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(54) **Title**: METHODS AND COMPOSITIONS USING FGF23 FUSION POLYPEPTIDES

(57) **Abstract**: The present disclosure is directed to methods, kits and compositions for preventing or treating age-related conditions or metabolic disorders. The fusion polypeptides of the disclosure include FGF23 or an active fragment thereof. In one embodiment, the fusion polypeptide comprises (a) a polypeptide comprising fibroblast growth factor 23 (FGF23), or a functionally active variant or derivative thereof, wherein FGF23 has a mutation at one or more of the positions Q 156, C206 and C244; and (b) either a modified Fc fragment having decreased affinity for Fc-gamma-receptor and/or increased serum half-life, or a polypeptide comprising at least one extracellular subdomain of a Klotho protein, or a functionally active variant or derivative thereof; and, optionally (c) a linker. The Klotho fusion proteins are useful in the treatment and prevention of a variety of age-related conditions and metabolic disorders. In another embodiment, the fusion polypeptide comprises a FGF (such as FGF23), or a functionally active variant or derivative thereof; and a modified Fc fragment, or a functionally active variant or derivative thereof. In various embodiments of the fusion polypeptides, FGF23 has mutations which decrease aggregation and protease-mediated cleavage.

METHODS AND COMPOSITIONS USING FGF23 FUSION POLYPEPTIDES

This application claims priority to U.S. Application Serial No. 12/696693, filed January 29, 2010, the contents of which are incorporated herein by reference in their entirety.

1. BACKGROUND

Fibroblast growth factors (FGFs) constitute a family of homologous polypeptide growth factors expressed in many organisms (Ornitz and Itoh, Genome Biol. 2: reviews, 3005.1-3005.12 (2001)). Among vertebrate species, FGFs are highly conserved in both gene structure and amino-acid sequence, having between 13-71% amino acid identity with one another. In humans, there are 22 known members of the FGF family (FGF15 is the mouse ortholog of human FGF19, hence there is no human FGF15). During early development, FGFs regulate cell proliferation, migration, and differentiation, but in the adult organism, FGFs maintain homeostasis, function in tissue repair, and respond to injury.

FGFs function as growth factors by binding and thereby activating cell-surface FGF receptors. FGF receptors (FGFRs) are tyrosine kinase receptors that activate signal transduction through autophosphorylation of FGFR, phosphorylation of FRS2 (FGF receptor substrate 2) and ERK1/2 (extracellular signal-regulated protein kinase 1/2), and activating Egr-1 (early growth response-1). FGFs also have a high affinity for heparin sulfate proteoglycans. When bound to FGFs, heparin sulfate enhances the activation of FGFRs.

The alpha-Klotho gene encodes a 130 kDa single pass type I transmembrane protein with an extracellular domain and a short cytoplasmic domain. The extracellular domain of alpha-Klotho protein comprises two subdomains termed, KL-D1 and KL-D2. These two subdomains share sequence homology to β-glucosidase of bacteria and plants. The extracellular domain of the alpha-Klotho protein may be bound to the cell surface by the transmembrane domain or may be cleaved and released into the extracellular milieu. Cleavage of the extracellular domain appears to be facilitated by local low extracellular Ca^{2+} concentrations.

In addition to alpha-Klotho, a homolog of alpha-Klotho, beta-Klotho, has been identified (Ito et al., Mech. Dev. 98:115-9 (2000)). Beta-Klotho is also a single pass type I transmembrane protein with extracellular KL-D1 and KL-D2 subdomains.

Modulation of alpha-Klotho expression has been demonstrated to produce aging related characteristics in mammals. Mice homozygous for a loss of function mutation in the alpha-Klotho gene develop characteristics resembling human aging, including shortened lifespan, skin atrophy, muscle wasting, arteriosclerosis, pulmonary emphysema and osteoporosis (Kuro-o et al., Nature, 390:45-51 (1997)). In contrast, overexpression of the alpha-Klotho gene in mice extends lifespan and increases resistance to oxidative stress relative to wild-type mice (Kurosu et al., Science 309:1829–1833 (2005); Yamamoto et al., J. Biol. Chem. 280:38029–38034 (2005)).

Recent studies have demonstrated strikingly similar biological characteristics between FGF23-deficient mice and alpha-Klotho-deficient mice (Shimada et al., J. Clin. Invest. 113:561-568 (2004); Yoshida et al. Endocrinology 143:683-689 (2002)), indicating functional crosstalk between FGF23 and alpha-Klotho. These studies led to the identification of alpha-Klotho as an obligatory partner of FGF23, in terms of both binding and signaling through its cognate FGF receptors (Urakawa et al., Nature 22:1524-6 (2007)). The alpha-Klotho gene is mainly expressed in kidney, parathyroid gland and choroid plexus. It is hypothesized that the tissue-specific expression of alpha-Klotho restricts activation of FGF23 signaling to those tissues.

Similar to FGF23/alpha-Klotho, beta-Klotho is an obligatory partner of FGF19 and FGF21, both in binding and in signaling through their respective cognate FGF receptors (Ogawa et al., Proc. Natl. Acad. Sci. USA 104:7432-7 (2007); Lin et al., J. Biol Chem. 282:27227-84 (2007); and Wu et al., J. Biol. Chem. 282:29069-72 (2007)). Such studies have also demonstrated the involvement of beta-Klotho in regulating tissue-specific metabolic activity. Beta-Klotho was initially shown to act with FGF21 as a cofactor for regulating carbohydrate and lipid metabolism in adipose tissue. Beta-Klotho in conjunction with FGF19 regulates bile acid metabolism in liver, thus explaining elevated bile synthesis in beta-Klotho deficient mice (Ito et al., J Clin Invest. 2005 Aug;115(8):2202-8).

U.S. Patent No. 6,579,850 describes polypeptides and compositions comprising an alpha-Klotho polypeptide. Human and mouse alpha-Klotho polypeptides are disclosed. The patent also disclosed that compositions comprising the polypeptides are useful in treating a syndrome resembling premature aging, treating adult diseases, and suppressing aging.

U.S. Patent No. 7,223,563 describes isolated nucleic acids encoding the FGF23 polypeptide sequence or recombinant cells comprising such an isolated nucleic acid. The

patent further relates to methods of diagnosing and treating hypophosphatemic and hyperphosphatemic disorders, osteoporosis, dermatomyositis, and coronary artery disease.

U.S. Patent No. 7,259,248 describes isolated nucleic acids encoding the FGF21 polypeptide sequence. The patent further relates to methods of diagnosing and treating liver disease, conditions related to thymic function, and methods of treating conditions of the testis.

2. SUMMARY OF THE INVENTION

The present disclosure is directed to methods, uses, kits and compositions for preventing or treating age-related conditions or metabolic disorders with fusion polypeptides or soluble polypeptides. The fusion polypeptides of the present disclosure are formed of a FGF (e.g., FGF23); and either a Klotho protein or an active fragment thereof (e.g., sKlotho) and/or a Fc fragment (e.g., FcLALA); and, optionally, a linker. In some embodiments, the FGF23 is mutated. In some embodiments, the present disclosure provides a Klotho fusion polypeptide comprising a Klotho protein or an active fragment thereof and a fibroblast growth factor or an active fragment thereof. In some embodiments, the fusion polypeptide comprises a Klotho polypeptide, a FGF (such as FGF23) and a modified Fc fragment. The Fc fragment can, for example, have decreased binding to Fc-gamma-receptor and increased serum half-life. Fusion proteins comprising sKlotho, FGF23 and FcLALA (a modified Fc fragment having decreased affinity for Fc-gamma-receptorand/or increased serum half-life) are described in SEQ ID NOs. 46, 47, 48, and 49. In some embodiments, the fusion polypeptide or protein comprises a FGF (e.g., FGF23), or a functionally active variant or derivative (e.g., a variant comprising at least one conservative amino acid substitution and/or one amino acid deletion) thereof; and a modified Fc fragment, or a functionally active variant or derivative (e.g., a variant comprising at least one conservative amino acid substitution and/or one amino acid deletion) thereof. Fusion proteins comprising FGF23 and FcLALA are described in SEQ ID NOs. 50, 51, 52 and 53. In some embodiments, the fusion polypeptide has one or more mutations in FGF23 which decrease aggregation and/or protease-mediated cleavage.

In a first aspect, the disclosure provides a fusion polypeptide having at least one extracellular subdomain of a Klotho protein and a fibroblast growth factor or an active fragment thereof. In some embodiments, the fusion further comprises a modified Fc fragment having decreased affinity (e.g., decreased Ka or increased Kd) for Fc-gamma-receptorand/or increased serum half-life. The Klotho extracellular domain may be derived

from either the alpha or beta Klotho isoforms. Further, although the FGF component of the Klotho fusion polypeptide is described primarily with reference to fibroblast growth factor-19, fibroblast growth factor-21 and fibroblast growth factor-23, it is contemplated that any of the twenty-three known FGFs can be used in practicing the disclosure. The reader of the instant application may assume that each of every combination of alpha or beta extracellular domain with each human FGF protein or an active fragment thereof are individually and specifically contemplated.

According to the present disclosure, the extracellular domain of the Klotho protein can include one or both of the KL-D1 and KL-D2 domains of a Klotho protein, or a functionally active variant or derivative (e.g., a variant comprising at least one conservative amino acid substitution and/or one amino acid deletion) thereof. In some embodiments, the Klotho fusion polypeptide of the disclosure has at least two extracellular subdomains of a Klotho protein, or a functionally active variant or derivative (e.g., a variant comprising at least one conservative amino acid substitution and/or one amino acid deletion) thereof. For example, the at least two extracellular subdomains can be at least two KL-D1 domains in tandem repeats, at least two KL-D2 domains in tandem repeats, or at least one KL-D1 domain and at least one KL-D2 domain. In various embodiments, the fusion polypeptide of the disclosure comprises amino acids 28-292 of the full length alpha Klotho protein, or amino acids 28-982 (SEQ ID NO: 7). In another embodiment, the fusion polypeptide of the disclosure comprises amino acids 52-997 of the full length beta Klotho protein.

In one embodiment of the present disclosure, the components of a fusion polypeptide comprise: (a) a polypeptide comprising fibroblast growth factor 23 (FGF23), or a functionally active variant or derivative (e.g., a variant comprising at least one conservative amino acid substitution and/or one amino acid deletion) thereof, wherein FGF23 has a mutation at one or more of the positions Q156, C206 and C244; and (b) either a modified Fc fragment having decreased affinity for Fc-gamma-receptor and/or increased serum half-life, or a polypeptide comprising at least one extracellular subdomain of a Klotho protein, or a functionally active variant or derivative (e.g., a variant comprising at least one conservative amino acid substitution and/or one amino acid deletion) thereof; and, optionally (c) a linker. The components can be, for example, chemically linked or fused in frame by a peptide bond. They may also linked via a linker. Non-limiting examples of polypeptide linker are SEQ ID NOs: 11, 12, 13, 14, 15, 16, 17, and 18. Such linkers may comprise at least one and up to about 30 repeats of SEQ ID

NOs:11, 12, 13, 14, 15, 16, 17 and 18. In another non-limiting embodiment, the fusion comprises (2) a FGF or an active fragment thereof and (3) a modified Fc fragment. The various components of the fuion can be operatively linked in any order; the polypeptide (1) can be operatively linked to the N-terminus of the polypeptide for (2) or (3); the polypeptide for (2) can be operatively linked to the N-terminus of the polypeptide for (1) or (3); the polypeptide for (3) can be operatively linked to the N-terminus of the polypeptide for (1) or (2).

According to the present disclosure, the extracellular subdomain of a Klotho protein, the fibroblast growth factor and the (optional) modified Fc fragment having decreased affinity for Fc-gamma-receptorand/or increased serum half-life can be operatively linked to one another in a variety of orientations and manners. For example, the extracellular subdomain of the Klotho protein can be operatively linked to the N-terminus of the fibroblast growth factor or alternatively the fibroblast growth factor can be operatively linked to the N-terminus of an extracellular subdomain of the Klotho protein.

In one embodiment, the present disclosure provides a fusion polypeptide comprising a sKlotho of a Klotho protein and a linker. In another embodiment, the present disclosure provides a fusion polypeptide comprising a sKlotho of the alpha Klotho protein and a linker. In another embodiment, the present disclosure provides a fusion polypeptide comprising a sKlotho of the beta Klotho protein and a linker. In yet another embodiment, the present disclosure provides a human FGF protein or an active fragment thereof (e.g., without signal peptide) and a linker. In one embodiment the disclosure provides fusion proteins, nucleic acid molecules or pharmaceutical composition for use in therapy or as medicament for use in the treatment of a pathological disorder. Pharmaceutical compositions comprising the fusion proteins of the disclosure and their uses for treating or preventing age-related conditions or metabolic disorders are also encompassed by the present disclosure. In some embodiments, the fusion protein further comprises a modified Fc fragment having decreased affinity for Fc-gamma-receptorand/or increased serum half-life.

In one embodiment, the present disclosure provides a fusion polypeptide comprising a sKlotho of alpha Klotho protein with signal peptide fused (directly or indirectly via a linker) to FGF-23. In another embodiment, the present disclosure provides a fusion polypeptide comprising a sKlotho of alpha Klotho protein without signal peptide fused (directly or indirectly via a linker) to FGF-23. In another

embodiment, the present disclosure provides sKlotho of alpha Klotho protein with signal peptide fused (directly or indirectly via a linker) to FGF-23 without signal peptide. In another embodiment, the present disclosure provides a fusion polypeptide comprising sKlotho of alpha Klotho protein without signal peptide fused (directly or indirectly via a linker) to FGF-23 without signal peptide. In some embodiments, the fusion protein further comprises a modified Fc fragment having decreased affinity for Fc-gamma-receptorand/or increased serum half-life.

In one embodiment, the present disclosure provides a fusion polypeptide comprising a sKlotho of alpha Klotho protein with signal peptide fused (directly or indirectly via a linker) to FGF-23 (R179Q) variant. In another embodiment, the present disclosure provides a fusion polypeptide comprising a sKlotho of alpha Klotho protein without signal peptide fused (directly or indirectly via a linker) to FGF-23 (R179Q) variant. In another embodiment, the present disclosure provides sKlotho of alpha Klotho protein with signal peptide fused (directly or indirectly via a linker) to FGF-23 (R179Q) variant without signal peptide. In another embodiment, the present disclosure provides a fusion polypeptide comprising sKlotho of alpha Klotho protein without signal peptide fused (directly or indirectly via a linker) to FGF-23 (R179Q) variant without signal peptide. In some embodiments, the fusion protein further comprises a modified Fc fragment having decreased affinity for Fc-gamma-receptorand/or increased serum half-life.

In one embodiment, the present disclosure provides a fusion polypeptide comprising: (a) a polypeptide comprising fibroblast growth factor 23 (FGF23), or a functionally active variant or derivative (e.g., a variant comprising at least one conservative amino acid substitution and/or one amino acid deletion) thereof, wherein FGF23 has a mutation at one or more of the positions Q156, C206 and C244; and (b) either a modified Fc fragment having decreased affinity for Fc-gamma-receptor and/or increased serum half-life, or a polypeptide comprising at least one extracellular subdomain of a Klotho protein, or a functionally active variant or derivative (e.g., a variant comprising at least one conservative amino acid substitution and/or one amino acid deletion) thereof; and, optionally (c) a linker. Such fusion polypeptides are disclosed in SEQ ID NOs: 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, and 68.

In one embodiment, the present disclosure provides a fusion polypeptide comprising (1) sKlotho of alpha Klotho protein with signal peptide, or a functionally active variant or derivative (e.g., a variant comprising at least one conservative amino

acid substitution and/or one amino acid deletion) thereof; (2) a linker; and (3) FGF-23 (R179Q) variant without signal peptide, or a functionally active variant or derivative (e.g., a variant comprising at least one conservative amino acid substitution and/or one amino acid deletion) thereof. In another embodiment, the present disclosure provides a fusion polypeptide comprising (1) sKlotho of alpha Klotho protein without signal peptide, or a functionally active variant or derivative (e.g., a variant comprising at least one conservative amino acid substitution and/or one amino acid deletion) thereof; (2) a linker; and (3) FGF-23 (R179Q) variant without signal peptide, or a functionally active variant or derivative (e.g., a variant comprising at least one conservative amino acid substitution and/or one amino acid deletion) thereof. In some embodiments, the fusion polypeptides of the disclosure are glycosylated. In some embodiments, the fusion protein further comprises a modified Fc fragment having decreased affinity for Fc-gamma-receptorand/or increased serum half-life.

In one embodiment, the present disclosure provides a fusion polypeptide comprising (1) sKlotho of alpha Klotho protein with signal peptide (SEQ ID NO: 44 or SEQ ID NO: 45), or a functionally active variant or derivative (e.g., a variant comprising at least one conservative amino acid substitution and/or one amino acid deletion) thereof (2) a linker comprising SEQ ID NO: 11; and (3) FGF-23 (R179Q) variant without signal peptide (SEQ ID NO: 43), or a functionally active variant or derivative (e.g., a variant comprising at least one conservative amino acid substitution and/or one amino acid deletion) thereof. In another embodiment, the present disclosure provides a fusion polypeptide comprising (1) sKlotho of alpha Klotho protein without signal peptide (SEQ ID NO: 7), or a functionally active variant or derivative (e.g., a variant comprising at least one conservative amino acid substitution and/or one amino acid deletion) thereof (2) a linker comprising SEQ ID NO: 11; and (3) FGF-23 (R179Q) variant without signal peptide (SEQ ID NO: 43), or a functionally active variant or derivative (e.g., a variant comprising at least one conservative amino acid substitution and/or one amino acid deletion) thereof In one embodiment, the present disclosure provides a fusion polypeptide comprising the amino acid sequence of SEQ ID NO: 19, 20, 40, or 41. In some embodiments, the fusion polypeptides of the disclosure are glycosylated.

In one embodiment, the present disclosure provides a fusion polypeptide comprising sKlotho of alpha Klotho protein with signal peptide (SEQ ID NO: 44 or SEQ ID NO: 45), or a functionally active variant or derivative (e.g., a variant comprising at least one conservative amino acid substitution and/or one amino acid deletion) thereof;

and a linker comprising SEQ ID NO: 11. In another embodiment, the present disclosure provides a fusion polypeptide comprising sKlotho of alpha Klotho protein without signal peptide (SEQ ID NO: 7); and a linker comprising SEQ ID NO: 11. In some embodiments, the fusion polypeptides of the disclosure are glycosylated. In some embodiments, the fusion protein further comprises a modified Fc fragment having decreased affinity for Fc-gamma-receptorand/or increased serum half-life.

In one embodiment, the present disclosure provides a fusion polypeptide comprising a human FGF protein or an active fragment thereof (e.g., without the signal peptide); and a linker comprising SEQ ID NO: 11. In some embodiments, the fusion polypeptides of the disclosure are glycosylated. In some embodiments, the fusion protein further comprises a modified Fc fragment having decreased affinity for Fc-gamma-receptorand/or increased serum half-life.

In one embodiment, the present disclosure provides a fusion polypeptide comprising a human FGF protein (e.g., FGF23) or an active fragment thereof (e.g., without the signal peptide); a linker (e.g., a linker comprising SEQ ID NO: 11); and sKlotho (with or without a signal peptide), or a functionally active variant or derivative (e.g., a variant comprising at least one conservative amino acid substitution and/or one amino acid deletion) thereof) or a Fc-gramma-receptor (e.g., FcLALA); wherein the FGF (e.g., FGF23) has one or more mutations at these residues: R179, Q156, C206, and/or C244. In various embodiments, the mutations are R179Q, Q156A, C206S, and/or C244S. Even though these mutations are conserved in the human, rhesus, bovine, mouse and rat FGF23, mutating them does not prevent FGF23 activity. Rather, mutating these amino acids unexpectedly enhances the qualities of the proteins, by reducing aggregation, reducing undesired protease-induced cleavage, and increasing protein production from cells. In various embodiments, the fusion protein comprising one or more FGF23 mutation is glycosylated.

In one embodiment, the present disclosure provides a pharmaceutical composition (e.g., in an intra-muscular administering form) comprising (e.g., as a sole pharmaceutically active ingredient) a fusion polypeptide (e.g., glycosylated or non-glycosylated) that comprises (1) FGF-23 (R179Q) variant without signal peptide (SEQ ID NO: 43), or a variant comprising additional mutations which reduce aggregation and/or protease-mediated cleavage, or a functionally active variant or derivative (e.g., a variant comprising at least one conservative amino acid substitution and/or one amino acid deletion) thereof (2) optionally, a linker comprising SEQ ID NO: 11; and (3) sKlotho of

alpha Klotho protein with signal peptide (SEQ ID NO: 44 or SEQ ID NO: 45), or a functionally active variant or derivative (e.g., a variant comprising at least one conservative amino acid substitution and/or one amino acid deletion) thereof or a modified Fc fragment having decreased affinity for Fc-gamma-receptorand/or increased serum half-life; and uses of the pharmaceutical composition in therapy or as medicament for the treatment of a pathological disorder, for example treating and/or preventing age-related conditions, such as muscular atrophy. In another embodiment, the present disclosure provides a pharmaceutical composition (e.g., in an intra-muscular administering form) comprising (e.g., as a sole pharmaceutically active ingredient) a fusion polypeptide (e.g., glycosylated or non-glycosylated) that comprises (1) FGF-23 (R179Q) variant without signal peptide (SEQ ID NO: 43), or a variant comprising additional mutations which reduce aggregation and/or protease-mediated cleavage, or a functionally active variant or derivative (e.g., a variant comprising at least one conservative amino acid substitution and/or one amino acid deletion) thereof (2) a linker comprising SEQ ID NO: 11; and (3) sKlotho of alpha Klotho protein without signal peptide (SEQ ID NO: 7), or a functionally active variant or derivative (e.g., a variant comprising at least one conservative amino acid substitution and/or one amino acid deletion) thereof, or a modified Fc fragment having decreased affinity for Fc-gamma-receptorand/or increased serum half-life, or a functionally active variant or derivative (e.g., a variant comprising at least one conservative amino acid substitution and/or one amino acid deletion) thereof; and uses of the pharmaceutical composition in therapy or as medicament for the treatment of a pathological disorder, for example treating and/or preventing age-related conditions, such as muscular atrophy. In one embodiment, the present disclosure provides a pharmaceutical composition (e.g., in an intra-muscular administering form) comprising (e.g., as a sole pharmaceutically active ingredient) a fusion polypeptide (e.g., glycosylated or non-glycosylated) comprising the amino acid sequence of SEQ ID NO: 19, 20, 40, or 41; and uses of the pharmaceutical composition in therapy or as medicament for the treatment of a pathological disorder, for example treating and/or preventing age-related conditions, such as muscular atrophy.

In one embodiment, the present disclosure provides a pharmaceutical composition (e.g., in an intra-muscular administering form) comprising (e.g., as a sole pharmaceutically active ingredient) a fusion polypeptide (e.g., glycosylated or non-glycosylated) that comprises sKlotho of alpha Klotho protein with signal peptide (SEQ ID NO: 44 or SEQ ID NO: 45); and a linker comprising SEQ ID NO: 11; and uses of the

pharmaceutical composition for treating and/or preventing age-related conditions, such as muscular atrophy. In another embodiment, the present disclosure provides a pharmaceutical composition (e.g., in an intra-muscular administering form) comprising (e.g., as a sole pharmaceutically active ingredient) a fusion polypeptide (e.g., glycosylated or non-glycosylated) comprising sKlotho of alpha Klotho protein without signal peptide (SEQ ID NO: 7); and a linker comprising SEQ ID NO: 11; and uses of the pharmaceutical composition in therapy or as medicament for the treatment of a pathological disorder,for example treating and/or preventing age-related conditions, such as muscular atrophy. In some embodiments, the fusion protein further comprises a modified Fc fragment.

In one embodiment, the present disclosure provides a pharmaceutical composition comprising (e.g., as a sole pharmaceutically active ingredient) a fusion polypeptide (e.g., glycosylated or non-glycosylated) that comprises a human FGF protein or an active fragment thereof (e.g., without the signal peptide); and a linker comprising SEQ ID NO: 11.

Pharmaceutical compositions comprising the fusion proteins of the disclosure and their uses in therapy or as medicament for the treatment of a pathological disorder therapy, for example treating or preventing age-related conditions (e.g., muscle atrophy) or metabolic disorders (e.g., diabete) are also encompassed by the present disclosure.

In one embodiment, the present disclosure provides a fusion polypeptide that is at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 96%, at least 97%, at least 98%, at least 99% identical to SEQ ID NO: 19. In another embodiment, the present disclosure provides a fusion polypeptide that is at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 96%, at least 97%, at least 98%, at least 99% identical to SEQ ID NO: 20.

In one embodiment, the present disclosure provides a fusion polypeptide that is at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 96%, at least 97%, at least 98%, at least 99% identical to SEQ ID NO: 40. In another embodiment, the present disclosure provides a fusion polypeptide that is at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 96%, at least 97%, at least 98%, at least 99% identical to SEQ ID NO: 41.

In one embodiment, the present disclosure provides a fusion polypeptide that is at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least

95%, at least 96%, at least 96%, at least 97%, at least 98%, at least 99% or 100% identical to SEQ ID NO: 46. In another embodiment, the present disclosure provides a fusion polypeptide that is at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 96%, at least 97%, at least 98%, at least 99% or 100% identical to SEQ ID NO: 47.

In another embodiment, the present disclosure provides a fusion polypeptide that is at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 96%, at least 97%, at least 98%, at least 99% or 100% identical to SEQ ID NO: 48. In another embodiment, the present disclosure provides a fusion polypeptide that is at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 96%, at least 97%, at least 98%, at least 99% or 100% identical to SEQ ID NO: 49.

In one embodiment, the present disclosure provides a fusion polypeptide that is at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 96%, at least 97%, at least 98%, at least 99% or 100% identical to SEQ ID NO: 50. In another embodiment, the present disclosure provides a fusion polypeptide that is at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 96%, at least 97%, at least 98%, at least 99% or 100% identical to SEQ ID NO: 51.

In one embodiment, the present disclosure provides a fusion polypeptide that is at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 96%, at least 97%, at least 98%, at least 99% or 100% identical to SEQ ID NO: 52. In another embodiment, the present disclosure provides a fusion polypeptide that is at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 96%, at least 97%, at least 98%, at least 99% or 100% identical to SEQ ID NO: 53.

In another embodiment, the present disclosure provides a fusion polypeptide that is at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 96%, at least 97%, at least 98%, at least 99% or 100% identical to SEQ ID NO: 54.

In another embodiment, the present disclosure provides a fusion polypeptide that is at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least

95%, at least 96%, at least 96%, at least 97%, at least 98%, at least 99% or 100% identical to SEQ ID NO: 55.

In another embodiment, the present disclosure provides a fusion polypeptide that is at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 96%, at least 97%, at least 98%, at least 99% or 100% identical to SEQ ID NO: 56.

In another embodiment, the present disclosure provides a fusion polypeptide that is at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 96%, at least 97%, at least 98%, at least 99% or 100% identical to SEQ ID NO: 57.

In another embodiment, the present disclosure provides a fusion polypeptide that is at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 96%, at least 97%, at least 98%, at least 99% or 100% identical to SEQ ID NO: 58.

In another embodiment, the present disclosure provides a fusion polypeptide that is at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 96%, at least 97%, at least 98%, at least 99% or 100% identical to SEQ ID NO: 59.

In another embodiment, the present disclosure provides a fusion polypeptide that is at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 96%, at least 97%, at least 98%, at least 99% or 100% identical to SEQ ID NO: 60.

In another embodiment, the present disclosure provides a fusion polypeptide that is at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 96%, at least 97%, at least 98%, at least 99% or 100% identical to SEQ ID NO: 61.

In another embodiment, the present disclosure provides a fusion polypeptide that is at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 96%, at least 97%, at least 98%, at least 99% or 100% identical to SEQ ID NO: 62.

In another embodiment, the present disclosure provides a fusion polypeptide that is at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 96%, at least 97%, at least 98%, at least 99% or 100% identical to SEQ ID NO: 63.

In another embodiment, the present disclosure provides a fusion polypeptide that is at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 96%, at least 97%, at least 98%, at least 99% or 100% identical to SEQ ID NO: 64.

In another embodiment, the present disclosure provides a fusion polypeptide that is at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 96%, at least 97%, at least 98%, at least 99% or 100% identical to SEQ ID NO: 65.

In another embodiment, the present disclosure provides a fusion polypeptide that is at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 96%, at least 97%, at least 98%, at least 99% or 100% identical to SEQ ID NO: 66.

In another embodiment, the present disclosure provides a fusion polypeptide that is at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 96%, at least 97%, at least 98%, at least 99% or 100% identical to SEQ ID NO: 67.

In another embodiment, the present disclosure provides a fusion polypeptide that is at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 96%, at least 97%, at least 98%, at least 99% or 100% identical to SEQ ID NO: 68.

In one embodiment, the present disclosure provides a fusion polypeptide comprising a sKlotho of beta Klotho protein with signal peptide fused (directly or indirectly via a linker) to FGF-19 or an active fragment thereof. In some embodiments, the fusion further comprises a modified Fc fragment having decreased affinity for Fc-gamma-receptor and/or increased serum half-life. In another embodiment, the present disclosure provides a fusion polypeptide comprising a sKlotho of beta Klotho protein without signal peptide fused (directly or indirectly via a linker) to FGF-19 or an active

fragment thereof. In another embodiment, the present disclosure provides a fusion polypeptide comprising a sKlotho of beta Klotho protein with signal peptide fused (directly or indirectly via a linker) to FGF-21 or an active fragment thereof. In another embodiment, the present disclosure provides a fusion polypeptide comprising a sKlotho of beta Klotho protein without signal peptide fused (directly or indirectly via a linker) to FGF-21 or an active fragment thereof.

The disclosure provides nucleic acid sequences encoding any of the Klotho fusion polypeptides described herein and host cells containing the nucleic acids. In some embodiments, the fusion further comprises a modified Fc fragment having decreased affinity for Fc-gamma-receptor and/or increased serum half-life.

The disclosure also provides composition having any of the Klotho fusion polypeptides contemplated herein. The compositions of the disclosure can further include heparin. In some embodiments, the fusion further comprises a modified Fc fragment having decreased affinity for Fc-gamma-receptor and/or increased serum half-life.

The disclosure also provides a method for treating or preventing an age-related condition in an individual. An individual (e.g., human) is administered a therapeutically effective dose of a pharmaceutical composition containing a Klotho fusion polypeptide, having at least one extracellular subdomain of a Klotho protein (e.g., alpha Klotho protein) and a fibroblast growth factor or an active fragment thereof so as to treat or prevent the age-related condition. In some embodiments, the fusion further comprises a modified Fc fragment having decreased affinity for Fc-gamma-receptor and/or increased serum half-life. In particular, the disclosure provides a method of treating or preventing muscle wasting comprising administering to an individual (e.g., human) an therapeutically effective amount of a fusion polypeptide having at least one extracellular subdomain of an alpha Klotho protein and a fibroblast growth factor (or an active fragment thereof).

Additionally, the disclosure provides a method for treating or preventing a metabolic disorder in an individual. An individual is administered a therapeutically effective dose of a pharmaceutical composition containing a fusion polypeptide of the disclosure, having at least one extracellular subdomain of a Klotho protein and a fibroblast growth factor (or an active fragment thereof) so as to treat the metabolic disorder. In some embodiments, the fusion further comprises a modified Fc fragment having decreased affinity for Fc-gamma-receptor and/or increased serum half-life. In particular, a fusion polypeptide of the disclosure having at least one extracellular

subdomain of a beta-Klotho protein and a fibroblast growth factor 21 is useful for treating a metabolic disorder.

Klotho-FGF23 fusion polypeptides of the disclosure can be used for treating or preventing hyperphosphatemia or calcinosis in an individual. In some embodiments, the fusion further comprises a modified Fc fragment having decreased affinity for Fc-gamma-receptor and/or increased serum half-life. A pharmacologically effective dose of a pharmaceutical composition containing the Klotho fusion polypeptide of the disclosure, having at least one extracellular subdomain of a Klotho protein and a fibroblast growth factor, is administered to treat or prevent hyperphosphatemia or calcinosis. In particular, a Klotho fusion polypeptide of the disclosure having at least one extracellular subdomain of an alpha Klotho protein and a fibroblast growth factor 23 is useful for treating hyperphosphatemia or calcinosis.

Klotho-FGF23 fusion polypeptides of the disclosure can be used for treating or preventing chronic renal disease or chronic renal failure in an individual. In some embodiments, the fusion further comprises a modified Fc fragment having decreased affinity for Fc-gamma-receptor and/or increased serum half-life. A therapeutically effective dose of a pharmaceutical composition containing the Klotho fusion polypeptide of the disclosure, having at least one extracellular subdomain of a Klotho protein (e.g., alpha Klotho protein) and a fibroblast growth factor, is administered to treat or prevent chronic renal disease or chronic renal failure.

Klotho-FGF23 fusion polypeptides of the disclosure can be used for treating or preventing cancer (e.g., breast cancer) in an individual. In some embodiments, the fusion further comprises a modified Fc fragment having decreased affinity for Fc-gamma-receptor and/or increased serum half-life. A therapeutically effective dose of a pharmaceutical composition containing the Klotho fusion polypeptide of the disclosure, having at least one extracellular subdomain of a Klotho protein (e.g., alpha Klotho protein) and a fibroblast growth factor, is administered to treat or prevent cancer or breast cancer.

The present disclosure provides fusion polypeptides comprising at least one extracellular subdomain of Klotho protein and a FGF or an active fragment thereof for use in medicine. In some embodiments, the fusion further comprises a modified Fc fragment having decreased affinity for Fc-gamma-receptor and/or increased serum half-life. In one embodiment, the present disclosure provides fusion polypeptides comprising at least one extracellular subdomain of Klotho protein and a FGF or an active fragment

thereof for use in treating or preventing muscle atrophy. The present disclosure also provides a method of treating or preventing an age related condition (e.g., muscle atrophy) comprising administering to an individual in need thereof a therapeutically effective dose of a pharmaceutical composition comprising a soluble Klotho protein.

The disclosure futhermore provides the above described peptides and fusion polypeptides or pharmaceutical compositions comprising said peptides for use in therapy, as a medicament or for use in the treatment of a pathological disorder, for example age-related condition, metabolic disorder, hyperphosphatemia or calcinosis, chronic renal disease or chronic renal failure or to prevent cancer or breast cancer, in an individual. Additonally, the disclosure further provides use of a polypeptide, nucleic acid or pharmaceutical composition of the invention in the manifacture of a medicament for the treatment of a pathological disorder, particularly for the treatment of the above mentioned disorders, preferably age related conditions like muscle atrophy.

The disclosure also includes kits for treating or preventing an age-related disorder or metabolic disorder in an individual. The kit includes instructions for use and a purified Klotho fusion polypeptide having at least one extracellular subdomain of a Klotho protein and a fibroblast growth factor. In some embodiments, the fusion further comprises a modified Fc fragment having decreased affinity for Fc-gamma-receptor and/or increased serum half-life.

The disclosure also provides a kit for producing a Klotho fusion polypeptide of the disclosure. The kit of the disclosure includes instructions for use and a nucleic acid encoding a Klotho fusion polypeptide, having at least one extracellular subdomain of Klotho protein and a fibroblast growth factor. In some embodiments, the fusion further comprises a modified Fc fragment having decreased affinity for Fc-gamma-receptor and/or increased serum half-life.

In one embodiment of the disclosure, the fusion polypeptide comprises: (a) a polypeptide comprising a fibroblast growth factor, or a functionally active variant or derivative (e.g., a variant comprising at least one conservative amino acid substitution and/or one amino acid deletion) thereof; and (b) a modified Fc fragment, or a functionally active variant or derivative (e.g., a variant comprising at least one conservative amino acid substitution and/or one amino acid deletion) thereof, having decreased affinity for Fc-gamma-receptor and/or increased serum half-life

In one embodiment of the disclosure, the polypeptide of (a) and the polypeptide of (b) are connected by a polypeptide linker. The linker can be repeated 1 to 30 times, or more.

In one embodiment of the disclosure, the polypeptide linker comprises an amino acid sequence selected from the group consisting of: SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, and SEQ ID NO: 18.

In one embodiment of the disclosure, the polypeptide of (a) is connected by a peptide bond to the N-terminus of said polypeptide linker, and the polypeptide of (b) is connected by a peptide bond to the C-terminus of said polypeptide linker.

In one embodiment of the disclosure, the fusion polypeptide further comprises a signal peptide.

In one embodiment of the disclosure, the signal peptide is the IgG signal peptide.

In one embodiment of the disclosure, the fibroblast growth factor is fibroblast growth factor-23 or a fibroblast growth factor-23 variant (R179Q).

In one embodiment of the disclosure, the fibroblast growth factor is fibroblast growth factor-19 or fibroblast growth factor-21.

In one embodiment of the disclosure, fusion polypeptide comprises an amino acid sequence which is 95% or more identical to the amino acid sequence of SEQ ID NO: 51, or SEQ ID NO: 53.

In one embodiment of the disclosure, fusion polypeptide comprises the amino acid sequence of SEQ ID NO: 51, or SEQ ID NO: 53.

In one embodiment of the disclosure, fusion polypeptide comprises FcLALA.

3. BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates several different embodiments of the Klotho fusion polypeptides of the disclosure. The represented fusion polypeptides include one or more Klotho extracellular subdomains operatively linked to a fibroblast growth factor. Polypeptides containing one or more Klotho extracellular subdomains include, for example, an extracellular domain of Klotho (e.g., aa 1 to 982 of human Klotho), or an active fragment of Klotho.

Figure 2 illustrates the amino acid and nucleic acid sequences of several Klotho fusion polypeptides of the disclosure and components thereof (e.g., Klotho extracellular

domain, FGF). Fusion proteins comprising sKlotho, FGF23 and FcLALA (a modified Fc fragment having decreased affinity for Fc-gamma-receptor and/or increased serum half-life) are described in SEQ ID NOs. 46, 47, 48, and 49. Fusion proteins comprising FGF23 and FcLALA are described in SEQ ID NOs. 50, 51, 52 and 53.

Figures 3A-3C depict protein expression of an sKlotho-FGF23 fusion protein. Figure 3A shows that sKlotho-FGF23 fusion protein was detected in conditioned media by Western blotting with anti-FGF23 antibodies. Figure 3B shows that sKlotho-FGF23 fusion protein was detected in conditioned media by SDS-PAGE and Coomassie blue staining Figure 3C shows a highly purified sKlotho-FGF23-6xHis fusion protein, analyzed by SDS-PAGE and Coomassie blue staining.

Figure 4 illustrates the results of an Egr-1 luciferase assay comparing the activation level of Egr-1 in cells treated with conditioned media containing either a Klotho fusion polypeptide, a FGF 23 polypeptide only, a soluble Klotho (sKlotho) polypeptide only, and a soluble Klotho polypeptide in combination with a FGF 23 polypeptide in the absence or presence of heparin (20 μg/ml).

Figures 5A-5B depict the results of an Egr-1 luciferase assay comparing the activation level of Egr-1 in cells treated with purified Klotho fusion polypeptide, FGF 23 polypeptide, or soluble Klotho polypeptide in the absence or presence of heparin. Figure 5A shows an the results of an experiment comparing the activation level of Egr-1 in cells treated with FGF 23 alone, sKlotho-His (10 nM or 20 nM) and a combination of FGF 23 and sKlotho-His (10 nM or 20 nM) in the absence or presence of heparin (20 μg/ml). Figure 5B shows Egr-1 luciferase reporter activity in cells treated with sKlotho-FGF23-His fusion (0 nM, 0.6 nM, 1.21 nM, 2.41 nM, 4.83 nM, 9.65 nM, and 19.3 nM).

Figures 6A-6B illustrate the effect of treatment with a purified sKlotho fusion polypeptide on C2C12 muscle cells. Figure 6A shows measurements of myotube diameter in C2C12 muscle cells treated with either IGF-1 (10 nM), FGF2 (20ng/ml), or a purified Klotho fusion polypeptide (20 nM), in the absence or presence of dexamethasone (100 μM). Figure 6B shows the phosphorylation of signaling pathway proteins in C2C12 muscle cells by IGF-1 (10 nM), FGF2 (20ng/ml), or a purified Klotho fusion polypeptide (20 nM), in the absence or presence of rapamycin (40 nM).

Figure 7 shows activation of EGR-1-luc reporter gene by sKlotho-FGF23(R179Q)-FcLALA fusion proteins.

Figure 8 shows the activation of EGR-1-luc reporter gene by FGF23(R179Q)-FcLALA proteins.

Figure 9 shows the pharmacokinetic profile of FGF23(R179Q) vs FGF23(R179Q)-FcLALAv2.

Figures 10A and 10B show the in vivo efficacy of sKlotho-FGF23 fusion in enhancing muscle growth after dexamethasone-induced muscle atrophy.

Figure 11. This figure shows activation of EGR-1-luc reporter gene by FGF23(R179Q)-FcLALA and Q156A, C206S, C244S and C206S/C244S mutants.

Figure 12 shows protein qualities and dimerization of WT (wild-type), Q156A, C206S, C244S and C206S/C244S mutants of FGF23(R179Q)-FcLaLa.

4. DETAILED DESCRIPTION

The present disclosure is directed to methods, kits and compositions for preventing or treating age-related conditions and metabolic disorders; and to the use of said compostions in therapy, as a medicament or for use in the treatment of a pathological disorder. The fusion polypeptides of the disclosure include a Klotho protein or active fragment thereof. In some embodiments, the fusion polypeptides of the disclosure include a Klotho protein or an active fragment thereof operatively linked to a fibroblast growth factor polypeptide or active fragment thereof. In some embodiments, the fusion further comprises a modified Fc fragment with decreased ability to bind FcRn and/or increased stability in serum. In another embodiment, the fusion polypeptide comprises a FGF (e.g., FGF23) and a modified Fc fragment with decreased ability to bind FcRn and/or increased stability in serum.

The fusion proteins or sKlotho of the present disclosure are useful in the treatment and prevention of a variety of age-related conditions including sarcopenia, skin atrophy, muscle wasting, brain atrophy, atherosclerosis, arteriosclerosis, pulmonary emphysema, osteoporosis, osteoarthritis, immunologic incompetence, high blood pressure, dementia, Huntington's disease, Alzheimer's disease, cataracts, age-related macular degeneration, prostate cancer, stroke, diminished life expectancy, memory loss, wrinkles, impaired kidney function, and age-related hearing loss; and metabolic disorders including Type II Diabetes, Metabolic Syndrome, hyperglycemia, and obesity.

The present disclosure is based at least in part on the finding that despite the physical constraints (e.g., large size of both the Klotho and FGF polypeptides) the Klotho-FGF fusion polypeptides are highly effective in activating an FGF receptor. This finding is unexpected given that fusion of these two proteins would likely interfere with the heterodimerization and thus the activities of the proteins; e.g., the binding domains of the proteins may be perturbed by the fusion or the proteins may be mis-oriented spatially if put together in a "cis" formation.

The fusion polypeptides described herein are advantageous because they allow the administration of a single therapeutic protein that has enhanced activity compared to Klotho or FGF administered alone or together as separate polypeptides. The use of Klotho and FGF as a single fusion polypeptide rather than as two separate polypeptides (i.e., a Klotho polypeptide and a separate FGF polypeptide) is more effective at activating the FGF receptor.

Definitions

"Klotho polypeptide", "Klotho protein", or "Klotho" as used herein, includes active fragments, derivatives, mimetics, variants and chemically modified compounds or hybrids thereof of wild-type "Klotho". A Klotho active fragment has the ability to bind to an FGF polypeptide. Generally, a Klotho active polypeptide contains at least a Klotho subdomain (e.g., KL-D1 and KL-D2). Wild-type Klotho has the amino acid sequence as is found in nature. Example Klotho polypeptides suitable for use with the present disclosure include alpha-Klotho (SEQ ID NO: 2) and beta-Klotho (SEQ ID NO: 4). Nucleotide and amino acid sequences of the alpha-Klotho and beta-Klotho are found in the GenBank database at Accession No. NM_004795; NP_004786 and NM_175737; NP__783864, respectively. Klotho polypeptides include those described in U.S. Patent No. 6,579,850, the content of which is herein incorporated by reference in its entirety. The Klotho polypeptides include those from other species besides humans, including alpha-Klotho from mouse (NP_038851), rat (NP_112626), rabbit (NP_001075692) and beta-Klotho from mouse (NP_112457). Species predicted to have alpha-Klotho include chimpanzee (XP_522655), macaque (XP_001101127), horse (XP_001495662), cow (XP_001252500), platypus (XP_001510981), and chicken (XP_417105). Species predicted to have beta-Klotho include chimpanzee (XP_526550), macaque (XP_001091413), horse (XP_001495248), dog (XP_536257), rat (XP_001078178), platypus (XP_001512722), and chicken (XP_423224). The Klotho polypeptides have an

amino acid sequence that is substantially identical to the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4; i.e., at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identical at the amino acid sequences of SEQ ID NO: 2 or SEQ ID NO: 4, or active fragment thereof.

"Fusion polypeptide" or "fusion protein", as used herein, shall mean a polypeptide comprising two or more different polypeptides or active fragments thereof that are not naturally present in the same polypeptide. In some embodiments, the two or more different polypeptides are operatively linked together covalently, e.g., chemically linked or fused in frame by a peptide bond. As used herein a "Klotho fusion polypeptide" is a fusion polypeptide which includes an amino acid sequence from a Klotho polypeptide or active fragment thereof. A fusion polypeptide can comprise, as non-limiting examples, Klotho (e.g., sKlotho), FGF (e.g., FG23), and (optionally) a modified Fc fragment (e.g., a modified Fc fragment with decreased binding affinity to FC-gamma-receptor and/or increased serum half-life). Examples of this type of fusion polypeptide are presented in SEQ ID NOs. 46 to 49. In another embodiment, the fusion proteins comprise FGF (e.g., FGF23) and a modified Fc (e.g., FcLALA). Fusion proteins comprising FGF23 and FcLALA are described in SEQ ID NOs. 50, 51, 52 and 53. FcLALA is a Fc fragment with a LALA mutation (L234A, L235A), which triggers ADCC with lowered efficiency, and binds and activates human complement weakly. Hessell et al. 2007 Nature 449:101-104.

"Fibroblast growth factor" and "FGF" are used interchangeably herein and shall refer to polypeptides that regulate cell proliferation, migration, differentiation, homeostasis, tissue repair and response to injury in an animal, including a human subject. FGFs have the ability to bind to a fibroblast growth factor receptor and regulate its activity, including autophosphorylation of FGFR, phosphorylation of FRS2 (FGF receptor substrate 2) and ERK1/2 (extracellular signal-regulated protein kinase 1/2), and activating Egr-1 (early growth response-1). The term "FGF" includes active fragments, derivatives, mimetics, variants and chemically modified compounds or hybrids thereof of wild-type "FGF", e.g., as known in the art and as described in U.S. Patent No. 7,223,563 and U.S. Patent No. 7,259,248, the contents of which are incorporated by reference in their entirety. Wild-type FGF has an amino acid sequence as is found in nature. Example fibroblast growth factors suitable for use with the present disclosure include fibroblast growth factor-19 (FGF19; SEQ ID NO: 31), fibroblast growth factor-21 (FGF21; SEQ ID NO: 33), and fibroblast growth factor-23 (FGF23; SEQ ID NO: 35). The FGF

polypeptides include those from other species besides humans, including murine FGFs. Generally, FGF polypeptides have an amino acid sequence that is substantially identical to the amino acid sequence of SEQ ID NO: 31, SEQ ID NO: 33 or SEQ ID NO: 35; i.e., having an amino acid sequence is which is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more or 100% identical to the amino acid sequences of SEQ ID NO: 31 SEQ ID NO: 33 or SEQ ID NO: 35, or active fragments thereof. Additional non-limiting examples of FGF, particularly FGF23, are provided at aa 1002-1228 of SEQ ID NO: 47; aa 1002-1228 of SEQ ID NO: 49; aa 1-251 of SEQ ID NO: 51, and aa 1-251 of SEQ ID NO: 53; and sequences which are at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more or 100% identical to these sequences. Nucleotides encoding these sequences are provided in SEQ ID NOs: 46, 48, 50 and 52.

The term "FGF", includes active fragments of the full-length polypeptide. Active FGF fragments that are able to bind to their corresponding FGF receptors are known in the art and also contemplated for use in the present disclosure. One skilled in the art would appreciate, based on the sequences disclosed herein, that overlapping fragments of the FGFs can be generated using standard recombinant technology, for example, that described in Sambrook et al. (1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, New York) and Ausubel et al. (1997, Current Protocols in Molecular Biology, Green & Wiley, New York). One skilled in the art would appreciate, based on the disclosure presented herein, that the biological activity of FGF fragments could be tested by methods well known in the art and described herein, including binding to the FGF receptor. Similarly, cell culture models which possess the necessary FGF signal transduction machinery (i.e. FGF receptor) may be transfected with FGF fragments and subsequently tested for alterations in FGF signaling, relative to wild type FGF.

FGFs are grouped into seven subfamilies based on the homology of the FGF core homology domain (approximately 120 amino acids long), which is flanked by N- and C-terminal sequences that are highly variable in both length and primary sequence, particularly among different FGF subfamilies (Goetz et al., Molecular and Cellular Biology, 2007, Vol. 27, 3417-3428). An FGF active polypeptide generally contains at least an FGF core homology domain. In some embodiments, an FGF active polypeptide may contain, in addition to an FGF core homology domain, flanking sequences which may confer additional specificity in binding FGF receptors. FGF19, FGF21, and FGF23 are grouped in the FGF19 subfamily because the core region of these ligands share high

sequence identity relative to other FGFs (FGF19 v. FGF21: 38% identity; FGF19 v. FGF23: 36% identity). FGF19 subfamily members act analogously to signaling molecules of the endocrine system and regulate diverse physiological processes uncommon to classical FGFs (e.g., FGF19: energy and bile acid homeostasis; FGF21: glucose and lipid metabolism; and FGF 23: phosphate and vitamin D homeostasis).

"Fibroblast growth factor receptor" and "FGFR" as used herein refer to any one of FGFRs 1-4 known in the art, or splice variants thereof (e.g., FGFR1c). Example fibroblast growth factor receptors suitable for use with the present disclosure include fibroblast growth factor receptor-19 (e.g., FGFR4-beta Klotho), fibroblast growth factor receptor-21 (e.g., FGFR1c-alpha Klotho), and fibroblast growth factor receptor-23 (e.g., FGFR1c-alpha Klotho, FGFR3-alpha Klotho, FGFR4-alpha Klotho).

"Extracellular domain", as used herein, refers to the fragment of a transmembrane protein existing outside of a cell (e.g., not including the intracellular or transmembrane region). The "extracellular domain of the Klotho protein", "soluble Klotho", or "sKlotho" (e.g., SEQ ID NO: 7; SEQ ID NO: 39), refers to an extracellular domain of the Klotho polypeptide that is capable of binding a fibroblast growth factor, and/or capable of enabling the binding of a fibroblast growth factor to a fibroblast growth factor receptor by binding to the fibroblast growth factor. The Klotho extracellular domain corresponds to amino acid residues 28-982 of the full length alpha Klotho sequence (SEQ ID NO: 2) and to amino acid residues 52-997 of the full length beta Klotho sequence (SEQ ID NO: 4).

"Extracellular subdomain of Klotho protein" and "extracellular subdomain of Klotho protein" are used interchangeably herein and shall refer to a region in the extracellular domain of the Klotho polypeptide that is capable of binding a fibroblast growth factor, and/or is capable of enabling the binding of a fibroblast growth factor to a fibroblast growth factor receptor by binding to the fibroblast growth factor. In various embodiments, the fusion comprises a polypeptide comprising at least one extracellular subdomain of a Klotho protein; a polypeptide comprising a fibroblast growth factor; and, optionally, a modified Fc fragment having decreased affinity for Fc-gamma-receptor and/or increased serum half-life. The Klotho extracellular domain has two homologous subdomains that are repeated, i.e., KL-D1 (SEQ ID NO: 5) and KL-D2 (SEQ ID NO: 6). KL-D1 and KL-D2 correspond respectively to amino acid residues 58-506 and 517-953 of the full length alpha Klotho polypeptide (SEQ ID NO: 2) and respectively to amino acid residues 77-508 and 571-967 of the full length beta Klotho polypeptide (SEQ ID NO: 4) and are suitable for use with the present disclosure. Generally, a polypeptide that

contains at least one Klotho subdomain is a Klotho active polypeptide. The Klotho extracellular subdomain for use with the polypeptide of the disclosure may be an alpha Klotho or beta Klotho KL-D1 domain with an amino acid sequence that is substantially identical to the amino acid sequence of SEQ ID NO: 5 or SEQ ID NO: 37, respectively. Further, the Klotho KL-D1 domain may have an amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence of SEQ ID NO: 5 or SEQ ID NO: 37. The Klotho extracellular subdomain may also be an alpha or beta Klotho polypeptide KL-D2 domain that is substantially identical to the amino acid sequence of SEQ ID NO: 6 or SEQ ID NO: 38, respectively. In a further embodiment, the KL-D2 domain has an amino acid sequence that is at least at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence of SEQ ID NO: 6 or SEQ ID NO: 38. In some embodiments, the fusion comprises at least two extracellular subdomains of the Klotho protein (e.g., KL-D1 and KL-D2; KL-D1 and KL-D1 in tandem repeats; KL-D2 and KL-D2 in tandem repeats, etc.).

"Modified Fc fragment", as used herein, shall mean an Fc fragment of an antibody comprising a modified sequence. The Fc fragment is a portion of an antibody comprising the CH2, CH3 and part of the hinge region. The modified Fc fragment can be derived from, for example, IgG1, IgG2, IgG3, or IgG4. FcLALA is a modified Fc fragment with a LALA mutation (L234A, L235A), which triggers ADCC with lowered efficiency, and binds and activates human complement weakly. Hessell et al. 2007 Nature 449:101-104. Additional modifications to the Fc fragment are described in, for example, U.S. Patent No. 7,217,798. For example, in various modified Fc fragments: (a) amino acid residue 250 is glutamic acid and amino acid residue 428 is phenylalanine; or (b) amino acid residue 250 is glutamine and amino acid residue 428 is phenylalanine; or (c) amino acid residue 250 is glutamine and amino acid residue 428 is leucine. In some embodiments, amino acid residues 250 and 428 differ from the residues present in an unmodified Fc-fusion protein by amino acid residue 250 being glutamic acid or glutamine and amino acid residue 428 being leucine or phenylalanine, and wherein amino acid residues are numbered by the EU numbering system, as described in U.S. Patent No. 7,217,798. In some embodiments, the modified Fc-fusion protein has a higher affinity for FcRn at pH 6.0 than at pH 8.0. Preferably, the modified Fc fragment has decreased affinity to FcRn and/or increased serum half-life. Non-limiting examples of modified Fc fragments include that at aa (amino acids) 1234-1459 of SEQ ID NO: 47; aa 1234 to 1450 of SEQ

ID NO: 49; aa 257 to 482 of SEQ ID NO: 51; and aa 257 to 473 of SEQ ID NO: 53; and sequences which are at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more or 100% identical to these sequences. Nucleotides encoding these sequences are provided in SEQ ID NOs: 46, 48, 50 and 52.

"Signal peptide", as used herein, shall mean a peptide chain (3-60 amino acids long) that directs the post-translational transport of a protein to the endoplasmic reticulum and may be cleaved off. Example signal peptides suitable for use with the present disclosure include the Klotho signal peptide (SEQ ID NO: 19) and the IgG signal peptide (SEQ ID NO: 20). Note that upon secretion and cleavage by the producer cell line, the signal peptide (e.g., of the peptides corresponding to SEQ ID NO: 19 and SEQ ID NO: 20) is cleaved off. Thus, after secretion and cleavage of the signal peptide by the producer cell lines, the peptide of SEQ ID NO: 19 would generate the peptide of SEQ ID NO: 41.

"Linker", as used herein, shall mean a functional group (e.g., chemical or polypeptide) that covalently attaches two or more polypeptides or nucleic acids so that they are connected with one another. As used herein, a "peptide linker" refers to one or more amino acids used to couple two proteins together (e.g., to couple the extracellular domain of Klotho and fibroblast growth factor-23). Peptide linkers suitable for use with the present disclosure include, but are not limited to, polypeptides with amino acid sequences represented by SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17 and SEQ ID NO: 18. A polypeptide linker can comprise at least 1 and up to about 30 repeats of any of these amino acid sequences.

"Operatively linked", as used herein, shall mean the linking of two or more biomolecules so that the biological functions, activities, and/or structure associated with the biomolecules are at least retained. In reference to polypeptides, the term means that the linking of two or more polypeptides results in a fusion polypeptide that retains at least some of the respective individual activities of each polypeptide component. The two or more polypeptides may be linked directly or via a linker. In reference to nucleic acids, the term means that a first polynucleotide is positioned adjacent to a second polynucleotide that directs transcription of the first polynucleotide when appropriate molecules (e.g., transcriptional activator proteins) are bound to the second polynucleotide.

"Specifically binds", as used herein, shall refer to the ability of a first molecule to bind to a target molecule out of many, different types of molecules to which it may be

exposed because of the ability of the first molecule to adopt a particular structure conducive to forming non-covalent interactions between itself and the other target molecule. The first molecule binds to the target forming a stable complex while there is substantially less recognition, contact, or complex formation of the first molecule with any other non-specific molecules.

"Polypeptide variant" or "protein variant", as used herein, refers to polypeptides in which one or more amino acids have been substituted by different amino acids from a reference sequence. It is well understood in the art that some amino acids may be substituted by others with broadly similar properties without changing the nature of the activity of the polypeptide (conservative substitutions) as described hereinafter. These terms also encompass polypeptides in which one or more amino acids have been added or deleted, or replaced with different amino acids, e.g., protein isoforms. An example variant of fibroblast growth factor-23 suitable for use with the present disclosure is the fibroblast growth factor-23 variant (R179Q).

"Pharmaceutical composition", as used herein, shall mean a composition containing a compound (e.g., a fusion polypeptide of the disclosure) that may be administered to treat or prevent a disease or disorder in an individual.

"Individual" or "subject", as used herein, shall refer to a mammal, including, but not limited to, a human or non-human mammal, such as a bovine, equine, canine, ovine, or feline.

"Treat", as used herein, shall mean decrease, suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disease. In the context of the disclosure, the administration of the polypeptides of the disclosure may be used to treat age-related conditions, including sarcopenia, skin atrophy, muscle wasting, brain atrophy, atherosclerosis, arteriosclerosis, pulmonary emphysema, osteoporosis, osteoarthritis, immunologic incompetence, high blood pressure, dementia, Huntington's disease, Alzheimer's disease, cataracts, age-related macular degeneration, prostate cancer, stroke, diminished life expectancy, memory loss, wrinkles, impaired kidney function, and age-related hearing loss; and metabolic disorders, including Type II Diabetes, Metabolic Syndrome, hyperglycemia, and obesity.

"Prevent", as used herein, shall refer to a decrease in the occurrence of a disorder or decrease in the risk of acquiring a disorder or its associated symptoms in a subject. In the context of the disclosure, the administration of the polypeptides of the disclosure may be used to prevent age-related conditions, including sarcopenia, skin atrophy, muscle

wasting, brain atrophy, atherosclerosis, arteriosclerosis, pulmonary emphysema, osteoporosis, osteoarthritis, immunologic incompetence, high blood pressure, dementia, Huntington's disease, Alzheimer's disease, cataracts, age-related macular degeneration, prostate cancer, stroke, diminished life expectancy, memory loss, wrinkles, impaired kidney function, and age-related hearing loss; and metabolic disorders, including Type II Diabetes, Metabolic Syndrome, hyperglycemia, and obesity. The prevention may be complete, e.g., the total absence of an age-related condition or metabolic disorder. The prevention may also be partial, such that the likelihood of the occurrence of the age-related condition or metabolic disorder in a subject is less likely to occur than had the subject not received the present disclosure.

"Disease", as used herein, shall mean any condition or disorder that damages or interferes with the normal function of a cell, tissue, or organ.

"Age-related condition", as used herein, shall mean any disease or disorder whose incidence in a population or severity in an individual correlates with the progression of age. In one embodiment, the age-related condition is a disease or disorder whose incidence is at least 1.5 fold higher among human individuals greater than 60 years of age relative to human individuals between the ages of 30-40 and in a selected population of greater than 100,000 individuals. Age-related conditions relevant to the present disclosure include, but are not limited to, sarcopenia, skin atrophy, muscle wasting, brain atrophy, atherosclerosis, arteriosclerosis, pulmonary emphysema, osteoporosis, osteoarthritis, immunologic incompetence, high blood pressure, dementia, Huntington's disease, Alzheimer's disease, cataracts, age-related macular degeneration, prostate cancer, stroke, diminished life expectancy, memory loss, wrinkles, impaired kidney function, and age-related hearing loss.

"Metabolic disorder", as used herein, shall mean any disease or disorder that damages or interferes with normal function in a cell, tissue, or organ by affecting the production of energy in cells or the accumulation of toxins in a cell, tissue, organ, or individual. Metabolic disorders relevant to the present disclosure include, but are not limited to, Type II Diabetes, Metabolic Syndrome, hyperglycemia, and obesity.

