stewart and Young, Solid Phase Peptide Synthesis, 2d.Ed., Pierce Chemical Co. (1984); Tam et al., J Am Chem Soc, 105:6442, (1983); Merrifield, Science 232:341-347 (1986); Barany and Merrifield, The Peptides, Gross and Meienhofer, eds, Academic Press, New York, 1-284; Barany et al., Int J Pep Protein Res, 30:705-739 (1987).

The polypeptides and proteins of the present invention can be purified according to protein purification techniques are well known to those of skill in the art. These techniques involve, at one level, the crude fractionation of the proteinaceous and non-proteinaceous fractions. Having separated the peptide polypeptides from other proteins, the peptide or polypeptide of interest can be further purified using chromatographic and electrophoretic techniques to achieve partial or complete purification (or purification to homogeneity). The term "isolated polypeptide" or "purified polypeptide" as used herein, is intended to refer to a composition, isolatable from other components, wherein the polypeptide is purified to any degree relative to its naturally-obtainable state. A purified polypeptide therefore also refers to a polypeptide that is free from the environment in which it may naturally occur. Generally, "purified" will refer to a polypeptide composition that has been subjected to fractionation to remove various other components, and which composition substantially retains its expressed biological activity. Where the term "substantially purified" is used, this designation will refer to a peptide or polypeptide composition in which the polypeptide or peptide forms the major component of the composition, such as constituting about 50%, about 60%, about 70%, about 80%, about 85%, or about 90% or more of the proteins in the composition.

Various techniques suitable for use in purification will be well known to those of skill in the art. These include, for example, precipitation with ammonium sulphate, PEG, antibodies (immunoprecipitation) and the like or by heat denaturation, followed by centrifugation; chromatography such as affinity chromatography (Protein-A columns), ion exchange, gel filtration, reverse phase, hydroxylapatite, hydrophobic interaction chromatography; isoelectric focusing; gel electrophoresis; and combinations of these techniques. As is generally known in the art, it is believed that the order of conducting the various purification steps may be changed, or that certain steps may be omitted, and still result in a suitable method for the preparation of a substantially purified polypeptide. Exemplary purification steps are provided in the Examples below.

Various methods for quantifying the degree of purification of polypeptide will be known to those of skill in the art in light of the present disclosure. These include, for example, determining the specific binding activity of an active fraction, or assessing the amount of peptide or polypeptide within a fraction by SDS/PAGE analysis. A preferred method for assessing the purity of a polypeptide fraction is to calculate the binding activity of the fraction, to compare it to the binding activity of the initial extract, and to thus calculate the degree of purification, herein assessed by a "-fold purification number." The actual units used to represent the amount of binding activity will, of course, be dependent upon the particular assay technique chosen to follow the purification and whether or not the polypeptide or peptide exhibits a detectable binding activity.

Variant activin type IIB polypeptides bind to ligands that activate muscle-degradation cascades. vActRIIB polypeptides capable of binding and inhibiting the activity of the ligands activin A, myostatin, and/or GDF-11, have therapeutic potential against the diseases that involve muscle atrophy, as well as the treatment of certain cancers, and other diseases as shown in the Examples below.

However, aggregation can occur when expressing or purifying wild-type ActRIIB or ActRIIB5 polypeptides. This aggregation includes structured oligomer formation during expression and non-structured aggregate generation both during expression and after polypeptide purification.

The combined approaches of structure analysis, molecular modeling, and mass spectrometry have indicated that multimerization may arise in ActRIIB polypeptides via intermolecular disulfide bond formation aided by electrostatic and hydrogen bonding interactions between nonglycosylated ActRIIB polypeptides. Significant hydrogen bonds

exist at the interface of two ActRIIB molecules; between E28 side chain in one ActRIIB and R40 side chain in the other ActRIIB, for example. In addition, critical electrostatic interactions exist between E28 in one ActRIIB and R40 in the other ActRIIB.

These electrostatic interactions may significantly contribute to increase the population of temporal ActRIIB dimers, resulting in promotion of noncovalent and/or covalent bond formation between ActRIIB units. The interaction between residues 28 and 40 is the most critical among these interactions as these two residues are involved in double hydrogen bonds and a strong electrostatic interaction. The residues 28 and 40 are involved in ActRIIB:ActRIIB interactions and not in ActRIIB:ligand interactions. Thus, residues 28 and 40 can be substituted with non-native amino acids according to invention, to improve the solubility, and reduce the aggregation of the receptor polypeptides. Therefore, E28 and R40 were substituted respectively with other possible natural amino acids, expressed, and tested by Biacore as shown below. Biacore determined binding are shown in Tables 1A and 1B in Example 2 below. Furthermore, percent aggregation of the vActRIIB polypeptides are determined below.

The results in the Examples below show reduced aggregation for vActRIIB polypeptides and proteins having the amino acid substitutions described herein, while retaining the ability to bind and neutralize myostatin, activin A, or GDF-11.

Antibodies

The present invention further includes antibodies which bind to variant ActRIIB polypeptides, including those that specifically bind to the vActRIIB polypeptides of the present invention. As used herein the term "specifically binds" refers to antibodies having a binding affinity (Ka) for vActRIIB polypeptides of 10^6 M^{-1} or greater. As used herein, the term "antibody" refers to intact antibodies including polyclonal antibodies (see, for example Antibodies: A Laboratory Manual, Harlow and Lane (eds), Cold Spring Harbor Press, (1988)), and monoclonal antibodies (see, for example, U.S. Patent Nos. RE 32,011, 4,902,614, 4,543,439, and 4,411,993, and Monoclonal Antibodies: A New Dimension in Biological Analysis, Plenum Press, Kennett, McKearn and Bechtol (eds.) (1980)). As used herein, the term "antibody" also refers to a fragment of an antibody such as F(ab), F(ab'), $F(ab')_2$, Fv, Fc, and single chain antibodies which are produced by recombinant DNA techniques or by enzymatic or chemical cleavage of intact antibodies. The term "antibody" also refers to bispecific or bifunctional antibodies, which are an artificial

hybrid antibody having two different heavy/light chain pairs and two different binding sites. Bispecific antibodies can be produced by a variety of methods including fusion of hybridomas or linking of Fab' fragments. (See Songsivilai et al, Clin. Exp. Immunol. 79:315-321 (1990), Kostelny et al., J. Immunol.148:1547-1553 (1992)).

As used herein the term "antibody" also refers to chimeric antibodies, that is, antibodies having a human constant antibody immunoglobin domain coupled to one or more non-human variable antibody immunoglobin domain, or fragments thereof (see, for example, U.S. Patent No. 5,595,898 and U.S. Patent No. 5,693,493). Antibodies also refers to "humanized" antibodies (see, for example, U.S. Pat. No. 4,816,567 and WO 94/10332), minibodies (WO 94/09817), maxibodies, and antibodies produced by transgenic animals, in which a transgenic animal containing a proportion of the human antibody producing genes but deficient in the production of endogenous antibodies are capable of producing human antibodies (see, for example, Mendez et al., Nature Genetics 15:146-156 (1997), and U.S. Patent No. 6,300,129). The term "antibodies" also includes multimeric antibodies, or a higher order complex of proteins such as heterdimeric antibodies, and anti-idiotypic antibodies. "Antibodies" also includes anti-idiotypic antibodies. The antibodies against v ActRIIB can be used, for example, to identify and quantitate vActRIIB *in vitro* and *in vivo*.

Also included are polyclonal antibodies from any mammal, for example mouse and rat antibodies, and rabbit antibodies, that bind specifically to the vActRIIB polypeptides described herein, including SEQ ID NO: 4, 6, 8, 10, 12, 14, 16, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 52, 54, 56, 60, 62, 64, 66, 68, 70, 72, 87, 88, 91, 93, 95, and 97.

Such antibodies find use as research tools and in quantitative assays for detecting and assaying the polypeptides disclosed herein. Such antibodies are made using methods described above and as known in the art.

Pharmaceutical Compositions

Pharmaceutical compositions containing the vActRIIB proteins and polypeptides of the present invention are also provided. Such compositions comprise a therapeutically or prophylactically effective amount of the polypeptide or protein in admixture with pharmaceutically acceptable materials, and physiologically acceptable formulation materials. The pharmaceutical composition may contain formulation materials for modifying, maintaining or preserving, for example, the pH, osmolarity, viscosity, clarity,

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

The optimal pharmaceutical composition will be determined by one skilled in the art depending upon, for example, the intended route of administration, delivery format, and desired dosage. See for example, Remington's Pharmaceutical Sciences, *supra*. Such compositions may influence the physical state, stability, rate of *in vivo* release, and rate of *in vivo* clearance of the polypeptide. For example, suitable compositions may be water for injection, physiological saline solution for parenteral administration.

The primary vehicle or carrier in a pharmaceutical composition may be either aqueous or non-aqueous in nature. For example, a suitable vehicle or carrier may be water for injection, physiological saline solution or artificial cerebrospinal fluid, possibly supplemented with other materials common in compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary

vehicles. Other exemplary pharmaceutical compositions comprise Tris buffer of about pH 7.0-8.5, or acetate buffer of about pH 4.0-5.5, which may further include sorbitol or a suitable substitute thereof. In one embodiment of the present invention, compositions may be prepared for storage by mixing the selected composition having the desired degree of purity with optional formulation agents (Remington's Pharmaceutical Sciences, supra) in the form of a lyophilized cake or an aqueous solution. Further, the therapeutic composition may be formulated as a lyophilizate using appropriate excipients such as sucrose.

The formulations can be delivered in a variety of methods, for example, by inhalation therapy, orally, or by injection. When parenteral administration is contemplated, the therapeutic compositions for use in this invention may be in the form of a pyrogen-free, parenterally acceptable aqueous solution comprising the desired polypeptide in a pharmaceutically acceptable vehicle. A particularly suitable vehicle for parenteral injection is sterile distilled water in which a polypeptide is formulated as a sterile, isotonic solution, properly preserved. Yet another preparation can involve the formulation of the desired molecule with an agent, such as injectable microspheres, bio-erodible particles, polymeric compounds (polylactic acid, polyglycolic acid), beads, or liposomes, that provides for the controlled or sustained release of the product which may then be delivered via a depot injection. Hyaluronic acid may also be used, and this may have the effect of promoting sustained duration in the circulation. Other suitable means for the introduction of the desired molecule include implantable drug delivery devices.

In another aspect, pharmaceutical formulations suitable for injectable administration may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiologically buffered saline. Aqueous injection suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils, such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate, triglycerides, or liposomes. Non-lipid polycationic amino polymers may also be used for delivery. Optionally, the suspension may also contain suitable stabilizers or agents to increase the solubility of the compounds and allow for the preparation of highly concentrated solutions. In another embodiment, a pharmaceutical composition may be formulated for inhalation. Inhalation

solutions may also be formulated with a propellant for aerosol delivery. In yet another embodiment, solutions may be nebulized. Pulmonary administration is further described in PCT Application No. PCT/US94/001875, which describes pulmonary delivery of chemically modified proteins.

It is also contemplated that certain formulations may be administered orally. In one embodiment of the present invention, molecules that are administered in this fashion can be formulated with or without those carriers customarily used in the compounding of solid dosage forms such as tablets and capsules. For example, a capsule may be designed to release the active portion of the formulation at the point in the gastrointestinal tract when bioavailability is maximized and pre-systemic degradation is minimized. Additional agents can be included to facilitate absorption of the therapeutic molecule. Diluents, flavorings, low melting point waxes, vegetable oils, lubricants, suspending agents, tablet disintegrating agents, and binders may also be employed. Pharmaceutical compositions for oral administration can also be formulated using pharmaceutically acceptable carriers well known in the art in dosages suitable for oral administration. Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for ingestion by the patient.

Pharmaceutical preparations for oral use can be obtained through combining active compounds with solid excipient and processing the resultant mixture of granules (optionally, after grinding) to obtain tablets or dragee cores. Suitable auxiliaries can be added, if desired. Suitable excipients include carbohydrate or protein fillers, such as sugars, including lactose, sucrose, mannitol, and sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose, such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; gums, including arabic and tragacanth; and proteins, such as gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, and alginic acid or a salt thereof, such as sodium alginate.

Dragee cores may be used in conjunction with suitable coatings, such as concentrated sugar solutions, which may also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for product identification or to characterize the quantity of active compound, *i.e.*, dosage.

Pharmaceutical preparations that can be used orally also include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating, such as glycerol or sorbitol. Push-fit capsules can contain active ingredients mixed with fillers or binders, such as lactose or starches, lubricants, such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid, or liquid polyethylene glycol with or without stabilizers.

Additional pharmaceutical compositions will be evident to those skilled in the art, including formulations involving polypeptides in sustained- or controlled-delivery formulations. Techniques for formulating a variety of other sustained- or controlled-delivery means, such as liposome carriers, bio-erodible microparticles or porous beads and depot injections, are also known to those skilled in the art. See for example, PCT/US93/00829 that describes controlled release of porous polymeric microparticles for the delivery of pharmaceutical compositions. Additional examples of sustained-release preparations include semipermeable polymer matrices in the form of shaped articles, e.g. films, or microcapsules. Sustained release matrices may include polyesters, hydrogels, polylactides (U.S. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman et al., Biopolymers, 22:547-556 (1983), poly (2-hydroxyethyl-methacrylate) (Langer et al., J. Biomed. Mater. Res., 15:167-277, (1981); Langer et al., Chem. Tech.,12:98-105(1982)), ethylene vinyl acetate (Langer et al., supra) or poly-D(-)-3-hydroxybutyric acid (EP 133,988). Sustained-release compositions also include liposomes, which can be prepared by any of several methods known in the art. See e.g., Eppstein *et al.*, PNAS (USA), 82:3688 (1985); EP 36,676; EP 88,046; EP 143,949.

The pharmaceutical composition to be used for *in vivo* administration typically must be sterile. This may be accomplished by filtration through sterile filtration membranes. Where the composition is lyophilized, sterilization using this method may be conducted either prior to or following lyophilization and reconstitution. The composition for parenteral administration may be stored in lyophilized form or in solution. In addition, parenteral compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Once the pharmaceutical composition has been formulated, it may be stored in sterile vials as a solution, suspension, gel, emulsion, solid, or a dehydrated or lyophilized

powder. Such formulations may be stored either in a ready-to-use form or in a form (e.g., lyophilized) requiring reconstitution prior to administration.

In a specific embodiment, the present invention is directed to kits for producing a single-dose administration unit. The kits may each contain both a first container having a dried protein and a second container having an aqueous formulation. Also included within the scope of this invention are kits containing single and multi-chambered pre-filled syringes (*e.g.*, liquid syringes and lyosyringes).

An effective amount of a pharmaceutical composition to be employed therapeutically will depend, for example, upon the therapeutic context and objectives. One skilled in the art will appreciate that the appropriate dosage levels for treatment will thus vary depending, in part, upon the molecule delivered, the indication for which the polypeptide is being used, the route of administration, and the size (body weight, body surface or organ size) and condition (the age and general health) of the patient. Accordingly, the clinician may titer the dosage and modify the route of administration to obtain the optimal therapeutic effect. A typical dosage may range from about 0.1mg/kg to up to about 100 mg/kg or more, depending on the factors mentioned above. Polypeptide compositions may be preferably injected or administered intravenously. Long-acting pharmaceutical compositions may be administered every three to four days, every week, or biweekly depending on the half-life and clearance rate of the particular formulation. The frequency of dosing will depend upon the pharmacokinetic parameters of the polypeptide in the formulation used. Typically, a composition is administered until a dosage is reached that achieves the desired effect. The composition may therefore be administered as a single dose, or as multiple doses (at the same or different concentrations/dosages) over time, or as a continuous infusion. Further refinement of the appropriate dosage is routinely made. Appropriate dosages may be ascertained through use of appropriate dose-response data.

The route of administration of the pharmaceutical composition is in accord with known methods, e.g. orally, through injection by intravenous, intraperitoneal, intracerebral (intra-parenchymal), intracerebroventricular, intramuscular, intra-ocular, intraarterial, intraportal, intralesional routes, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, or intraperitoneal; as well as intranasal, enteral, topical, sublingual, urethral, vaginal, or rectal means, by sustained release systems or by implantation devices. Where desired, the compositions may be administered by bolus injection or continuously by

infusion, or by implantation device. Alternatively or additionally, the composition may be administered locally via implantation of a membrane, sponge, or another appropriate material on to which the desired molecule has been absorbed or encapsulated. Where an implantation device is used, the device may be implanted into any suitable tissue or organ, and delivery of the desired molecule may be via diffusion, timed-release bolus, or continuous administration.

In some cases, the vActRIIB polypeptides of the present invention can be delivered by implanting certain cells that have been genetically engineered, using methods such as those described herein, to express and secrete the polypeptide. Such cells may be animal or human cells, and may be autologous, heterologous, or xenogeneic. Optionally, the cells may be immortalized. In order to decrease the chance of an immunological response, the cells may be encapsulated to avoid infiltration of surrounding tissues. The encapsulation materials are typically biocompatible, semi-permeable polymeric enclosures or membranes that allow the release of the polypeptide product(s) but prevent the destruction of the cells by the patient's immune system or by other detrimental factors from the surrounding tissues.

vActRIIB gene therapy *in vivo* is also envisioned wherein a nucleic acid molecule encoding vActRIIB, or a derivative of vActRIIB is introduced directly into the subject. For example, a nucleic acid sequence encoding a vActRIIB is introduced into target cells via local injection of a nucleic acid construct with or without an appropriate delivery vector, such as an adeno-associated virus vector. Alternative viral vectors include, but are not limited to, retroviruses, adenovirus, herpes simplex, virus and papilloma virus vectors. Physical transfer of the virus vector may be achieved *in vivo* by local injection of the desired nucleic acid construct or other appropriate delivery vector containing the desired nucleic acid sequence, liposome-mediated transfer, direct injection (naked DNA), or microparticle bombardment (gene-gun).

Uses of vActRIIB Compositions

The present invention provides methods and pharmaceutical compositions for reducing or neutralizing the amount or activity of myostatin, activin A, or GDF-11 *in vivo* and *in vitro* by contacting the polypeptides with vActRIIB polypeptide. vActRIIB polypeptides have a high affinity for myostatin, activin A, and GDF-11, and are capable of reducing and inhibiting the biological activities of at least one of myostatin, activin A and

GDF-11. In some embodiments, the vActRIIB polypeptides exhibit improved activity compared with the wild type ActRIIB polypeptides. This is demonstrated in the Examples below.

In one aspect, the present invention provides methods and reagents for treating myostatin-related and/or activin A related disorders in a subject in need of such a treatment by administering an effective dosage of a vActRIIB composition to the subject. As used herein the term "subject" refers to any animal, such as mammals including humans.

The compositions of the present invention are used to increase lean muscle mass as a percentage of body weight and decrease fat mass as percentage of body weight.

The disorders that can be treated by a vActRIIB composition include but are not limited to various forms of muscle wasting, as well as metabolic disorders such as diabetes and related disorders, and bone degenerative diseases such as osteoporosis. The vActRIIB compositions have been demonstrated to be effective in treating muscle wasting disorders in various disease models set forth in Example 3 below. This demonstrated in the treatment of muscle wasting in inhibin-α knockout mice, treatment of muscle wasting in colon-26 cancer cachexia models, prevention of muscular atrophy in hind limb suspension model, treatment of OXV female showing increase in lean muscle mass, decrease in fat mass and increase in bone mineral content.

Muscle wasting disorders also include dystrophies such as Duchenne's muscular dystrophy, progressive muscular dystrophy, Becker's type muscular dystrophy, Dejerine-Landouzy muscular dystrophy, Erb's muscular dystrophy, and infantile neuroaxonal muscular dystrophy. Additional muscle wasting disorders arise from chronic diseases or disorders such as amyotrophic lateral sclerosis, congestive obstructive pulmonary disease, cancer, AIDS, renal failure, organ atrophy, androgen deprivation, and rheumatoid arthritis.

Over-expression of myostatin and/or activin may contribute to cachexia, a severe muscle and fat wasting syndrome. The effectiveness of the vActRIIB polypeptides in treating cachexias in animal models is shown in Example 3 below. Cachexia also arises due to rheumatoid arthritis, diabetic nephropathy, renal failure, chemotherapy, injury due to burns, as well as other causes. In another example, serum and intramuscular concentrations of myostatin-immunoreactive protein was found to be increased in men exhibiting AIDS-related muscle wasting and was inversely related to fat-free mass (Gonzalez-Cadavid et al., PNAS USA 95: 14938-14943 (1998)). Myostatin levels have

also been shown to increase in response to burns injuries, resulting in a catabolic muscle effect (Lang et al, FASEB J 15, 1807-1809 (2001)). Additional conditions resulting in muscle wasting may arise from inactivity due to disability such as confinement in a wheelchair, prolonged bed rest due to stroke, illness, spinal chord injury, bone fracture or trauma, and muscular atrophy in a microgravity environment (space flight). For example, plasma myostatin immunoreactive protein was found to increase after prolonged bed rest (Zachwieja et al. J Gravit Physiol. 6(2):11(1999). It was also found that the muscles of rats exposed to a microgravity environment during a space shuttle flight expressed an increased amount of myostatin compared with the muscles of rats which were not exposed (Lalani et al., J.Endocrin 167 (3):417-28 (2000)).

In addition, age-related increases in fat to muscle ratios, and age-related muscular atrophy appear to be related to myostatin. For example, the average serum myostatin-immunoreactive protein increased with age in groups of young (19-35 yr old), middle-aged (36-75 yr old), and elderly (76-92 yr old) men and women, while the average muscle mass and fat-free mass declined with age in these groups (Yarasheski et al. J Nutr Aging 6(5):343-8 (2002)). In addition, myostatin has now been found to be expressed at low levels in heart muscle and expression is upregulated in cardiomyocytes after infarct (Sharma et al., J Cell Physiol. 180 (1):1-9 (1999)). Therefore, reducing myostatin levels in the heart muscle may improve recovery of heart muscle after infarct.

Myostatin also appears to influence metabolic disorders including type 2 diabetes, noninsulin-dependent diabetes mellitus, hyperglycemia, and obesity. For example, lack of myostatin has been shown to improve the obese and diabetic phenotypes of two mouse models (Yen *et al. FASEB J. 8*:479 (1994). It has been demonstrated in U.S. application serial no: 11/590,962, U.S. application publication No: 2007/0117130, AAV-ActRIIB5 vectors increases the muscle to fat ratio in an animal, in particular for obese animal models. The vActRIIB polypeptides of the present disclosure, such as SEQ ID NO: 4, 6, 8, 10, 12, 14, 16, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 52, 54, 56, 60, 62, 64, 66, 68, 70, 72, 87, 88, 91, 93, 95 are suitable for such uses. Therefore, decreasing fat composition by administering the compositions of the present invention will improve diabetes, obesity, and hyperglycemic conditions in animals. In addition, compositions containing the vActRIIB polypeptides may decrease food intake in obese individuals, as demonstrated in U.S. application serial no: 11/590,962, U.S. application publication No: 2007/0117130 for the ActRIIB5 polypeptide.

Administering the ActRIIB polypeptides of the present invention may improve bone strength and reduce osteoporosis and other degenerative bone diseases. This has been demonstrated in the OVX mouse model described below. It has been also been found, for example, that myostatin-deficient mice showed increased mineral content and density of the mouse humerus and increased mineral content of both trabecular and cortical bone at the regions where the muscles attach, as well as increased muscle mass (Hamrick et al. Calcif Tissue Int 71(1):63-8 (2002)). In addition, the vActRIIB compositions of the present invention can be used to treat the effects of androgen deprivation such as androgen deprivation therapy used for the treatment of prostate cancer.