An "effective dose" or "effective amount" is an amount sufficient to effect a beneficial or desired clinical result. In the context of the disclosure, it is an amount of a Klotho fusion polypeptide or sKlotho effective to produce the intended pharmacological, therapeutic or preventive result. A therapeutically effective dose results in the prevention or amelioration of the disorder or one or more symptoms of the disorder, (e.g., an age-

related condition or metabolic disorder). Therapeutically effective doses will vary depending upon the subject and disease condition being treated, the weight and age of the subject, the severity of the disease condition, the manner of administration and the like which can be readily be determined by one of ordinary skill in the art.

"Klotho nucleic acid molecule", as used herein is a gene encoding a Klotho protein. An example human Klotho gene is provided at GenBank Accession No. NM_004795 (SEQ ID NO: 1). Additional non-limiting examples of Klotho are provided at aa 1-982 of SEQ ID NO: 47 and aa 1-982 of SEQ ID NO: 49; and sequences which are at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more or 100% identical to these sequences.

"Fragment", as used herein, refers to a portion of a polypeptide or nucleic acid molecule. This portion contains, preferably, at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more of the entire length of the reference nucleic acid molecule or polypeptide. A fragment may contain 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000 or up to 3000 nucleotides or amino acids.

The term "substantially identical" refers to a polypeptide or nucleic acid molecule exhibiting at least 50% identity to a reference amino acid sequence (for example, any one of the amino acid sequences described herein) or nucleic acid sequence (for example, any one of the nucleic acid sequences described herein). Preferably, such a sequence is at least 60%, 70%, 75%, 80% or 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical at the amino acid level or nucleic acid to the sequence used for comparison.

The present disclosure is directed to methods, kits and compositions for preventing or treating age-related conditions and metabolic disorders; and to the use of said compostions in therapy, as a medicament or for use in the treatment of a pathological disorder. In some embodiments, the disclosure provides a fusion polypeptide having at least one extracellular subdomain of a Klotho protein. In some embodiments, the fusion polypeptides further comprise a fibroblast growth factor or an active fragment thereof. In some embodiments, the fusion further comprises a modified Fc fragment having decreased affinity for Fc-gamma-receptorand/or increased serum half-life. In other embodiments, the fusion comprises an FGF (e.g., FGF19, FGF21, FGF23 or FGF23 variant R179Q) fused to a modified Fc (e.g., FcLALA). FcLALA is a Fc fragment with a LALA mutation (L234A, L235A), which triggers ADCC with lowered efficiency, and binds and activates human complement weakly. The Klotho extracellular domain may be

derived from either the alpha or beta Klotho isoforms. Further, although the FGF component of the Klotho fusion polypeptide is described primarily with reference to fibroblast growth factor-19, fibroblast growth factor-21 and fibroblast growth factor-23, it is contemplated that any of the twenty-three known FGFs or an active fragment thereof can be used in practicing the disclosure.

The extracellular domain of the Klotho protein can include one or both of the KL-D1 and KL-D2 domains of a Klotho protein. In some embodiments, the Klotho fusion polypeptide has at least two extracellular subdomains of a Klotho protein. For example, the at least two extracellular subdomains can be at least two KL-D1 domains in tandem repeats, at least two KL-D2 domains in tandem repeats, or at least one KL-D1 domain and at least one KL-D2 domain.

The extracellular subdomain of a Klotho protein and the fibroblast growth factor (or an active fragment thereof) can be operatively linked to one another in a variety of orientations and manners. For example, the extracellular subdomain of the Klotho protein can be operatively linked to the N-terminus of the fibroblast growth factor or alternatively the fibroblast growth factor can be operatively linked to the N-terminus of the at least one extracellular subdomain of the Klotho protein.

The fusion polypeptide of the disclosure may include one or both of the Klotho extracellular domains, i.e., KL-D1 (SEQ ID NO: 5) and KL-D2 (SEQ ID NO: 6). KL-D1 and KL-D2 correspond respectively to amino acid residues 58-506 and 517-953 of the full length alpha Klotho polypeptide (SEQ ID NO: 2) and to amino acid residues 77-508 and 571-967 of the full length beta Klotho polypeptide (SEQ ID NO: 4) and are suitable for use with the present disclosure. The Klotho fusion polypeptide may have a KL-D1 domain of an alpha Klotho polypeptide having an amino acid sequence that is substantially identical to the amino acid sequence of SEQ ID NO: 5 or of a beta Klotho polypeptide having an amino acid sequence that is substantially identical to the amino acid sequence of SEQ ID NO: 37. Specifically, the Klotho fusion polypeptide may have an amino acid sequence that is at least at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identical to SEQ ID NO: 5 or SEQ ID NO: 37. The Klotho fusion polypeptide may have a KL-D2 domain of an alpha Klotho polypeptide with an amino acid sequence that is substantially identical to the amino acid sequence of SEQ ID NO: 6 or of a beta Klotho polypeptide having an amino acid sequence that is substantially identical to the amino acid sequence of SEQ ID NO: 38. Specifically,, the Klotho fusion

polypeptide may have an amino acid sequence that is at least at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identical to SEQ ID NO: 6 or SEQ ID NO: 38, respectively.

In some embodiments, the Klotho fusion polypeptide of the disclosure is soluble and is capable of binding to an FGF receptor.

The Klotho fusion polypeptides of the disclosure can contain a polypeptide linker which connects the polypeptide having at least one extracellular subdomain of a Klotho protein and the fibroblast growth factor and the (optional) modified Fc fragment. Suitable linkers are well known in the art and generally contain several Gly and several Ser residues, e.g., $(Gly_4\ Ser)_3$ (SEQ ID NO: 11), Gly_4 Ser polypeptide (SEQ ID NO: 12), Gly (SEQ ID NO: 13), Gly Gly (SEQ ID NO: 14), Gly Ser (SEQ ID NO: 15), Gly_2 Ser (SEQ ID NO: 16), Ala (SEQ ID NO: 17), and Ala Ala (SEQ ID NO: 18). In some embodiments, the linker will have at least 2 and up to about 30 repeats of an amino acid sequence represented by any one of SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, or SEQ ID NO: 18.

When a polypeptide linker is present in the Klotho fusion polypeptide of the disclosure, the polypeptide having at least one extracellular subdomain of a Klotho protein may be connected by a peptide bond to the N-terminus of the linker polypeptide with the FGF connected by a peptide bond to the C-terminus of the polypeptide linker. Alternatively, the FGF may be connected by a peptide bond to the N-terminus of the linker polypeptide with the polypeptide having at least one extracellular subdomain of Klotho connected by a peptide bond to the C-terminus of the polypeptide linker. A chemical linker can also be used to link the two polypeptides.

The Klotho fusion polypeptide of the disclosure may include a signal peptide. Example signal peptides for use with the Klotho fusion polypeptide include, but are not limited to the Klotho signal peptide (SEQ ID NO: 8) and the IgG signal peptide (SEQ ID NO: 9).

In some embodiments, the disclosure provides a fusion between a FGF (e.g., FGF19, FGF21, FGF23, or FGF23 variant R179Q) and a modified Fc (e.g., FcLALA). The fusion can also optionally comprise linkers between the FGF and Fc portions. The fusion can also optionally comprise a signal peptide. In various embodiments, the disclosure encompasses nucleic acids encoding these fusion polypeptides, vectors comprising these nucleic acids, and host cells containing these nucleic acids.

4.1. Klotho and Fibroblast growth factor polypeptides

The Klotho fusion polypeptides of the disclosure are expected to exhibit biological activities comparable to FGF in nature, such as binding to an FGF receptor and inducing the phosphorylation of an FGF receptor, FRS2 (FGF receptor substrate 2) and ERK1/2 (extracellular signal-regulated protein kinase 1/2) and activating Egr-1 (early growth response-1) gene. FGF is a secreted peptide growth factor that binds the FGF receptor. The amino acid and nucleic acid sequences of FGF are readily available to those of skill in the art. For example, example nucleotide sequences for FGF19, FGF21, and FGF23 can be found in the GenBank database at Accession numbers: NM_005117, NM_019113, and NM_020638, respectively, and herein as SEQ ID NOs: 30, 32, and 34, respectively. Example amino sequences for FGF19, FGF21, and FGF23 can be found in the GenBank database at Accession numbers: NP_005108, NP_061986, and NP_065689, respectively, and herein as SEQ ID NOs: 31, 35, and 35, respectively. Additionally, FGF may include one or more alterations which aid in the expression of the protein, e.g., the FGF23 (R179Q) variant (SEQ ID NO: 36).

The Klotho protein is a 130 kDa single pass type I transmembrane protein with an extracellular domain and a short cytoplasmic domain. The amino acid and nucleic acid sequences of Klotho are readily available to those of skill in the art. For example, example nucleotide sequences for alpha-Klotho and beta-Klotho can be found in the GenBank database at Accession numbers: NM_004795 and NM_175737, respectively, and herein as SEQ ID NOs: 7 and 8, respectively. Example amino acid sequences for alpha-Klotho and beta-Klotho can be found in the GenBank database at Accession numbers: NP_004786 and NP_783864, respectively, and herein as SEQ ID NOs: 2 and 4, respectively.

The Klotho fusion polypeptide of the disclosure can bind to a fibroblast growth factor receptor and has an alpha-Klotho or beta-Klotho extracellular domain operatively linked to either fibroblast growth factor-19 (SEQ ID NO: 31), fibroblast growth factor-21 (SEQ ID NO: 33), fibroblast growth factor-23 (SEQ ID NO: 35), or variants thereof (which include fibroblast growth factor-23 variant (R179Q) (SEQ ID NO: 36)).

Specifically, the Klotho fusion polypeptide of the disclosure may include an alpha-Klotho (SEQ ID NO: 2) which is operatively coupled to fibroblast growth factor-23 (SEQ ID NO: 35) or fibroblast growth factor-23 variant (R179Q) (SEQ ID NO: 36). Additionally, the Klotho fusion polypeptide of the disclosure may have beta-Klotho (SEQ ID NO: 4), which is operatively coupled to fibroblast growth factor-19 (SEQ ID NO: 31).

The Klotho fusion polypeptide of the disclosure may include a beta-Klotho (SEQ ID NO: 4), which is operatively coupled to fibroblast growth factor-21 (SEQ ID NO: 33).

The disclosure includes homologs of the various Klotho and FGF genes and proteins encoded by those genes. A "homolog," in reference to a gene refers to a nucleotide sequence that is substantially identical over at least part of the gene or to its complementary strand or a part thereof, provided that the nucleotide sequence encodes a protein that has substantially the same activity/function as the protein encoded by the gene which it is a homolog of. Homologs of the genes described herein can be identified by percent identity between amino acid or nucleotide sequences for putative homologs and the sequences for the genes or proteins encoded by them (e.g., nucleotide sequences for genes encoding Klotho and FGF or their complementary strands). Percent identity may be determined, for example, by visual inspection or by using various computer programs known in the art or as described herein. Sequence identity is typically measured using sequence analysis software (for example, Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, Wis. 53705, BLAST, BESTFIT, GAP, or PILEUP/PRETTYBOX programs). Such software matches identical or similar sequences by assigning degrees of homology to various substitutions, deletions, and/or other modifications. Conservative amino acid substitutions typically include substitutions within the following groups:

glycine and alanine;

valine, isoleucine and leucine;

aspartic acid, glutamic acid, asparagine and glutamine;

serine and threonine;

lysine and arginine; and

phenylalanine and tyrosine.

Thus, mutating a glycine to alanine would be a conservative amino acid substititon, as would mutating an alanine to a glycine; mutating a valine to an isoleucine or leucine would be a conservative amino acid substation, as would replacing an isoleucine with valine or leucine, as would replacing leucine with valine or isoleucine, etc. The disclosure provides variants of all the amino acid sequences disclosed herein with at least one conservative amino acid substitution.

In an example approach to determining the degree of identity, a BLAST program may be used, with a probability score between e^{-3} and e^{-100} indicating a closely related sequence.

In one embodiment, the present disclosure provides a fusion polypeptide of SEQ ID NO: 19.

In another embodiment, the present disclosure provides a fusion polypeptide of SEQ ID NO: 20.

In one embodiment, the present disclosure provides a fusion polypeptide of SEQ ID NO: 40.

In another embodiment, the present disclosure provides a fusion polypeptide of SEQ ID NO: 41, or a variant thereof comprising at least one conservative amino acid substition.

In one embodiment, the present disclosure provides a fusion polypeptide of SEQ ID NO: 46.

In another embodiment, the present disclosure provides a fusion polypeptide of SEQ ID NO: 47, or a variant thereof comprising at least one conservative amino acid substition.

In another embodiment, the present disclosure provides a fusion polypeptide of SEQ ID NO: 48.

In another embodiment, the present disclosure provides a fusion polypeptide of SEQ ID NO: 49, or a variant thereof comprising at least one conservative amino acid substition.

In one embodiment, the present disclosure provides a fusion polypeptide of SEQ ID NO: 50.

In another embodiment, the present disclosure provides a fusion polypeptide of SEQ ID NO: 51, or a variant thereof comprising at least one conservative amino acid substition.

In one embodiment, the present disclosure provides a fusion polypeptide of SEQ ID NO: 52.

In another embodiment, the present disclosure provides a fusion polypeptide of SEQ ID NO: 53, or a variant thereof comprising at least one conservative amino acid substition.

In another embodiment, the present disclosure provides a fusion polypeptide of SEQ ID NO: 54, or a variant thereof comprising at least one conservative amino acid substition.

In another embodiment, the present disclosure provides a fusion polypeptide of SEQ ID NO: 55, or a variant thereof comprising at least one conservative amino acid substition.

In another embodiment, the present disclosure provides a fusion polypeptide of SEQ ID NO: 56, or a variant thereof comprising at least one conservative amino acid substition.

In another embodiment, the present disclosure provides a fusion polypeptide of SEQ ID NO: 57, or a variant thereof comprising at least one conservative amino acid substition.

In another embodiment, the present disclosure provides a fusion polypeptide of SEQ ID NO: 58, or a variant thereof comprising at least one conservative amino acid substition.

In another embodiment, the present disclosure provides a fusion polypeptide of SEQ ID NO: 59, or a variant thereof comprising at least one conservative amino acid substition.

In another embodiment, the present disclosure provides a fusion polypeptide of SEQ ID NO: 60, or a variant thereof comprising at least one conservative amino acid substition.

In another embodiment, the present disclosure provides a fusion polypeptide of SEQ ID NO: 61, or a variant thereof comprising at least one conservative amino acid substition.

In another embodiment, the present disclosure provides a fusion polypeptide of SEQ ID NO: 62, or a variant thereof comprising at least one conservative amino acid substition.

In another embodiment, the present disclosure provides a fusion polypeptide of SEQ ID NO: 63, or a variant thereof comprising at least one conservative amino acid substition.

In another embodiment, the present disclosure provides a fusion polypeptide of SEQ ID NO: 64, or a variant thereof comprising at least one conservative amino acid substition.

In another embodiment, the present disclosure provides a fusion polypeptide of SEQ ID NO: 65, or a variant thereof comprising at least one conservative amino acid substition.

In another embodiment, the present disclosure provides a fusion polypeptide of SEQ ID NO: 66, or a variant thereof comprising at least one conservative amino acid substition.

In another embodiment, the present disclosure provides a fusion polypeptide of SEQ ID NO: 67, or a variant thereof comprising at least one conservative amino acid substition.

In another embodiment, the present disclosure provides a fusion polypeptide of SEQ ID NO: 68, or a variant thereof comprising at least one conservative amino acid substition.

As used herein, the terms "homology" and "homologous" are not limited to designate proteins having a theoretical common genetic ancestor, but includes proteins which may be genetically unrelated that have, nonetheless, evolved to perform similar functions and/or have similar structures. Functional homology to the various proteins described herein also encompasses proteins that have an activity of the corresponding protein of which it is a homolog. For proteins to have functional homology, it is not required that they have significant identity in their amino acid sequences, but, rather, proteins having functional homology are so defined by having similar or identical activities. For example, with respect to a Klotho molecule, the polypeptide should have the functional characteristics of binding to an FGF polypeptide and enable the binding of the FGF to an FGFR. With respect to an FGF molecule, the polypeptide should have the functional characteristics of binding to an FGFR and causing the activation of FGFR (e.g., phosphorylation). Assays for assessing FGF binding to the FGF receptor and/or activation of the FGF signaling pathway are known in the art and described herein (See Example 2). Assays for assessing Klotho activity are also known in the art and described

herein (e.g., binding to a FGF polypeptide). Proteins with structural homology are defined as having analogous tertiary (or quaternary) structure and do not necessarily require amino acid identity or nucleic acid identity for the genes encoding them. In certain circumstances, structural homologs may include proteins which maintain structural homology only at the active site or binding site of the protein.

In addition to structural and functional homology, the present disclosure further encompasses proteins having amino acid identity to the various Klotho and FGF amino acid sequences described herein. To determine the percent identity/homology of two amino acid sequences, the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in the amino acid sequence of one protein for optimal alignment with the amino acid sequence of another protein). The amino acid residues at corresponding amino acid positions are then compared. When a position in one sequence is occupied by the same amino acid residue as the corresponding position in the other, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % identity= # of identical positions/total # of positions multiplied by 100).

The amino acid sequences of molecules of the disclosure described herein have an amino acid sequence which is at least about 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or more identical or homologous to an amino acid sequence described herein.

The nucleic acid sequences of molecules of the disclosure described herein have a nucleotide sequence which hybridizes to or is at least about 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or more identical or homologous to a nucleotide sequence described herein.

Nucleic acid molecules appropriate for use in the fusion polypeptides of the disclosure may have a Klotho or FGF nucleotide sequence which hybridizes under stringent conditions to the complement of a nucleic acid molecule encoding Klotho or FGF, respectively. As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences at least about 70%, 80%, 85%, 90% or more homologous to each other typically remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found in Ausubel et al. *Current Protocols in Molecular Biology*, Wiley Interscience, New York (2001), 6.3.1-6.3.6. A specific, non-limiting example of stringent hybridization conditions are hybridization in 6X sodium

chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2 X SSC, 0.1% SDS at 50-65°C.

4.2. Klotho-FGF fusion polypeptides of the disclosure

In some embodiments of the disclosure, a Klotho fusion polypeptide has a polypeptide chain having a first polypeptide sequence of a Klotho polypeptide or an active fragment thereof and a second polypeptide sequence encoding FGF or an active fragment thereof. In some embodiments, the fusion further comprises a modified Fc fragment having decreased affinity for Fc-gamma-receptor and/or increased serum half-life.

The disclosure includes fusion polypeptides which are at least about 95% or more homologous to an amino acid sequence presented in SEQ ID NO: 19-28. The amino acid sequence of SEQ ID NO: 19 encodes a Klotho fusion polypeptide having a Klotho extracellular domain N-terminally linked to the FGF23 (R179Q) variant (SEQ ID NO: 36). The amino acid sequence of SEQ ID NO: 20 encodes a Klotho fusion polypeptide having an IgG signal peptide N-terminally linked to a Klotho extracellular domain lacking a signal peptide N-terminally linked to the FGF23 (R179Q) variant. The amino acid sequence of SEQ ID NO: 21 encodes a Klotho fusion polypeptide having a KL-D1 extracellular subdomain N-terminally linked to the FGF23 (R179Q) variant. The amino acid sequence of SEQ ID NO: 22 encodes a Klotho fusion polypeptide having a KL-D2 extracellular subdomain N-terminally linked to the FGF23 (R179Q) variant. The amino acid sequence of SEQ ID NO: 23 encodes a Klotho fusion polypeptide having two KL-D1 extracellular subdomains N-terminally linked to the FGF23 (R179Q) variant. The amino acid sequence of SEQ ID NO: 24 encodes a Klotho fusion polypeptide having two KL-D2 extracellular subdomains N-terminally linked to the FGF23 (R179Q) variant. The amino acid sequence of SEQ ID NO: 25 encodes a Klotho fusion polypeptide having the FGF23 (R179Q) variant N-terminally linked to a Klotho extracellular domain. The amino acid sequence of SEQ ID NO: 26 encodes a Klotho fusion polypeptide having the FGF23 (R179Q) variant N-terminally linked to a KL-D1 extracellular subdomain. The amino acid sequence of SEQ ID NO: 27 encodes a Klotho fusion polypeptide having the FGF23 (R179Q) variant N-terminally linked to a KL-D2 extracellular subdomain. The amino acid sequence of SEQ ID NO: 28 encodes a Klotho fusion polypeptide having the FGF23 (R179Q) variant N-terminally linked to two KL-D1 extracellular subdomains. The amino acid sequence of SEQ ID NO: 29 encodes a Klotho fusion polypeptide having the FGF23

(R179Q) variant N-terminally linked to two KL-D2 extracellular subdomains. In some embodiments, the fusion further comprises a modified Fc fragment having decreased affinity for Fc-gamma-receptor and/or increased serum half-life.

The Klotho fusion polypeptide of the disclosure may include an amino acid sequence which is at least about 95% identical to the amino acid sequence set forth in SEQ ID NO: 7. The amino acid sequence of SEQ ID NO: 7 encodes a Klotho extracellular domain lacking a signal peptide. In some embodiments, the fusion further comprises a modified Fc fragment having decreased affinity for Fc-gamma-receptor and/or increased serum half-life.

The subject fusion proteins are described herein and can be made using methods known in the art. For example, the fusion polypeptides of the disclosure may be constructed as described in U.S. No. Patent 6,194,177. The use of Klotho polypeptides is described in U.S. Patent No. 6,579,850. The use of FGF nucleic acid molecules is described in U.S. Patent No. 7,223,563.

In some embodiments, a nucleic acid molecule encoding the Klotho is cloned by PCR and ligated, in frame, with a nucleic acid molecule encoding FGF. In some embodiments, the fusion further comprises a modified Fc fragment having decreased affinity for Fc-gamma-receptor and/or increased serum half-life. The nucleic acid encoding the fusion polypeptide is operatively linked to a promoter to allow for expression. The nucleic acid molecule encoding the fusion polypeptide is subsequently transfected into a host cell for expression. The sequence of the final construct can be confirmed by sequencing.

When preparing the fusion proteins of the present disclosure, a nucleic acid molecule encoding an extracellular subdomain of Klotho will be fused in frame to the nucleic acid molecule encoding FGF and the (optional) nucleic acid encoding the modified Fc fragment. Expression of the resulting nucleic acid molecule results in the extracellular subdomain of Klotho being fused N-terminal in relation to the FGF polypeptide. Fusions are also possible in which the extracellular subdomain of Klotho is fused C-terminal in relation to the FGF polypeptide. Methods for making fusion proteins are well known in the art.

The fusion polypeptides of the disclosure have at least two polypeptides that are covalently linked, in which one polypeptide comes from one protein sequence or domain, e.g., Klotho, and the other polypeptide comes from another protein sequence or domain, e.g., FGF. In some embodiments, the fusion further comprises a modified Fc fragment

having decreased affinity for Fc-gamma-receptor and/or increased serum half-life. In another embodiment, the disclosure comprises a FGF fused to a modified Fc fragment. Klotho and/or FGF and/or the (optional) modified Fc fragment, of the fusion polypeptides of the disclosure, can be joined by methods well known to those of skill in the art. These methods include both chemical and recombinant means.

Nucleic acids encoding the domains to be incorporated into the fusion polypeptides of the disclosure can be obtained using routine techniques in the field of recombinant genetics. Basic texts disclosing the general methods of use in this disclosure include Sambrook and Russell, Molecular Cloning, A Laboratory Manual (3rd ed. 2001); Kriegler, Gene Transfer and Expression: A Laboratory Manual (1990); and Current Protocols in Molecular Biology (Ausubel et al., eds., 1994-1999). In nucleic acids encoding a Klotho fusion polypeptide of the disclosure, the nucleic acid sequence encoding alpha-Klotho or beta-Klotho, represented by SEQ ID NO: 1 and SEQ ID NO: 3, respectively, may be used. In nucleic acids encoding a Klotho fusion polypeptide, the nucleic acid sequence encoding FGF19, FGF21, or FGF23, represented by SEQ ID NO: 30, SEQ ID NO: 32 and SEQ ID NO: 34, respectively, may be used. Nucleic acid sequences of molecules of the disclosure described herein comprise a nucleotide sequence which hybridizes to or is at least about 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or more identical or homologous to SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 30, SEQ ID NO: 32, or SEQ ID NO: 34.

Nucleic acid sequences that encode the various components of the fusion [Klotho, and/or FGF peptide and/or the (optional) modified Fc fragment] can be obtained using any of a variety of methods. For example, the nucleic acid sequences encoding the polypeptides may be cloned from cDNA and genomic DNA libraries by hybridization with probes, or isolated using amplification techniques with oligonucleotide primers. More commonly, amplification techniques are used to amplify and isolate the Klotho and FGF sequences using a DNA or RNA template (see, e.g., Dieffenfach & Dveksler, PCR Primers: A Laboratory Manual (1995)). Alternatively, overlapping oligonucleotides can be produced synthetically and joined to produce one or more of the domains. Nucleic acids encoding Klotho or FGF can also be isolated from expression libraries using antibodies as probes.

According to the present disclosure, the various components of the fusion [Klotho, and/or, FGF and/or the (optional) modified Fc fragment] can be linked either directly or via a covalent linker, including amino acid linkers, such as a polyglycine linker, or

another type of chemical linker, including, carbohydrate linkers, lipid linkers, fatty acid linkers, polyether linkers, such as PEG, etc. (See for example, Hermanson, Bioconjugate techniques (1996)). The polypeptides forming the fusion/fusion polypeptide are typically linked C-terminus to N-terminus, although they can also be linked C-terminus to C-terminus, N-terminus to N-terminus, or N-terminus to C-terminus. One or more polypeptide domains may be inserted at an internal location within a fusion polypeptide of the disclosure. The polypeptides of the fusion protein can be in any order. The fusion polypeptides may be produced by covalently linking a chain of amino acids from one protein sequence, e.g., an extracellular subdomain of Klotho, to a chain of amino acids from another protein sequence, e.g., FGF, by preparing a recombinant polynucleotide contiguously encoding the fusion protein. The different chains of amino acids in a fusion protein may be directly spliced together or may be indirectly spliced together via a chemical linking group or an amino acid linking group. The amino acid linking group can be about 200 amino acids or more in length, or generally 1 to 100 amino acids. In some embodiments, proline residues are incorporated into the linker to prevent the formation of significant secondary structural elements by the linker. Linkers can often be flexible amino acid subsequences that are synthesized as part of a recombinant fusion protein. Such flexible linkers are known to persons of skill in the art.

According to the present disclosure, the amino acid sequences of the fusion [an extracellular subdomain of Klotho and/or the FGF and/or the (optional) modified Fc fragment] may be linked via a peptide linker. Example peptide linkers are well known in the art and described herein. For example, peptide linkers generally include several Gly and several Ser residues, such as: $(Gly_4\ Ser)_3$ (SEQ ID NO: 11), Gly_4 Ser polypeptide (SEQ ID NO: 12), Gly (SEQ ID NO: 13), Gly Gly (SEQ ID NO: 14), Gly Ser (SEQ ID NO: 15), Gly_2 Ser (SEQ ID NO: 16), Ala (SEQ ID NO: 17), and Ala Ala (SEQ ID NO: 18). Specifically, a peptide linker for use in a fusion protein of the disclosure may act as a flexible hinge.

The signal sequence of Klotho or FGF may be excluded prior to incorporation of Klotho into a fusion protein of the disclosure. The signal sequence for Klotho or FGF of the fusion protein may be included, e.g., the polypeptide represented by SEQ ID NO: 19. However, such sequences may also be omitted and replaced with the signal sequence of a different protein, e.g., the IgG signal sequence (SEQ ID NO: 9). Generally, the pharmaceutical compositions of the disclosure will contain the mature form of Klotho and FGF.

Generally, introns are excluded from either one or both the Klotho or the FGF moieties prior to incorporation into a fusion polypeptide.

The fusion polypeptides of the disclosure may include one or more polymers covalently attached to one or more reactive amino acid side chains. By way of example, not limitation, such polymers include polyethylene glycol (PEG), which can be attached to one or more free cysteine sulfhydryl residues, thereby blocking the formation of disulfide bonds and aggregation when the protein is exposed to oxidizing conditions. In addition, PEGylation of the fusion polypeptides of the disclosure is expected to provide such improved properties as increased half-life, solubility, and protease resistance. The fusion polypeptides of the disclosure may alternatively be modified by the covalent addition of polymers to free amino groups such as the lysine epsilon or the N-terminal amino group. Particular specific cysteines and lysines for covalent modification will be those not involved in receptor binding, heparin binding, or in proper protein folding. It will be apparent to one skilled in the art that the methods for assaying the biochemical and/or biological activity of the fusion polypeptides may be employed in order to determine if modification of a particular amino acid residue affects the activity of the protein as desired. Other similar suitable modifications are contemplated and known in the art.

The disclosure is also directed to the expression of a fusion polypeptide that is at least about 95% or more homologous to an amino acid sequence presented in SEQ ID NO: 19-28.

The present disclosure encompasses a fusion polypeptide comprising: (a) a polypeptide comprising at least one extracellular subdomain of a Klotho protein, or a functionally active variant or derivative thereof; (b) a polypeptide comprising a fibroblast growth factor, or a functionally active variant or derivative thereof; and (c) a modified Fc fragment having decreased affinity for Fc-gamma-receptor and/or increased serum half-life. By "a functionally active variant or derivative thereof" is meant a variant or derivative comprising a longer, shorter or altered amino acid sequence than the corresponding wild-type polypeptide, while retaining the biological activity. Thus "a functionally active variant or derivative" of an extracellular subdomain of a Klotho protein or a fibroblast growth factor comprises fewer, more, or an altered amino acid sequence than a wild-type extracellular subdomain of a Klotho protein or a fibroblast growth factor, but still retains at least one biological activity of the wild-type polypeptide sequence. A functionally active variant or derivative of a polypeptide disclosed herein

can also comprise the same amino acid sequence of a polypeptide disclosed herein, but vary in post-translational modification (e.g., pegylation, methylation and/or glycosylation), or have additional moieties or elements added to it. In various embodiments, the variant or derivative of FGF23 comprises R179Q or does not.

In one embodiment, a functionally active variant or derivative polypeptide includes an amino acid sequence at least about 60% identical to a sequence disclosed herein (e.g., at least one extracellular domain of a Klotho protein or a fibroblast growth factor). Preferably, the polypeptide is at least 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% or more identical to a sequence disclosed herein.

As used herein, percent identity of two amino acid sequences (or of two nucleic acid sequences) is determined using the algorithm of Karlin and Altschul (PNAS USA 87:2264-2268, 1990), modified as in Karlin and Altschul, PNAS USA 90:5873-5877, 1993). Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul et al. (J. Mol. Biol. 215:403-410, 1990). BLAST nucleotide searches are performed with the NBLAST program, score=100, wordlength=12. BLAST protein searches are performed with the XBLAST program, score=50, wordlength=3. To obtain gapped alignment for comparison purposes GappedBLAST is utilized as described in Altschul et al. (Nucleic Acids Res. 25:3389-3402, 1997). When utilizing BLAST and GappedBLAST programs the default parameters of the respective programs (e.g., XBLAST and NBLAST) are used to obtain nucleotide sequences homologous to a nucleic acid molecule of the invention.

Identity or identical means amino acid sequence (or nucleic acid sequence) similarity and has an art recognized meaning. Sequences with identity share identical or similar amino acids (or nucleic acids). Thus, a candidate sequence sharing 85% amino acid sequence identity with a reference sequence requires that, following alignment of the candidate sequence with the reference sequence, 85% of the amino acids in the candidate sequence are identical to the corresponding amino acids in the reference sequence, and/or constitute conservative amino acid changes.

Functionally active variants of a polypeptide disclosed herein retain substantially the same functional activity of the original polypeptide or fragment. Naturally occurring functionally active variants such as allelic variants and species variants and non-naturally

occurring functionally active variants are included in the invention and can be produced by, for example, mutagenesis techniques or by direct synthesis.

A functionally active variant or derivative differs by about or at least, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60 or more amino acid residues from a polypeptide disclosed herein. Where this comparison requires alignment the sequences are aligned for maximum homology. The site of variation can occur anywhere in the polypeptide, as long as activity substantially similar to a polypeptide disclosed herein.

Guidance concerning how to make variants and derivatives with phenotypically silent amino acid substitutions is provided in Bowie et al., Science, 247:1306-1310 (1990), which teaches that there are two main strategies for studying the tolerance of an amino acid sequence to change.

The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, the amino acid positions which have been conserved between species can be identified. See e.g., FIG. 5. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions in which substitutions have been tolerated by natural selection indicate positions which are not critical for protein function. Thus, positions tolerating amino acid substitution can be modified while still maintaining specific binding activity of the polypeptide.

The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site-directed mutagenesis or alanine-scanning mutagenesis (the introduction of single alanine mutations at every residue in the molecule) can be used (Cunningham et al., Science, 244:1081-1085 (1989)).

Methods of introducing a mutation into amino acids of a protein is well known to those skilled in the art. See, e.g., Ausubel (ed.), Current Protocols in Molecular Biology, John Wiley and Sons, Inc. (1994); T. Maniatis, E. F. Fritsch and J. Sambrook, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor laboratory, Cold Spring Harbor, N.Y. (1989)). Mutations can also be introduced using commercially available kits such as "QuikChange.TM. Site-Directed Mutagenesis Kit" (Stratagene). The generation of a

polypeptide functionally active variant or derivative to a polypeptide by replacing an amino acid that does not influence the function of a polypeptide can be accomplished by one skilled in the art.

A variant or derivative can have, for example, one or more conservative substitutions while still retaining at least one biological activity. A conservative substitution is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. In general, the following groups of amino acids represent conservative changes: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his.

Particular example variants and derivatives include, without limitation, functionally active variants and derivatives of a polypeptide comprising at least one extracellular subdomain of a Klotho protein, e.g., a polypeptide comprising at least about 100, 150, 200, 250, 300, 350, 375, 400, or 425 contiguous amino acids of an extracellular domain of Klotho (e.g., SEQ ID NO: 5 or 6), with no more than about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60 or more amino acid residue differences from the wild-type sequence (as disclosed in SEQ ID NO: 5 or 6), while retaining at least one biological activity of the wild-type polypeptide. For example, a functionally active variant or derivative of a polypeptide comprising at least one extracellular subdomain of a Klotho protein comprises a polypeptide comprising at least about 400 contiguous amino acids of SEQ ID NO: 5 or 6, with no more than about 100 amino acid residue differences. For example, a functionally active variant or derivative of a polypeptide comprising at least one extracellular subdomain of a Klotho protein comprises a polypeptide comprising at least about 400 contiguous amino acids of SEQ ID NO: 5 or 6, with no more than about 50 amino acid residue differences. For example, a functionally active variant or derivative of a polypeptide comprising at least one extracellular subdomain of a Klotho protein comprises a polypeptide comprising at least about 425 contiguous amino acids of SEQ ID NO: 5 or 6, with no more than about 25 amino acid residue differences. For example, a functionally active variant or derivative of a polypeptide comprising at least one extracellular subdomain of a Klotho protein comprises a polypeptide comprising at least about 425 contiguous amino acids of SEQ ID NO: 5 or 6, with no more than about 10 amino acid residue differences. In

another example, a functionally active variant or derivative of a polypeptide comprising at least one extracellular subdomain of a Klotho protein comprises a polypeptide comprising at least about 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 925, 950 or 982 contiguous amino acids of SEQ ID NO: 7, with no more than about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 75, 80, 85, 90, 95, 100, 110, 120, 140, 150, 160, 170, 180, 190, or 200 amino acid residue differences from the wild-type sequence. For example, a functionally active variant or derivative of a polypeptide comprising at least one extracellular subdomain of a Klotho protein comprises a polypeptide comprising at least about 500 contiguous amino acids of SEQ ID NO: 7, with no more than about 100 amino acid residue differences. For example, a functionally active variant or derivative of a polypeptide comprising at least one extracellular subdomain of a Klotho protein comprises a polypeptide comprising at least about 600 contiguous amino acids of SEQ ID NO: 7, with no more than about 100 amino acid residue differences. For example, a functionally active variant or derivative of a polypeptide comprising at least one extracellular subdomain of a Klotho protein comprises a polypeptide comprising at least about 700 contiguous amino acids of SEQ ID NO: 7, with no more than about 100 amino acid residue differences. For example, a functionally active variant or derivative of a polypeptide comprising at least one extracellular subdomain of a Klotho protein comprises a polypeptide comprising at least about 800 contiguous amino acids of SEQ ID NO: 7, with no more than about 100 amino acid residue differences. For example, a functionally active variant or derivative of a polypeptide comprising at least one extracellular subdomain of a Klotho protein comprises a polypeptide comprising at least about 900 contiguous amino acids of SEQ ID NO: 7, with no more than about 100 amino acid residue differences. For example, a functionally active variant or derivative of a polypeptide comprising at least one extracellular subdomain of a Klotho protein comprises a polypeptide comprising at least about 900 contiguous amino acids of SEQ ID NO: 7, with no more than about 50 amino acid residue differences.

Particular example variants and derivatives include, without limitation, functionally active variants and derivatives of a polypeptide comprising a fibroblast growth factor, e.g., a polypeptide comprising at least about 100, 125, 150, 150, 175, 200, 225, or 250 contiguous amino acids of a fibroblast growth factor, e.g., FGF19 (SEQ ID NO: 31), FGF21 (SEQ ID NO: 33), or FGF23 (SEQ ID NO: 35), with no more than about

1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60 or more amino acid residue differences from the wild-type sequence (as disclosed in SEQ ID NOs: 31, 33 or 35), while retaining at least one biological activity of the wild-type polypeptide. In various embodiments, the variant or derivative can comprise the R179Q variation or not. For example, a functionally active variant or derivative of a polypeptide comprising a fibroblast growth factor comprises a polypeptide comprising at least about 150 contiguous amino acids of SEQ ID NOs: 31, 33 or 35, with no more than about 25 amino acid residue differences. For example, a functionally active variant or derivative of a polypeptide comprising a fibroblast growth factor comprises a polypeptide comprising at least about 175 contiguous amino acids of SEQ ID NOs: 31, 33 or 35, with no more than about 25 amino acid residue differences. For example, a functionally active variant or derivative of a polypeptide comprising a fibroblast growth factor comprises a polypeptide comprising at least about 200 contiguous amino acids of SEQ ID NOs: 31, 33 or 35, with no more than about 25 amino acid residue differences. For example, a functionally active variant or derivative of a polypeptide comprising a fibroblast growth factor comprises a polypeptide comprising at least about 225 contiguous amino acids of SEQ ID NO: 35, with no more than about 50 amino acid residue differences. For example, a functionally active variant or derivative of a polypeptide comprising a fibroblast growth factor comprises a polypeptide comprising at least about 225 contiguous amino acids of SEQ ID NO: 35, with no more than about 25 amino acid residue differences.

4.3. Expression of fusion polypeptides of the disclosure

In order to express the fusion protein of the disclosure, DNA molecules obtained by any of the methods described herein or those that are known in the art, can be inserted into appropriate expression vectors by techniques well known in the art. For example, a double stranded cDNA can be cloned into a suitable vector by homopolymeric tailing or by restriction enzyme linking involving the use of synthetic DNA linkers or by blunt-ended ligation. DNA ligases are usually used to ligate the DNA molecules and undesirable joining can be avoided by treatment with alkaline phosphatase.

Therefore, the disclosure includes vectors (e.g., recombinant plasmids and bacteriophages) that include nucleic acid molecules (e.g., genes or recombinant nucleic acid molecules encoding genes) as described herein. The term "recombinant vector"

includes a vector (e.g., plasmid, phage, phasmid, virus, cosmid, fosmid, or other purified nucleic acid vector) that has been altered, modified or engineered such that it contains greater, fewer or different nucleic acid sequences than those included in the native or natural nucleic acid molecule from which the recombinant vector was derived. For example, a recombinant vector may include a nucleotide sequence encoding a Klotho-FGF23 fusion operatively linked to regulatory sequences, e.g., promoter sequences, terminator sequences and/or artificial ribosome binding sites (RBSs), as defined herein. Recombinant vectors which allow for expression of the genes or nucleic acids included in them are referred to as "expression vectors."

For eukaryotic hosts, different transcriptional and translational regulatory sequences may be employed, depending on the nature of the host. They may be derived from viral sources, such as adenovirus, bovine papilloma virus, Simian virus or the like, where the regulatory signals are associated with a particular gene which has a high level of expression. Examples include, but are not limited to, the TK promoter of the Herpes virus, the SV40 early promoter, the yeast gal4 gene promoter, etc. Transcriptional initiation regulatory signals may be selected which allow for repression or activation, so that expression of the genes can be modulated.

In some of the molecules of the disclosure described herein, one or more DNA molecules having a nucleotide sequence encoding one or more polypeptide chains of a fusion polypeptide are operatively linked to one or more regulatory sequences, which are capable of integrating the desired DNA molecule into a host cell. Cells which have been stably transformed by the introduced DNA can be selected, for example, by introducing one or more markers which allow for selection of host cells which contain the expression vector. A selectable marker gene can either be linked directly to a nucleic acid sequence to be expressed, or be introduced into the same cell by co-transfection. Additional elements may also be needed for optimal synthesis of proteins described herein. It would be apparent to one of ordinary skill in the art which additional elements to use.

Factors of importance in selecting a particular plasmid or viral vector include, but are not limited to, the ease with which recipient cells that contain the vector are recognized and selected from those recipient cells which do not contain the vector; the number of copies of the vector which are desired in a particular host; and whether it is desirable to be able to "shuttle" the vector between host cells of different species.

Once the vector(s) is constructed to include a DNA sequence for expression, it may be introduced into an appropriate host cell by one or more of a variety of suitable

methods that are known in the art, including but not limited to, for example, transformation, transfection, conjugation, protoplast fusion, electroporation, calcium phosphate-precipitation, direct microinjection, etc.

Host cells may either be prokaryotic or eukaryotic. Examples of eukaryotic host cells include, for example, mammalian cells, such as human, monkey, mouse, and Chinese hamster ovary (CHO) cells. Such cells facilitate post-translational modifications of proteins, including, for example, correct folding or glycosylation. Additionally, yeast cells can also be used to express fusion polypeptides of the disclosure. Like most mammalian cells, yeast cells also enable post-translational modifications of proteins, including, for example, glycosylation. A number of recombinant DNA strategies exist which utilize strong promoter sequences and high copy number plasmids that can be utilized for production of proteins in yeast. Yeast transcription and translation machinery can recognize leader sequences on cloned mammalian gene products, thereby enabling the secretion of peptides bearing leader sequences (i.e., pre-peptides). A particularmethod of high-yield production of the fusion polypeptides of the disclosure is through the use of dihydrofolate reductase (DHFR) amplification in DHFR-deficient CHO cells, by the use of successively increasing levels of methotrexate as described in U.S. Patent No. 4,889,803. The polypeptide obtained may be in a glycosylated form.

After the introduction of one or more vector(s), host cells are usually grown in a selective medium, which selects for the growth of vector-containing cells. Purification of the recombinant proteins can be carried out by any of the methods known in the art or described herein, for example, any conventional procedures involving extraction, precipitation, chromatography and electrophoresis. A further purification procedure that may be used for purifying proteins is affinity chromatography using monoclonal antibodies which bind a target protein. Generally, crude preparations containing a recombinant protein are passed through a column on which a suitable monoclonal antibody is immobilized. The protein usually binds to the column via the specific antibody while the impurities pass through. After washing the column, the protein is eluted from the gel by changing pH or ionic strength, for example.

4.4. Assays for assessing fusion polypeptide activity

Assays described herein (See Example 2) and those known in the art can be used for detecting Klotho or FGF activity of the fusion polypeptides of the disclosure. Suitable activity assays include receptor binding assays, cellular proliferation assays and cell

signaling assays. For example, a binding assay which may be used for determining whether a fusion polypeptide has Klotho or FGF activity includes, assaying the binding of a fusion polypeptide to an FGF receptor. FGF receptor binding assays include, but are not limited to, both competitive and non-competitive assay. For example, FGF receptor binding can be detected by contacting cells expressing an FGF receptor with a labeled FGF (for example, radio-active label) and increasing concentrations of an unlabeled Klotho-FGF fusion polypeptide. The two ligands that compete for binding to the same receptor are added to a reaction mixture containing the cell. The cells are subsequently washed and labeled FGF is measured. A decrease in the amount of the labeled FGF to its receptor in the presence of the unlabeled fusion polypeptide is indicative of binding of the Klotho-FGF fusion polypeptide to the receptor. Alternatively, the Klotho-FGF fusion polypeptide may be labeled and direct binding of the fusion polypeptide to the cell is detected.

Klotho or FGF activity can also be measured by determining whether the fusion polypeptide induces a cellular response. For example, in some embodiments, an assay for detecting the biological activity of a Klotho-FGF fusion polypeptide involves contacting cells which express an FGF receptor with a fusion polypeptide, assaying a cellular response such as, for example, cell proliferation or Egr-1 activation, myotube diameter in C2C12 cells, and comparing the cellular response in the presence and absence of the fusion polypeptide. An increase in the cellular response in the presence of the fusion polypeptide complex relative to the absence indicates that the fusion polypeptide has biological activity. Also, an increase in a downstream signaling event from the receptor can also be measured as indicia of biological activity (e.g., phosphorylation of FGFR, FRS2, ERK1/2, p70S6K etc.).

4.5 Pharmaceutical compositions and methods of treatment

The disclosure also pertains to pharmaceutical compositions containing one or more fusion polypeptides of the disclosure and a pharmaceutically acceptable diluent or carrier. The pharmaceutical compositions can further include a pharmaceutically effective dose of heparin. Such pharmaceutical compositions may be included in a kit or container. Such kit or container may be packaged with instructions pertaining to the extended *in vivo* half-life or the *in vitro* shelf life of the fusion polypeptides. Optionally associated with such kit or container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or

biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. Such compositions may be used in methods of treating, preventing, or ameliorating a disease or a disease symptom (e.g., age-related condition or metabolic disorder) in a patient, preferably a mammal and most preferably a human, by administering the pharmaceutical composition to the patient.

In general, a therapeutically effective amount of a pharmaceutical composition of the disclosure is from about 0.0001 mg/kg to 0.001 mg/kg; 0.001 mg/kg to about 10 mg/kg body weight or from about 0.02 mg/kg to about 5 mg/kg body weight. Commonly, a therapeutically effective amount of a fusion polypeptide is from about 0.001 mg to about 0.01 mg, about 0.01 mg to about 100 mg, or from about 100 mg to about 1000 mg, for example. Preferably, a therapeutically effective amount of a fusion polypeptide is from about 0.001 mg/kg to 2mg/kg.

The optimal pharmaceutical formulations for a fusion polypeptide can be determined by one or ordinary skilled in the art depending upon the route of administration and desired dosage. (See, for example, Remington's Pharmaceutical Sciences, 18th Ed. (1990), Mack Publishing Co., Easton, Pa., the entire disclosure of which is hereby incorporated by reference).

The fusion polypeptides of the disclosure may be administered as a pharmaceutical composition that may be in the form of a solid, liquid or gas (aerosol). Typical routes of administration may include, without limitation, oral, topical, parenteral, sublingual, rectal, vaginal, intradermal and intranasal. Parenteral administration includes subcutaneous injections, intravenous, intramuscular, intraperitoneal, intrapleural, intrasternal injection or infusion techniques. Preferably, the compositions are administered parenterally. More preferably, the compositions are administered intravenously. Pharmaceutical compositions of the disclosure can be formulated so as to allow a polypeptide of the disclosure to be bioavailable upon administration of the composition to a subject. Compositions can take the form of one or more dosage units, where, for example, a tablet can be a single dosage unit, and a container of a polypeptide of the disclosure in aerosol form can hold a plurality of dosage units.

Materials used in preparing the pharmaceutical compositions can be non-toxic in the amounts used. It will be evident to those of ordinary skill in the art that the optimal dosage of the active ingredient(s) in the pharmaceutical composition will depend on a variety of factors. Relevant factors include, without limitation, the type of subject (e.g., human), the overall health of the subject, the type of age-related condition or metabolic

disorder the subject in need of treatment of, the use of the composition as part of a multi-drug regimen, the particular form of the polypeptide of the disclosure, the manner of administration, and the composition employed.

The pharmaceutically acceptable carrier or vehicle may be particulate, so that the compositions are, for example, in tablet or powder form. The carrier(s) can be liquid, with the compositions being, for example, an oral syrup or injectable liquid. In addition, the carrier(s) can be gaseous, so as to provide an aerosol composition useful in, e.g., inhalatory administration.

The term "carrier" refers to a diluent, adjuvant or excipient, with which a polypeptide of the disclosure is administered. Such pharmaceutical carriers can be liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. The carriers can be saline, gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea, and the like. In addition, auxiliary, stabilizing, thickening, lubricating and coloring agents can be used. In one embodiment, when administered to a subject, the polypeptides of the disclosure and pharmaceutically acceptable carriers are sterile. Water is a particular carrier when the polypeptide of the disclosure is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical carriers also include excipients such as starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The present compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents.

The composition may be intended for oral administration, and if so, the composition is preferably in solid or liquid form, where semi-solid, semi-liquid, suspension and gel forms are included within the forms considered herein as either solid or liquid.

As a solid composition for oral administration, the composition can be formulated into a powder, granule, compressed tablet, pill, capsule, chewing gum, wafer or the like form. Such a solid composition typically contains one or more inert diluents. In addition, one or more of the following can be present: binders such as ethyl cellulose, carboxymethylcellulose, microcrystalline cellulose, or gelatin; excipients such as starch, lactose or dextrins, disintegrating agents such as alginic acid, sodium alginate, Primogel,

corn starch and the like; lubricants such as magnesium stearate or Sterotex; glidants such as colloidal silicon dioxide; sweetening agents such as sucrose or saccharin, a flavoring agent such as peppermint, methyl salicylate or orange flavoring, and a coloring agent.

When the pharmaceutical composition is in the form of a capsule, e.g., a gelatin capsule, it can contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol, cyclodextrin or a fatty oil.

The pharmaceutical composition can be in the form of a liquid, e.g., an elixir, syrup, solution, emulsion or suspension. The liquid can be useful for oral administration or for delivery by injection. When intended for oral administration, a composition can contain one or more of a sweetening agent, preservatives, dye/colorant and flavour enhancer. In a composition for administration by injection, one or more of a surfactant, preservative, wetting agent, dispersing agent, suspending agent, buffer, stabilizer and isotonic agent can also be included.

The liquid compositions of the disclosure, whether they are solutions, suspensions or other like form, can also include one or more of the following: sterile diluents such as water for injection, saline solution, preferably physiological saline, Ringer's solution, isotonic sodium chloride, fixed oils such as synthetic mono or digylcerides which can serve as the solvent or suspending medium, polyethylene glycols, glycerin, cyclodextrin, propylene glycol or other solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. A parenteral composition can be enclosed in an ampoule, a disposable syringe or a multiple-dose vial made of glass, plastic or other material. Physiological saline is a particular specific adjuvant. An injectable composition is preferably sterile.

The pharmaceutical compositions contain an effective amount of a compound of the disclosure (e.g., fusion polypeptide) such that a suitable dosage will be obtained. The pharmaceutical compositions may contain the known effective amount of the compounds as currently prescribed for their respective disorders.

The route of administration of the polypeptide of the disclosure used in the prophylactic and/or therapeutic regimens which will be effective in the prevention, treatment, and/or management of a age-related condition or metabolic disorder can be based on the currently prescribed routes of administration for other therapeutics known in the art. The polypeptides of the disclosure can be administered by any convenient route,

for example, by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.). Administration can be systemic or local. Various delivery systems are known, e.g., microparticles, microcapsules, capsules, etc., and may be useful for administering a polypeptide of the disclosure. More than one polypeptides of the disclosure may be administered to a subject. Methods of administration may include, but are not limited to, oral administration and parenteral administration; parenteral administration including, but not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, sublingual, intranasal, intracerebral, intraventricular, intrathecal, intravaginal, transdermal, rectally, by inhalation, or topically to the ears, nose, eyes, or skin.

The polypeptides of the disclosure may be administered parenterally. Specifically, the polypeptides of the disclosure may be administered intravenously.

Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent, or via perfusion in a fluorocarbon or synthetic pulmonary surfactant. The polypeptides of the disclosure can also be formulated as a suppository, with traditional binders and carriers such as triglycerides.

The polypeptides of the disclosure can be delivered in a controlled release system. For example, a pump can be used (see Sefton, *CRC Crit. Ref. Biomed. Eng.* 1987, *14*, 201; Buchwald *et al.*, Surgery 1980, *88*: 507; Saudek *et al.*, *N. Engl. J. Med.* 1989, 321: 574). Polymeric materials can also be used for controlled release of the polypeptides of the disclosure (see *Medical Applications of Controlled Release*, Langer and Wise (eds.), CRC Pres., Boca Raton, FL, 1974; *Controlled Drug Bioavailability, Drug Product Design and Performance*, Smolen and Ball (eds.), Wiley, New York, 1984; Ranger and Peppas, *J. Macromol. Sci. Rev. Macromol. Chem.* 1983, *23*, 61; *see also* Levy *et al.*, *Science* 1985, *228*, 190; During *et al.*, *Ann. Neurol.*, 1989, *25*, 351; Howard *et al.*, *J. Neurosurg.*, 1989, *71*, 105). Specifically, a controlled-release system can be placed in proximity of the target of the polypeptides of the disclosure, e.g., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in *Medical Applications of Controlled Release*, *supra*, vol. 2, 1984, pp. 115-138). Other controlled-release systems discussed in the review by Langer (*Science* 1990, *249*, 1527-1533) can be used.

Polymeric materials used to achieve controlled or sustained release of the polypeptides of the disclosure are disclosed, e.g., in U.S. Patent No. 5,679,377; U.S. Patent No. 5,916,597; U.S. Patent No. 5,912,015; U.S. Patent No. 5,989,463; U.S. Patent

No. 5,128,326; PCT Publication No. WO 99/15154; and PCT Publication No. WO 99/20253. Examples of polymers used in sustained release formulations include, but are not limited to, poly(2-hydroxy ethyl methacrylate), poly(methyl methacrylate), poly(acrylic acid), poly(ethylene-co-vinyl acetate), poly(methacrylic acid), polyglycolides (PLG), polyanhydrides, poly(N-vinyl pyrrolidone), poly(vinyl alcohol), polyacrylamide, poly(ethylene glycol), polylactides (PLA), poly(lactide-co-glycolides) (PLGA), and polyorthoesters. Preferably, the polymer used in a sustained release formulation is inert, free of leachable impurities, stable on storage, sterile, and biodegradable.

In general, a therapeutically effective amount of a pharmaceutical composition of the disclosure is from about 0.0001 mg/kg to 0.001 mg/kg; 0.001 mg/kg to about 10 mg/kg body weight or from about 0.02 mg/kg to about 5 mg/kg body weight.

In other embodiments, the prophylactic and/or therapeutic regimen involves administering to a patient one or more doses of an effective amount of a polypeptide of the disclosure, wherein the dose of an effective amount achieves a plasma level of at least 0.01 μg/mL to at least 400 μg/mL of the polypeptide of the disclosure.

A prophylactic and/or therapeutic regimen may involve administering to a patient a plurality of doses of an effective amount of a polypeptide of the disclosure, wherein the plurality of doses maintains a plasma level of at least 0.01 μg/mL, to 400 μg/mL of the polypeptide of the disclosure. The prophylactic and/or therapeutic regimen may be administered for at least 1 day, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months or 9 months.

The prophylactic and/or therapeutic regimen may involve administration of a polypeptide of the disclosure in combination with one or more additional therapeutics. The recommended dosages of the one or more therapeutics currently used for the prevention, treatment, and/or management of an age-related condition or metabolic disorder can be obtained from any reference in the art including, but not limited to, Hardman *et al.*, eds., *Goodman & Gilman's The Pharmacological Basis Of Basis Of Therapeutics, 10th ed.*, McGraw-Hill, New York, 2001; *Physician's Desk Reference* (60th ed., 2006), which is incorporated herein by reference in its entirety.

The disclosure includes methods of treating disorders wherein agonistic activity of Klotho protein and FGF are desirable. The disclosure furthermore includes the use of the disclosed proteins, fusion proteins, nucleic acid molecules or pharmaceutical composition in therapy or as medicament for the treatment of a pathological disorder wherein agonistic

activity of Klotho protein and FGF are desirable. Examples of such methods or uses of the disclosure include, but are not limited to age-related condition or metabolic disorders.

The disclosure includes methods for treating or preventing an age-related condition in an individual; and the use of the disclosed proteins, fusion proteins, nucleic acid molecules or pharmaceutical composition in therapy or as medicament for treating or preventing an age-related condition in an individual. An individual in need of treatment is administered a pharmacologically effective dose of a pharmaceutical composition containing a Klotho fusion polypeptide, having at least one extracellular subdomain of a Klotho protein and a fibroblast growth factor and an (optional) modified Fc fragment, so as to treat or prevent the age-related condition. In some embodiments, the Klotho fusion polypeptide is co-administered with a pharmacologically effective dose of heparin. Age-related conditions include sarcopenia, skin atrophy, muscle wasting, brain atrophy, atherosclerosis, arteriosclerosis, pulmonary emphysema, osteoporosis, osteoarthritis, immunologic incompetence, high blood pressure, dementia, Huntington's disease, Alzheimer's disease, cataracts, age-related macular degeneration, prostate cancer, stroke, diminished life expectancy, memory loss, wrinkles, impaired kidney function, and age-related hearing loss. In some embodiments, the Klotho fusion polypeptide contains at least one extracellular domain of an alpha Klotho protein. In a particular embodiment, a Klotho fusion protein containing at least one extracellular domain of alpha Klotho protein and fibroblast growth factor 23 is administered to an individual in need of treatment for muscle wasting.

The disclosure is also directed to a method for treating or preventing a metabolic disorder in an individual; and to the use of the disclosed proteins, fusion proteins, nucleic acid molecules or pharmaceutical composition in therapy or as medicament for treating or preventing metabolic disorder in an individual. An individual in need of treatment is administered a pharmacologically effective dose of a pharmaceutical composition containing a Klotho fusion polypeptide, having at least one extracellular subdomain of a Klotho protein and a fibroblast growth factor so as to treat the metabolic disorder, and an (optional) modified Fc fragment having decreased binding to FcRn and/or increased serum half-life and/or stability. In some embodiments, the Klotho fusion polypeptide is co-administered with a pharmacologically effective dose of heparin. The method may be used in the treatment or prevention of Type II Diabetes, Metabolic Syndrome, hyperglycemia, and obesity. In a particular embodiment, a Klotho fusion protein containing at least one extracellular domain of a beta-Klotho protein and fibroblast

growth factor 21 is administered to an individual in need of treatment for a metabolic disorder.

The disclosure also provides methods for treating or preventing hyperphosphatemia or calcinosis in an individual; and the use of the disclosed proteins, fusion proteins, nucleic acid molecules or pharmaceutical composition in therapy or as medicament for treating or preventing hyperphosphatemia or calcinosis in an individual. An individual in need of treatment is administered a pharmacologically effective dose of a pharmaceutical composition containing a Klotho fusion polypeptide, having at least one extracellular subdomain of a Klotho protein, a fibroblast growth factor and an (optional) modified Fc fragment so as to treat hyperphosphatemia or calcinosis. In some embodiments, the Klotho fusion polypeptide is co-administered with a pharmacologically effective dose of heparin. In a particular embodiment, a Klotho fusion protein containing at least one extracellular domain of an alpha Klotho protein and fibroblast growth factor 23 and an (optional) modified Fc fragment is administered to an individual in need of treatment for a hyperphosphatemia or calcinosis.

The disclosure is also directed to a method for treating or preventing chronic renal disease or chronic renal failure in an individual; and to the use of the disclosed proteins, fusion proteins, nucleic acid molecules or pharmaceutical composition in therapy or as medicament for treating or preventing chronic renal disease or chronic renal failure in an individual. An individual in need of treatment is administered a pharmacologically effective dose of a pharmaceutical composition containing a Klotho fusion polypeptide, having at least one extracellular subdomain of a Klotho protein, a fibroblast growth factor and an (optional) modified Fc fragment so as to treat chronic renal disease or chronic renal failure. In some embodiments, the Klotho fusion polypeptide is co-administered with a pharmacologically effective dose of heparin. In some embodiments, a Klotho fusion protein containing at least one extracellular domain of an alpha Klotho protein is administered to an individual in need of treatment for chronic renal disease or chronic renal failure.

The disclosure also includes methods for treating or preventing cancer in an individual; and the use of the disclosed proteins, fusion proteins, nucleic acid molecules or pharmaceutical composition in therapy or as medicament for treating or preventing cancer in an individual. An individual in need of treatment is administered a pharmacologically effective dose of a pharmaceutical composition containing a Klotho fusion polypeptide, having at least one extracellular subdomain of a Klotho protein, a

fibroblast growth factor and an (optional) modified Fc fragment so as to treat cancer. The method may be used in the treatment or prevention of breast cancer. In some embodiments, the Klotho fusion polypeptide is co-administered with a pharmacologically effective dose of heparin. In some embodiments, a Klotho fusion protein containing at least one extracellular domain of an alpha Klotho protein is administered to an individual in need of treatment for cancer.

In methods of treating disorders by administering a pharmaceutical composition containing a Klotho fusion polypeptide; or when using pharmaceutical composition containing a Klotho fusion polypeptide in therapy, the Klotho fusion polypeptide and an (optional) modified Fc fragment has at least one extracellular subdomain of a Klotho protein and a fibroblast growth factor. In a particular embodiment, the Klotho fusion protein contains at least one extracellular domain of a beta Klotho protein and fibroblast growth factor 21.

In another embodiment, the fusion comprises a FGF (e.g., FGF19, FGF21, FGF23 or FGF23 variant) and a modified Fc fragment with decreased binding to FcRn and/or increased serum stability. This type of fusion can be used in various diseases, as described above, or used to treat or prevent any FGF-related disease known in the art. The fusion can be administered to an individual in need thereof.

The fusion polypeptide compositions can be administered according to any method of administration known to those of skill in the art and described herein. Particular specific methods of administration include subcutaneous or intravenous. Other effective modes of administration are described herein.

4.6. Methods of Treatment and Assays for Assessing Efficacy

Methods or uses of the disclosure which provide administering the fusion polypeptides described herein to an individual can be used to treat a variety of disorders including an age-related disorder or a metabolic disorder. Without being limited by any particular theory, fusion polypeptides may be used to treat disorders in which there is dysregulation of Klotho or FGF. Example disorders include metabolic disorders and age-related disorders. For example, both FGF23 or Klotho knock-out mice display a variety of similar phenotypes including, low physical activity, growth retardation, muscle wasting, skin atrophy, atherosclerosis, short life spans, etc. (See Razzaque and Lanske, *J. of Endrocrinology*, 194:1-10 (2007), which is herein incorporated by reference).

In particular, fusion polypeptides of the disclosure are particularly useful in the treatment of aging-related disorders, including muscle wasting. Without being bound to theory, the ability of Klotho and FGF23 to control mineral (e.g., phosphate and calcium) and vitamin D homeostasis may be the means by which these proteins modulate aging and muscle atrophy.

On the other hand, fusion polypeptides of the disclosure may be used for treating a metabolic disorder. For example, beta-Klotho and FGF19 have been shown to control bile acid homeostasis by regulating cholesterol 7-α-hydroxylase (CYP7A1). A non-limiting example of bile homeostasis disorder is cholestasis. The beta-Klotho and FGF21 have been shown to induce lipolysis in adipocytes and, therefore, reduced fat storage and increased glucose uptake. Non-limiting examples of lipolysis/fat storage disorders are obesity and associated metabolic and cardiovascular diseases.

Based at least in part on the finding that FGF23 is able to stimulate excretion of phosphate in the urine and thereby reduce phosphate levels in the serum, Klotho-FGF23 fusion polypeptides of the disclosure can be used for treating or preventing hyperphosphatemia or calcinosis in an individual. For example, it has been shown that a homozygous missense mutation in Klotho resulting in a deficiency in Klotho in a patient can cause severe tumoral calcinosis and artery calcification (Ichikawa et al., *J. Clin. Invest.* 117:2684-2691 (2007), which is herein incorporated by reference). An individual is administered a pharmacologically effective dose of a pharmaceutical composition containing the Klotho fusion polypeptide, having at least one extracellular subdomain of a Klotho protein, a fibroblast growth factor and an (optional) modified Fc fragment so as to treat or prevent hyperphosphatemia or calcinosis. In particular, a Klotho fusion polypeptide containing at least one extracellular domain of an alpha Klotho protein, a fibroblast growth factor and an (optional) modified Fc fragment is useful for treating hyperphosphatemia or calcinosis.

Klotho fusion polypeptides of the disclosure can also be used for treating or preventing chronic renal disease or chronic renal failure in an individual. For example, it has been shown that Klotho expression is reduced in kidney of patients with chronic renal failure, compared to that in unaffected kidneys (Koh et al., *Biochem. Biophys. Res. Comm.* 280:1015-1020 (2001), which is herein incorporated by reference). An individual is administered a pharmacologically effective dose of a pharmaceutical composition containing the Klotho fusion polypeptide, having at least one extracellular subdomain of a Klotho protein, a fibroblast growth factor and an (optional) modified Fc fragment so as to

treat or prevent chronic renal disease or chronic renal failure. In particular, a Klotho fusion polypeptide containing at least one extracellular domain of an alpha Klotho protein is useful for treating chronic renal disease or chronic renal failure.

Klotho fusion polypeptides of the disclosure can also be used for treating or preventing cancer in an individual. For example, it has been shown that Klotho expression is reduced in breast cancer tissue, compared to normal breast cancer tissue (Wolf et al., *Oncogene* (2008) advance online publication, which is herein incorporated by reference). An individual is administered a pharmacologically effective dose of a pharmaceutical composition containing the Klotho fusion polypeptide, having at least one extracellular subdomain of a Klotho protein, a fibroblast growth factor and an (optional) modified Fc fragment so as to treat or prevent cancer or breast cancer. In particular, a Klotho fusion protein containing at least one extracellular domain of an alpha Klotho protein is useful for treating cancer or breast cancer.

Methods for evaluating the efficacy and/or determining the effective dose of a Klotho fusion polypeptide of the disclosure on an age-related disorder or metabolic disorder include organismal based assays, e.g., using a mammal (e.g., a mouse, rat, primate, or some other non-human), or other animal (e.g., Xenopus, zebrafish, or an invertebrate such as a fly or nematode). The Klotho fusion polypeptide can be administered to the organism once or as a regimen (regular or irregular). A parameter of the organism is then evaluated, e.g., an age-associated parameter. Klotho fusion polypeptides that are of interest result in a change in the parameter relative to a reference, e.g., a parameter of a control organism. Other parameters (e.g., related to toxicity, clearance, and pharmacokinetics) can also be evaluated.

The Klotho fusion polypeptide of the disclosure may be evaluated using an animal that has a particular disorder, e.g., a disorder described herein, e.g., an age-related disorder, a metabolic disorder. These disorders can also provide a sensitized system in which the test polypeptide's effects on physiology can be observed. Example disorders include: denervation, disuse atrophy; metabolic disorders (e.g., disorder of obese and/or diabetic animals such as db/db mouse and ob/ob mouse); cerebral, liver ischemia; cisplatin/taxol/vincristine models; various tissue (xenograph) transplants; transgenic bone models; pain syndromes (include inflammatory and neuropathic disorders); Paraquat, genotoxic, and oxidative stress models; and tumor I models.

For measuring an age-related disorder, the animal model can be an animal that has an altered phenotype when calorically restricted. For example, F344 rats provide a useful

assay system for evaluating a Klotho fusion polypeptide. When calorically restricted, F344 rats have a 0 to 10% incidence of nephropathy. However, when fed ad libitum, they have a 60 to 100% incidence of nephropathy.

To evaluate a Klotho fusion polypeptide of the disclosure, it is administered to the animal (e.g., an F344 rat or other suitable animal) and a parameter of the animal is evaluated, e.g., after a period of time. The animal can be fed ad libitum or normally (e.g., not under caloric restriction, although some parameters can be evaluated under such conditions). Typically, a cohort of such animals is used for the assay. Generally, a test polypeptide can be indicated as favorably altering lifespan regulation in the animal if the test polypeptide affects the parameter in the direction of the phenotype of a similar animal subject to caloric restriction. Such test polypeptides may cause at least some of the lifespan regulatory effects of caloric restriction, e.g., a subset of such effects, without having to deprive the organism of caloric intake.

The parameter to be tested may be an age-associated or disease associated parameter, e.g., a symptom of the disorder associated with the animal model. For example, the test polypeptide can be administered to a SH Rat, and blood pressure is monitored. A test polypeptide that is favorably indicated can cause an amelioration of the symptom relative to a similar reference animal not treated with the polypeptide. Other parameters relevant to a disorder or to aging can include: antioxidant levels (e.g., antioxidant enzyme levels or activity), stress resistance (e.g., paraquat resistance), core body temperature, glucose levels, insulin levels, thyroid-stimulating hormone levels, prolactin levels, and leutinizing hormone levels.

To measure the effectiveness of the polypeptides of the disclosure for treating an age-related disorder, an animal having decreased Klotho expression may be used, e.g., mouse with a mutant Klotho; See Kuroo, et al. Nature, 390; 45 (1997) and U.S. Pub. No. 2003/0119910, both of which are herein incorporated by reference in their entirety. For example, the test polypeptide is administered to the mutant mouse and age-related parameters are monitored. A test polypeptide that is favorably indicated can cause an amelioration of the symptom relative to a similar reference animal not treated with the polypeptide. A parameter relevant to a metabolic disorder or to aging can be assessed by measurement of body weight, examination on the acquisition of reproductive ability, measurement of blood sugar level, observation of life span, observation of skin, observation of motor functions such as walking, and the like. The assessment can also be made by measurement of thymus weight, observation of the size of calcified nodules

formed on the inner surface of thoracic cavity, and the like. Further, quantitative determination of mRNA for the Klotho gene or Klotho protein is also useful for the assessment.

Still other in vivo models and organismal assays include evaluating an animal for a metabolic parameter, e.g., a parameter relevant to an insulin disorder, type II diabetes. Example metabolic parameters include: glucose concentration, insulin concentration, and insulin sensitivity.

Another example system features tumors, e.g., in an animal model. The tumors can be spontaneous or induced. For example, the tumors can be developed from cells that have a variety of genetic constitutions, e.g., they can be p53+ or p53-. It is also possible to use organisms that an autoimmune disorder, e.g., an NZB mouse, which is predisposed to SLE. To evaluate features of bone disease, it is possible, for example, to use an animal that has an ovariectomy as a model,. e.g., for osteoporosis. Similarly, for joint disease, the model can be based on adjuvant arthritis (e.g., mice can be immunized with cartilage proteoglycans, high mobility group proteins, streptococcal cell wall material, or collagens); for kidney disease, kd/kd mice can be used. Animal models of cognition, particularly learning and memory are also available. Animal models of diabetes and its complications are also available, e.g., the streptozotocin model. Canine models can be used, for example, for evaluating stroke and ischemia.

In assessing whether a test polypeptide is capable of altering life span regulation, a number of age-associated parameters or biomarkers can be monitored or evaluated. Example age associated parameters include: (i) lifespan of the cell or the organism; (ii) presence or abundance of a gene transcript or gene product in the cell or organism that has a biological age dependent expression pattern; (iii) resistance of the cell or organism to stress; (iv) one so or more metabolic parameters of the cell or organism (example parameters include circulating insulin levels, blood glucose levels; fat content; core body temperature and so forth); (v) proliferative capacity of the cell or a set of cells present in the organism; and (vi) physical appearance or behavior of the cell or organism.

The term "average lifespan" refers to the average of the age of death of a cohort of organisms. In some cases, the "average lifespan" is assessed using a cohort of genetically identical organisms under controlled environmental conditions. Deaths due to mishap are discarded. Where average lifespan cannot be determined (e.g., for humans) under controlled environmental conditions, reliable statistical information (e.g., from actuarial tables) for a sufficiently large population can be used as the average lifespan.

Characterization of molecular differences between two such organisms, e.g., one reference organism and one organism treated with a Klotho fusion polypeptide can reveal a difference in the physiological state of the organisms. The reference organism and the treated organism are typically the same chronological age. The term "chronological age" as used herein refers to time elapsed since a preselected event, such as conception, a defined embryological or fetal stage, or, more preferably, birth. A variety of criteria can be used to determine whether organisms are of the "same" chronological age for the comparative analysis. Typically, the degree of accuracy required is a function of the average lifespan of a wildtype organism. For example, for the nematode *C. elegans*, for which the laboratory wildtype strain N2 lives an to average of about 16 days under some controlled conditions, organisms of the same age may have lived for the same number of days. For mice, organism of the same age may have lived for the same number of weeks or months; for primates or humans, the same number of years (or within 2, 3, or 5 years); and so forth. Generally, organisms of the same chronological age may have lived for an amount of time within 15, 10, 5, 3, 2 or 1% of the average lifespan of a wildtype organism of that species. Preferably, the organisms are adult organisms, e.g., the organisms have lived for at least an amount of time in which the average wildtype organism has matured to an age at which it is competent to reproduce.

The organismal screening assay can be performed before the organisms exhibit overt physical features of aging. For example, the organisms may be adults that have lived only 10, 30, 40, 50, 60, or 70% of the average lifespan of a wildtype organism of the same species. Age-associated changes in metabolism, immune competence, and chromosomal structure have been reported. Any of these changes can be evaluated, either in a test subject (e.g., for an organism based assay), or for a patient (e.g., prior, during or after treatment with a therapeutic described herein.

A marker associated with caloric restriction can also be evaluated in a subject organism of a screening assay (or a treated subject). Although these markers may not be age-associated, they may be indicative of a physiological state that is altered when the Klotho pathway is modulated. The marker can be an mRNA or protein whose abundance changes in calorically restricted animals. WO01/12851 and U.S. Patent No. 6,406, 853 describe example markers. Cellular models derived from cells of an animal described herein or analogous to an animal model described herein can be used for a cell-based assay.

Models for evaluating the effect of a test polypeptide on muscle atrophy include: 1) rat medial gastrocnemius muscle mass loss resulting from denervation, e.g., by severing the right sciatic nerve at mid-thigh; 2) rat medial gastrocnemius muscle mass loss resulting from immobilization, e.g., by fixed the right ankle joint at 90 degrees of flexion; 3) rat medial gastrocnemius muscle mass loss resulting from hind limb suspension; (see, e.g., U.S. 2003-0129686); 4) skeletal muscle atrophy resulting from treatment with the cachectic cytokine, interleukin-1 (IL-1) (R. N. Cooney, S. R. Kimball, T. C. Vary, *Shock* 7, 1-16 (1997)); and 5) skeletal muscle atrophy resulting from treatment with the glucocorticoid, dexamethasone (A. L. Goldberg, *J. Biol. Chem.* 244, 3223-9 (1969).)

Example animal models for AMD include: laser-induced mouse model simulating exudative (wet) macular degeneration Bora *et al., Proc. Natl. Acad. Sci.* U S A., 100:2679-84 (2003); a transgenic mouse expressing a mutated form of cathepsin D resulting in features associated with the "geographic atrophy" form of AMD (Rakoczy *et al., Am. J. Pathol.*, 161:1515-24 (2002)); and a transgenic mouse over expressing VEGF in the retinal pigment epithelium resulting in CNV. Schwesinger *et al., Am. J. Pathol.* 158:1161-72 (2001).

Example animal models of Parkinson's disease include primates rendered Parkinsonian by treatment with the dopaminergic neurotoxin 1-methyl-4 phenyl 1,2,3,6-tetrahydropyridine (MPTP) (see, e.g., U.S. Patent Publication No. 20030055231 and Wichmann *et al., Ann. N.Y. Acad. Sci.*, 991:199-213 (2003); 6-hydroxydopamine-lesioned rats (e.g., Lab. Anim. Sci.,49:363-71 (1999)) ; and transgenic invertebrate models (e.g., Lakso *et al., J. Neurochem.* 86:165-72 (2003) and Link, *Mech. Ageing Dev.*, 122:1639-49 (2001)).

Example molecular models of Type II diabetes include: a transgenic mouse having defective Nkx-2.2 or Nkx-6.1; (U.S. Patent No. 6,127,598); Zucker Diabetic Fatty fa/fa (ZDF) rat. (U.S. Patent No. 6,569,832); and Rhesus monkeys, which spontaneously develop obesity and subsequently frequently progress to overt type 2 diabetes (Hotta *et al., Diabetes*, 50:1126-33 (2001); and a transgenic mouse with a dominant-negative IGF-I receptor (KR-IGF-IR) having Type 2 diabetes-like insulin resistance.

Example animal and cellular models for neuropathy include: vincristine induced sensory-motor neuropathy in mice (U.S. Patent No. 5,420,112) or rabbits (Ogawa *et al., Neurotoxicology,* 21:501-11 (2000)); a streptozotocin (STZ)-diabetic rat for study of

autonomic neuropathy (Schmidt *et al., Am. J. Pathol.*, 163:21-8 (2003)); and a progressive motor neuropathy (pmn) mouse (Martin *et al., Genomics*, 75:9-16 (2001)).

Example animal models of hyperphosphatemia or tumoral calcinosis include Klotho knockout mice and FGF23 knockout mice (Yoshida et al., *Endocrinology* 143:683-689 (2002)).

Example animal models of chronic renal disease or chronic renal failure include COL4A3+/-mice (Beirowski et al., *J. Am. Soc. Nephrol.* 17:1986-1994 (2006)).

Example animal models of cancer include the transplantation or implantation of cancer cells or tissue into nude mice, as is known in the art (Giovanella et al., *Adv. Cancer Res.* 44:69-120 (1985)). For example, animal models of breast cancer include nude mice transplanted or implanted with breast cancer cells or tissue (e.g., Yue et al., *Cancer Res.* 54:5092-5095 (1994); Glinsky et al., *Cancer Res.* 56:5319-5324 (1996); Visonneau *Am. J. Path.* 152:1299-1311 (1998)).

The compositions can be administered to a subject, e.g., an adult subject, particularly a healthy adult subject or a subject having an age-related disease. In the latter case, the method can include evaluating a subject, e.g., to characterize a symptom of an age-related disease or other disease marker, and thereby identifying a subject as having a neurodegenerative disease, e.g., Alzheimer's or an age-related disease or being pre-disposed to such a disease.

Skeletal Muscle Atrophy

Methods or uses of the disclosure which provide administering the Klotho fusion polypeptide to an individual can be used to treat skeletal muscle atrophy. Muscle atrophy includes numerous neuromuscular, metabolic, immunological and neurological disorders and diseases as well as starvation, nutritional deficiency, metabolic stress, diabetes, aging, muscular dystrophy, or myopathy. Muscle atrophy occurs during the aging process. Muscle atrophy also results from reduced use or disuse of the muscle. Symptoms include a decline in skeletal muscle tissue mass. In human males, muscle mass declines by one-third between the ages of 50 and 80. Some molecular features of muscle atrophy include the upregulation of ubiquitin ligases, and the loss of myofibrillar proteins (Furuno et al., *J. Biol. Chem.*, 265:8550-8557, 1990). The breakdown of these proteins can be followed, e.g., by measuring 3-methyl-histidine production, which is a specific constituent of actin, and in certain muscles of myosin (Goodman, Biochem. J. 241:121-12, 1987 and Lowell, et al., Metabolism, 35:1121-112, 1986; Stein and Schluter, *Am. J. Physiol. Endocrinol.*

Metab. 272: E688-E696, 1997). Release of creatine kinase (a cell damage marker) (Jackson, et al., Neurology, 41: 101 104, 1991) can also be indicative.

Non-insulin-dependent Diabetes

Methods or uses of the disclosure which provide administering the Klotho fusion polypeptide to an individual can be used to treat Non-insulin-dependent Diabetes. Non-insulin-dependent Diabetes is also called "adult onset" diabetes and Type 2 diabetes. Type 2 diabetes also includes "non-obese type 2" and "obese type 2." Type II diabetes can be characterized by (1) reduced pancreatic-beta-islet-cell secretion of insulin such that less than necessary amounts of insulin are produced to keep blood glucose levels in balance and/or (2) "insulin resistance," wherein the body fails to respond normally to insulin. (U.S. Patent No. 5,266,561 and U.S. Patent No. 6,518,069) . For example, glucose-stimulated insulin levels typically fail to rise above 4.0 nmol/L. (U.S. Patent No. 5,266,561). Example symptoms of Type II diabetes include: hyperglycemia while fasting (U.S. Patent No. 5,266,561); fatigue; excessive thirst; frequent urination; blurred vision; and an increased rate of infections. Molecular indications of Type II diabetes include islet amyloid deposition in the pancreases.

Neuropathy

Neuropathy can include a central and/or peripheral nerve dysfunction caused by systemic disease, hereditary condition or toxic agent affecting motor, sensory, sensorimotor or autonomic nerves. (see, e.g., US Patent Application No. 20030013771). Symptoms can vary depending upon the cause of the nerve damage and the particular types of nerves affected. For example, symptoms of motor neuropathy include clumsiness in performing physical tasks or as muscular weakness, exhaustion after minor exertion, difficulty in standing or walking and attenuation or absence of a neuromuscular reflex. (U.S. Patent Application No. 20030013771) symptoms of autonomic neuropathy include constipation, cardiac irregularities and attenuation of the postural hypotensive reflex. (U.S. Patent Application No. 20030013771), symptoms of sensory neuropathy include pain and numbness; tingling in the hands, legs or feet; and extreme sensitivity to touch, and symptoms of retinopathy include blurred vision, sudden loss of vision, black spots, and flashing lights.

Alzheimer's Disease

Methods or uses of the disclosure which provide administering the Klotho fusion polypeptide to an individual can be used to treat Alzheimer's Disease (AD). Alzheimer's Disease is a complex neurodegenerative disease that results in the irreversible loss of neurons. It provides merely one example of a neurodegenerative disease that is also an age-related condition. Clinical hallmarks of Alzheimer's Disease include progressive impairment in memory, judgment, orientation to physical surroundings, and language. Neuropathological hallmarks of AD include region-specific neuronal loss, amyloid plaques, and neurofibrillary tangles. Amyloid plaques are extracellular plaques containing the amyloid peptide (also known as Ap, or Ap42), which is a cleavage product of the, 8-amyloid precursor protein (also known as APP). Neurofibrillary tangles are insoluble intracellular aggregates composed of filaments of the abnormally hyperphosphorylated microtubule-associated protein, taut Amyloid plaques and neurofibrillary tangles may contribute to secondary events that lead to neuronal loss by apoptosis (Clark and Karlawish, *Ann. Intern. Med.* 138(5):400-410 (2003). For example, p-amyloid induces caspase-2-dependent apoptosis in cultured neurons (Troy *et al. J Neurosci.* 20(4):1386-1392). The deposition of plaques in viva may trigger apoptosis of proximal neurons in a similar manner.

A variety of criteria, including genetic, biochemical, physiological, and cognitive criteria, can be used to evaluate AD in a subject. Symptoms and diagnosis of AD are known to medical practitioners. Some example symptoms and markers of AD are presented below. Information about these indications and other indications known to be associated with AD can be used as an "AD-related parameter." An AD related parameter can include qualitative or quantitative information. An example of quantitative information is a numerical value of one or more dimensions, e.g., a concentration of a protein or a tomographic map. Qualitative information can include an assessment, e.g., a physician's comments or a binary ("yes"/"no") and so forth. An AD-related parameter includes information that indicates that the subject is not diagnosed with AD or does not have a particular indication of AD, e.g., a cognitive test result that is not typical of AD or a genetic APOE polymorphism not associated with AD.

Progressive cognitive impairment is a hallmark of AD. This impairment can present as decline in memory, judgment, decision making, orientation to physical surroundings, and language (Nussbaum and Ellis, *New Eng J. Med.* 348(14):1356 35 1364 (2003)). Exclusion of other forms of dementia can assist in making a diagnosis of AD. Neuronal death leads to progressive cerebral atrophy in AD patients. Imaging

techniques (e.g., magnetic resonance imaging, or computer assisted tomography) can be used to detect AD-associated lesions in the brain and/or brain atrophy.

AD patients may exhibit biochemical abnormalities that result from the pathology of the disease. For example, levels of tan protein in the cerebrospinal fluid is elevated in AD patients (Andreasen, N. *et al. Arch Neurol.* 58:349-350 (2001)).

Levels of amyloid beta 42 (A,B42) peptide can be reduced in CSF of AD patients. Levels of Ap42 can be increased in the plasma of AD patients (Ertekein-Taner, N., *et al. Science* 290:2303 2304 (2000)). Techniques to detect biochemical abnormalities in a sample from a subject include cellular, immunological, and other biological methods known in the art. For general guidance, see, e.g., techniques described in Sambrook & Russell, Molecular Cloning: A Laboratory Manual, 3r Edition, Cold Spring Harbor Laboratory, N.Y. (2001), Ausubel et al., Current Protocols in Molecular Biology (Greene Publishing Associates and Wiley Interscience, N.Y. (1989), (Harrow, E. and Lane, D. (1988) Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY), and updated editions thereof.

For example, antibodies, other immunoglobulins, and other specific binding ligands can be used to detect a biomolecule, e.g., a protein or other antigen associated with AD. For example, one or more specific antibodies can be used to probe a sample. Various formats are possible, e.g., ELISAs, fluorescence-based assays, Western blots, and protein arrays. Methods of producing polypeptide arrays are described in the art, e.g., in De Wildt et al. (2000). *Nature Biotech.* 18, 989-994; Lucking et al. (1999). *Anal. Biochem.* 270, 103-111; Ge, H. (2000). *Nucleic Acids Res.* 28, e3, I-VII; MacBeath, G., and Schreiber, S.L. (2000). *Science* 289, 1760 to 1 763; and WO 99/5 1 773A1.

In one assay, a non-human animal model of AD (e.g., a mouse model) is used, e.g., to evaluate a polypeptide or a therapeutic regimen. For example, U.S. Patent No. 6,509,515 describes one such model animal which is naturally able to be used with learning and memory tests. The animal expresses an amyloid precursor protein (APP) sequence at a level in brain tissues such that the animal develops a progressive neurologic disorder within a short period of time from birth, generally within a year from birth, preferably within 2 to 6 months, from birth. The APP protein sequence is introduced into the animal, or an ancestor of the animal, at an embryonic stage, preferably the one cell, or fertilized oocyte, stage, and generally not later than about the 8-cell stage. The zygote or embryo is then developed to term in a pseudo-pregnant as foster female. The amyloid precursor protein genes are introduced into an animal embryo so as to be chromosomally

incorporated in a state which results in super endogenous expression of the amyloid precursor protein and the development of a progressive necrologic disease in the cortico-limbic areas of the brain, areas of the brain which are prominently affected in progressive necrologic disease states such as AD. The gliosis and clinical manifestations in affected transgenic animals model necrologic disease. The progressive aspects of the neurologic disease are characterized by diminished exploratory and/or locomotor behavior and diminished deoxyglucose uptake/utilization and hypertrophic gliosis in the cortico-limbic regions of the brain. Further, the changes that are seen are similar to those that are seen in some aging animals. Other animal models are also described in US 5,387,742; 5,877,399; 6,358,752; and 6, 187,992.

Parkinson's Disease

Methods or uses of the disclosure which provide administering the Klotho fusion polypeptide to an individual can be used to treat Parkinson's Disease. Parkinson's disease includes neurodegeneration of dopaminergic neurons in the substantia nigra resulting in the degeneration of the nigrostriatal dopamine system that regulates motor function. This pathology, in turn, leads to motor dysfunctions.(see, e.g., and Lotharius *et al., Nat. Rev. Neurosci.*, 3:932-42 (2002)). Example motor symptoms include: akinesia, stooped posture, gait difficulty, postural instability, catalepsy, muscle rigidity, and tremor. Example non-motor symptoms include: depression, lack of motivation, passivity, dementia and gastrointestinal dysfunction (see, e. g., Fahn, *Ann. N.Y. Acad. Sci.*, 991:1-14 (2003) and Pfeiffer, *Lancet Neurol.*, 2:107-16 (2003)) Parkinson's has been observed in 0.5 to 1 percent of persons 65 to 69 years of age and 1 to 3 percent among persons 80 years of age and older. (see, e.g., Nussbaum *et al., N. Engl. J. Med.*, 348:1356-64 (2003)). Molecular markers of Parkinson's disease include reduction in aromatic L amino acid decarboxylase (AADC) (see, e.g., US App.. No. 20020172664); and loss of dopamine content in the nigrostriatal neurons (see, e.g., Fahn, Ann. *N.Y. Acad. Sci.*, 991:1-14 (2003) and Lotharius et al., Nat. Rev. Neurosci., 3:932-42 (2002)). In some familial cases, PD is linked to mutations in single genes encoding alpha-synuclein and parkin (an E3 ubiquitin ligase) proteins. (e.g., Riess et al., J. Neurol. 250 Suppl 1:I3 10 (2003) and Nussbaum et al., N. Engl. J. Med., 348:1356-64 (2003)). A missense mutation in a neuron-specific C-terminal ubiquitin hydrolase gene is also associated with Parkinson's. (e.g., Nussbaum et al., N. Engl. J. Med., 348:1356-64 (2003))

Huntington's Disease

Methods or uses of the disclosure which provide administering the Klotho fusion polypeptide to an individual can be used to treat Huntington's Disease. Methods for evaluating the efficacy and/or determining the effective dose of a Klotho fusion polypeptide on Huntington's Disease include organismal based assays, e.g., using a mammal (e.g., a mouse, rat, primate, or some other non-human), or other animal (e.g., Xenopus, zebrafish, or an invertebrate such as a fly or nematode). A number of animal model system for Huntington's disease are available. See, e.g., Brouillet, Functional *Neurology* 15(4): 239-251 (2000); Ona *et al. Nature* 399: 263-267 (1999), Bates *et al. Hum Mol Genet.* 6(10):1633-7 (1997); Hansson *et al. J. of Neurochemistry* 78: 694-703; and Rubinsztein, D. C., *Trends in Genetics*, Vol. 1S, No. 4, pp. 202-209 (a review on various animal and non-human models of HD).

An example of such an animal model is the transgenic mouse strain is the R6/2 line (Mangiarini et al. Cell 87: 493-506 (1996)). The R6/2 mice are transgenic Huntington's disease mice, which over-express exon 1 of the human HD gene (under the control of the endogenous promoter). The exon 1 of the R6/2 human HD gene has an expanded CAG/polyglutamine repeat lengths (150 CAG repeats on average). These mice develop a progressive, ultimately fatal neurological disease with many features of human Huntington's disease. Abnormal aggregates, constituted in part by the N terminal part of Huntingtin (encoded by HD exon 1), are observed in R6/2 mice, both 45 in the cytoplasm and nuclei of cells (Davies *et al. Cell* 90: 537-548 (1997)). For example, the human Huntingtin protein in the transgenic animal is encoded by a gene that includes at least 55 CAG repeats and more preferably about 150 CAG repeats. These transgenic animals can develop a Huntington's disease-like phenotype.

These transgenic mice are characterized by reduced weight gain, reduced lifespan and motor impairment characterized by abnormal gait, resting tremor, hindlimb clasping and hyperactivity from 8 to 10 weeks after birth (for example the R6/2 strain; see Mangiarini et al. *Cell* 87: 493-506 (1996)). The phenotype worsens progressively toward hypokinesia. The brains of these transgenic mice also demonstrate neurochemical and histological abnormalities, such as changes in neurotransmitter receptors (glutamate, dopaminergic), decreased concentration of N-acetylaspartate (a marker of neuronal integrity) and reduced striatum and brain size. Accordingly, evaluating can include assessing parameters related to neurotransmitter levels, neurotransmitter receptor levels, brain size and striatum size. In addition, abnormal aggregates containing the transgenic

part of or full-length human Huntingtin protein are present in the brain tissue of these animals (e.g., the R6/2 transgenic mouse strain). See, e.g., Mangiarini *et al. Cell* 87: 493-506 (1996), Davies *et al. Cell* 90: 537-548 (1997), Brouillet, Functional Neurology 15(4): 239-251 (2000) and *Cha et al. Proc. Natl. Acad. Sci.* USA 95: 6480-6485 (1998).

To test the effect of the test polypeptide or known polypeptide described in the application in an animal model, different concentrations of test polypeptide are administered to the transgenic animal, for example by injecting the test polypeptide into circulation of the animal. A Huntington's disease-like symptom may be evaluated in the animal. The progression of the Huntington's disease-like symptoms, e.g., as described above for the mouse model, is then monitored to determine whether treatment with the test polypeptide results in reduction or delay of symptoms. In another assay, disaggregation of the Huntingtin protein aggregates in these animals is monitored. The animal can then be sacrificed and brain slices are obtained. The brain slices are then analyzed for the presence of aggregates containing the transgenic human Huntingtin protein, a portion thereof, or a fusion protein comprising human Huntingtin protein, or a portion thereof. This analysis can includes, for example, staining the slices of brain tissue with anti-Huntingtin antibody and adding a secondary antibody conjugated with FITC which recognizes the anti-Huntington's antibody (e.g., the anti-Huntingtin antibody is mouse anti-human antibody and the secondary antibody is specific for human antibody) and visualizing the protein aggregates by fluorescent microscopy.

A variety of methods are available to evaluate and/or monitor Huntington's disease. A variety of clinical symptoms and indicia for the disease are known. Huntington's disease causes a movement disorder, psychiatric difficulties and cognitive changes. The degree, age of onset, and manifestation of these symptoms can vary. The movement disorder can include quick, random, dance-like movements called chorea.

Example motor evaluations include: ocular pursuit, saccade initiation, saccade velocity, dysarthria, tongue protrusion, finger tap ability, pronate/supinate, a lo fist-hand-palm sequence, rigidity of arms, bradykinesia, maximal dystonia (trunk, upper and lower extremities), maximal chorea (e.g., trunk, face, upper and lower extremities), gait, tandem walking, and retropulsion. An example treatment can cause a change in the Total Motor Score 4 (TMS-4), a subscale of the UHDRS, e.g., over a one-year period.

Cancer

Methods or uses of the disclosure which provide administering the Klotho fusion polypeptide to an individual can be used to treat cacner. Cancer includes any disease that is caused by or results in inappropriately high levels of cell division, inappropriately low levels of apoptosis, or both. Examples of cancers include, without limitation, leukemias (e.g., acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute monocytic leukemia, acute erythroleukemia, chronic leukemia, chronic myelocytic leukemia, chronic lymphocytic leukemia), polycythemia vera, lymphoma (Hodgkin's disease, non-Hodgkin's disease), Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors such as sarcomas and carcinomas (e.g., fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, nile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, uterine cancer, testicular cancer, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodenroglioma, schwannoma, meningioma, melanoma, neuroblastoma, and retinoblastoma). Lymphoproliferative disorders are also considered to be proliferative diseases.

All patents, patent applications, and published references cited herein are hereby incorporated by reference in their entirety. While this disclosure has been particularly shown and described with references to embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the disclosure encompassed by the appended claims.

5. EXAMPLES

Example 1. Expression and purification of Klotho fusion polypeptides

Expression of the Klotho fusion polypeptide

The polypeptides of the disclosure were made by transiently transfecting HEK293T cells with an expression vector encoding a Klotho fusion polypeptide having the extracellular domain of alpha Klotho and the FGF23 (R179Q) variant. Conditioned media containing expressed polypeptides were generated by transient transfection of the respective expression plasmids for Klotho, FGF23, and the Klotho-FGF23(R179Q) fusion protein. The transfections were performed in 6-well plates using Lipofectamine 2000 (Invitrogen, Cat # 11668-019). Five hours after transfection, the transfection mix was replaced with 3 ml DMEM plus 1% FBS. Conditioned media were collected 72 hours after the addition of 3 ml DMEM plus 1% FBS. Samples of conditioned medium from various transiently transfected HEK293T cells were separated by SDS-polyacrylamide gel electrophoresis (SDS-PAGE) and analyzed by Western blot (Figure 3A) or stained with Coomassie blue (Figure 3B).

SDS-polyacrylamide gel electrophoresis was performed on various samples (lane 1, Control; lane 2, FGF23; lane 3, sKlotho; lanes 4-6, sKlotho-FGF23). Coomassie blue staining revealed the expression of a high, >180 kDa band (Figure 3B, indicated by arrow on the right) that was not present in lanes 1-3, which contained samples that had not been transfected with the vector encoding the Klotho fusion polypeptide. The quality of the Klotho fusion polypeptide secreted into the media was evaluated by Western blot (Figure 3A). An anti-FGF23 rat monoclonal IgG2A (R&D Systems, Cat# MAB26291) was used as the primary antibody to detect the Klotho fusion polypeptides by Western blot. The Western blot confirmed that the additional bands observed in the Coomassie stained gels were Klotho fusion polypeptides. The Western blot confirmed that the Klotho fusion polypeptides had the expected molecular weight for the Klotho fusion polypeptide. This analysis shows the expression of the Klotho-FGF23(R179Q) fusion protein.

Purification of the Klotho fusion polypeptide

The polypeptides of the disclosure were purified from conditioned media from a culture of HEK293T cells transiently transfected with an expression vector encoding a Klotho fusion polypeptide having the extracellular domain of alpha Klotho and the FGF23 R179Q variant. To generate conditioned medium, an expression vector encoding sKlotho-FGF23-6xHis was transfected (500 μg DNA in 18 ml of OptiMEM 1 (GIBCO, Cat #11058) mixed with 18 ml of 2 μg/ml polyethlinimine (PEI) into HEK293 cells grown in suspension in expression medium (464 ml of HEK293T cells at 10^6 cells/ml in Freestype 293 expression medium (GIBCO, Cat #12338)). After transfection, the culture was allowed to grow (120 hours; 37°C in a 5% CO_2 incubator; shaking at 125 rpm). At

the end of incubation, conditioned medium was harvested by centrifugation (1000 rpm for five minutes). The conditioned medium was then applied to a nickel-agarose column. The sKlotho-FGF23-6xHis bound tightly to the column and was eluted with 50 mM imidazole. The resulting purified material was then dialyzed in PBS to remove imidazole. A sample of the purified sKlotho-FGF23-6xHis was separated by SDS-PAGE (lane 1, purified sKlotho-FGF23-6xHis; lane 2, molecular weight marker) and analyzed by staining with Coomassie blue (Figure 3C). The stained SDS-PAGE gel confirmed that the purified sKlotho-FGF23-6xHis had the expected molecular weight. The inability to detect bands corresponding to proteins other than full-length sKlotho-FGF23-6xHis in the lane loaded with the purified material also showed that the sKlotho-FGF23-6xHis was purified.

Example 2. *In vitro* assay assessing the activity of the Klotho fusion polypeptide.

Egr-1-luciferase

The biological activity of the expressed alpha Klotho fusion polypeptide was tested in Egr-1-luciferase reporter assays. Binding of the Klotho fusion polypeptide to the FGF23 receptor resulted in the downstream activation of Egr-1 and the expression of a luciferase reporter regulated by the Egr-1 promoter. The Egr-1-luciferase reporter gene was constructed based on that reported by Urakawa et al. (Nature, 2006, Vol 444, 770-774). HEK293T cells seeded in 48-well poly-D-lysine plate were transfected with the Egr-1-luciferase reporter gene together with a transfection normalization reporter gene (Renilla luciferase). Five hours after transfection of the Egr-1 luciferase reporter gene, the transfection mix was replaced with 3 ml DMEM plus 1% FBS. Conditioned media were collected 72 hours after the addition of 3 ml DMEM plus 1% FBS. Five hours later, the transfection mix was replaced with a sample to be tested for activity. In initial experiments, 50% conditioned medium (alone or containing Klotho, FGF23, Klotho and FGF23, and the Klotho-FGF23(R179Q) fusion protein) and 50% DMEM with 1% FBS in the presence or absence of 20 μg/ml heparin (Sigma, Cat#H8537; dissolved in DMEM as 2 mg/ml stock) were tested in the Egr-1-luciferase reporter assays (Figure 4). Further experiments used defined quantities of the purified polypeptides (Figures 5A and 5B). Cells were lysed 20 hours later in passive lysis buffer (Promega, Cat #E194A) and luciferase activities were determined using Dual-Glo Luciferase Assay System (Promega, Cat #E2940).

In initial experiments, Klotho fusion polypeptide activity was demonstrated in unfractionated conditioned medium. Using the Egr-1-luciferase reporter gene (Figure 4) these experiments quantified the fold changes in the expression of the luciferase reporter. Conditioned medium containing a combination of FGF23 and the extracellular domain of Klotho protein activated Egr-1-luciferase, but conditioned medium containing only FGF23 or conditioned medium containing only the extracellular domain of Klotho, did not activate Egr-1-luciferase. Conditioned medium containing the fusion protein sKlotho-FGF23(R179Q) activated the Egr-1-luciferase reporter gene in contrast to conditioned media containing either FGF23 or Klotho alone. In these experiments, conditioned medium containing the fusion protein sKlotho-FGF23(R179Q) activated the Egr-1-luciferase reporter gene significantly better than conditioned medium containing a combination of FGF23 and Klotho. In the presence of heparin, the inductions by conditioned medium containing the fusion protein sKlotho-FGF23(R179Q) and the conditioned medium containing a combination of FGF23 and Klotho were significantly enhanced. Table 1 lists the relative expression of various FGF-Klotho fusion polypeptides in conditioned medium and the relative activity of the unfractionated conditioned medium corresponding to the various FGF-Klotho fusion polypeptides in Egr-1-luciferase reporter assays.

Table 1. Expression and Activities of sKlotho-FGF23 fusion variants

	sKlotho-FGF23 fusion constructs	Expression	Activity in Egr-1-luc reporter gene
1	sKlotho-FGF23	good	yes
2	IgG sp-sKlotho-FGF23	good	yes
3	sKL-D1-FGF23	good	no
4	sKL-D2-FGF23	no	n.a.
5	s(KL-D1)2-FGF23	good	no
6	sKL-D1/D2-FGF23	no	n.a.
7	ssKlotho(ΔN-26)-FGF23	poor	no*
8	sKLD1-D2(Δ692-965)-FGF23	poor	no*
9	sKL-D1-D2(Δ507-798)-FGF23	poor	no*
10	FGF23-sKlotho	poor	no*

* lack of activity may be the result of low expression

Egr-1-luciferase reporter assays were also performed using defined quantities of proteins purified from the conditioned medium, using the purification procedure as described in Example 1. Consistent with previous results using unfractionated conditioned medium containing the expressed polypeptides, treatment with a combination of purified FGF23 and sKlotho resulted in luciferase reporter activity, but treatment with purified FGF23 alone did not (Figure 5A). The luciferase reporter activity from the combination of purified FGF23 and sKlotho was further dependent on the dose of purified sKlotho, and the effect could be enhanced by the presence of heparin (20 μg/ml). An effect of the sKlotho-FGF23-6xHis fusion polypeptide on luciferase activity could be detected at concentrations as low as about 1.21 nM (1.2 fold change) and at least up to about 19.3 nM (2.4 fold change) in Egr-1-luciferase reporter assays (Figure 5B). The activity of the sKlotho-FGF23-6xHis fusion polypeptide on luciferase activity was significantly enhanced in the presence of heparin (20 μg/ml). In the presence of heparin, the effect of the sKlotho-FGF23-6xHis fusion polypeptide on luciferase activity could be detected at a concentration as low as about 0.6 nM (2.0 fold change). The result showed that purified sKlotho-FGF23-6xHis dose-dependently induced the EGR-1-luc reporter gene, and that treatment with sKlotho-FGF23-6xHis.

Example 3. *In vitro* assay assessing the effect of the Klotho fusion polypeptide on muscle cells.

The biological effect of the expressed Klotho fusion polypeptide was tested on C2C12 myoblasts. Treatment of C2C12 myoblasts with IGF-1, FGF2, or sKlotho-FGF23 resulted in myotube growth and phosphorylation of signaling proteins. C2C12 myoblasts were seeded at a density of 40,000 cells/well in 6-well poly-D-lysine and fibronectin coated plates in growth medium (3 parts DMEM and 1 part F12), 10% FBS, 1% Glut; 1% P/S; 1% Linolic acid; 0.1% ITS: [insulin (10 mg/ml), transferrin (5.5 mg/ml), and selenium (5 ng/ml)]. After myoblasts reached confluence (3 days), medium was changed into differentiation medium (DMED with 2% horse serum; 1% Glut; 1% P/S).

For the myotube diameter experiments, three days after confluent media was changed into differentiation medium, cells were treated with IGF-1 (10 nM), FGF2 (20 ng/ml) or sKlotho-FGF23 (20 nM) in the absence or presence of dexamethasone (100 μM) for 24 hours in differentiation medium. At the end of treatment, cells were fixed

with glutaraldehyde (5% in PBS) and multiple fluorescent images were collected. Myotube diameter was measured using the Pipeline Pilot program to determine hypertrophy or atrophy.

For the signaling protein phosphorylation,experiments, three days after confluent media was changed into differentiation medium, cells were starved for four hours with DMEM without FBS and then treated with IGF-1 (10 nM), FGF2 (20 ng/ml) or sKlotho-FGF23 (20 nM) in the absence or presence of Rapamycin (40 nM) for 30 min. Cells were lysed in RIPA buffer in the presence of protease and phosphatase inhibitors. Western blot analysis was carried out and membranes were probed with different antibodies as indicated in the figure and developed on X-ray films, which were scanned.

The results of this study showed that sKlotho-FGF23 resulted in an increase in myotube diameter compared to the control and induced C2C12 myotube hypertrophy similar to results for IGF-1 and FGF2 (Figure 5A). In addition, treatment with sKlotho-FGF23, IGF-1, and FGF2 could partially reverse myotube atrophy induced by dexamethasone, based on measurements of myotube diameter. No difference was observed between sKlotho-FGF23 and FGF2 on myotube morphology (measured by thickness of the myotubes) in the absence or presence of dexamethasone. The trophic effects of sKlotho-FGF23, IGF-1, and FGF2 were statistically significant.

Consistent with the effects on C2C12 myotubes, sKlotho-FGF23 fusion protein signaling led to the phosphorylation of p70S6K and ERK, but not AKT or FoxO, in C2C12 myotubes (Figure 5B). The effect of sKlotho-FGF23 on signaling was similar to that of FGF2, but was distinct from that of IGF-1. The extent of ERK phosphorylation by sKlotho-FGF23 was observed to be less than that of IGF-1 or FGF2. The phosphorylation of p70S6K by sKlotho-FGF23 was rapamycin sensitive. In the experiments involving C2C12 cells, heparin was not required to activate signaling. These results show that a sKlotho-FGF23 fusion polypeptide activated signaling in C2C12 myotubes.

Example 4. Fusion polypeptides comprising sKlotho, FGF23 and FcLALA

Various fusion polypeptides are constructed using sKlotho, FGF23, and a modified Fc fragment of an antibody. These modified Fc molecules have altered (decreased) binding to FcRn and thus increased serum half-life. They also have modified bioavailability and alterered transport to mucosal surfaces and other targets in the body. In this example, the FGF23 and sKlotho are fused to FcLALA, which is described in U.S. Patent No. 7,217,798 and Hessell et al. 2007 Nature 449:101-104, Intervening between the various components of these fusion polypeptides are linkers, as described in Lode et

al. 1998 Proc. Natl. Acad. Sci. USA 95: 2475-2480. These fusions are inserted into constructs, e.g., pcDNA3.1
(Invitrogen, Carlsbad, CA), and expressed in HEK293 cells.

A. sKlotho-FGF23-FcLALA v1

A fusion is constructed which comprises: sKlotho, a linker, FGF23, another linker, and FcLALA. This embodiment, designated sKlotho-FGF23-FcLALA v1, is presented in SEQ ID NOs: 46 and 47, below.

The nucleotide sequence of sKlotho-FGF23-FcLALA v1 (wherein initiation **A**TG as 1) is presented as SEQ ID NO: 46.

The amino acid sequence of sKlotho-FGF23-FcLALA v1 is presented below as SEQ ID NO: 47.

In this sequence, the various components of the fusion are as follows:

sKlotho: 1-982; Linker1: 983-1001; FGF23: 1002-1228; Linker 2; 1229-1233; FcLALA: 1234-1459.

B. sKlotho-FGF23-FcLALA v2

A fusion is constructed which comprises: sKlotho, a linker, FGF23, another linker, and FcLALA. This embodiment is designated sKlotho-FGF23-FcLALA v2 and presented as SEQ ID NOs: 48 and 49, below.

The nucleotide sequence of sKlotho-FGF23-FcLALA v2 (wherein initiation **A**TG as 1) is presented as SEQ ID NO: 48.

The amino acid sequence of sKlotho-FGF23-FcLALA v2 is presented below as SEQ ID NO: 49.

In this sequence, the various components of the fusion are as follows:

sKlotho: (aa or amino acids) 1-982; Linker 1: 983-1001; FGF23: 1002-1228; Linker 2; 1229-1233; FcLALA: 1234-1450.

Other fusion polypeptides can be constructed by combining in various combinations the FGF, Klotho, modified Fc fragments, and (optionally) linker sequences, and variants and derivatives thereof, as described herein or known in the art.

Example 5. Fusion polypeptides comprising FGF23 and FcLALA.

Various fusion polypeptides are constructed using FGF23, and a modified Fc fragment of an antibody, as described in U.S. Patent No. 7,217,798. These modified Fc molecules have altered (decreased) binding to FcRn and thus increased serum half-life. They also have modified bioavailability and alterered transport to mucosal surfaces and

other targets in the body. In this example, FGF23 is fused to FcLALA, Intervening between the various components of these fusion polypeptides are linkers, as described in Lode et al. 1998 Proc. Natl. Acad. Sci. USA 95: 2475-2480. These fusions are inserted constructs, e.g., pcDNA3.1 (Invitrogen, Carlsbad, CA), and expressed in HEK293 cells.

C. FGF23-FcLALA v1

A fusion is constructed which comprises: FGF23, a linker, and FcLALA. This construct is designated FGF23-FcLALA v1 and presented below as SEQ ID NOs: 50 and 51.

The nucleotide sequence of FGF23-FcLALA v1 (wherein initiation ATG as 1) is presented below as SEQ ID NO: 50.

The amino acid sequence of FGF23(R179Q)-FcLALAv1 is presented below as SEQ ID NO: 51.

In this sequence, the various components of the fusion are as follows:

FGF23: (aa) 1-251; Linker: 252-256; FcLALA: 257-482.

D. FGF23-FcLALA v2

A fusion is constructed which comprises: FGF23-FcLALA v2, which comprises FGF23 and FcLALA.

The nucleotide sequence of FGF23-FcLALA v2 (wherein initiation ATG as 1) is presented below as SEQ ID NO: 52.

The amino acid sequence of FGF23(R179Q)-FcLALAv2 is presented below as SEQ ID NO: 53.

In this sequence, the various components of the fusion are as follows:

FGF23: 1-251; Linker: 252-256; FcLALA: 257-473.

Other fusion polypeptides can be constructed by combining in various combinations the FGF sequences, modified Fc fragments, and (optionally) linkers, and variants and derivatives thereof, as described herein or known in the art.

E. Activation of Egr-1-luc reporter gene by sKlotho-FGF23(R179Q)-FcLALA fusion proteins; activation of Egr-1-luc reporter gene by FGF23(R179Q)-FcLALA proteins; and pharmacokinetic profile of FGF23(R179Q) vs FGF23(R179Q)-FcLaLav2 are determined.

Figure 7 shows the activation of Egr-1-luc reporter gene by sKlotho-FGF23(R179Q)-FcLALA fusion proteins. HEK293T cells are transiently transfected with the Egr-1-luc reporter gene and incubated with the indicated conditioned media in the absence or

presence of 20 μg/ml heparin. Luciferase activities are then determined 18 hours later. The result shows that sklotho-FGF23-FcLALA fusion proteins induces the reporter gene activity. These inductions are significantly enhanced in the presence of heparin. sKF-Fcv1: sKlotho-FGF23-FcLALAv1; sKF-Fcv2: sKlotho-FGF23-FcLALAv2

Figure 8 shows the activation of Egr-1-luc reporter gene by FGF23(R179Q)-FcLALA proteins. HEK293T cells are transiently transfected with the Egr-1-luc reporter gene together with the full-length transmembrane form of Klotho and incubated with the indicated 30% conditioned media. Luciferase activities are then determined 18 hours later. The results show that FGF23-FcLALA fusion proteins induce the reporter gene activity in a similar manner as the FGF23.

Figure 9 shows the pharmacokinetic profile of FGF23(R179Q) vs FGF23(R179Q)-FcLALAv2. Four mice per group are injected subcutaneously with FGF23(R179Q)-6xHis or FGF23(R179Q)-FcLALAv2 at 2 mg/kg. At the indicated times, serum samples are collected and analyzed for FGF23 by ELISA. FGF23(R179Q)-FcLALA concentration in serum remains elevated at the 24 hr time point, while FGF23(R179Q)-6xHis is back to basal level. This results indicate that with the addition of FcLALA, the in vivo half-life of FGF23(R179Q) is significantly improved.

Example 6. In vivo efficacy of sKlotho-FGF23 fusion in enhancing muscle growth after dexamethasone-induced muscle atrophy

Experimental data shows that intramuscular injection of sKlotho-FGF23 significantly enhanced growth of muscle mass after dexamethasone-induced muscle atrophy. In this experiment, the peptide corresponding to that of SEQ ID NO: 41 is used.

Figure 10 shows absolute weights (A) and percent weight change (B) of the gastrocnemius-soleus-plantaris (GSP) muscles showing that intramuscular injection of sKlotho-FGF23 (KLOFGF) significantly enhanced regrowth of muscle mass after dexamethasone (DEX)-induced muscle atrophy compared with intramuscular injection of sKlotho (sKLO) or phosphate buffered saline (PBS).

Eighty male C57BL/6 mice, aged 15 weeks, are randomized by body weight into 8 groups each of 10 mice. Four groups receive water without DEX (W21d) while the other

four receive DEX in drinking water at 2.4 mg/kg/day for three weeks (D21d). After the three weeks, DEX treatment is stopped and one W21d and one D21d group is immediately sacrificed to establish the degree of muscle atrophy induced by the DEX treatment. The remaining three groups of W21d or D21d mice are allowed to recover for another 14 days (R14d) during which period they receive an intramuscular injection of 2x50 µl of PBS, sKlotho-FGF23 (KLOFGF; 1.6 mg/ml), or sKlotho (sKLO; 1.6 mg/ml), respectively, every other day into the right gastrocnemius-soleus-plantaris muscle complex. The mice are sacrificed 24h after the last intramuscular injection and the muscle weights determined and expressed as absolute weight (A) or percent change compared to the W21d+PBS group.

These data show the in vivo efficacy of sKlotho-FGF23 fusion in enhancing muscle growth after dexamethasone-induced muscle atrophy.

Example 7. Additional mutations in the FGF23 portion of fusion proteins which reduce aggregation, reduce undesired protease-induced cleavage, and increase production

Several mutations are investigated within the FGF23 portion of sKlotho-FGF23 and FGF23-FcLaLa fusion polypeptides. These include Q156, C206 and C244 (wherein the number is based on the FGF23 amino acid sequence). Example individual mutations include Q156A, C206S and C244S, and mutations at any of these sites can be combined with a mutation at R179 (e.g., R179Q). Example sequences are provided in SEQ ID NO: 54 to 68 of Figure 2.

C206 and C244 are suspected to be involved in dimerization; and Q156 is a site identified by the inventors as a protease sensitive site. Mutating these amino acids to any other amino acid enhances the qualities of the proteins, by reducing aggregation, reducing undesired protease-induced cleavage, and increasing protein production from cells, without interfering with FGF23 activity. This is an unexpected result, as these three positions are conserved in the FGF23 proteins found in human, rhesus, bovine, mouse and rat. This conservation is shown below in the comparison between SEQ ID NOs: 69, 70, 71, 72 and 73, with the Q156, C206 and C244 in bold, underlined font.

```
hFGF23          MLGARLRLWVCALCSVCSMSVLRAYPNASPLLGSSWGGLIHLYTATARNSYHLQIHKNGH
rhesus          MLGARLRLWVCALCSVCSMSVIRAYPNASPLLGSSWGGLIHLYTATARNSYHLQIHKNGH
bovine          MLGARLGLWVCTLSCV-----VQAYPNSSPLLGSSWGGLTHLYTATARNSYHLQIHGDGH
mouse           MLGTCLRLLVGVLCTVCSLGTARAYPDTSPLLGSNWGSLTHLYTATARTSYHLQIHRDGH
rat             MLGACLRLLVGALCTVCSLGTARAYSDTSPLLGSNWGSLTHLYTATARNSYHLQIHRDGH

hFGF23          VDGAPHQTIYSALMIRSEDAGFVVITGVMSRRYLCMDFRGNIFGSHYFDPENCRFQHQTL
rhesus          VDGAPHQTIYSALMIRSEDAGFVVITGVMSRRYLCMDFRGNIFGSHYFNPENCRFRHWTL
bovine          VDGSPQQTVYSALMIRSEDAGFVVITGVMSRRYLCMDFTGNIFGSHHFSPESCRFRQRTL
mouse           VDGTPHQTIYSALMITSEDAGSVVITGAMTRRFLCMDLHGNIFGSLHFSPENCKFRQWTL
rat             VDGTPHQTIYSALMITSEDAGSVVIIGAMTRRFLCMDLRGNIFGSYHFSPENCRFRQWTL

hFGF23          ENGYDVYHSPQYHFLVSLGRAKRAFLPGMNPPPYSQFLSRRNEIPLIHFNTPI-PRRHTR
rhesus          ENGYDVYHSPQHHFLVSLGRAKRAFLPGMNPPPYSQFLSRRNEIPLIHFNTPR-PRRHTR
bovine          ENGYDVYHSPQHRFLVSLGRAKRAFLPGTNPPPYAQFLSRRNEIPLPHFAATARPRRHTR
mouse           ENGYDVYLSQKHHYLVSLGRAKRIFQPGTNPPPFSQFLARRNEVPLLHFYTVR-PRRHTR
rat             ENGYDVYLSPKHHYLVSLGRSKRIFQPGTNPPPFSQFLARRNEVPLLHFYTAR-PRRHTR

hFGF23          SAEDDSERDPLNVLKPRARMTPAPASCSQELPSAEDNSPMASDPLGVVRGGRVNTHAGGT
rhesus          SAEDDSERDPLNVLKPRARMTPAPASCSQELPSAEDNSPVASDPLGVVRGGRVNTHAGGT
bovine          SAHDSG--DPLSVLKPRARATPVPAACSQELPSAEDSGPAASDPLGVLRGHRLDVRAGSA
mouse           SAEDPPERDPLNVLKPRPRATPVPVSCSRELPSAEEGGPAASDPLGVLRRGRGDARGGAG
rat             SAEDPPERDPLNVLKPRPRATPIPVSCSRELPSAEEGGPAASDPLGVLRRGRGDARRGAG

hFGF23          GPEGCRPFAKFI (SEQ ID NO: 69)
rhesus          GPEACRPFPKFI (SEQ ID NO: 70)
bovine          GAERCRPFPGFA (SEQ ID NO: 71)
mouse           GADRCRPFPRFV (SEQ ID NO: 72)
rat             GTDRCRPFPRFV (SEQ ID NO: 73)
```

The fact that these three mutations do not prevent FGF23 activity is shown in Figure 11. This figure shows activation of Egr-1-luc reporter gene by FGF23(R179Q)-FcLALA and Q156A, C206S, C244S and C206S/C244S mutants.

HEK293T cells are transiently transfected with the EGR-1-luc reporter gene together with the full-length transmembrane form of Klotho and indicated FGF23-FcLaLa mutants. Luciferase activities are then determined 18 hours later. The results show that C206S, C244S, C206S/C244S (three independent clones) and Q156A (three independent clones) mutants are equally effective as FGF23-FcLALA fusion proteins in activating EGR-1-Luc reporter gene activity.

Data showing that mutating C244 and C206 alter dimerization and aggregation of FGF23 is shown in Figure 12. This figure shows protein qualities of WT, Q156A, C206S, C244S and C206S/C244S mutants of FGF23(R179Q)-FcLaLa. Conditioned medium from HEK293T cells transient transfected with the indicated FGF23-FcLaLa expression vectors are analyzed by Western blot using an FGF23 antibody. The result shows that C206S/C244S mutation prevents protein dimerization and Q156A mutation has reduced proteolytic fragments.

Thus, surprisingly, even though these Q156, C206 and C244 residues are conserved across species, they can mutated without reducing FGF23 activity and can enhance the qualities of the protein by reducing aggregation and cleavage and by improving production.

Unless defined otherwise, the technical and scientific terms used herein have the same meaning as that usually understood by a specialist familiar with the field to which the disclosure belongs.

Unless indicated otherwise, all methods, steps, techniques and manipulations that are not specifically described in detail can be performed and have been performed in a manner known per se, as will be clear to the skilled person. Reference is for example again made to the standard handbooks and the general background art mentioned herein and to the further references cited therein.

Claims to the invention are non-limiting and are provided below.

Although particular embodiments and claims have been disclosed herein in detail, this has been done by way of example for purposes of illustration only, and is not intended to be limiting with respect to the scope of the appended claims, or the scope of subject matter of claims of any corresponding future application. In particular, it is contemplated by the inventors that various substitutions, alterations, and modifications may be made to the disclosure without departing from the spirit and scope of the disclosure as defined by the claims. The choice of nucleic acid starting material or clone of interest is believed to be a matter of routine for a person of ordinary skill in the art with knowledge of the embodiments described herein. Other aspects, advantages, and modifications considered to be within the scope of the following claims. Redrafting of claim scope in later filed corresponding applications may be due to limitations by the patent laws of various countries and should not be interpreted as giving up subject matter of the claims.