The present invention also provides methods and compositions for increasing muscle mass in food animals by administering an effective dosage of the vActRIIB proteins to the animal. Since the mature C-terminal myostatin polypeptide is identical in all species tested, vActRIIB polypeptides would be expected to be effective for increasing muscle mass and reducing fat in any agriculturally important species including cattle, chicken, turkeys, and pigs.

The vActRIIB polypeptides and compositions of the present invention also antagonize the activity of activin A. Activin A is known to be expressed in certain types of cancers, particularly gonadal tumors such as ovarian carcinomas, and to cause severe cachexia. (Ciprano et al. Endocrinol 141 (7):2319-27 (2000), Shou et al., Endocrinol 138 (11):5000-5 (1997); Coerver et al, Mol Endocrinol 10(5):534-43 (1996); Ito et al. British J Cancer 82(8):1415-20 (2000), Lambert-Messerlian, et al, Gynecologic Oncology 74:93-7 (1999). In Example 3 below, the vActRIIB polypeptides of the present invention have been demonstrated to be effective in treating severe cachexia, reducing tumor size, and prolonging survival in inhibin-α knockout mice models and colon-26 cancer cachexia mouse models. Therefore, the compositions of the present disclosure can be used to treat conditions related to activin A overexpression, as well as myostatin expression, such as cachexia from certain cancers and the treatment of certain gonadal type tumors.

The compositions of the present disclosure may be used alone or in combination with other therapeutic agents to enhance their therapeutic effects or decrease potential side effects. These properties include increased activity, increased solubility, reduced degradation, increased half-life, reduced toxicity, and reduced immunogenicity. Thus the compositions of the present disclosure are useful for extended treatment regimes. In addition, the properties of hydrophilicity and hydrophobicity of the compounds of the

invention are well balanced, thereby enhancing their utility for both *in vitro* and especially *in vivo* uses. Specifically, compounds of the disclosure have an appropriate degree of solubility in aqueous media that permits absorption and bioavailability in the body, while also having a degree of solubility in lipids that permits the compounds to traverse the cell membrane to a putative site of action, such as a particular muscle mass.

In addition, the vActRIIB polypeptides of the present invention are useful for detecting and quantitating myostatin, activin A, or GDF-11 in any number of assays. In general, the ActRIIB polypeptides of the present invention are useful as capture agents to bind and immobilize myostatin, activin A, or GDF-11 in a variety of assays, similar to those described, for example, in Asai, ed., Methods in Cell Biology, 37, Antibodies in Cell Biology, Academic Press, Inc., New York (1993). The polypeptides may be labeled in some manner or may react with a third molecule such as an antibody which is labeled to enable myostatin to be detected and quantitated. For example, a polypeptide or a third molecule can be modified with a detectable moiety, such as biotin, which can then be bound by a fourth molecule, such as enzyme-labeled streptavidin, or other proteins. (Akerstrom, *J Immunol* 135:2589 (1985); Chaubert, *Mod Pathol* 10:585 (1997)).

The invention having been described, the following examples are offered by way of illustration, and not limitation.

Example 1

Expression and Purification of vActRIIB Polypeptides

The following methods were used for expressing and purifying the variant ActRIIB polypeptides.

The cDNA of the human activin type IIB receptor was isolated from a cDNA library of human testis origin (Clontech, Inc.) and cloned as described in U.S. application serial no: 11/590,962, U.S. application publication No: 2007/0117130.

Determination of amino acid substitutions

The combined approaches of structure analysis, molecular modeling, and mass spectrometry indicated that aggregation (oligomerization) may arise in ActRIIB through intermolecular disulfide bond formation triggered by electrostatic and H-bonding interactions between nonglycosylated ActRIIB molecules. The residues 28 and 40 were

determined to be involved in ActRIIB:ActRIIB interactions and not in ActRIIB interactions with its ligands.

Initially, E28 and R40 on ActRIIB-Fc were substituted with A at each position. Light scattering and mass spectrometry analyses confirmed that the fraction of fully glycosylated vActRIIB-IgG1Fc, E28A, and vActRIIB-IgG1Fc R40A was significantly increased compared to wild-type protein. E28A and R40A vActRIIB-IgG1Fc were incubated at 37 °C for 6 days, resulting little or no aggregation compared to wild type. Amino acid substitutions at positions 28 and 40 (with respect to SEQ ID NO: 2 and 18 with the signal sequence) were made to alleviate or prevent aggregation that can occur during expression or purification of the wild-type ActRIIB (SEQ ID NO: 2 and 18). This aggregation has been identified as structured oligomer formation during expression and non-structured aggregate generation both during expression and after protein purification.

Aggregation at different stages of the production and purification processes was determined using size exclusion chromatography according to the procedure below.

The following exemplary method was used to produce the variant ActRIIB polypeptides (vActRIIB and vActRIIB5). Polynucleotides encoding the vActRIIB, E28W (SEQ ID NO: 23) were fused to polynucleotides encoding human IgG1 Fc domain (SEQ ID NO: 82) or polynucleotides encoding human IgG2 Fc (SEQ ID NO: 84), via a hinge linker sequence (nucleotides encoding SEQ ID NO: 79) using PCR overlap extension using primers containing the mutation resulting in E28W. The full polynucleotide sequence is SEQ ID NO: 61. Double stranded DNA fragments were subcloned into pTT5 (Biotechnology Research Institute, National Research Council Canada (NRCC), 6100 Avenue Royalmount, Montréal (Québec) Canada H4P 2R2), pDSRα (described in WO/9014363) and/or derivatives of pDSRα. In other embodiments, polynucleotides encoding vActRIIB polypeptides were attached to polynucleotides encoding linker GGGGS (SEQ ID NO: 75) or multimers thereof, and or hinge linkers (such as SEQ ID NO: 79).

Transient expression of engineered vActRIIB-Fc and vActRIIB5-Fc was carried out as follows.

The engineered variants of the above two molecules were expressed transiently in serum-free suspension adapted 293-6E cells (National Research Council of Canada, Ottawa, Canada) maintained in FreeStyle™ medium (Invitrogen Corporation, Carlsbad, CA) supplemented with 250 μg/ml geneticin (Invitrogen) and 0.1% Pluronic F68

(Invitrogen). Transfections were performed as 1L cultures. Briefly, the cell inoculum was grown to 1.1×10^6 cells/ml in a 4L fernbach shake flask (Corning, Inc.). The shake flask culture was maintained on an Innova 2150 shaker platform (News Brunswick Scientific, Edison, NJ) at 65 RPM which was placed in a humidified incubator maintained at 37°C and 5% CO_2. At the time of transfection, the 293-6E cells were diluted to 1.0×10^6 cells/ml.

The transfection complexes were formed in 100 ml FreeStyle medium. 1 mg plasmid DNA was first added to the medium followed by 3 ml of FuGene HD transfection reagent (Roche Applied Science, Indianapolis, IN). The transfection complex was incubated at room temperature for approximately 15 minutes and then added to the cells in the shake flask. Twenty-hour hours post transfection, 20% (w/v) of peptone TN1 (OrganoTechnie S.A., TeknieScience, QC, Canada) was added to reach a final concentration of 0.5% (w/v). The transfection/expression was performed for 4-7 days, after which the conditioned medium was harvested by centrifugation at 4,000 RPM for 60 minutes at 4°C.

Stable transfection and expression was carried out as follows. The vActRIIB-human (hu) IgG2-Fc cell lines were created by transfecting stable CHO host cells with the expression plasmids pDC323-vActRIIB (E28W)-huIgG2 Fc and pDC324-vActRIIB (E28W)-huIgG2 Fc (according to Bianchi et al., Biotech and Bioengineering, 84(4):439-444 (2003)) using a standard electroporation procedure. After transfection of the host cell line with the expression plasmids the cells were grown in serum-free selection medium without GHT for 2-3 weeks to allow for selection of the plasmid and recovery of the cells. Cell are selected until they achieved greater than 85% viability. This pool of transfected cells was then cultured in medium containing 150 nM methotrexate.

Cell Line Cloning

A cell bank was made of selected clones according to the following procedure. An amplified pool of stable transfected cells was seeded in 96-well plates, and candidate clones were evaluated for growth and productivity performance in small-scale studies. Pre-master cell banks (PMCB) of approximately 60 vials were prepared from the chosen clone. All PMCBs were tested for sterility, mycoplasma and viruses.

A vActRIIB-Fc expressing cell line was scaled up using a typical fed-batch process. Cells were inoculated into a Wave bioreactor (Wave Biotech LLC). Culture was fed three times with bolus feeds. 10L were harvested on day 10, the remainder was harvested on day 11; both harvests underwent depth filtration followed by sterile filtration. The conditioned media was filtered through a 10 inch 0.45/0.2 micron pre filter, followed by a filtration through a 6 inch 0.2 micron filter.

Protein Purification

Approximately 5 L of the conditioned medium containing ActRIIB-Fc (both IgG1 and IgG2), ActRIIB5-Fc (both IgG1 and IgG2), and variants of these were concentrated using a 5 ft^2 10K membrane tangential flow filter (Pall). The concentrated material was applied to a 5 mL Protein A High Performance Column™ (GE Healthcare) which had been equilibrated with PBS (Dulbecco's with no magnesium chloride or calcium chloride). After washing the column with the equilibration buffer until the absorbance at 280 nm (OD_{280}) was less than 0.1, the bound protein was eluted with 0.1 M glycine-HCl, pH 2.7, and immediately neutralized with 1 M Tris-HCl, pH 8.5. The neutralized eluted pool was concentrated to a volume of 1 ml and applied to a 320ml Sephacryl -200 column (GE Healthcare) that was equilibrated in PBS (Dulbecco's with no magnesium chloride or calcium chloride. A 4-20% SDS PAGE gels (Invitrogen) were run to determine which fractions to pool. These polypeptides were tested for activity, and degree of aggregation, as shown below.

Optionally, the polypeptides can be further purified, using for example, using a Shp-Sepharose column. Concentration was determined using OD280.

Example 2

In vitro Activity assays

Samples of vActRIIB polypeptides purified as described above were diluted with phosphate-buffered saline (PBS: 2.67 mM potassium chloride, 138 mM sodium chloride, 1.47 mM potassium phosphate monobasic, 8.1 mM sodium phosphate dibasic, pH 7.4) to 0.2 mg/ml, incubated at 37 °C for 6 days, then applied to MALDI-MS (matrix-assisted laser desorption/ionization mass spectrometry), SEC and/or SEC-LS analyses. The aggregation of the wt and variant polypeptides after the protein A purification step were

determined using SEC or SEC-LS, and the molecular weight of the molecules confirmed using the MALDI-MS procedure described below.

Size exclusion chromatography (SEC). Experiments were performed on an Agilent 1100 HPLC system with two columns (TOSOHAAS G3000swxl, 7.8 x 300 mm) in tandem. 2x PBS was used as the mobile phase at 0.5 ml/minute.

Size exclusion chromatography-light scattering (SEC-LS). Experiments were performed on an Agilent 1100 HPLC system with a Superdex-200 gel filtration column (Amersham Pharmacia, Waukesha, WI). The samples were then passed through a Wyatt miniDawn LS laser light scattering detector and Wyatt Optilab DSP Refractometer (Wyatt Technology Co., Santa Barbara, CA) to determine the molecular mass. PBS was used as the mobile phase at 0.4 ml/minute.

Matrix-Assisted laser Desorption /Ionization Mass Spectrometry. Samples were mixed (1:1) with sinapinic acid and applied to MALDI-MS (Applied Biosystems Voyager System 2009). This procedure was used to check molecular weight of the molecules.

Determination of binding affinity, and IC_{50} values for activin and myostatin were obtained as described below.

Qualitative BIAcore® Assay. E28 and R40 were substituted respectively with other natural amino acids in fusions with IgG1 Fc as described above. These were generated with or without linkers, as shown in the Tables below. Each vActRIIB-IgG1Fc sample from conditioned media was captured on goat anti-human IgG1 Fc antibody (Jackson Immuno Research, cat# 109-005-098, lot 63550) coated CM5 surface. 20 nM of Activin A was injected over captured sample surfaces using BIACore2000 (BIACore Life Sciences, Piscataway, New Jersey). The resulting sensorgrams were normalized to the captured RL (500 RU) of vActRIIB-IgG1Fc variants. The normalized binding response (RU) for some variants are shown in Table 2, and is further described below. Relative binding affinity for activin was also determined by Biacore measurements using conditioned media obtained from mammalian cell expression. Activin A (20 nM) was used to capture soluble receptor polypeptide in the conditioned media and measured SPR signals were normalized. Normalized SPR of +++++: > 60, ++++: 40 – 60, +++: 20 – 40, ++: 10 – 20, +: 5 – 10, -: <5.

Table 1A and Table 1B summarize the results of the relative binding data. The table below shows that certain embodiments of the vActRIIB-IgG1Fc in particular bound to activin A with higher affinity than wild type, or retained comparable affinity with the wild type.

Table IA

Wild-type and Engineered ActRIIB-IgG1 Fc Binding (Stable Transfectants)

CHO	Expression	Molecule	Res28	Res40	Linker (SEQ ID NO: 75)	Relative activin binding
CHO	Stable	ActRIIB5	none (E28)	None	none	+++
CHO	Stable	ActRIIB5	E28A	None	none	+++
CHO	Stable	ActRIIB5	E28A	None	GGGGS	+++
CHO	Stable	ActRIIB5	none	R40A	GGGGS	+++
CHO	Stable	ActRIIB5	E28W	R40A	GGGGS	++++
CHO	Stable	ActRIIB	none (E28)	None	GGGGS	++++
CHO	Stable	ActRIIB	E28A	None	GGGGS	+++
CHO	Stable	ActRIIB	E28A	None	2(GGGGS)	+++
COS	Stable	ActRIIB	none (E28)	None	none	++
COS	Stable	ActRIIB	E28A	None	none	++
COS	Stable	ActRIIB	none (E28)	R40A	none	++

Table IB

Wild-type and Engineered ActRIIB-IgG1 Fc Binding (Transient Transfectants)

COS	Transient	ActRIIB	E28W	none (R40)	GGGGS	+++++
COS	Transient	ActRIIB	E28Y	none (R40)	GGGGS	+++++
COS	Transient	ActRIIB	none (E28)	R40G	GGGGS	+++
COS	Transient	ActRIIB	E28F	none (R40)	GGGGS	+++
COS	Transient	ActRIIB	none (E28)	none (R40)	GGGGS	+
COS	Transient	ActRIIB	none (E28)	none (R40)	GGGGS	+
CHO	Transient	ActRIIB	E28A	none (R40)	none	-
COS	Transient	ActRIIB	E28T	none (R40)	GGGGS	-
COS	Transient	ActRIIB	E28Q	none (R40)	GGGGS	+
COS	Transient	ActRIIB	E28S	none (R40)	GGGGS	-
COS	Transient	ActRIIB	E28D	none (R40)	GGGGS	-
COS	Transient	ActRIIB	E28V	none (R40)	GGGGS	+
COS	Transient	ActRIIB	E28I	none (R40)	GGGGS	++
COS	Transient	ActRIIB	E28L	none (R40)	GGGGS	+
COS	Transient	ActRIIB	E28C	none (R40)	GGGGS	-
COS	Transient	ActRIIB	E28G	none (R40)	GGGGS	-
COS	Transient	ActRIIB	E28P	none (R40)	GGGGS	-
COS	Transient	ActRIIB	E28R	none (R40)	GGGGS	-
COS	Transient	ActRIIB	E28N	none (R40)	GGGGS	-
COS	Transient	ActRIIB	E28A	none (R40)	GGGGS	+
COS	Transient	ActRIIB	E28M	none (R40)	GGGGS	++
COS	Transient	ActRIIB	E28K	none (R40)	GGGGS	+
COS	Transient	ActRIIB	E28H	none (R40)	GGGGS	+
COS	Transient	ActRIIB	none (E28)	R40Q	GGGGS	+
COS	Transient	ActRIIB	none (E28)	R40P	GGGGS	-
CHO	Transient	ActRIIB	none(E28)	R40A	GGGGS	+
COS	Transient	ActRIIB	none (E28)	R40L	GGGGS	-
COS	Transient	ActRIIB	none (E28)	R40T	GGGGS	-
COS	Transient	ActRIIB	none (E28)	R40F	GGGGS	-
COS	Transient	ActRIIB	none (E28)	R40Y	GGGGS	-
COS	Transient	ActRIIB	none (E28)	R40V	GGGGS	-
COS	Transient	ActRIIB	none(E28)	R40S	GGGGS	-
COS	Transient	ActRIIB	none(E28)	R40M	GGGGS	+
COS	Transient	ActRIIB	none (E28)	R40H	GGGGS	++
COS	Transient	ActRIIB	none (E28)	R40I	GGGGS	-
COS	Transient	ActRIIB	none (E28)	R40C	GGGGS	-

COS	Transient	ActRIIB	none (E28)	R40K	GGGGS	++
COS	Transient	ActRIIB	none (E28)	R40N	GGGGS	++

C2C12 Cell Based Activity Assay

vActRIIB5-IgG1Fc and vActRIIB-IgG1Fc variants were generated as described above. The ability of these variants to inhibit the binding of activin A or myostatin to the activin IIB receptor was tested using a cell based activity assay as described below.

A myostatin/activin/GDF-11-responsive reporter cell line was generated by transfection of C2C12 myoblast cells (ATCC No: CRL-1772) with a pMARE-luc construct. The pMARE-luc construct is made by cloning twelve repeats of the CAGA sequence, representing the myostatin/activin response elements (Dennler et al. EMBO 17: 3091-3100 (1998)) into a pLuc-MCS reporter vector (Stratagene cat # 219087) upstream of the TATA box. The C2C12 cells naturally express activin receptor IIB on their cell surface. When myostatin/activinA/GDF-11 binds the cell receptors, the Smad pathway is activated, and phosphorylated Smad binds to the response element (Macias-Silva et al. Cell 87:1215 (1996)), resulting in the expression of the luciferase gene. Luciferase activity was then measured using a commercial luciferase reporter assay kit (cat # E4550, Promega, Madison, WI) according to manufacturer's protocol. A stable line of C2C12 cells that has been transfected with pMARE-luc (C2C12/pMARE) was used to measure activity according to the following procedure. Reporter cells were plated into 96 well cultures. Screening using dilutions of the wild type and variant ActRIIB-IgG1 Fc fusions constructed as described above was performed with the concentration fixed at 4 nM activin. Activin A was pre-incubated with the receptors at several concentrations. Activin activity was measured by determining the luciferase activity in the treated cultures. The IC_{50} values were determined for each polypeptide. These are shown in Table 2. The same procedure was followed for ActRIIB-huIgG2 Fc fusions produced as described above for the determination of myostatin. Protein A purified wt and variants were used in the determination of IC_{50} values for myostatin using the same methodology. For this determination, the polypeptides were pre-incubated with 4 nM myostatin. In addition, the degree of aggregation was determined using the procedures described above. These values are given in Table 3 below.

Out of the set of ActRIIB5-IgG1 Fc variants that are listed in Table 1A, several ActRIIB-IgG1 Fc variants and three ActRIIB5-IgG1 Fc variants together with the wild type polypeptides were further purified and analyzed by SPR (surface plasmon resonance)

at 20 nM activin A. Table 2 shows the SPR binding affinity of selected vActRIIB-IgG1 Fc polypeptides for activin. Activin A (20 nM) was used to capture vActRIIB polypeptides in the samples and measured SPR signals were normalized. IC_{50} values were obtained from cell-based activin inhibition assays described above. Standard errors are less than 10% for all results.

Table 2

Variant	SPR normalized RU (RU = response unit)	IC_{50} (nM) Activin
ActRIIB-IgG1Fc (SEQ ID NO:58)	35	8.20
vActRIIB-IgG1Fc, E28A (SEQ ID NO:60)	20	25.30
vActRIIB-IgG1Fc, E28W (SEQ ID NO:62)	128	2.07
vActRIIB-IgG1Fc, E28Y (SEQ ID NO:64)	115	2.10
vActRIIB-IgG1Fc, R40G (SEQ ID NO:66)	18	
ActRIIB5-IgG1Fc (SEQ ID NO:68)	37	
vActRIIB5-IgG1Fc, E28A (SEQ ID NO:70)	8	
vActRIIB5-IgG1Fc, E28W (SEQ ID NO:72)	45	16.86

As shown above in Table 2 above, the IC_{50} value of vActRIIB-IgG1Fc (E28W) for blocking activin was 2.07 nM and the IC_{50} value of vActRIIB-IgG1Fc (E28Y) was 2.1 nM compared to wild type. Furthermore, the E28W and E28Y variants of vActRIIB-IgG1Fc were stable and not aggregated once purified.

The IC_{50} value in a myostatin blocking cell based assay was determined for additional variant polypeptides as well. These variants were the mature truncated vActRIIB polypeptides lacking the signal sequence and the first six amino acids of the N-terminal. These sequences are shown in Table 3. Table 3 show the percent aggregation of

the protein after protein A purification, and the IC_{50} value with respect to myostatin. It can be seen that the percent aggregation is much less for the variant polypeptides compared with the wild type. Similar results were obtained for mature truncated vActRIIB polypeptides without the signal sequence and the N-terminal four amino acids, and with identical substitutions as shown below.

Table 3

ActRIIB-Fc Variant	ActRIIB	Linker—Hinge	IgG2 Fc	% aggregation	IC_{50} (nM) for myostatin cell based assay
hActRIIB-hIgG$_2$Fc (SEQ ID NO: 89)	ETRE[25]CIYYNANWELERT NQSGLERCEGEQDKRLHC YASWRNSSGTIELVKKGC WLDDFNCYDRQECVATEE NPQVYFCCCEGNFCNERF THLPEAGGPEVTYEPPPTA PT (SEQ ID NO: 86)	GGGGS VECPPC P (SEQ ID NO:79)	APPVAGPSVFLFPP KPKDTLMISRTPE VTCVVVDVSHEDP EVQFNWYVDGVE VHNAKTKPREEQF NSTFRVVSVLTVV HQDWLNGKEYKC KVSNKGLPAPEIK TISKTKGQPREPQ VYTLPPSREEMTK NQVSLTCLVKGFY PSDIAVEWESNGQ PENNYKTTPPMLD SDGSFFLYSKLTV DKSRWQQGNVFS CSVMHEALHNHY TQKSLSLSPGK (SEQ ID NO: 80)	13%	1.1
hActRIIB-hIgG$_2$Fc (E28W) (SEQ ID NO:91)	ETRW[25]CIYYNANWELERT NQSGLRCEGEQDKRLHCY ASWRNSSGTIELVKKGCW LDDFNCYDRQECVATEEN PQVYFCCCEGNFCNERFT HLPEAGGPEVTYEPPPTAP T (SEQ ID NO: 87)	GGGSV ECPPCP (SEQ ID NO:79)	APPVAGPSVFLFPP KPKDTLMISRTPE VTCVVVDVSHEDP EVQFNWYVDGVE VHNAKTKPREEQF NSTFRVVSVLTVV HQDWLNGKEYKC KVSNKGLPAPIEK TISKTKGQPREPQ VYTLPPSREEMTK NQVSLTCLVKGFY PSDIAVEWESNGQ PENNYKTTPPMLD SDGSFFLYSKLTV DKSRWQQGNVFS CSVMHEALHNHY TQKSLSLSPGK (SEQ ID NO: 80)	2%	0.9
hActRIIB-	ETRY[25]CIYYNANWELERT NQSGLERCEGEQDKRLHC	GGGGS VECPPC	APPVAGPSVFLFPP KPKDTLMISRTPE	4%	1.0

hIgG$_2$Fc (E28Y) (SEQ ID NO: 93)	YASWRNSSGTIELVKKGC WLDDFCYDRQECVATEEN PQVYFCCCEGNFCNERFT HLPEAGGPEVTYEPPPTAP T (SEQ ID NO:88)	P (SEQ ID NO:79)	VTCVVVDVSHEDP EVQFNWYVDGVE VHNAKTKPREEQF NSTFRVVSVLTVV HQDWLNGKEYKC KVSNKGLPAPIEK TISKTKGQPREPQ VYTLPPSREEMTK NQVSLTCLVKGFY PSDIAVEWESNGQ PENNYKTTPPMLD SDGSFFLYSKLTV DKSRWQQGNVFS CSVMHEALHNHY TQKSLSLSPGK (SEQ ID NO: 80)		

Table 4 identifies the sequences corresponding to SEQ ID NO:1-99 in the sequence listing.