SEQUENCE LISTING (Figure 2)

Human Klotho nucleic acid sequence (NM_004795) (SEQ ID NO: 1)
Protein coding region: 9-3047

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Klotho amino acid sequence (NP_004786) (SEQ ID NO: 2)

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beta-Klotho nucleic acid sequence (NM_175737) (SEQ ID NO: 3)
Protein coding region: 98-3232

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1621 ttctttaaaa gagtccacgc cagatgtgca gggccagttt ccctgtgact tctcctgggg
1681 tgtcactgaa tctgttctta agcccgagtc tgtggcttcg tccccacagt tcagcgatcc
1741 tcatctgtac gtgtggaacg ccactggcaa cagactgttg caccgagtgg aaggggtgag
1801 gctgaaaaca cgacccgctc aatgcacaga ttttgtaaac atcaaaaaac aacttgagat
1861 gttggcaaga atgaaagtca cccactaccg gtttgctctg gattgggcct cggtccttcc
1921 cactggcaac ctgtccgcgg tgaaccgaca ggccctgagg tactacaggt gcgtggtcag
1981 tgaggggctg aagcttggca tctccgcgat ggtcaccctg tattatccga cccacgccca
2041 cctaggcctc cccgagcctc tgttgcatgc cgacgggtgg ctgaacccat cgacggccga
2101 ggccttccag gcctacgctg ggctgtgctt ccaggagctg ggggacctgg tgaagctctg
2161 gatcaccatc aacgagccta accggctaag tgacatctac aaccgctctg gcaacgacac
2221 ctacggggcg gcgcacaacc tgctggtggc ccacgccctg gcctggcgcc tctacgaccg
2281 gcagttcagg ccctcacagc gcggggccgt gtcgctgtcg ctgcacgcgg actgggcgga
2341 acccgccaac ccctatgctg actcgcactg gagggcggcc gagcgcttcc tgcagttcga
2401 gatcgcctgg ttcgccgagc cgctcttcaa gaccggggac taccccgcgg ccatgaggga
2461 atacattgcc tccaagcacc gacgggggct ttccagctcg gccctgccgc gcctcaccga
2521 ggccgaaagg aggctgctca agggcacggt cgacttctgc gcgctcaacc acttcaccac
2581 taggttcgtg atgcacgagc agctggccgg cagccgctac gactcggaca gggacatcca
2641 gtttctgcag gacatcaccc gcctgagctc ccccacgcgc ctggctgtga ttccctgggg
2701 ggtgcgcaag ctgctgcggt gggtccggag gaactacggc gacatggaca tttacatcac
2761 cgccagtggc atcgacgacc aggctctgga ggatgaccgg ctccggaagt actacctagg
```

```
2821 gaagtacctt caggaggtgc tgaaagcata cctgattgat aaagtcagaa tcaaaggcta
2881 ttatgcattc aaactggctg aagagaaatc taaacccaga tttggattct tcacatctga
2941 ttttaaagct aaatcctcaa tacaatttta caacaaagtg atcagcagca ggggcttccc
3001 ttttgagaac agtagttcta gatgcagtca gacccaagaa aatacagagt gcactgtctg
3061 cttattcctt gtgcagaaga aaccactgat attcctgggt tgttgcttct tctccaccct
3121 ggttctactc ttatcaattg ccatttttca aaggcagaag agaagaaagt tttggaaagc
3181 aaaaaactta caacacatac cattaaagaa aggcaagaga gttgttagct aaactgatct
3241 gtctgcatga tagacagttt aaaaattcat cccagttcc
```

beta-Klotho amino acid sequence (NP_783864) (SEQ ID NO: 4)

```
   1 mkpgcaagsp gnewiffstd eittryrntm sngglqrsvi lsalillrav tgfsgdgrai
  61 wsknpnftpv nesqlflydt fpknffwgig tgalqvegsw kkdgkgpsiw dhfihthlkn
 121 vsstngssds yiflekdlsa ldfigvsfyq fsiswprlfp dgivtvanak glqyystlld
 181 alvlrniepi vtlyhwdlpl alqekyggwk ndtiidifnd yatycfqmfg drvkywitih
 241 npylvawhgy gtgmhapgek gnlaavytvg hnlikahskv whnynthfrp hqkgwlsitl
 301 gshwiepnrs entmdifkcq qsmvsvlgwf anpihgdgdy pegmrkklfs vlpifseaek
 361 hemrgtadff afsfgpnnfk plntmakmgq nvslnlreal nwikleynnp riliaengwf
 421 tdsrvktedt taiymmknfl sqvlqairld eirvfgytaw slldgfewqd aytirrglfy
 481 vdfnskqker kpkssahyyk qiirengfsl kestpdvqgq fpcdfswgvt esvlkpesva
 541 sspqfsdphl yvwnatgnrl lhrvegvrlk trpaqctdfv nikkqlemla rmkvthyrfa
 601 ldwasvlptg nlsavnrqal ryyrcvvseg lklgisamvt lyypthahlg lpepllhadg
 661 wlnpstaeaf qayaglcfqe lgdlvklwit inepnrlsdi ynrsgndtyg aahnllvaha
 721 lawrlydrqf rpsqrgavsl slhadwaepa npyadshwra aerflqfeia wfaeplfktg
 781 dypaamreyi askhrrglss salprlteae rrllkgtvdf calnhfttrf vmheqlagsr
 841 ydsdrdiqfl qditrlsspt rlavipwgvr kllrwvrrny gdmdiyitas giddqaledd
 901 rlrkyylgky lqevlkayli dkvrikgyya fklaeekskp rfgfftsdfk akssiqfynk
 961 vissrgfpfe nsssrcsqtq entectvclf lvqkkplifl gccffstlvl llsiaifqrq
1021 krrkfwkakn lqhiplkkgk rvvs
```

Human Klotho domain 1 (KL-D1) amino acid sequence (SEQ ID NO: 5)

```
  58                                                            qgt
  61 fpdgflwavg saayqteggw qqhgkgasiw dtfthhplap pgdsrnaslp lgapsplqpa
 121 tgdvasdsyn nvfrdtealr elgvthyrfs iswarvlpng sagvpnregl ryyrrllerl
 181 relgvqpvvt lyhwdlpqrl qdayggwanr aladhfrdya elcfrhfggq vkywitidnp
 241 yvvawhgyat grlapgirgs prlgylvahn lllahakvwh lyntsfrptq ggqvsialss
 301 hwinprrmtd hsikecqksl dfvlgwfakp vfidgdypes mknnlssilp dftesekkfi
 361 kgtadffalc fgptlsfqll dphmkfrqle spnlrqllsw idlefnhpqi fivengwfvs
 421 gttkrddaky myylkkfime tlkaikldgv dvigytawsl mdgfewhrgy sirrglfyvd
 481 flsqdkmllp kssalfyqkl iekngf
```

Human Klotho domain 2 (KL-D2) amino acid sequence (SEQ ID NO: 6)

```
 517                                          gtfp cdfawgvvdn yiqvdttlsq
 541 ftdlnvylwd vhhskrlikv dgvvtkkrks ycvdfaaiqp qiallqemhv thfrfsldwa
 601 lilplgnqsq vnhtilqyyr cmaselvrvn itpvvalwqp mapnqglprl larqgawenp
 661 ytalafaeya rlcfqelghh vklwitmnep ytrnmtysag hnllkahala whvynekfrh
 721 aqngkisial qadwiepacp fsqkdkevae rvlefdigwl aepifgsgdy pwvmrdwlnq
 781 rnnfllpyft edekkliqgt fdflalshyt tilvdseked pikyndylev qemtditwln
 841 spsqvavvpw glrkvlnwlk fkygdlpmyi isngiddglh aeddqlrvyy mqnyinealk
 901 ahildginlc gyfaysfndr taprfglyry aadqfepkas mkhyrkiids ngf
```

Klotho extracellular domain (without signal peptide) amino acid sequence (SEQ ID NO: 7)

```
  28                                     epgdgaq twarfsrppa peaaglfqgt
  61 fpdgflwavg saayqteggw qqhgkgasiw dtfthhplap pgdsrnaslp lgapsplqpa
 121 tgdvasdsyn nvfrdtealr elgvthyrfs iswarvlpng sagvpnregl ryyrrllerl
```

```
181 relgvqpvvt lyhwdlpqrl qdayggwanr aladhfrdya elcfrhfggq vkywitidnp
241 yvvawhgyat grlapgirgs prlgylvahn lllahakvwh lyntsfrptq ggqvsialss
301 hwinprrmtd hsikecqksl dfvlgwfakp vfidgdypes mknnlssilp dftesekkfi
361 kgtadffalc fgptlsfqll dphmkfrqle spnlrqllsw idlefnhpqi fivengwfvs
421 gttkrddaky myylkkfime tlkaikldgv dvigytawsl mdgfewhrgy sirrglfyvd
481 flsqdkmllp kssalfyqkl ieknqfpplp enqplegtfp cdfawgvvdn yiqvdttlsq
541 ftdlnvylwd vhhskrlikv dgvvtkkrks ycvdfaaiqp qiallqemhv thfrfsldwa
601 lilplgnqsq vnhtilqyyr cmaselvrvn itpvvalwqp mapnqglprl larqgawenp
661 ytalafaeya rlcfqelghh vklwitmnep ytrnmtysag hnllkahala whvynekfrh
721 aqngkisial qadwiepacp fsqkdkevae rvlefdigwl aepifgsgdy pwvmrdwlnq
781 rnnfllpyft edekkliqgt fdflalshyt tilvdseked pikyndylev qemtditwln
841 spsqvavvpw glrkvlnwlk fkygdlpmyi isngiddglh aeddqlrvyy mqnyinealk
901 ahildginlc gyfaysfndr taprfglyry aadqfepkas mkhyrkiids ngfpgpetle
961 rfcpeeftvc tecsffhtrk sl
```

Klotho signal peptide amino acid sequence (SEQ ID NO: 8)

```
1 mpasapprrp rppppslsll lvllglggrr lra
```

IgG signal peptide amino acid sequence (SEQ ID NO: 9)

```
1 msvltqvlal lllwltgtrc rrlra
```

$(Gly_4\ Ser)_3$ polypeptide linker nucleic acid sequence (SEQ ID NO: 10)

```
1 ggaggtggag gttcaggagg tggaggttca ggaggtggag gttca
```

$(Gly_4\ Ser)_3$ polypeptide linker amino acid sequence (SEQ ID NO: 11)

```
1 GGGGSGGGGS GGGGS
```

$(Gly_4\ Ser)$ polypeptide linker amino acid sequence (SEQ ID NO: 12)

```
1 GGGGS
```

(Gly) polypeptide linker amino acid sequence (SEQ ID NO: 13)

```
1 G
```

(Gly Gly) polypeptide linker amino acid sequence (SEQ ID NO: 14)

```
1 GG
```

(Gly Ser) polypeptide linker amino acid sequence (SEQ ID NO: 15)

```
1 GS
```

$(Gly_2\ Ser)$ polypeptide linker amino acid sequence (SEQ ID NO: 16)

```
1 GGS
```

(Ala) polypeptide linker amino acid sequence (SEQ ID NO: 17)

1 A

(Ala Ala) polypeptide linker amino acid sequence (SEQ ID NO: 18)

1 AA

Klotho signal peptide-Klotho extracellular domain-FGF23 (R179Q) amino acid sequence (SEQ ID NO: 19)

```
   1 MPASAPPRRP RPPPPSLSLL LVLLGLGGRR LRAEPGDGAQ TWARFSRPPA
  51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
 101 PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
 151 ISWARVLPNG SAGVPNREGL RYYRRLLERL RELGVQPVVT LYHWDLPQRL
 201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
 251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
 301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP
 351 DFTESEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
 401 IDLEFNHPQI FIVENGWFVS GTTKRDDAKY MYYLKKFIME TLKAIKLDGV
 451 DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD FLSQDKMLLP KSSALFYQKL
 501 IEKNGFPPLP ENQPLEGTFP CDFAWGVVDN YIQVDTTLSQ FTDLNVYLWD
 551 VHHSKRLIKV DGVVTKKRKS YCVDFAAIQP QIALLQEMHV THFRFSLDWA
 601 LILPLGNQSQ VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL
 651 LARQGAWENP YTALAFAEYA RLCFQELGHH VKLWITMNEP YTRNMTYSAG
 701 HNLLKAHALA WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE
 751 RVLEFDIGWL AEPIFGSGDY PWVMRDWLNQ RNNFLLPYFT EDEKKLIQGT
 801 FDFLALSHYT TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW
 851 GLRKVLNWLK FKYGDLPMYI ISNGIDDGLH AEDDQLRVYY MQNYINEALK
 901 AHILDGINLC GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIIDS
 951 NGFPGPETLE RFCPEEFTVC TECSFFHTRK SLGSGGGGSG GGGSGGGGSL
1001 KYPNASPLLG SSWGGLIHLY TATARNSYHL QIHKNGHVDG APHQTIYSAL
1051 MIRSEDAGFV VITGVMSRRY LCMDFRGNIF GSHYFDPENC RFQHQTLENG
1101 YDVYHSPQYH FLVSLGRAKR AFLPGMNPPP YSQFLSRRNE IPLIHFNTPI
1151 PRRHTQSAED DSERDPLNVL KPRARMTPAP ASCSQELPSA EDNSPMASDP
1201 LGVVRGGRVN THAGGTGPEG CRPFAKFI*
```

IgG signal peptide-Klotho extracellular domain-FGF23 (R179Q) amino acid sequence (SEQ ID NO: 20)

```
   1 MSVLTQVLAL LLLWLTGLGG RRLRAEPGDG AQTWARFSRP PAPEAAGLFQ
  51 GTFPDGFLWA VGSAAYQTEG GWQQHGKGAS IWDTFTHHPL APPGDSRNAS
 101 LPLGAPSPLQ PATGDVASDS YNNVFRDTEA LRELGVTHYR FSISWARVLP
 151 NGSAGVPNRE GLRYYRRLLE RLRELGVQPV VTLYHWDLPQ RLQDAYGGWA
 201 NRALADHFRD YAELCFRHFG GQVKYWITID NPYVVAWHGY ATGRLAPGIR
 251 GSPRLGYLVA HNLLLAHAKV WHLYNTSFRP TQGGQVSIAL SSHWINPRRM
 301 TDHSIKECQK SLDFVLGWFA KPVFIDGDYP ESMKNNLSSI LPDFTESEKK
 351 FIKGTADFFA LCFGPTLSFQ LLDPHMKFRQ LESPNLRQLL SWIDLEFNHP
 401 QIFIVENGWF VSGTTKRDDA KYMYYLKKFI METLKAIKLD GVDVIGYTAW
 451 SLMDGFEWHR GYSIRRGLFY VDFLSQDKML LPKSSALFYQ KLIEKNGFPP
 501 LPENQPLEGT FPCDFAWGVV DNYIQVDTTL SQFTDLNVYL WDVHHSKRLI
 551 KVDGVVTKKR KSYCVDFAAI QPQIALLQEM HVTHFRFSLD WALILPLGNQ
 601 SQVNHTILQY YRCMASELVR VNITPVVALW QPMAPNQGLP RLLARQGAWE
 651 NPYTALAFAE YARLCFQELG HHVKLWITMN EPYTRNMTYS AGHNLLKAHA
 701 LAWHVYNEKF RHAQNGKISI ALQADWIEPA CPFSQKDKEV AERVLEFDIG
 751 WLAEPIFGSG DYPWVMRDWL NQRNNFLLPY FTEDEKKLIQ GTFDFLALSH
 801 YTTILVDSEK EDPIKYNDYL EVQEMTDITW LNSPSQVAVV PWGLRKVLNW
 851 LKFKYGDLPM YIISNGIDDG LHAEDDQLRV YYMQNYINEA LKAHILDGIN
 901 LCGYFAYSFN DRTAPRFGLY RYAADQFEPK ASMKHYRKII DSNGFPGPET
 951 LERFCPEEFT VCTECSFFHT RKSLGSGGGG SGGGGSGGGG SLKYPNASPL
```

```
1001 LGSSWGGLIH LYTATARNSY HLQIHKNGHV DGAPHQTIYS ALMIRSEDAG
1051 FVVITGVMSR RYLCMDFRGN IFGSHYFDPE NCRFQHQTLE NGYDVYHSPQ
1101 YHFLVSLGRA KRAFLPGMNP PPYSQFLSRR NEIPLIHFNT PIPRRHTQSA
1151 EDDSERDPLN VLKPRARMTP APASCSQELP SAEDNSPMAS DPLGVVRGGR
1201 VNTHAGGTGP EGCRPFAKFI *
```

KL-D1-FGF23 (R179Q) amino acid sequence (SEQ ID NO: 21)

```
   1 MPASAPPRRP RPPPPSLSLL LVLLGLGGRR LRAEPGDGAQ TWARFSRPPA
  51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
 101 PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
 151 ISWARVLPNG SAGVPNREGL RYYRRLLERL RELGVQPVVT LYHWDLPQRL
 201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
 251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
 301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP
 351 DFTESEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
 401 IDLEFNHPQI FIVENGWFVS GTTKRDDAKY MYYLKKFIME TLKAIKLDGV
 451 DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD FLSQDKMLLP KSSALFYQKL
 501 IEKNGFPPLP ENQPLEGSGG GGSGGGGSGG GGSLKYPNAS PLLGSSWGGL
 551 IHLYTATARN SYHLQIHKNG HVDGAPHQTI YSALMIRSED AGFVVITGVM
 601 SRRYLCMDFR GNIFGSHYFD PENCRFQHQT LENGYDVYHS PQYHFLVSLG
 651 RAKRAFLPGM NPPPYSQFLS RRNEIPLIHF NTPIPRRHTQ SAEDDSERDP
 701 LNVLKPRARM TPAPASCSQE LPSAEDNSPM ASDPLGVVRG GRVNTHAGGT
 751 GPEGCRPFAK FI*
```

KL-D2-FGF23 (R179Q) amino acid sequence (SEQ ID NO: 22)

```
   1 MPASAPPRRP RPPPPSLSLL LVLLGLGGRR LPLPENQPLE GTFPCDFAWG
  51 VVDNYIQVDT TLSQFTDLNV YLWDVHHSKR LIKVDGVVTK KRKSYCVDFA
 101 AIQPQIALLQ EMHVTHFRFS LDWALILPLG NQSQVNHTIL QYYRCMASEL
 151 VRVNITPVVA LWQPMAPNQG LPRLLARQGA WENPYTALAF AEYARLCFQE
 201 LGHHVKLWIT MNEPYTRNMT YSAGHNLLKA HALAWHVYNE KFRHAQNGKI
 251 SIALQADWIE PACPFSQKDK EVAERVLEFD IGWLAEPIFG SGDYPWVMRD
 301 WLNQRNNFLL PYFTEDEKKL IQGTFDFLAL SHYTTILVDS EKEDPIKYND
 351 YLEVQEMTDI TWLNSPSQVA VVPWGLRKVL NWLKFKYGDL PMYIISNGID
 401 DGLHAEDDQL RVYYMQNYIN EALKAHILDG INLCGYFAYS FNDRTAPRFG
 451 LYRYAADQFE PKASMKHYRK IIDSNGFPGP ETLERFCPEE FTVCTECSFF
 501 HTRKSLGSGG GGSGGGGSGG GGSLKYPNAS PLLGSSWGGL IHLYTATARN
 551 SYHLQIHKNG HVDGAPHQTI YSALMIRSED AGFVVITGVM SRRYLCMDFR
 601 GNIFGSHYFD PENCRFQHQT LENGYDVYHS PQYHFLVSLG RAKRAFLPGM
 651 NPPPYSQFLS RRNEIPLIHF NTPIPRRHTQ SAEDDSERDP LNVLKPRARM
 701 TPAPASCSQE LPSAEDNSPM ASDPLGVVRG GRVNTHAGGT GPEGCRPFAK
 751 FI*
```

$(KL\text{-}D1)_2$-FGF23 (R179Q) amino acid sequence (SEQ ID NO: 23)

```
   1 MPASAPPRRP RPPPPSLSLL LVLLGLGGRR LRAEPGDGAQ TWARFSRPPA
  51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
 101 PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
 151 ISWARVLPNG SAGVPNREGL RYYRRLLERL RELGVQPVVT LYHWDLPQRL
 201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
 251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
 301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP
 351 DFTESEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
 401 IDLEFNHPQI FIVENGWFVS GTTKRDDAKY MYYLKKFIME TLKAIKLDGV
 451 DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD FLSQDKMLLP KSSALFYQKL
 501 IEKNGFPPLP ENQPLEGSGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW
 551 DTFTHHPLAP PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR
 601 ELGVTHYRFS ISWARVLPNG SAGVPNREGL RYYRRLLERL RELGVQPVVT
 651 LYHWDLPQRL QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP
```

```
 701 YVVAWHGYAT GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ
 751 GGQVSIALSS HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES
 801 MKNNLSSILP DFTESEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE
 851 SPNLRQLLSW IDLEFNHPQI FIVENGWFVS GTTKRDDAKY MYYLKKFIME
 901 TLKAIKLDGV DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD FLSQDKMLLP
 951 KSSALFYQKL IEKNGFPEFG SGGGGSGGGG SGGGGSLKYP NASPLLGSSW
1001 GGLIHLYTAT ARNSYHLQIH KNGHVDGAPH QTIYSALMIR SEDAGFVVIT
1051 GVMSRRYLCM DFRGNIFGSH YFDPENCRFQ HQTLENGYDV YHSPQYHFLV
1101 SLGRAKRAFL PGMNPPPYSQ FLSRRNEIPL IHFNTPIPRR HTQSAEDDSE
1151 RDPLNVLKPR ARMTPAPASC SQELPSAEDN SPMASDPLGV VRGGRVNTHA
1201 GGTGPEGCRP FAKFI*
```

$(KL\text{-}D2)_2$-FGF23 (R179Q) amino acid sequence (SEQ ID NO: 24)

```
   1 MPASAPPRRP RPPPPSLSLL LVLLGLGGRR LPLPENQPLE GTFPCDFAWG
  51 VVDNYIQVDT TLSQFTDLNV YLWDVHHSKR LIKVDGVVTK KRKSYCVDFA
 101 AIQPQIALLQ EMHVTHFRFS LDWALILPLG NQSQVNHTIL QYYRCMASEL
 151 VRVNITPVVA LWQPMAPNQG LPRLLARQGA WENPYTALAF AEYARLCFQE
 201 LGHHVKLWIT MNEPYTRNMT YSAGHNLLKA HALAWHVYNE KFRHAQNGKI
 251 SIALQADWIE PACPFSQKDK EVAERVLEFD IGWLAEPIFG SGDYPWVMRD
 301 WLNQRNNFLL PYFTEDEKKL IQGTFDFLAL SHYTTILVDS EKEDPIKYND
 351 YLEVQEMTDI TWLNSPSQVA VVPWGLRKVL NWLKFKYGDL PMYIISNGID
 401 DGLHAEDDQL RVYYMQNYIN EALKAHILDG INLCGYFAYS FNDRTAPRFG
 451 LYRYAADQFE PKASMKHYRK IIDSNGFPGP ETLERFCPEE FTVCTECSFF
 501 HTRKSLGTFP CDFAWGVVDN YIQVDTTLSQ FTDLNVYLWD VHHSKRLIKV
 551 DGVVTKKRKS YCVDFAAIQP QIALLQEMHV THFRFSLDWA LILPLGNQSQ
 601 VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL LARQGAWENP
 651 YTALAFAEYA RLCFQELGHH VKLWITMNEP YTRNMTYSAG HNLLKAHALA
 701 WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE RVLEFDIGWL
 751 AEPIFGSGDY PWVMRDWLNQ RNNFLLPYFT EDEKKLIQGT FDFLALSHYT
 801 TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW GLRKVLNWLK
 851 FKYGDLPMYI ISNGIDDGLH AEDDQLRVYY MQNYINEALK AHILDGINLC
 901 GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIIDS NGFGSGGGGS
 951 GGGGSGGGGS LKYPNASPLL GSSWGGLIHL YTATARNSYH LQIHKNGHVD
1001 GAPHQTIYSA LMIRSEDAGF VVITGVMSRR YLCMDFRGNI FGSHYFDPEN
1051 CRFQHQTLEN GYDVYHSPQY HFLVSLGRAK RAFLPGMNPP PYSQFLSRRN
1101 EIPLIHFNTP IPRRHTQSAE DDSERDPLNV LKPRARMTPA PASCSQELPS
1151 AEDNSPMASD PLGVVRGGRV NTHAGGTGPE GCRPFAKFI*
```

FGF23 (R179Q) -Klotho extracellular domain amino acid sequence (SEQ ID NO: 25)

```
   1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNS
  51 YHLQIHKNGH VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
 101 NIFGSHYFDP ENCRFQHQTL ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN
 151 PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
 201 PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGCRPFAKF
 251 IGSGGGGSGG GGSGGGGSLK EPGDGAQTWA RFSRPPAPEA AGLFQGTFPD
 301 GFLWAVGSAA YQTEGGWQQH GKGASIWDTF THHPLAPPGD SRNASLPLGA
 351 PSPLQPATGD VASDSYNNVF RDTEALRELG VTHYRFSISW ARVLPNGSAG
 401 VPNREGLRYY RRLLERLREL GVQPVVTLYH WDLPQRLQDA YGGWANRALA
 451 DHFRDYAELC FRHFGGQVKY WITIDNPYVV AWHGYATGRL APGIRGSPRL
 501 GYLVAHNLLL AHAKVWHLYN TSFRPTQGGQ VSIALSSHWI NPRRMTDHSI
 551 KECQKSLDFV LGWFAKPVFI DGDYPESMKN NLSSILPDFT ESEKKFIKGT
 601 ADFFALCFGP TLSFQLLDPH MKFRQLESPN LRQLLSWIDL EFNHPQIFIV
 651 ENGWFVSGTT KRDDAKYMYY LKKFIMETLK AIKLDGVDVI GYTAWSLMDG
 701 FEWHRGYSIR RGLFYVDFLS QDKMLLPKSS ALFYQKLIEK NGFPPLPENQ
 751 PLEGTFPCDF AWGVVDNYIQ VDTTLSQFTD LNVYLWDVHH SKRLIKVDGV
 801 VTKKRKSYCV DFAAIQPQIA LLQEMHVTHF RFSLDWALIL PLGNQSQVNH
 851 TILQYYRCMA SELVRVNITP VVALWQPMAP NQGLPRLLAR QGAWENPYTA
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```
 901 LAFAEYARLC FQELGHHVKL WITMNEPYTR NMTYSAGHNL LKAHALAWHV
 951 YNEKFRHAQN GKISIALQAD WIEPACPFSQ KDKEVAERVL EFDIGWLAEP
1001 IFGSGDYPWV MRDWLNQRNN FLLPYFTEDE KKLIQGTFDF LALSHYTTIL
1051 VDSEKEDPIK YNDYLEVQEM TDITWLNSPS QVAVVPWGLR KVLNWLKFKY
1101 GDLPMYIISN GIDDGLHAED DQLRVYYMQN YINEALKAHI LDGINLCGYF
1151 AYSFNDRTAP RFGLYRYAAD QFEPKASMKH YRKIIDSNGF PGPETLERFC
1201 PEEFTVCTEC SFFHTRKSL*
```

FGF23 (R179Q) -KL-D1 amino acid sequence (SEQ ID NO: 26)

```
   1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNS
  51 YHLQIHKNGH VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
 101 NIFGSHYFDP ENCRFQHQTL ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN
 151 PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
 201 PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGCRPFAKF
 251 IQGTFPDGFL WAVGSAAYQT EGGWQQHGKG ASIWDTFTHH PLAPPGDSRN
 301 ASLPLGAPSP LQPATGDVAS DSYNNVFRDT EALRELGVTH YRFSISWARV
 351 LPNGSAGVPN REGLRYYRRL LERLRELGVQ PVVTLYHWDL PQRLQDAYGG
 401 WANRALADHF RDYAELCFRH FGGQVKYWIT IDNPYVVAWH GYATGRLAPG
 451 IRGSPRLGYL VAHNLLLAHA KVWHLYNTSF RPTQGGQVSI ALSSHWINPR
 501 RMTDHSIKEC QKSLDFVLGW FAKPVFIDGD YPESMKNNLS SILPDFTESE
 551 KKFIKGTADF FALCFGPTLS FQLLDPHMKF RQLESPNLRQ LLSWIDLEFN
 601 HPQIFIVENG WFVSGTTKRD DAKYMYYLKK FIMETLKAIK LDGVDVIGYT
 651 AWSLMDGFEW HRGYSIRRGL FYVDFLSQDK MLLPKSSALF YQKLIEKNGF
 652 *
```

FGF23 (R179Q) -KL-D2 amino acid sequence (SEQ ID NO: 27)

```
   1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNS
  51 YHLQIHKNGH VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
 101 NIFGSHYFDP ENCRFQHQTL ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN
 151 PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
 201 PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGCRPFAKF
 251 IGTFPCDFAW GVVDNYIQVD TTLSQFTDLN VYLWDVHHSK RLIKVDGVVT
 301 KKRKSYCVDF AAIQPQIALL QEMHVTHFRF SLDWALILPL GNQSQVNHTI
 351 LQYYRCMASE LVRVNITPVV ALWQPMAPNQ GLPRLLARQG AWENPYTALA
 401 FAEYARLCFQ ELGHHVKLWI TMNEPYTRNM TYSAGHNLLK AHALAWHVYN
 451 EKFRHAQNGK ISIALQADWI EPACPFSQKD KEVAERVLEF DIGWLAEPIF
 501 GSGDYPWVMR DWLNQRNNFL LPYFTEDEKK LIQGTFDFLA LSHYTTILVD
 551 SEKEDPIKYN DYLEVQEMTD ITWLNSPSQV AVVPWGLRKV LNWLKFKYGD
 601 LPMYIISNGI DDGLHAEDDQ LRVYYMQNYI NEALKAHILD GINLCGYFAY
 651 SFNDRTAPRF GLYRYAADQF EPKASMKHYR KIIDSNGF*
```

FGF23 (R179Q) -$(KL\text{-}D1)_2$ amino acid sequence (SEQ ID NO: 28)

```
   1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNS
  51 YHLQIHKNGH VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
 101 NIFGSHYFDP ENCRFQHQTL ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN
 151 PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
 201 PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGCRPFAKF
 251 IQGTFPDGFL WAVGSAAYQT EGGWQQHGKG ASIWDTFTHH PLAPPGDSRN
 301 ASLPLGAPSP LQPATGDVAS DSYNNVFRDT EALRELGVTH YRFSISWARV
 351 LPNGSAGVPN REGLRYYRRL LERLRELGVQ PVVTLYHWDL PQRLQDAYGG
 401 WANRALADHF RDYAELCFRH FGGQVKYWIT IDNPYVVAWH GYATGRLAPG
 451 IRGSPRLGYL VAHNLLLAHA KVWHLYNTSF RPTQGGQVSI ALSSHWINPR
 501 RMTDHSIKEC QKSLDFVLGW FAKPVFIDGD YPESMKNNLS SILPDFTESE
 551 KKFIKGTADF FALCFGPTLS FQLLDPHMKF RQLESPNLRQ LLSWIDLEFN
 601 HPQIFIVENG WFVSGTTKRD DAKYMYYLKK FIMETLKAIK LDGVDVIGYT
 651 AWSLMDGFEW HRGYSIRRGL FYVDFLSQDK MLLPKSSALF YQKLIEKNGF
 701 QGTFPDGFLW AVGSAAYQTE GGWQQHGKGA SIWDTFTHHP LAPPGDSRNA
```

```
 751 SLPLGAPSPL QPATGDVASD SYNNVFRDTE ALRELGVTHY RFSISWARVL
 801 PNGSAGVPNR EGLRYYRRLL ERLRELGVQP VVTLYHWDLP QRLQDAYGGW
 851 ANRALADHFR DYAELCFRHF GGQVKYWITI DNPYVVAWHG YATGRLAPGI
 901 RGSPRLGYLV AHNLLLAHAK VWHLYNTSFR PTQGGQVSIA LSSHWINPRR
 951 MTDHSIKECQ KSLDFVLGWF AKPVFIDGDY PESMKNNLSS ILPDFTESEK
1001 KFIKGTADFF ALCFGPTLSF QLLDPHMKFR QLESPNLRQL LSWIDLEFNH
1051 PQIFIVENGW FVSGTTKRDD AKYMYYLKKF IMETLKAIKL DGVDVIGYTA
1101 WSLMDGFEWH RGYSIRRGLF YVDFLSQDKM LLPKSSALFY QKLIEKNGF*
```

FGF23 (R179Q) -(KL-D2)$_2$ amino acid sequence (SEQ ID NO: 29)

```
   1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNS
  51 YHLQIHKNGH VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
 101 NIFGSHYFDP ENCRFQHQTL ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN
 151 PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
 201 PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGCRPFAKF
 251 IGTFPCDFAW GVVDNYIQVD TTLSQFTDLN VYLWDVHHSK RLIKVDGVVT
 301 KKRKSYCVDF AAIQPQIALL QEMHVTHFRF SLDWALILPL GNQSQVNHTI
 351 LQYYRCMASE LVRVNITPVV ALWQPMAPNQ GLPRLLARQG AWENPYTALA
 401 FAEYARLCFQ ELGHHVKLWI TMNEPYTRNM TYSAGHNLLK AHALAWHVYN
 451 EKFRHAQNGK ISIALQADWI EPACPFSQKD KEVAERVLEF DIGWLAEPIF
 501 GSGDYPWVMR DWLNQRNNFL LPYFTEDEKK LIQGTFDFLA LSHYTTILVD
 551 SEKEDPIKYN DYLEVQEMTD ITWLNSPSQV AVVPWGLRKV LNWLKFKYGD
 601 LPMYIISNGI DDGLHAEDDQ LRVYYMQNYI NEALKAHILD GINLCGYFAY
 651 SFNDRTAPRF GLYRYAADQF EPKASMKHYR KIIDSNGFGT FPCDFAWGVV
 701 DNYIQVDTTL SQFTDLNVYL WDVHHSKRLI KVDGVVTKKR KSYCVDFAAI
 751 QPQIALLQEM HVTHFRFSLD WALILPLGNQ SQVNHTILQY YRCMASELVR
 801 VNITPVVALW QPMAPNQGLP RLLARQGAWE NPYTALAFAE YARLCFQELG
 851 HHVKLWITMN EPYTRNMTYS AGHNLLKAHA LAWHVYNEKF RHAQNGKISI
 901 ALQADWIEPA CPFSQKDKEV AERVLEFDIG WLAEPIFGSG DYPWVMRDWL
 951 NQRNNFLLPY FTEDEKKLIQ GTFDFLALSH YTTILVDSEK EDPIKYNDYL
1001 EVQEMTDITW LNSPSQVAVV PWGLRKVLNW LKFKYGDLPM YIISNGIDDG
1051 LHAEDDQLRV YYMQNYINEA LKAHILDGIN LCGYFAYSFN DRTAPRFGLY
1101 RYAADQFEPK ASMKHYRKII DSNGF*
```

FGF19 nucleic acid sequence (NM_005117) (SEQ ID NO: 30)
Protein coding region (464-1114)

```
   1 gctcccagcc aagaacctcg gggccgctgc gcggtgggga ggagttcccc gaaacccggc
  61 cgctaagcga ggcctcctcc tcccgcagat ccgaacggcc tgggcggggt caccccggct
 121 gggacaagaa gccgccgcct gcctgcccgg gcccggggag ggggctgggg ctggggccgg
 181 aggcggggtg tgagtgggtg tgtgcggggg gcggaggctt gatgcaatcc cgataagaaa
 241 tgctcgggtg tcttgggcac ctacccgtgg ggcccgtaag gcgctactat ataaggctgc
 301 cggcccggag ccgccgcgcc gtcagagcag gagcgctgcg tccaggatct agggccacga
 361 ccatcccaac ccggcactca cagccccgca gcgcatcccg gtcgccgccc agcctcccgc
 421 acccccatcg ccggagctgc gccgagagcc ccagggaggt gccatgcgga gcgggtgtgt
 481 ggtggtccac gtatggatcc tggccggcct ctggctggcc gtggccgggc gccccctcgc
 541 cttctcggac gcggggcccc acgtgcacta cggctggggc gaccccatcc gcctgcggca
 601 cctgtacacc tccggccccc acgggctctc cagctgcttc ctgcgcatcc gtgccgacgg
 661 cgtcgtggac tgcgcgcggg gccagagcgc gcacagtttg ctggagatca aggcagtcgc
 721 tctgcggacc gtggccatca agggcgtgca cagcgtgcgg tacctctgca tgggcgccga
 781 cggcaagatg caggggctgc ttcagtactc ggaggaagac tgtgctttcg aggaggagat
 841 ccgcccagat ggctacaatg tgtaccgatc cgagaagcac cgcctcccgg tctccctgag
 901 cagtgccaaa cagcggcagc tgtacaagaa cagaggcttt cttccactct ctcatttcct
 961 gcccatgctg cccatggtcc cagaggagcc tgaggacctc aggggccact tggaatctga
1021 catgttctct tcgcccctgg agaccgacag catggaccca tttgggcttg tcaccggact
1081 ggaggccgtg aggagtccca gctttgagaa gtaactgaga ccatgcccgg gcctcttcac
1141 tgctgccagg ggctgtggta cctgcagcgt gggggacgtg cttctacaag aacagtcctg
1201 agtccacgtt ctgtttagct ttaggaagaa acatctagaa gttgtacata ttcagagttt
1261 tccattggca gtgccagttt ctagccaata gacttgtctg atcataacat tgtaagcctg
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1321 tagcttgccc agctgctgcc tgggccccca ttctgctccc tcgaggttgc tggacaagct
1381 gctgcactgt ctcagttctg cttgaatacc tccatcgatg gggaactcac ttcctttgga
1441 aaaattctta tgtcaagctg aaattctcta atttttttctc atcacttccc caggagcagc
1501 cagaagacag gcagtagttt taatttcagg aacaggtgat ccactctgta aaacagcagg
1561 taaatttcac tcaaccccat gtgggaattg atctatatct ctacttccag ggaccatttg
1621 cccttcccaa atccctccag gccagaactg actggagcag gcatggccca ccaggcttca
1681 ggagtagggg aagcctggag ccccactcca gccctgggac aacttgagaa ttccccctga
1741 ggccagttct gtcatggatg ctgtcctgag aataacttgc tgtcccggtg tcacctgctt
1801 ccatctccca gcccaccagc cctctgccca cctcacatgc ctccccatgg attggggcct
1861 cccaggcccc ccaccttatg tcaacctgca cttcttgttc aaaaatcagg aaaagaaaag
1921 atttgaagac cccaagtctt gtcaataact tgctgtgtgg aagcagcggg ggaagaccta
1981 gaacccttc cccagcactt ggttttccaa catgatattt atgagtaatt tattttgata
2041 tgtacatctc ttatttttctt acattattta tgcccccaaa ttatatttat gtatgtaagt
2101 gaggtttgtt ttgtatatta aaatggagtt tgtttgtaaa aaaaaaaaaa aaaaaaa
```

FGF19 amino acid sequence (NP_005108) (SEQ ID NO: 31)

```
  1 MRSGCVVVHV WILAGLWLAV AGRPLAFSDA GPHVHYGWGD PIRLRHLYTS GPHGLSSCFL
 61 RIRADGVVDC ARGQSAHSLL EIKAVALRTV AIKGVHSVRY LCMGADGKMQ GLLQYSEEDC
121 AFEEEIRPDG YNVYRSEKHR LPVSLSSAKQ RQLYKNRGFL PLSHFLPMLP MVPEEPEDLR
181 GHLESDMFSS PLETDSMDPF GLVTGLEAVR SPSFEK
```

FGF21 nucleic acid sequence (NM_019113) (SEQ ID NO: 32)
Protein coding region 151-780

```
  1 CTGTCAGCTG AGGATCCAGC CGAAAGAGGA GCCAGGCACT CAGGCCACCT GAGTCTACTC
 61 ACCTGGACAA CTGGAATCTG GCACCAATTC TAAACCACTC AGCTTCTCCG AGCTCACACC
121 CCGGAGATCA CCTGAGGACC CGAGCCATTG ATGGACTCGG ACGAGACCGG GTTCGAGCAC
181 TCAGGACTGT GGGTTTCTGT GCTGGCTGGT CTTCTGCTGG GAGCCTGCCA GGCACACCCC
241 ATCCCTGACT CCAGTCCTCT CCTGCAATTC GGGGGCCAAG TCCGGCAGCG GTACCTCTAC
301 ACAGATGATG CCCAGCAGAC AGAAGCCCAC CTGGAGATCA GGGAGGATGG GACGGTGGGG
361 GGCGCTGCTG ACCAGAGCCC CGAAAGTCTC CTGCAGCTGA AAGCCTTGAA GCCGGGAGTT
421 ATTCAAATCT TGGGAGTCAA GACATCCAGG TTCCTGTGCC AGCGGCCAGA TGGGGCCCTG
481 TATGGATCGC TCCACTTTGA CCCTGAGGCC TGCAGCTTCC GGGAGCTGCT TCTTGAGGAC
541 GGATACAATG TTTACCAGTC CGAAGCCCAC GGCCTCCCGC TGCACCTGCC AGGGAACAAG
601 TCCCCACACC GGGACCCTGC ACCCCGAGGA CCAGCTCGCT TCCTGCCACT ACCAGGCCTG
661 CCCCCCGCAC TCCCGGAGCC ACCCGGAATC CTGGCCCCCC AGCCCCCCGA TGTGGGCTCC
721 TCGGACCCTC TGAGCATGGT GGGACCTTCC CAGGGCCGAA GCCCCAGCTA CGCTTCCTGA
781 AGCCAGAGGC TGTTTACTAT GACATCTCCT CTTTATTTAT TAGGTTATTT ATCTTATTTA
841 TTTTTTTATT TTTCTTACTT GAGATAATAA AGAGTTCCAG AGGAGAAAAA AAAAAAAAAA
901 AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA
```

FGF21 amino acid sequence (NP_061986) (SEQ ID NO: 33)

```
  1 MDSDETGFEH SGLWVSVLAG LLLGACQAHP IPDSSPLLQF GGQVRQRYLY TDDAQQTEAH
 61 LEIREDGTVG GAADQSPESL LQLKALKPGV IQILGVKTSR FLCQRPDGAL YGSLHFDPEA
121 CSFRELLLED GYNVYQSEAH GLPLHLPGNK SPHRDPAPRG PARFLPLPGL PPALPEPPGI
181 LAPQPPDVGS SDPLSMVGPS QGRSPSYAS
```

FGF23 nucleic acid sequence (NM_020638) (SEQ ID NO: 34)
Protein coding region 147-902

```
  1 cggcaaaaag gagggaatcc agtctaggat cctcacacca gctacttgca agggagaagg
 61 aaaaggccag taaggcctgg gccaggagag tcccgacagg agtgtcaggt ttcaatctca
121 gcaccagcca ctcagagcag ggcacgatgt tgggggcccg cctcaggctc tgggtctgtg
181 ccttgtgcag cgtctgcagc atgagcgtcc tcagagccta tcccaatgcc tccccactgc
241 tcggctccag ctggggtggc ctgatccacc tgtacacagc cacagccagg aacagctacc
301 acctgcagat ccacaagaat ggccatgtgg atggcgcacc ccatcagacc atctacagtg
361 ccctgatgat cagatcagag gatgctggct ttgtggtgat tacaggtgtg atgagcagaa
```

```
 421 gatacctctg catggatttc agaggcaaca tttttggatc acactatttc gacccggaga
 481 actgcaggtt ccaacaccag acgctggaaa acgggtacga cgtctaccac tctcctcagt
 541 atcacttcct ggtcagtctg ggccgggcga agagagcctt cctgccaggc atgaacccac
 601 ccccgtactc ccagttcctg tcccggagga acgagatccc cctaattcac ttcaacaccc
 661 ccataccacg gcggcacacc cggagcgccg aggacgactc ggagcgggac cccctgaacg
 721 tgctgaagcc ccgggcccgg atgaccccgg ccccggcctc ctgttcacag gagctcccga
 781 gcgccgagga caacagcccg atggccagtg acccattagg ggtggtcagg ggcggtcgag
 841 tgaacacgca cgctgggggа acgggcccgg aaggctgccg ccccttcgcc aagttcatct
 901 agggtcgctg gaagggcacc ctctttaacc catccctcag caaacgcagc tcttcccaag
 961 gaccaggtcc cttgacgttc cgaggatggg aaaggtgaca ggggcatgta tggaatttgc
1021 tgcttctctg gggtcccttc cacaggaggt cctgtgagaa ccaacctttg aggcccaagt
1081 catggggttt caccgccttc ctcactccat atagaacacc tttcccaata ggaaacccca
1141 acaggtaaac tagaaatttc cccttcatga aggtagagag aaggggtctc tcccaacata
1201 tttctcttcc ttgtgcctct cctctttatc acttttaagc ataaaaaaaa aaaaaaaaaa
1261 aaaaaaaaaa aaaagcagtg ggttcctgag ctcaagactt tgaaggtgta gggaagagga
1321 aatcggagat cccagaagct tctccactgc cctatgcatt tatgttagat gccccgatcc
1381 cactggcatt tgagtgtgca aaccttgaca ttaacagctg aatggggcaa gttgatgaaa
1441 acactacttt caagccttcg ttcttccttg agcatctctg gggaagagct gtcaaaagac
1501 tggtggtagg ctggtgaaaa cttgacagct agacttgatg cttgctgaaa tgaggcagga
1561 atcataatag aaaactcagc ctccctacag ggtgagcacc ttctgtctcg ctgtctccct
1621 ctgtgcagcc acagccagag ggcccagaat ggccccactc tgttcccaag cagttcatga
1681 tacagcctca ccttttggcc ccatctctgg tttttgaaaa tttggtctaa ggaataaata
1741 gcttttacac tggctcacga aaatctgccc tgctagaatt tgcttttcaa aatggaaata
1801 aattccaact ctcctaagag gcatttaatt aaggctctac ttccaggttg agtaggaatc
1861 cattctgaac aaactacaaa aatgtgactg ggaaaggggc tttgagagac tgggactgct
1921 ctgggttagg ttttctgtgg actgaaaaat cgtgtccttt tctctaaatg aagtggcatc
1981 aaggactcag ggggaaagaa atcaggggac atgttataga agttatgaaa agacaaccac
2041 atggtcaggc tcttgtctgt ggtctctagg gctctgcagc agcagtggct cttcgattag
2101 ttaaaactct cctaggctga cacatctggg tctcaatccc cttggaaatt cttggtgcat
2161 taaatgaagc cttaccccat tactgcggtt cttcctgtaa gggggctcca ttttcctccc
2221 tctctttaaa tgaccaccta aaggacagta tattaacaag caaagtcgat tcaacaacag
2281 cttcttccca gtcacttttt tttttctcac tgccatcaca tactaacctt atactttgat
2341 ctattctttt tggttatgag agaaatgttg ggcaactgtt tttacctgat ggttttaagc
2401 tgaacttgaa ggactggttc ctattctgaa acagtaaaac tatgtataat agtatatagc
2461 catgcatggc aaatatttta atatttctgt tttcatttcc tgttggaaat attatcctgc
2521 ataatagcta ttggaggctc ctcagtgaaa gatcccaaaa ggattttggt ggaaaactag
2581 ttgtaatctc acaaactcaa cactaccatc aggggttttc tttatggcaa agccaaaata
2641 gctcctacaa tttcttatat ccctcgtcat gtggcagtat ttatttattt atttggaagt
2701 ttgcctatcc ttctatattt atagatattt ataaaaatgt aacccctttt tcctttcttc
2761 tgtttaaaat aaaaataaaa tttatctcag cttctgttag cttatcctct ttgtagtact
2821 acttaaaagc atgtcggaat ataagaataa aaaggattat gggaggggaa cattagggaa
2881 atccagagaa ggcaaaattg aaaaaaagat tttagaattt taaaattttc aaagatttct
2941 tccattcata aggagactca atgattttaa ttgatctaga cagaattatt taagttttat
3001 caatattgga tttctggt
```

FGF23 amino acid sequence (NP_065689) (SEQ ID NO: 35)

```
  1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNS YHLQIHKNGH
 61 VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG NIFGSHYFDP ENCRFQHQTL
121 ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN PPPYSQFLSR RNEIPLIHFN TPIPRRHTRS
181 AEDDSERDPL NVLKPRARMT PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG
241 PEGCRPFAKF I
```

FGF23 (R179Q) amino acid sequence (SEQ ID NO: 36)

```
  1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNS YHLQIHKNGH
 61 VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG NIFGSHYFDP ENCRFQHQTL
121 ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS
181 AEDDSERDPL NVLKPRARMT PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG
241 PEGCRPFAKF I
```

Human beta-Klotho domain 1 (b-KL-D1) amino acid sequence (SEQ ID NO: 37)

```
 77                    ydt fpknffwgig tgalqvegsw kkdgkgpsiw dhfihthlkn
121 vsstngssds yiflekdlsa ldfigvsfyq fsiswprlfp dgivtvanak glqyystlld
181 alvlrniepi vtlyhwdlpl alqekyggwk ndtiidifnd yatycfqmfg drvkywitih
241 npylvawhgy gtgmhapgek gnlaavytvg hnlikahskv whnynthfrp hqkgwlsitl
301 gshwiepnrs entmdifkcq qsmvsvlgwf anpihgdgdy pegmrkklfs vlpifseaek
361 hemrgtadff afsfgpnnfk plntmakmgq nvslnlreal nwikleynnp riliaengwf
421 tdsrvktedt taiymmknfl sqvlqairld eirvfgytaw slldgfewqd aytirrglfy
481 vdfnskqker kpkssahyyk qiirengf
```

Human beta-Klotho domain 2 (b-KL-D2) amino acid sequence (SEQ ID NO: 38)

```
571                                   trpaqctdfv nikkqlemla
rmkvthyrfa
601 ldwasvlptg nlsavnrqal ryyrcvvseg lklgisamvt lyypthahlg
lpepllhadg
661 wlnpstaeaf qayaglcfqe lgdlvklwit inepnrlsdi ynrsgndtyg
aahnllvaha
721 lawrlydrqf rpsqrgavsl slhadwaepa npyadshwra aerflqfeia
wfaeplfktg
781 dypaamreyi askhrrglss salprlteae rrllkgtvdf calnhfttrf
vmheqlagsr
841 ydsdrdiqfl qditrlsspt rlavipwgvr kllrwvrrny gdmdiyitas
giddqaledd
901 rlrkyylgky lqevlkayli dkvrikgyya fklaeekskp rfgfftsdfk
akssiqfynk
961 vissrgf
```

Beta-Klotho extracellular domain (without signal peptide) amino acid sequence (SEQ ID NO: 39)

```
 52                                                     gfsgdgrai
 61 wsknpnftpv nesqlflydt fpknffwgig tgalqvegsw kkdgkgpsiw dhfihthlkn
121 vsstngssds yiflekdlsa ldfigvsfyq fsiswprlfp dgivtvanak glqyystlld
181 alvlrniepi vtlyhwdlpl alqekyggwk ndtiidifnd yatycfqmfg drvkywitih
241 npylvawhgy gtgmhapgek gnlaavytvg hnlikahskv whnynthfrp hqkgwlsitl
301 gshwiepnrs entmdifkcq qsmvsvlgwf anpihgdgdy pegmrkklfs vlpifseaek
361 hemrgtadff afsfgpnnfk plntmakmgq nvslnlreal nwikleynnp riliaengwf
421 tdsrvktedt taiymmknfl sqvlqairld eirvfgytaw slldgfewqd aytirrglfy
481 vdfnskqker kpkssahyyk qiirengfsl kestpdvqgq fpcdfswgvt esvlkpesva
541 sspqfsdphl yvwnatgnrl lhrvegvrlk trpaqctdfv nikkqlemla rmkvthyrfa
601 ldwasvlptg nlsavnrqal ryyrcvvseg lklgisamvt lyypthahlg lpepllhadg
661 wlnpstaeaf qayaglcfqe lgdlvklwit inepnrlsdi ynrsgndtyg aahnllvaha
721 lawrlydrqf rpsqrgavsl slhadwaepa npyadshwra aerflqfeia wfaeplfktg
781 dypaamreyi askhrrglss salprlteae rrllkgtvdf calnhfttrf vmheqlagsr
841 ydsdrdiqfl qditrlsspt rlavipwgvr kllrwvrrny gdmdiyitas giddqaledd
901 rlrkyylgky lqevlkayli dkvrikgyya fklaeekskp rfgfftsdfk akssiqfynk
961 vissrgfpfe nsssrcsqtq entectvclf lvqkkpl
```

sKlotho without signal peptide – FGF23 amino acid sequence (without signal peptide) (SEQ ID NO: 40)

```
                                      EPGDGAQ TWARFSRPPA
 51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
101 PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
151 ISWARVLPNG SAGVPNREGL RYYRRLLERL RELGVQPVVT LYHWDLPQRL
```

```
 201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
 251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
 301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP
 351 DFTESEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
 401 IDLEFNHPQI FIVENGWFVS GTTKRDDAKY MYYLKKFIME TLKAIKLDGV
 451 DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD FLSQDKMLLP KSSALFYQKL
 501 IEKNGFPPLP ENQPLEGTFP CDFAWGVVDN YIQVDTTLSQ FTDLNVYLWD
 551 VHHSKRLIKV DGVVTKKRKS YCVDFAAIQP QIALLQEMHV THFRFSLDWA
 601 LILPLGNQSQ VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL
 651 LARQGAWENP YTALAFAEYA RLCFQELGHH VKLWITMNEP YTRNMTYSAG
 701 HNLLKAHALA WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE
 751 RVLEFDIGWL AEPIFGSGDY PWVMRDWLNQ RNNFLLPYFT EDEKKLIQGT
 801 FDFLALSHYT TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW
 851 GLRKVLNWLK FKYGDLPMYI ISNGIDDGLH AEDDQLRVYY MQNYINEALK
 901 AHILDGINLC GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIIDS
 951 NGFPGPETLE RFCPEEFTVC TECSFFHTRK SLGSGGGGSG GGGSGGGGSL
1001 KYPNASPLLG SSWGGLIHLY TATARNSYHL QIHKNGHVDG APHQTIYSAL
1051 MIRSEDAGFV VITGVMSRRY LCMDFRGNIF GSHYFDPENC RFQHQTLENG
1101 YDVYHSPQYH FLVSLGRAKR AFLPGMNPPP YSQFLSRRNE IPLIHFNTPI
1151 PRRHTRSAED DSERDPLNVL KPRARMTPAP ASCSQELPSA EDNSPMASDP
1201 LGVVRGGRVN THAGGTGPEG CRPFAKFI*
```

sKlotho without signal peptide -FGF23 (R179Q) (without signal peptide) amino acid sequence (SEQ ID NO: 41)

```
                                          EPGDGAQ TWARFSRPPA
  51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
 101 PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
 151 ISWARVLPNG SAGVPNREGL RYYRRLLERL RELGVQPVVT LYHWDLPQRL
 201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
 251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
 301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP
 351 DFTESEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
 401 IDLEFNHPQI FIVENGWFVS GTTKRDDAKY MYYLKKFIME TLKAIKLDGV
 451 DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD FLSQDKMLLP KSSALFYQKL
 501 IEKNGFPPLP ENQPLEGTFP CDFAWGVVDN YIQVDTTLSQ FTDLNVYLWD
 551 VHHSKRLIKV DGVVTKKRKS YCVDFAAIQP QIALLQEMHV THFRFSLDWA
 601 LILPLGNQSQ VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL
 651 LARQGAWENP YTALAFAEYA RLCFQELGHH VKLWITMNEP YTRNMTYSAG
 701 HNLLKAHALA WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE
 751 RVLEFDIGWL AEPIFGSGDY PWVMRDWLNQ RNNFLLPYFT EDEKKLIQGT
 801 FDFLALSHYT TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW
 851 GLRKVLNWLK FKYGDLPMYI ISNGIDDGLH AEDDQLRVYY MQNYINEALK
 901 AHILDGINLC GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIIDS
 951 NGFPGPETLE RFCPEEFTVC TECSFFHTRK SLGSGGGGSG GGGSGGGGSL
1001 KYPNASPLLG SSWGGLIHLY TATARNSYHL QIHKNGHVDG APHQTIYSAL
1051 MIRSEDAGFV VITGVMSRRY LCMDFRGNIF GSHYFDPENC RFQHQTLENG
1101 YDVYHSPQYH FLVSLGRAKR AFLPGMNPPP YSQFLSRRNE IPLIHFNTPI
1151 PRRHTQSAED DSERDPLNVL KPRARMTPAP ASCSQELPSA EDNSPMASDP
1201 LGVVRGGRVN THAGGTGPEG CRPFAKFI*
```

FGF23 without signal peptide (SEQ ID NO: 42)

```
                                YPNASP LLGSSWGGLI HLYTATARNS YHLQIHKNGH
  61 VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG NIFGSHYFDP ENCRFQHQTL
 121 ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN PPPYSQFLSR RNEIPLIHFN TPIPRRHTRS
 181 AEDDSERDPL NVLKPRARMT PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG
 241 PEGCRPFAKF I
```

FGF23(R179Q) without signal peptide (SEQ ID NO: 43)

```
                                YPNASP LLGSSWGGLI HLYTATARNS YHLQIHKNGH
 61 VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG NIFGSHYFDP ENCRFQHQTL
121 ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS
181 AEDDSERDPL NVLKPRARMT PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG
241 PEGCRPFAKF I
```

sKlotho with Klotho signal peptide (SEQ ID NO: 44)

```
  1 MPASAPPRRP RPPPPSLSLL LVLLGLGGRR LRAEPGDGAQ TWARFSRPPA
 51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
101 PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
151 ISWARVLPNG SAGVPNREGL RYYRRLLERL RELGVQPVVT LYHWDLPQRL
201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP
351 DFTESEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
401 IDLEFNHPQI FIVENGWFVS GTTKRDDAKY MYYLKKFIME TLKAIKLDGV
451 DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD FLSQDKMLLP KSSALFYQKL
501 IEKNGFPPLP ENQPLEGTFP CDFAWGVVDN YIQVDTTLSQ FTDLNVYLWD
551 VHHSKRLIKV DGVVTKKRKS YCVDFAAIQP QIALLQEMHV THFRFSLDWA
601 LILPLGNQSQ VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL
651 LARQGAWENP YTALAFAEYA RLCFQELGHH VKLWITMNEP YTRNMTYSAG
701 HNLLKAHALA WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE
751 RVLEFDIGWL AEPIFGSGDY PWVMRDWLNQ RNNFLLPYFT EDEKKLIQGT
801 FDFLALSHYT TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW
851 GLRKVLNWLK FKYGDLPMYI ISNGIDDGLH AEDDQLRVYY MQNYINEALK
901 AHILDGINLC GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIIDS
951 NGFPGPETLE RFCPEEFTVC TECSFFHTRK SL
```

sKlotho with IgG Signal peptide (SEQ ID NO: 45)

```
  1 MSVLTQVLAL LLLWLTGLGG RRLRAEPGDG AQTWARFSRP PAPEAAGLFQ
 51 GTFPDGFLWA VGSAAYQTEG GWQQHGKGAS IWDTFTHHPL APPGDSRNAS
101 LPLGAPSPLQ PATGDVASDS YNNVFRDTEA LRELGVTHYR FSISWARVLP
151 NGSAGVPNRE GLRYYRRLLE RLRELGVQPV VTLYHWDLPQ RLQDAYGGWA
201 NRALADHFRD YAELCFRHFG GQVKYWITID NPYVVAWHGY ATGRLAPGIR
251 GSPRLGYLVA HNLLLAHAKV WHLYNTSFRP TQGGQVSIAL SSHWINPRRM
301 TDHSIKECQK SLDFVLGWFA KPVFIDGDYP ESMKNNLSSI LPDFTESEKK
351 FIKGTADFFA LCFGPTLSFQ LLDPHMKFRQ LESPNLRQLL SWIDLEFNHP
401 QIFIVENGWF VSGTTKRDDA KYMYYLKKFI METLKAIKLD GVDVIGYTAW
451 SLMDGFEWHR GYSIRRGLFY VDFLSQDKML LPKSSALFYQ KLIEKNGFPP
501 LPENQPLEGT FPCDFAWGVV DNYIQVDTTL SQFTDLNVYL WDVHHSKRLI
551 KVDGVVTKKR KSYCVDFAAI QPQIALLQEM HVTHFRFSLD WALILPLGNQ
601 SQVNHTILQY YRCMASELVR VNITPVVALW QPMAPNQGLP RLLARQGAWE
651 NPYTALAFAE YARLCFQELG HHVKLWITMN EPYTRNMTYS AGHNLLKAHA
701 LAWHVYNEKF RHAQNGKISI ALQADWIEPA CPFSQKDKEV AERVLEFDIG
751 WLAEPIFGSG DYPWVMRDWL NQRNNFLLPY FTEDEKKLIQ GTFDFLALSH
801 YTTILVDSEK EDPIKYNDYL EVQEMTDITW LNSPSQVAVV PWGLRKVLNW
851 LKFKYGDLPM YIISNGIDDG LHAEDDQLRV YYMQNYINEA LKAHILDGIN
901 LCGYFAYSFN DRTAPRFGLY RYAADQFEPK ASMKHYRKII DSNGFPGPET
951 LERFCPEEFT VCTECSFFHT RKSL*
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sKlotho-FGF23-FcLALA v1 (SEQ ID NO: 46)

```
   1 ATGCCCGCCA GCGCCCCGCC GCGCCGCCCG CGGCCGCCGC CGCCGTCGCT
     GTCGCTGCTG
  61 CTGGTGCTGC TGGGCCTGGG CGGCCGCCGC CTGCGTGCGG AGCCGGGCGA
     CGGCGCGCAG
 121 ACCTGGGCCC GTTTCTCGCG GCCTCCTGCC CCCGAGGCCG CGGGCCTCTT
     CCAGGGCACC
 181 TTCCCCGACG GCTTCCTCTG GGCCGTGGGC AGCGCCGCCT ACCAGACCGA
     GGGCGGCTGG
 241 CAGCAGCACG GCAAGGGTGC GTCCATCTGG GATACGTTCA CCCACCACCC
     CCTGGCACCC
 301 CCGGGAGACT CCCGGAACGC CAGTCTGCCG TTGGGCGCCC CGTCGCCGCT
     GCAGCCCGCC
 361 ACCGGGGACG TAGCCAGCGA CAGCTACAAC AACGTCTTCC GCGACACGGA
     GGCGCTGCGC
 421 GAGCTCGGGG TCACTCACTA CCGCTTCTCC ATCTCGTGGG CGCGAGTGCT
     CCCCAATGGC
 481 AGCGCGGGCG TCCCCAACCG CGAGGGGCTG CGCTACTACC GGCGCCTGCT
     GGAGCGGCTG
 541 CGGGAGCTGG GCGTGCAGCC CGTGGTCACC CTGTACCACT GGGACCTGCC
     CCAGCGCCTG
 601 CAGGACGCCT ACGGCGGCTG GGCCAACCGC GCCCTGGCCG ACCACTTCAG
     GGATTACGCG
 661 GAGCTCTGCT TCCGCCACTT CGGCGGTCAG GTCAAGTACT GGATCACCAT
     CGACAACCCC
 721 TACGTGGTGG CCTGGCACGG CTACGCCACC GGGCGCCTGG CCCCCGGCAT
     CCGGGGCAGC
 781 CCGCGGCTCG GGTACCTGGT GGCGCACAAC CTCCTCCTGG CTCATGCCAA
     AGTCTGGCAT
 841 CTCTACAATA CTTCTTTCCG TCCCACTCAG GGAGGTCAGG TGTCCATTGC
     CCTAAGCTCT
 901 CACTGGATCA ATCCTCGAAG AATGACCGAC CACAGCATCA AAGAATGTCA
     AAAATCTCTG
 961 GACTTTGTAC TAGGTTGGTT TGCCAAACCC GTATTTATTG ATGGTGACTA
     TCCCGAGAGC
1021 ATGAAGAATA ACCTTTCATC TATTCTGCCT GATTTTACTG AATCTGAGAA
     AAAGTTCATC
1081 AAAGGAACTG CTGACTTTTT TGCTCTTTGC TTTGGACCCA CCTTGAGTTT
     TCAACTTTTG
1141 GACCCTCACA TGAAGTTCCG CCAATTGGAA TCTCCCAACC TGAGGCAACT
     GCTTTCCTGG
1201 ATTGACCTTG AATTTAACCA TCCTCAAATA TTTATTGTGG AAAATGGCTG
     GTTTGTCTCA
1261 GGGACCACCA AGAGAGATGA TGCCAAATAT ATGTATTACC TCAAAAAGTT
     CATCATGGAA
1321 ACCTTAAAAG CCATCAAGCT GGATGGGGTG GATGTCATCG GGTATACCGC
     ATGGTCCCTC
1381 ATGGATGGTT TCGAGTGGCA CAGAGGTTAC AGCATCAGGC GTGGACTCTT
     CTATGTTGAC
1441 TTTCTAAGCC AGGACAAGAT GTTGTTGCCA AAGTCTTCAG CCTTGTTCTA
     CCAAAAGCTG
1501 ATAGAGAAAA ATGGCTTCCC TCCTTTACCT GAAAATCAGC CCCTAGAAGG
     GACATTTCCC
1561 TGTGACTTTG CTTGGGGAGT TGTTGACAAC TACATTCAAG TAGATACCAC
     TCTGTCTCAG
1621 TTTACCGACC TGAATGTTTA CCTGTGGGAT GTCCACCACA GTAAAAGGCT
     TATTAAAGTG
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1681 GATGGGGTTG TGACCAAGAA GAGGAAATCC TACTGTGTTG ACTTTGCTGC
CATCCAGCCC
1741 CAGATCGCTT TACTCCAGGA AATGCACGTT ACACATTTTC GCTTCTCCCT
GGACTGGGCC
1801 CTGATTCTCC CTCTGGGTAA CCAGTCCCAG GTGAACCACA CCATCCTGCA
GTACTATCGC
1861 TGCATGGCCA GCGAGCTTGT CCGTGTCAAC ATCACCCCAG TGGTGGCCCT
GTGGCAGCCT
1921 ATGGCCCCGA ACCAAGGACT GCCGCGCCTC CTGGCCAGGC AGGGCGCCTG
GGAGAACCCC
1981 TACACTGCCC TGGCCTTTGC AGAGTATGCC CGACTGTGCT TTCAAGAGCT
CGGCCATCAC
2041 GTCAAGCTTT GGATAACGAT GAATGAGCCG TATACAAGGA ATATGACATA
CAGTGCTGGC
2101 CACAACCTTC TGAAGGCCCA TGCCCTGGCT TGGCATGTGT ACAATGAAAA
GTTTAGGCAT
2161 GCTCAGAATG GGAAAATATC CATAGCCTTG CAGGCTGATT GGATAGAACC
TGCCTGCCCT
2221 TTCTCCCAAA AGGACAAAGA GGTGGCCGAG AGAGTTTTGG AATTTGACAT
TGGCTGGCTG
2281 GCTGAGCCCA TTTTCGGCTC TGGAGATTAT CCATGGGTGA TGAGGGACTG
GCTGAACCAA
2341 AGAAACAATT TTCTTCTTCC TTATTTCACT GAAGATGAAA AAAAGCTAAT
CCAGGGTACC
2401 TTTGACTTTT TGGCTTTAAG CCATTATACC ACCATCCTTG TAGACTCAGA
AAAAGAAGAT
2461 CCAATAAAAT ACAATGATTA CCTAGAAGTG CAAGAAATGA CCGACATCAC
GTGGCTCAAC
2521 TCCCCCAGTC AGGTGGCGGT AGTGCCCTGG GGGTTGCGCA AAGTGCTGAA
CTGGCTGAAG
2581 TTCAAGTACG GAGACCTCCC CATGTACATA ATATCCAACG GAATCGATGA
CGGGCTGCAT
2641 GCTGAGGACG ACCAGCTGAG GGTGTATTAT ATGCAGAATT ACATAAACGA
AGCTCTCAAA
2701 GCCCACATAC TGGATGGTAT CAATCTTTGC GGATACTTTG CTTATTCGTT
TAACGACCGC
2761 ACAGCTCCGA GGTTTGGCCT CTATCGTTAT GCTGCAGATC AGTTTGAGCC
CAAGGCATCC
2821 ATGAAACATT ACAGGAAAAT TATTGACAGC AATGGTTTCC CGGGCCCAGA
AACTCTGGAA
2881 AGATTTTGTC CAGAAGAATT CACCGTGTGT ACTGAGTGCA GTTTTTTTCA
CACCCGAAAG
2941 TCTTTAGGAT CCGGAGGTGG AGGTTCAGGA GGTGGAGGTT CAGGAGGTGG
AGGTTCACTT
3001 AAGTATCCCA ATGCCTCCCC ACTGCTCGGC TCCAGCTGGG GTGGCCTGAT
CCACCTGTAC
3061 ACAGCCACAG CCAGGAACAG CTACCACCTG CAGATCCACA AGAATGGCCA
TGTGGATGGC
3121 GCACCCCATC AGACCATCTA CAGTGCCCTG ATGATCAGAT CAGAGGATGC
TGGCTTTGTG
3181 GTGATTACAG GTGTGATGAG CAGAAGATAC CTCTGCATGG ATTTCAGAGG
CAACATTTTT
3241 GGATCACACT ATTTCGACCC GGAGAACTGC AGGTTCCAAC ACCAGACGCT
GGAAAACGGG
3301 TACGACGTCT ACCACTCTCC TCAGTATCAC TTCCTGGTCA GTCTGGGCCG
GGCGAAGAGA
3361 GCCTTCCTGC CAGGCATGAA CCCACCCCCG TACTCCCAGT TCCTGTCCCG
GAGGAACGAG
3421 ATCCCCCTAA TTCACTTCAA CACCCCCATA CCACGGCGGC ACACCCAGAG
CGCCGAGGAC
3481 GACTCGGAGC GGGACCCCCT GAACGTGCTG AAGCCCCGGG CCCGGATGAC
CCCGGCCCCG

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3541 GCCTCCTGTT CACAGGAGCT CCCGAGCGCC GAGGACAACA GCCCGATGGC
     CAGTGACCCA
3601 TTAGGGGTGG TCAGGGGCGG TCGAGTGAAC ACGCACGCTG GGGGAACGGG
     CCCGGAAGGC
3661 TGCCGCCCCT TCGCCAAGTT CATCGGAGGT GGAGGTTCAA AAACCCACAC
     GTGTCCTCCT
3721 TGTCCTGCCC CAGAAGCAGC AGGTGGTCCA TCAGTTTTTC TTTTCCCTCC
     CAAACCCAAG
3781 GATACGCTGA TGATCTCTCG CACGCCTGAG GTGACATGCG TCGTAGTAGA
     CGTGAGCCAC
3841 GAAGATCCCG AGGTGAAGTT CAATTGGTAT GTGGACGGAG TAGAAGTGCA
     TAACGCGAAA
3901 ACTAAGCCGC GCGAGGAACA ATATAACAGT ACTTACAGGG TGGTATCCGT
     GCTCACAGTC
3961 CTGCACCAGG ACTGGCTGAA CGGTAAGGAA TACAAGTGCA AAGTAAGCAA
     CAAGGCACTT
4021 CCCGCGCCTA TTGAGAAAAC AATCTCCAAG GCGAAGGGAC AACCAAGAGA
     ACCTCAGGTT
4081 TACACTCTCC CGCCTTCCAG GGAAGAGATG ACCAAAAAATC AAGTTTCCCT
     GACTTGCCTC
4141 GTCAAAGGAT TCTACCCTTC CGACATTGCT GTTGAATGGG AAAGCAATGG
     ACAACCAGAG
4201 AACAACTACA AGACAACACC CCCGGTGCTG GATAGTGACG GATCTTTCTT
     TCTCTACTCA
4261 AAGCTGACCG TGGATAAGTC CAGGTGGCAG CAGGGAAACG TGTTTTCCTG
     CTCTGTCATG
4321 CATGAAGCGC TGCATAATCA CTATACCCAG AAGTCTCTGA GCTTGAGCCC
     AGGCAAGTAA
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sKlotho-FGF23-FcLALA v1 (SEQ ID NO: 47)

```
   1 MPASAPPRRP RPPPPSLSLL LVLLGLGGRR LRAEPGDGAQ TWARFSRPPA
  51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
 101 PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
 151 ISWARVLPNG SAGVPNREGL RYYRRLLERL RELGVQPVVT LYHWDLPQRL
 201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
 251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
 301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP
 351 DFTESEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
 401 IDLEFNHPQI FIVENGWFVS GTTKRDDAKY MYYLKKFIME TLKAIKLDGV
 451 DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD FLSQDKMLLP KSSALFYQKL
 501 IEKNGFPPLP ENQPLEGTFP CDFAWGVVDN YIQVDTTLSQ FTDLNVYLWD
 551 VHHSKRLIKV DGVVTKKRKS YCVDFAAIQP QIALLQEMHV THFRFSLDWA
 601 LILPLGNQSQ VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL
 651 LARQGAWENP YTALAFAEYA RLCFQELGHH VKLWITMNEP YTRNMTYSAG
 701 HNLLKAHALA WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE
 751 RVLEFDIGWL AEPIFGSGDY PWVMRDWLNQ RNNFLLPYFT EDEKKLIQGT
 801 FDFLALSHYT TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW
 851 GLRKVLNWLK FKYGDLPMYI ISNGIDDGLH AEDDQLRVYY MQNYINEALK
 901 AHILDGINLC GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIIDS
 951 NGFPGPETLE RFCPEEFTVC TECSFFHTRK SLGSGGGGSG GGGSGGGGSL
1001 KYPNASPLLG SSWGGLIHLY TATARNSYHL QIHKNGHVDG APHQTIYSAL
1051 MIRSEDAGFV VITGVMSRRY LCMDFRGNIF GSHYFDPENC RFQHQTLENG
1101 YDVYHSPQYH FLVSLGRAKR AFLPGMNPPP YSQFLSRRNE IPLIHFNTPI
1151 PRRHTQSAED DSERDPLNVL KPRARMTPAP ASCSQELPSA EDNSPMASDP
1201 LGVVRGGRVN THAGGTGPEG CRPFAKFIGG GGSKTHTCPP CPAPEAAGGP
1251 SVFLFPPKPK DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK
1301 TKPREEQYNS TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK
1351 AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA VEWESNGQPE
1401 NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ
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1451 KSLSLSPGK*

sKlotho-FGF23-FcLALA v2 (SEQ ID NO: 48)

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   1 ATGCCCGCCA GCGCCCCGCC GCGCCGCCCG CGGCCGCCGC CGCCGTCGCT
     GTCGCTGCTG
  61 CTGGTGCTGC TGGGCCTGGG CGGCCGCCGC CTGCGTGCGG AGCCGGGCGA
     CGGCGCGCAG
 121 ACCTGGGCCC GTTTCTCGCG GCCTCCTGCC CCCGAGGCCG CGGGCCTCTT
     CCAGGGCACC
 181 TTCCCCGACG GCTTCCTCTG GGCCGTGGGC AGCGCCGCCT ACCAGACCGA
     GGGCGGCTGG
 241 CAGCAGCACG GCAAGGGTGC GTCCATCTGG GATACGTTCA CCCACCACCC
     CCTGGCACCC
 301 CCGGGAGACT CCCGGAACGC CAGTCTGCCG TTGGGCGCCC CGTCGCCGCT
     GCAGCCCGCC
 361 ACCGGGGACG TAGCCAGCGA CAGCTACAAC AACGTCTTCC GCGACACGGA
     GGCGCTGCGC
 421 GAGCTCGGGG TCACTCACTA CCGCTTCTCC ATCTCGTGGG CGCGAGTGCT
     CCCCAATGGC
 481 AGCGCGGGCG TCCCCAACCG CGAGGGGCTG CGCTACTACC GGCGCCTGCT
     GGAGCGGCTG
 541 CGGGAGCTGG GCGTGCAGCC CGTGGTCACC CTGTACCACT GGGACCTGCC
     CCAGCGCCTG
 601 CAGGACGCCT ACGGCGGCTG GGCCAACCGC GCCCTGGCCG ACCACTTCAG
     GGATTACGCG
 661 GAGCTCTGCT TCCGCCACTT CGGCGGTCAG GTCAAGTACT GGATCACCAT
     CGACAACCCC
 721 TACGTGGTGG CCTGGCACGG CTACGCCACC GGGCGCCTGG CCCCCGGCAT
     CCGGGGCAGC
 781 CCGCGGCTCG GGTACCTGGT GGCGCACAAC CTCCTCCTGG CTCATGCCAA
     AGTCTGGCAT
 841 CTCTACAATA CTTCTTTCCG TCCCACTCAG GGAGGTCAGG TGTCCATTGC
     CCTAAGCTCT
 901 CACTGGATCA ATCCTCGAAG AATGACCGAC CACAGCATCA AAGAATGTCA
     AAAATCTCTG
 961 GACTTTGTAC TAGGTTGGTT TGCCAAACCC GTATTTATTG ATGGTGACTA
     TCCCGAGAGC
1021 ATGAAGAATA ACCTTTCATC TATTCTGCCT GATTTTACTG AATCTGAGAA
     AAAGTTCATC
1081 AAAGGAACTG CTGACTTTTT TGCTCTTTGC TTTGGACCCA CCTTGAGTTT
     TCAACTTTTG
1141 GACCCTCACA TGAAGTTCCG CCAATTGGAA TCTCCCAACC TGAGGCAACT
     GCTTTCCTGG
1201 ATTGACCTTG AATTTAACCA TCCTCAAATA TTTATTGTGG AAAATGGCTG
     GTTTGTCTCA
1261 GGGACCACCA AGAGAGATGA TGCCAAATAT ATGTATTACC TCAAAAAGTT
     CATCATGGAA
1321 ACCTTAAAAG CCATCAAGCT GGATGGGGTG GATGTCATCG GGTATACCGC
     ATGGTCCCTC
1381 ATGGATGGTT TCGAGTGGCA CAGAGGTTAC AGCATCAGGC GTGGACTCTT
     CTATGTTGAC
1441 TTTCTAAGCC AGGACAAGAT GTTGTTGCCA AAGTCTTCAG CCTTGTTCTA
     CCAAAAGCTG
1501 ATAGAGAAAA ATGGCTTCCC TCCTTTACCT GAAAATCAGC CCCTAGAAGG
     GACATTTCCC
1561 TGTGACTTTG CTTGGGGAGT TGTTGACAAC TACATTCAAG TAGATACCAC
     TCTGTCTCAG
1621 TTTACCGACC TGAATGTTTA CCTGTGGGAT GTCCACCACA GTAAAAGGCT
     TATTAAAGTG
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1681 GATGGGGTTG TGACCAAGAA GAGGAAATCC TACTGTGTTG ACTTTGCTGC
CATCCAGCCC
1741 CAGATCGCTT TACTCCAGGA AATGCACGTT ACACATTTTC GCTTCTCCCT
GGACTGGGCC
1801 CTGATTCTCC CTCTGGGTAA CCAGTCCCAG GTGAACCACA CCATCCTGCA
GTACTATCGC
1861 TGCATGGCCA GCGAGCTTGT CCGTGTCAAC ATCACCCCAG TGGTGGCCCT
GTGGCAGCCT
1921 ATGGCCCCGA ACCAAGGACT GCCGCGCCTC CTGGCCAGGC AGGGCGCCTG
GGAGAACCCC
1981 TACACTGCCC TGGCCTTTGC AGAGTATGCC CGACTGTGCT TTCAAGAGCT
CGGCCATCAC
2041 GTCAAGCTTT GGATAACGAT GAATGAGCCG TATACAAGGA ATATGACATA
CAGTGCTGGC
2101 CACAACCTTC TGAAGGCCCA TGCCCTGGCT TGGCATGTGT ACAATGAAAA
GTTTAGGCAT
2161 GCTCAGAATG GGAAAATATC CATAGCCTTG CAGGCTGATT GGATAGAACC
TGCCTGCCCT
2221 TTCTCCCAAA AGGACAAAGA GGTGGCCGAG AGAGTTTTGG AATTTGACAT
TGGCTGGCTG
2281 GCTGAGCCCA TTTTCGGCTC TGGAGATTAT CCATGGGTGA TGAGGGACTG
GCTGAACCAA
2341 AGAAACAATT TTCTTCTTCC TTATTTCACT GAAGATGAAA AAAAGCTAAT
CCAGGGTACC
2401 TTTGACTTTT TGGCTTTAAG CCATTATACC ACCATCCTTG TAGACTCAGA
AAAAGAAGAT
2461 CCAATAAAAT ACAATGATTA CCTAGAAGTG CAAGAAATGA CCGACATCAC
GTGGCTCAAC
2521 TCCCCCAGTC AGGTGGCGGT AGTGCCCTGG GGGTTGCGCA AAGTGCTGAA
CTGGCTGAAG
2581 TTCAAGTACG GAGACCTCCC CATGTACATA ATATCCAACG GAATCGATGA
CGGGCTGCAT
2641 GCTGAGGACG ACCAGCTGAG GGTGTATTAT ATGCAGAATT ACATAAACGA
AGCTCTCAAA
2701 GCCCACATAC TGGATGGTAT CAATCTTTGC GGATACTTTG CTTATTCGTT
TAACGACCGC
2761 ACAGCTCCGA GGTTTGGCCT CTATCGTTAT GCTGCAGATC AGTTTGAGCC
CAAGGCATCC
2821 ATGAAACATT ACAGGAAAAT TATTGACAGC AATGGTTTCC CGGGCCCAGA
AACTCTGGAA
2881 AGATTTTGTC CAGAAGAATT CACCGTGTGT ACTGAGTGCA GTTTTTTTCA
CACCCGAAAG
2941 TCTTTAGGAT CCGGAGGTGG AGGTTCAGGA GGTGGAGGTT CAGGAGGTGG
AGGTTCACTT
3001 AAGTATCCCA ATGCCTCCCC ACTGCTCGGC TCCAGCTGGG GTGGCCTGAT
CCACCTGTAC
3061 ACAGCCACAG CCAGGAACAG CTACCACCTG CAGATCCACA AGAATGGCCA
TGTGGATGGC
3121 GCACCCCATC AGACCATCTA CAGTGCCCTG ATGATCAGAT CAGAGGATGC
TGGCTTTGTG
3181 GTGATTACAG GTGTGATGAG CAGAAGATAC CTCTGCATGG ATTTCAGAGG
CAACATTTTT
3241 GGATCACACT ATTTCGACCC GGAGAACTGC AGGTTCCAAC ACCAGACGCT
GGAAAACGGG
3301 TACGACGTCT ACCACTCTCC TCAGTATCAC TTCCTGGTCA GTCTGGGCCG
GGCGAAGAGA
3361 GCCTTCCTGC CAGGCATGAA CCCACCCCCG TACTCCCAGT TCCTGTCCCG
GAGGAACGAG
3421 ATCCCCCTAA TTCACTTCAA CACCCCCATA CCACGGCGGC ACACCCAGAG
CGCCGAGGAC
3481 GACTCGGAGC GGGACCCCCT GAACGTGCTG AAGCCCCGGG CCCGGATGAC
CCCGGCCCCG

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3541 GCCTCCTGTT CACAGGAGCT CCCGAGCGCC GAGGACAACA GCCCGATGGC
    CAGTGACCCA
3601 TTAGGGGTGG TCAGGGGCGG TCGAGTGAAC ACGCACGCTG GGGGAACGGG
    CCCGGAAGGC
3661 TGCCGCCCCT TCGCCAAGTT CATCGGAGGT GGAGGTTCAG CCCCAGAAGC
    AGCAGGTGGT
3721 CCATCAGTTT TTCTTTTCCC TCCCAAACCC AAGGATACGC TGATGATCTC
    TCGCACGCCT
3781 GAGGTGACAT GCGTCGTAGT AGACGTGAGC CACGAAGATC CCGAGGTGAA
    GTTCAATTGG
3841 TATGTGGACG GAGTAGAAGT GCATAACGCG AAAACTAAGC CGCGCGAGGA
    ACAATATAAC
3901 AGTACTTACA GGGTGGTATC CGTGCTCACA GTCCTGCACC AGGACTGGCT
    GAACGGTAAG
3961 GAATACAAGT GCAAAGTAAG CAACAAGGCA CTTCCCGCGC CTATTGAGAA
    AACAATCTCC
4021 AAGGCGAAGG GACAACCAAG AGAACCTCAG GTTTACACTC TCCCGCCTTC
    CAGGGAAGAG
4081 ATGACCAAAA ATCAAGTTTC CCTGACTTGC CTCGTCAAAG GATTCTACCC
    TTCCGACATT
4141 GCTGTTGAAT GGGAAAGCAA TGGACAACCA GAGAACAACT ACAAGACAAC
    ACCCCCGGTG
4201 CTGGATAGTG ACGGATCTTT CTTTCTCTAC TCAAAGCTGA CCGTGGATAA
    GTCCAGGTGG
4261 CAGCAGGGAA ACGTGTTTTC CTGCTCTGTC ATGCATGAAG CGCTGCATAA
    TCACTATACC
4321 CAGAAGTCTC TGAGCTTGAG CCCAGGCAAG TAA
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sKlotho-FGF23-FcLALA v2 (SEQ ID NO: 49)

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   1 MPASAPPRRP RPPPPSLSLL LVLLGLGGRR LRAEPGDGAQ TWARFSRPPA
  51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
 101 PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
 151 ISWARVLPNG SAGVPNREGL RYYRRLLERL RELGVQPVVT LYHWDLPQRL
 201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
 251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
 301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP
 351 DFTESEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
 401 IDLEFNHPQI FIVENGWFVS GTTKRDDAKY MYYLKKFIME TLKAIKLDGV
 451 DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD FLSQDKMLLP KSSALFYQKL
 501 IEKNGFPPLP ENQPLEGTFP CDFAWGVVDN YIQVDTTLSQ FTDLNVYLWD
 551 VHHSKRLIKV DGVVTKKRKS YCVDFAAIQP QIALLQEMHV THFRFSLDWA
 601 LILPLGNQSQ VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL
 651 LARQGAWENP YTALAFAEYA RLCFQELGHH VKLWITMNEP YTRNMTYSAG
 701 HNLLKAHALA WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE
 751 RVLEFDIGWL AEPIFGSGDY PWVMRDWLNQ RNNFLLPYFT EDEKKLIQGT
 801 FDFLALSHYT TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW
 851 GLRKVLNWLK FKYGDLPMYI ISNGIDDGLH AEDDQLRVYY MQNYINEALK
 901 AHILDGINLC GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIIDS
 951 NGFPGPETLE RFCPEEFTVC TECSFFHTRK SLGSGGGGSG GGGSGGGGSL
1001 KYPNASPLLG SSWGGLIHLY TATARNSYHL QIHKNGHVDG APHQTIYSAL
1051 MIRSEDAGFV VITGVMSRRY LCMDFRGNIF GSHYFDPENC RFQHQTLENG
1101 YDVYHSPQYH FLVSLGRAKR AFLPGMNPPP YSQFLSRRNE IPLIHFNTPI
1151 PRRHTQSAED DSERDPLNVL KPRARMTPAP ASCSQELPSA EDNSPMASDP
1201 LGVVRGGRVN THAGGTGPEG CRPFAKFIGG GGSAPEAAGG PSVFLFPPKP
1251 KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
1301 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ
1351 VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV
1401 LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK
1451 *
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FGF23-FcLALA v1 (SEQ ID NO: 50)

```
   1 ATGTTGGGGG CCCGCCTCAG GCTCTGGGTC TGTGCCTTGT GCAGCGTCTG
     CAGCATGAGC
  61 GTCCTCAGAG CCTATCCCAA TGCCTCCCCA CTGCTCGGCT CCAGCTGGGG
     TGGCCTGATC
 121 CACCTGTACA CAGCCACAGC CAGGAACAGC TACCACCTGC AGATCCACAA
     GAATGGCCAT
 181 GTGGATGGCG CACCCCATCA GACCATCTAC AGTGCCCTGA TGATCAGATC
     AGAGGATGCT
 241 GGCTTTGTGG TGATTACAGG TGTGATGAGC AGAAGATACC TCTGCATGGA
     TTTCAGAGGC
 301 AACATTTTTG GATCACACTA TTTCGACCCG GAGAACTGCA GGTTCCAACA
     CCAGACGCTG
 361 GAAAACGGGT ACGACGTCTA CCACTCTCCT CAGTATCACT TCCTGGTCAG
     TCTGGGCCGG
 421 GCGAAGAGAG CCTTCCTGCC AGGCATGAAC CCACCCCCGT ACTCCCAGTT
     CCTGTCCCGG
 481 AGGAACGAGA TCCCCCTAAT TCACTTCAAC ACCCCCATAC CACGGCGGCA
     CACCCAGAGC
 541 GCCGAGGACG ACTCGGAGCG GGACCCCCTG AACGTGCTGA AGCCCCGGGC
     CCGGATGACC
 601 CCGGCCCCGG CCTCCTGTTC ACAGGAGCTC CCGAGCGCCG AGGACAACAG
     CCCGATGGCC
 661 AGTGACCCAT TAGGGGTGGT CAGGGGCGGT CGAGTGAACA CGCACGCTGG
     GGGAACGGGC
 721 CCGGAAGGCT GCCGCCCCTT CGCCAAGTTC ATCGGAGGTG GAGGTTCAAA
     AACCCACACG
 781 TGTCCTCCTT GTCCTGCCCC AGAAGCAGCA GGTGGTCCAT CAGTTTTTCT
     TTTCCCTCCC
 841 AAACCCAAGG ATACGCTGAT GATCTCTCGC ACGCCTGAGG TGACATGCGT
     CGTAGTAGAC
 901 GTGAGCCACG AAGATCCCGA GGTGAAGTTC AATTGGTATG TGGACGGAGT
     AGAAGTGCAT
 961 AACGCGAAAA CTAAGCCGCG CGAGGAACAA TATAACAGTA CTTACAGGGT
     GGTATCCGTG
1021 CTCACAGTCC TGCACCAGGA CTGGCTGAAC GGTAAGGAAT ACAAGTGCAA
     AGTAAGCAAC
1081 AAGGCACTTC CCGCGCCTAT TGAGAAAACA ATCTCCAAGG CGAAGGGACA
     ACCAAGAGAA
1141 CCTCAGGTTT ACACTCTCCC GCCTTCCAGG GAAGAGATGA CCAAAAATCA
     AGTTTCCCTG
1201 ACTTGCCTCG TCAAAGGATT CTACCCTTCC GACATTGCTG TTGAATGGGA
     AAGCAATGGA
1261 CAACCAGAGA ACAACTACAA GACAACACCC CCGGTGCTGG ATAGTGACGG
     ATCTTTCTTT
1321 CTCTACTCAA AGCTGACCGT GGATAAGTCC AGGTGGCAGC AGGGAAACGT
     GTTTTCCTGC
1381 TCTGTCATGC ATGAAGCGCT GCATAATCAC TATACCCAGA AGTCTCTGAG
     CTTGAGCCCA
1441 GGCAAGTAA
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FGF23(R179Q)-FcLALAv1 (SEQ ID NO: 51)

```
   1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNS
  51 YHLQIHKNGH VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
 101 NIFGSHYFDP ENCRFQHQTL ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN
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151 PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
201 PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGCRPFAKF
251 IGGGGSKTHT CPPCPAPEAA GGPSVFLFPP KPKDTLMISR TPEVTCVVVD
301 VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN
351 GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR EEMTKNQVSL
401 TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS
451 RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK*
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FGF23-FcLALA v2 (SEQ ID NO: 52)

```
  1 ATGTTGGGGG CCCGCCTCAG GCTCTGGGTC TGTGCCTTGT GCAGCGTCTG
    CAGCATGAGC
 61 GTCCTCAGAG CCTATCCCAA TGCCTCCCCA CTGCTCGGCT CCAGCTGGGG
    TGGCCTGATC
121 CACCTGTACA CAGCCACAGC CAGGAACAGC TACCACCTGC AGATCCACAA
    GAATGGCCAT
181 GTGGATGGCG CACCCCATCA GACCATCTAC AGTGCCCTGA TGATCAGATC
    AGAGGATGCT
241 GGCTTTGTGG TGATTACAGG TGTGATGAGC AGAAGATACC TCTGCATGGA
    TTTCAGAGGC
301 AACATTTTTG GATCACACTA TTTCGACCCG GAGAACTGCA GGTTCCAACA
    CCAGACGCTG
361 GAAAACGGGT ACGACGTCTA CCACTCTCCT CAGTATCACT TCCTGGTCAG
    TCTGGGCCGG
421 GCGAAGAGAG CCTTCCTGCC AGGCATGAAC CCACCCCCGT ACTCCCAGTT
    CCTGTCCCGG
481 AGGAACGAGA TCCCCCTAAT TCACTTCAAC ACCCCCATAC CACGGCGGCA
    CACCCAGAGC
541 GCCGAGGACG ACTCGGAGCG GGACCCCCTG AACGTGCTGA AGCCCCGGGC
    CCGGATGACC
601 CCGGCCCCGG CCTCCTGTTC ACAGGAGCTC CCGAGCGCCG AGGACAACAG
    CCCGATGGCC
661 AGTGACCCAT TAGGGGTGGT CAGGGGCGGT CGAGTGAACA CGCACGCTGG
    GGGAACGGGC
721 CCGGAAGGCT GCCGCCCCTT CGCCAAGTTC ATCGGAGGTG GAGGTTCAGC
    CCCAGAAGCA
781 GCAGGTGGTC CATCAGTTTT TCTTTTCCCT CCCAAACCCA AGGATACGCT
    GATGATCTCT
841 CGCACGCCTG AGGTGACATG CGTCGTAGTA GACGTGAGCC ACGAAGATCC
    CGAGGTGAAG
901 TTCAATTGGT ATGTGGACGG AGTAGAAGTG CATAACGCGA AAACTAAGCC
    GCGCGAGGAA
961 CAATATAACA GTACTTACAG GGTGGTATCC GTGCTCACAG TCCTGCACCA
    GGACTGGCTG
1021 AACGGTAAGG AATACAAGTG CAAAGTAAGC AACAAGGCAC TTCCCGCGCC
    TATTGAGAAA
1081 ACAATCTCCA AGGCGAAGGG ACAACCAAGA GAACCTCAGG TTTACACTCT
    CCCGCCTTCC
1141 AGGGAAGAGA TGACCAAAAA TCAAGTTTCC CTGACTTGCC TCGTCAAAGG
    ATTCTACCCT
1201 TCCGACATTG CTGTTGAATG GGAAAGCAAT GGACAACCAG AGAACAACTA
    CAAGACAACA
1261 CCCCCGGTGC TGGATAGTGA CGGATCTTTC TTTCTCTACT CAAAGCTGAC
    CGTGGATAAG
1321 TCCAGGTGGC AGCAGGGAAA CGTGTTTTCC TGCTCTGTCA TGCATGAAGC
    GCTGCATAAT
1381 CACTATACCC AGAAGTCTCT GAGCTTGAGC CCAGGCAAGT AA
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FGF23(R179Q)-FcLALAv2 (SEQ ID NO: 53)

```
  1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNS
 51 YHLQIHKNGH VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
101 NIFGSHYFDP ENCRFQHQTL ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN
151 PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
201 PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGCRPFAKF
251 IGGGGSAPEA AGGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK
301 FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS
351 NKALPAPIEK TISKAKGQPR EPQVYTLPPS REEMTKNQVS LTCLVKGFYP
401 SDIAVEWESN GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS
451 CSVMHEALHN HYTQKSLSLS PGK*
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Amino acid sequence of sKlotho-FGF23 (R1156Q, C1183S) (SEQ ID NO: 54)
sKlotho: aa [amino acid] 1-982; Linker1: aa 983-1001; FGF23: aa 1002-1228

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   1 MPASAPPRRP RPPPPSLSLL LVLLGLGGRR LRAEPGDGAQ TWARFSRPPA
  51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
 101 PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
 151 ISWARVLPNG SAGVPNREGL RYYRRLLERL RELGVQPVVT LYHWDLPQRL
 201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
 251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
 301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP
 351 DFTESEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
 401 IDLEFNHPQI FIVENGWFVS GTTKRDDAKY MYYLKKFIME TLKAIKLDGV
 451 DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD FLSQDKMLLP KSSALFYQKL
 501 IEKNGFPPLP ENQPLEGTFP CDFAWGVVDN YIQVDTTLSQ FTDLNVYLWD
 551 VHHSKRLIKV DGVVTKKRKS YCVDFAAIQP QIALLQEMHV THFRFSLDWA
 601 LILPLGNQSQ VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL
 651 LARQGAWENP YTALAFAEYA RLCFQELGHH VKLWITMNEP YTRNMTYSAG
 701 HNLLKAHALA WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE
 751 RVLEFDIGWL AEPIFGSGDY PWVMRDWLNQ RNNFLLPYFT EDEKKLIQGT
 801 FDFLALSHYT TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW
 851 GLRKVLNWLK FKYGDLPMYI ISNGIDDGLH AEDDQLRVYY MQNYINEALK
 901 AHILDGINLC GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIIDS
 951 NGFPGPETLE RFCPEEFTVC TECSFFHTRK SLGSGGGGSG GGGSGGGGSL
1001 KYPNASPLLG SSWGGLIHLY TATARNSYHL QIHKNGHVDG APHQTIYSAL
1051 MIRSEDAGFV VITGVMSRRY LCMDFRGNIF GSHYFDPENC RFQHQTLENG
1101 YDVYHSPQYH FLVSLGRAKR AFLPGMNPPP YSQFLSRRNE IPLIHFNTPI
1151 PRRHTQSAED DSERDPLNVL KPRARMTPAP ASSSQELPSA EDNSPMASDP
1201 LGVVRGGRVN THAGGTGPEG CRPFAKFI*
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Amino acid sequence of sKlotho-FGF23 (R1156Q, C1221S) (SEQ ID NO: 55)

sKlotho: 1-982; Linker1: 983-1001; FGF23: 1002-1228;

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   1 MPASAPPRRP RPPPPSLSLL LVLLGLGGRR LRAEPGDGAQ TWARFSRPPA
  51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
 101 PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
 151 ISWARVLPNG SAGVPNREGL RYYRRLLERL RELGVQPVVT LYHWDLPQRL
 201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
 251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
 301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP
 351 DFTESEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
 401 IDLEFNHPQI FIVENGWFVS GTTKRDDAKY MYYLKKFIME TLKAIKLDGV
 451 DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD FLSQDKMLLP KSSALFYQKL
 501 IEKNGFPPLP ENQPLEGTFP CDFAWGVVDN YIQVDTTLSQ FTDLNVYLWD
 551 VHHSKRLIKV DGVVTKKRKS YCVDFAAIQP QIALLQEMHV THFRFSLDWA
 601 LILPLGNQSQ VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL
 651 LARQGAWENP YTALAFAEYA RLCFQELGHH VKLWITMNEP YTRNMTYSAG
 701 HNLLKAHALA WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE
 751 RVLEFDIGWL AEPIFGSGDY PWVMRDWLNQ RNNFLLPYFT EDEKKLIQGT
 801 FDFLALSHYT TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW
 851 GLRKVLNWLK FKYGDLPMYI ISNGIDDGLH AEDDQLRVYY MQNYINEALK
 901 AHILDGINLC GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIIDS
 951 NGFPGPETLE RFCPEEFTVC TECSFFHTRK SLGSGGGGSG GGGSGGGGSL
1001 KYPNASPLLG SSWGGLIHLY TATARNSYHL QIHKNGHVDG APHQTIYSAL
1051 MIRSEDAGFV VITGVMSRRY LCMDFRGNIF GSHYFDPENC RFQHQTLENG
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54067A

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1101 YDVYHSPQYH FLVSLGRAKR AFLPGMNPPP YSQFLSRRNE IPLIHFNTPI
1151 PRRHTQSAED DSERDPLNVL KPRARMTPAP ASCSQELPSA EDNSPMASDP
1201 LGVVRGGRVN THAGGTGPEG SRPFAKFI*
```

Amino acid sequence of sKlotho-FGF23 (R1156Q, Q1133A) (SEQ ID NO: 56)

sKlotho: 1-982; Linker1: 983-1001; FGF23: 1002-1228

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   1 MPASAPPRRP RPPPPSLSLL LVLLGLGGRR LRAEPGDGAQ TWARFSRPPA
  51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
 101 PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
 151 ISWARVLPNG SAGVPNREGL RYYRRLLERL RELGVQPVVT LYHWDLPQRL
 201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
 251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
 301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP
 351 DFTESEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
 401 IDLEFNHPQI FIVENGWFVS GTTKRDDAKY MYYLKKFIME TLKAIKLDGV
 451 DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD FLSQDKMLLP KSSALFYQKL
 501 IEKNGFPPLP ENQPLEGTFP CDFAWGVVDN YIQVDTTLSQ FTDLNVYLWD
 551 VHHSKRLIKV DGVVTKKRKS YCVDFAAIQP QIALLQEMHV THFRFSLDWA
 601 LILPLGNQSQ VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL
 651 LARQGAWENP YTALAFAEYA RLCFQELGHH VKLWITMNEP YTRNMTYSAG
 701 HNLLKAHALA WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE
 751 RVLEFDIGWL AEPIFGSGDY PWVMRDWLNQ RNNFLLPYFT EDEKKLIQGT
 801 FDFLALSHYT TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW
 851 GLRKVLNWLK FKYGDLPMYI ISNGIDDGLH AEDDQLRVYY MQNYINEALK
 901 AHILDGINLC GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIIDS
 951 NGFPGPETLE RFCPEEFTVC TECSFFHTRK SLGSGGGGSG GGGSGGGGSL
1001 KYPNASPLLG SSWGGLIHLY TATARNSYHL QIHKNGHVDG APHQTIYSAL
1051 MIRSEDAGFV VITGVMSRRY LCMDFRGNIF GSHYFDPENC RFQHQTLENG
1101 YDVYHSPQYH FLVSLGRAKR AFLPGMNPPP YSAFLSRRNE IPLIHFNTPI
1151 PRRHTQSAED DSERDPLNVL KPRARMTPAP ASCSQELPSA EDNSPMASDP
1201 LGVVRGGRVN THAGGTGPEG CRPFAKFI*
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Amino acid sequence of sKlotho-FGF23 (R1156Q, C1183S, C1221S) (SEQ ID NO: 57)

sKlotho: 1-982; Linker1: 983-1001; FGF23: 1002-1228

```
   1 MPASAPPRRP RPPPPSLSLL LVLLGLGGRR LRAEPGDGAQ TWARFSRPPA
  51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
 101 PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
 151 ISWARVLPNG SAGVPNREGL RYYRRLLERL RELGVQPVVT LYHWDLPQRL
 201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
 251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
 301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP
 351 DFTESEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
 401 IDLEFNHPQI FIVENGWFVS GTTKRDDAKY MYYLKKFIME TLKAIKLDGV
 451 DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD FLSQDKMLLP KSSALFYQKL
 501 IEKNGFPPLP ENQPLEGTFP CDFAWGVVDN YIQVDTTLSQ FTDLNVYLWD
 551 VHHSKRLIKV DGVVTKKRKS YCVDFAAIQP QIALLQEMHV THFRFSLDWA
 601 LILPLGNQSQ VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL
 651 LARQGAWENP YTALAFAEYA RLCFQELGHH VKLWITMNEP YTRNMTYSAG
 701 HNLLKAHALA WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE
 751 RVLEFDIGWL AEPIFGSGDY PWVMRDWLNQ RNNFLLPYFT EDEKKLIQGT
 801 FDFLALSHYT TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW
 851 GLRKVLNWLK FKYGDLPMYI ISNGIDDGLH AEDDQLRVYY MQNYINEALK
 901 AHILDGINLC GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIIDS
 951 NGFPGPETLE RFCPEEFTVC TECSFFHTRK SLGSGGGGSG GGGSGGGGSL
```

54067A

```
1001 KYPNASPLLG SSWGGLIHLY TATARNSYHL QIHKNGHVDG APHQTIYSAL
1051 MIRSEDAGFV VITGVMSRRY LCMDFRGNIF GSHYFDPENC RFQHQTLENG
1101 YDVYHSPQYH FLVSLGRAKR AFLPGMNPPP YSQFLSRRNE IPLIHFNTPI
1151 PRRHTQSAED DSERDPLNVL KPRARMTPAP ASSSQELPSA EDNSPMASDP
1201 LGVVRGGRVN THAGGTGPEG SRPFAKFI*
```

Amino acid sequence of sKlotho-FGF23 (R1156Q, C1183S, C1221S, Q1133A) (SEQ ID NO: 58)

sKlotho: 1-982; Linker1: 983-1001; FGF23: 1002-1228

```
   1 MPASAPPRRP RPPPPSLSLL LVLLGLGGRR LRAEPGDGAQ TWARFSRPPA
  51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
 101 PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
 151 ISWARVLPNG SAGVPNREGL RYYRRLLERL RELGVQPVVT LYHWDLPQRL
 201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
 251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
 301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP
 351 DFTESEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
 401 IDLEFNHPQI FIVENGWFVS GTTKRDDAKY MYYLKKFIME TLKAIKLDGV
 451 DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD FLSQDKMLLP KSSALFYQKL
 501 IEKNGFPPLP ENQPLEGTFP CDFAWGVVDN YIQVDTTLSQ FTDLNVYLWD
 551 VHHSKRLIKV DGVVTKKRKS YCVDFAAIQP QIALLQEMHV THFRFSLDWA
 601 LILPLGNQSQ VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL
 651 LARQGAWENP YTALAFAEYA RLCFQELGHH VKLWITMNEP YTRNMTYSAG
 701 HNLLKAHALA WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE
 751 RVLEFDIGWL AEPIFGSGDY PWVMRDWLNQ RNNFLLPYFT EDEKKLIQGT
 801 FDFLALSHYT TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW
 851 GLRKVLNWLK FKYGDLPMYI ISNGIDDGLH AEDDQLRVYY MQNYINEALK
 901 AHILDGINLC GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIIDS
 951 NGFPGPETLE RFCPEEFTVC TECSFFHTRK SLGSGGGGSG GGGSGGGGSL
1001 KYPNASPLLG SSWGGLIHLY TATARNSYHL QIHKNGHVDG APHQTIYSAL
1051 MIRSEDAGFV VITGVMSRRY LCMDFRGNIF GSHYFDPENC RFQHQTLENG
1101 YDVYHSPQYH FLVSLGRAKR AFLPGMNPPP YSAFLSRRNE IPLIHFNTPI
1151 PRRHTQSAED DSERDPLNVL KPRARMTPAP ASSSQELPSA EDNSPMASDP
1201 LGVVRGGRVN THAGGTGPEG SRPFAKFI*
```

Amino acid sequence of FGF23(R179Q; C206S)-FcLALAv1 (SEQ ID NO: 59)

FGF23: 1-251; Linker: 252-256; FcLALA: 257-482

```
   1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNS
  51 YHLQIHKNGH VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
 101 NIFGSHYFDP ENCRFQHQTL ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN
 151 PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
 201 PAPASSSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGCRPFAKF
 251 IGGGGSKTHT CPPCPAPEAA GGPSVFLFPP KPKDTLMISR TPEVTCVVVD
 301 VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN
 351 GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR EEMTKNQVSL
 401 TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS
 451 RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK*
```

Amino acid sequence of FGF23(R179Q, C244S)-FcLALAv1 (SEQ ID NO: 60)

FGF23: 1-251; Linker: 252-256; FcLALA: 257-482

```
  1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNS
 51 YHLQIHKNGH VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
101 NIFGSHYFDP ENCRFQHQTL ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN
151 PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
201 PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGSRPFAKF
251 IGGGGSKTHT CPPCPAPEAA GGPSVFLFPP KPKDTLMISR TPEVTCVVVD
301 VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN
351 GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR EEMTKNQVSL
401 TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS
451 RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK*
```

Amino acid sequence of FGF23(R179Q, Q156A)-FcLALAv1 (SEQ ID NO: 61)

FGF23: 1-251; Linker: 252-256; FcLALA: 257-482

```
  1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNS
 51 YHLQIHKNGH VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
101 NIFGSHYFDP ENCRFQHQTL ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN
151 PPPYSAFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
201 PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGCRPFAKF
251 IGGGGSKTHT CPPCPAPEAA GGPSVFLFPP KPKDTLMISR TPEVTCVVVD
301 VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN
351 GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR EEMTKNQVSL
401 TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS
451 RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK*
```

Amino acid sequence of FGF23(R179Q, C206S, C244S)-FcLALAv1 (SEQ ID NO: 62)

FGF23: 1-251; Linker: 252-256; FcLALA: 257-482

```
  1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNS
 51 YHLQIHKNGH VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
101 NIFGSHYFDP ENCRFQHQTL ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN
151 PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
201 PAPASSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGSRPFAKF
251 IGGGGSKTHT CPPCPAPEAA GGPSVFLFPP KPKDTLMISR TPEVTCVVVD
301 VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN
351 GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR EEMTKNQVSL
401 TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS
451 RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK*
```

Amino acid sequence of FGF23(R179Q, C206S, C244S, Q156A)-FcLALAv1 (SEQ ID NO: 63)

FGF23: 1-251; Linker: 252-256; FcLALA: 257-482

```
  1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNS
 51 YHLQIHKNGH VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
101 NIFGSHYFDP ENCRFQHQTL ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN
151 PPPYSAFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
201 PAPASSSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGSRPFAKF
251 IGGGGSKTHT CPPCPAPEAA GGPSVFLFPP KPKDTLMISR TPEVTCVVVD
301 VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN
351 GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR EEMTKNQVSL
401 TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS
451 RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK*
```

Amino acid sequence of FGF23(R179Q, C206S)-FcLALAv2 (SEQ ID NO: 64)

FGF23: 1-251; Linker: 252-256; FcLALA: 257-473

```
  1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNS
 51 YHLQIHKNGH VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
101 NIFGSHYFDP ENCRFQHQTL ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN
151 PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
201 PAPASSSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGCRPFAKF
251 IGGGGSAPEA AGGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK
301 FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS
351 NKALPAPIEK TISKAKGQPR EPQVYTLPPS REEMTKNQVS LTCLVKGFYP
401 SDIAVEWESN GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS
451 CSVMHEALHN HYTQKSLSLS PGK*
```

Amino acid sequence of FGF23(R179Q,C244S)-FcLALAv2 (SEQ ID NO: 65)

FGF23: 1-251; Linker: 252-256; FcLALA: 257-473

```
  1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNS
 51 YHLQIHKNGH VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
101 NIFGSHYFDP ENCRFQHQTL ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN
151 PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
201 PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGSRPFAKF
251 IGGGGSAPEA AGGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK
301 FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS
351 NKALPAPIEK TISKAKGQPR EPQVYTLPPS REEMTKNQVS LTCLVKGFYP
401 SDIAVEWESN GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS
```

451 CSVMHEALHN HYTQKSLSLS PGK*

Amino acid sequence of FGF23(R179Q,Q156A)-FcLALAv2 (SEQ ID NO: 66)

FGF23: 1-251; Linker: 252-256; FcLALA: 257-473

```
  1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNS
 51 YHLQIHKNGH VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
101 NIFGSHYFDP ENCRFQHQTL ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN
151 PPPYSAFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
201 PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGCRPFAKF
251 IGGGGSAPEA AGGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK
301 FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS
351 NKALPAPIEK TISKAKGQPR EPQVYTLPPS REEMTKNQVS LTCLVKGFYP
401 SDIAVEWESN GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS
451 CSVMHEALHN HYTQKSLSLS PGK*
```

Amino acid sequence of FGF23(R179Q, C206S, C244S)-FcLALAv2 (SEQ ID NO: 67)

FGF23: 1-251; Linker: 252-256; FcLALA: 257-473

```
  1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNS
 51 YHLQIHKNGH VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
101 NIFGSHYFDP ENCRFQHQTL ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN
151 PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
201 PAPASSSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGSRPFAKF
251 IGGGGSAPEA AGGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK
301 FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS
351 NKALPAPIEK TISKAKGQPR EPQVYTLPPS REEMTKNQVS LTCLVKGFYP
401 SDIAVEWESN GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS
451 CSVMHEALHN HYTQKSLSLS PGK*
```

Amino acid sequence of FGF23(R179Q, C206S, C244S, Q156A)-FcLALAv2 (SEQ ID NO: 68)

FGF23: 1-251; Linker: 252-256; FcLALA: 257-473

```
  1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNS
 51 YHLQIHKNGH VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
101 NIFGSHYFDP ENCRFQHQTL ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN
151 PPPYSAFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
201 PAPASSSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGSRPFAKF
251 IGGGGSAPEA AGGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK
301 FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS
351 NKALPAPIEK TISKAKGQPR EPQVYTLPPS REEMTKNQVS LTCLVKGFYP
401 SDIAVEWESN GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS
```

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451 CSVMHEALHN HYTQKSLSLS PGK*

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A fusion polypeptide comprising: (a) a polypeptide comprising fibroblast growth factor 23 (FGF23), or a functionally active variant or derivative thereof, wherein FGF23 has a mutation at one or more of the positions Q156, C206 and C244; and (b) either a modified Fc fragment having decreased affinity for Fc-gamma-receptor and/or increased serum half-life, or a polypeptide comprising at least one extracellular subdomain of a Klotho protein, or a functionally active variant or derivative thereof; and, optionally (c) a linker.

2. The fusion polypeptide of claim 1, wherein the polypeptide of (a) is operatively linked to the N-terminus of the polypeptide of (b).

3. The fusion polypeptide of claim 1 or claim 2, wherein the polypeptide of (b) is operatively linked to the N-terminus of the polypeptide of (a).

4. The fusion polypeptide of any one of claims 1 to 3, wherein the polypeptide of (a) and the polypeptide of (b) are connected by a polypeptide linker.

5. The fusion polypeptide of claim 4, wherein the polypeptide linker comprises an amino acid sequence selected from the group consisting of: SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, and SEQ ID NO: 18.

6. The fusion polypeptide of claim 4, wherein the polypeptide linker comprises at least 1 and up to about 30 repeats of an amino acid sequence selected from the group consisting of: SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, and SEQ ID NO: 18.

7. The fusion polypeptide of claim 4, wherein the polypeptide of (a) is connected by a peptide bond to the N-terminus of said polypeptide linker, and the polypeptide of (b) is connected by a peptide bond to the C-terminus of said polypeptide linker.

8. The fusion polypeptide of claim 4, wherein the polypeptide of (a) is connected by a peptide bond to the C-terminus of said polypeptide linker, and the polypeptide of (b) is connected by a peptide bond to the N-terminus of said polypeptide linker.

9. The fusion polypeptide of any one of claims 1 to 8, wherein the extracellular subdomain of the Klotho protein is a KL-D 1 domain or a KL-D2 domain.

10. The fusion polypeptide of any one of claims 1 to 9, wherein the polypeptide of (a) comprises at least two extracellular subdomains of the Klotho protein.

11. The fusion polypeptide of claim 10, wherein the at least two extracellular subdomains of the Klotho protein are at least two KL-Dl domains in tandem repeats.

12. The fusion polypeptide of claim 10, wherein the at least two extracellular subdomains of the Klotho protein are at least two KL-D2 domains in tandem repeats.

13. The fusion polypeptide of claim 10, wherein the at least two extracellular subdomains of Klotho protein comprise a KL-Dl domain and a KL-D2 domain.

14. The fusion polypeptide of any one of claims 1 to 10, wherein the polypeptide of (a) is the extracellular domain of the Klotho protein.

15. The fusion polypeptide of any one of claims 1 to 4, further comprising a signal peptide.

16. The fusion polypeptide of claim 15, wherein the signal peptide is the Klotho signal peptide.

17. The fusion polypeptide of claim 15, wherein the signal peptide is the IgG signal peptide.

18. The fusion polypeptide of any one of claims 1 to 17 that specifically binds to a fibroblast growth factor receptor.

19. The fusion polypeptide of any one of claims 1 to 18, wherein the Klotho protein is alpha-Klotho.

20. The fusion polypeptide of any one of claims 1 to 18, wherein the Klotho protein is beta-Klotho.

21. The fusion polypeptide of claim 19, wherein the fibroblast growth factor is fibroblast growth factor-23 (FGF23) or a fibroblast growth factor-23 variant (R179Q).

22. The fusion polypeptide of any one of claims 1 to 21 comprising an amino acid sequence which is 95% or more identical to the amino acid sequence of SEQ ID NO: 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, or 68.

23. The fusion polypeptide of claim 1 having the amino acid sequence of SEQ ID NO: 58, or SEQ ID NO: 68.

24. The fusion polypeptide of any one of claims 1 to 23 comprising FcLALA.

25. A pharmaceutical composition comprising the fusion polypeptide of any one of claims 1 to 24 and a pharmaceutically acceptable carrier.

26. A nucleic acid comprising a sequence that encodes the fusion polypeptide of any one of claims 1 to 24.

27. A host cell containing the nucleic acid of claim 26.

28. A vector comprising the nucleic acid of claim 26.

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29. A method for treating or preventing an age-related condition in an individual, comprising administering to an individual in need thereof a therapeutically effective dose of a pharmaceutical composition comprising a fusion polypeptide comprising: (a) a polypeptide comprising fibroblast growth factor 23 (FGF23), or a functionally active variant or derivative thereof, wherein FGF23 has a mutation at one or more of the positions Q156, C206 and C244; and (b) either a modified Fc fragment having decreased affinity for Fc-gamma-receptor and/or increased serum half- life, or a polypeptide comprising at least one extracellular subdomain of a Klotho protein, or a functionally active variant or derivative thereof; and, optionally (c) a linker.

30. The method of claim 29, wherein the age-related condition is selected from the group consisting of sarcopenia, skin atrophy, muscle wasting, brain atrophy, atherosclerosis, arteriosclerosis, pulmonary emphysema, osteoporosis, osteoarthritis, immunologic incompetence, high blood pressure, dementia, Huntington's disease, Alzheimer's disease, cataracts, age-related macular degeneration, prostate cancer, stroke, diminished life expectancy, memory loss, wrinkles, impaired kidney function, and age-related hearing loss.

31. The method of claim 30, wherein the age-related condition is muscle wasting, the Klotho protein is alpha Klotho protein, and the fibroblast growth factor is fibroblast growth factor 23.

32. A method for treating or preventing a metabolic disorder in an individual, comprising administering to an individual in need thereof a therapeutically effective dose of a pharmaceutical composition comprising a fusion polypeptide, comprising: (a) a polypeptide comprising fibroblast growth factor 23 (FGF23), or a functionally active variant or derivative thereof, wherein FGF23 has a mutation at one or more of the positions Q156, C206 and C244; and (b) either a modified Fc fragment having decreased affinity for Fc-gamma-receptor and/or increased serum half- life, or a polypeptide comprising at least one extracellular subdomain of a Klotho protein, or a functionally active variant or derivative thereof; and, optionally (c) a linker.

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33. The method of claim 32, wherein the metabolic disorder is selected from the group consisting of Type II Diabetes, Metabolic Syndrome, hyperglycemia, and obesity.

34. A method for treating or preventing hyperphosphatemia or calcinosis in an individual, comprising administering to an individual in need thereof a therapeutically effective dose of a pharmaceutical composition comprising a fusion polypeptide, comprising: (a) a polypeptide comprising fibroblast growth factor 23 (FGF23), or a functionally active variant or derivative thereof, wherein FGF23 has a mutation at one or more of the positions Q156, C206 and C244; and (b) either a modified Fc fragment having decreased affinity for Fc-gamma-receptor and/or increased serum half-life, or a polypeptide comprising at least one extracellular subdomain of a Klotho protein, or a functionally active variant or derivative thereof; and, optionally (c) a linker.

35. The method of claim 34, wherein the fusion polypeptide comprises: (a) a polypeptide that comprises at least one extracellular subdomain of an alpha Klotho protein; and (b) a polypeptide that comprises a fibroblast growth factor 23.

36. A method for treating or preventing chronic renal disease or chronic renal failure in an individual, comprising administering to an individual in need thereof a therapeutically effective dose of a pharmaceutical composition comprising a fusion polypeptide, comprising: (a) a polypeptide comprising fibroblast growth factor 23 (FGF23), or a functionally active variant or derivative thereof, wherein FGF23 has a mutation at one or more of the positions Q156, C206 and C244; and (b) either a modified Fc fragment having decreased affinity for Fc-gamma-receptor and/or increased serum half-life, or a polypeptide comprising at least one extracellular subdomain of a Klotho protein, or a functionally active variant or derivative thereof; and, optionally (c) a linker.

37. A method for treating or preventing cancer in an individual, comprising administering to an individual in need thereof a therapeutically effective dose of a pharmaceutical composition comprising a fusion polypeptide, comprising: (a) a polypeptide comprising fibroblast growth factor 23 (FGF23), or a functionally active variant or derivative thereof, wherein FGF23 has a mutation at one or more of the positions

Q156, C206 and C244; and (b) either a modified Fc fragment having decreased affinity for Fc-gamma-receptor and/or increased serum half-life, or a polypeptide comprising at least one extracellular subdomain of a Klotho protein, or a functionally active variant or derivative thereof; and, optionally (c) a linker.

38. The method of claim 37, wherein the cancer is breast cancer.

39. The method of any one of claims 29, 32, 34, 36 and 37, wherein the Klotho protein is an alpha Klotho protein.

40. The fusion polypeptide of any one of claims 1 to 24 or the method of any one of claims 29 to 39, wherein the Klotho protein is a human Klotho protein.

41. Use of the fusion polypeptide of any one of claims 1 to 24 in the manufacture of a medicament for treating or preventing muscle atrophy, an age-related condition, a metabolic disorder, hyperphosphatemia, calcinosis, chronic renal disease, chronic renal failure or cancer.

42. A method of treating or preventing muscle atrophy comprising administering to an individual in need thereof a therapeutically effective dose of a pharmaceutical composition comprising a soluble Klotho fusion protein of SEQ ID NO: 47, or SEQ ID NO: 49.

43. A method of treating or preventing muscle atrophy comprising administering to an individual in need thereof a therapeutically effective dose of a pharmaceutical composition comprising (a) a polypeptide comprising fibroblast growth factor 23 (FGF23), or a functionally active variant or derivative thereof, wherein FGF23 has a mutation at one or more of the positions Q156, C206 and C244; and (b) either a modified Fc fragment having decreased affinity for Fc-gamma-receptor and/or increased serum half-life, or a polypeptide comprising at least one extracellular subdomain of a Klotho protein, or a functionally active variant or derivative thereof; and, optionally (c) a linker.

44. The fusion polypeptide of claim 1 or the method of any one of claims 29, 32, 34,

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36, 37, 42 and 43, substantially as herein described.

REPLACEMENT SHEET

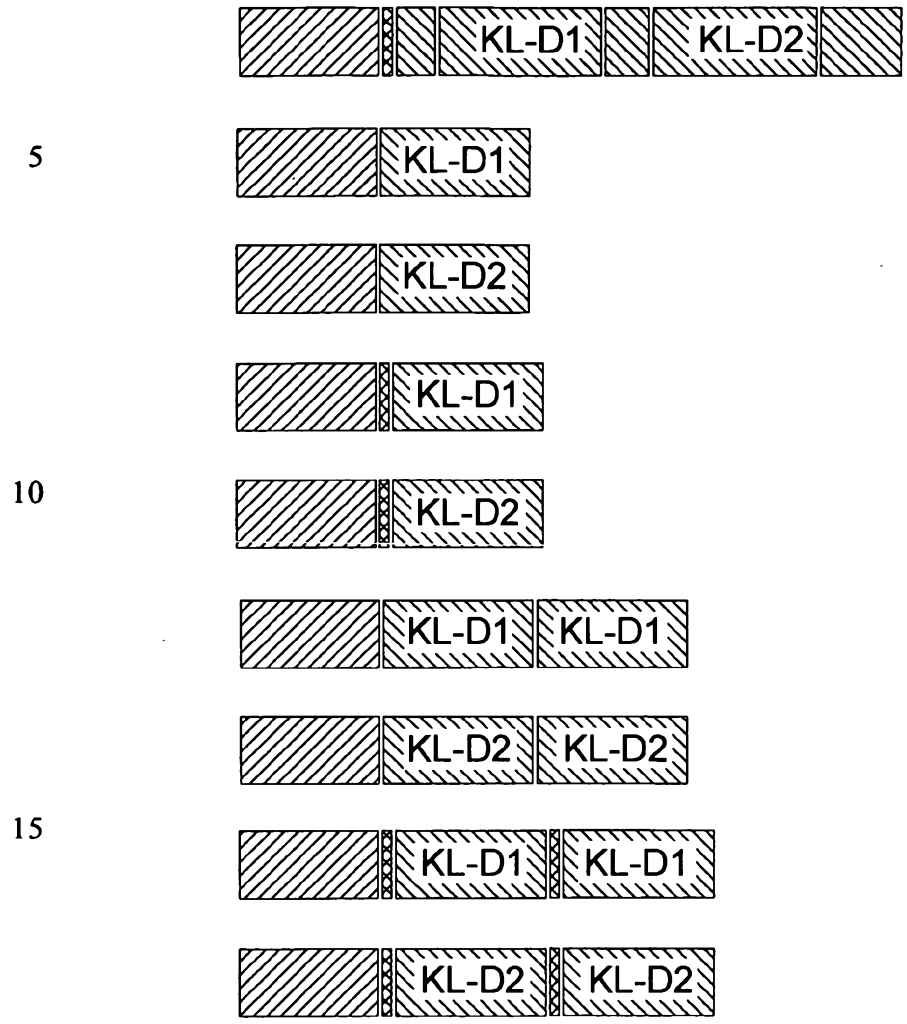
Figure 1

: Klotho (extracellular domain) or active fragment of Klotho;

: FGF23 (R179Q), FGF23, FGF 19, FGF21; : linker; : IgG signal peptide.

REPLACEMENT SHEET

Figure 1 (continued)



: Klotho (extracellular domain) or active fragment of Klotho;

: FGF23 (R179Q), FGF23, FGF 19, FGF21; : linker; : IgG signal peptide.

REPLACEMENT SHEET

Figure 2

Human Klotho nucleic acid sequence (NM_004795) (SEQ ID NO: 1)
Protein coding region: 9-3047