Table 4

SEQ ID NO	Description
1	ActRIIB5 extracellular domain, polynucleotide
2	ActRIIB5 extracellular domain, polypeptide
3	vActRIIB5 E28A polynucleotide
4	vActRIIB5 E28A polypeptide
5	vActRIIB5 E28A and R40A polynucleotide
6	vActRIIB5 E28A and R40A polypeptide
7	vActRIIB5 E28W polynucleotide
8	vActRIIB5 E28W polypeptide
9	vActRIIB5 E28Y polynucleotide
10	vActRIIB5 E28Y polypeptide
11	vActRIIB5 E28X wherein X is A, F, Q, V, I, L, M, K, H, W or Y polynucleotide
12	vActRIIB5 E28X wherein X is A, F, Q, V, I, L, M, K, H, W or Y polypeptide
13	vActRIIB5 E28X and R40X, wherein X(28) is A, F, Q, V, I, L, M, K, H, W or Y wherein X(40) is A, G, Q, M, H, K or N polynucleotide
14	vActRIIB5 E28X and R40X, wherein X(28) is A, F, Q, V, I, L, M, K, H, W or Y wherein X(40) is A, G, Q, M, H, K or N polypeptide
15	vActRIIB5 R40X wherein X is G, Q, M, H, K or N polynucleotide
16	vActRIIB5 R40X wherein X is G, Q, M, H, K or N polypeptide

17	ActRIIB extracellular domain, polynucleotide
18	ActRIIB extracellular domain, polypeptide
19	vActRIIB E28A polynucleotide
20	vActRIIB E28A polypeptide
21	vActRIIB E28A and R40A polynucleotide
22	vActRIIB E28A and R40A polypeptide
23	vActRIIB E28W polynucleotide
24	vActRIIB E28W polypeptide
25	vActRIIB E28Y polynucleotide
26	vActRIIB E28Y polypeptide
27	vActRIIB E28X wherein X is A, F, Q, V, I, L, M, K, H, W or Y polynucleotide
28	vActRIIB E28X wherein X is A, F, Q, V, I, L, M, K, H, W or Y polypeptide
29	vActRIIB E28X and R40X, wherein X(28) is A, F, Q, V, I, L, M, K, H, Y or W wherein X(40) is A, G, Q, M, H, K or N polynucleotide
30	vActRIIB E28X and R40X, wherein X(28) is A, F, Q, V, I, L, M, K, H, Y or W wherein X(40) is A, G, Q, M, H, K or N polypeptide
31	vActRIIB R40X wherein X is G, Q, M, H, K or N polynucleotide
32	vActRIIB R40X wherein X is G, Q, M, H, K or N polypeptide
33	vActRIIB R64A, E28A polynucleotide
34	vActRIIB R64A, E28A polypeptide
35	vActRIIB R64A, E28A and R40A polynucleotide
36	vActRIIB R64A, E28A and R40A polypeptide
37	vActRIIB R64A, E28W polynucleotide
38	vActRIIB R64A, E28W polypeptide
39	vActRIIB R64A, E28Y polynucleotide
40	vActRIIB R64A, E28Y polypeptide
41	vActRIIB R64A, E28X wherein X is A, F, Q, V, I, L, M, K, H, Y or W polynucleotide
42	vActRIIB R64A, E28X wherein X is A, F, Q, V, I, L, M, K, H, Y or W polypeptide
43	vActRIIB R64A, E28X and R40X, wherein X(28) is A, F, Q, V, I, L, M, K, H, W or Y wherein X(40) is A, G, Q, M, H, K or N polynucleotide
44	vActRIIB R64A, E28X and R40X, wherein X(28) is A, F, Q, V, I, L, M, K, H, W or Y wherein X(40) is A, G, Q, M, H, K or N polypeptide
45	vActRIIB R64A, R40X wherein X is G, Q, M, H, K or N polynucleotide
46	vActRIIB R64A, R40X wherein X is G, Q, M, H, K or N polypeptide
47	Sequence Accession NP_001097 (Wild type ActRIIB) polypeptide
48	Sequence Accession NM_002192 (Activin A) polypeptide
49	Sequence Accession AAB86694 (Myostatin) polypeptide

50	Sequence Accession O95390 (GDF-11) polypeptide
51	vActRIIB5 E28X and R40X, wherein X = any amino acid polynucleotide
52	vActRIIB5 E28X and R40X, wherein X = any amino acid polypeptide
53	vActRIIB E28X and R40X, wherein X = any amino acid polynucleotide
54	vActRIIB E28X and R40X, wherein X = any amino acid polypeptide
55	vActRIIB R64A, E28X and R40X, wherein X = any amino acid polynucleotide
56	vActRIIB R64A, E28X and R40X, wherein X = any amino acid polypeptide
57	ActRIIB-IgG1Fc mature polynucleotide
58	ActRIIB-IgG1Fc mature polypeptide
59	vActRIIB-IgG1Fc E28A (E10A) mature polynucleotide
60	vActRIIB-IgG1Fc E28A (E10A) mature polypeptide
61	vActRIIB-IgG1Fc E28W (E10W) mature polynucleotide
62	vActRIIB-IgG1Fc E28W (E10W) mature polypeptide
63	vActRIIB-IgG1Fc E28Y (E10Y) mature polynucleotide
64	vActRIIB-IgG1Fc E28Y (E10Y) mature polypeptide
65	vActRIIB-IgG1Fc R40G (R22G) mature polynucleotide
66	vActRIIB-IgG1Fc mature R40G (R22G) mature polypeptide
67	vActRIIB5-IgG1Fc mature polynucleotide
68	vActRIIB5-IgG1Fc mature polypeptide
69	vActRIIB5-IgG1Fc E28A (E10A) mature polynucleotide
70	vActRIIB5-IgG1Fc E28A (E10A) mature polypeptide
71	vActRIIB5-IgG1Fc E28W (E10W) mature polynucleotide E10W
72	vActRIIB5-IgG1Fc E28W (E10W) mature polypeptide E10W
73	Signal sequence shown in Figures 1 and 2
74	Alternative signal sequence
75	Linker
76	Complete hinge regions for IgG1
77	Complete hinge region for IgG2
78	Complete hinge region for IgG4
79	Hinge linker
80	IgG2 Fc polypeptide
81	IgG2 Fc nucleotide degenerate
82	IgG1 Fc polypeptide
83	IgG1 Fc polynucleotide
84	IgG4 Fc polypeptide
85	IgG4 Fc polynucleotide—degenerate
86	ActRIIB mature truncated wt polypeptide
87	vActRIIB (E4W) (E28W) mature truncated polypeptide
88	vActRIIB (E4Y) (E28Y) mature truncated polypeptide
89	ActRIIB-IgG2Fc mature truncated polypeptide
90	ActRIIB-IgG2 Fc mature truncated polynucleotide degenerate
91	vActRIIB-IgG2Fc (E4W) E28W mature truncated polypeptide
92	vActRIIB-IgG2Fc (E4W) E28W mature truncated polynucleotide
93	vActRIIB-IgG2Fc (E4Y) E28Y mature truncated polypeptide
94	vActRIIB-IgG2Fc (E4Y) E28Y mature truncated polynucleotide
95	vActRIIB-IgG2 Fc (E4A) E28A mature truncated polypeptide

96	vActRIIB-IgG2 Fc (E4A) E28A mature truncated polynucleotide degenerate
97	vActRIIB—IgG2 Fc (E4X) E28X—wherein X is A, F, Q, V, I, L, M, K, H, W or Y mature truncated polypeptide
98	Figure 1—ActRIIB-IgG1 Fc
99	Figure 2—ActRIIB5-IgG1 Fc

Example 3
In vivo Treatments using vActRIIB

All of the following animal studies were carried out using the mature truncated vActRIIB-IgG2 Fc (E28W) polypeptide, (SEQ ID NO: 91), according to the procedures described below.

Treatment of muscle wasting in Inhibin-α Deficient Mice

Inhibin-α is a naturally occurring inhibitor of activin A. Mice lacking inhibin-α show significantly elevated activin A levels in circulation and suffer from a lethal wasting syndrome which is associated with the spontaneous formation of tumors such as ovarian, testicular cancers and adrenal cancers (Matzuk et al., PNAS 91(19):8817-21 (1994), Cipriano et al. Endocrinology 121(7): 2319-27(2000), Matzuk et al., Nature 360(6402):313-9 (1992)). For the following experiments, inhibin-α knockout mice (C57BL/6J) were obtained from Charles River Laboratories. The effects of the vActRIIB-IgG2 Fc E28W (SEQ ID NO: 91) (hereinafter E28W, or E28W polypeptide, or soluble receptor E28W) on body weight and muscle mass was examined in inhibin-α knockout mice. A 14-day single-injection study in 8-week-old male inhibin-α knockout mice was performed. At 8 weeks of age, the male inhibin-α knockout mice had lost more than 25% of body weight compared to age-matched wild-type littermate control mice. 5 of the knockout mice were given a single subcutaneous injection of E28W (30 mg/kg), while 5 knockout mice were subcutaneously administered an equal volume of PBS (vehicle) on day 0. As a baseline control, 5 age-matched wild-type mice were administered a single subcutaneous injection of vehicle on day 0. The mice were weighed at day 0, day 7 and day 14. At the end of day 14, all the mice were sacrificed, and their lean carcass weights and calf muscle mass were analyzed via necropsy. Over the 14-day study period, the average body weight of the vehicle-treated knockout mice dropped by approximately 1.1 g from 22.5 g on day 0 to 21.4 g on day 14. In contrast, the average body weight of the E28W-treated knockout mice showed a dramatic gain by 11 g from 22.1 g on day 0 to 33.1 g on day 14. Terminal necropsy analysis revealed that the E28W polypeptide virtually

doubled the lean carcass weight and calf muscle mass in the inhibin-α knockout mice, as shown below. The average lean carcass weight of the E28W-treated knockout mice was approximately 14.9 g compared with approximately 8.0 g for the vehicle-treated knockout mice, and approximately 12.1 g for vehicle-treated wild-type control mice. The average calf muscle weight (from both legs) of the E28W-treated knockout mice was approximately 426 mg compared with approximately 209 mg for the vehicle-treated knockout mice, and approximately 324 mg for vehicle-treated wild-type control mice. These results demonstrate the effectiveness of the E28W polypeptide for the treatment of disease states of weight loss and muscle wasting and are summarized in the Table below.

	WT plus Vehicle	KO plus Vehicle	KO plus E28W
Body Weight	28.64 +/- 1.11	21.36 +/- 0.99*	33.10 +/- 1.56 *#
Lean Carcass (g)	12.07 +/- 0.36	8.00 +/- 0.29*	14.90 +/- 0.77 *#
Calf Muscle (g)	0.324 +/- 0.014	0.209 +/- 0.012*	0.426 +/- 0.024*#

*: P<0.05 vs. WT + Veh; #: P<0.05 vs. KO + Veh.

The effects of the administration of the E28W polypeptide on the rates of formation of testicular and ovarian tumors were examined in male and female inhibin-α KO mice, respectively. In this study, 11 of the inhibin-α knockout mice, including 8-week-old males (n=5) and 9-week-old females (n=6), were treated with a single subcutaneous injection of E28W (30 mg/kg), while another 11 of the inhibin-α knockout mice, including age-matched males (n=5) and females (n=6) received a single injection of an equal volume of PBS (vehicle). In addition, 11 of the wild-type littermate control mice, including age-matched males (n=5) and females (n=6) were administered a single injection of vehicle. Two weeks after the treatment, the mice were sacrificed and subjected to necropsy to examine the rates of formation of visually identifiable testicular and ovarian tumors. It was observed that 10 of the 11 vehicle-treated knockout mice developed identifiable tumors. Specifically, testicular and ovarian tumor formations were found in 5 out of the 5 males and 5 out of the 6 females examined, respectively. The sizes of these tumors were found to be 2-3 fold larger than the corresponding normal testis or ovary in wild-type control mice. This is shown in Figure 3. Only 10% (1 out of 11) of the E28W-treated inhibin-α knockout mice showed visible tumor formation. Specifically, in females, 1 out of 6 of the E28W-treated knockout mice developed an identifiable ovarian tumor, whereas 5 out of the 6 of the untreated female knockouts had little or no change in the size

or gross morphology of the ovary compared with age-matched wild-type controls. 5 out of 5 of the E28W-treated male knockout mice showed no visible tumors with little or no change in the size or gross morphology of the testis in comparison to the age-matched wild-type controls. These results demonstrate that E28W administration was effective in reducing the formation of testicular and ovarian tumors in the inhibin-α KO mice, suggesting a clinical utility for the soluble receptor therapy in cancer treatment.

The effectiveness of the E28W polypeptide in treating anorexia was examined in male inhibin-α knockout mice. In this study, food consumption in the inhibin-α knockout mice (n=5) was significantly reduced compared to that of the age-matched wild-type mice (n=10). It was observed that the food intake of the E28W treated inhibin-α knockout mice was significantly increased during a 3-week period examined. The average weekly food intake in the E28W-treated knockout mice increased to a level slightly higher than that in the age-matched wild-type control mice, and was about 50% greater than the average weekly food intake of the knockout mice treated with the vehicle. Thus, the data show that the E28W treatment was highly effective in ameliorating anorexia in the inhibin-α KO mice.

The effect of the E28W treatment on survival was examined in male and female inhibin-α KO mice, respectively. For males, 25 inhibin-α KO mice around 50 days of age were administered the E28W polypeptide (10 mg/kg/wk, SC), while 26 age-matched inhibin-α KO mice received vehicle (PBS). 19 aged-matched wild-type male mice received vehicle and were used as baseline control. The vehicle-treated knockout mice started dying on day 15 of the study (around 65 days of age). By day 34 of the experiment (around 84 days of age), 50 % of the vehicle-treated knockout mice had died, and by day 78 (around 128 days of age), 100% of them had died. In contrast, none of the 25 knockout mice treated with the E28W polypeptide, or of the 19 wild-type control mice treated with vehicle, died before day 78 of the study (around 128 days of age). In the E28W-treated knockout mice, 1 out of 25 died on day 78 of the study (around 128 days of age) and 24 out of 25 survived beyond day 100 (around 150 days of age). No vehicle-treated wild type mice died during the 100-day study period. Similar survival results were obtained in female inhibin-α KO mice. 22 of female inhibin-α KO mice of approximately 50 days of age were treated with E28W (10 mg/kg/wk, SC), while 23 female inhibin-α KO mice of the same age were treated with PBS (vehicle). In the meantime, 17 of wild type female

control mice were treated with vehicle. The vehicle-treated female knockout mice began dying on day 40 of the study (around 90 days of age). By day 58 of the experiment (around 108 days of age), 50% of the vehicle-treated female knockout mice had died, and by day 86 of the study (about 136 days of age) 100% of them had died. In contrast, only about 5% (1 out of 22) of the E28W-treated female knockout mice had died while about 90% (20 out of 22) survived beyond day 120 of the study (about 170 days of age). No vehicle-treated wild type mice died during the 120-day study period. Therefore, the data demonstrate that the E28W polypeptide therapy is effective in dramatically prolonging the survival of both male and female inhibin-α knockout mice. A schematic plot of the survival curves for both the male and female knockout mice is provided in Figure 4.

Treatment of muscle wasting in colon-26 tumor bearing mice

Colon-26 tumor bearing mice is a widely used preclinical animal model for studying cancer cachexia (Fujita et al., Int J Cancer 68(5):637-43 (1996), Kwak et al., Cancer Research 64(22):8193-8 (2004)). The effect of E28W polypeptide on body weight change, muscle mass and survival rate were studied in the tumor-bearing mice. Colon-26 (C-26) tumor cells were subcutaneously implanted into 40 10-week-old, male CDF1 mice at 0.5 x 10^6 cells per mouse. The tumor implantation was performed on day 0. Beginning on day 5 after tumor implantation, twenty C-26 mice were treated weekly with a subcutaneous injection of 10 mg/kg vActRIIB IgG2 Fc E28W (SEQ ID NO: 91), while twenty C-26 mice were treated with a vehicle (PBS). At the same time 10 age and weight matched normal mice were treated with a vehicle (PBS) only. Body weight and food intake were determined 3 times per week. The tumor-bearing mice were inspected twice daily for survival. Tumor sizes were measured using calipers (Ultra-Cal IV IP65 electronic caliper, Fred V Fowler Co. Boston MA) connected to a PC computer and values were automatically recorded to a worksheet in a Microsoft Excel data file. As shown in Figure 5, two weeks after tumor implantation, the mice bearing C-26 tumors developed severe cachexia and lost their body weight dramatically. E28W treatment effectively mitigated the body weight loss in the tumor-bearing mice. The average body weight of the tumor-bearing mice treated with E28W was significantly higher than that of the tumor-bearing mice treated with vehicle ($p<0.001$, from day 7 to day 33 after tumor-inoculation. Unpaired T test, Graph pad Software Inc. San Diego CA).

There was no difference in tumor size between the E28W polypeptide treated and vehicle treated groups indicating that the treatment had no effect on C-26 tumor growth. Terminal necropsy analysis showed that the average lean carcass mass and calf muscle weight of the E28W -treated C-26 tumor-bearing mice were significantly higher than those of the tumor-bearing mice treated with vehicle ($p<0.001$ for both lean carcass and calf muscle). The effect of the E28W on survival of the C-26 tumor-bearing mice is shown in Figure 6. The vehicle treated mice began dying at about day 14 post tumor implantation. At day 35 post tumor implantation, all 20 vehicle treated C-26 tumor-bearing mice died; however 17 out of 20 C-26 tumor-bearing mice treated with E28W were still surviving. Thus, the E28W treatment led to a significant prolongation of survival of the C-26 tumor-bearing mice ($p<0.0001$, chi-square test). Therefore, the E28W polypeptide was not only effective in maintaining body weight and muscle mass but also in prolonging the survival of the C-26 tumor-bearing mice.

Treatment of Hindlimb Suspension Mice

The hindlimb suspension mouse model was used to examine the effect of the vActRIIB-IgG2 Fc E28W (SEQ ID NO: 91) on muscle mass in disuse state. Hindlimb suspension procedure is essentially the same as previously reported by Carlson CJ el al (Carlson CJ, Booth FW and Gordon SE: Am J Physiol Regul Integr Comp Physiol. 277: R601-RR606, 1999). Nine-week-old female C57BL/6 mice were used for the study. A total of 60 mice were divided into three groups as follows: 1. Non-suspended baseline control group (20 mice) treated with vehicle (PBS), 2. Hindlimb suspension group (20 mice) treated with vehicle, and 3. Hindlimb suspension mice group (20 mice) treated with vActRIIB-IgG2 Fc, E28W. Specifically, a single SC injection of either 30 mg/kg of vActRIIB-IgG 2 Fc E28W or vehicle was given to the above described groups respectively, at the time of the initiation of hindlimb suspension. Body weight changes were measured longitudinally 2-3 times per week. 5 mice from each group were sacrificed at the following 4 different time points: day 1, day 3, day 7 and day 14. Calf muscle weights were determined via necropsy.

As shown in the Table below, hindlimb suspension led to a significant loss in body weight up to 10%. Treatment of the hindlimb suspended mice with vActRIIB-IgG2 Fc E28W led to a significant body weight gain to a level higher than either the vehicle treated

hindlimb suspension group or the non-suspended baseline control group as analyzed by ANOVA measurement. During the two-week study period, the average body weight gain of the vActRIIB-IgG2 Fc E28W (SEQ ID NO: 91) treatment group was 12.6% in comparison to the 0.2% drop in the vehicle-treated suspension group and 4.8% weight gain in the non-suspened baseline control group, resepctively. Time-course necropsy results showed that the hindlimb muscle mass changed in parallel to the body weights. Treatment of the suspended mice with vActRIIB-IgG2 Fc (E28W) completely mitigated the muscle loss. Therefore, the results of this experiment show that E28W is effective in the treatment of muscle atrophy associated with disuse.

Group/days (body weight change %)	day 3 (%)	day 7 (%)	day 14 (%)
Non-HS + PBS	2.4%	2.9%	4.8%
HS + vehicle	-10.0%	-3.0%	-0.2%
HS + E28W, 30 mg/ml	-9.7%	2.1%	12.6%

Treatment of OVX Mice

Ovariectomized female C57Bl6 mice (OVX) are considered to be a model for female hypogonadism and osteoporesis. 24 female C57Bl6 mice were ovariectomized at age 3 months and allowed to recover for 3 months. At age 6 months, 24 OVX mice as well as 24 age-matched sham operated control C57Bl6 mice were measured for longitudinal changes in body weight, muscle, and fat mass by NMR and bone mass (PIXImus—GE LUNAR Corporation) over a 3 month treatment period. At the end of the period, the animals were sacrificed, and the bone tissues harvested during terminal necropsy and subjected to Faxitron X-ray and microCT (Faxitron X-ray Corporation and GE Medical system) analysis. It was demonstrated to the E28W variant receptor (SEQ ID NO: 91) was effective at increasing body weight, specifically lean skeletal muscle mass, and bone mass, while decreasing fat content of the mice to the level seen in non-ovariectomized mice. Specifically, over a 12 week period, lean muscle mass was increased from 20 g to 27.0 g for OVX mice treated with E28W, compared with 20 g to 27.5 g for sham operated mice treated with E28W, compared with almost no increase in lean muscle mass for OVX plus vehicle or sham plus vehicle (about 19 grams for OVX plus vehicle and about 20 g for wild type plus vehicle). In the same study, OVX mice treated with E28W showed reduced fat mass from 8 g average per animal to about 4 g

average per animal, comparable with the sham operated animals, by the end of the 12 week study. The OVX mice treated with the vehicle, in contrast, did not lose fat mass at any time during the study. Finally, bone mass was increased in the OVX mice treated with E28W compared with vehicle treated OVX mice. Analysis of femur/tibia BMC (Bone mineral content) of the dissected bone harvested during terminal necropsy was determined by pQCT analysis (Peripheral Quantitative Computed Tomography). The OVX mice treated with E28W increased BMC of about 0.045 g/cm to about 0.055 g/cm at the end of the 12 week study, which is comparable to the final BMC of sham operated vehicle treated animals. The OVX mice treated with vehicle showed about the same BMC of 0.045 g/cm at the end of the 12 week study. The E28W treated wild type mice showed an increase of BMC from about 0.054 g/cm to about 0.065 g/cm at the end of the 12 week study. These studies demonstrate the effectiveness of the E28W polypeptide as potential treatments of frailty, osteoporesis, and obesity in aging.

The present invention is not to be limited in scope by the specific embodiments described herein, which are intended as single illustrations of individual aspects of the invention, and functionally equivalent methods and components are within the scope of the invention. Indeed, various modifications of the invention, in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the appended claims.