```
   1 cgcgcagcat gcccgccagc gccccgccgc gccgcccgcg gccgccgccg ccgtcgctgt
  61 cgctgctgct ggtgctgctg ggcctgggcg gccgccgcct gcgtgcggag ccgggcgacg
 121 gcgcgcagac ctgggcccgt ttctcgcggc ctcctgcccc cgaggccgcg ggcctcttcc
 181 agggcacctt ccccgacggc ttcctctggg ccgtgggcag cgccgcctac cagaccgagg
 241 gcggctggca gcagcacggc aagggtgcgt ccatctggga tacgttcacc caccaccccc
 301 tggcaccccc gggagactcc cggaacgcca gtctgccgtt gggcgccccg tcgccgctgc
 361 agcccgccac cggggacgta gccagcgaca gctacaacaa cgtcttccgc gacacggagg
 421 cgctgcgcga gctcggggtc actcactacc gcttctccat ctcgtgggcg cgagtgctcc
 481 ccaatggcag cgcgggcgtc cccaaccgcg aggggctgcg ctactaccgg cgcctgctgg
 541 agcggctgcg ggagctgggc gtgcagcccg tggtcaccct gtaccactgg gacctgcccc
 601 agcgcctgca ggacgcctac ggcggctggg ccaaccgcgc cctggccgac cacttcaggg
 661 attacgcgga gctctgcttc cgccacttcg gcggtcaggt caagtactgg atcaccatcg
 721 acaaccccta cgtggtggcc tggcacggct acgccaccgg gcgcctggcc cccggcatcc
 781 ggggcagccc gcggctcggg tacctggtgg cgcacaacct cctcctggct catgccaaag
 841 tctggcatct ctacaatact tctttccgtc ccactcaggg aggtcaggtg tccattgccc
 901 taagctctca ctggatcaat cctcgaagaa tgaccgacca cagcatcaaa gaatgtcaaa
 961 aatctctgga ctttgtacta ggttggtttg ccaaacccgt atttattgat ggtgactatc
1021 ccgagagcat gaagaataac ctttcatcta ttctgcctga ttttactgaa tctgagaaaa
1081 agttcatcaa aggaactgct gacttttttg ctctttgctt tggacccacc ttgagttttc
1141 aacttttgga ccctcacatg aagttccgcc aattggaatc tcccaacctg aggcaactgc
1201 tttcctggat tgaccttgaa tttaaccatc ctcaaatatt tattgtggaa aatggctggt
1261 ttgtctcagg gaccaccaag agagatgatg ccaaatatat gtattacctc aaaaagttca
1321 tcatggaaac cttaaaagcc atcaagctgg atggggtgga tgtcatcggg tataccgcat
1381 ggtccctcat ggatggtttc gagtggcaca gaggttacag catcaggcgt ggactcttct
1441 atgttgactt tctaagccag gacaagatgt tgttgccaaa gtcttcagcc ttgttctacc
1501 aaaagctgat agagaaaaat ggcttccctc ctttacctga aaatcagccc ctagaaggga
1561 catttccctg tgactttgct tggggagttg ttgacaacta cattcaagta gataccactc
1621 tgtctcagtt taccgacctg aatgtttacc tgtgggatgt ccaccacagt aaaaggctta
1681 ttaaagtgga tggggttgtg accaagaaga ggaaatccta ctgtgttgac tttgctgcca
1741 tccagcccca gatcgcttta ctccaggaaa tgcacgttac acattttcgc ttctccctgg
1801 actgggccct gattctccct ctgggtaacc agtcccaggt gaaccacacc atcctgcagt
1861 actatcgctg catggccagc gagcttgtcc gtgtcaacat caccccagtg gtggccctgt
1921 ggcagcctat ggccccgaac caaggactgc cgcgcctcct ggccaggcag ggcgcctggg
1981 agaaccccta cactgccctg gcctttgcag agtatgcccg actgtgcttt caagagctcg
2041 gccatcacgt caagctttgg ataacgatga atgagccgta tacaaggaat atgacataca
2101 gtgctggcca caaccttctg aaggcccatg ccctggcttg gcatgtgtac aatgaaaagt
2161 ttaggcatgc tcagaatggg aaaatatcca tagccttgca ggctgattgg atagaacctg
2221 cctgcccttt ctcccaaaag gacaaagagg tggccgagag agttttggaa tttgacattg
2281 gctggctggc tgagcccatt ttcggctctg gagattatcc atgggtgatg agggactggc
2341 tgaaccaaag aaacaatttt cttcttcctt atttcactga agatgaaaaa aagctaatcc
2401 agggtacctt tgacttttta gctttaagcc attataccac catccttgta gactcagaaa
2461 aagaagatcc aataaaatac aatgattacc tagaagtgca agaaatgacc gacatcacgt
2521 ggctcaactc ccccagtcag gtggcggtag tgccctgggg gttgcgcaaa gtgctgaact
2581 ggctgaagtt caagtacgga gacctcccca tgtacataat atccaacgga atcgatgacg
2641 ggctgcatgc tgaggacgac cagctgaggg tgtattatat gcagaattac ataaacgaag
2701 ctctcaaagc ccacatactg gatggtatca atctttgcgg atactttgct tattcgttta
2761 acgaccgcac agctccgagg tttggcctct atcgttatgc tgcagatcag tttgagccca
2821 aggcatccat gaaacattac aggaaaatta ttgacagcaa tggtttcccg ggcccagaaa
2881 ctctggaaag attttgtcca gaagaattca ccgtgtgtac tgagtgcagt ttttttcaca
2941 cccgaaagtc tttactggct ttcatagctt ttctattttt tgcttctatt atttctctct
3001 cccttatatt ttactactcg aagaaaggca gaagaagtta caaatagttc tgaacatttt
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REPLACEMENT SHEET

```
3061 tctattcatt cattttgaaa taattatgca gacacatcag ctgttaacca tttgcacctc
3121 taagtgttgt gaaactgtaa atttcataca tttgacttct agaaaacatt tttgtggctt
3181 atgacagagg ttttgaaatg ggcatagggtg atcgtaaaat attgaataat gcgaatagtg
3241 cctgaatttg ttctcttttt gggtgattaa aaaactgaca ggcactataa tttctgtaac
3301 acactaacaa aagcatgaaa aataggaacc acaccaatgc aacatttgtg cagaaatttg
3361 aatgacaaga ttaggaatat tttcttctgc acccacttct aaatttaatg tttttctgga
3421 agtagtaatt gcaagagttc gaatagaaag ttatgtacca agtaaccatt tctcagctgc
3481 cataataatg cctagtggct tcccctctgt caaatctagt ttcctatgga aaagaagatg
3541 gcagatacag gagagacgac agagggtcct aggctggaat gttcctttcg aaagcaatgc
3601 ttctatcaaa tactagtatt aatttatgta tctggttaat gacatacttg gagagcaaat
3661 tatggaaatg tgtattttat atgatttttg aggtcctgtc taaaccctgt gtccctgagg
3721 gatctgtctc actggcatct tgttgagggc cttgcacata ggaaactttt gataagtatc
3781 tgcggaaaaa caaacatgaa tcctgtgata ttgggctctt caggaagcat aaagcaattg
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3901 gtgcaacatt atgattaatc tgattataca ccatttttga gcagatcttg gaatgaatga
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4021 actttctatt ctttagctgt actgtaattt ctttgagttg atagttttac aaattcttaa
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4141 tattttatgt ttttgctgct acttctgtgg aagtagcttt gaactagttt tactttgaac
4201 tttcacgctg aaacatgcta gtgatatcta gaaagggcta attaggtctc atcctttaat
4261 gccccttaaa taagtcttgc tgattttcag acagggaagt ctctctatta cactggagct
4321 gttttataga taagtcaata ttgtatcagg caagataaac caatgtcata acaggcattg
4381 ccaacctcac tgacacaggg tcatagtgta taataatata ctgtactata taatatatca
4441 tctttagagg tatgattttt tcatgaaaga taagcttttg gtaatattca ttttaaagtg
4501 gacttattaa aattggatgc tagagaatca agtttatttt atgtatatat ttttctgatt
4561 ataagagtaa tatatgttca ttgtaaaaat ttttaaaaca cagaaactat atgcaaagaa
4621 aaaataaaaa ttatctataa tctcagaacc cagaaatagc cactattaac atttcctacg
4681 tattttattt tacatagatc atattgtata tagttagtat ctttattaat ttttattatg
4741 aaactttcct ttgtcattat tagtcttcaa aagcatgatt tttaatagtt gttgagtatt
4801 ccaccacagg aatgtatcac aacttaaccg ttcccgtttg ttagactagt ttcttattaa
4861 tgttgatgaa tgttgtttaa aaataatttt gttgctacat ttactttaat ttccttgact
4921 gtaaagagaa gtaattttgc tccttgataa agtattatat taataataaa tctgcctgca
4981 acttttgcc ttctttcata atc
```

Klotho amino acid sequence (NP_004786) (SEQ ID NO: 2)

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  1 MPASAPPRRP RPPPPSLSLL LVLLGLGGRR LRAEPGDGAQ TWARFSRPPA PEAAGLFQGT
 61 FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP PGDSRNASLP LGAPSPLQPA
121 TGDVASDSYN NVFRDTEALR ELGVTHYRFS ISWARVLPNG SAGVPNREGL RYYRRLLERL
181 RELGVQPVVT LYHWDLPQRL QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP
241 YVVAWHGYAT GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP DFTESEKKFI
361 KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW IDLEFNHPQI FIVENGWFVS
421 GTTKRDDAKY MYYLKKFIME TLKAIKLDGV DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD
481 FLSQDKMLLP KSSALFYQKL IEKNGFPPLP ENQPLEGTFP CDFAWGVVDN YIQVDTTLSQ
541 FTDLNVYLWD VHHSKRLIKV DGVVTKKRKS YCVDFAAIQP QIALLQEMHV THFRFSLDWA
601 LILPLGNQSQ VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL LARQGAWENP
661 YTALAFAEYA RLCFQELGHH VKLWITMNEP YTRNMTYSAG HNLLKAHALA WHVYNEKFRH
721 AQNGKISIAL QADWIEPACP FSQKDKEVAE RVLEFDIGWL AEPIFGSGDY PWVMRDWLNQ
781 RNNFLLPYFT EDEKKLIQGT FDFLALSHYT TILVDSEKED PIKYNDYLEV QEMTDITWLN
841 SPSQVAVVPW GLRKVLNWLK FKYGDLPMYI ISNGIDDGLH AEDDQLRVYY MQNYINEALK
901 AHILDGINLC GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIIDS NGFPGPETLE
961 RFCPEEFTVC TECSFFHTRK SLLAFIAFLF FASIISLSLI FYYSKKGRRS YK
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REPLACEMENT SHEET

beta-Klotho nucleic acid sequence (NM_175737) (SEQ ID NO: 3)
Protein coding region: 98-3232

```
   1 atcctcagtc tcccagttca agctaatcat tgacagagct ttacaatcac aagcttttac
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 121 atctccaggg aatgaatgga ttttcttcag cactgatgaa ataaccacac gctataggaa
 181 tacaatgtcc aacgggggat tgcaaagatc tgtcatcctg tcagcactta ttctgctacg
 241 agctgttact ggattctctg gagatggaag agctatatgg tctaaaaatc ctaattttac
 301 tccggtaaat gaaagtcagc tgtttctcta tgacactttc cctaaaaact ttttctgggg
 361 tattgggact ggagcattgc aagtggaagg gagttggaag aaggatggaa aaggaccttc
 421 tatatgggat catttcatcc acacacacct taaaaatgtc agcagcacga atggttccag
 481 tgacagttat atttttctgg aaaaagactt atcagccctg gattttatag gagtttcttt
 541 ttatcaattt tcaatttcct ggccaaggct tttccccgat ggaatagtaa cagttgccaa
 601 cgcaaaaggt ctgcagtact acagtactct tctggacgct ctagtgctta gaaacattga
 661 acctatagtt actttatacc actgggattt gcctttggca ctacaagaaa aatatggggg
 721 gtggaaaaat gataccataa tagatatctt caatgactat gccacatact gtttccagat
 781 gtttggggac cgtgtcaaat attggattac aattcacaac ccatatctag tggcttggca
 841 tgggtatggg acaggtatgc atgcccctgg agagaaggga aatttagcag ctgtctacac
 901 tgtgggacac aacttgatca aggctcactc gaaagtttgg cataactaca acacacattt
 961 ccgcccacat cagaagggtt ggttatcgat cacgttggga tctcattgga tcgagccaaa
1021 ccggtcggaa aacacgatgg atatattcaa atgtcaacaa tccatggttt ctgtgcttgg
1081 atggtttgcc aaccctatcc atggggatgg cgactatcca gaggggatga gaaagaagtt
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1201 tttctttgcc ttttcttttg gacccaacaa cttcaagccc ctaaacacca tggctaaaat
1261 gggacaaaat gtttcactta atttaagaga agcgctgaac tggattaaac tggaatacaa
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1381 agacaccacg gccatctaca tgatgaagaa tttcctcagc caggtgcttc aagcaataag
1441 gttagatgaa atacgagtgt ttggttatac tgcctggtct ctcctggatg gctttgaatg
1501 gcaggatgct tacaccatcc gccgaggatt attttatgtg gattttaaca gtaaacagaa
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1681 tgtcactgaa tctgttctta agcccgagtc tgtggcttcg tccccacagt tcagcgatcc
1741 tcatctgtac gtgtggaacg ccactggcaa cagactgttg caccgagtgg aaggggtgag
1801 gctgaaaaca cgacccgctc aatgcacaga ttttgtaaac atcaaaaaac aacttgagat
1861 gttggcaaga atgaaagtca cccactaccg gtttgctctg gattgggcct cggtccttcc
1921 cactggcaac ctgtccgcgg tgaaccgaca ggccctgagg tactacaggt gcgtggtcag
1981 tgaggggctg aagcttggca tctccgcgat ggtcaccctg tattatccga cccacgccca
2041 cctaggcctc cccgagcctc tgttgcatgc cgacgggtgg ctgaacccat cgacggccga
2101 ggccttccag gcctacgctg ggctgtgctt ccaggagctg ggggacctgg tgaagctctg
2161 gatcaccatc aacgagccta accggctaag tgacatctac aaccgctctg gcaacgacac
2221 ctacggggcg gcgcacaacc tgctggtggc ccacgccctg gcctggcgcc tctacgaccg
2281 gcagttcagg ccctcacagc gcggggccgt gtcgctgtcg ctgcacgcgg actgggcgga
2341 acccgccaac ccctatgctg actcgcactg gagggcggcc gagcgcttcc tgcagttcga
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2521 ggccgaaagg aggctgctca agggcacggt cgacttctgc gcgctcaacc acttcaccac
2581 taggttcgtg atgcacgagc agctggccgg cagccgctac gactcggaca gggacatcca
2641 gtttctgcag gacatcaccc gcctgagctc ccccacgcgc ctggctgtga ttccctgggg
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2761 cgccagtggc atcgacgacc aggctctgga ggatgaccgg ctccggaagt actacctagg
2821 gaagtacctt caggaggtgc tgaaagcata cctgattgat aaagtcagaa tcaaaggcta
2881 ttatgcattc aaactggctg aagagaaatc taaacccaga tttggattct tcacatctga
2941 ttttaaagct aaatcctcaa tacaatttta caacaaagtg atcagcagca ggggcttccc
3001 ttttgagaac agtagttcta gatgcagtca gacccaagaa aatacagagt gcactgtctg
3061 cttattcctt gtgcagaaga aaccactgat attcctgggt tgttgcttct tctccaccct
3121 ggttctactc ttatcaattg ccatttttca aaggcagaag agaagaaagt tttggaaagc
```

REPLACEMENT SHEET

```
3181 aaaaaactta caacacatac cattaaagaa aggcaagaga gttgttagct aaactgatct
3241 gtctgcatga tagacagttt aaaaattcat cccagttcc
```

beta-Klotho amino acid sequence (NP_783864) (SEQ ID NO: 4)

```
   1 mkpgcaagsp gnewiffstd eittryrntm sngglqrsvi lsalillrav tgfsgdgrai
  61 wsknpnftpv nesqlflydt fpknffwgig tgalqvegsw kkdgkgpsiw dhfihthlkn
 121 vsstngssds yiflekdlsa ldfigvsfyq fsiswprlfp dgivtvanak glqyystlld
 181 alvlrniepi vtlyhwdlpl alqekyggwk ndtiidifnd yatycfqmfg drvkywitih
 241 npylvawhgy gtgmhapgek gnlaavytvg hnlikahskv whnynthfrp hqkgwlsitl
 301 gshwiepnrs entmdifkcq qsmvsvlgwf anpihgdgdy pegmrkklfs vlpifseaek
 361 hemrgtadff afsfgpnnfk plntmakmgq nvslnlreal nwikleynnp riliaengwf
 421 tdsrvktedt taiymmknfl sqvlqairld eirvfgytaw slldgfewqd aytirrglfy
 481 vdfnskqker kpkssahyyk qiirengfsl kestpdvqgq fpcdfswgvt esvlkpesva
 541 sspqfsdphl yvwnatgnrl lhrvegvrlk trpaqctdfv nikkqlemla rmkvthyrfa
 601 ldwasvlptg nlsavnrqal ryyrcvvseg lklgisamvt lyypthahlg lpepllhadg
 661 wlnpstaeaf qayaglcfqe lgdlvklwit inepnrlsdi ynrsgndtyg aahnllvaha
 721 lawrlydrqf rpsqrgavsl slhadwaepa npyadshwra aerflqfeia wfaeplfktg
 781 dypaamreyi askhrrglss salprlteae rrllkgtvdf calnhfttrf vmheqlagsr
 841 ydsdrdiqfl qditrlsspt rlavipwgvr kllrwvrrny gdmdiyitas giddqaledd
 901 rlrkyylgky lqevlkayli dkvrikgyya fklaeekskp rfgfftsdfk akssiqfynk
 961 vissrgfpfe nsssrcsqtq entectvclf lvqkkplifl gccffstlvl llsiaifqrq
1021 krrkfwkakn lqhiplkkgk rvvs
```

Human Klotho domain 1 (KL-D1) amino acid sequence (SEQ ID NO: 5)

```
  58                                                              qgt
  61 fpdgflwavg saayqteggw qqhgkgasiw dtfthhplap pgdsrnaslp lgapsplqpa
 121 tgdvasdsyn nvfrdtealr elgvthyrfs iswarvlpng sagvpnregl ryyrrllerl
 181 relgvqpvvt lyhwdlpqrl qdayggwanr aladhfrdya elcfrhfggq vkywitidnp
 241 yvvawhgyat grlapgirgs prlgylvahn lllahakvwh lyntsfrptq ggqvsialss
 301 hwinprrmtd hsikecqksl dfvlgwfakp vfidgdypes mknnlssilp dftesekkfi
 361 kgtadffalc fgptlsfqll dphmkfrqle spnlrqllsw idlefnhpqi fivengwfvs
 421 gttkrddaky myylkkfime tlkaikldgv dvigytawsl mdgfewhrgy sirrglfyvd
 481 flsqdkmllp kssalfyqkl iekngf
```

Human Klotho domain 2 (KL-D2) amino acid sequence (SEQ ID NO: 6)

```
 517                                          gtfp cdfawgvvdn yiqvdttlsq
 541 ftdlnvylwd vhhskrlikv dgvvtkkrks ycvdfaaiqp qiallqemhv thfrfsldwa
 601 lilplgnqsq vnhtilqyyr cmaselvrvn itpvvalwqp mapnqglprl larqgawenp
 661 ytalafaeya rlcfqelghh vklwitmnep ytrnmtysag hnllkahala whvynekfrh
 721 aqngkisial qadwiepacp fsqkdkevae rvlefdigwl aepifgsgdy pwvmrdwlnq
 781 rnnfllpyft edekkliqgt fdflalshyt tilvdseked pikyndylev qemtditwln
 841 spsqvavvpw glrkvlnwlk fkygdlpmyi isngiddglh aeddqlrvyy mqnyinealk
 901 ahildginlc gyfaysfndr taprfglyry aadqfepkas mkhyrkiids ngf
```

Klotho extracellular domain (without signal peptide) amino acid sequence (SEQ ID NO: 7)

```
  28                                       epgdgaq twarfsrppa peaaglfqgt
  61 fpdgflwavg saayqteggw qqhgkgasiw dtfthhplap pgdsrnaslp lgapsplqpa
 121 tgdvasdsyn nvfrdtealr elgvthyrfs iswarvlpng sagvpnregl ryyrrllerl
 181 relgvqpvvt lyhwdlpqrl qdayggwanr aladhfrdya elcfrhfggq vkywitidnp
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REPLACEMENT SHEET

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241 yvvawhgyat grlapgirgs prlgylvahn lllahakvwh lyntsfrptq ggqvsialss
301 hwinprrmtd hsikecqksl dfvlgwfakp vfidgdypes mknnlssilp dftesekkfi
361 kgtadffalc fgptlsfqll dphmkfrqle spnlrqllsw idlefnhpqi fivengwfvs
421 gttkrddaky myylkkfime tlkaikldgv dvigytawsl mdgfewhrgy sirrglfyvd
481 flsqdkmllp kssalfyqkl iekngfpplp enqplegtfp cdfawgvvdn yiqvdttlsq
541 ftdlnvylwd vhhskrlikv dgvvtkkrks ycvdfaaiqp qiallqemhv thfrfsldwa
601 lilplgnqsq vnhtilqyyr cmaselvrvn itpvvalwqp mapnqglprl larqgawenp
661 ytalafaeya rlcfqelghh vklwitmnep ytrnmtysag hnllkahala whvynekfrh
721 aqngkisial qadwiepacp fsqkdkevae rvlefdigwl aepifgsgdy pwvmrdwlnq
781 rnnfllpyft edekkliqgt fdflalshyt tilvdseked pikyndylev qemtditwln
841 spsqvavvpw glrkvlnwlk fkygdlpmyi isngiddglh aeddqlrvyy mqnyinealk
901 ahildginlc gyfaysfndr taprfglyry aadqfepkas mkhyrkiids ngfpgpetle
961 rfcpeeftvc tecsffhtrk sl
```

Klotho signal peptide amino acid sequence (SEQ ID NO: 8)

```
1 mpasapprrp rppppslsll lvllglggrr lra
```

IgG signal peptide amino acid sequence (SEQ ID NO: 9)

```
1 msvltqvlal lllwltgtrc rrlra
```

$(Gly_4\ Ser)_3$ polypeptide linker nucleic acid sequence (SEQ ID NO: 10)

```
1 ggaggtggag gttcaggagg tggaggttca ggaggtggag gttca
```

$(Gly_4\ Ser)_3$ polypeptide linker amino acid sequence (SEQ ID NO: 11)

```
1 GGGGSGGGGS GGGGS
```

$(Gly_4\ Ser)$ polypeptide linker amino acid sequence (SEQ ID NO: 12)

```
1 GGGGS
```

(Gly) polypeptide linker amino acid sequence (SEQ ID NO: 13)

```
1 G
```

(Gly Gly) polypeptide linker amino acid sequence (SEQ ID NO: 14)

```
1 GG
```

(Gly Ser) polypeptide linker amino acid sequence (SEQ ID NO: 15)

```
1 GS
```

$(Gly_2\ Ser)$ polypeptide linker amino acid sequence (SEQ ID NO: 16)

```
1 GGS
```

REPLACEMENT SHEET

(Ala) polypeptide linker amino acid sequence (SEQ ID NO: 17)

1 A

(Ala Ala) polypeptide linker amino acid sequence (SEQ ID NO: 18)

1 AA

Klotho signal peptide-Klotho extracellular domain-FGF23 (R179Q) amino acid sequence (SEQ ID NO: 19)

```
   1 MPASAPPRRP RPPPPSLSLL LVLLGLGGRR LRAEPGDGAQ TWARFSRPPA
  51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
 101 PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
 151 ISWARVLPNG SAGVPNREGL RYYRRLLERL RELGVQPVVT LYHWDLPQRL
 201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
 251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
 301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP
 351 DFTESEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
 401 IDLEFNHPQI FIVENGWFVS GTTKRDDAKY MYYLKKFIME TLKAIKLDGV
 451 DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD FLSQDKMLLP KSSALFYQKL
 501 IEKNGFPPLP ENQPLEGTFP CDFAWGVVDN YIQVDTTLSQ FTDLNVYLWD
 551 VHHSKRLIKV DGVVTKKRKS YCVDFAAIQP QIALLQEMHV THFRFSLDWA
 601 LILPLGNQSQ VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL
 651 LARQGAWENP YTALAFAEYA RLCFQELGHH VKLWITMNEP YTRNMTYSAG
 701 HNLLKAHALA WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE
 751 RVLEFDIGWL AEPIFGSGDY PWVMRDWLNQ RNNFLLPYFT EDEKKLIQGT
 801 FDFLALSHYT TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW
 851 GLRKVLNWLK FKYGDLPMYI ISNGIDDGLH AEDDQLRVYY MQNYINEALK
 901 AHILDGINLC GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIIDS
 951 NGFPGPETLE RFCPEEFTVC TECSFFHTRK SLGSGGGGSG GGGSGGGGSL
1001 KYPNASPLLG SSWGGLIHLY TATARNSYHL QIHKNGHVDG APHQTIYSAL
1051 MIRSEDAGFV VITGVMSRRY LCMDFRGNIF GSHYFDPENC RFQHQTLENG
1101 YDVYHSPQYH FLVSLGRAKR AFLPGMNPPP YSQFLSRRNE IPLIHFNTPI
1151 PRRHTQSAED DSERDPLNVL KPRARMTPAP ASCSQELPSA EDNSPMASDP
1201 LGVVRGGRVN THAGGTGPEG CRPFAKFI*
```

IgG signal peptide-Klotho extracellular domain-FGF23 (R179Q) amino acid sequence (SEQ ID NO: 20)

```
   1 MSVLTQVLAL LLLWLTGLGG RRLRAEPGDG AQTWARFSRP PAPEAAGLFQ
  51 GTFPDGFLWA VGSAAYQTEG GWQQHGKGAS IWDTFTHHPL APPGDSRNAS
 101 LPLGAPSPLQ PATGDVASDS YNNVFRDTEA LRELGVTHYR FSISWARVLP
 151 NGSAGVPNRE GLRYYRRLLE RLRELGVQPV VTLYHWDLPQ RLQDAYGGWA
 201 NRALADHFRD YAELCFRHFG GQVKYWITID NPYVVAWHGY ATGRLAPGIR
 251 GSPRLGYLVA HNLLLAHAKV WHLYNTSFRP TQGGQVSIAL SSHWINPRRM
 301 TDHSIKECQK SLDFVLGWFA KPVFIDGDYP ESMKNNLSSI LPDFTESEKK
 351 FIKGTADFFA LCFGPTLSFQ LLDPHMKFRQ LESPNLRQLL SWIDLEFNHP
 401 QIFIVENGWF VSGTTKRDDA KYMYYLKKFI METLKAIKLD GVDVIGYTAW
 451 SLMDGFEWHR GYSIRRGLFY VDFLSQDKML LPKSSALFYQ KLIEKNGFPP
 501 LPENQPLEGT FPCDFAWGVV DNYIQVDTTL SQFTDLNVYL WDVHHSKRLI
 551 KVDGVVTKKR KSYCVDFAAI QPQIALLQEM HVTHFRFSLD WALILPLGNQ
```

REPLACEMENT SHEET

```
 601 SQVNHTILQY YRCMASELVR VNITPVVALW QPMAPNQGLP RLLARQGAWE
 651 NPYTALAFAE YARLCFQELG HHVKLWITMN EPYTRNMTYS AGHNLLKAHA
 701 LAWHVYNEKF RHAQNGKISI ALQADWIEPA CPFSQKDKEV AERVLEFDIG
 751 WLAEPIFGSG DYPWVMRDWL NQRNNFLLPY FTEDEKKLIQ GTFDFLALSH
 801 YTTILVDSEK EDPIKYNDYL EVQEMTDITW LNSPSQVAVV PWGLRKVLNW
 851 LKFKYGDLPM YIISNGIDDG LHAEDDQLRV YYMQNYINEA LKAHILDGIN
 901 LCGYFAYSFN DRTAPRFGLY RYAADQFEPK ASMKHYRKII DSNGFPGPET
 951 LERFCPEEFT VCTECSFFHT RKSLGSGGGG SGGGGSGGGG SLKYPNASPL
1001 LGSSWGGLIH LYTATARNSY HLQIHKNGHV DGAPHQTIYS ALMIRSEDAG
1051 FVVITGVMSR RYLCMDFRGN IFGSHYFDPE NCRFQHQTLE NGYDVYHSPQ
1101 YHFLVSLGRA KRAFLPGMNP PPYSQFLSRR NEIPLIHFNT PIPRRHTQSA
1151 EDDSERDPLN VLKPRARMTP APASCSQELP SAEDNSPMAS DPLGVVRGGR
1201 VNTHAGGTGP EGCRPFAKFI *
```

KL-D1-FGF23 (R179Q) amino acid sequence (SEQ ID NO: 21)

```
   1 MPASAPPRRP RPPPPSLSLL LVLLGLGGRR LRAEPGDGAQ TWARFSRPPA
  51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
 101 PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
 151 ISWARVLPNG SAGVPNREGL RYYRRLLERL RELGVQPVVT LYHWDLPQRL
 201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
 251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
 301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP
 351 DFTESEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
 401 IDLEFNHPQI FIVENGWFVS GTTKRDDAKY MYYLKKFIME TLKAIKLDGV
 451 DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD FLSQDKMLLP KSSALFYQKL
 501 IEKNGFPPLP ENQPLEGSGG GGSGGGGSGG GGSLKYPNAS PLLGSSWGGL
 551 IHLYTATARN SYHLQIHKNG HVDGAPHQTI YSALMIRSED AGFVVITGVM
 601 SRRYLCMDFR GNIFGSHYFD PENCRFQHQT LENGYDVYHS PQYHFLVSLG
 651 RAKRAFLPGM NPPPYSQFLS RRNEIPLIHF NTPIPRRHTQ SAEDDSERDP
 701 LNVLKPRARM TPAPASCSQE LPSAEDNSPM ASDPLGVVRG GRVNTHAGGT
 751 GPEGCRPFAK FI*
```

KL-D2-FGF23 (R179Q) amino acid sequence (SEQ ID NO: 22)

```
   1 MPASAPPRRP RPPPPSLSLL LVLLGLGGRR LPLPENQPLE GTFPCDFAWG
  51 VVDNYIQVDT TLSQFTDLNV YLWDVHHSKR LIKVDGVVTK KRKSYCVDFA
 101 AIQPQIALLQ EMHVTHFRFS LDWALILPLG NQSQVNHTIL QYYRCMASEL
 151 VRVNITPVVA LWQPMAPNQG LPRLLARQGA WENPYTALAF AEYARLCFQE
 201 LGHHVKLWIT MNEPYTRNMT YSAGHNLLKA HALAWHVYNE KFRHAQNGKI
 251 SIALQADWIE PACPFSQKDK EVAERVLEFD IGWLAEPIFG SGDYPWVMRD
 301 WLNQRNNFLL PYFTEDEKKL IQGTFDFLAL SHYTTILVDS EKEDPIKYND
 351 YLEVQEMTDI TWLNSPSQVA VVPWGLRKVL NWLKFKYGDL PMYIISNGID
 401 DGLHAEDDQL RVYYMQNYIN EALKAHILDG INLCGYFAYS FNDRTAPRFG
 451 LYRYAADQFE PKASMKHYRK IIDSNGFPGP ETLERFCPEE FTVCTECSFF
 501 HTRKSLGSGG GGSGGGGSGG GGSLKYPNAS PLLGSSWGGL IHLYTATARN
 551 SYHLQIHKNG HVDGAPHQTI YSALMIRSED AGFVVITGVM SRRYLCMDFR
 601 GNIFGSHYFD PENCRFQHQT LENGYDVYHS PQYHFLVSLG RAKRAFLPGM
 651 NPPPYSQFLS RRNEIPLIHF NTPIPRRHTQ SAEDDSERDP LNVLKPRARM
 701 TPAPASCSQE LPSAEDNSPM ASDPLGVVRG GRVNTHAGGT GPEGCRPFAK
 751 FI*
```

$(KL\text{-}D1)_2$-FGF23 (R179Q) amino acid sequence (SEQ ID NO: 23)

```
   1 MPASAPPRRP RPPPPSLSLL LVLLGLGGRR LRAEPGDGAQ TWARFSRPPA
```

REPLACEMENT SHEET

```
  51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
 101 PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
 151 ISWARVLPNG SAGVPNREGL RYYRRLLERL RELGVQPVVT LYHWDLPQRL
 201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
 251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
 301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP
 351 DFTESEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
 401 IDLEFNHPQI FIVENGWFVS GTTKRDDAKY MYYLKKFIME TLKAIKLDGV
 451 DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD FLSQDKMLLP KSSALFYQKL
 501 IEKNGFPPLP ENQPLEGSGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW
 551 DTFTHHPLAP PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR
 601 ELGVTHYRFS ISWARVLPNG SAGVPNREGL RYYRRLLERL RELGVQPVVT
 651 LYHWDLPQRL QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP
 701 YVVAWHGYAT GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ
 751 GGQVSIALSS HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES
 801 MKNNLSSILP DFTESEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE
 851 SPNLRQLLSW IDLEFNHPQI FIVENGWFVS GTTKRDDAKY MYYLKKFIME
 901 TLKAIKLDGV DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD FLSQDKMLLP
 951 KSSALFYQKL IEKNGFPEFG SGGGGSGGGG SGGGGSLKYP NASPLLGSSW
1001 GGLIHLYTAT ARNSYHLQIH KNGHVDGAPH QTIYSALMIR SEDAGFVVIT
1051 GVMSRRYLCM DFRGNIFGSH YFDPENCRFQ HQTLENGYDV YHSPQYHFLV
1101 SLGRAKRAFL PGMNPPPYSQ FLSRRNEIPL IHFNTPIPRR HTQSAEDDSE
1151 RDPLNVLKPR ARMTPAPASC SQELPSAEDN SPMASDPLGV VRGGRVNTHA
1201 GGTGPEGCRP FAKFI*
```

$(KL\text{-}D2)_2$-FGF23 (R179Q) amino acid sequence (SEQ ID NO: 24)

```
   1 MPASAPPRRP RPPPPSLSLL LVLLGLGGRR LPLPENQPLE GTFPCDFAWG
  51 VVDNYIQVDT TLSQFTDLNV YLWDVHHSKR LIKVDGVVTK KRKSYCVDFA
 101 AIQPQIALLQ EMHVTHFRFS LDWALILPLG NQSQVNHTIL QYYRCMASEL
 151 VRVNITPVVA LWQPMAPNQG LPRLLARQGA WENPYTALAF AEYARLCFQE
 201 LGHHVKLWIT MNEPYTRNMT YSAGHNLLKA HALAWHVYNE KFRHAQNGKI
 251 SIALQADWIE PACPFSQKDK EVAERVLEFD IGWLAEPIFG SGDYPWVMRD
 301 WLNQRNNFLL PYFTEDEKKL IQGTFDFLAL SHYTTILVDS EKEDPIKYND
 351 YLEVQEMTDI TWLNSPSQVA VVPWGLRKVL NWLKFKYGDL PMYIISNGID
 401 DGLHAEDDQL RVYYMQNYIN EALKAHILDG INLCGYFAYS FNDRTAPRFG
 451 LYRYAADQFE PKASMKHYRK IIDSNGFPGP ETLERFCPEE FTVCTECSFF
 501 HTRKSLGTFP CDFAWGVVDN YIQVDTTLSQ FTDLNVYLWD VHHSKRLIKV
 551 DGVVTKKRKS YCVDFAAIQP QIALLQEMHV THFRFSLDWA LILPLGNQSQ
 601 VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL LARQGAWENP
 651 YTALAFAEYA RLCFQELGHH VKLWITMNEP YTRNMTYSAG HNLLKAHALA
 701 WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE RVLEFDIGWL
 751 AEPIFGSGDY PWVMRDWLNQ RNNFLLPYFT EDEKKLIQGT FDFLALSHYT
 801 TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW GLRKVLNWLK
 851 FKYGDLPMYI ISNGIDDGLH AEDDQLRVYY MQNYINEALK AHILDGINLC
 901 GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIIDS NGFGSGGGGS
 951 GGGGSGGGGS LKYPNASPLL GSSWGGLIHL YTATARNSYH LQIHKNGHVD
1001 GAPHQTIYSA LMIRSEDAGF VVITGVMSRR YLCMDFRGNI FGSHYFDPEN
1051 CRFQHQTLEN GYDVYHSPQY HFLVSLGRAK RAFLPGMNPP PYSQFLSRRN
1101 EIPLIHFNTP IPRRHTQSAE DDSERDPLNV LKPRARMTPA PASCSQELPS
1151 AEDNSPMASD PLGVVRGGRV NTHAGGTGPE GCRPFAKFI*
```

FGF23 (R179Q) -Klotho extracellular domain amino acid sequence (SEQ ID NO: 25)

```
   1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNS
```

REPLACEMENT SHEET

```
  51 YHLQIHKNGH VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
 101 NIFGSHYFDP ENCRFQHQTL ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN
 151 PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
 201 PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGCRPFAKF
 251 IGSGGGGSGG GGSGGGGSLK EPGDGAQTWA RFSRPPAPEA AGLFQGTFPD
 301 GFLWAVGSAA YQTEGGWQQH GKGASIWDTF THHPLAPPGD SRNASLPLGA
 351 PSPLQPATGD VASDSYNNVF RDTEALRELG VTHYRFSISW ARVLPNGSAG
 401 VPNREGLRYY RRLLERLREL GVQPVVTLYH WDLPQRLQDA YGGWANRALA
 451 DHFRDYAELC FRHFGGQVKY WITIDNPYVV AWHGYATGRL APGIRGSPRL
 501 GYLVAHNLLL AHAKVWHLYN TSFRPTQGGQ VSIALSSHWI NPRRMTDHSI
 551 KECQKSLDFV LGWFAKPVFI DGDYPESMKN NLSSILPDFT ESEKKFIKGT
 601 ADFFALCFGP TLSFQLLDPH MKFRQLESPN LRQLLSWIDL EFNHPQIFIV
 651 ENGWFVSGTT KRDDAKYMYY LKKFIMETLK AIKLDGVDVI GYTAWSLMDG
 701 FEWHRGYSIR RGLFYVDFLS QDKMLLPKSS ALFYQKLIEK NGFPPLPENQ
 751 PLEGTFPCDF AWGVVDNYIQ VDTTLSQFTD LNVYLWDVHH SKRLIKVDGV
 801 VTKKRKSYCV DFAAIQPQIA LLQEMHVTHF RFSLDWALIL PLGNQSQVNH
 851 TILQYYRCMA SELVRVNITP VVALWQPMAP NQGLPRLLAR QGAWENPYTA
 901 LAFAEYARLC FQELGHHVKL WITMNEPYTR NMTYSAGHNL LKAHALAWHV
 951 YNEKFRHAQN GKISIALQAD WIEPACPFSQ KDKEVAERVL EFDIGWLAEP
1001 IFGSGDYPWV MRDWLNQRNN FLLPYFTEDE KKLIQGTFDF LALSHYTTIL
1051 VDSEKEDPIK YNDYLEVQEM TDITWLNSPS QVAVVPWGLR KVLNWLKFKY
1101 GDLPMYIISN GIDDGLHAED DQLRVYYMQN YINEALKAHI LDGINLCGYF
1151 AYSFNDRTAP RFGLYRYAAD QFEPKASMKH YRKIIDSNGF PGPETLERFC
1201 PEEFTVCTEC SFFHTRKSL*
```

FGF23 (R179Q) -KL-D1 amino acid sequence (SEQ ID NO: 26)

```
   1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNS
  51 YHLQIHKNGH VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
 101 NIFGSHYFDP ENCRFQHQTL ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN
 151 PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
 201 PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGCRPFAKF
 251 IQGTFPDGFL WAVGSAAYQT EGGWQQHGKG ASIWDTFTHH PLAPPGDSRN
 301 ASLPLGAPSP LQPATGDVAS DSYNNVFRDT EALRELGVTH YRFSISWARV
 351 LPNGSAGVPN REGLRYYRRL LERLRELGVQ PVVTLYHWDL PQRLQDAYGG
 401 WANRALADHF RDYAELCFRH FGGQVKYWIT IDNPYVVAWH GYATGRLAPG
 451 IRGSPRLGYL VAHNLLLAHA KVWHLYNTSF RPTQGGQVSI ALSSHWINPR
 501 RMTDHSIKEC QKSLDFVLGW FAKPVFIDGD YPESMKNNLS SILPDFTESE
 551 KKFIKGTADF FALCFGPTLS FQLLDPHMKF RQLESPNLRQ LLSWIDLEFN
 601 HPQIFIVENG WFVSGTTKRD DAKYMYYLKK FIMETLKAIK LDGVDVIGYT
 651 AWSLMDGFEW HRGYSIRRGL FYVDFLSQDK MLLPKSSALF YQKLIEKNGF
 652 *
```

FGF23 (R179Q) -KL-D2 amino acid sequence (SEQ ID NO: 27)

```
   1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNS
  51 YHLQIHKNGH VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
 101 NIFGSHYFDP ENCRFQHQTL ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN
 151 PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
 201 PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGCRPFAKF
 251 IGTFPCDFAW GVVDNYIQVD TTLSQFTDLN VYLWDVHHSK RLIKVDGVVT
 301 KKRKSYCVDF AAIQPQIALL QEMHVTHFRF SLDWALILPL GNQSQVNHTI
 351 LQYYRCMASE LVRVNITPVV ALWQPMAPNQ GLPRLLARQG AWENPYTALA
 401 FAEYARLCFQ ELGHHVKLWI TMNEPYTRNM TYSAGHNLLK AHALAWHVYN
 451 EKFRHAQNGK ISIALQADWI EPACPFSQKD KEVAERVLEF DIGWLAEPIF
```

REPLACEMENT SHEET

```
 501 GSGDYPWVMR DWLNQRNNFL LPYFTEDEKK LIQGTFDFLA LSHYTTILVD
 551 SEKEDPIKYN DYLEVQEMTD ITWLNSPSQV AVVPWGLRKV LNWLKFKYGD
 601 LPMYIISNGI DDGLHAEDDQ LRVYYMQNYI NEALKAHILD GINLCGYFAY
 651 SFNDRTAPRF GLYRYAADQF EPKASMKHYR KIIDSNGF*
```

FGF23 (R179Q) -(KL-D1)$_2$ amino acid sequence (SEQ ID NO: 28)

```
   1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNS
  51 YHLQIHKNGH VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
 101 NIFGSHYFDP ENCRFQHQTL ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN
 151 PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
 201 PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGCRPFAKF
 251 IQGTFPDGFL WAVGSAAYQT EGGWQQHGKG ASIWDTFTHH PLAPPGDSRN
 301 ASLPLGAPSP LQPATGDVAS DSYNNVFRDT EALRELGVTH YRFSISWARV
 351 LPNGSAGVPN REGLRYYRRL LERLRELGVQ PVVTLYHWDL PQRLQDAYGG
 401 WANRALADHF RDYAELCFRH FGGQVKYWIT IDNPYVVAWH GYATGRLAPG
 451 IRGSPRLGYL VAHNLLLAHA KVWHLYNTSF RPTQGGQVSI ALSSHWINPR
 501 RMTDHSIKEC QKSLDFVLGW FAKPVFIDGD YPESMKNNLS SILPDFTESE
 551 KKFIKGTADF FALCFGPTLS FQLLDPHMKF RQLESPNLRQ LLSWIDLEFN
 601 HPQIFIVENG WFVSGTTKRD DAKYMYYLKK FIMETLKAIK LDGVDVIGYT
 651 AWSLMDGFEW HRGYSIRRGL FYVDFLSQDK MLLPKSSALF YQKLIEKNGF
 701 QGTFPDGFLW AVGSAAYQTE GGWQQHGKGA SIWDTFTHHP LAPPGDSRNA
 751 SLPLGAPSPL QPATGDVASD SYNNVFRDTE ALRELGVTHY RFSISWARVL
 801 PNGSAGVPNR EGLRYYRRLL ERLRELGVQP VVTLYHWDLP QRLQDAYGGW
 851 ANRALADHFR DYAELCFRHF GGQVKYWITI DNPYVVAWHG YATGRLAPGI
 901 RGSPRLGYLV AHNLLLAHAK VWHLYNTSFR PTQGGQVSIA LSSHWINPRR
 951 MTDHSIKECQ KSLDFVLGWF AKPVFIDGDY PESMKNNLSS ILPDFTESEK
1001 KFIKGTADFF ALCFGPTLSF QLLDPHMKFR QLESPNLRQL LSWIDLEFNH
1051 PQIFIVENGW FVSGTTKRDD AKYMYYLKKF IMETLKAIKL DGVDVIGYTA
1101 WSLMDGFEWH RGYSIRRGLF YVDFLSQDKM LLPKSSALFY QKLIEKNGF*
```

FGF23 (R179Q) -(KL-D2)$_2$ amino acid sequence (SEQ ID NO: 29)

```
   1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNS
  51 YHLQIHKNGH VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
 101 NIFGSHYFDP ENCRFQHQTL ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN
 151 PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
 201 PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGCRPFAKF
 251 IGTFPCDFAW GVVDNYIQVD TTLSQFTDLN VYLWDVHHSK RLIKVDGVVT
 301 KKRKSYCVDF AAIQPQIALL QEMHVTHFRF SLDWALILPL GNQSQVNHTI
 351 LQYYRCMASE LVRVNITPVV ALWQPMAPNQ GLPRLLARQG AWENPYTALA
 401 FAEYARLCFQ ELGHHVKLWI TMNEPYTRNM TYSAGHNLLK AHALAWHVYN
 451 EKFRHAQNGK ISIALQADWI EPACPFSQKD KEVAERVLEF DIGWLAEPIF
 501 GSGDYPWVMR DWLNQRNNFL LPYFTEDEKK LIQGTFDFLA LSHYTTILVD
 551 SEKEDPIKYN DYLEVQEMTD ITWLNSPSQV AVVPWGLRKV LNWLKFKYGD
 601 LPMYIISNGI DDGLHAEDDQ LRVYYMQNYI NEALKAHILD GINLCGYFAY
 651 SFNDRTAPRF GLYRYAADQF EPKASMKHYR KIIDSNGFGT FPCDFAWGVV
 701 DNYIQVDTTL SQFTDLNVYL WDVHHSKRLI KVDGVVTKKR KSYCVDFAAI
 751 QPQIALLQEM HVTHFRFSLD WALILPLGNQ SQVNHTILQY YRCMASELVR
 801 VNITPVVALW QPMAPNQGLP RLLARQGAWE NPYTALAFAE YARLCFQELG
 851 HHVKLWITMN EPYTRNMTYS AGHNLLKAHA LAWHVYNEKF RHAQNGKISI
 901 ALQADWIEPA CPFSQKDKEV AERVLEFDIG WLAEPIFGSG DYPWVMRDWL
 951 NQRNNFLLPY FTEDEKKLIQ GTFDFLALSH YTTILVDSEK EDPIKYNDYL
1001 EVQEMTDITW LNSPSQVAVV PWGLRKVLNW LKFKYGDLPM YIISNGIDDG
1051 LHAEDDQLRV YYMQNYINEA LKAHILDGIN LCGYFAYSFN DRTAPRFGLY
1101 RYAADQFEPK ASMKHYRKII DSNGF*
```

REPLACEMENT SHEET

FGF19 nucleic acid sequence (NM_005117) (SEQ ID NO: 30)
Protein coding region (464-1114)

```
   1 gctcccagcc aagaacctcg gggccgctgc gcggtgggga ggagttcccc gaaacccggc
  61 cgctaagcga ggcctcctcc tcccgcagat ccgaacggcc tgggcggggt caccccggct
 121 gggacaagaa gccgccgcct gcctgcccgg gcccggggag ggggctgggg ctggggccgg
 181 aggcggggtg tgagtgggtg tgtgcggggg gcggaggctt gatgcaatcc cgataagaaa
 241 tgctcgggtg tcttgggcac ctacccgtgg ggcccgtaag gcgctactat ataaggctgc
 301 cggcccggag ccgccgcgcc gtcagagcag gagcgctgcg tccaggatct agggccacga
 361 ccatcccaac ccggcactca cagccccgca gcgcatcccg gtcgccgccc agcctcccgc
 421 acccccatcg ccggagctgc gccgagagcc ccagggaggt gccatgcgga gcgggtgtgt
 481 ggtggtccac gtatggatcc tggccggcct ctggctggcc gtggccgggc gccccctcgc
 541 cttctcggac gcggggcccc acgtgcacta cggctggggc gaccccatcc gcctgcggca
 601 cctgtacacc tccggccccc acgggctctc cagctgcttc ctgcgcatcc gtgccgacgg
 661 cgtcgtggac tgcgcgcggg gccagagcgc gcacagtttg ctggagatca aggcagtcgc
 721 tctgcggacc gtggccatca agggcgtgca cagcgtgcgg tacctctgca tgggcgccga
 781 cggcaagatg caggggctgc ttcagtactc ggaggaagac tgtgctttcg aggaggagat
 841 ccgcccagat ggctacaatg tgtaccgatc cgagaagcac cgcctcccgg tctccctgag
 901 cagtgccaaa cagcggcagc tgtacaagaa cagaggcttt cttccactct ctcatttcct
 961 gcccatgctg cccatggtcc cagaggagcc tgaggacctc aggggccact tggaatctga
1021 catgttctct tcgccctgg agaccgacag catggaccca tttgggcttg tcaccggact
1081 ggaggccgtg aggagtccca gctttgagaa gtaactgaga ccatgcccgg gcctcttcac
1141 tgctgccagg ggctgtggta cctgcagcgt gggggacgtg cttctacaag aacagtcctg
1201 agtccacgtt ctgtttagct ttaggaagaa acatctagaa gttgtacata ttcagagttt
1261 tccattggca gtgccagttt ctagccaata gacttgtctg atcataacat tgtaagcctg
1321 tagcttgccc agctgctgcc tgggccccca ttctgctccc tcgaggttgc tggacaagct
1381 gctgcactgt ctcagttctg cttgaatacc tccatcgatg gggaactcac ttcctttgga
1441 aaaattctta tgtcaagctg aaattctcta attttttctc atcacttccc caggagcagc
1501 cagaagacag gcagtagttt taatttcagg aacaggtgat ccactctgta aaacagcagg
1561 taaatttcac tcaaccccat gtgggaattg atctatatct ctacttccag ggaccatttg
1621 cccttcccaa atcccttccag gccagaactg actggagcag gcatggccca ccaggcttca
1681 ggagtagggg aagcctggag ccccactcca gccctgggac aacttgagaa ttccccctga
1741 ggccagtttct gtcatggatg ctgtcctgag aataacttgc tgtcccggtg tcacctgctt
1801 ccatctccca gcccaccagc cctctgccca cctcacatgc ctccccatgg attggggcct
1861 cccaggcccc ccaccttatg tcaacctgca cttcttgttc aaaaatcagg aaaagaaaag
1921 atttgaagac cccaagtctt gtcaataact tgctgtgtgg aagcagcggg ggaagaccta
1981 gaaccctttc cccagcactt ggttttccaa catgatattt atgagtaatt tattttgata
2041 tgtacatctc ttattttctt acattattta tgcccccaaa ttatatttat gtatgtaagt
2101 gaggtttgtt ttgtatatta aaatggagtt tgtttgtaaa aaaaaaaaaa aaaaaaa
```

FGF19 amino acid sequence (NP_005108) (SEQ ID NO: 31)

```
   1 MRSGCVVVHV WILAGLWLAV AGRPLAFSDA GPHVHYGWGD PIRLRHLYTS GPHGLSSCFL
  61 RIRADGVVDC ARGQSAHSLL EIKAVALRTV AIKGVHSVRY LCMGADGKMQ GLLQYSEEDC
 121 AFEEEIRPDG YNVYRSEKHR LPVSLSSAKQ RQLYKNRGFL PLSHFLPMLP MVPEEPEDLR
 181 GHLESDMFSS PLETDSMDPF GLVTGLEAVR SPSFEK
```

FGF21 nucleic acid sequence (NM_019113) (SEQ ID NO: 32)
Protein coding region 151-780

```
   1 CTGTCAGCTG AGGATCCAGC CGAAAGAGGA GCCAGGCACT CAGGCCACCT GAGTCTACTC
  61 ACCTGGACAA CTGGAATCTG GCACCAATTC TAAACCACTC AGCTTCTCCG AGCTCACACC
 121 CCGGAGATCA CCTGAGGACC CGAGCCATTG ATGGACTCGG ACGAGACCGG GTTCGAGCAC
```

REPLACEMENT SHEET

```
181 TCAGGACTGT GGGTTTCTGT GCTGGCTGGT CTTCTGCTGG GAGCCTGCCA GGCACACCCC
241 ATCCCTGACT CCAGTCCTCT CCTGCAATTC GGGGGCCAAG TCCGGCAGCG GTACCTCTAC
301 ACAGATGATG CCCAGCAGAC AGAAGCCCAC CTGGAGATCA GGGAGGATGG GACGGTGGGG
361 GGCGCTGCTG ACCAGAGCCC CGAAAGTCTC CTGCAGCTGA AAGCCTTGAA GCCGGGAGTT
421 ATTCAAATCT TGGGAGTCAA GACATCCAGG TTCCTGTGCC AGCGGCCAGA TGGGGCCCTG
481 TATGGATCGC TCCACTTTGA CCCTGAGGCC TGCAGCTTCC GGGAGCTGCT TCTTGAGGAC
541 GGATACAATG TTTACCAGTC CGAAGCCCAC GGCCTCCCGC TGCACCTGCC AGGGAACAAG
601 TCCCCACACC GGGACCCTGC ACCCCGAGGA CCAGCTCGCT TCCTGCCACT ACCAGGCCTG
661 CCCCCCGCAC TCCCGGAGCC ACCCGGAATC CTGGCCCCCC AGCCCCCCGA TGTGGGCTCC
721 TCGGACCCTC TGAGCATGGT GGGACCTTCC CAGGGCCGAA GCCCCAGCTA CGCTTCCTGA
781 AGCCAGAGGC TGTTTACTAT GACATCTCCT CTTTATTTAT TAGGTTATTT ATCTTATTTA
841 TTTTTTTATT TTTCTTACTT GAGATAATAA AGAGTTCCAG AGGAGAAAAA AAAAAAAAAA
901 AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA
```

FGF21 amino acid sequence (NP_061986) (SEQ ID NO: 33)

```
  1 MDSDETGFEH SGLWVSVLAG LLLGACQAHP IPDSSPLLQF GGQVRQRYLY TDDAQQTEAH
 61 LEIREDGTVG GAADQSPESL LQLKALKPGV IQILGVKTSR FLCQRPDGAL YGSLHFDPEA
121 CSFRELLLED GYNVYQSEAH GLPLHLPGNK SPHRDPAPRG PARFLPLPGL PPALPEPPGI
181 LAPQPPDVGS SDPLSMVGPS QGRSPSYAS
```

FGF23 nucleic acid sequence (NM_020638) (SEQ ID NO: 34)
Protein coding region 147-902

```
   1 cggcaaaaag gagggaatcc agtctaggat cctcacacca gctacttgca agggagaagg
  61 aaaaggccag taaggcctgg gccaggagag tcccgacagg agtgtcaggt ttcaatctca
 121 gcaccagcca ctcagagcag ggcacgatgt tgggggcccg cctcaggctc tgggtctgtg
 181 ccttgtgcag cgtctgcagc atgagcgtcc tcagagccta tcccaatgcc tccccactgc
 241 tcggctccag ctggggtggc ctgatccacc tgtacacagc cacagccagg aacagctacc
 301 acctgcagat ccacaagaat ggccatgtgg atggcgcacc ccatcagacc atctacagtg
 361 ccctgatgat cagatcagag gatgctggct ttgtggtgat tacaggtgtg atgagcagaa
 421 gatacctctg catggatttc agaggcaaca tttttggatc acactatttc gacccggaga
 481 actgcaggtt ccaacaccag acgctggaaa acgggtacga cgtctaccac tctcctcagt
 541 atcacttcct ggtcagtctg ggccgggcga agagagcctt cctgccaggc atgaacccac
 601 ccccgtactc ccagttcctg tcccggagga acgagatccc cctaattcac ttcaacaccc
 661 ccataccacg gcggcacacc cggagcgccg aggacgactc ggagcgggac cccctgaacg
 721 tgctgaagcc ccgggcccgg atgaccccgg ccccggcctc ctgttcacag gagctcccga
 781 gcgccgagga caacagcccg atggccagtg acccattagg ggtggtcagg ggcggtcgag
 841 tgaacacgca cgctgggggа acgggcccgg aaggctgccg cccttcgcc aagttcatct
 901 agggtcgctg gaagggcacc ctctttaacc catccctcag caaacgcagc tcttcccaag
 961 gaccaggtcc cttgacgttc cgaggatggg aaaggtgaca ggggcatgta tggaatttgc
1021 tgcttctctg gggtcccttc cacaggaggt cctgtgagaa ccaacctttg aggcccaagt
1081 catggggttt caccgccttc ctcactccat atagaacacc tttcccaata ggaaacccca
1141 acaggtaaac tagaaatttc cccttcatga aggtagagag aaggggtctc tcccaacata
1201 tttctcttcc ttgtgcctct cctctttatc acttttaagc ataaaaaaaa aaaaaaaaaa
1261 aaaaaaaaaa aaaagcagtg ggttcctgag ctcaagactt tgaaggtgta gggaagagga
1321 aatcggagat cccagaagct tctccactgc cctatgcatt tatgttagat gccccgatcc
1381 cactggcatt tgagtgtgca aaccttgaca ttaacagctg aatggggcaa gttgatgaaa
1441 acactacttt caagccttcg ttcttccttg agcatctctg gggaagagct gtcaaaagac
1501 tggtggtagg ctggtgaaaa cttgacagct agacttgatg cttgctgaaa tgaggcagga
1561 atcataatag aaaactcagc ctccctacag ggtgagcacc ttctgtctcg ctgtctccct
1621 ctgtgcagcc acagccagag ggcccagaat ggccccactc tgttcccaag cagttcatga
1681 tacagcctca ccttttggcc ccatctctgg ttttgaaaa tttggtctaa ggaataaata
1741 gcttttacac tggctcacga aaatctgccc tgctagaatt tgcttttcaa aatggaaata
1801 aattccaact ctcctaagag gcatttaatt aaggctctac ttccaggttg agtaggaatc
```

REPLACEMENT SHEET

```
1861 cattctgaac aaactacaaa aatgtgactg ggaagggggc tttgagagac tgggactgct
1921 ctgggttagg ttttctgtgg actgaaaaat cgtgtccttt tctctaaatg aagtggcatc
1981 aaggactcag ggggaaagaa atcaggggac atgttataga agttatgaaa agacaaccac
2041 atggtcaggc tcttgtctgt ggtctctagg gctctgcagc agcagtggct cttcgattag
2101 ttaaaactct cctaggctga cacatctggg tctcaatccc cttggaaatt cttggtgcat
2161 taaatgaagc cttaccccat tactgcggtt cttcctgtaa gggggctcca ttttcctccc
2221 tctctttaaa tgaccaccta aaggacagta tattaacaag caaagtcgat tcaacaacag
2281 cttcttccca gtcacttttt tttttctcac tgccatcaca tactaacctt atactttgat
2341 ctattctttt tggttatgag agaaatgttg ggcaactgtt tttacctgat ggttttaagc
2401 tgaacttgaa ggactggttc ctattctgaa acagtaaaac tatgtataat agtatatagc
2461 catgcatggc aaatatttta atatttctgt tttcatttcc tgttggaaat attatcctgc
2521 ataatagcta ttggaggctc ctcagtgaaa gatcccaaaa ggattttggt ggaaaactag
2581 ttgtaatctc acaaactcaa cactaccatc aggggttttc tttatggcaa agccaaaata
2641 gctcctacaa tttcttatat ccctcgtcat gtggcagtat ttatttattt atttggaagt
2701 ttgcctatcc ttctatattt atagatattt ataaaaatgt aacccctttt tcctttcttc
2761 tgtttaaaat aaaaataaaa tttatctcag cttctgttag cttatcctct ttgtagtact
2821 acttaaaagc atgtcggaat ataagaataa aaaggattat gggaggggaa cattagggaa
2881 atccagagaa ggcaaaattg aaaaaaagat tttagaattt taaaattttc aaagatttct
2941 tccattcata aggagactca atgattttaa ttgatctaga cagaattatt taagttttat
3001 caatattgga tttctggt
```

FGF23 amino acid sequence (NP_065689) (SEQ ID NO: 35)

```
   1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNS YHLQIHKNGH
  61 VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG NIFGSHYFDP ENCRFQHQTL
 121 ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN PPPYSQFLSR RNEIPLIHFN TPIPRRHTRS
 181 AEDDSERDPL NVLKPRARMT PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG
 241 PEGCRPFAKF I
```

FGF23 (R179Q) amino acid sequence (SEQ ID NO: 36)

```
   1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNS YHLQIHKNGH
  61 VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG NIFGSHYFDP ENCRFQHQTL
 121 ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS
 181 AEDDSERDPL NVLKPRARMT PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG
 241 PEGCRPFAKF I
```

Human beta-Klotho domain 1 (b-KL-D1) amino acid sequence (SEQ ID NO: 37)

```
  77                    ydt fpknffwgig tgalqvegsw kkdgkgpsiw dhfihthlkn
 121 vsstngssds yiflekdlsa ldfigvsfyq fsiswprlfp dgivtvanak glqyystlld
 181 alvlrniepi vtlyhwdlpl alqekyggwk ndtiididfnd yatycfqmfg drvkywitih
 241 npylvawhgy gtgmhapgek gnlaavytvg hnlikahskv whnynthfrp hqkgwlsitl
 301 gshwiepnrs entmdifkcq qsmvsvlgwf anpihgdgdy pegmrkklfs vlpifseaek
 361 hemrgtadff afsfgpnnfk plntmakmgq nvslnlreal nwikleynnp riliaengwf
 421 tdsrvktedt taiymmknfl sqvlqairld eirvfgytaw slldgfewqd aytirrglfy
 481 vdfnskqker kpkssahyyk qiirengf
```

Human beta-Klotho domain 2 (b-KL-D2) amino acid sequence (SEQ ID NO: 38)

```
 571                                trpaqctdfv nikkqlemla rmkvthyrfa
 601 ldwasvlptg nlsavnrqal ryyrcvvseg lklgisamvt lyypthahlg lpepllhadg
 661 wlnpstaeaf qayaglcfqe lgdlvklwit inepnrlsdi ynrsgndtyg aahnllvaha
 721 lawrlydrqf rpsqrgavsl slhadwaepa npyadshwra aerflqfeia wfaeplfktg
```

REPLACEMENT SHEET

```
781 dypaamreyi askhrrglss salprlteae rrllkgtvdf calnhfttrf vmheqlagsr
841 ydsdrdiqfl qditrlsspt rlavipwgvr kllrwvrrny gdmdiyitas giddqaledd
901 rlrkyylgky lqevlkayli dkvrikgyya fklaeekskp rfgfftsdfk akssiqfynk
961 vissrgf
```

Beta-Klotho extracellular domain (without signal peptide) amino acid sequence (SEQ ID NO: 39)

```
 52                                                            gfsgdgrai
 61 wsknpnftpv nesqlflydt fpknffwgig tgalqvegsw kkdgkgpsiw dhfihthlkn
121 vsstngssds yiflekdlsa ldfigvsfyq fsiswprlfp dgivtvanak glqyystlld
181 alvlrniepi vtlyhwdlpl alqekyggwk ndtiidifnd yatycfqmfg drvkywitih
241 npylvawhgy gtgmhapgek gnlaavytvg hnlikahskv whnynthfrp hqkgwlsitl
301 gshwiepnrs entmdifkcq qsmvsvlgwf anpihgdgdy pegmrkklfs vlpifseaek
361 hemrgtadff afsfgpnnfk plntmakmgq nvslnlreal nwikleynnp riliaengwf
421 tdsrvktedt taiymmknfl sqvlqairld eirvfgytaw slldgfewqd aytirrglfy
481 vdfnskqker kpkssahyyk qiirengfsl kestpdvqgq fpcdfswgvt esvlkpesva
541 sspqfsdphl yvwnatgnrl lhrvegvrlk trpaqctdfv nikkqlemla rmkvthyrfa
601 ldwasvlptg nlsavnrqal ryyrcvvseg lklgisamvt lyypthahlg lpepllhadg
661 wlnpstaeaf qayaglcfqe lgdlvklwit inepnrlsdi ynrsgndtyg aahnllvaha
721 lawrlydrqf rpsqrgavsl slhadwaepa npyadshwra aerflqfeia wfaeplfktg
781 dypaamreyi askhrrglss salprlteae rrllkgtvdf calnhfttrf vmheqlagsr
841 ydsdrdiqfl qditrlsspt rlavipwgvr kllrwvrrny gdmdiyitas giddqaledd
901 rlrkyylgky lqevlkayli dkvrikgyya fklaeekskp rfgfftsdfk akssiqfynk
961 vissrgfpfe nsssrcsqtq entectvclf lvqkkpl
```

sKlotho without signal peptide – FGF23 amino acid sequence (without signal peptide) (SEQ ID NO: 40)

```
                                                 EPGDGAQ TWARFSRPPA
 51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
101 PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
151 ISWARVLPNG SAGVPNREGL RYYRRLLERL RELGVQPVVT LYHWDLPQRL
201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP
351 DFTESEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
401 IDLEFNHPQI FIVENGWFVS GTTKRDDAKY MYYLKKFIME TLKAIKLDGV
451 DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD FLSQDKMLLP KSSALFYQKL
501 IEKNGFPPLP ENQPLEGTFP CDFAWGVVDN YIQVDTTLSQ FTDLNVYLWD
551 VHHSKRLIKV DGVVTKKRKS YCVDFAAIQP QIALLQEMHV THFRFSLDWA
601 LILPLGNQSQ VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL
651 LARQGAWENP YTALAFAEYA RLCFQELGHH VKLWITMNEP YTRNMTYSAG
701 HNLLKAHALA WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE
751 RVLEFDIGWL AEPIFGSGDY PWVMRDWLNQ RNNFLLPYFT EDEKKLIQGT
801 FDFLALSHYT TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW
851 GLRKVLNWLK FKYGDLPMYI ISNGIDDGLH AEDDQLRVYY MQNYINEALK
901 AHILDGINLC GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIIDS
951 NGFPGPETLE RFCPEEFTVC TECSFFHTRK SLGSGGGGSG GGGSGGGGSL
1001 KYPNASPLLG SSWGGLIHLY TATARNSYHL QIHKNGHVDG APHQTIYSAL
1051 MIRSEDAGFV VITGVMSRRY LCMDFRGNIF GSHYFDPENC RFQHQTLENG
1101 YDVYHSPQYH FLVSLGRAKR AFLPGMNPPP YSQFLSRRNE IPLIHFNTPI
1151 PRRHTRSAED DSERDPLNVL KPRARMTPAP ASCSQELPSA EDNSPMASDP
1201 LGVVRGGRVN THAGGTGPEG CRPFAKFI*
```

REPLACEMENT SHEET

sKlotho without signal peptide -FGF23 (R179Q) (without signal peptide) amino acid sequence (SEQ ID NO: 41)

```
                                                EPGDGAQ TWARFSRPPA
  51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
 101 PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
 151 ISWARVLPNG SAGVPNREGL RYYRRLLERL RELGVQPVVT LYHWDLPQRL
 201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
 251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
 301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP
 351 DFTESEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
 401 IDLEFNHPQI FIVENGWFVS GTTKRDDAKY MYYLKKFIME TLKAIKLDGV
 451 DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD FLSQDKMLLP KSSALFYQKL
 501 IEKNGFPPLP ENQPLEGTFP CDFAWGVVDN YIQVDTTLSQ FTDLNVYLWD
 551 VHHSKRLIKV DGVVTKKRKS YCVDFAAIQP QIALLQEMHV THFRFSLDWA
 601 LILPLGNQSQ VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL
 651 LARQGAWENP YTALAFAEYA RLCFQELGHH VKLWITMNEP YTRNMTYSAG
 701 HNLLKAHALA WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE
 751 RVLEFDIGWL AEPIFGSGDY PWVMRDWLNQ RNNFLLPYFT EDEKKLIQGT
 801 FDFLALSHYT TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW
 851 GLRKVLNWLK FKYGDLPMYI ISNGIDDGLH AEDDQLRVYY MQNYINEALK
 901 AHILDGINLC GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIIDS
 951 NGFPGPETLE RFCPEEFTVC TECSFFHTRK SLGSGGGGSG GGGSGGGGSL
1001 KYPNASPLLG SSWGGLIHLY TATARNSYHL QIHKNGHVDG APHQTIYSAL
1051 MIRSEDAGFV VITGVMSRRY LCMDFRGNIF GSHYFDPENC RFQHQTLENG
1101 YDVYHSPQYH FLVSLGRAKR AFLPGMNPPP YSQFLSRRNE IPLIHFNTPI
1151 PRRHTQSAED DSERDPLNVL KPRARMTPAP ASCSQELPSA EDNSPMASDP
1201 LGVVRGGRVN THAGGTGPEG CRPFAKFI*
```

FGF23 without signal peptide (SEQ ID NO:42)

```
                                  YPNASP LLGSSWGGLI HLYTATARNS YHLQIHKNGH
  61 VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG NIFGSHYFDP ENCRFQHQTL
 121 ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN PPPYSQFLSR RNEIPLIHFN TPIPRRHTRS
 181 AEDDSERDPL NVLKPRARMT PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG
 241 PEGCRPFAKF I
```

FGF23(R179Q) without signal peptide (SEQ ID NO:43)

```
                                  YPNASP LLGSSWGGLI HLYTATARNS YHLQIHKNGH
  61 VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG NIFGSHYFDP ENCRFQHQTL
 121 ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS
 181 AEDDSERDPL NVLKPRARMT PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG
 241 PEGCRPFAKF I
```

REPLACEMENT SHEET

sKlotho with Klotho signal peptide (SEQ ID NO:44)

```
  1 MPASAPPRRP RPPPPSLSLL LVLLGLGGRR LRAEPGDGAQ TWARFSRPPA
 51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
101 PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
151 ISWARVLPNG SAGVPNREGL RYYRRLLERL RELGVQPVVT LYHWDLPQRL
201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP
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sKlotho with IgG Signal peptide (SEQ ID NO:45)

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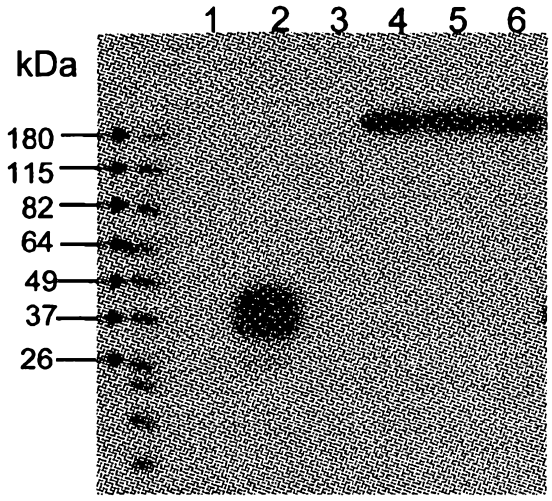
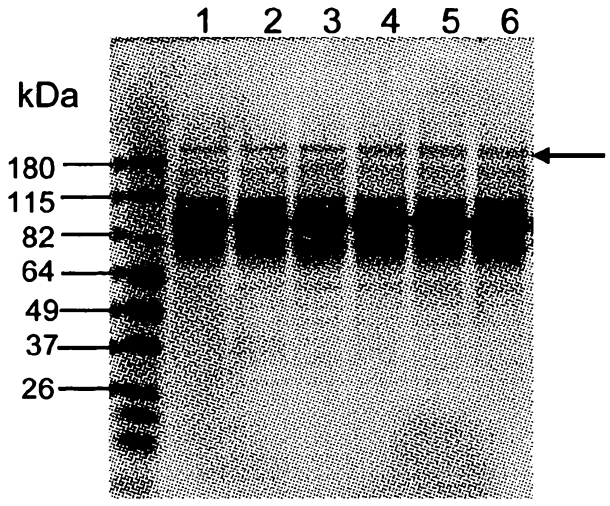


lane 1, Ctrl; lane 2, FGF23; lane 3, sKlotho; lanes 4-6, sKlotho-FGF23

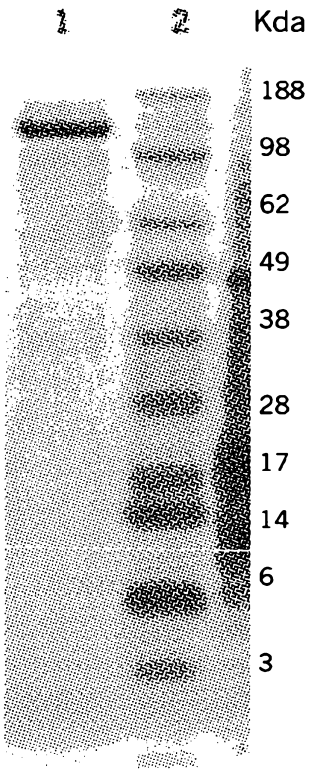
Figure 3B



lane 1, Ctrl; lane 2, FGF23; lane 3, sKlotho; lanes 4-6, sKlotho-FGF23

REPLACEMENT SHEET

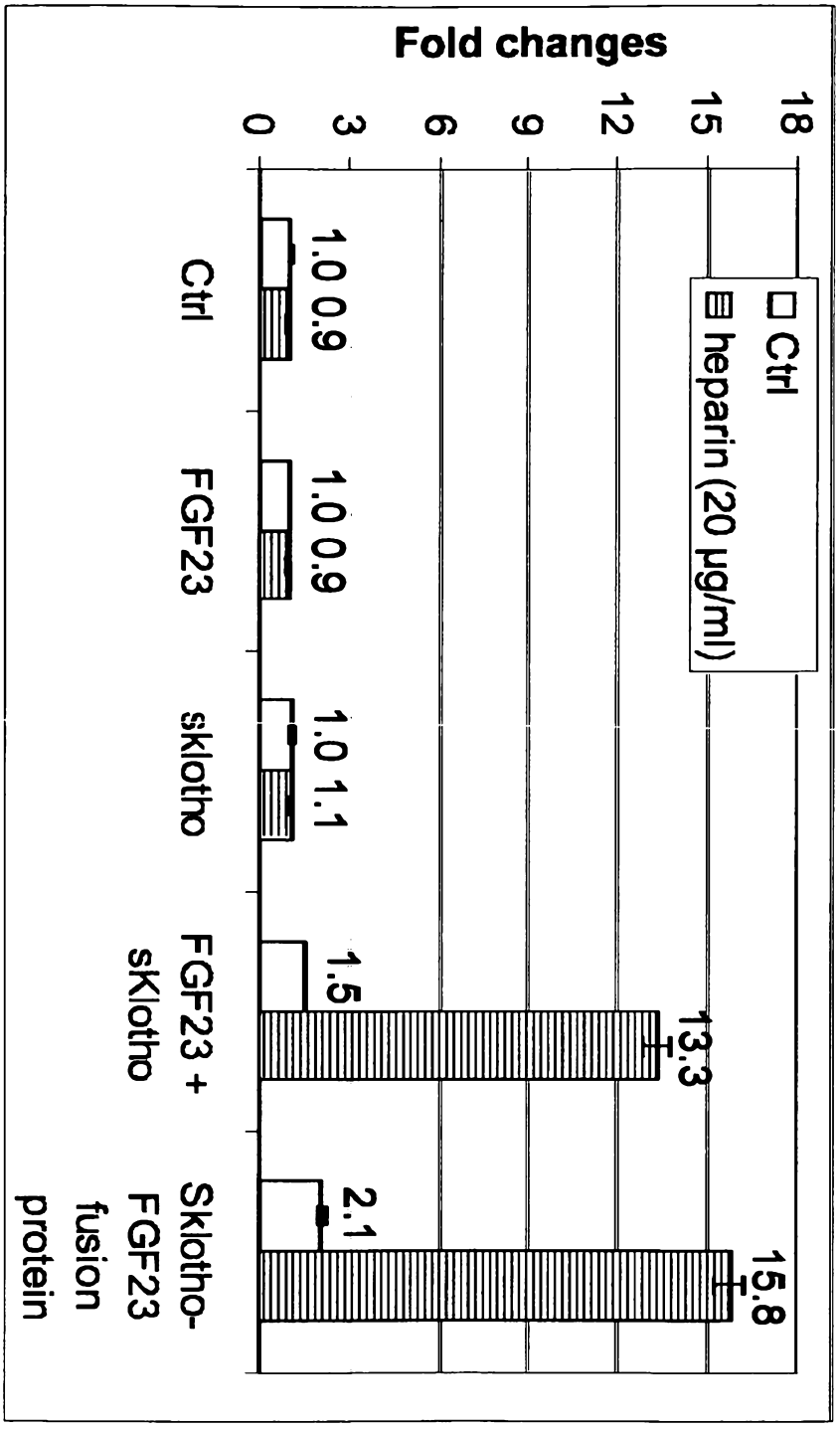
Figure 3C



lane 1, purified sKlotho-FGF23-6xHis;
lane 2, molecular weight marker

REPLACEMENT SHEET

Figure 4



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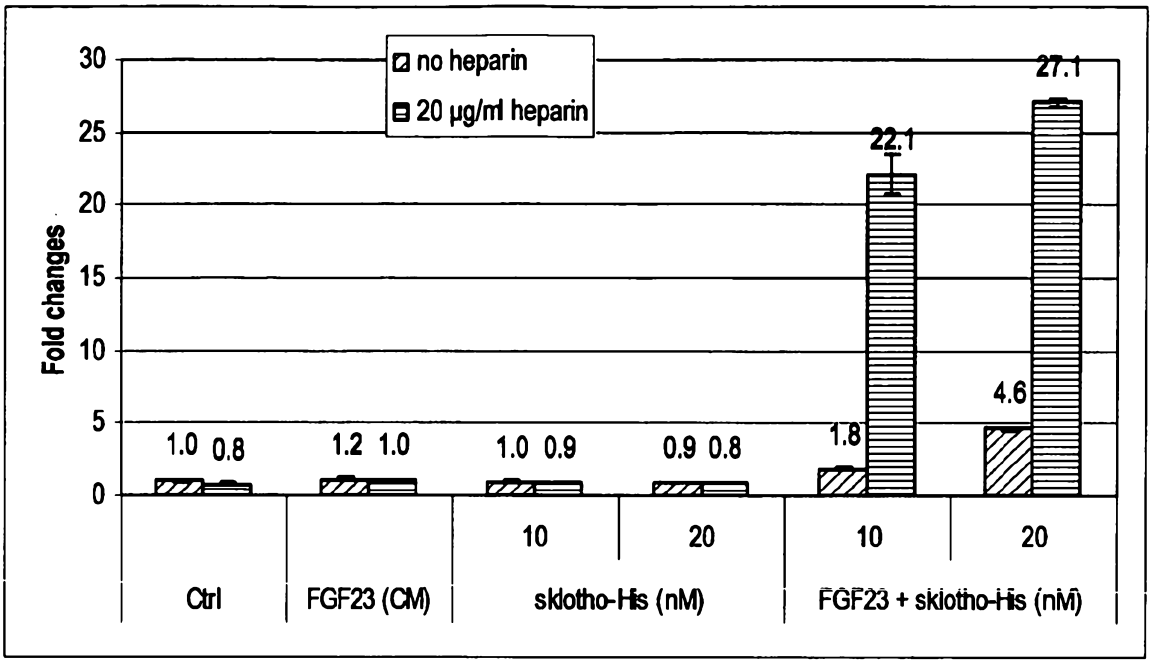

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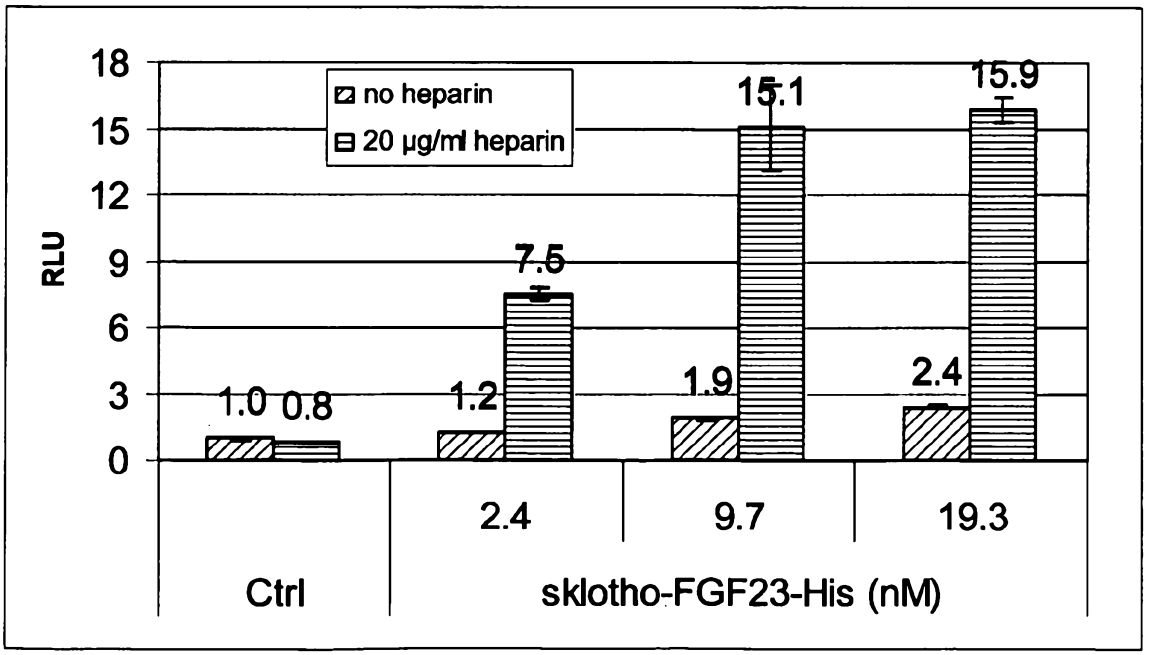

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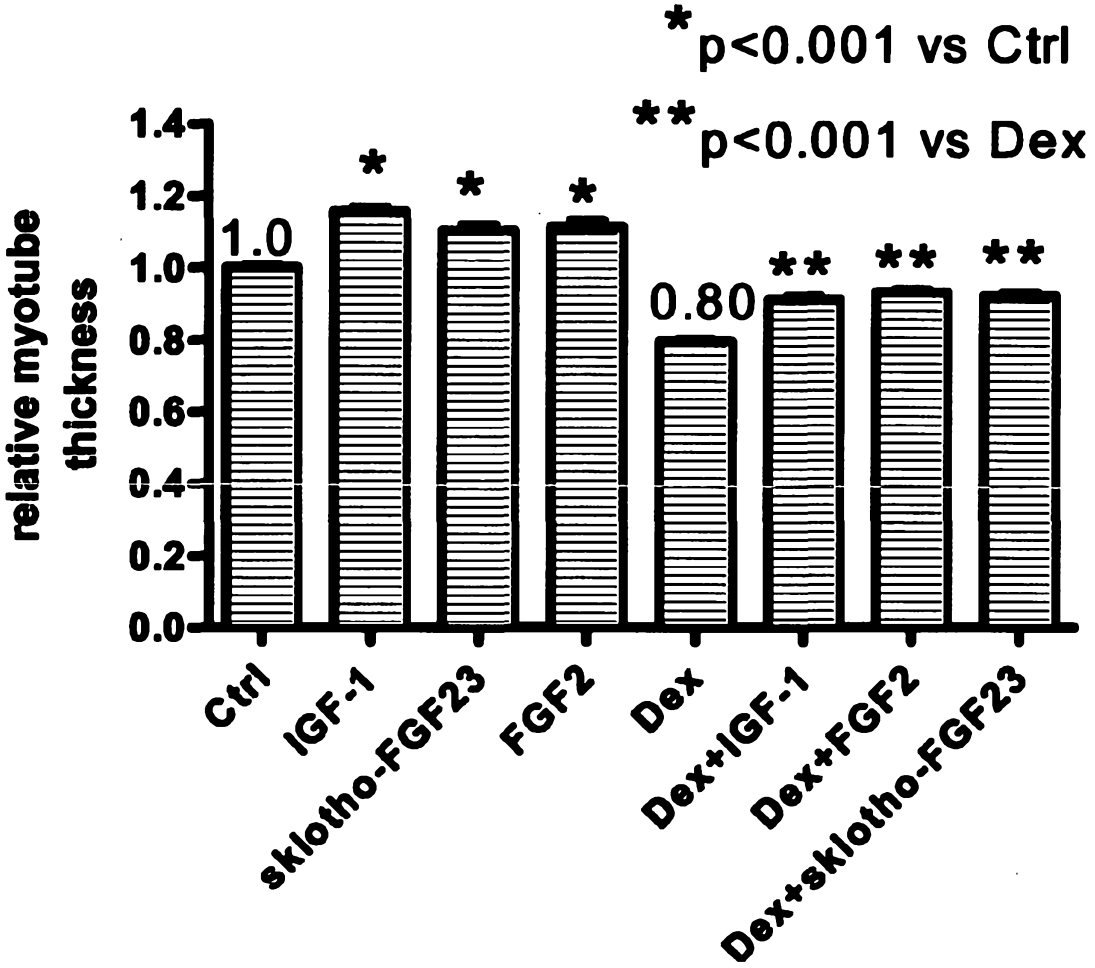

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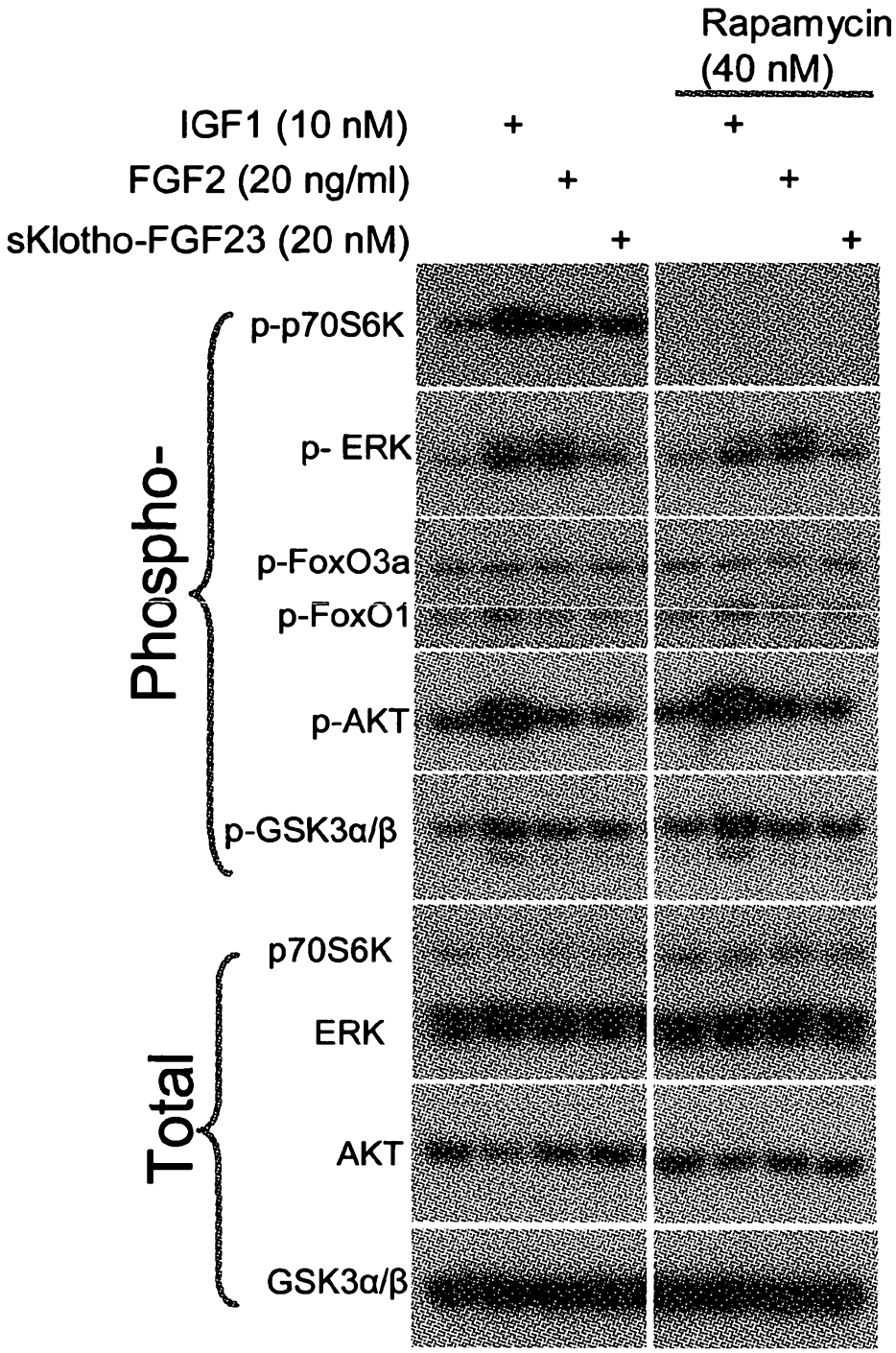

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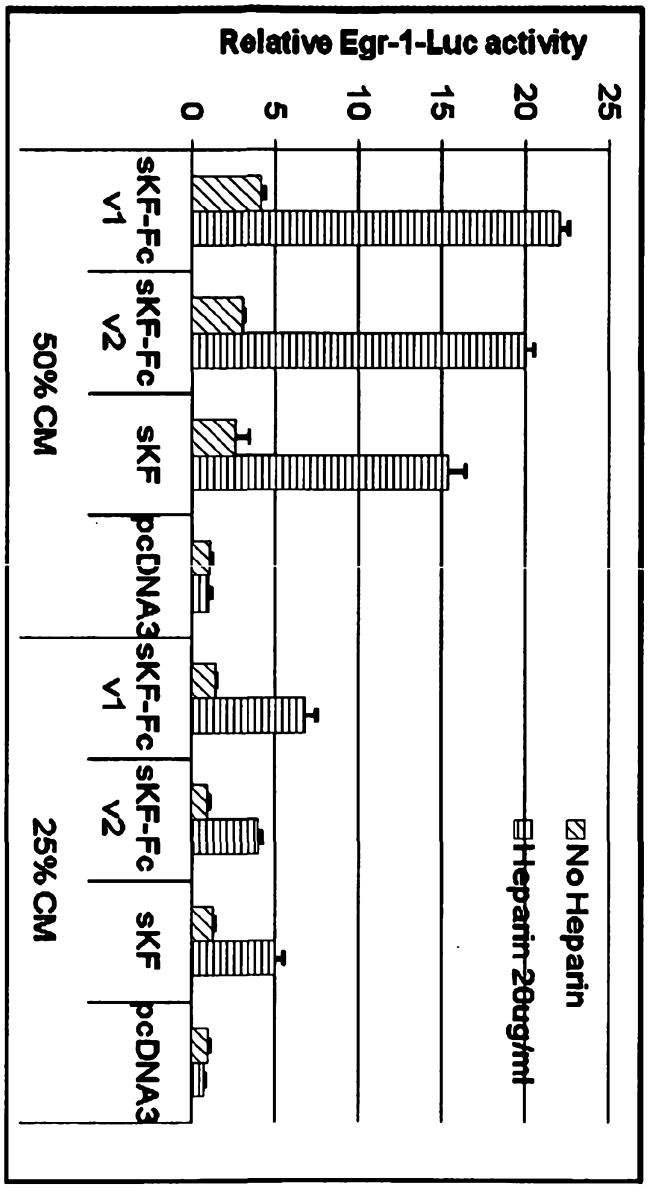

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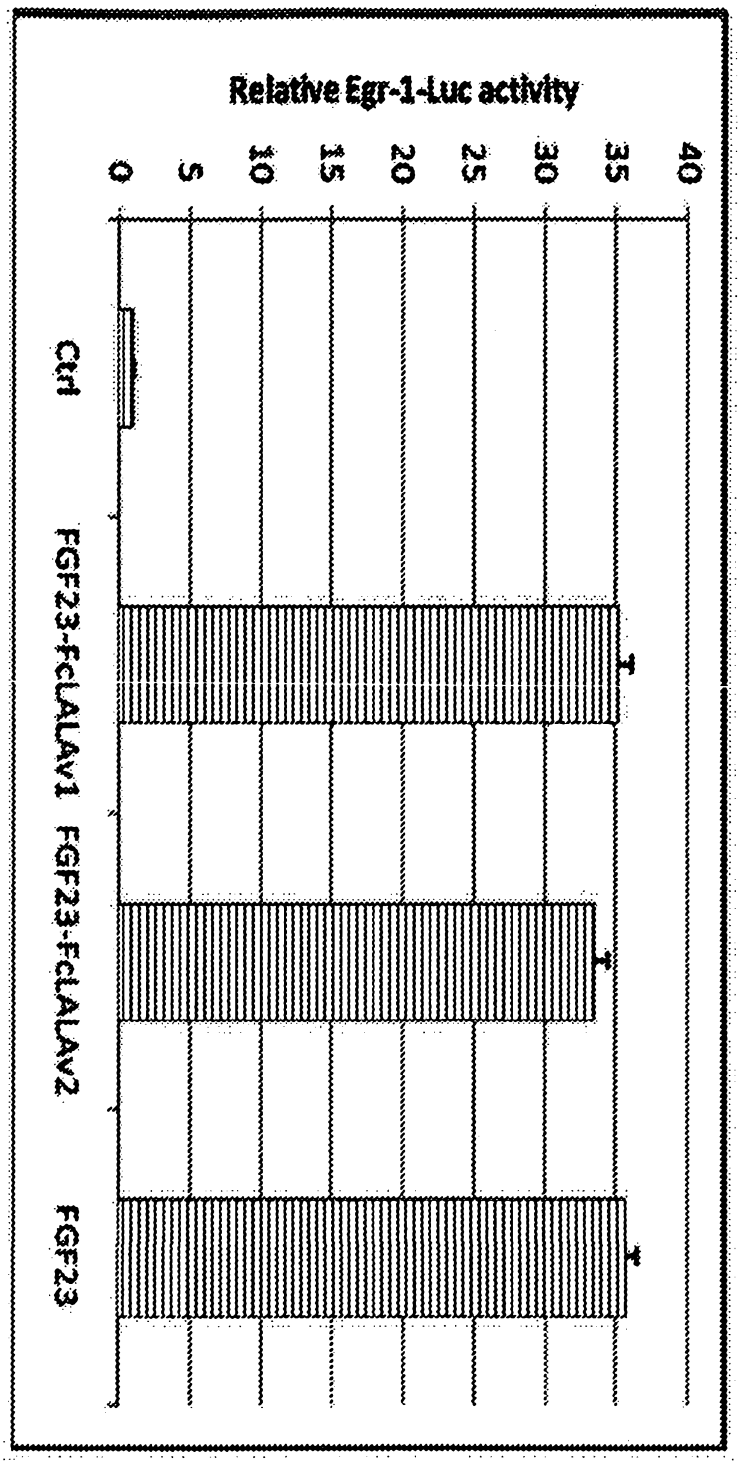
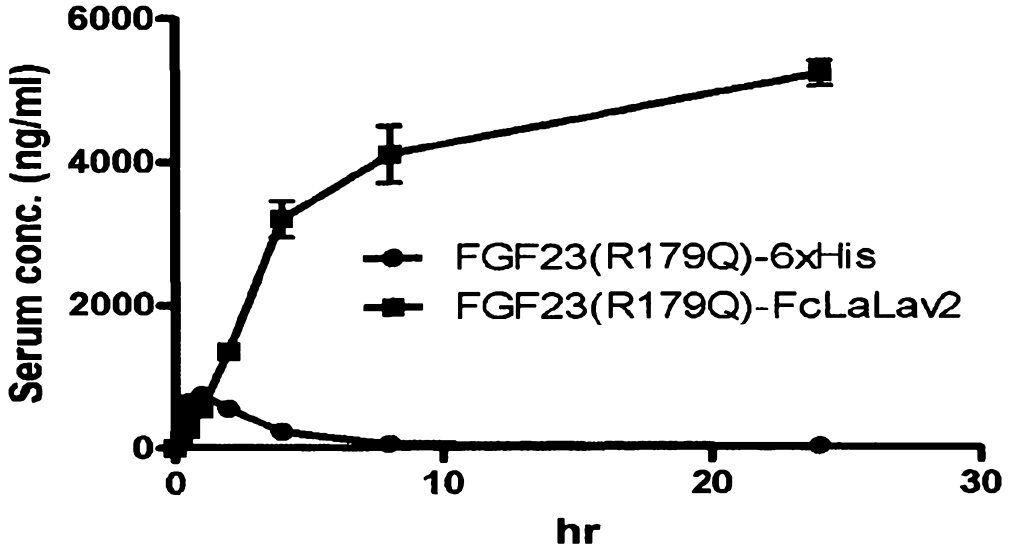


Figure 8

REPLACEMENT SHEET

Figure 9



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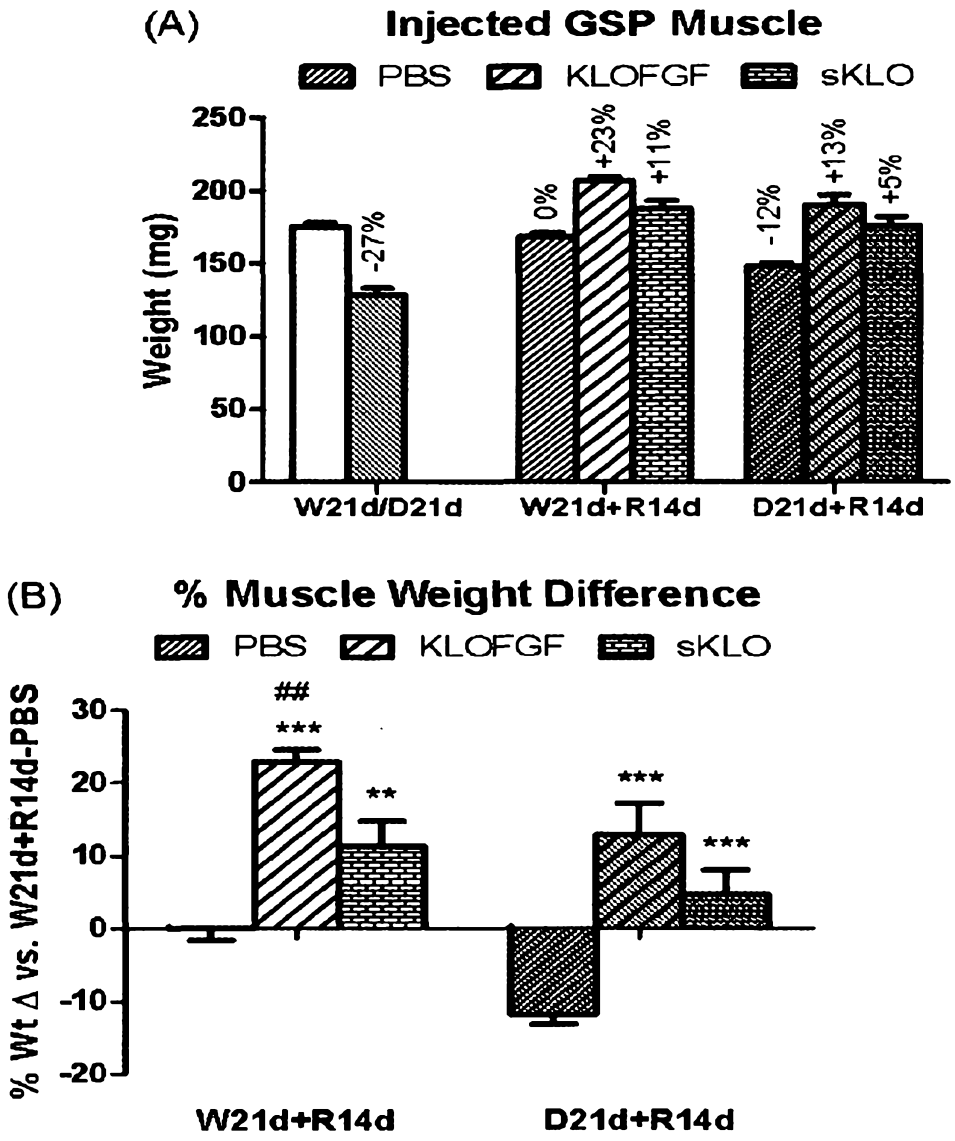

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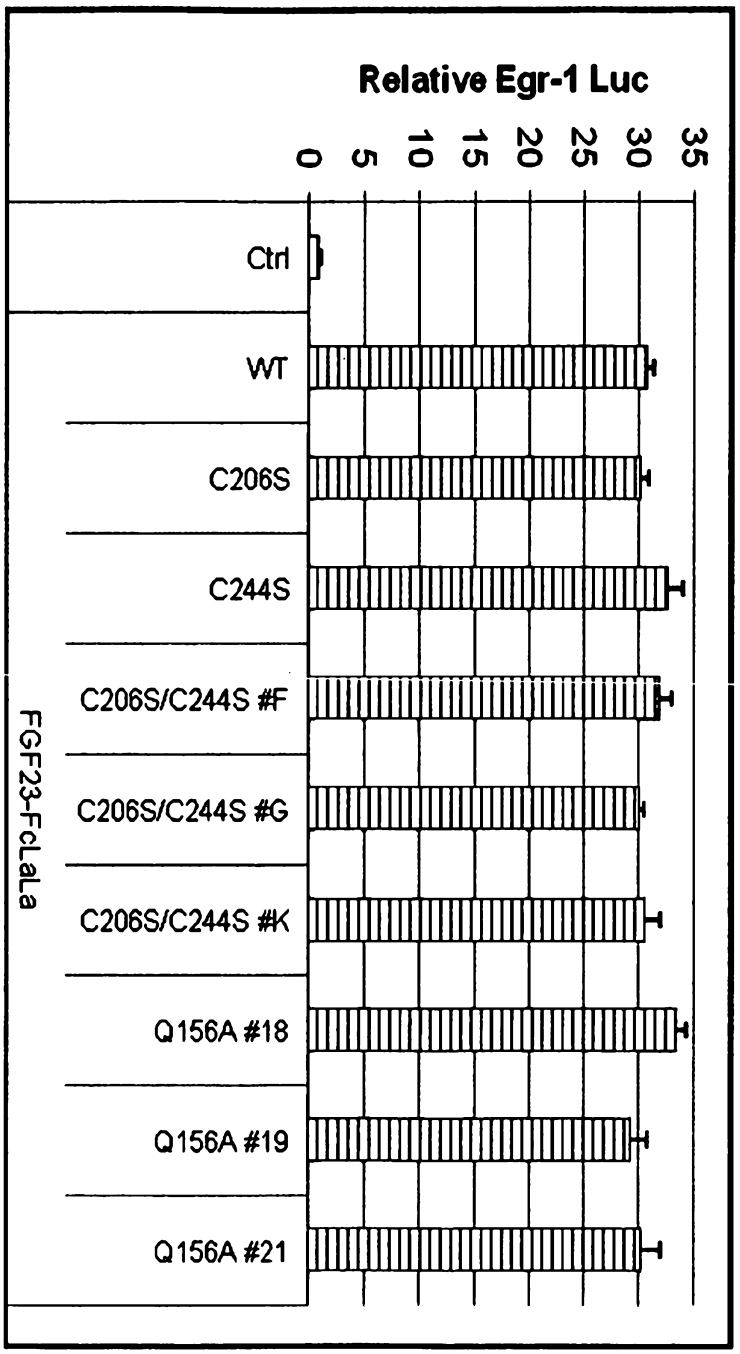
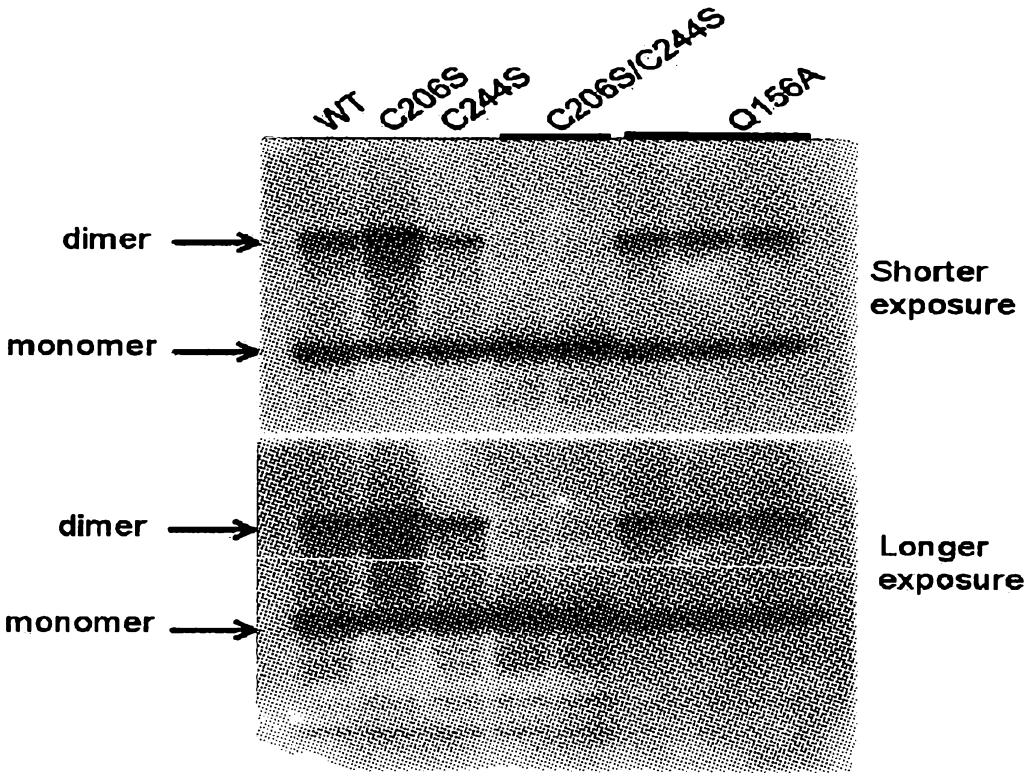


Figure 11

REPLACEMENT SHEET

Figure 12



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Asp Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe
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Leu Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr
785                 790                 795                 800

Phe Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser
                805                 810                 815

Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu
            820                 825                 830

Met Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val
        835                 840                 845

Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly
    850                 855                 860

Asp Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His
865                 870                 875                 880

Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn
                885                 890                 895

Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr
            900                 905                 910

Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr
        915                 920                 925

Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr
    930                 935                 940

Arg Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu
945                 950                 955                 960

Arg Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe
                965                 970                 975

His Thr Arg Lys Ser Leu Leu Ala Phe Ile Ala Phe Leu Phe Phe Ala
            980                 985                 990
```

Ser Ile Ile Ser Leu Ser Leu Ile Phe Tyr Tyr Ser Lys Lys Gly Arg
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Arg Ser Tyr Lys
    1010

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<212> DNA
<213> Homo Sapiens

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atctccaggg aatgaatgga ttttcttcag cactgatgaa ataaccacac gctataggaa 180

tacaatgtcc aacgggggat tgcaaagatc tgtcatcctg tcagcactta ttctgctacg 240

agctgttact ggattctctg gagatggaag agctatatgg tctaaaaatc ctaattttac 300

tccggtaaat gaaagtcagc tgtttctcta tgacactttc cctaaaaact ttttctgggg 360

tattgggact ggagcattgc aagtggaagg gagttggaag aaggatggaa aaggaccttc 420

tatatgggat catttcatcc acacacacct taaaaatgtc agcagcacga atggttccag 480

tgacagttat atttttctgg aaaaagactt atcagccctg gattttatag gagtttcttt 540

ttatcaattt tcaatttcct ggccaaggct tttccccgat ggaatagtaa cagttgccaa 600

cgcaaaaggt ctgcagtact acagtactct tctggacgct ctagtgctta gaaacattga 660

acctatagtt actttatacc actgggattt gcctttggca ctacaagaaa aatatggggg 720

gtggaaaaat gataccataa tagatatctt caatgactat gccacatact gtttccagat 780

gtttggggac cgtgtcaaat attggattac aattcacaac ccatatctag tggcttggca 840

tgggtatggg acaggtatgc atgcccctgg agagaaggga aatttagcag ctgtctacac 900

tgtgggacac aacttgatca aggctcactc gaaagtttgg cataactaca acacacattt 960

ccgcccacat cagaagggtt ggttatcgat cacgttggga tctcattgga tcgagccaaa 1020

ccggtcggaa aacacgatgg atatattcaa atgtcaacaa tccatggttt ctgtgcttgg 1080

atggtttgcc aaccctatcc atggggatgg cgactatcca gaggggatga gaaagaagtt 1140

gttctccgtt ctacccattt tctctgaagc agagaagcat gagatgagag gcacagctga 1200

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caaccctcga atcttgattg ctgagaatgg ctggttcaca gacagtcgtg tgaaaacaga 1380

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gttagatgaa atacgagtgt ttggttatac tgcctggtct ctcctggatg gctttgaatg 1500

gcaggatgct tacaccatcc gccgaggatt attttatgtg gattttaaca gtaaacagaa 1560

agagcggaaa cctaagtctt cagcacacta ctacaaacag atcatacgag aaaatggttt 1620

ttctttaaaa gagtccacgc cagatgtgca gggccagttt ccctgtgact tctcctgggg 1680

tgtcactgaa tctgttctta agcccgagtc tgtggcttcg tccccacagt tcagcgatcc 1740

tcatctgtac gtgtggaacg ccactggcaa cagactgttg caccgagtgg aaggggtgag 1800

gctgaaaaca cgacccgctc aatgcacaga ttttgtaaac atcaaaaaac aacttgagat 1860

gttggcaaga atgaaagtca cccactaccg gtttgctctg gattgggcct cggtccttcc 1920

cactggcaac ctgtccgcgg tgaaccgaca ggccctgagg tactacaggt gcgtggtcag 1980

tgaggggctg aagcttggca tctccgcgat ggtcaccctg tattatccga cccacgccca 2040

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ggccttccag gcctacgctg ggctgtgctt ccaggagctg ggggacctgg tgaagctctg 2160

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ctacggggcg gcgcacaacc tgctggtggc ccacgccctg gcctggcgcc tctacgaccg 2280

gcagttcagg ccctcacagc gcggggccgt gtcgctgtcg ctgcacgcgg actgggcgga 2340

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gtttctgcag gacatcaccc gcctgagctc ccccacgcgc ctggctgtga ttccctgggg 2700

ggtgcgcaag ctgctgcggt gggtccggag gaactacggc gacatggaca tttacatcac 2760

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ggttctactc ttatcaattg ccatttttca aaggcagaag agaagaaagt tttggaaagc 3180

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<400> 4

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Met Lys Pro Gly Cys Ala Ala Gly Ser Pro Gly Asn Glu Trp Ile Phe
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Phe Ser Thr Asp Glu Ile Thr Thr Arg Tyr Arg Asn Thr Met Ser Asn
            20                  25                  30

Gly Gly Leu Gln Arg Ser Val Ile Leu Ser Ala Leu Ile Leu Leu Arg
        35                  40                  45

Ala Val Thr Gly Phe Ser Gly Asp Gly Arg Ala Ile Trp Ser Lys Asn
    50                  55                  60

Pro Asn Phe Thr Pro Val Asn Glu Ser Gln Leu Phe Leu Tyr Asp Thr
65                  70                  75                  80

Phe Pro Lys Asn Phe Phe Trp Gly Ile Gly Thr Gly Ala Leu Gln Val
                85                  90                  95

Glu Gly Ser Trp Lys Lys Asp Gly Lys Gly Pro Ser Ile Trp Asp His
            100                 105                 110

Phe Ile His Thr His Leu Lys Asn Val Ser Ser Thr Asn Gly Ser Ser
        115                 120                 125

Asp Ser Tyr Ile Phe Leu Glu Lys Asp Leu Ser Ala Leu Asp Phe Ile
    130                 135                 140

Gly Val Ser Phe Tyr Gln Phe Ser Ile Ser Trp Pro Arg Leu Phe Pro
145                 150                 155                 160

Asp Gly Ile Val Thr Val Ala Asn Ala Lys Gly Leu Gln Tyr Tyr Ser
                165                 170                 175

Thr Leu Leu Asp Ala Leu Val Leu Arg Asn Ile Glu Pro Ile Val Thr
            180                 185                 190

Leu Tyr His Trp Asp Leu Pro Leu Ala Leu Gln Glu Lys Tyr Gly Gly
        195                 200                 205

Trp Lys Asn Asp Thr Ile Ile Asp Ile Phe Asn Asp Tyr Ala Thr Tyr
    210                 215                 220
```

```
Cys Phe Gln Met Phe Gly Asp Arg Val Lys Tyr Trp Ile Thr Ile His
225                 230                 235                 240

Asn Pro Tyr Leu Val Ala Trp His Gly Tyr Gly Thr Gly Met His Ala
                245                 250                 255

Pro Gly Glu Lys Gly Asn Leu Ala Ala Val Tyr Thr Val Gly His Asn
            260                 265                 270

Leu Ile Lys Ala His Ser Lys Val Trp His Asn Tyr Asn Thr His Phe
        275                 280                 285

Arg Pro His Gln Lys Gly Trp Leu Ser Ile Thr Leu Gly Ser His Trp
    290                 295                 300

Ile Glu Pro Asn Arg Ser Glu Asn Thr Met Asp Ile Phe Lys Cys Gln
305                 310                 315                 320

Gln Ser Met Val Ser Val Leu Gly Trp Phe Ala Asn Pro Ile His Gly
                325                 330                 335

Asp Gly Asp Tyr Pro Glu Gly Met Arg Lys Lys Leu Phe Ser Val Leu
            340                 345                 350

Pro Ile Phe Ser Glu Ala Glu Lys His Glu Met Arg Gly Thr Ala Asp
        355                 360                 365

Phe Phe Ala Phe Ser Phe Gly Pro Asn Asn Phe Lys Pro Leu Asn Thr
    370                 375                 380

Met Ala Lys Met Gly Gln Asn Val Ser Leu Asn Leu Arg Glu Ala Leu
385                 390                 395                 400

Asn Trp Ile Lys Leu Glu Tyr Asn Asn Pro Arg Ile Leu Ile Ala Glu
                405                 410                 415

Asn Gly Trp Phe Thr Asp Ser Arg Val Lys Thr Glu Asp Thr Thr Ala
            420                 425                 430

Ile Tyr Met Met Lys Asn Phe Leu Ser Gln Val Leu Gln Ala Ile Arg
        435                 440                 445

Leu Asp Glu Ile Arg Val Phe Gly Tyr Thr Ala Trp Ser Leu Leu Asp
    450                 455                 460

Gly Phe Glu Trp Gln Asp Ala Tyr Thr Ile Arg Arg Gly Leu Phe Tyr
465                 470                 475                 480
```

```
Val Asp Phe Asn Ser Lys Gln Lys Glu Arg Lys Pro Lys Ser Ser Ala
                485                 490                 495

His Tyr Tyr Lys Gln Ile Ile Arg Glu Asn Gly Phe Ser Leu Lys Glu
            500                 505                 510

Ser Thr Pro Asp Val Gln Gly Gln Phe Pro Cys Asp Phe Ser Trp Gly
        515                 520                 525

Val Thr Glu Ser Val Leu Lys Pro Glu Ser Val Ala Ser Ser Pro Gln
    530                 535                 540

Phe Ser Asp Pro His Leu Tyr Val Trp Asn Ala Thr Gly Asn Arg Leu
545                 550                 555                 560

Leu His Arg Val Glu Gly Val Arg Leu Lys Thr Arg Pro Ala Gln Cys
                565                 570                 575

Thr Asp Phe Val Asn Ile Lys Lys Gln Leu Glu Met Leu Ala Arg Met
            580                 585                 590

Lys Val Thr His Tyr Arg Phe Ala Leu Asp Trp Ala Ser Val Leu Pro
        595                 600                 605

Thr Gly Asn Leu Ser Ala Val Asn Arg Gln Ala Leu Arg Tyr Tyr Arg
    610                 615                 620

Cys Val Val Ser Glu Gly Leu Lys Leu Gly Ile Ser Ala Met Val Thr
625                 630                 635                 640

Leu Tyr Tyr Pro Thr His Ala His Leu Gly Leu Pro Glu Pro Leu Leu
                645                 650                 655

His Ala Asp Gly Trp Leu Asn Pro Ser Thr Ala Glu Ala Phe Gln Ala
            660                 665                 670

Tyr Ala Gly Leu Cys Phe Gln Glu Leu Gly Asp Leu Val Lys Leu Trp
        675                 680                 685

Ile Thr Ile Asn Glu Pro Asn Arg Leu Ser Asp Ile Tyr Asn Arg Ser
    690                 695                 700

Gly Asn Asp Thr Tyr Gly Ala Ala His Asn Leu Leu Val Ala His Ala
705                 710                 715                 720

Leu Ala Trp Arg Leu Tyr Asp Arg Gln Phe Arg Pro Ser Gln Arg Gly
                725                 730                 735
```

```
Ala Val Ser Leu Ser Leu His Ala Asp Trp Ala Glu Pro Ala Asn Pro
            740                 745                 750

Tyr Ala Asp Ser His Trp Arg Ala Ala Glu Arg Phe Leu Gln Phe Glu
        755                 760                 765

Ile Ala Trp Phe Ala Glu Pro Leu Phe Lys Thr Gly Asp Tyr Pro Ala
    770                 775                 780

Ala Met Arg Glu Tyr Ile Ala Ser Lys His Arg Arg Gly Leu Ser Ser
785                 790                 795                 800

Ser Ala Leu Pro Arg Leu Thr Glu Ala Glu Arg Arg Leu Leu Lys Gly
                805                 810                 815

Thr Val Asp Phe Cys Ala Leu Asn His Phe Thr Thr Arg Phe Val Met
            820                 825                 830

His Glu Gln Leu Ala Gly Ser Arg Tyr Asp Ser Asp Arg Asp Ile Gln
        835                 840                 845

Phe Leu Gln Asp Ile Thr Arg Leu Ser Ser Pro Thr Arg Leu Ala Val
    850                 855                 860

Ile Pro Trp Gly Val Arg Lys Leu Leu Arg Trp Val Arg Arg Asn Tyr
865                 870                 875                 880

Gly Asp Met Asp Ile Tyr Ile Thr Ala Ser Gly Ile Asp Asp Gln Ala
                885                 890                 895

Leu Glu Asp Asp Arg Leu Arg Lys Tyr Tyr Leu Gly Lys Tyr Leu Gln
            900                 905                 910

Glu Val Leu Lys Ala Tyr Leu Ile Asp Lys Val Arg Ile Lys Gly Tyr
        915                 920                 925

Tyr Ala Phe Lys Leu Ala Glu Glu Lys Ser Lys Pro Arg Phe Gly Phe
    930                 935                 940

Phe Thr Ser Asp Phe Lys Ala Lys Ser Ser Ile Gln Phe Tyr Asn Lys
945                 950                 955                 960

Val Ile Ser Ser Arg Gly Phe Pro Phe Glu Asn Ser Ser Ser Arg Cys
                965                 970                 975