CLAIMS

What is claimed is:

1. An isolated protein comprising a variant activin IIB receptor polypeptide (vActRIIB) wherein said polypeptide is selected from the group consisting of:

(a) a polypeptide having the polypeptide sequence set forth in SEQ ID NO: 18, except for a single amino acid substitution at position 28, wherein the substitution is selected from any one of A, F, Q, V, I, L, M, K, H, W and Y for E;

(b) a polypeptide having the polypeptide sequence set forth in amino acids 19 through 134 of SEQ ID NO: 18, except for a single amino acid substitution at position 28, wherein the substitution is selected from any one of A, F, Q, V, I, L, M, K, H, W and Y for E;

(c) a polypeptide having the polypeptide sequence set forth in amino acids 23 through 134 of SEQ ID NO: 18, except for a single amino acid substitution at position 28, wherein the substitution is selected from any one of A, F, Q, V, I, L, M, K, H, W and Y for E;

(d) a polypeptide having the polypeptide sequence set forth in amino acids 25 through 134 of SEQ ID NO: 18, except for a single amino acid substitution at position 28, wherein the substitution is selected from any one of A, F, Q, V, I, L, M, K, H, W and Y for E;

(e) a polypeptide having at least 90% identity to any one of (a) through (d), wherein the substitution at position 28 is selected from any one of A, F, Q, V, I, L, M, K, H, W and Y for E, and wherein the polypeptide is capable of binding myostatin, activin A, or GDF-11.

2. An isolated protein comprising a variant activin IIB receptor polypeptide (vActRIIB) wherein said polypeptide is selected from the group consisting of:

(a) a polypeptide having the polypeptide sequence set forth in SEQ ID NO: 2, except for a single amino acid substitution at position 28, wherein the substitution is selected from any one of A, F, Q, V, I, L, M, K, H, W and Y for E;

(b) a polypeptide having the polypeptide sequence set forth in amino acids 19 through 160 of SEQ ID NO: 2, except for a single amino acid substitution at position 28, wherein the substitution is selected from any one of A, F, Q, V, I, L, M, K, H, W and Y for E;

(c) a polypeptide having the polypeptide sequence set forth in amino acids 23 through 160 of SEQ ID NO: 2, except for a single amino acid substitution at position 28, wherein the substitution is selected from any one of A, F, Q, V, I, L, M, K, H, W and Y for E;

(d) a polypeptide having the polypeptide sequence set forth in amino acids 25 through 160 of SEQ ID NO: 2, except for a single amino acid substitution at position 28, wherein the substitution is selected from any one of A, F, Q, V, I, L, M, K, H, W and Y for E;

(e) a polypeptide having at least 90% identity to any one of (a) through (c), wherein the substitution at position 28 is selected from any one of A, F, Q, V, I, L, M, K, H, W and Y for E, and wherein the polypeptide is capable of binding myostatin, activin A, or GDF-11.

3. An isolated protein comprising a variant activin IIB receptor polypeptide (vActRIIB) wherein said polypeptide is selected from the group consisting of:

(a) a polypeptide having the polypeptide sequence set forth in SEQ ID NO: 2, or SEQ ID NO: 18, except for a single amino acid substitution at position 28, wherein the substitution is selected from one of A, F, Q, V, I, L, M, K, H, W and Y for E, and a single amino acid substitution at position 40, wherein the substitution is selected from A, G, Q, M, H, K and N for R;

(b) a polypeptide having the polypeptide sequence set forth in amino acids 19 through 160 of SEQ ID NO: 2, or 19 through 134 of SEQ ID NO: 18, except for a single amino acid substitution at position 28, wherein the substitution is selected from one of A, F, Q, V, I, L, M, K, H, W and Y for E, and a single amino acid substitution at position 40, wherein the substitution is selected from A, G, Q, M, H, K and N for R;

(c) a polypeptide having the polypeptide sequence set forth in amino acids 23 through 160 of SEQ ID NO: 2, or 23 through 134 of SEQ ID NO: 18, except for a single

amino acid substitution at position 28, wherein the substitution is selected from one of A, F, Q, V, I, L, M, K, H, W and Y for E, and a single amino acid substitution at position 40, wherein the substitution is selected from A, G, Q, M, H, K and N for R;

(d) a polypeptide having the polypeptide sequence set forth in amino acids 25 through 160 of SEQ ID NO: 2, or 25 through 134 for SEQ ID NO: 18, except for a single amino acid substitution at position 28, wherein the substitution is selected from one of A, F, Q, V, I, L, M, K, H, W and Y for E, and a single amino acid substitution at position 40, wherein the substitution is selected from A, G, Q, M, H, K and N for R;

(e) a polypeptide having at least 90% identity to any one of (a) through (d), wherein the substitution at position 28 is selected from any one of A, F, Q, V, I, L, M, K, H, W and Y for E, and wherein the substitution at position 40 is selected from a single amino acid substitution at position 40, wherein the substitution is selected from A, G, Q, M, H, K and N for R, and wherein the polypeptide is capable of binding myostatin, activin A, or GDF-11.

4. An isolated protein comprising a variant activin IIB receptor polypeptide (vActRIIB) wherein said polypeptide is selected from the group consisting of:

(a) a polypeptide having the polypeptide sequence set forth in SEQ ID NO: 2, or SEQ ID NO: 18, except for a single amino acid substitution at position 40, wherein the substitution is selected from A, G, Q, M, H, K and N for R;

(b) a polypeptide having the polypeptide sequence set forth in amino acids 19 through 160 of SEQ ID NO: 2, or 19 through 134 of SEQ ID NO: 18, except for a single amino acid substitution at position 40, wherein the substitution is selected from A, G, Q, M, H, K and N for R;

(c) a polypeptide having the polypeptide sequence set forth in amino acids 23 through 160 of SEQ ID NO: 2, or 23 through 134 for SEQ ID NO: 18, except for a single amino acid substitution at position 40, wherein the substitution is selected from A, G, Q, M, H, K and N for R;

(d) a polypeptide having the polypeptide sequence set forth in amino acids 25 through 160 of SEQ ID NO: 2, or 25 through 134 for SEQ ID NO: 18, except for a single

amino acid substitution at position 40, wherein the substitution is selected from A, G, Q, M, H, K and N for R;

(e) a polypeptide having at least 90% identity to any one of (a) through (d), wherein the substitution at position 40 is selected from A, G, Q, M, H, K and N for R, and wherein the polypeptide is capable of binding myostatin, activin A, or GDF-11.

5. The isolated protein of any one of claims 1 through 4, wherein the substitution is at position 28 is selected from A, W or Y for E.

6. The isolated protein of any one of claims 1 through 5, wherein the polypeptide further comprises the substitution A for R at position 64.

7. The isolated protein of any one of claims 1 to 6, wherein the polypeptide has the sequence selected from the group consisting of SEQ ID NO: 4, 6, 8, 10, 12, 14, 16, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 52, 54, 56, 87 and 88.

8. The isolated protein of claim 1, wherein the polypeptide has the sequence selected from the group consisting of SEQ ID NO: 20, 24, 26, 28, 34, 38, 40, 42, 87 and 88.

9. The isolated protein of any one of claims 1 to 8, wherein the polypeptide is fused to at least one heterologous polypeptide.

10. The isolated protein of claim 9, wherein the heterologous polypeptide is a human Fc domain.

11. The isolated protein of claim 10, wherein the protein further comprises a linker.

12. The protein of claim 11, wherein the protein has the sequence selected from the group consisting of SEQ ID NO: 60, 62, 64, 66, 70, 72, 87, 88, 91, 93, 95, and 97.

13. The protein of claim 11, wherein the protein has the sequence set forth in SEQ ID NO: 91.

14. A pharmaceutical composition comprising an effective amount of the protein of any one of claims 1 through 13 in admixture with a pharmaceutically acceptable carrier.

15. An isolated nucleic acid molecule comprised a polynucleotide encoding the protein of any one of claims 1 through 13.

16. The isolated nucleic acid molecule of claim 15, comprising a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the sequence selected from the group consisting of SEQ ID NO: 3, 5, 7, 9, 11, 13, 15, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 51, 53, 59, 61, 63, 65, 69, 71, 92, 94, and 96 or its complement; and

(b) a polynucleotide encoding a polypeptide having the sequence selected from the group consisting of SEQ ID NO: 4, 6, 8, 10, 12, 14, 16, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 52, 54, 56, 60, 62, 64, 66, 70, 72, 87, 88, 91, 93, 95 and 97.

17. An isolated nucleic acid molecule comprising a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the sequence selected from the group consisting of SEQ ID NO: 19, 23, 25, 27, 33, 37, 39, 41, 59, 61, 63, 92, 94, and 96, or its complement, and

(b) a polynucleotide encoding a polypeptide having the sequence selected from the group consisting of SEQ ID NO: 20, 24, 26, 28, 34, 38, 40, 42, 60, 62, 64, 87, 88, 91, 93, 95, and 97.

18. A recombinant expression vector comprising the nucleic acids of any one of claims 15, 16, or 17.

19. A recombinant host cell comprising the vector of claim 18.

20. A method of producing the protein of any one of claims 1 through 13, comprising culturing the host cell of claim 19, thereby expressing the protein.

21. Use of the protein of any one of claims 1-13 or the composition of claim 14 in the manufacture of a medicament for treating a subject in need of myostatin inhibition.

22. Use of the protein of any one of claims 1-13 or the composition of claim 14 in the manufacture of a medicament for treating a subject in need of increasing lean muscle mass or increasing the ratio of lean muscle mass to fat mass.

23. Use of the protein of any one of claims 1-13 or the composition of claim 14 in the manufacture of a medicament for treating a muscle-wasting disease or disorder in a subject in need of such treatment.

24. The use of claim 23, wherein the muscle-wasting disease or disorder is selected from muscular dystrophy, amyotrophic lateral sclerosis, congestive obstructive pulmonary disease, chronic heart failure, cancer cachexia, AIDS, cachexia due to renal failure, uremia, cachexia due to rheumatoid arthritis, age-related sarcopenia, organ atrophy, carpal tunnel syndrome, androgen deprivation, cachexia due to burns injury, diabetic nephropathy, and muscle-wasting due to prolonged bed rest, spinal chord injury, stroke, bone fracture, aging or exposure to micro-gravity.

25. Use of the protein of any one of claims 1-13 or the composition of claim 14 in the manufacture of a medicament for treating a metabolic disorder in a subject in need of such treatment.

26. The use of claim 25, wherein the metabolic disorder is selected from diabetes, obesity, hyperglycemia, and bone loss.

27. Use of the protein of any one of claims 1-13 or the composition of claim 14 in the manufacture of a medicament for treating a disease in which activin is over-expressed in a subject in need of such treatment.

28. The use of claim 27, wherein the disease is cancer.

29. Use of the vector of claim 18 in the manufacture of a medicament for treating a muscle wasting disorder or metabolic disorder in a subject in need of such a treatment, wherein the vector is capable of directing expression of vActRIIB polypeptides in the subject.

SEQUENCE LISTING

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Sun, Jeonghoon
Tam, Lei-Ting Tony
Han, HQ
Kwak, Keith Soo-Nyung
Zhou, Xiaolan

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            20                  25                  30

aac gcc aac tgg gag ctg gag cgc acc aac cag agc ggc ctg gag cgc   144
Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln Ser Gly Leu Glu Arg
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gac ttc aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac   288
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
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ccc cag gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc   336
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110

ttc act cat ttg cca gag gct ggg ggc ccg gaa gga ccc tgg gcc tcc   384
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Gly Pro Trp Ala Ser
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        35                  40                  45
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg
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65                  70                  75                  80
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
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Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
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Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Gly Pro Trp Ala Ser
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Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Ala Cys Ile Tyr Tyr
            20                  25                  30

aac gcc aac tgg gag ctg gag cgc acc aac cag agc ggc ctg gag cgc   144
Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln Ser Gly Leu Glu Arg
        35                  40                  45

tgc gaa ggc gag cag gac aag cgg ctg cac tgc tac gcc tcc tgg cgc   192
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 65                  70                  75                  80

gac ttc aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac   288
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                85                  90                  95

ccc cag gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc   336
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110

ttc act cat ttg cca gag gct ggg ggc ccg gaa gga ccc tgg gcc tcc   384
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Gly Pro Trp Ala Ser
        115                 120                 125

acc acc atc ccc tct ggt ggg cct gaa gcc act gca gct gct gga gat   432
Thr Thr Ile Pro Ser Gly Gly Pro Glu Ala Thr Ala Ala Ala Gly Asp
    130                 135                 140

caa ggc tcg ggg gcg ctt tgg ctg tgt ctg gaa ggc cca gct cat gaa   480
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        35                  40                  45
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg
    50                  55                  60
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65                  70                  75                  80
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                85                  90                  95

Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Gly Pro Trp Ala Ser
        115                 120                 125
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Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Ala Cys Ile Tyr Tyr
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aac gcc aac tgg gag ctg gag gcn acc aac cag agc ggc ctg gag cgc   144
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tgc gaa ggc gag cag gac aag cgg ctg cac tgc tac gcc tcc tgg cgc   192
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg
    50                  55                  60

aac agc tct ggc acc atc gag ctc gtg aag aag ggc tgc tgg cta gat   240
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
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gac ttc aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac   288
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
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ccc cag gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc   336
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Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
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Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
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        35                  40                  45

tgc gaa ggc gag cag gac aag cgg ctg cac tgc tac gcc tcc tgg cgc   192
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg
    50                  55                  60

aac agc tct ggc acc atc gag ctc gtg aag aag ggc tgc tgg cta gat   240
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gac ttc aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac   288

Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
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ccc cag gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc   336
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
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ttc act cat ttg cca gag gct ggg ggc ccg gaa gga ccc tgg gcc tcc   384
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acc acc atc ccc tct ggt ggg cct gaa gcc act gca gct gct gga gat   432
Thr Thr Ile Pro Ser Gly Gly Pro Glu Ala Thr Ala Ala Ala Gly Asp
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Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
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Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
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Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Gly Pro Trp Ala Ser
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ccc cag gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc   336
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100   105   110

ttc act cat ttg cca gag gct ggg ggc ccg gaa gga ccc tgg gcc tcc   384
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Gly Pro Trp Ala Ser
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acc acc atc ccc tct ggt ggg cct gaa gcc act gca gct gct gga gat   432

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    50                  55                  60
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65                  70                  75                  80
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                85                  90                  95
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Gly Pro Trp Ala Ser
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Thr Thr Ile Pro Ser Gly Gly Pro Glu Ala Thr Ala Ala Ala Gly Asp
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<222> (1)...(480)

<400> 11

```
atg acg gcg ccc tgg gtg gcc ctc gcc ctc ctc tgg gga tcg ctg tgc   48
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Cys
 1               5                  10                  15

gcc ggc tct ggg cgt ggg gag gct gag aca cgg nnn tgc atc tac tac   96
Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Xaa Cys Ile Tyr Tyr
            20                  25                  30

aac gcc aac tgg gag ctg gag cgc acc aac cag agc ggc ctg gag cgc   144
Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln Ser Gly Leu Glu Arg
        35                  40                  45

tgc gaa ggc gag cag gac aag cgg ctg cac tgc tac gcc tcc tgg cgc   192
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg
    50                  55                  60
```

```
aac agc tct ggc acc atc gag ctc gtg aag aag ggc tgc tgg cta gat   240
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
 65                  70                  75                  80

gac ttc aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac   288
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                85                  90                  95

ccc cag gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc   336
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110

ttc act cat ttg cca gag gct ggg ggc ccg gaa gga ccc tgg gcc tcc   384
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Gly Pro Trp Ala Ser
        115                 120                 125

acc acc atc ccc tct ggt ggg cct gaa gcc act gca gct gct gga gat   432
Thr Thr Ile Pro Ser Gly Gly Pro Glu Ala Thr Ala Ala Ala Gly Asp
    130                 135                 140

caa ggc tcg ggg gcg ctt tgg ctg tgt ctg gaa ggc cca gct cat gaa   480

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

<210> 12
<211> 160
<212> PRT
<213> Homo sapiens

<220>
<221> VARIANT
<222> 28
<223> Xaa = Ala OR Phe OR Gln OR Val OR Ile OR Leu OR
Met OR Lys OR His OR Trp OR Tyr

<400> 12

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

<210> 13
<211> 480
<212> DNA
<213> Homo sapiens

<220>
<221> variation

<222> (82)...(84)
<223> n = a, c, t, or g

<220>
<221> variation
<222> (118)...(120)
<223> n = a, c, t, or g

<220>
<221> CDS
<222> (1)...(480)

<400> 13
atg acg gcg ccc tgg gtg gcc ctc gcc ctc ctc tgg gga tcg ctg tgc 48

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

gcc ggc tct ggg cgt ggg gag gct gag aca cgg nnn tgc atc tac tac 96
Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Xaa Cys Ile Tyr Tyr
20 25 30

aac gcc aac tgg gag ctg gag nnn acc aac cag agc ggc ctg gag cgc 144
Asn Ala Asn Trp Glu Leu Glu Xaa Thr Asn Gln Ser Gly Leu Glu Arg
35 40 45

tgc gaa ggc gag cag gac aag cgg ctg cac tgc tac gcc tcc tgg cgc 192
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg
50 55 60

aac agc tct ggc acc atc gag ctc gtg aag aag ggc tgc tgg cta gat 240
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65 70 75 80

gac ttc aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac 288
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
85 90 95

ccc cag gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc 336
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
100 105 110

ttc act cat ttg cca gag gct ggg ggc ccg gaa gga ccc tgg gcc tcc 384
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Gly Pro Trp Ala Ser
115 120 125

acc acc atc ccc tct ggt ggg cct gaa gcc act gca gct gct gga gat 432
Thr Thr Ile Pro Ser Gly Gly Pro Glu Ala Thr Ala Ala Ala Gly Asp
130 135 140

caa ggc tcg ggg gcg ctt tgg ctg tgt ctg gaa ggc cca gct cat gaa 480
Gln Gly Ser Gly Ala Leu Trp Leu Cys Leu Glu Gly Pro Ala His Glu
145 150 155 160

<210> 14
<211> 160
<212> PRT
<213> Homo sapiens

<220>
<221> VARIANT
<222> 28
<223> Xaa = Ala OR Phe OR Gln OR Val OR Ile OR Leu OR
Met OR Lys OR His OR Trp OR Tyr

<220>

<221> VARIANT
<222> 40
<223> Xaa = Ala OR Gly OR Gln OR Met OR His OR Lys OR
Asn

<400> 14

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

<210> 15
<211> 480
<212> DNA
<213> Homo sapiens

<220>
<221> variation
<222> (118)...(120)
<223> n = a, c, t, or g

<220>
<221> CDS
<222> (1)...(480)

<400> 15

```
atg acg gcg ccc tgg gtg gcc ctc gcc ctc ctc tgg gga tcg ctg tgc   48
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Cys
 1               5                  10                  15

gcc ggc tct ggg cgt ggg gag gct gag aca cgg gag tgc atc tac tac   96
Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Glu Cys Ile Tyr Tyr
            20                  25                  30

aac gcc aac tgg gag ctg gag nnn acc aac cag agc ggc ctg gag cgc   144
Asn Ala Asn Trp Glu Leu Glu Xaa Thr Asn Gln Ser Gly Leu Glu Arg
        35                  40                  45

tgc gaa ggc gag cag gac aag cgg ctg cac tgc tac gcc tcc tgg cgc   192
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg
    50                  55                  60

aac agc tct ggc acc atc gag ctc gtg aag aag ggc tgc tgg cta gat   240
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65                  70                  75                  80

gac ttc aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac   288
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                85                  90                  95

ccc cag gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc   336
```

```
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110

ttc act cat ttg cca gag gct ggg ggc ccg gaa gga ccc tgg gcc tcc   384
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Gly Pro Trp Ala Ser
        115                 120                 125

acc acc atc ccc tct ggt ggg cct gaa gcc act gca gct gct gga gat   432
Thr Thr Ile Pro Ser Gly Gly Pro Glu Ala Thr Ala Ala Ala Gly Asp
    130                 135                 140

caa ggc tcg ggg gcg ctt tgg ctg tgt ctg gaa ggc cca gct cat gaa   480
Gln Gly Ser Gly Ala Leu Trp Leu Cys Leu Glu Gly Pro Ala His Glu
145                 150                 155                 160



<210> 16
<211> 160
<212> PRT
<213> Homo sapiens

<220>
<221> VARIANT
<222> 40
<223> Xaa = Gly OR Gln OR Met OR His OR Lys OR Asn

<400> 16
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Cys
 1               5                  10                  15
Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Glu Cys Ile Tyr Tyr
            20                  25                  30
Asn Ala Asn Trp Glu Leu Glu Xaa Thr Asn Gln Ser Gly Leu Glu Arg
        35                  40                  45
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg
    50                  55                  60
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65                  70                  75                  80
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                85                  90                  95
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Gly Pro Trp Ala Ser
        115                 120                 125
Thr Thr Ile Pro Ser Gly Gly Pro Glu Ala Thr Ala Ala Ala Gly Asp
    130                 135                 140
Gln Gly Ser Gly Ala Leu Trp Leu Cys Leu Glu Gly Pro Ala His Glu
145                 150                 155                 160


<210> 17
<211> 402
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)...(402)

<400> 17
atg acg gcg ccc tgg gtg gcc ctc gcc ctc ctc tgg gga tcg ctg tgc   48
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Cys
 1               5                  10                  15

gcc ggc tct ggg cgt ggg gag gct gag aca cgg gag tgc atc tac tac   96
Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Glu Cys Ile Tyr Tyr
            20                  25                  30
```

```
aac gcc aac tgg gag ctg gag cgc acc aac cag agc ggc ctg gag cgc   144
Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln Ser Gly Leu Glu Arg
         35                  40                  45

tgc gaa ggc gag cag gac aag cgg ctg cac tgc tac gcc tcc tgg cgc   192
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg
     50                  55                  60

aac agc tct ggc acc atc gag ctc gtg aag aag ggc tgc tgg cta gat   240
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
 65                  70                  75                  80

gac ttc aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac   288
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                 85                  90                  95

ccc cag gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc   336
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110

ttc act cat ttg cca gag gct ggg ggc ccg gaa gtc acg tac gag cca   384
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro
        115                 120                 125

ccc ccg aca gcc ccc acc                                           402
Pro Pro Thr Ala Pro Thr
    130
```

<210> 18
<211> 134
<212> PRT
<213> Homo sapiens

<400> 18

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

Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65                  70                  75                  80
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                85                  90                  95
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro
        115                 120                 125
Pro Pro Thr Ala Pro Thr
    130
```

<210> 19
<211> 402
<212> DNA
<213> Homo sapiens

<220>
<221> variation
<222> 84
<223> n = a, c, t, or g

<220>

<221> CDS
<222> (1)...(402)

<400> 19
```
atg acg gcg ccc tgg gtg gcc ctc gcc ctc ctc tgg gga tcg ctg tgc   48
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Cys
 1               5                  10                  15

gcc ggc tct ggg cgt ggg gag gct gag aca cgg gcn tgc atc tac tac   96
Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Ala Cys Ile Tyr Tyr
            20                  25                  30

aac gcc aac tgg gag ctg gag cgc acc aac cag agc ggc ctg gag cgc   144
Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln Ser Gly Leu Glu Arg
        35                  40                  45

tgc gaa ggc gag cag gac aag cgg ctg cac tgc tac gcc tcc tgg cgc   192
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg
    50                  55                  60

aac agc tct ggc acc atc gag ctc gtg aag aag ggc tgc tgg cta gat   240
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65                  70                  75                  80

gac ttc aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac   288
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                85                  90                  95

ccc cag gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc   336
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110

ttc act cat ttg cca gag gct ggg ggc ccg gaa gtc acg tac gag cca   384
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro
        115                 120                 125

ccc ccg aca gcc ccc acc                                           402
Pro Pro Thr Ala Pro Thr
    130
```

<210> 20
<211> 134
<212> PRT
<213> Homo sapiens

<400> 20
```
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Cys
 1               5                  10                  15
Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Ala Cys Ile Tyr Tyr
            20                  25                  30
Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln Ser Gly Leu Glu Arg
        35                  40                  45
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg
    50                  55                  60
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65                  70                  75                  80
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                85                  90                  95
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro
        115                 120                 125
Pro Pro Thr Ala Pro Thr
    130
```

<210> 21
<211> 402
<212> DNA
<213> Homo sapiens

<220>
<221> variation
<222> 84
<223> n = a, c, t, or g

<220>
<221> variation
<222> 120
<223> n = a, c, t, or g

<220>
<221> CDS
<222> (1)...(402)

<400> 21

```
atg acg gcg ccc tgg gtg gcc ctc gcc ctc ctc tgg gga tcg ctg tgc   48
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Cys
 1               5                  10                  15

gcc ggc tct ggg cgt ggg gag gct gag aca cgg gcn tgc atc tac tac   96
Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Ala Cys Ile Tyr Tyr
            20                  25                  30

aac gcc aac tgg gag ctg gag gcn acc aac cag agc ggc ctg gag cgc   144
Asn Ala Asn Trp Glu Leu Glu Ala Thr Asn Gln Ser Gly Leu Glu Arg
        35                  40                  45

tgc gaa ggc gag cag gac aag cgg ctg cac tgc tac gcc tcc tgg cgc   192
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg
    50                  55                  60

aac agc tct ggc acc atc gag ctc gtg aag aag ggc tgc tgg cta gat   240
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65                  70                  75                  80

gac ttc aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac   288
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                85                  90                  95

ccc cag gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc   336
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110

ttc act cat ttg cca gag gct ggg ggc ccg gaa gtc acg tac gag cca   384
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro
        115                 120                 125

ccc ccg aca gcc ccc acc                                           402
Pro Pro Thr Ala Pro Thr
    130
```

<210> 22
<211> 134
<212> PRT
<213> Homo sapiens

<400> 22

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

```
        35                  40                  45
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg
    50                  55                  60
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65                  70                  75                  80
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                85                  90                  95
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro
        115                 120                 125
Pro Pro Thr Ala Pro Thr
    130
```

<210> 23
<211> 402
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)...(402)

<400> 23

```
atg acg gcg ccc tgg gtg gcc ctc gcc ctc ctc tgg gga tcg ctg tgc   48
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Cys
 1               5                  10                  15

gcc ggc tct ggg cgt ggg gag gct gag aca cgg tgg tgc atc tac tac   96
Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Trp Cys Ile Tyr Tyr
            20                  25                  30

aac gcc aac tgg gag ctg gag cgc acc aac cag agc ggc ctg gag cgc   144
Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln Ser Gly Leu Glu Arg
        35                  40                  45

tgc gaa ggc gag cag gac aag cgg ctg cac tgc tac gcc tcc tgg cgc   192
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg
    50                  55                  60

aac agc tct ggc acc atc gag ctc gtg aag aag ggc tgc tgg cta gat   240
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65                  70                  75                  80

gac ttc aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac   288
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                85                  90                  95

ccc cag gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc   336
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110

ttc act cat ttg cca gag gct ggg ggc ccg gaa gtc acg tac gag cca   384
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro
        115                 120                 125

ccc ccg aca gcc ccc acc                                          402
Pro Pro Thr Ala Pro Thr
    130
```

<210> 24
<211> 134
<212> PRT
<213> Homo sapiens

<400> 24

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

Pro Pro Thr Ala Pro Thr
    130
```

<210> 25
<211> 402
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)...(402)

<400> 25

```
atg acg gcg ccc tgg gtg gcc ctc gcc ctc ctc tgg gga tcg ctg tgc   48
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Cys
 1               5                  10                  15

gcc ggc tct ggg cgt ggg gag gct gag aca cgg tac tgc atc tac tac   96
Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Tyr Cys Ile Tyr Tyr
            20                  25                  30

aac gcc aac tgg gag ctg gag cgc acc aac cag agc ggc ctg gag cgc   144
Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln Ser Gly Leu Glu Arg
        35                  40                  45

tgc gaa ggc gag cag gac aag cgg ctg cac tgc tac gcc tcc tgg cgc   192
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg
    50                  55                  60

aac agc tct ggc acc atc gag ctc gtg aag aag ggc tgc tgg cta gat   240
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65                  70                  75                  80

gac ttc aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac   288
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                85                  90                  95

ccc cag gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc   336
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110

ttc act cat ttg cca gag gct ggg ggc ccg gaa gtc acg tac gag cca   384
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro
        115                 120                 125

ccc ccg aca gcc ccc acc                                           402
Pro Pro Thr Ala Pro Thr
    130
```

<210> 26
<211> 134
<212> PRT
<213> Homo sapiens

<400> 26
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Cys
 1   5   10   15
Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Tyr Cys Ile Tyr Tyr
            20   25   30
Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln Ser Gly Leu Glu Arg
        35   40   45
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg
    50   55   60
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65   70   75   80
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                85   90   95
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100   105   110
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro
        115   120   125

Pro Pro Thr Ala Pro Thr
    130

<210> 27
<211> 402
<212> DNA
<213> Homo sapiens

<220>
<221> variation
<222> (82)...(84)
<223> n = a, c, t, or g

<220>
<221> CDS
<222> (1)...(402)

<400> 27
atg acg gcg ccc tgg gtg gcc ctc gcc ctc ctc tgg gga tcg ctg tgc   48
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Cys
 1   5   10   15

gcc ggc tct ggg cgt ggg gag gct gag aca cgg nnn tgc atc tac tac   96
Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Xaa Cys Ile Tyr Tyr
            20   25   30

aac gcc aac tgg gag ctg gag cgc acc aac cag agc ggc ctg gag cgc   144
Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln Ser Gly Leu Glu Arg
        35   40   45

tgc gaa ggc gag cag gac aag cgg ctg cac tgc tac gcc tcc tgg cgc   192
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg
    50   55   60

aac agc tct ggc acc atc gag ctc gtg aag aag ggc tgc tgg cta gat   240
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65   70   75   80

gac ttc aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac   288
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                85   90   95

ccc cag gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc   336
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg

100 105 110

ttc act cat ttg cca gag gct ggg ggc ccg gaa gtc acg tac gag cca 384
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro
115 120 125

ccc ccg aca gcc ccc acc 402
Pro Pro Thr Ala Pro Thr
130

<210> 28
<211> 134
<212> PRT
<213> Homo sapiens

<220>
<221> VARIANT
<222> 28
<223> Xaa = Ala OR Phe OR Gln OR Val OR Ile OR Leu OR
Met OR Lys OR His OR Trp OR Tyr

<400> 28
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Cys
1 5 10 15
Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Xaa Cys Ile Tyr Tyr
20 25 30
Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln Ser Gly Leu Glu Arg
35 40 45
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg
50 55 60
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65 70 75 80
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
85 90 95
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
100 105 110
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro
115 120 125
Pro Pro Thr Ala Pro Thr
130

<210> 29
<211> 402
<212> DNA
<213> Homo sapiens

<220>
<221> variation
<222> (82)...(84)
<223> n = a, c, t, or g

<220>
<221> variation
<222> (118)...(120)
<223> n = a, c, t, or g

<220>
<221> CDS
<222> (1)...(402)

<400> 29
atg acg gcg ccc tgg gtg gcc ctc gcc ctc ctc tgg gga tcg ctg tgc 48
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Cys
1 5 10 15

gcc ggc tct ggg cgt ggg gag gct gag aca cgg nnn tgc atc tac tac 96

```
Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Xaa Cys Ile Tyr Tyr
              20                  25                  30

aac gcc aac tgg gag ctg gag nnn acc aac cag agc ggc ctg gag cgc   144
Asn Ala Asn Trp Glu Leu Glu Xaa Thr Asn Gln Ser Gly Leu Glu Arg
          35                  40                  45

tgc gaa ggc gag cag gac aag cgg ctg cac tgc tac gcc tcc tgg cgc   192

Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg
      50                  55                  60

aac agc tct ggc acc atc gag ctc gtg aag aag ggc tgc tgg cta gat   240
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
 65                  70                  75                  80

gac ttc aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac   288
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                 85                  90                  95

ccc cag gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc   336
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110

ttc act cat ttg cca gag gct ggg ggc ccg gaa gtc acg tac gag cca   384
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro
        115                 120                 125

ccc ccg aca gcc ccc acc                                           402
Pro Pro Thr Ala Pro Thr
    130


<210> 30
<211> 134
<212> PRT
<213> Homo sapiens

<220>
<221> VARIANT
<222> 28
<223> Xaa = Ala OR Phe OR Gln OR Val OR Ile OR Leu OR
      Met OR Lys OR His OR Tyr OR Trp

<220>
<221> VARIANT
<222> 40
<223> Xaa = Ala OR Gly OR Gln OR Met OR His OR Lys OR
      Asn

<400> 30
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Cys
 1               5                  10                  15
Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Xaa Cys Ile Tyr Tyr
            20                  25                  30
Asn Ala Asn Trp Glu Leu Glu Xaa Thr Asn Gln Ser Gly Leu Glu Arg
        35                  40                  45
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg
    50                  55                  60
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65                  70                  75                  80
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                85                  90                  95
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro
        115                 120                 125
Pro Pro Thr Ala Pro Thr
```

130

<210> 31
<211> 402
<212> DNA
<213> Homo sapiens

<220>
<221> variation
<222> (118)...(120)
<223> n = a, c, t, or g

<220>
<221> CDS
<222> (1)...(402)

<400> 31
atg acg gcg ccc tgg gtg gcc ctc gcc ctc ctc tgg gga tcg ctg tgc 48
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Cys
1 5 10 15

gcc ggc tct ggg cgt ggg gag gct gag aca cgg gag tgc atc tac tac 96
Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Glu Cys Ile Tyr Tyr
20 25 30

aac gcc aac tgg gag ctg gag nnn acc aac cag agc ggc ctg gag cgc 144
Asn Ala Asn Trp Glu Leu Glu Xaa Thr Asn Gln Ser Gly Leu Glu Arg
35 40 45

tgc gaa ggc gag cag gac aag cgg ctg cac tgc tac gcc tcc tgg cgc 192
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg
50 55 60

aac agc tct ggc acc atc gag ctc gtg aag aag ggc tgc tgg cta gat 240
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65 70 75 80

gac ttc aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac 288
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
85 90 95

ccc cag gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc 336
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
100 105 110

ttc act cat ttg cca gag gct ggg ggc ccg gaa gtc acg tac gag cca 384
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro
115 120 125

ccc ccg aca gcc ccc acc 402
Pro Pro Thr Ala Pro Thr
130

<210> 32
<211> 134
<212> PRT
<213> Homo sapiens

<220>
<221> VARIANT
<222> 40
<223> Xaa = Gly OR Gln OR Met OR His OR Lys OR Asn

<400> 32
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Cys
1 5 10 15

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

<210> 33
<211> 402
<212> DNA
<213> Homo sapiens

<220>
<221> variation
<222> 84
<223> n = a, c, t, or g

<220>
<221> variation
<222> 192
<223> n = a, c, t, or g

<220>
<221> CDS
<222> (1)...(402)

<400> 33

```
atg acg gcg ccc tgg gtg gcc ctc gcc ctc ctc tgg gga tcg ctg tgc   48
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Cys
 1               5                  10                  15

gcc ggc tct ggg cgt ggg gag gct gag aca cgg gcn tgc atc tac tac   96
Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Ala Cys Ile Tyr Tyr
            20                  25                  30

aac gcc aac tgg gag ctg gag cgc acc aac cag agc ggc ctg gag cgc   144
Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln Ser Gly Leu Glu Arg
        35                  40                  45

tgc gaa ggc gag cag gac aag cgg ctg cac tgc tac gcc tcc tgg gcn   192
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Ala
    50                  55                  60

aac agc tct ggc acc atc gag ctc gtg aag aag ggc tgc tgg cta gat   240

Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
 65                  70                  75                  80

gac ttc aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac   288
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                85                  90                  95

ccc cag gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc   336
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110

ttc act cat ttg cca gag gct ggg ggc ccg gaa gtc acg tac gag cca   384
```

```
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro
        115                 120                 125

ccc ccg aca gcc ccc acc                                         402
Pro Pro Thr Ala Pro Thr
    130
```

<210> 34
<211> 134
<212> PRT
<213> Homo sapiens

<400> 34

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

<210> 35
<211> 402
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)...(402)

<220>
<221> variation
<222> 84
<223> n = a, c, t, or g

<400> 35

```
atg acg gcg ccc tgg gtg gcc ctc gcc ctc ctc tgg gga tcg ctg tgc   48
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Cys
 1               5                  10                  15

gcc ggc tct ggg cgt ggg gag gct gag aca cgg gcn tgc atc tac tac   96
Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Ala Cys Ile Tyr Tyr
            20                  25                  30

aac gcc aac tgg gag ctg gag gcn acc aac cag agc ggc ctg gag cgc   144
Asn Ala Asn Trp Glu Leu Glu Ala Thr Asn Gln Ser Gly Leu Glu Arg
        35                  40                  45

tgc gaa ggc gag cag gac aag cgg ctg cac tgc tac gcc tcc tgg gcn   192
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Ala
    50                  55                  60

aac agc tct ggc acc atc gag ctc gtg aag aag ggc tgc tgg cta gat   240
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65                  70                  75                  80
```

```
gac ttc aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac   288
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                 85                  90                  95

ccc cag gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc   336
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110

ttc act cat ttg cca gag gct ggg ggc ccg gaa gtc acg tac gag cca   384
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro
        115                 120                 125

ccc ccg aca gcc ccc acc                                           402
Pro Pro Thr Ala Pro Thr
    130
```

<210> 36
<211> 134
<212> PRT
<213> Homo sapiens

<400> 36

```
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Cys
 1               5                  10                  15
Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Ala Cys Ile Tyr Tyr
            20                  25                  30

Asn Ala Asn Trp Glu Leu Glu Ala Thr Asn Gln Ser Gly Leu Glu Arg
        35                  40                  45
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Ala
    50                  55                  60
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65                  70                  75                  80
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                85                  90                  95
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro
        115                 120                 125
Pro Pro Thr Ala Pro Thr
    130
```

<210> 37
<211> 402
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)...(402)

<220>
<221> variation
<222> 192
<223> n = a, c, t, or g

<400> 37

```
atg acg gcg ccc tgg gtg gcc ctc gcc ctc ctc tgg gga tcg ctg tgc   48
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Cys
 1               5                  10                  15

gcc ggc tct ggg cgt ggg gag gct gag aca cgg tgg tgc atc tac tac   96
Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Trp Cys Ile Tyr Tyr
            20                  25                  30
```

```
aac gcc aac tgg gag ctg gag cgc acc aac cag agc ggc ctg gag cgc   144
Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln Ser Gly Leu Glu Arg
          35                  40                  45

tgc gaa ggc gag cag gac aag cgg ctg cac tgc tac gcc tcc tgg gcn   192
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Ala
      50                  55                  60

aac agc tct ggc acc atc gag ctc gtg aag aag ggc tgc tgg cta gat   240
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
 65                  70                  75                  80

gac ttc aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac   288
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                 85                  90                  95

ccc cag gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc   336
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110

ttc act cat ttg cca gag gct ggg ggc ccg gaa gtc acg tac gag cca   384

Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro
        115                 120                 125

ccc ccg aca gcc ccc acc                                          402
Pro Pro Thr Ala Pro Thr
    130
```

<210> 38
<211> 134
<212> PRT
<213> Homo sapiens

<400> 38

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

<210> 39
<211> 402
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)...(402)

<400> 39

```
atg acg gcg ccc tgg gtg gcc ctc gcc ctc ctc tgg gga tcg ctg tgc   48
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Cys
 1               5                  10                  15

gcc ggc tct ggg cgt ggg gag gct gag aca cgg tac tgc atc tac tac   96
Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Tyr Cys Ile Tyr Tyr
            20                  25                  30

aac gcc aac tgg gag ctg gag cgc acc aac cag agc ggc ctg gag cgc   144
Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln Ser Gly Leu Glu Arg
        35                  40                  45

tgc gaa ggc gag cag gac aag cgg ctg cac tgc tac gcc tcc tgg gcn   192
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Ala
    50                  55                  60

aac agc tct ggc acc atc gag ctc gtg aag aag ggc tgc tgg cta gat   240
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65                  70                  75                  80

gac ttc aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac   288
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                85                  90                  95

ccc cag gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc   336
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110

ttc act cat ttg cca gag gct ggg ggc ccg gaa gtc acg tac gag cca   384

Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro
        115                 120                 125

ccc ccg aca gcc ccc acc                                           402
Pro Pro Thr Ala Pro Thr
    130
```

<210> 40
<211> 134
<212> PRT
<213> Homo sapiens

<400> 40

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

<210> 41
<211> 402
<212> DNA
<213> Homo sapiens

<220>
<221> variation
<222> (82)...(84)
<223> n = a, c, t, or g

<220>
<221> CDS
<222> (1)...(402)

<400> 41
```
atg acg gcg ccc tgg gtg gcc ctc gcc ctc ctc tgg gga tcg ctg tgc   48
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Cys
 1               5                  10                  15

gcc ggc tct ggg cgt ggg gag gct gag aca cgg nnn tgc atc tac tac   96
Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Xaa Cys Ile Tyr Tyr
            20                  25                  30

aac gcc aac tgg gag ctg gag cgc acc aac cag agc ggc ctg gag cgc   144
Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln Ser Gly Leu Glu Arg
        35                  40                  45

tgc gaa ggc gag cag gac aag cgg ctg cac tgc tac gcc tcc tgg gcn   192
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Ala
    50                  55                  60

aac agc tct ggc acc atc gag ctc gtg aag aag ggc tgc tgg cta gat   240
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65                  70                  75                  80

gac ttc aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac   288
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                85                  90                  95

ccc cag gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc   336
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110

ttc act cat ttg cca gag gct ggg ggc ccg gaa gtc acg tac gag cca   384
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro
        115                 120                 125

ccc ccg aca gcc ccc acc                                           402
Pro Pro Thr Ala Pro Thr
    130
```

<210> 42
<211> 134
<212> PRT
<213> Homo sapiens

<220>
<221> VARIANT
<222> 28
<223> Xaa = Ala OR Phe OR Gln OR Val OR Ile OR Leu OR
Met OR Lys OR His OR Tyr OR Trp

<400> 42
```
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Cys
 1               5                  10                  15
Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Xaa Cys Ile Tyr Tyr
            20                  25                  30
Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln Ser Gly Leu Glu Arg
        35                  40                  45
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Ala
    50                  55                  60
```

```
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65                  70                  75                  80
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                85                  90                  95
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro
        115                 120                 125
Pro Pro Thr Ala Pro Thr
    130
```

<210> 43
<211> 402
<212> DNA
<213> Homo sapiens

<220>
<221> variation
<222> (82)...(84)
<223> n = a, c, t, or g

<220>
<221> variation
<222> (118)...(120)
<223> n = a, c, t, or g

<220>
<221> CDS
<222> (1)...(402)

<400> 43

```
atg acg gcg ccc tgg gtg gcc ctc gcc ctc ctc tgg gga tcg ctg tgc   48
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Cys
 1               5                  10                  15

gcc ggc tct ggg cgt ggg gag gct gag aca cgg nnn tgc atc tac tac   96
Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Xaa Cys Ile Tyr Tyr
            20                  25                  30

aac gcc aac tgg gag ctg gag nnn acc aac cag agc ggc ctg gag cgc   144
Asn Ala Asn Trp Glu Leu Glu Xaa Thr Asn Gln Ser Gly Leu Glu Arg
        35                  40                  45

tgc gaa ggc gag cag gac aag cgg ctg cac tgc tac gcc tcc tgg gcn   192
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Ala
    50                  55                  60

aac agc tct ggc acc atc gag ctc gtg aag aag ggc tgc tgg cta gat   240
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65                  70                  75                  80

gac ttc aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac   288
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                85                  90                  95

ccc cag gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc   336
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110

ttc act cat ttg cca gag gct ggg ggc ccg gaa gtc acg tac gag cca   384
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro
        115                 120                 125

ccc ccg aca gcc ccc acc                                          402
Pro Pro Thr Ala Pro Thr
    130
```

<210> 44
<211> 134
<212> PRT
<213> Homo sapiens

<220>
<221> VARIANT
<222> 28
<223> Xaa = Ala OR Phe OR Gln OR Val OR Ile OR Leu OR
Met OR Lys OR His OR Trp OR Tyr

<220>
<221> VARIANT
<222> 40
<223> Xaa = Ala OR Gly OR Gln OR Met OR His OR Lys OR
Asn

<400> 44
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Cys
1 5 10 15
Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Xaa Cys Ile Tyr Tyr
20 25 30
Asn Ala Asn Trp Glu Leu Glu Xaa Thr Asn Gln Ser Gly Leu Glu Arg
35 40 45
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Ala
50 55 60
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65 70 75 80
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
85 90 95
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
100 105 110
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro
115 120 125
Pro Pro Thr Ala Pro Thr
130

<210> 45
<211> 402
<212> DNA
<213> Homo sapiens

<220>
<221> variation
<222> (118)...(120)
<223> n = a, c, t, or g

<220>
<221> CDS
<222> (1)...(402)

<400> 45
atg acg gcg ccc tgg gtg gcc ctc gcc ctc ctc tgg gga tcg ctg tgc 48
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Cys
1 5 10 15

gcc ggc tct ggg cgt ggg gag gct gag aca cgg gag tgc atc tac tac 96
Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Glu Cys Ile Tyr Tyr
20 25 30

aac gcc aac tgg gag ctg gag nnn acc aac cag agc ggc ctg gag cgc 144
Asn Ala Asn Trp Glu Leu Glu Xaa Thr Asn Gln Ser Gly Leu Glu Arg
35 40 45

tgc gaa ggc gag cag gac aag cgg ctg cac tgc tac gcc tcc tgg gcn 192

```
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Ala
     50                  55                  60

aac agc tct ggc acc atc gag ctc gtg aag aag ggc tgc tgg cta gat   240
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
 65                  70                  75                  80

gac ttc aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac   288
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                 85                  90                  95

ccc cag gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc   336
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110

ttc act cat ttg cca gag gct ggg ggc ccg gaa gtc acg tac gag cca   384
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro
        115                 120                 125

ccc ccg aca gcc ccc acc                                          402
Pro Pro Thr Ala Pro Thr
    130
```

<210> 46
<211> 134
<212> PRT
<213> Homo sapiens

<220>
<221> VARIANT
<222> 40
<223> Xaa = Gly OR Glu OR Met OR His OR Lys OR Asn

<400> 46

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

Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro
        115                 120                 125
Pro Pro Thr Ala Pro Thr
    130
```

<210> 47
<211> 512
<212> PRT
<213> Homo sapiens

<400> 47

```
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Cys
 1               5                  10                  15

Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Glu Cys Ile Tyr Tyr
            20                  25                  30
Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln Ser Gly Leu Glu Arg
```

```
        35                  40                  45
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg
    50                  55                  60
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65                  70                  75                  80
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                85                  90                  95
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro
        115                 120                 125
Pro Pro Thr Ala Pro Thr Leu Leu Thr Val Leu Ala Tyr Ser Leu Leu
    130                 135                 140
Pro Ile Gly Gly Leu Ser Leu Ile Val Leu Leu Ala Phe Trp Met Tyr
145                 150                 155                 160
Arg His Arg Lys Pro Pro Tyr Gly His Val Asp Ile His Glu Asp Pro
                165                 170                 175
Gly Pro Pro Pro Pro Ser Pro Leu Val Gly Leu Lys Pro Leu Gln Leu
            180                 185                 190
Leu Glu Ile Lys Ala Arg Gly Arg Phe Gly Cys Val Trp Lys Ala Gln
        195                 200                 205
Leu Met Asn Asp Phe Val Ala Val Lys Ile Phe Pro Leu Gln Asp Lys
    210                 215                 220
Gln Ser Trp Gln Ser Glu Arg Glu Ile Phe Ser Thr Pro Gly Met Lys
225                 230                 235                 240
His Glu Asn Leu Leu Gln Phe Ile Ala Ala Glu Lys Arg Gly Ser Asn
                245                 250                 255
Leu Glu Val Glu Leu Trp Leu Ile Thr Ala Phe His Asp Lys Gly Ser
            260                 265                 270
Leu Thr Asp Tyr Leu Lys Gly Asn Ile Ile Thr Trp Asn Glu Leu Cys
        275                 280                 285
His Val Ala Glu Thr Met Ser Arg Gly Leu Ser Tyr Leu His Glu Asp
    290                 295                 300
Val Pro Trp Cys Arg Gly Glu Gly His Lys Pro Ser Ile Ala His Arg
305                 310                 315                 320
Asp Phe Lys Ser Lys Asn Val Leu Leu Lys Ser Asp Leu Thr Ala Val
                325                 330                 335
Leu Ala Asp Phe Gly Leu Ala Val Arg Phe Glu Pro Gly Lys Pro Pro
            340                 345                 350
Gly Asp Thr His Gly Gln Val Gly Thr Arg Arg Tyr Met Ala Pro Glu
        355                 360                 365
Val Leu Glu Gly Ala Ile Asn Phe Gln Arg Asp Ala Phe Leu Arg Ile
    370                 375                 380
Asp Met Tyr Ala Met Gly Leu Val Leu Trp Glu Leu Val Ser Arg Cys
385                 390                 395                 400
Lys Ala Ala Asp Gly Pro Val Asp Glu Tyr Met Leu Pro Phe Glu Glu
                405                 410                 415
Glu Ile Gly Gln His Pro Ser Leu Glu Glu Leu Gln Glu Val Val Val
            420                 425                 430
His Lys Lys Met Arg Pro Thr Ile Lys Asp His Trp Leu Lys His Pro
        435                 440                 445
Gly Leu Ala Gln Leu Cys Val Thr Ile Glu Glu Cys Trp Asp His Asp
    450                 455                 460
Ala Glu Ala Arg Leu Ser Ala Gly Cys Val Glu Glu Arg Val Ser Leu
465                 470                 475                 480
Ile Arg Arg Ser Val Asn Gly Thr Thr Ser Asp Cys Leu Val Ser Leu
                485                 490                 495

Val Thr Ser Val Thr Asn Val Asp Leu Pro Pro Lys Glu Ser Ser Ile
            500                 505                 510
```

<210> 48
<211> 426
<212> PRT
<213> Homo sapiens

<400> 48

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

Met Leu Tyr Tyr Asp Asp Gly Gln Asn Ile Ile Lys Lys Asp Ile Gln
                405                 410                 415
Asn Met Ile Val Glu Glu Cys Gly Cys Ser
            420                 425


<210> 49
<211> 375
<212> PRT
<213> Homo sapiens

<400> 49
Met Gln Lys Leu Gln Leu Cys Val Tyr Ile Tyr Leu Phe Met Leu Ile
 1               5                  10                  15
Val Ala Gly Pro Val Asp Leu Asn Glu Asn Ser Glu Gln Lys Glu Asn
            20                  25                  30
Val Glu Lys Glu Gly Leu Cys Asn Ala Cys Thr Trp Arg Gln Asn Thr
```

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


<210> 50
<211> 217
<212> PRT
<213> Homo sapiens

<400> 50
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
 1               5                  10                  15
Pro Lys Asp Ile Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45
Val Gly Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
        115                 120                 125
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
```

```
    130                 135                 140
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205
Lys Ser Leu Ser Leu Ser Pro Gly Lys
    210                 215
```

<210> 51
<211> 480
<212> DNA
<213> Homo sapiens

<220>
<221> variation
<222> (1)...(480)
<223> n = a, c, t, or g

<220>
<221> CDS
<222> (1)...(480)

<400> 51

```
atg acg gcg ccc tgg gtg gcc ctc gcc ctc ctc tgg gga tcg ctg tgc   48
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Cys
 1               5                  10                  15

gcc ggc tct ggg cgt ggg gag gct gag aca cgg nnn tgc atc tac tac   96
Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Xaa Cys Ile Tyr Tyr
            20                  25                  30

aac gcc aac tgg gag ctg gag nnn acc aac cag agc ggc ctg gag cgc   144
Asn Ala Asn Trp Glu Leu Glu Xaa Thr Asn Gln Ser Gly Leu Glu Arg
        35                  40                  45

tgc gaa ggc gag cag gac aag cgg ctg cac tgc tac gcc tcc tgg cgc   192
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg
    50                  55                  60

aac agc tct ggc acc atc gag ctc gtg aag aag ggc tgc tgg cta gat   240
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65                  70                  75                  80

gac ttc aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac   288
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                85                  90                  95

ccc cag gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc   336
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110

ttc act cat ttg cca gag gct ggg ggc ccg gaa gga ccc tgg gcc tcc   384
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Gly Pro Trp Ala Ser
        115                 120                 125

acc acc atc ccc tct ggt ggg cct gaa gcc act gca gct gct gga gat   432
Thr Thr Ile Pro Ser Gly Gly Pro Glu Ala Thr Ala Ala Ala Gly Asp
    130                 135                 140

caa ggc tcg ggg gcg ctt tgg ctg tgt ctg gaa ggc cca gct cat gaa   480
Gln Gly Ser Gly Ala Leu Trp Leu Cys Leu Glu Gly Pro Ala His Glu
145                 150                 155                 160
```

<210> 52
<211> 160
<212> PRT
<213> Homo sapiens

<220>
<221> VARIANT
<222> 28
<223> Xaa = any amino acid

<220>
<221> VARIANT
<222> 40
<223> Xaa = any amino acid

<400> 52
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Cys
 1   5   10   15
Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Xaa Cys Ile Tyr Tyr
            20   25   30
Asn Ala Asn Trp Glu Leu Glu Xaa Thr Asn Gln Ser Gly Leu Glu Arg
        35   40   45
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg
    50   55   60
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65   70   75   80
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                85   90   95
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100   105   110
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Gly Pro Trp Ala Ser
        115   120   125
Thr Thr Ile Pro Ser Gly Gly Pro Glu Ala Thr Ala Ala Ala Gly Asp
    130   135   140
Gln Gly Ser Gly Ala Leu Trp Leu Cys Leu Glu Gly Pro Ala His Glu
145   150   155   160

<210> 53
<211> 402
<212> DNA
<213> Homo sapiens

<220>
<221> variation
<222> (1)...(402)
<223> n = a, c, t, or g

<220>
<221> CDS
<222> (1)...(402)

<400> 53
atg acg gcg ccc tgg gtg gcc ctc gcc ctc ctc tgg gga tcg ctg tgc   48
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Cys
 1   5   10   15

gcc ggc tct ggg cgt ggg gag gct gag aca cgg nnn tgc atc tac tac   96
Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Xaa Cys Ile Tyr Tyr
            20   25   30

aac gcc aac tgg gag ctg gag nnn acc aac cag agc ggc ctg gag cgc   144
Asn Ala Asn Trp Glu Leu Glu Xaa Thr Asn Gln Ser Gly Leu Glu Arg
        35   40   45

tgc gaa ggc gag cag gac aag cgg ctg cac tgc tac gcc tcc tgg cgc   192

```
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg
     50                  55                  60

aac agc tct ggc acc atc gag ctc gtg aag aag ggc tgc tgg cta gat   240
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
 65                  70                  75                  80

gac ttc aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac   288
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                85                  90                  95

ccc cag gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc   336
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110

ttc act cat ttg cca gag gct ggg ggc ccg gaa gtc acg tac gag cca   384
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro
        115                 120                 125

ccc ccg aca gcc ccc acc                                          402
Pro Pro Thr Ala Pro Thr
    130
```

<210> 54
<211> 134
<212> PRT
<213> Homo sapiens

<220>
<221> VARIANT
<222> 28
<223> Xaa = any amino acid

<220>
<221> VARIANT
<222> 40
<223> Xaa = any amino acid

<400> 54

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

<210> 55
<211> 402
<212> DNA
<213> Homo sapiens

<220>
<221> variation
<222> (1)...(402)

<223> n = a, c, t, or g

<220>
<221> CDS
<222> (1)...(402)

<400> 55

```
atg acg gcg ccc tgg gtg gcc ctc gcc ctc ctc tgg gga tcg ctg tgc   48
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Cys
 1               5                  10                  15

gcc ggc tct ggg cgt ggg gag gct gag aca cgg nnn tgc atc tac tac   96
Ala Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Xaa Cys Ile Tyr Tyr
            20                  25                  30

aac gcc aac tgg gag ctg gag nnn acc aac cag agc ggc ctg gag cgc   144
Asn Ala Asn Trp Glu Leu Glu Xaa Thr Asn Gln Ser Gly Leu Glu Arg
        35                  40                  45

tgc gaa ggc gag cag gac aag cgg ctg cac tgc tac gcc tcc tgg gcn   192
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Ala
    50                  55                  60

aac agc tct ggc acc atc gag ctc gtg aag aag ggc tgc tgg cta gat   240
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65                  70                  75                  80

gac ttc aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac   288
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                85                  90                  95

ccc cag gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc   336
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110

ttc act cat ttg cca gag gct ggg ggc ccg gaa gtc acg tac gag cca   384
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro
        115                 120                 125

ccc ccg aca gcc ccc acc                                           402
Pro Pro Thr Ala Pro Thr
    130
```

<210> 56
<211> 134
<212> PRT
<213> Homo sapiens

<220>
<221> VARIANT
<222> 28
<223> Xaa = any amino acid

<220>
<221> VARIANT
<222> 40
<223> Xaa = any amino acid

<400> 56

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

```
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65                  70                  75                  80
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                85                  90                  95
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro
        115                 120                 125

Pro Pro Thr Ala Pro Thr
    130
```

<210> 57
<211> 1044
<212> DNA
<213> Homo sapiens

<400> 57

```
tct ggg cgt ggg gag gct gag aca cgg gag tgc atc tac tac aac gcc   48
Ser Gly Arg Gly Glu Ala Glu Thr Arg Glu Cys Ile Tyr Tyr Asn Ala
 1               5                  10                  15

aac tgg gag ctg gag cgc acc aac cag agc ggc ctg gag cgc tgc gaa   96
Asn Trp Glu Leu Glu Arg Thr Asn Gln Ser Gly Leu Glu Arg Cys Glu
            20                  25                  30

ggc gag cag gac aag cgg ctg cac tgc tac gcc tcc tgg cgc aac agc   144
Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg Asn Ser
        35                  40                  45

tct ggc acc atc gag ctc gtg aag aag ggc tgc tgg cta gat gac ttc   192
Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp Asp Phe
    50                  55                  60

aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac ccc cag   240
Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn Pro Gln
65                  70                  75                  80

gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc ttc act   288
Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg Phe Thr
                85                  90                  95

cat ttg cca gag gct ggg ggc ccg gaa gtc acg tac gag cca ccc ccg   336
His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro Pro Pro
            100                 105                 110

aca gcc ccc act gga gga gga gga tct gac aaa act cac aca tgc cca   384
Thr Ala Pro Thr Gly Gly Gly Gly Ser Asp Lys Thr His Thr Cys Pro
        115                 120                 125

ccg tgc cca gca cct gaa ctc ctg ggg gga ccg tca gtc ttc ctc ttc   432

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
    130                 135                 140

ccc cca aaa ccc aag gac atc ctc atg atc tcc cgg acc cct gag gtc   480
Pro Pro Lys Pro Lys Asp Ile Leu Met Ile Ser Arg Thr Pro Glu Val
145                 150                 155                 160

aca tgc gtg gtg gtg gac gtg agc cac gaa gac cct gag gtc aag ttc   528
Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
                165                 170                 175

aac tgg tac gtg ggc ggc gtg gag gtg cat aat gcc aag aca aag ccg   576
Asn Trp Tyr Val Gly Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
            180                 185                 190
```

```
cgg gag gag cag tac aac agc acg tac cgt gtg gtc agc gtc ctc acc   624
Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
        195                 200                 205

gtc ctg cac cag gac tgg ctg aat ggc aag gag tac aag tgc aag gtc   672
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
    210                 215                 220

tcc aac aaa gcc ctc cca gcc ccc atc gag aaa acc atc tcc aaa gcc   720
Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
225                 230                 235                 240

aaa ggg cag ccc cga gaa cca cag gtg tac acc ctg ccc cca tcc cgg   768
Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
                245                 250                 255

gat gag ctg acc aag aac cag gtc agc ctg acc tgc ctg gtc aaa ggc   816
Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
            260                 265                 270

ttc tat ccc agc gac atc gcc gtg gag tgg gag agc aat ggg cag ccg   864
Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
        275                 280                 285

gag aac aac tac aag acc acg cct ccc gtg ctg gac tcc gac ggc tcc   912
Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
    290                 295                 300

ttc ttc ctc tac agc aag ctc acc gtg gac aag agc agg tgg cag cag   960
Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
305                 310                 315                 320

ggg aac gtc ttc tca tgc tcc gtg atg cat gag gct ctg cac aac cac   1008
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
                325                 330                 335

tac acg cag aag agc ctc tcc ctg tct ccg ggt aaa tga               1044
Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys  *
            340                 345
```

<210> 58
<211> 348
<212> PRT
<213> Homo sapiens

<400> 58

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

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
    130                 135                 140
Pro Pro Lys Pro Lys Asp Ile Leu Met Ile Ser Arg Thr Pro Glu Val
145                 150                 155                 160
```

```
Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
                165                 170                 175
Asn Trp Tyr Val Gly Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
            180                 185                 190
Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
        195                 200                 205
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
    210                 215                 220
Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
225                 230                 235                 240
Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
                245                 250                 255
Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
            260                 265                 270
Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
        275                 280                 285
Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
    290                 295                 300
Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
305                 310                 315                 320
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
                325                 330                 335
Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
            340                 345
```

<210> 59
<211> 1044
<212> DNA
<213> Homo sapiens

<400> 59

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tct ggg cgt ggg gag gct gag aca cgg gcg tgc atc tac tac aac gcc   48
Ser Gly Arg Gly Glu Ala Glu Thr Arg Ala Cys Ile Tyr Tyr Asn Ala
1               5                   10                  15

aac tgg gag ctg gag cgc acc aac cag agc ggc ctg gag cgc tgc gaa   96
Asn Trp Glu Leu Glu Arg Thr Asn Gln Ser Gly Leu Glu Arg Cys Glu
            20                  25                  30

ggc gag cag gac aag cgg ctg cac tgc tac gcc tcc tgg cgc aac agc   144
Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg Asn Ser
        35                  40                  45

tct ggc acc atc gag ctc gtg aag aag ggc tgc tgg cta gat gac ttc   192
Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp Asp Phe
    50                  55                  60

aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac ccc cag   240
Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn Pro Gln
65                  70                  75                  80

gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc ttc act   288
Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg Phe Thr
                85                  90                  95

cat ttg cca gag gct ggg ggc ccg gaa gtc acg tac gag cca ccc ccg   336
His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro Pro Pro
            100                 105                 110

aca gcc ccc act gga gga gga gga tct gac aaa act cac aca tgc cca   384
Thr Ala Pro Thr Gly Gly Gly Gly Ser Asp Lys Thr His Thr Cys Pro
        115                 120                 125

ccg tgc cca gca cct gaa ctc ctg ggg gga ccg tca gtc ttc ctc ttc   432
Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
    130                 135                 140
```

```
ccc cca aaa ccc aag gac atc ctc atg atc tcc cgg acc cct gag gtc   480
Pro Pro Lys Pro Lys Asp Ile Leu Met Ile Ser Arg Thr Pro Glu Val
145                 150                 155                 160

aca tgc gtg gtg gtg gac gtg agc cac gaa gac cct gag gtc aag ttc   528
Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
                165                 170                 175

aac tgg tac gtg ggc ggc gtg gag gtg cat aat gcc aag aca aag ccg   576
Asn Trp Tyr Val Gly Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
            180                 185                 190

cgg gag gag cag tac aac agc acg tac cgt gtg gtc agc gtc ctc acc   624
Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
        195                 200                 205

gtc ctg cac cag gac tgg ctg aat ggc aag gag tac aag tgc aag gtc   672
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
    210                 215                 220

tcc aac aaa gcc ctc cca gcc ccc atc gag aaa acc atc tcc aaa gcc   720
Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
225                 230                 235                 240

aaa ggg cag ccc cga gaa cca cag gtg tac acc ctg ccc cca tcc cgg   768
Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
                245                 250                 255

gat gag ctg acc aag aac cag gtc agc ctg acc tgc ctg gtc aaa ggc   816
Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
            260                 265                 270

ttc tat ccc agc gac atc gcc gtg gag tgg gag agc aat ggg cag ccg   864
Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
        275                 280                 285

gag aac aac tac aag acc acg cct ccc gtg ctg gac tcc gac ggc tcc   912
Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
    290                 295                 300

ttc ttc ctc tac agc aag ctc acc gtg gac aag agc agg tgg cag cag   960
Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
305                 310                 315                 320

ggg aac gtc ttc tca tgc tcc gtg atg cat gag gct ctg cac aac cac   1008
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
                325                 330                 335

tac acg cag aag agc ctc tcc ctg tct ccg ggt aaa tga               1044

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys  *
            340                 345


<210> 60
<211> 348
<212> PRT
<213> Homo sapiens

<400> 60
Ser Gly Arg Gly Glu Ala Glu Thr Arg Ala Cys Ile Tyr Tyr Asn Ala
1               5                   10                  15
Asn Trp Glu Leu Glu Arg Thr Asn Gln Ser Gly Leu Glu Arg Cys Glu
            20                  25                  30
Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg Asn Ser
        35                  40                  45
Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp Asp Phe
    50                  55                  60
```

```
Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn Pro Gln
65                  70                  75                  80
Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg Phe Thr
                85                  90                  95
His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro Pro Pro
            100                 105                 110
Thr Ala Pro Thr Gly Gly Gly Gly Ser Asp Lys Thr His Thr Cys Pro
        115                 120                 125
Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
    130                 135                 140
Pro Pro Lys Pro Lys Asp Ile Leu Met Ile Ser Arg Thr Pro Glu Val
145                 150                 155                 160
Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
                165                 170                 175
Asn Trp Tyr Val Gly Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
            180                 185                 190
Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
        195                 200                 205
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
    210                 215                 220
Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
225                 230                 235                 240
Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
                245                 250                 255

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
            260                 265                 270
Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
        275                 280                 285
Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
    290                 295                 300
Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
305                 310                 315                 320
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
                325                 330                 335
Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
            340                 345


<210> 61
<211> 1044
<212> DNA
<213> Homo sapiens

<400> 61
tct ggg cgt ggg gag gct gag aca cgg tgg tgc ctc tac tac aac gcc   48
Ser Gly Arg Gly Glu Ala Glu Thr Arg Trp Cys Leu Tyr Tyr Asn Ala
1               5                   10                  15

aac tgg gag ctg gag cgc acc aac cag agc ggc ctg gag cgc tgc gaa   96
Asn Trp Glu Leu Glu Arg Thr Asn Gln Ser Gly Leu Glu Arg Cys Glu
            20                  25                  30

ggc gag cag gac aag cgg ctg cac tgc tac gcc tcc tgg cgc aac agc   144
Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg Asn Ser
        35                  40                  45

tct ggc acc atc gag ctc gtg aag aag ggc tgc tgg cta gat gac ttc   192
Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp Asp Phe
    50                  55                  60

aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac ccc cag   240
Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn Pro Gln
65                  70                  75                  80

gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc ttc act   288
Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg Phe Thr
                85                  90                  95
```

```
cat ttg cca gag gct ggg ggc ccg gaa gtc acg tac gag cca ccc ccg   336
His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro Pro Pro
            100                 105                 110

aca gcc ccc act gga gga gga gga tct gac aaa act cac aca tgc cca   384
Thr Ala Pro Thr Gly Gly Gly Gly Ser Asp Lys Thr His Thr Cys Pro
        115                 120                 125

ccg tgc cca gca cct gaa ctc ctg ggg gga ccg tca gtc ttc ctc ttc   432
Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
    130                 135                 140

ccc cca aaa ccc aag gac atc ctc atg atc tcc cgg acc cct gag gtc   480
Pro Pro Lys Pro Lys Asp Ile Leu Met Ile Ser Arg Thr Pro Glu Val
145                 150                 155                 160

aca tgc gtg gtg gtg gac gtg agc cac gaa gac cct gag gtc aag ttc   528
Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
                165                 170                 175

aac tgg tac gtg ggc ggc gtg gag gtg cat aat gcc aag aca aag ccg   576
Asn Trp Tyr Val Gly Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
            180                 185                 190

cgg gag gag cag tac aac agc acg tac cgt gtg gtc agc gtc ctc acc   624
Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
        195                 200                 205

gtc ctg cac cag gac tgg ctg aat ggc aag gag tac aag tgc aag gtc   672
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
    210                 215                 220

tcc aac aaa gcc ctc cca gcc ccc att gag aaa acc atc tcc aaa gcc   720
Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
225                 230                 235                 240

aaa ggg cag ccc cga gaa cca cag gtg tac acc ctg ccc cca tcc cgg   768
Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
                245                 250                 255

gat gag ctg acc aag aac cag gtc agc ctg acc tgc ctg gtc aaa ggc   816
Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
            260                 265                 270

ttc tat ccc agc gac atc gcc gtg gag tgg gag agc aat ggg cag ccg   864
Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
        275                 280                 285

gag aac aac tac aag acc acg cct ccc gtg ctg gac tcc gac ggc tcc   912
Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
    290                 295                 300

ttc ttc ctc tac agc aag ctc acc gtg gac aag agc agg tgg cag cag   960
Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
305                 310                 315                 320

ggg aac gtc ttc tca tgc tcc gtg atg cat gag gct ctg cac aac cac   1008
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
                325                 330                 335

tac acg cag aag agc ctc tcc ctg tct ccg ggt aaa tga               1044
Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys  *
            340                 345
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<210> 62
<211> 348

<212> PRT
<213> Homo sapiens

<400> 62

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Ser Gly Arg Gly Glu Ala Glu Thr Arg Trp Cys Leu Tyr Tyr Asn Ala
1               5                  10                  15
Asn Trp Glu Leu Glu Arg Thr Asn Gln Ser Gly Leu Glu Arg Cys Glu
            20                  25                  30
Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg Asn Ser
        35                  40                  45

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

<210> 63
<211> 1044
<212> DNA
<213> Homo sapiens

<400> 63

```
tct ggg cgt ggg gag gct gag aca cgg tac tgc atc tac tac aac gcc   48
Ser Gly Arg Gly Glu Ala Glu Thr Arg Tyr Cys Ile Tyr Tyr Asn Ala
1               5                  10                  15

aac tgg gag ctg gag cgc acc aac cag agc ggc ctg gag cgc tgc gaa   96
Asn Trp Glu Leu Glu Arg Thr Asn Gln Ser Gly Leu Glu Arg Cys Glu
            20                  25                  30

ggc gag cag gac aag cgg ctg cac tgc tac gcc tcc tgg cgc aac agc   144
Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg Asn Ser
        35                  40                  45
```

```
tct ggc acc atc gag ctc gtg aag aag ggc tgc tgg cta gat gac ttc   192
Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp Asp Phe
    50                  55                  60

aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac ccc cag   240
Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn Pro Gln
65                  70                  75                  80

gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc ttc act   288
Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg Phe Thr
                85                  90                  95

cat ttg cca gag gct ggg ggc ccg gaa gtc acg tac gag cca ccc ccg   336
His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro Pro Pro
            100                 105                 110

aca gcc ccc act gga gga gga gga tct gac aaa act cac aca tgc cca   384
Thr Ala Pro Thr Gly Gly Gly Gly Ser Asp Lys Thr His Thr Cys Pro
        115                 120                 125

ccg tgc cca gca cct gaa ctc ctg ggg gga ccg tca gtc ttc ctc ttc   432
Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
    130                 135                 140

ccc cca aaa ccc aag gac atc ctc atg atc tcc cgg acc cct gag gtc   480
Pro Pro Lys Pro Lys Asp Ile Leu Met Ile Ser Arg Thr Pro Glu Val
145                 150                 155                 160

aca tgc gtg gtg gtg gac gtg agc cac gaa gac cct gag gtc aag ttc   528
Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
                165                 170                 175

aac tgg tac gtg ggc ggc gtg gag gtg cat aat gcc aag aca aag ccg   576
Asn Trp Tyr Val Gly Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
            180                 185                 190

cgg gag gag cag tac aac agc acg tac cgt gtg gtc agc gtc ctc acc   624
Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
        195                 200                 205

gtc ctg cac cag gac tgg ctg aat ggc aag gag tac aag tgc aag gtc   672
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
    210                 215                 220

tcc aac aaa gcc ctc cca gcc ccc atc gag aaa acc atc tcc aaa gcc   720
Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
225                 230                 235                 240

aaa ggg cag ccc cga gaa cca cag gtg tac acc ctg ccc cca tcc cgg   768
Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
                245                 250                 255

gat gag ctg acc aag aac cag gtc agc ctg acc tgc ctg gtc aaa ggc   816
Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
            260                 265                 270

ttc tat ccc agc gac atc gcc gtg gag tgg gag agc aat ggg cag ccg   864
Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
        275                 280                 285

gag aac aac tac aag acc acg cct ccc gtg ctg gac tcc gac ggc tcc   912
Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
    290                 295                 300

ttc ttc ctc tac agc aag ctc acc gtg gac aag agc agg tgg cag cag   906
Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
305                 310                 315                 320
```

```
ggg aac gtc ttc tca tgc tcc gtg atg cat gag gct ctg cac aac cac   1008
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
                325                 330                 335

tac acg cag aag agc ctc tcc ctg tct ccg ggt aaa tga               1044
Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys  *
            340                 345
```

<210> 64
<211> 348
<212> PRT
<213> Homo sapiens

<400> 64

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

<210> 65
<211> 1044
<212> DNA
<213> Homo sapiens

<400> 65

```
tct ggg cgt ggg gag gct gag aca cgg gag tgc atc tac tac aac gcc   48
Ser Gly Arg Gly Glu Ala Glu Thr Arg Glu Cys Ile Tyr Tyr Asn Ala
1               5                  10                  15

aac tgg gag ctg gag ggc acc aac cag agc ggc ctg gag cgc tgc gaa   96
Asn Trp Glu Leu Glu Gly Thr Asn Gln Ser Gly Leu Glu Arg Cys Glu
            20                  25                  30

ggc gag cag gac aag cgg ctg ccc tgc tac gcc tcc tgg cgc aac agc   144

Gly Glu Gln Asp Lys Arg Leu Pro Cys Tyr Ala Ser Trp Arg Asn Ser
        35                  40                  45

tct ggc ccc atc gag ctc gtg aag aag ggc tgc tgg cta gat gac ttc   192
Ser Gly Pro Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp Asp Phe
    50                  55                  60

aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac ccc cag   240
Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn Pro Gln
65                  70                  75                  80

gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc ttc act   288
Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg Phe Thr
                85                  90                  95

cat ttg cca gag gct ggg ggc ccg gaa gtc acg tac gag cca ccc ccg   336
His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro Pro Pro
            100                 105                 110

aca gcc ccc act gga gga gga gga tct gac aaa act cac aca tgc cca   384
Thr Ala Pro Thr Gly Gly Gly Gly Ser Asp Lys Thr His Thr Cys Pro
        115                 120                 125

ccg tgc cca gca cct gaa ctc ctg ggg gga ccg tca gtc ttc ctc ttc   432
Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
    130                 135                 140

ccc cca aaa ccc aag gac atc ctc atg atc tcc cgg acc cct gag gtc   480
Pro Pro Lys Pro Lys Asp Ile Leu Met Ile Ser Arg Thr Pro Glu Val
145                 150                 155                 160

aca tgc gtg gtg gtg gac gtg agc cac gaa gac cct gag gtc aag ttc   528
Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
                165                 170                 175

aac tgg tac gtg ggc ggc gtg gag gtg cat aat gcc aag aca aag ccg   576
Asn Trp Tyr Val Gly Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
            180                 185                 190

cgg gag gag cag tac aac agc acg tac cgt gtg gtc agc gtc ctc acc   624

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
        195                 200                 205

gtc ctg cac cag gac tgg ctg aat ggc aag gag tac aag tgc aag gtc   672
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
    210                 215                 220

tcc aac aaa gcc ctc cca gcc ccc atc gag aaa acc atc tcc aaa gcc   720
Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
225                 230                 235                 240

aaa ggg cag ccc cga gaa cca cag gtg tac acc ctg ccc cca tcc cgg   768
Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
                245                 250                 255

gat gag ctg acc aag aac cag gtc agc ctg acc tgc ctg gtc aaa ggc   816
Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
```

```
            260                 265                 270

ttc tat ccc agc gac atc gcc gtg gag tgg gag agc aat ggg cag ccg   864

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
        275                 280                 285

gag aac aac tac aag acc acg cct ccc gtg ctg gac tcc gac ggc tcc   912
Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
    290                 295                 300

ttc ttc ctc tac agc aag ctc acc gtg gac aag agc agg tgg cag cag   960
Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
305                 310                 315                 320

ggg aac gtc ttc tca tgc tcc gtg atg cat gag gct ctg cac aac cac   1008
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
                325                 330                 335

tac acg cag aag agc ctc tcc ctg tct ccg ggt aaa tga               1044
Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys  *
            340                 345


<210> 66
<211> 348
<212> PRT
<213> Homo sapiens

<400> 66
Ser Gly Arg Gly Glu Ala Glu Thr Arg Glu Cys Ile Tyr Tyr Asn Ala
1               5                   10                  15
Asn Trp Glu Leu Glu Gly Thr Asn Gln Ser Gly Leu Glu Arg Cys Glu
            20                  25                  30
Gly Glu Gln Asp Lys Arg Leu Pro Cys Tyr Ala Ser Trp Arg Asn Ser
        35                  40                  45
Ser Gly Pro Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp Asp Phe
    50                  55                  60
Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn Pro Gln
65                  70                  75                  80
Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg Phe Thr
                85                  90                  95
His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro Pro Pro
            100                 105                 110
Thr Ala Pro Thr Gly Gly Gly Gly Ser Asp Lys Thr His Thr Cys Pro
        115                 120                 125
Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
    130                 135                 140
Pro Pro Lys Pro Lys Asp Ile Leu Met Ile Ser Arg Thr Pro Glu Val
145                 150                 155                 160
Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
                165                 170                 175
Asn Trp Tyr Val Gly Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
            180                 185                 190
Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
        195                 200                 205
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
    210                 215                 220
Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
225                 230                 235                 240
Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
                245                 250                 255
Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
            260                 265                 270

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
        275                 280                 285
Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
```

```
    290                 295                 300
Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
305                 310                 315                 320
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
                325                 330                 335
Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
            340                 345
```

<210> 67
<211> 1125
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)...(1125)

<400> 67

```
tct ggg cgt ggg gag gct gag aca cgg gag tgc atc tac tac aac gcc   48
Ser Gly Arg Gly Glu Ala Glu Thr Arg Glu Cys Ile Tyr Tyr Asn Ala
 1               5                  10                  15

aac tgg gag ctg gag cgc acc aac cag agc ggc ctg gag cgc tgc gaa   96
Asn Trp Glu Leu Glu Arg Thr Asn Gln Ser Gly Leu Glu Arg Cys Glu
            20                  25                  30

ggc gag cag gac aag cgg ctg cac tgc tac gcc tcc tgg cgc aac agc   144
Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg Asn Ser
        35                  40                  45

tct ggc acc atc gag ctc gtg aag aag ggc tgc tgg cta gat gac ttc   192
Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp Asp Phe
    50                  55                  60

aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac ccc cag   240

Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn Pro Gln
 65                  70                  75                  80

gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc ttc act   288
Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg Phe Thr
                85                  90                  95

cat ttg cca gag gct ggg ggc ccg gaa gga ccc tgg gcc tcc acc acc   336
His Leu Pro Glu Ala Gly Gly Pro Glu Gly Pro Trp Ala Ser Thr Thr
            100                 105                 110

atc ccc tct ggt ggg cct gaa gcc act gca gct gct gga gat caa ggc   384
Ile Pro Ser Gly Gly Pro Glu Ala Thr Ala Ala Ala Gly Asp Gln Gly
        115                 120                 125

tcg ggg gcg ctt tgg ctg tgt ctg gaa ggc cca gct cat gaa gga gga   432
Ser Gly Ala Leu Trp Leu Cys Leu Glu Gly Pro Ala His Glu Gly Gly
    130                 135                 140

gga gga tct gac aaa act cac aca tgc cca ccg tgc cca gca cct gaa   480
Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
145                 150                 155                 160

ctc ctg ggg gga ccg tca gtc ttc ctc ttc ccc cca aaa ccc aag gac   528
Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
                165                 170                 175

acc ctc atg atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac   576
Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
            180                 185                 190
```

```
gtg agc cac gaa gac cct gag gtc aag ttc aac tgg tac gtg gac ggc   624
Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
        195                 200                 205

gtg gag gtg cat aat gcc aag aca aag ccg cgg gag gag cag tac aac   672
Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
    210                 215                 220

agc acg tac cgt gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg   720
Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
225                 230                 235                 240

ctg aat ggc aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca   768
Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
                245                 250                 255

gcc ccc atc gag aaa acc atc tcc aaa gcc aaa ggg cag ccc cga gaa   816
Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
            260                 265                 270

cca cag gtg tac acc ctg ccc cca tcc cgg gat gag ctg acc aag aac   864
Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
        275                 280                 285

cag gtc agc ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc   912
Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
    290                 295                 300

gcc gtg gag tgg gag agc aat ggg cag ccg gag aac aac tac aag acc   960

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
305                 310                 315                 320

acg cct ccc gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag   1008
Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
                325                 330                 335

ctc acc gtg gac aag agc agg tgg cag cag ggg aac gtc ttc tca tgc   1056
Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
            340                 345                 350

tcc gtg atg cat gag gct ctg cac aac cac tac acg cag aag agc ctc   1104
Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
        355                 360                 365

tcc ctg tct ccg ggt aaa tga                                      1125
Ser Leu Ser Pro Gly Lys  *
    370
```

<210> 68
<211> 374
<212> PRT
<213> Homo sapiens

<400> 68

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

```
His Leu Pro Glu Ala Gly Gly Pro Glu Gly Pro Trp Ala Ser Thr Thr
            100                 105                 110
Ile Pro Ser Gly Gly Pro Glu Ala Thr Ala Ala Ala Gly Asp Gln Gly
        115                 120                 125
Ser Gly Ala Leu Trp Leu Cys Leu Glu Gly Pro Ala His Glu Gly Gly
    130                 135                 140
Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
145                 150                 155                 160
Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
                165                 170                 175
Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
            180                 185                 190
Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
        195                 200                 205
Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
    210                 215                 220
Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
225                 230                 235                 240
Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
                245                 250                 255
Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
            260                 265                 270

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
        275                 280                 285
Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
    290                 295                 300
Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
305                 310                 315                 320
Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
                325                 330                 335
Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
            340                 345                 350
Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
        355                 360                 365
Ser Leu Ser Pro Gly Lys
    370
```

<210> 69
<211> 1125
<212> DNA
<213> Homo sapiens

<220>
<221> variation
<222> (1)...(1125)
<223> n = a, c, t, or g

<220>
<221> CDS
<222> (1)...(1125)

<400> 69

```
tct ggg cgt ggg gag gct gag aca cgg gcn tgc atc tac tac aac gcc   48
Ser Gly Arg Gly Glu Ala Glu Thr Arg Ala Cys Ile Tyr Tyr Asn Ala
 1               5                  10                  15

aac tgg gag ctg gag cgc acc aac cag agc ggc ctg gag cgc tgc gaa   96
Asn Trp Glu Leu Glu Arg Thr Asn Gln Ser Gly Leu Glu Arg Cys Glu
            20                  25                  30

ggc gag cag gac aag cgg ctg cac tgc tac gcc tcc tgg cgc aac agc   144
Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg Asn Ser
        35                  40                  45

tct ggc acc atc gag ctc gtg aag aag ggc tgc tgg cta gat gac ttc   192
Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp Asp Phe
```

```
     50                  55                  60

aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac ccc cag   240
Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn Pro Gln
 65                  70                  75                  80

gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc ttc act   288
Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg Phe Thr
                 85                  90                  95

cat ttg cca gag gct ggg ggc ccg gaa gga ccc tgg gcc tcc acc acc   336
His Leu Pro Glu Ala Gly Gly Pro Glu Gly Pro Trp Ala Ser Thr Thr
            100                 105                 110

atc ccc tct ggt ggg cct gaa gcc act gca gct gct gga gat caa ggc   384

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

tcg ggg gcg ctt tgg ctg tgt ctg gaa ggc cca gct cat gaa gga gga   432
Ser Gly Ala Leu Trp Leu Cys Leu Glu Gly Pro Ala His Glu Gly Gly
    130                 135                 140

gga gga tct gac aaa act cac aca tgc cca ccg tgc cca gca cct gaa   480
Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
145                 150                 155                 160

ctc ctg ggg gga ccg tca gtc ttc ctc ttc ccc cca aaa ccc aag gac   528
Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
                165                 170                 175

acc ctc atg atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac   576
Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
            180                 185                 190

gtg agc cac gaa gac cct gag gtc aag ttc aac tgg tac gtg gac ggc   624
Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
        195                 200                 205

gtg gag gtg cat aat gcc aag aca aag ccg cgg gag gag cag tac aac   672

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
    210                 215                 220

agc acg tac cgt gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg   720
Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
225                 230                 235                 240

ctg aat ggc aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca   768
Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
                245                 250                 255

gcc ccc atc gag aaa acc atc tcc aaa gcc aaa ggg cag ccc cga gaa   816
Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
            260                 265                 270

cca cag gtg tac acc ctg ccc cca tcc cgg gat gag ctg acc aag aac   864
Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
        275                 280                 285

cag gtc agc ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc   912
Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
    290                 295                 300

gcc gtg gag tgg gag agc aat ggg cag ccg gag aac aac tac aag acc   960
Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
305                 310                 315                 320
```

```
acg cct ccc gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag   1008
Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
                325                 330                 335

ctc acc gtg gac aag agc agg tgg cag cag ggg aac gtc ttc tca tgc   1056
Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
            340                 345                 350

tcc gtg atg cat gag gct ctg cac aac cac tac acg cag aag agc ctc   1104
Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
        355                 360                 365

tcc ctg tct ccg ggt aaa tga                                      1125
Ser Leu Ser Pro Gly Lys  *
    370
```

<210> 70
<211> 374
<212> PRT
<213> Homo sapiens

<400> 70

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

Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg Phe Thr
                85                  90                  95
His Leu Pro Glu Ala Gly Gly Pro Glu Gly Pro Trp Ala Ser Thr Thr
            100                 105                 110
Ile Pro Ser Gly Gly Pro Glu Ala Thr Ala Ala Ala Gly Asp Gln Gly
        115                 120                 125
Ser Gly Ala Leu Trp Leu Cys Leu Glu Gly Pro Ala His Glu Gly Gly
    130                 135                 140
Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
145                 150                 155                 160
Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
                165                 170                 175
Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
            180                 185                 190
Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
        195                 200                 205
Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
    210                 215                 220
Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
225                 230                 235                 240
Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
                245                 250                 255
Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
            260                 265                 270
Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
        275                 280                 285
Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
    290                 295                 300
Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
305                 310                 315                 320
Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
                325                 330                 335
Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
            340                 345                 350
```

```
Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
        355                 360                 365
Ser Leu Ser Pro Gly Lys
    370
```

<210> 71
<211> 1125
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)...(1125)

<400> 71

```
tct ggg cgt ggg gag gct gag aca cgg tgg tgc atc tac tac aac gcc   48
Ser Gly Arg Gly Glu Ala Glu Thr Arg Trp Cys Ile Tyr Tyr Asn Ala
 1               5                  10                  15

aac tgg gag ctg gag cgc acc aac cag agc ggc ctg gag cgc tgc gaa   96
Asn Trp Glu Leu Glu Arg Thr Asn Gln Ser Gly Leu Glu Arg Cys Glu
            20                  25                  30

ggc gag cag gac aag cgg ctg cac tgc tac gcc tcc tgg cgc aac agc   144
Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg Asn Ser
        35                  40                  45

tct ggc acc atc gag ctc gtg aag aag ggc tgc tgg cta gat gac ttc   192
Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp Asp Phe
    50                  55                  60

aac tgc tac gat agg cag gag tgt gtg gcc act gag gag aac ccc cag   240
Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn Pro Gln
65                  70                  75                  80

gtg tac ttc tgc tgc tgt gaa ggc aac ttc tgc aac gag cgc ttc act   288
Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg Phe Thr
                85                  90                  95

cat ttg cca gag gct ggg ggc ccg gaa gga ccc tgg gcc tcc acc acc   336
His Leu Pro Glu Ala Gly Gly Pro Glu Gly Pro Trp Ala Ser Thr Thr
            100                 105                 110

atc ccc tct ggt ggg cct gaa gcc act gca gct gct gga gat caa ggc   384
Ile Pro Ser Gly Gly Pro Glu Ala Thr Ala Ala Ala Gly Asp Gln Gly
        115                 120                 125

tcg ggg gcg ctt tgg ctg tgt ctg gaa ggc cca gct cat gaa gga gga   432
Ser Gly Ala Leu Trp Leu Cys Leu Glu Gly Pro Ala His Glu Gly Gly
    130                 135                 140

gga gga tct gac aaa act cac aca tgc cca ccg tgc cca gca cct gaa   480
Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
145                 150                 155                 160

ctc ctg ggg gga ccg tca gtc ttc ctc ttc ccc cca aaa ccc aag gac   528
Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
                165                 170                 175

acc ctc atg atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac   576
Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
            180                 185                 190

gtg agc cac gaa gac cct gag gtc aag ttc aac tgg tac gtg gac ggc   624
Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
        195                 200                 205
```

```
gtg gag gtg cat aat gcc aag aca aag ccg cgg gag gag cag tac aac   672
Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
    210                 215                 220

agc acg tac cgt gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg   720
Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
225                 230                 235                 240

ctg aat ggc aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca   768
Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
                245                 250                 255

gcc ccc atc gag aaa acc atc tcc aaa gcc aaa ggg cag ccc cga gaa   816
Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
            260                 265                 270

cca cag gtg tac acc ctg ccc cca tcc cgg gat gag ctg acc aag aac   864
Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
        275                 280                 285

cag gtc agc ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc   912
Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
    290                 295                 300

gcc gtg gag tgg gag agc aat ggg cag ccg gag aac aac tac aag acc   960
Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
305                 310                 315                 320

acg cct ccc gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag   1008
Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
                325                 330                 335

ctc acc gtg gac aag agc agg tgg cag cag ggg aac gtc ttc tca tgc   1056
Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
            340                 345                 350

tcc gtg atg cat gag gct ctg cac aac cac tac acg cag aag agc ctc   1104
Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
        355                 360                 365

tcc ctg tct ccg ggt aaa tga                                      1125
Ser Leu Ser Pro Gly Lys  *
    370
```

<210> 72
<211> 374
<212> PRT
<213> Homo sapiens

<400> 72

```
Ser Gly Arg Gly Glu Ala Glu Thr Arg Trp Cys Ile Tyr Tyr Asn Ala
 1               5                  10                  15
Asn Trp Glu Leu Glu Arg Thr Asn Gln Ser Gly Leu Glu Arg Cys Glu
            20                  25                  30

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

```
Ser Gly Ala Leu Trp Leu Cys Leu Glu Gly Pro Ala His Glu Gly Gly
    130                 135                 140
Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
145                 150                 155                 160
Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
                165                 170                 175
Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
            180                 185                 190
Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
        195                 200                 205
Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
    210                 215                 220
Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
225                 230                 235                 240
Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
                245                 250                 255
Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
            260                 265                 270
Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
        275                 280                 285
Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
    290                 295                 300
Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
305                 310                 315                 320
Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
                325                 330                 335
Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
            340                 345                 350
Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
        355                 360                 365
Ser Leu Ser Pro Gly Lys
    370
```

<210> 73
<211> 18
<212> PRT
<213> Homo sapiens

<400> 73
```
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Trp
 1               5                  10                  15
Pro Gly
```

<210> 74
<211> 18
<212> PRT
<213> Homo sapiens

<400> 74
```
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Cys
 1               5                  10                  15
Ala Gly
```

<210> 75
<211> 5
<212> PRT
<213> Homo sapiens

<400> 75
```
Gly Gly Gly Gly Ser
 1               5
```

<210> 76
<211> 15
<212> PRT
<213> Homo sapiens

<400> 76

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
1 5 10 15

<210> 77
<211> 12
<212> PRT
<213> Homo sapiens

<400> 77
Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro
1 5 10

<210> 78
<211> 12
<212> PRT
<213> Homo sapiens

<400> 78
Glu Ser Lys Thr Gly Pro Pro Cys Pro Ser Cys Pro
1 5 10

<210> 79
<211> 12
<212> PRT
<213> Homo sapiens

<400> 79
Gly Gly Gly Gly Ser Val Glu Cys Pro Pro Cys Pro
1 5 10

<210> 80
<211> 216
<212> PRT
<213> Homo sapiens

<400> 80
Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
1 5 10 15
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
20 25 30
Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
35 40 45
Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
50 55 60
Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln
65 70 75 80
Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
85 90 95
Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro
100 105 110
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
115 120 125
Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
130 135 140
Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
145 150 155 160

```
Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
                165                 170                 175
Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
            180                 185                 190
Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
        195                 200                 205
Ser Leu Ser Leu Ser Pro Gly Lys
    210                 215


<210> 81
<211> 648
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)...(648)

<220>
<221> misc_feature
<222> (1)...(648)
<223> n = a,c,t or g

<400> 81
gcn ccn ccn gtn gcn ggn ccn nnn gtn tty ytn tty ccn ccn aar ccn   48
Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
 1               5                  10                  15

aar gay acn ytn atg ath nnn nnn acn ccn gar gtn acn tgy gtn gtn   96
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
            20                  25                  30

gtn gay gtn nnn cay gar gay ccn gar gtn car tty aay tgg tay gtn   144

Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
        35                  40                  45

gay ggn gtn gar gtn cay aay gcn aar acn aar ccn nnn gar gar car   192
Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
    50                  55                  60

tty aay nnn acn tty nnn gtn gtn nnn gtn ytn acn gtn gtn cay car   240
Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln
65                  70                  75                  80

gay tgg ytn aay ggn aar gar tay aar tgy aar gtn nnn aay aar ggn   288
Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
                85                  90                  95

ytn ccn gcn ccn ath gar aar acn ath nnn aar acn aar ggn car ccn   336
Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro
            100                 105                 110

nnn gar ccn car gtn tay acn ytn ccn ccn nnn nnn gar gar atg acn   384
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
        115                 120                 125

aar aay car gtn nnn ytn acn tgy ytn gtn aar ggn tty tay ccn nnn   432
Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
    130                 135                 140

gay ath gcn gtn gar tgg gar nnn aay ggn car ccn gar aay aay tay   480
Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
145                 150                 155                 160

aar acn acn ccn ccn atg ytn gay nnn gay ggn nnn tty tty ytn tay   528
Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
```

```
                165                 170                 175

nnn aar ytn acn gtn gay aar nnn nnn tgg car car ggn aay gtn tty   576
Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
            180                 185                 190

nnn tgy nnn gtn atg cay gar gcn ytn cay aay cay tay acn car aar   624
Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
        195                 200                 205

nnn ytn nnn ytn nnn ccn ggn aar                                   648
Ser Leu Ser Leu Ser Pro Gly Lys
    210                 215


<210> 82
<211> 217
<212> PRT
<213> Homo sapiens

<400> 82
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
 1               5                  10                  15
Pro Lys Asp Ile Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

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


<210> 83
<211> 651
<212> DNA
<213> Homo sapiens

<400> 83
cctgaactcc tgggggacc gtcagtcttc ctcttccccc caaaacccaa ggacatcctc 60
atgatctccc ggaccctga ggtcacatgc gtggtggtgg acgtgagcca cgaagaccct 120
gaggtcaagt tcaactggta cgtgggcggc gtggaggtgc ataatgccaa gacaaagccg 180
cgggaggagc agtacaacag cacgtaccgt gtggtcagcg tcctcaccgt cctgcaccag 240
gactggctga atggcaagga gtacaagtgc aaggtctcca acaaagccct cccagccccc 300
atcgagaaaa ccatctccaa agccaaaggg cagccccgag aaccacaggt gtacaccctg 360
cccccatccc gggatgagct gaccaagaac caggtcagcc tgacctgcct ggtcaaaggc 420
ttctatccca gcgacatcgc cgtggagtgg gagagcaatg ggcagccgga gaacaactac 480
aagaccacgc ctcccgtgct ggactccgac ggctccttct tcctctacag caagctcacc 540
gtggacaaga gcaggtggca gcaggggaac gtcttctcat gctccgtgat gcatgaggct 600
```

ctgcacaacc actacacgca gaagagcctc tccctgtctc cgggtaaatg a 651

<210> 84
<211> 217
<212> PRT
<213> Homo sapiens

<400> 84

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

Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met
        115                 120                 125
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175
Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val
            180                 185                 190
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205
Lys Ser Leu Ser Leu Ser Leu Gly Lys
    210                 215
```

<210> 85
<211> 651
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)...(651)

<220>
<221> misc_feature
<222> (1)...(651)
<223> n = A,T,C or G

<400> 85

```
gcn ccn gar tty ytn ggn ggn ccn nnn gtn tty ytn tty ccn ccn aar   48
Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
 1               5                  10                  15

ccn aar gay acn ytn atg ath nnn nnn acn ccn gar gtn acn tgy gtn   96
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

gtn gtn gay gtn nnn car gar gay ccn gar gtn car tty aay tgg tay  144
Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
        35                  40                  45

gtn gay ggn gtn gar gtn cay aay gcn aar acn aar ccn nnn gar gar  192
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
```

```
    50                  55                  60

car tty aay nnn acn tay nnn gtn gtn nnn gtn ytn acn gtn ytn cay   240
Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

car gay tgg ytn aay ggn aar gar tay aar tgy aar gtn nnn aay aar   288
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

ggn ytn ccn nnn nnn ath gar aar acn ath nnn aar gcn aar ggn car   336
Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

ccn nnn gar ccn car gtn tay acn ytn ccn ccn nnn car gar gar atg   384
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met
        115                 120                 125

acn aar aay car gtn nnn ytn acn tgy ytn gtn aar ggn tty tay ccn   432
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

nnn gay ath gcn gtn gar tgg gar nnn aay ggn car ccn gar aay aay   480
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

tay aar acn acn ccn ccn gtn ytn gay nnn gay ggn nnn tty tty ytn   528
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

tay nnn nnn ytn acn gtn gay aar nnn nnn tgg car gar ggn aay gtn   576
Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val
            180                 185                 190

tty nnn tgy nnn gtn atg cay gar gcn ytn cay aay cay tay acn car   624
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

aar nnn ytn nnn ytn nnn ytn ggn aar                               651
Lys Ser Leu Ser Leu Ser Leu Gly Lys
    210                 215
```

<210> 86
<211> 110
<212> PRT
<213> Homo sapiens

<400> 86

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

<210> 87
<211> 110
<212> PRT

<213> Homo sapiens

<400> 87

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

<210> 88
<211> 110
<212> PRT
<213> Homo sapiens

<400> 88

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

Glu Gly Asn Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly
                85                  90                  95
Gly Pro Glu Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro Thr
            100                 105                 110
```

<210> 89
<211> 338
<212> PRT
<213> Homo sapiens

<400> 89

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

```
Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
                165                 170                 175
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
            180                 185                 190
Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys
        195                 200                 205
Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu
    210                 215                 220
Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
225                 230                 235                 240
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
                245                 250                 255
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
            260                 265                 270
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met
        275                 280                 285
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
    290                 295                 300
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
305                 310                 315                 320
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
                325                 330                 335
Gly Lys
```

<210> 90
<211> 1014
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)...(1014)

<400> 90

```
gag aca cgg gag tgc atc tac tac aac gcc aac tgg gag ctg gag cgc   48
Glu Thr Arg Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg
 1               5                  10                  15

acc aac cag agc ggc ctg gag cgc tgc gaa ggc gag cag gac aag cgg   96
Thr Asn Gln Ser Gly Leu Glu Arg Cys Glu Gly Glu Gln Asp Lys Arg
            20                  25                  30

ctg cac tgc tac gcc tcc tgg cgc aac agc tct ggc acc atc gag ctc   144
Leu His Cys Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu
        35                  40                  45

gtg aag aag ggc tgc tgg cta gat gac ttc aac tgc tac gat agg cag   192
Val Lys Lys Gly Cys Trp Leu Asp Asp Phe Asn Cys Tyr Asp Arg Gln
    50                  55                  60

gag tgt gtg gcc act gag gag aac ccc cag gtg tac ttc tgc tgc tgt   240
Glu Cys Val Ala Thr Glu Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys
65                  70                  75                  80

gag ggc aac ttc tgc aac gag cgc ttc act cat ttg cca gag gct ggg   288
Glu Gly Asn Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly
                85                  90                  95

ggc ccg gaa gtc acg tac gag cca ccc ccg aca gcc ccc acc gga gga   336
Gly Pro Glu Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro Thr Gly Gly
            100                 105                 110

gga gga tct gtc gag tgc cca ccg tgc cca gca cca cct gtg gca gga   384
Gly Gly Ser Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly
        115                 120                 125
```

```
ccg tca gtc ttc ctc ttc ccc cca aaa ccc aag gac acc ctc atg atc   432
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
    130                 135                 140

tcc cgg acc cct gag gtc acg tgc gtg gtg gtg gac gtg agc cac gaa   480
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
145                 150                 155                 160

gac ccc gag gtc cag ttc aac tgg tac gtg gac ggc gtg gag gtg cat   528
Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
                165                 170                 175

aat gcc aag aca aag cca cgg gag gag cag ttc aac agc acg ttc cgt   576
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
            180                 185                 190

gtg gtc agc gtc ctc acc gtt gtg cac cag gac tgg ctg aac ggc aag   624
Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys
        195                 200                 205

gag tac aag tgc aag gtc tcc aac aaa ggc ctc cca gcc ccc atc gag   672

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu
    210                 215                 220

aaa acc atc tcc aaa acc aaa ggg cag ccc cga gaa cca cag gtg tac   720
Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
225                 230                 235                 240

acc ctg ccc cca tcc cgg gag gag atg acc aag aac cag gtc agc ctg   768
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
                245                 250                 255

acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc gcc gtg gag tgg   816
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
            260                 265                 270

gag agc aat ggg cag ccg gag aac aac tac aag acc aca cct ccc atg   864
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met
        275                 280                 285

ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc acc gtg gac   912
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
    290                 295                 300

aag agc agg tgg cag cag ggg aac gtc ttc tca tgc tcc gtg atg cat   960
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
305                 310                 315                 320

gag gct ctg cac aac cac tac acg cag aag agc ctc tcc ctg tct ccg   1008
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
                325                 330                 335

ggt aaa                                                          1014
Gly Lys
```

<210> 91
<211> 338
<212> PRT
<213> Homo sapiens

<400> 91

```
Glu Thr Arg Trp Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg
 1               5                  10                  15
Thr Asn Gln Ser Gly Leu Glu Arg Cys Glu Gly Glu Gln Asp Lys Arg
            20                  25                  30
```

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

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
145                 150                 155                 160
Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
                165                 170                 175
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
            180                 185                 190
Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys
        195                 200                 205
Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu
    210                 215                 220
Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
225                 230                 235                 240
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
                245                 250                 255
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
            260                 265                 270
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met
        275                 280                 285
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
    290                 295                 300
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
305                 310                 315                 320
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
                325                 330                 335
Gly Lys
```

<210> 92
<211> 1014
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)...(1014)

<400> 92

```
gag aca cgg tgg tgc atc tac tac aac gcc aac tgg gag ctg gag cgc   48
Glu Thr Arg Trp Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg
 1               5                  10                  15

acc aac cag agc ggc ctg gag cgc tgc gaa ggc gag cag gac aag cgg   96
Thr Asn Gln Ser Gly Leu Glu Arg Cys Glu Gly Glu Gln Asp Lys Arg
            20                  25                  30

ctg cac tgc tac gcc tcc tgg cgc aac agc tct ggc acc atc gag ctc   144
Leu His Cys Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu
        35                  40                  45

gtg aag aag ggc tgc tgg cta gat gac ttc aac tgc tac gat agg cag   192
Val Lys Lys Gly Cys Trp Leu Asp Asp Phe Asn Cys Tyr Asp Arg Gln
    50                  55                  60
```

```
gag tgt gtg gcc act gag gag aac ccc cag gtg tac ttc tgc tgc tgt   240
Glu Cys Val Ala Thr Glu Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys
65                  70                  75                  80

gag ggc aac ttc tgc aac gag cgc ttc act cat ttg cca gag gct ggg   288
Glu Gly Asn Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly
                85                  90                  95

ggc ccg gaa gtc acg tac gag cca ccc ccg aca gcc ccc acc gga gga   336
Gly Pro Glu Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro Thr Gly Gly
            100                 105                 110

gga gga tct gtc gag tgc cca ccg tgc cca gca cca cct gtg gca gga   384
Gly Gly Ser Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly
        115                 120                 125

ccg tca gtc ttc ctc ttc ccc cca aaa ccc aag gac acc ctc atg atc   432
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
    130                 135                 140

tcc cgg acc cct gag gtc acg tgc gtg gtg gtg gac gtg agc cac gaa   480
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
145                 150                 155                 160

gac ccc gag gtc cag ttc aac tgg tac gtg gac ggc gtg gag gtg cat   528
Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
                165                 170                 175

aat gcc aag aca aag cca cgg gag gag cag ttc aac agc acg ttc cgt   576
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
            180                 185                 190

gtg gtc agc gtc ctc acc gtt gtg cac cag gac tgg ctg aac ggc aag   624
Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys
        195                 200                 205

gag tac aag tgc aag gtc tcc aac aaa ggc ctc cca gcc ccc atc gag   672
Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu
    210                 215                 220

aaa acc atc tcc aaa acc aaa ggg cag ccc cga gaa cca cag gtg tac   720
Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
225                 230                 235                 240

acc ctg ccc cca tcc cgg gag gag atg acc aag aac cag gtc agc ctg   768
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
                245                 250                 255

acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc gcc gtg gag tgg   816
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
            260                 265                 270

gag agc aat ggg cag ccg gag aac aac tac aag acc aca cct ccc atg   864
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met
        275                 280                 285

ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc acc gtg gac   912
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
    290                 295                 300

aag agc agg tgg cag cag ggg aac gtc ttc tca tgc tcc gtg atg cat   960
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
305                 310                 315                 320

gag gct ctg cac aac cac tac acg cag aag agc ctc tcc ctg tct ccg   1008
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
                325                 330                 335
```

ggt aaa 1014
Gly Lys

<210> 93
<211> 338
<212> PRT
<213> Homo sapiens

<400> 93
Glu Thr Arg Tyr Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg
1 5 10 15
Thr Asn Gln Ser Gly Leu Glu Arg Cys Glu Gly Glu Gln Asp Lys Arg
20 25 30
Leu His Cys Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu
35 40 45
Val Lys Lys Gly Cys Trp Leu Asp Asp Phe Asn Cys Tyr Asp Arg Gln
50 55 60
Glu Cys Val Ala Thr Glu Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys
65 70 75 80
Glu Gly Asn Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly
85 90 95
Gly Pro Glu Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro Thr Gly Gly
100 105 110
Gly Gly Ser Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly
115 120 125
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
130 135 140
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
145 150 155 160

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
165 170 175
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
180 185 190
Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys
195 200 205
Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu
210 215 220
Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
225 230 235 240
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
245 250 255
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
260 265 270
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met
275 280 285
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
290 295 300
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
305 310 315 320
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
325 330 335
Gly Lys

<210> 94
<211> 1014
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)...(1014)

<400> 94

```
gag aca cgg tac tgc atc tac tac aac gcc aac tgg gag ctg gag cgc   48
Glu Thr Arg Tyr Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg
 1               5                  10                  15

acc aac cag agc ggc ctg gag cgc tgc gaa ggc gag cag gac aag cgg   96
Thr Asn Gln Ser Gly Leu Glu Arg Cys Glu Gly Glu Gln Asp Lys Arg
            20                  25                  30

ctg cac tgc tac gcc tcc tgg cgc aac agc tct ggc acc atc gag ctc  144
Leu His Cys Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu
        35                  40                  45

gtg aag aag ggc tgc tgg cta gat gac ttc aac tgc tac gat agg cag  192
Val Lys Lys Gly Cys Trp Leu Asp Asp Phe Asn Cys Tyr Asp Arg Gln
    50                  55                  60

gag tgt gtg gcc act gag gag aac ccc cag gtg tac ttc tgc tgc tgt  240
Glu Cys Val Ala Thr Glu Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys
65                  70                  75                  80

gag ggc aac ttc tgc aac gag cgc ttc act cat ttg cca gag gct ggg  288
Glu Gly Asn Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly
                85                  90                  95

ggc ccg gaa gtc acg tac gag cca ccc ccg aca gcc ccc acc gga gga  336
Gly Pro Glu Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro Thr Gly Gly
            100                 105                 110

gga gga tct gtc gag tgc cca ccg tgc cca gca cca cct gtg gca gga  384
Gly Gly Ser Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly
        115                 120                 125

ccg tca gtc ttc ctc ttc ccc cca aaa ccc aag gac acc ctc atg atc  432
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
    130                 135                 140

tcc cgg acc cct gag gtc acg tgc gtg gtg gtg gac gtg agc cac gaa  480
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
145                 150                 155                 160

gac ccc gag gtc cag ttc aac tgg tac gtg gac ggc gtg gag gtg cat  528
Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
                165                 170                 175

aat gcc aag aca aag cca cgg gag gag cag ttc aac agc acg ttc cgt  576
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
            180                 185                 190

gtg gtc agc gtc ctc acc gtt gtg cac cag gac tgg ctg aac ggc aag  624
Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys
        195                 200                 205

gag tac aag tgc aag gtc tcc aac aaa ggc ctc cca gcc ccc atc gag  672
Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu
    210                 215                 220

aaa acc atc tcc aaa acc aaa ggg cag ccc cga gaa cca cag gtg tac  720
Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
225                 230                 235                 240

acc ctg ccc cca tcc cgg gag gag atg acc aag aac cag gtc agc ctg  768
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
                245                 250                 255

acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc gcc gtg gag tgg  816
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
            260                 265                 270
```

```
gag agc aat ggg cag ccg gag aac aac tac aag acc aca cct ccc atg   864
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met
        275                 280                 285

ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc acc gtg gac   912
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
    290                 295                 300

aag agc agg tgg cag cag ggg aac gtc ttc tca tgc tcc gtg atg cat   960
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
305                 310                 315                 320

gag gct ctg cac aac cac tac acg cag aag agc ctc tcc ctg tct ccg   1008
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
                325                 330                 335

ggt aaa                                                          1014
Gly Lys
```

<210> 95
<211> 338
<212> PRT
<213> Homo sapiens

<400> 95

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

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
                165                 170                 175
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
            180                 185                 190
Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys
        195                 200                 205
Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu
    210                 215                 220
Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
225                 230                 235                 240
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
                245                 250                 255
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
            260                 265                 270
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met
        275                 280                 285
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
    290                 295                 300
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
```

```
305                 310                 315                 320
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
                325                 330                 335
Gly Lys
```

<210> 96
<211> 1014
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)...(1014)

<220>
<221> misc_feature
<222> (1)...(1014)
<223> n = a,t,c or g

<400> 96

```
gar acn nnn gcn tgy ath tay tay aay gcn aay tgg gar ytn gar nnn   48
Glu Thr Arg Ala Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg
 1               5                  10                  15

acn aay car nnn ggn ytn gar nnn tgy gar ggn gar car gay aar nnn   96
Thr Asn Gln Ser Gly Leu Glu Arg Cys Glu Gly Glu Gln Asp Lys Arg
            20                  25                  30

ytn cay tgy tay gcn nnn tgg nnn aay nnn nnn ggn acn ath gar ytn   144
Leu His Cys Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu
        35                  40                  45

gtn aar aar ggn tgy tgg ytn gay gay tty aay tgy tay gay nnn car   192
Val Lys Lys Gly Cys Trp Leu Asp Asp Phe Asn Cys Tyr Asp Arg Gln
    50                  55                  60

gar tgy gtn gcn acn gar gar aay ccn car gtn tay tty tgy tgy tgy   240
Glu Cys Val Ala Thr Glu Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys
65                  70                  75                  80

gar ggn aay tty tgy aay gar nnn tty acn cay ytn ccn gar gcn ggn   288
Glu Gly Asn Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly
                85                  90                  95

ggn ccn gar gtn acn tay gar ccn ccn ccn acn gcn ccn acn ggn ggn   336
Gly Pro Glu Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro Thr Gly Gly
            100                 105                 110

ggn ggn nnn gtn gar tgy ccn ccn tgy ccn gcn ccn ccn gtn gcn ggn   384
Gly Gly Ser Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly
        115                 120                 125

ccn nnn gtn tty ytn tty ccn ccn aar ccn aar gay acn ytn atg ath   432
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
    130                 135                 140

nnn nnn acn ccn gar gtn acn tgy gtn gtn gtn gay gtn nnn cay gar   480
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
145                 150                 155                 160

gay ccn gar gtn car tty aay tgg tay gtn gay ggn gtn gar gtn cay   528
Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
                165                 170                 175

aay gcn aar acn aar ccn nnn gar gar car tty aay nnn acn tty nnn   576
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
```

```
            180                 185                 190

gtn gtn nnn gtn ytn acn gtn gtn cay car gay tgg ytn aay ggn aar   624
Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys
        195                 200                 205

gar tay aar tgy aar gtn nnn aay aar ggn ytn ccn gcn ccn ath gar   672
Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu
    210                 215                 220

aar acn ath nnn aar acn aar ggn car ccn nnn gar ccn car gtn tay   720
Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
225                 230                 235                 240

acn ytn ccn ccn nnn nnn gar gar atg acn aar aay car gtn nnn ytn   768
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
                245                 250                 255

acn tgy ytn gtn aar ggn tty tay ccn nnn gay ath gcn gtn gar tgg   816
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
            260                 265                 270

gar nnn aay ggn car ccn gar aay aay tay aar acn acn ccn ccn atg   864
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met
        275                 280                 285

ytn gay nnn gay ggn nnn tty tty ytn tay nnn aar ytn acn gtn gay   912
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
    290                 295                 300

aar nnn nnn tgg car car ggn aay gtn tty nnn tgy nnn gtn atg cay   960
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
305                 310                 315                 320

gar gcn ytn cay aay cay tay acn car aar nnn ytn nnn ytn nnn ccn   1008
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
                325                 330                 335

ggn aar                                                          1014
Gly Lys
```

<210> 97
<211> 338
<212> PRT
<213> Homo sapiens

<220>
<221> VARIANT
<222> 4
<223> Xaa = Ala OR Phe OR Gln OR Val OR Ile OR Leu OR
Met OR Lys OR His OR Trp OR Tyr

<400> 97

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

Glu Gly Asn Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly
                85                  90                  95
```

```
Gly Pro Glu Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro Thr Gly Gly
            100                 105                 110
Gly Gly Ser Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly
        115                 120                 125
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
    130                 135                 140
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
145                 150                 155                 160
Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
                165                 170                 175
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
            180                 185                 190
Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys
        195                 200                 205
Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu
    210                 215                 220
Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
225                 230                 235                 240
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
                245                 250                 255
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
            260                 265                 270
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met
        275                 280                 285
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
    290                 295                 300
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
305                 310                 315                 320

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
                325                 330                 335
Gly Lys



<210> 98
<211> 367
<212> PRT
<213> Homo sapiens

<220>
<221> VARIANT
<222> 64
<223> Xaa = Ala OR Arg

<400> 98
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Trp
 1               5                  10                  15
Pro Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Glu Cys Ile Tyr Tyr
            20                  25                  30
Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln Ser Gly Leu Glu Arg
        35                  40                  45
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Xaa
    50                  55                  60
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65                  70                  75                  80
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                85                  90                  95

Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro
        115                 120                 125
Pro Pro Thr Ala Pro Thr Gly Gly Gly Gly Ser Val Asp Lys Thr His
    130                 135                 140
Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
145                 150                 155                 160
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
```

```
                165                 170                 175
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            180                 185                 190
Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        195                 200                 205
Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
    210                 215                 220
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
225                 230                 235                 240
Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
                245                 250                 255
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            260                 265                 270
Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        275                 280                 285
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    290                 295                 300
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
305                 310                 315                 320
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
                325                 330                 335
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            340                 345                 350
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        355                 360                 365


<210> 99
<211> 392
<212> PRT
<213> Homo sapiens

<220>
<221> VARIANT
<222> 64
<223> Xaa = Ala OR Arg

<400> 99
Met Thr Ala Pro Trp Val Ala Leu Ala Leu Leu Trp Gly Ser Leu Typ
 1               5                  10                  15
Pro Gly Ser Gly Arg Gly Glu Ala Glu Thr Arg Glu Cys Ile Tyr Tyr
            20                  25                  30
Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gly Ser Gly Leu Glu Arg
        35                  40                  45
Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Xaa
    50                  55                  60
Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65                  70                  75                  80
Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                85                  90                  95
Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110
Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Gly Pro Trp Ala Ser
        115                 120                 125
Thr Thr Ile Pro Ser Gly Gly Pro Glu Ala Thr Ala Ala Ala Gly Asp
    130                 135                 140
Gln Gly Ser Gly Ala Leu Trp Leu Cys Leu Glu Gly Pro Ala His Glu
145                 150                 155                 160
Gly Gly Gly Gly Ser Val Asp Lys Thr His Thr Cys Pro Pro Cys Pro
                165                 170                 175
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
            180                 185                 190
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
        195                 200                 205
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
    210                 215                 220
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
225                 230                 235                 240
```

```
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
                245                 250                 255
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
            260                 265                 270
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
        275                 280                 285
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
    290                 295                 300
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
305                 310                 315                 320
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
                325                 330                 335
Tyr Leu Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
            340                 345                 350
Tyr Ser Lys Leu Thr Val Asp Lys Ser Trp Gln Gln Gly Asn Val Phe
        355                 360                 365
Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
    370                 375                 380
Ser Leu Ser Leu Ser Pro Gly Lys
385                 390
```

81