Ser Gln Thr Gln Glu Asn Thr Glu Cys Thr Val Cys Leu Phe Leu Val
```

980 985 990

Gln Lys Lys Pro Leu Ile Phe Leu Gly Cys Cys Phe Phe Ser Thr Leu
995 1000 1005

Val Leu Leu Leu Ser Ile Ala Ile Phe Gln Arg Gln Lys Arg Arg
1010 1015 1020

Lys Phe Trp Lys Ala Lys Asn Leu Gln His Ile Pro Leu Lys Lys
1025 1030 1035

Gly Lys Arg Val Val Ser
1040

<210> 5
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<212> PRT
<213> Homo Sapiens

<400> 5

Gln Gly Thr Phe Pro Asp Gly Phe Leu Trp Ala Val Gly Ser Ala Ala
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Tyr Gln Thr Glu Gly Gly Trp Gln Gln His Gly Lys Gly Ala Ser Ile
20 25 30

Trp Asp Thr Phe Thr His His Pro Leu Ala Pro Pro Gly Asp Ser Arg
35 40 45

Asn Ala Ser Leu Pro Leu Gly Ala Pro Ser Pro Leu Gln Pro Ala Thr
50 55 60

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

Ala Leu Arg Glu Leu Gly Val Thr His Tyr Arg Phe Ser Ile Ser Trp
85 90 95

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

Leu Arg Tyr Tyr Arg Arg Leu Leu Glu Arg Leu Arg Glu Leu Gly Val
115 120 125

Gln Pro Val Val Thr Leu Tyr His Trp Asp Leu Pro Gln Arg Leu Gln
130 135 140

Asp Ala Tyr Gly Gly Trp Ala Asn Arg Ala Leu Ala Asp His Phe Arg

145 150 155 160

Asp Tyr Ala Glu Leu Cys Phe Arg His Phe Gly Gly Gln Val Lys Tyr
165 170 175

Trp Ile Thr Ile Asp Asn Pro Tyr Val Val Ala Trp His Gly Tyr Ala
180 185 190

Thr Gly Arg Leu Ala Pro Gly Ile Arg Gly Ser Pro Arg Leu Gly Tyr
195 200 205

Leu Val Ala His Asn Leu Leu Leu Ala His Ala Lys Val Trp His Leu
210 215 220

Tyr Asn Thr Ser Phe Arg Pro Thr Gln Gly Gly Gln Val Ser Ile Ala
225 230 235 240

Leu Ser Ser His Trp Ile Asn Pro Arg Arg Met Thr Asp His Ser Ile
245 250 255

Lys Glu Cys Gln Lys Ser Leu Asp Phe Val Leu Gly Trp Phe Ala Lys
260 265 270

Pro Val Phe Ile Asp Gly Asp Tyr Pro Glu Ser Met Lys Asn Asn Leu
275 280 285

Ser Ser Ile Leu Pro Asp Phe Thr Glu Ser Glu Lys Lys Phe Ile Lys
290 295 300

Gly Thr Ala Asp Phe Phe Ala Leu Cys Phe Gly Pro Thr Leu Ser Phe
305 310 315 320

Gln Leu Leu Asp Pro His Met Lys Phe Arg Gln Leu Glu Ser Pro Asn
325 330 335

Leu Arg Gln Leu Leu Ser Trp Ile Asp Leu Glu Phe Asn His Pro Gln
340 345 350

Ile Phe Ile Val Glu Asn Gly Trp Phe Val Ser Gly Thr Thr Lys Arg
355 360 365

Asp Asp Ala Lys Tyr Met Tyr Tyr Leu Lys Lys Phe Ile Met Glu Thr
370 375 380

Leu Lys Ala Ile Lys Leu Asp Gly Val Asp Val Ile Gly Tyr Thr Ala
385 390 395 400

Trp Ser Leu Met Asp Gly Phe Glu Trp His Arg Gly Tyr Ser Ile Arg
405 410 415

Arg Gly Leu Phe Tyr Val Asp Phe Leu Ser Gln Asp Lys Met Leu Leu
420 425 430

Pro Lys Ser Ser Ala Leu Phe Tyr Gln Lys Leu Ile Glu Lys Asn Gly
435 440 445

Phe

<210> 6
<211> 437
<212> PRT
<213> Homo Sapiens

<400> 6

Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp Asn Tyr Ile
1 5 10 15

Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn Val Tyr Leu
20 25 30

Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp Gly Val Val
35 40 45

Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala Ile Gln Pro
50 55 60

Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe Arg Phe Ser
65 70 75 80

Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser Gln Val Asn
85 90 95

His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu Leu Val Arg
100 105 110

Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met Ala Pro Asn
115 120 125

Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp Glu Asn Pro
130 135 140

Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys Phe Gln Glu
145 150 155 160

```
Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu Pro Tyr Thr
                165                 170                 175

Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys Ala His Ala
            180                 185                 190

Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala Gln Asn Gly
        195                 200                 205

Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro Ala Cys Pro
    210                 215                 220

Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu Glu Phe Asp
225                 230                 235                 240

Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp Tyr Pro Trp
                245                 250                 255

Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu Leu Pro Tyr
            260                 265                 270

Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe Asp Phe Leu
        275                 280                 285

Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu Lys Glu Asp
    290                 295                 300

Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met Thr Asp Ile
305                 310                 315                 320

Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro Trp Gly Leu
                325                 330                 335

Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly Asp Leu Pro Met
            340                 345                 350

Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His Ala Glu Asp Asp
        355                 360                 365

Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn Glu Ala Leu Lys
    370                 375                 380

Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr Phe Ala Tyr Ser
385                 390                 395                 400

Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr Arg Tyr Ala Ala
                405                 410                 415
```

```
Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr Arg Lys Ile Ile
            420                 425                 430


Asp Ser Asn Gly Phe
        435


<210>  7
<211>  949
<212>  PRT
<213>  Homo Sapiens

<400>  7

Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro Pro
1               5                   10                  15


Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly Phe
            20                  25                  30


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


Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro
    50                  55                  60


Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala
65                  70                  75                  80


Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr
                85                  90                  95


Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr
            100                 105                 110


His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser
        115                 120                 125


Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu
    130                 135                 140


Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His
145                 150                 155                 160


Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn
                165                 170                 175


Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg
            180                 185                 190
```

```
His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr
        195                 200                 205

Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile
    210                 215                 220

Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu
225                 230                 235                 240

Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr
                245                 250                 255

Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro
            260                 265                 270

Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp
        275                 280                 285

Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr
    290                 295                 300

Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr
305                 310                 315                 320

Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu
                325                 330                 335

Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys
            340                 345                 350

Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile
        355                 360                 365

Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp
    370                 375                 380

Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr
385                 390                 395                 400

Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly
                405                 410                 415

Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu
            420                 425                 430

Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe
        435                 440                 445
```

```
Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr
    450                 455                 460

Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln
465                 470                 475                 480

Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp
                485                 490                 495

Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn
            500                 505                 510

Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp
        515                 520                 525

Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala
    530                 535                 540

Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe
545                 550                 555                 560

Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser
                565                 570                 575

Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu
            580                 585                 590

Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met
        595                 600                 605

Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp
    610                 615                 620

Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys
625                 630                 635                 640

Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu
                645                 650                 655

Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys
            660                 665                 670

Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala
        675                 680                 685

Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro
```

690 695 700

Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu
705 710 715 720

Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp
725 730 735

Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu
740 745 750

Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe
755 760 765

Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu
770 775 780

Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met
785 790 795 800

Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro
805 810 815

Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly Asp
820 825 830

Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His Ala
835 840 845

Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn Glu
850 855 860

Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr Phe
865 870 875 880

Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr Arg
885 890 895

Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr Arg
900 905 910

Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu Arg
915 920 925

Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe His
930 935 940

Thr Arg Lys Ser Leu
945

<210> 8
<211> 33
<212> PRT
<213> Homo Sapiens

<400> 8

Met Pro Ala Ser Ala Pro Pro Arg Arg Pro Arg Pro Pro Pro Pro Ser
1 5 10 15

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

Ala

<210> 9
<211> 25
<212> PRT
<213> Homo Sapiens

<400> 9

Met Ser Val Leu Thr Gln Val Leu Ala Leu Leu Leu Leu Trp Leu Thr
1 5 10 15

Gly Thr Arg Cys Arg Arg Leu Arg Ala
20 25

<210> 10
<211> 45
<212> DNA
<213> Homo Sapiens

<400> 10
ggaggtggag gttcaggagg tggaggttca ggaggtggag gttca 45

<210> 11
<211> 15
<212> PRT
<213> Homo Sapiens

<400> 11

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

<210> 12
<211> 5
<212> PRT
<213> Homo Sapiens

<400> 12

Gly Gly Gly Gly Ser
1   5

<210> 13
<211> 1
<212> PRT
<213> Homo Sapiens

<400> 13

Gly
1

<210> 14
<211> 2
<212> PRT
<213> Homo Sapiens

<400> 14

Gly Gly
1

<210> 15
<211> 2
<212> PRT
<213> Homo Sapiens

<400> 15

Gly Ser
1

<210> 16
<211> 3
<212> PRT
<213> Homo Sapiens

<400> 16

Gly Gly Ser
1

<210> 17
<211> 1
<212> PRT
<213> Homo Sapiens

<400> 17

Ala
1

<210> 18
<211> 2

<212> PRT
<213> Homo Sapiens

<400> 18

Ala Ala
1

<210> 19
<211> 1228
<212> PRT
<213> Homo Sapiens

<400> 19

Met Pro Ala Ser Ala Pro Pro Arg Arg Pro Arg Pro Pro Pro Pro Ser
1 5 10 15

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

Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro
35 40 45

Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly
50 55 60

Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp
65 70 75 80

Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His
85 90 95

Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly
100 105 110

Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser
115 120 125

Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val
130 135 140

Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly
145 150 155 160

Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu
165 170 175

Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr
180 185 190

```
His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala
        195                 200                 205

Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe
    210                 215                 220

Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro
225                 230                 235                 240

Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly
                245                 250                 255

Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu
            260                 265                 270

Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro
        275                 280                 285

Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn
    290                 295                 300

Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu
305                 310                 315                 320

Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp
                325                 330                 335

Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe
            340                 345                 350

Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala
        355                 360                 365

Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met
    370                 375                 380

Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp
385                 390                 395                 400

Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly
                405                 410                 415

Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr
            420                 425                 430

Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp
        435                 440                 445
```

```
Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe
    450                 455                 460

Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp
465                 470                 475                 480

Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe
                485                 490                 495

Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn
            500                 505                 510

Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val
        515                 520                 525

Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu
    530                 535                 540

Asn Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val
545                 550                 555                 560

Asp Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala
                565                 570                 575

Ala Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His
            580                 585                 590

Phe Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln
        595                 600                 605

Ser Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser
    610                 615                 620

Glu Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro
625                 630                 635                 640

Met Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala
                645                 650                 655

Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu
            660                 665                 670

Cys Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn
        675                 680                 685

Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu
```

690 695 700

Lys Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His
705 710 715 720

Ala Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu
725 730 735

Pro Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val
740 745 750

Leu Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly
755 760 765

Asp Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe
770 775 780

Leu Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr
785 790 795 800

Phe Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser
805 810 815

Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu
820 825 830

Met Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val
835 840 845

Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly
850 855 860

Asp Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His
865 870 875 880

Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn
885 890 895

Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr
900 905 910

Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr
915 920 925

Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr
930 935 940

```
Arg Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu
945                 950                 955                 960

Arg Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe
                965                 970                 975

His Thr Arg Lys Ser Leu Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
            980                 985                 990

Gly Ser Gly Gly Gly Gly Ser Leu  Lys Tyr Pro Asn Ala  Ser Pro Leu
        995                 1000                1005

Leu Gly  Ser Ser Trp Gly Gly  Leu Ile His Leu Tyr  Thr Ala Thr
    1010                1015                1020

Ala Arg  Asn Ser Tyr His Leu  Gln Ile His Lys Asn  Gly His Val
    1025                1030                1035

Asp Gly  Ala Pro His Gln Thr  Ile Tyr Ser Ala Leu  Met Ile Arg
    1040                1045                1050

Ser Glu  Asp Ala Gly Phe Val  Val Ile Thr Gly Val  Met Ser Arg
    1055                1060                1065

Arg Tyr  Leu Cys Met Asp Phe  Arg Gly Asn Ile Phe  Gly Ser His
    1070                1075                1080

Tyr Phe  Asp Pro Glu Asn Cys  Arg Phe Gln His Gln  Thr Leu Glu
    1085                1090                1095

Asn Gly  Tyr Asp Val Tyr His  Ser Pro Gln Tyr His  Phe Leu Val
    1100                1105                1110

Ser Leu  Gly Arg Ala Lys Arg  Ala Phe Leu Pro Gly  Met Asn Pro
    1115                1120                1125

Pro Pro  Tyr Ser Gln Phe Leu  Ser Arg Arg Asn Glu  Ile Pro Leu
    1130                1135                1140

Ile His  Phe Asn Thr Pro Ile  Pro Arg Arg His Thr  Gln Ser Ala
    1145                1150                1155

Glu Asp  Asp Ser Glu Arg Asp  Pro Leu Asn Val Leu  Lys Pro Arg
    1160                1165                1170

Ala Arg  Met Thr Pro Ala Pro  Ala Ser Cys Ser Gln  Glu Leu Pro
    1175                1180                1185
```

Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu Gly Val
1190 1195 1200

Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly Pro
1205 1210 1215

Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile
1220 1225

<210> 20
<211> 1220
<212> PRT
<213> Homo Sapiens

<400> 20

Met Ser Val Leu Thr Gln Val Leu Ala Leu Leu Leu Leu Trp Leu Thr
1 5 10 15

Gly Leu Gly Gly Arg Arg Leu Arg Ala Glu Pro Gly Asp Gly Ala Gln
20 25 30

Thr Trp Ala Arg Phe Ser Arg Pro Pro Ala Pro Glu Ala Ala Gly Leu
35 40 45

Phe Gln Gly Thr Phe Pro Asp Gly Phe Leu Trp Ala Val Gly Ser Ala
50 55 60

Ala Tyr Gln Thr Glu Gly Gly Trp Gln Gln His Gly Lys Gly Ala Ser
65 70 75 80

Ile Trp Asp Thr Phe Thr His His Pro Leu Ala Pro Pro Gly Asp Ser
85 90 95

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

Thr Gly Asp Val Ala Ser Asp Ser Tyr Asn Asn Val Phe Arg Asp Thr
115 120 125

Glu Ala Leu Arg Glu Leu Gly Val Thr His Tyr Arg Phe Ser Ile Ser
130 135 140

Trp Ala Arg Val Leu Pro Asn Gly Ser Ala Gly Val Pro Asn Arg Glu
145 150 155 160

Gly Leu Arg Tyr Tyr Arg Arg Leu Leu Glu Arg Leu Arg Glu Leu Gly
165 170 175

```
Val Gln Pro Val Val Thr Leu Tyr His Trp Asp Leu Pro Gln Arg Leu
            180                 185                 190

Gln Asp Ala Tyr Gly Gly Trp Ala Asn Arg Ala Leu Ala Asp His Phe
        195                 200                 205

Arg Asp Tyr Ala Glu Leu Cys Phe Arg His Phe Gly Gly Gln Val Lys
    210                 215                 220

Tyr Trp Ile Thr Ile Asp Asn Pro Tyr Val Val Ala Trp His Gly Tyr
225                 230                 235                 240

Ala Thr Gly Arg Leu Ala Pro Gly Ile Arg Gly Ser Pro Arg Leu Gly
                245                 250                 255

Tyr Leu Val Ala His Asn Leu Leu Leu Ala His Ala Lys Val Trp His
            260                 265                 270

Leu Tyr Asn Thr Ser Phe Arg Pro Thr Gln Gly Gly Gln Val Ser Ile
        275                 280                 285

Ala Leu Ser Ser His Trp Ile Asn Pro Arg Arg Met Thr Asp His Ser
    290                 295                 300

Ile Lys Glu Cys Gln Lys Ser Leu Asp Phe Val Leu Gly Trp Phe Ala
305                 310                 315                 320

Lys Pro Val Phe Ile Asp Gly Asp Tyr Pro Glu Ser Met Lys Asn Asn
                325                 330                 335

Leu Ser Ser Ile Leu Pro Asp Phe Thr Glu Ser Glu Lys Lys Phe Ile
            340                 345                 350

Lys Gly Thr Ala Asp Phe Phe Ala Leu Cys Phe Gly Pro Thr Leu Ser
        355                 360                 365

Phe Gln Leu Leu Asp Pro His Met Lys Phe Arg Gln Leu Glu Ser Pro
    370                 375                 380

Asn Leu Arg Gln Leu Leu Ser Trp Ile Asp Leu Glu Phe Asn His Pro
385                 390                 395                 400

Gln Ile Phe Ile Val Glu Asn Gly Trp Phe Val Ser Gly Thr Thr Lys
                405                 410                 415

Arg Asp Asp Ala Lys Tyr Met Tyr Tyr Leu Lys Lys Phe Ile Met Glu
            420                 425                 430
```

```
Thr Leu Lys Ala Ile Lys Leu Asp Gly Val Asp Val Ile Gly Tyr Thr
        435                 440                 445

Ala Trp Ser Leu Met Asp Gly Phe Glu Trp His Arg Gly Tyr Ser Ile
    450                 455                 460

Arg Arg Gly Leu Phe Tyr Val Asp Phe Leu Ser Gln Asp Lys Met Leu
465                 470                 475                 480

Leu Pro Lys Ser Ser Ala Leu Phe Tyr Gln Lys Leu Ile Glu Lys Asn
                485                 490                 495

Gly Phe Pro Pro Leu Pro Glu Asn Gln Pro Leu Glu Gly Thr Phe Pro
            500                 505                 510

Cys Asp Phe Ala Trp Gly Val Val Asp Asn Tyr Ile Gln Val Asp Thr
        515                 520                 525

Thr Leu Ser Gln Phe Thr Asp Leu Asn Val Tyr Leu Trp Asp Val His
    530                 535                 540

His Ser Lys Arg Leu Ile Lys Val Asp Gly Val Val Thr Lys Lys Arg
545                 550                 555                 560

Lys Ser Tyr Cys Val Asp Phe Ala Ala Ile Gln Pro Gln Ile Ala Leu
                565                 570                 575

Leu Gln Glu Met His Val Thr His Phe Arg Phe Ser Leu Asp Trp Ala
            580                 585                 590

Leu Ile Leu Pro Leu Gly Asn Gln Ser Gln Val Asn His Thr Ile Leu
        595                 600                 605

Gln Tyr Tyr Arg Cys Met Ala Ser Glu Leu Val Arg Val Asn Ile Thr
    610                 615                 620

Pro Val Val Ala Leu Trp Gln Pro Met Ala Pro Asn Gln Gly Leu Pro
625                 630                 635                 640

Arg Leu Leu Ala Arg Gln Gly Ala Trp Glu Asn Pro Tyr Thr Ala Leu
                645                 650                 655

Ala Phe Ala Glu Tyr Ala Arg Leu Cys Phe Gln Glu Leu Gly His His
            660                 665                 670

Val Lys Leu Trp Ile Thr Met Asn Glu Pro Tyr Thr Arg Asn Met Thr
```

675 680 685

Tyr Ser Ala Gly His Asn Leu Leu Lys Ala His Ala Leu Ala Trp His
690 695 700

Val Tyr Asn Glu Lys Phe Arg His Ala Gln Asn Gly Lys Ile Ser Ile
705 710 715 720

Ala Leu Gln Ala Asp Trp Ile Glu Pro Ala Cys Pro Phe Ser Gln Lys
725 730 735

Asp Lys Glu Val Ala Glu Arg Val Leu Glu Phe Asp Ile Gly Trp Leu
740 745 750

Ala Glu Pro Ile Phe Gly Ser Gly Asp Tyr Pro Trp Val Met Arg Asp
755 760 765

Trp Leu Asn Gln Arg Asn Asn Phe Leu Leu Pro Tyr Phe Thr Glu Asp
770 775 780

Glu Lys Lys Leu Ile Gln Gly Thr Phe Asp Phe Leu Ala Leu Ser His
785 790 795 800

Tyr Thr Thr Ile Leu Val Asp Ser Glu Lys Glu Asp Pro Ile Lys Tyr
805 810 815

Asn Asp Tyr Leu Glu Val Gln Glu Met Thr Asp Ile Thr Trp Leu Asn
820 825 830

Ser Pro Ser Gln Val Ala Val Val Pro Trp Gly Leu Arg Lys Val Leu
835 840 845

Asn Trp Leu Lys Phe Lys Tyr Gly Asp Leu Pro Met Tyr Ile Ile Ser
850 855 860

Asn Gly Ile Asp Asp Gly Leu His Ala Glu Asp Asp Gln Leu Arg Val
865 870 875 880

Tyr Tyr Met Gln Asn Tyr Ile Asn Glu Ala Leu Lys Ala His Ile Leu
885 890 895

Asp Gly Ile Asn Leu Cys Gly Tyr Phe Ala Tyr Ser Phe Asn Asp Arg
900 905 910

Thr Ala Pro Arg Phe Gly Leu Tyr Arg Tyr Ala Ala Asp Gln Phe Glu
915 920 925

```
Pro Lys Ala Ser Met Lys His Tyr Arg Lys Ile Ile Asp Ser Asn Gly
    930                 935                 940

Phe Pro Gly Pro Glu Thr Leu Glu Arg Phe Cys Pro Glu Glu Phe Thr
945                 950                 955                 960

Val Cys Thr Glu Cys Ser Phe Phe His Thr Arg Lys Ser Leu Gly Ser
                965                 970                 975

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
            980                 985                 990

Lys Tyr Pro Asn Ala Ser Pro Leu  Leu Gly Ser Ser Trp  Gly Gly Leu
        995                 1000                1005

Ile His  Leu Tyr Thr Ala Thr  Ala Arg Asn Ser Tyr  His Leu Gln
    1010                1015                1020

Ile His  Lys Asn Gly His Val  Asp Gly Ala Pro His  Gln Thr Ile
    1025                1030                1035

Tyr Ser  Ala Leu Met Ile Arg  Ser Glu Asp Ala Gly  Phe Val Val
    1040                1045                1050

Ile Thr  Gly Val Met Ser Arg  Arg Tyr Leu Cys Met  Asp Phe Arg
    1055                1060                1065

Gly Asn  Ile Phe Gly Ser His  Tyr Phe Asp Pro Glu  Asn Cys Arg
    1070                1075                1080

Phe Gln  His Gln Thr Leu Glu  Asn Gly Tyr Asp Val  Tyr His Ser
    1085                1090                1095

Pro Gln  Tyr His Phe Leu Val  Ser Leu Gly Arg Ala  Lys Arg Ala
    1100                1105                1110

Phe Leu  Pro Gly Met Asn Pro  Pro Pro Tyr Ser Gln  Phe Leu Ser
    1115                1120                1125

Arg Arg  Asn Glu Ile Pro Leu  Ile His Phe Asn Thr  Pro Ile Pro
    1130                1135                1140

Arg Arg  His Thr Gln Ser Ala  Glu Asp Asp Ser Glu  Arg Asp Pro
    1145                1150                1155

Leu Asn  Val Leu Lys Pro Arg  Ala Arg Met Thr Pro  Ala Pro Ala
    1160                1165                1170
```

```
Ser Cys  Ser Gln Glu Leu Pro  Ser Ala Glu Asp Asn  Ser Pro Met
    1175                1180                1185


Ala Ser  Asp Pro Leu Gly Val  Val Arg Gly Gly Arg  Val Asn Thr
    1190                1195                1200


His Ala  Gly Gly Thr Gly Pro  Glu Gly Cys Arg Pro  Phe Ala Lys
    1205                1210                1215


Phe Ile
    1220


<210>  21
<211>  762
<212>  PRT
<213>  Homo Sapiens

<400>  21

Met Pro Ala Ser Ala Pro Pro Arg Arg Pro Arg Pro Pro Pro Pro Ser
1               5                  10                  15


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


Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro
        35                  40                  45


Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly
    50                  55                  60


Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp
65                  70                  75                  80


Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His
                85                  90                  95


Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly
            100                 105                 110


Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser
        115                 120                 125


Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val
    130                 135                 140


Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly
145                 150                 155                 160
```

```
Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu
                165                 170                 175

Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr
            180                 185                 190

His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala
        195                 200                 205

Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe
    210                 215                 220

Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro
225                 230                 235                 240

Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly
                245                 250                 255

Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu
            260                 265                 270

Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro
        275                 280                 285

Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn
    290                 295                 300

Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu
305                 310                 315                 320

Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp
                325                 330                 335

Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe
            340                 345                 350

Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala
        355                 360                 365

Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met
    370                 375                 380

Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp
385                 390                 395                 400

Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly
                405                 410                 415
```

```
Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr
            420                 425                 430

Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp
        435                 440                 445

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

Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp
465                 470                 475                 480

Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe
                485                 490                 495

Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn
            500                 505                 510

Gln Pro Leu Glu Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        515                 520                 525

Gly Gly Gly Gly Ser Leu Lys Tyr Pro Asn Ala Ser Pro Leu Leu Gly
    530                 535                 540

Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg Asn
545                 550                 555                 560

Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala Pro
                565                 570                 575

His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala Gly
            580                 585                 590

Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met Asp
        595                 600                 605

Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn Cys
    610                 615                 620

Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His Ser
625                 630                 635                 640

Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala Phe
                645                 650                 655

Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg Arg
```

660 665 670

Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg His
675 680 685

Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val Leu
690 695 700

Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln Glu
705 710 715 720

Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu Gly
725 730 735

Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly Pro
740 745 750

Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile
755 760

<210> 22
<211> 752
<212> PRT
<213> Homo Sapiens

<400> 22

Met Pro Ala Ser Ala Pro Pro Arg Arg Pro Arg Pro Pro Pro Pro Ser
1 5 10 15

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

Leu Pro Glu Asn Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala
35 40 45

Trp Gly Val Val Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln
50 55 60

Phe Thr Asp Leu Asn Val Tyr Leu Trp Asp Val His His Ser Lys Arg
65 70 75 80

Leu Ile Lys Val Asp Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys
85 90 95

Val Asp Phe Ala Ala Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met
100 105 110

His Val Thr His Phe Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro

115 120 125

Leu Gly Asn Gln Ser Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg
130 135 140

Cys Met Ala Ser Glu Leu Val Arg Val Asn Ile Thr Pro Val Val Ala
145 150 155 160

Leu Trp Gln Pro Met Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala
165 170 175

Arg Gln Gly Ala Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu
180 185 190

Tyr Ala Arg Leu Cys Phe Gln Glu Leu Gly His His Val Lys Leu Trp
195 200 205

Ile Thr Met Asn Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly
210 215 220

His Asn Leu Leu Lys Ala His Ala Leu Ala Trp His Val Tyr Asn Glu
225 230 235 240

Lys Phe Arg His Ala Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala
245 250 255

Asp Trp Ile Glu Pro Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val
260 265 270

Ala Glu Arg Val Leu Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile
275 280 285

Phe Gly Ser Gly Asp Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln
290 295 300

Arg Asn Asn Phe Leu Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu
305 310 315 320

Ile Gln Gly Thr Phe Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile
325 330 335

Leu Val Asp Ser Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu
340 345 350

Glu Val Gln Glu Met Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln
355 360 365

```
Val Ala Val Val Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys
    370                 375                 380

Phe Lys Tyr Gly Asp Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp
385                 390                 395                 400

Asp Gly Leu His Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln
                405                 410                 415

Asn Tyr Ile Asn Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn
            420                 425                 430

Leu Cys Gly Tyr Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg
        435                 440                 445

Phe Gly Leu Tyr Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser
    450                 455                 460

Met Lys His Tyr Arg Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro
465                 470                 475                 480

Glu Thr Leu Glu Arg Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu
                485                 490                 495

Cys Ser Phe Phe His Thr Arg Lys Ser Leu Gly Ser Gly Gly Gly Gly
            500                 505                 510

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu Lys Tyr Pro Asn
        515                 520                 525

Ala Ser Pro Leu Leu Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr
    530                 535                 540

Thr Ala Thr Ala Arg Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly
545                 550                 555                 560

His Val Asp Gly Ala Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile
                565                 570                 575

Arg Ser Glu Asp Ala Gly Phe Val Val Ile Thr Gly Val Met Ser Arg
            580                 585                 590

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

Phe Asp Pro Glu Asn Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly
    610                 615                 620
```

```
Tyr Asp Val Tyr His Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly
625                 630                 635                 640

Arg Ala Lys Arg Ala Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser
                645                 650                 655

Gln Phe Leu Ser Arg Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr
            660                 665                 670

Pro Ile Pro Arg Arg His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg
        675                 680                 685

Asp Pro Leu Asn Val Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro
    690                 695                 700

Ala Ser Cys Ser Gln Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met
705                 710                 715                 720

Ala Ser Asp Pro Leu Gly Val Val Arg Gly Gly Arg Val Asn Thr His
                725                 730                 735

Ala Gly Gly Thr Gly Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile
            740                 745                 750


<210>  23
<211>  1215
<212>  PRT
<213>  Homo Sapiens

<400>  23

Met Pro Ala Ser Ala Pro Pro Arg Arg Pro Arg Pro Pro Pro Pro Ser
1               5                   10                  15

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

Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro
        35                  40                  45

Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly
    50                  55                  60

Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp
65                  70                  75                  80

Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His
                85                  90                  95
```

```
Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly
            100                 105                 110

Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser
        115                 120                 125

Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val
    130                 135                 140

Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly
145                 150                 155                 160

Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu
                165                 170                 175

Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr
            180                 185                 190

His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala
        195                 200                 205

Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe
    210                 215                 220

Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro
225                 230                 235                 240

Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly
                245                 250                 255

Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu
            260                 265                 270

Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro
        275                 280                 285

Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn
    290                 295                 300

Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu
305                 310                 315                 320

Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp
                325                 330                 335

Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe
            340                 345                 350
```

```
Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala
        355                 360                 365

Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met
    370                 375                 380

Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp
385                 390                 395                 400

Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly
                405                 410                 415

Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr
            420                 425                 430

Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp
        435                 440                 445

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

Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp
465                 470                 475                 480

Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe
                485                 490                 495

Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn
            500                 505                 510

Gln Pro Leu Glu Gly Ser Gly Thr Phe Pro Asp Gly Phe Leu Trp Ala
        515                 520                 525

Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln Gln His Gly
    530                 535                 540

Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro Leu Ala Pro
545                 550                 555                 560

Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala Pro Ser Pro
                565                 570                 575

Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr Asn Asn Val
            580                 585                 590

Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr His Tyr Arg
```

595 600 605

Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser Ala Gly Val
610 615 620

Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu Glu Arg Leu
625 630 635 640

Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His Trp Asp Leu
645 650 655

Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn Arg Ala Leu
660 665 670

Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg His Phe Gly
675 680 685

Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr Val Val Ala
690 695 700

Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile Arg Gly Ser
705 710 715 720

Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu Ala His Ala
725 730 735

Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr Gln Gly Gly
740 745 750

Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro Arg Arg Met
755 760 765

Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp Phe Val Leu
770 775 780

Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr Pro Glu Ser
785 790 795 800

Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr Glu Ser Glu
805 810 815

Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu Cys Phe Gly
820 825 830

Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys Phe Arg Gln
835 840 845

```
Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile Asp Leu Glu
    850                 855                 860

Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp Phe Val Ser
865                 870                 875                 880

Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr Leu Lys Lys
                885                 890                 895

Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly Val Asp Val
            900                 905                 910

Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu Trp His Arg
        915                 920                 925

Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe Leu Ser Gln
    930                 935                 940

Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr Gln Lys Leu
945                 950                 955                 960

Ile Glu Lys Asn Gly Phe Pro Glu Phe Gly Ser Gly Gly Gly Gly Ser
                965                 970                 975

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu Lys Tyr Pro Asn Ala
            980                 985                 990

Ser Pro Leu Leu Gly Ser Ser Trp  Gly Gly Leu Ile His  Leu Tyr Thr
        995                 1000                1005

Ala Thr  Ala Arg Asn Ser Tyr  His Leu Gln Ile His  Lys Asn Gly
    1010                1015                1020

His Val  Asp Gly Ala Pro His  Gln Thr Ile Tyr Ser  Ala Leu Met
    1025                1030                1035

Ile Arg  Ser Glu Asp Ala Gly  Phe Val Val Ile Thr  Gly Val Met
    1040                1045                1050

Ser Arg  Arg Tyr Leu Cys Met  Asp Phe Arg Gly Asn  Ile Phe Gly
    1055                1060                1065

Ser His  Tyr Phe Asp Pro Glu  Asn Cys Arg Phe Gln  His Gln Thr
    1070                1075                1080

Leu Glu  Asn Gly Tyr Asp Val  Tyr His Ser Pro Gln  Tyr His Phe
    1085                1090                1095
```

```
Leu Val  Ser Leu Gly Arg Ala  Lys Arg Ala Phe Leu  Pro Gly Met
    1100                1105                1110


Asn Pro  Pro Pro Tyr Ser Gln  Phe Leu Ser Arg Arg  Asn Glu Ile
    1115                1120                1125


Pro Leu  Ile His Phe Asn Thr  Pro Ile Pro Arg Arg  His Thr Gln
    1130                1135                1140


Ser Ala  Glu Asp Asp Ser Glu  Arg Asp Pro Leu Asn  Val Leu Lys
    1145                1150                1155


Pro Arg  Ala Arg Met Thr Pro  Ala Pro Ala Ser Cys  Ser Gln Glu
    1160                1165                1170


Leu Pro  Ser Ala Glu Asp Asn  Ser Pro Met Ala Ser  Asp Pro Leu
    1175                1180                1185


Gly Val  Val Arg Gly Gly Arg  Val Asn Thr His Ala  Gly Gly Thr
    1190                1195                1200


Gly Pro  Glu Gly Cys Arg Pro  Phe Ala Lys Phe Ile
    1205                1210                1215


<210>  24
<211>  1189
<212>  PRT
<213>  Homo Sapiens

<400>  24

Met Pro Ala Ser Ala Pro Pro Arg Arg Pro Arg Pro Pro Pro Pro Ser
1               5                  10                  15


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


Leu Pro Glu Asn Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala
        35                  40                  45


Trp Gly Val Val Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln
    50                  55                  60


Phe Thr Asp Leu Asn Val Tyr Leu Trp Asp Val His His Ser Lys Arg
65                  70                  75                  80


Leu Ile Lys Val Asp Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys
                85                  90                  95
```

```
Val Asp Phe Ala Ala Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met
            100                 105                 110

His Val Thr His Phe Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro
        115                 120                 125

Leu Gly Asn Gln Ser Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg
    130                 135                 140

Cys Met Ala Ser Glu Leu Val Arg Val Asn Ile Thr Pro Val Val Ala
145                 150                 155                 160

Leu Trp Gln Pro Met Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala
                165                 170                 175

Arg Gln Gly Ala Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu
            180                 185                 190

Tyr Ala Arg Leu Cys Phe Gln Glu Leu Gly His His Val Lys Leu Trp
        195                 200                 205

Ile Thr Met Asn Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly
    210                 215                 220

His Asn Leu Leu Lys Ala His Ala Leu Ala Trp His Val Tyr Asn Glu
225                 230                 235                 240

Lys Phe Arg His Ala Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala
                245                 250                 255

Asp Trp Ile Glu Pro Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val
            260                 265                 270

Ala Glu Arg Val Leu Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile
        275                 280                 285

Phe Gly Ser Gly Asp Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln
    290                 295                 300

Arg Asn Asn Phe Leu Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu
305                 310                 315                 320

Ile Gln Gly Thr Phe Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile
                325                 330                 335

Leu Val Asp Ser Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu
            340                 345                 350
```

```
Glu Val Gln Glu Met Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln
        355                 360                 365

Val Ala Val Val Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys
    370                 375                 380

Phe Lys Tyr Gly Asp Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp
385                 390                 395                 400

Asp Gly Leu His Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln
                405                 410                 415

Asn Tyr Ile Asn Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn
            420                 425                 430

Leu Cys Gly Tyr Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg
        435                 440                 445

Phe Gly Leu Tyr Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser
    450                 455                 460

Met Lys His Tyr Arg Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro
465                 470                 475                 480

Glu Thr Leu Glu Arg Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu
                485                 490                 495

Cys Ser Phe Phe His Thr Arg Lys Ser Leu Gly Thr Phe Pro Cys Asp
            500                 505                 510

Phe Ala Trp Gly Val Val Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu
        515                 520                 525

Ser Gln Phe Thr Asp Leu Asn Val Tyr Leu Trp Asp Val His His Ser
    530                 535                 540

Lys Arg Leu Ile Lys Val Asp Gly Val Val Thr Lys Lys Arg Lys Ser
545                 550                 555                 560

Tyr Cys Val Asp Phe Ala Ala Ile Gln Pro Gln Ile Ala Leu Leu Gln
                565                 570                 575

Glu Met His Val Thr His Phe Arg Phe Ser Leu Asp Trp Ala Leu Ile
            580                 585                 590

Leu Pro Leu Gly Asn Gln Ser Gln Val Asn His Thr Ile Leu Gln Tyr
```

595 600 605

Tyr Arg Cys Met Ala Ser Glu Leu Val Arg Val Asn Ile Thr Pro Val
610 615 620

Val Ala Leu Trp Gln Pro Met Ala Pro Asn Gln Gly Leu Pro Arg Leu
625 630 635 640

Leu Ala Arg Gln Gly Ala Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe
645 650 655

Ala Glu Tyr Ala Arg Leu Cys Phe Gln Glu Leu Gly His His Val Lys
660 665 670

Leu Trp Ile Thr Met Asn Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser
675 680 685

Ala Gly His Asn Leu Leu Lys Ala His Ala Leu Ala Trp His Val Tyr
690 695 700

Asn Glu Lys Phe Arg His Ala Gln Asn Gly Lys Ile Ser Ile Ala Leu
705 710 715 720

Gln Ala Asp Trp Ile Glu Pro Ala Cys Pro Phe Ser Gln Lys Asp Lys
725 730 735

Glu Val Ala Glu Arg Val Leu Glu Phe Asp Ile Gly Trp Leu Ala Glu
740 745 750

Pro Ile Phe Gly Ser Gly Asp Tyr Pro Trp Val Met Arg Asp Trp Leu
755 760 765

Asn Gln Arg Asn Asn Phe Leu Leu Pro Tyr Phe Thr Glu Asp Glu Lys
770 775 780

Lys Leu Ile Gln Gly Thr Phe Asp Phe Leu Ala Leu Ser His Tyr Thr
785 790 795 800

Thr Ile Leu Val Asp Ser Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp
805 810 815

Tyr Leu Glu Val Gln Glu Met Thr Asp Ile Thr Trp Leu Asn Ser Pro
820 825 830

Ser Gln Val Ala Val Val Pro Trp Gly Leu Arg Lys Val Leu Asn Trp
835 840 845

```
Leu Lys Phe Lys Tyr Gly Asp Leu Pro Met Tyr Ile Ile Ser Asn Gly
    850                 855                 860

Ile Asp Asp Gly Leu His Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr
865                 870                 875                 880

Met Gln Asn Tyr Ile Asn Glu Ala Leu Lys Ala His Ile Leu Asp Gly
                885                 890                 895

Ile Asn Leu Cys Gly Tyr Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala
            900                 905                 910

Pro Arg Phe Gly Leu Tyr Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys
        915                 920                 925

Ala Ser Met Lys His Tyr Arg Lys Ile Ile Asp Ser Asn Gly Phe Gly
    930                 935                 940

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
945                 950                 955                 960

Leu Lys Tyr Pro Asn Ala Ser Pro Leu Leu Gly Ser Ser Trp Gly Gly
                965                 970                 975

Leu Ile His Leu Tyr Thr Ala Thr Ala Arg Asn Ser Tyr His Leu Gln
            980                 985                 990

Ile His Lys Asn Gly His Val Asp  Gly Ala Pro His Gln  Thr Ile Tyr
        995                 1000                1005

Ser Ala  Leu Met Ile Arg Ser  Glu Asp Ala Gly Phe  Val Val Ile
    1010                1015                1020

Thr Gly  Val Met Ser Arg Arg  Tyr Leu Cys Met Asp  Phe Arg Gly
    1025                1030                1035

Asn Ile  Phe Gly Ser His Tyr  Phe Asp Pro Glu Asn  Cys Arg Phe
    1040                1045                1050

Gln His  Gln Thr Leu Glu Asn  Gly Tyr Asp Val Tyr  His Ser Pro
    1055                1060                1065

Gln Tyr  His Phe Leu Val Ser  Leu Gly Arg Ala Lys  Arg Ala Phe
    1070                1075                1080

Leu Pro  Gly Met Asn Pro Pro  Pro Tyr Ser Gln Phe  Leu Ser Arg
    1085                1090                1095
```

```
Arg Asn  Glu Ile Pro Leu Ile  His Phe Asn Thr Pro  Ile Pro Arg
    1100                1105                1110


Arg His  Thr Gln Ser Ala Glu  Asp Asp Ser Glu Arg  Asp Pro Leu
    1115                1120                1125


Asn Val  Leu Lys Pro Arg Ala  Arg Met Thr Pro Ala  Pro Ala Ser
    1130                1135                1140


Cys Ser  Gln Glu Leu Pro Ser  Ala Glu Asp Asn Ser  Pro Met Ala
    1145                1150                1155


Ser Asp  Pro Leu Gly Val Val  Arg Gly Gly Arg Val  Asn Thr His
    1160                1165                1170


Ala Gly  Gly Thr Gly Pro Glu  Gly Cys Arg Pro Phe  Ala Lys Phe
    1175                1180                1185


Ile



<210>  25
<211>  1219
<212>  PRT
<213>  Homo Sapiens

<400>  25

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


Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
            20                  25                  30


Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
        35                  40                  45


Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
    50                  55                  60


Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65                  70                  75                  80


Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
                85                  90                  95


Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
            100                 105                 110
```

```
Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
        115                 120                 125

Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
    130                 135                 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
145                 150                 155                 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
                165                 170                 175

His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
            180                 185                 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
        195                 200                 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
    210                 215                 220

Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225                 230                 235                 240

Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile Gly Ser Gly Gly Gly
                245                 250                 255

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu Lys Glu Pro
            260                 265                 270

Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro Pro Ala Pro
        275                 280                 285

Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly Phe Leu Trp
    290                 295                 300

Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln Gln His
305                 310                 315                 320

Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro Leu Ala
                325                 330                 335

Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala Pro Ser
            340                 345                 350

Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr Asn Asn
        355                 360                 365
```

```
Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr His Tyr
    370                 375                 380

Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser Ala Gly
385                 390                 395                 400

Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu Glu Arg
                405                 410                 415

Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His Trp Asp
            420                 425                 430

Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn Arg Ala
        435                 440                 445

Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg His Phe
    450                 455                 460

Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr Val Val
465                 470                 475                 480

Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile Arg Gly
                485                 490                 495

Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu Ala His
            500                 505                 510

Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr Gln Gly
        515                 520                 525

Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro Arg Arg
    530                 535                 540

Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp Phe Val
545                 550                 555                 560

Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr Pro Glu
                565                 570                 575

Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr Glu Ser
            580                 585                 590

Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu Cys Phe
        595                 600                 605

Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys Phe Arg
```

610 615 620

Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile Asp Leu
625 630 635 640

Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp Phe Val
645 650 655

Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr Leu Lys
660 665 670

Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly Val Asp
675 680 685

Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu Trp His
690 695 700

Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe Leu Ser
705 710 715 720

Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr Gln Lys
725 730 735

Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln Pro Leu
740 745 750

Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp Asn Tyr
755 760 765

Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn Val Tyr
770 775 780

Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp Gly Val
785 790 795 800

Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala Ile Gln
805 810 815

Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe Arg Phe
820 825 830

Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser Gln Val
835 840 845

Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu Leu Val
850 855 860

```
Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met Ala Pro
865                 870                 875                 880

Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp Glu Asn
                885                 890                 895

Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys Phe Gln
            900                 905                 910

Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu Pro Tyr
        915                 920                 925

Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys Ala His
    930                 935                 940

Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala Gln Asn
945                 950                 955                 960

Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro Ala Cys
                965                 970                 975

Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu Glu Phe
            980                 985                 990

Asp Ile Gly Trp Leu Ala Glu Pro  Ile Phe Gly Ser Gly  Asp Tyr Pro
        995                 1000                1005

Trp Val  Met Arg Asp Trp Leu  Asn Gln Arg Asn Asn  Phe Leu Leu
    1010                1015                1020

Pro Tyr  Phe Thr Glu Asp Glu  Lys Lys Leu Ile Gln  Gly Thr Phe
    1025                1030                1035

Asp Phe  Leu Ala Leu Ser His  Tyr Thr Thr Ile Leu  Val Asp Ser
    1040                1045                1050

Glu Lys  Glu Asp Pro Ile Lys  Tyr Asn Asp Tyr Leu  Glu Val Gln
    1055                1060                1065

Glu Met  Thr Asp Ile Thr Trp  Leu Asn Ser Pro Ser  Gln Val Ala
    1070                1075                1080

Val Val  Pro Trp Gly Leu Arg  Lys Val Leu Asn Trp  Leu Lys Phe
    1085                1090                1095

Lys Tyr  Gly Asp Leu Pro Met  Tyr Ile Ile Ser Asn  Gly Ile Asp
    1100                1105                1110
```

```
Asp Gly  Leu His Ala Glu Asp  Asp Gln Leu Arg Val  Tyr Tyr Met
    1115                 1120                 1125


Gln Asn  Tyr Ile Asn Glu Ala  Leu Lys Ala His Ile  Leu Asp Gly
    1130                 1135                 1140


Ile Asn  Leu Cys Gly Tyr Phe  Ala Tyr Ser Phe Asn  Asp Arg Thr
    1145                 1150                 1155


Ala Pro  Arg Phe Gly Leu Tyr  Arg Tyr Ala Ala Asp  Gln Phe Glu
    1160                 1165                 1170


Pro Lys  Ala Ser Met Lys His  Tyr Arg Lys Ile Ile  Asp Ser Asn
    1175                 1180                 1185


Gly Phe  Pro Gly Pro Glu Thr  Leu Glu Arg Phe Cys  Pro Glu Glu
    1190                 1195                 1200


Phe Thr  Val Cys Thr Glu Cys  Ser Phe Phe His Thr  Arg Lys Ser
    1205                 1210                 1215


Leu



<210>  26
<211>  700
<212>  PRT
<213>  Homo Sapiens

<400>  26

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


Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
            20                  25                  30


Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
        35                  40                  45


Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
    50                  55                  60


Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65                  70                  75                  80


Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
                85                  90                  95
```

```
Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
            100                 105                 110

Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
        115                 120                 125

Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
    130                 135                 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
145                 150                 155                 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
                165                 170                 175

His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
            180                 185                 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
        195                 200                 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
    210                 215                 220

Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225                 230                 235                 240

Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile Gln Gly Thr Phe Pro
                245                 250                 255

Asp Gly Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly
            260                 265                 270

Gly Trp Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr
        275                 280                 285

His His Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro
    290                 295                 300

Leu Gly Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser
305                 310                 315                 320

Asp Ser Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu
                325                 330                 335

Gly Val Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro
            340                 345                 350
```

```
Asn Gly Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg
        355                 360                 365

Arg Leu Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr
    370                 375                 380

Leu Tyr His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly
385                 390                 395                 400

Trp Ala Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu
                405                 410                 415

Cys Phe Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp
            420                 425                 430

Asn Pro Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala
        435                 440                 445

Pro Gly Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn
    450                 455                 460

Leu Leu Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe
465                 470                 475                 480

Arg Pro Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp
                485                 490                 495

Ile Asn Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys
            500                 505                 510

Ser Leu Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp
        515                 520                 525

Gly Asp Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro
    530                 535                 540

Asp Phe Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe
545                 550                 555                 560

Phe Ala Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro
                565                 570                 575

His Met Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu
            580                 585                 590

Ser Trp Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu
```

595 600 605

Asn Gly Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr
610 615 620

Met Tyr Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys
625 630 635 640

Leu Asp Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp
645 650 655

Gly Phe Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr
660 665 670

Val Asp Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala
675 680 685

Leu Phe Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe
690 695 700

<210> 27
<211> 688
<212> PRT
<213> Homo Sapiens

<400> 27

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

Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
20 25 30

Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
35 40 45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
50 55 60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65 70 75 80

Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
85 90 95

Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
100 105 110

Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His

```
        115                 120                 125

Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
    130                 135                 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
145                 150                 155                 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
                165                 170                 175

His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
            180                 185                 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
        195                 200                 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
    210                 215                 220

Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225                 230                 235                 240

Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile Gly Thr Phe Pro Cys
                245                 250                 255

Asp Phe Ala Trp Gly Val Val Asp Asn Tyr Ile Gln Val Asp Thr Thr
            260                 265                 270

Leu Ser Gln Phe Thr Asp Leu Asn Val Tyr Leu Trp Asp Val His His
        275                 280                 285

Ser Lys Arg Leu Ile Lys Val Asp Gly Val Val Thr Lys Lys Arg Lys
    290                 295                 300

Ser Tyr Cys Val Asp Phe Ala Ala Ile Gln Pro Gln Ile Ala Leu Leu
305                 310                 315                 320

Gln Glu Met His Val Thr His Phe Arg Phe Ser Leu Asp Trp Ala Leu
                325                 330                 335

Ile Leu Pro Leu Gly Asn Gln Ser Gln Val Asn His Thr Ile Leu Gln
            340                 345                 350

Tyr Tyr Arg Cys Met Ala Ser Glu Leu Val Arg Val Asn Ile Thr Pro
        355                 360                 365
```

```
Val Val Ala Leu Trp Gln Pro Met Ala Pro Asn Gln Gly Leu Pro Arg
    370                 375                 380

Leu Leu Ala Arg Gln Gly Ala Trp Glu Asn Pro Tyr Thr Ala Leu Ala
385                 390                 395                 400

Phe Ala Glu Tyr Ala Arg Leu Cys Phe Gln Glu Leu Gly His His Val
                405                 410                 415

Lys Leu Trp Ile Thr Met Asn Glu Pro Tyr Thr Arg Asn Met Thr Tyr
            420                 425                 430

Ser Ala Gly His Asn Leu Leu Lys Ala His Ala Leu Ala Trp His Val
        435                 440                 445

Tyr Asn Glu Lys Phe Arg His Ala Gln Asn Gly Lys Ile Ser Ile Ala
    450                 455                 460

Leu Gln Ala Asp Trp Ile Glu Pro Ala Cys Pro Phe Ser Gln Lys Asp
465                 470                 475                 480

Lys Glu Val Ala Glu Arg Val Leu Glu Phe Asp Ile Gly Trp Leu Ala
                485                 490                 495

Glu Pro Ile Phe Gly Ser Gly Asp Tyr Pro Trp Val Met Arg Asp Trp
            500                 505                 510

Leu Asn Gln Arg Asn Asn Phe Leu Leu Pro Tyr Phe Thr Glu Asp Glu
        515                 520                 525

Lys Lys Leu Ile Gln Gly Thr Phe Asp Phe Leu Ala Leu Ser His Tyr
    530                 535                 540

Thr Thr Ile Leu Val Asp Ser Glu Lys Glu Asp Pro Ile Lys Tyr Asn
545                 550                 555                 560

Asp Tyr Leu Glu Val Gln Glu Met Thr Asp Ile Thr Trp Leu Asn Ser
                565                 570                 575

Pro Ser Gln Val Ala Val Val Pro Trp Gly Leu Arg Lys Val Leu Asn
            580                 585                 590

Trp Leu Lys Phe Lys Tyr Gly Asp Leu Pro Met Tyr Ile Ile Ser Asn
        595                 600                 605

Gly Ile Asp Asp Gly Leu His Ala Glu Asp Asp Gln Leu Arg Val Tyr
    610                 615                 620
```

```
Tyr Met Gln Asn Tyr Ile Asn Glu Ala Leu Lys Ala His Ile Leu Asp
625                 630                 635                 640


Gly Ile Asn Leu Cys Gly Tyr Phe Ala Tyr Ser Phe Asn Asp Arg Thr
                645                 650                 655


Ala Pro Arg Phe Gly Leu Tyr Arg Tyr Ala Ala Asp Gln Phe Glu Pro
            660                 665                 670


Lys Ala Ser Met Lys His Tyr Arg Lys Ile Ile Asp Ser Asn Gly Phe
        675                 680                 685


<210>  28
<211>  1149
<212>  PRT
<213>  Homo Sapiens

<400>  28

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


Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
            20                  25                  30


Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
        35                  40                  45


Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
    50                  55                  60


Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65                  70                  75                  80


Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
                85                  90                  95


Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
            100                 105                 110


Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
        115                 120                 125


Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
    130                 135                 140


Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
145                 150                 155                 160
```

```
Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
                165                 170                 175

His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
            180                 185                 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
        195                 200                 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
    210                 215                 220

Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225                 230                 235                 240

Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile Gln Gly Thr Phe Pro
                245                 250                 255

Asp Gly Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly
            260                 265                 270

Gly Trp Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr
        275                 280                 285

His His Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro
    290                 295                 300

Leu Gly Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser
305                 310                 315                 320

Asp Ser Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu
                325                 330                 335

Gly Val Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro
            340                 345                 350

Asn Gly Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg
        355                 360                 365

Arg Leu Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr
    370                 375                 380

Leu Tyr His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly
385                 390                 395                 400

Trp Ala Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu
                405                 410                 415
```

```
Cys Phe Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp
            420                 425                 430

Asn Pro Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala
        435                 440                 445

Pro Gly Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn
    450                 455                 460

Leu Leu Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe
465                 470                 475                 480

Arg Pro Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp
                485                 490                 495

Ile Asn Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys
            500                 505                 510

Ser Leu Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp
        515                 520                 525

Gly Asp Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro
    530                 535                 540

Asp Phe Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe
545                 550                 555                 560

Phe Ala Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro
                565                 570                 575

His Met Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu
            580                 585                 590

Ser Trp Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu
        595                 600                 605

Asn Gly Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr
    610                 615                 620

Met Tyr Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys
625                 630                 635                 640

Leu Asp Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp
                645                 650                 655

Gly Phe Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr
```

```
            660                 665                 670

Val Asp Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala
        675                 680                 685

Leu Phe Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Gln Gly Thr Phe
    690                 695                 700

Pro Asp Gly Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu
705                 710                 715                 720

Gly Gly Trp Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe
                725                 730                 735

Thr His His Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu
            740                 745                 750

Pro Leu Gly Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala
        755                 760                 765

Ser Asp Ser Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu
    770                 775                 780

Leu Gly Val Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu
785                 790                 795                 800

Pro Asn Gly Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr
                805                 810                 815

Arg Arg Leu Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val
            820                 825                 830

Thr Leu Tyr His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly
        835                 840                 845

Gly Trp Ala Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu
    850                 855                 860

Leu Cys Phe Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile
865                 870                 875                 880

Asp Asn Pro Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu
                885                 890                 895

Ala Pro Gly Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His
            900                 905                 910
```

```
Asn Leu Leu Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser
        915                 920                 925

Phe Arg Pro Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His
    930                 935                 940

Trp Ile Asn Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln
945                 950                 955                 960

Lys Ser Leu Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile
                965                 970                 975

Asp Gly Asp Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu
            980                 985                 990

Pro Asp Phe Thr Glu Ser Glu Lys  Lys Phe Ile Lys Gly  Thr Ala Asp
        995                 1000                1005

Phe Phe  Ala Leu Cys Phe Gly  Pro Thr Leu Ser Phe  Gln Leu Leu
    1010                1015                1020

Asp Pro  His Met Lys Phe Arg  Gln Leu Glu Ser Pro  Asn Leu Arg
    1025                1030                1035

Gln Leu  Leu Ser Trp Ile Asp  Leu Glu Phe Asn His  Pro Gln Ile
    1040                1045                1050

Phe Ile  Val Glu Asn Gly Trp  Phe Val Ser Gly Thr  Thr Lys Arg
    1055                1060                1065

Asp Asp  Ala Lys Tyr Met Tyr  Tyr Leu Lys Lys Phe  Ile Met Glu
    1070                1075                1080

Thr Leu  Lys Ala Ile Lys Leu  Asp Gly Val Asp Val  Ile Gly Tyr
    1085                1090                1095

Thr Ala  Trp Ser Leu Met Asp  Gly Phe Glu Trp His  Arg Gly Tyr
    1100                1105                1110

Ser Ile  Arg Arg Gly Leu Phe  Tyr Val Asp Phe Leu  Ser Gln Asp
    1115                1120                1125

Lys Met  Leu Leu Pro Lys Ser  Ser Ala Leu Phe Tyr  Gln Lys Leu
    1130                1135                1140

Ile Glu  Lys Asn Gly Phe
    1145
```

<210> 29
<211> 1125
<212> PRT
<213> Homo Sapiens

<400> 29

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

Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
            20                  25                  30

Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
        35                  40                  45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
    50                  55                  60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65                  70                  75                  80

Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
                85                  90                  95

Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
            100                 105                 110

Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
        115                 120                 125

Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
    130                 135                 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
145                 150                 155                 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
                165                 170                 175

His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
            180                 185                 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
        195                 200                 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
    210                 215                 220
```

```
Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225                 230                 235                 240

Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile Gly Thr Phe Pro Cys
                245                 250                 255

Asp Phe Ala Trp Gly Val Val Asp Asn Tyr Ile Gln Val Asp Thr Thr
            260                 265                 270

Leu Ser Gln Phe Thr Asp Leu Asn Val Tyr Leu Trp Asp Val His His
        275                 280                 285

Ser Lys Arg Leu Ile Lys Val Asp Gly Val Val Thr Lys Lys Arg Lys
    290                 295                 300

Ser Tyr Cys Val Asp Phe Ala Ala Ile Gln Pro Gln Ile Ala Leu Leu
305                 310                 315                 320

Gln Glu Met His Val Thr His Phe Arg Phe Ser Leu Asp Trp Ala Leu
                325                 330                 335

Ile Leu Pro Leu Gly Asn Gln Ser Gln Val Asn His Thr Ile Leu Gln
            340                 345                 350

Tyr Tyr Arg Cys Met Ala Ser Glu Leu Val Arg Val Asn Ile Thr Pro
        355                 360                 365

Val Val Ala Leu Trp Gln Pro Met Ala Pro Asn Gln Gly Leu Pro Arg
    370                 375                 380

Leu Leu Ala Arg Gln Gly Ala Trp Glu Asn Pro Tyr Thr Ala Leu Ala
385                 390                 395                 400

Phe Ala Glu Tyr Ala Arg Leu Cys Phe Gln Glu Leu Gly His His Val
                405                 410                 415

Lys Leu Trp Ile Thr Met Asn Glu Pro Tyr Thr Arg Asn Met Thr Tyr
            420                 425                 430

Ser Ala Gly His Asn Leu Leu Lys Ala His Ala Leu Ala Trp His Val
        435                 440                 445

Tyr Asn Glu Lys Phe Arg His Ala Gln Asn Gly Lys Ile Ser Ile Ala
    450                 455                 460

Leu Gln Ala Asp Trp Ile Glu Pro Ala Cys Pro Phe Ser Gln Lys Asp
465                 470                 475                 480
```

Lys Glu Val Ala Glu Arg Val Leu Glu Phe Asp Ile Gly Trp Leu Ala
485 490 495

Glu Pro Ile Phe Gly Ser Gly Asp Tyr Pro Trp Val Met Arg Asp Trp
500 505 510

Leu Asn Gln Arg Asn Asn Phe Leu Leu Pro Tyr Phe Thr Glu Asp Glu
515 520 525

Lys Lys Leu Ile Gln Gly Thr Phe Asp Phe Leu Ala Leu Ser His Tyr
530 535 540

Thr Thr Ile Leu Val Asp Ser Glu Lys Glu Asp Pro Ile Lys Tyr Asn
545 550 555 560

Asp Tyr Leu Glu Val Gln Glu Met Thr Asp Ile Thr Trp Leu Asn Ser
565 570 575

Pro Ser Gln Val Ala Val Val Pro Trp Gly Leu Arg Lys Val Leu Asn
580 585 590

Trp Leu Lys Phe Lys Tyr Gly Asp Leu Pro Met Tyr Ile Ile Ser Asn
595 600 605

Gly Ile Asp Asp Gly Leu His Ala Glu Asp Asp Gln Leu Arg Val Tyr
610 615 620

Tyr Met Gln Asn Tyr Ile Asn Glu Ala Leu Lys Ala His Ile Leu Asp
625 630 635 640

Gly Ile Asn Leu Cys Gly Tyr Phe Ala Tyr Ser Phe Asn Asp Arg Thr
645 650 655

Ala Pro Arg Phe Gly Leu Tyr Arg Tyr Ala Ala Asp Gln Phe Glu Pro
660 665 670

Lys Ala Ser Met Lys His Tyr Arg Lys Ile Ile Asp Ser Asn Gly Phe
675 680 685

Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp Asn Tyr Ile
690 695 700

Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn Val Tyr Leu
705 710 715 720

Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp Gly Val Val

725 730 735

Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala Ile Gln Pro
740 745 750

Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe Arg Phe Ser
755 760 765

Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser Gln Val Asn
770 775 780

His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu Leu Val Arg
785 790 795 800

Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met Ala Pro Asn
805 810 815

Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp Glu Asn Pro
820 825 830

Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys Phe Gln Glu
835 840 845

Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu Pro Tyr Thr
850 855 860

Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys Ala His Ala
865 870 875 880

Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala Gln Asn Gly
885 890 895

Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro Ala Cys Pro
900 905 910

Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu Glu Phe Asp
915 920 925

Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp Tyr Pro Trp
930 935 940

Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu Leu Pro Tyr
945 950 955 960

Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe Asp Phe Leu
965 970 975

```
Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu Lys Glu Asp
            980                 985                 990

Pro Ile Lys Tyr Asn Asp Tyr Leu  Glu Val Gln Glu Met  Thr Asp Ile
        995                 1000                1005

Thr Trp  Leu Asn Ser Pro Ser  Gln Val Ala Val Val  Pro Trp Gly
    1010                1015                1020

Leu Arg  Lys Val Leu Asn Trp  Leu Lys Phe Lys Tyr  Gly Asp Leu
    1025                1030                1035

Pro Met  Tyr Ile Ile Ser Asn  Gly Ile Asp Asp Gly  Leu His Ala
    1040                1045                1050

Glu Asp  Asp Gln Leu Arg Val  Tyr Tyr Met Gln Asn  Tyr Ile Asn
    1055                1060                1065

Glu Ala  Leu Lys Ala His Ile  Leu Asp Gly Ile Asn  Leu Cys Gly
    1070                1075                1080

Tyr Phe  Ala Tyr Ser Phe Asn  Asp Arg Thr Ala Pro  Arg Phe Gly
    1085                1090                1095

Leu Tyr  Arg Tyr Ala Ala Asp  Gln Phe Glu Pro Lys  Ala Ser Met
    1100                1105                1110

Lys His  Tyr Arg Lys Ile Ile  Asp Ser Asn Gly Phe
    1115                1120                1125
```

<210> 30
<211> 2157
<212> DNA
<213> Homo Sapiens

<400> 30

```
gctcccagcc aagaacctcg gggccgctgc gcggtgggga ggagttcccc gaaacccggc     60

cgctaagcga ggcctcctcc tcccgcagat ccgaacggcc tgggcggggt caccccggct    120

gggacaagaa gccgccgcct gcctgcccgg gcccggggag ggggctgggg ctggggccgg    180

aggcggggtg tgagtgggtg tgtgcggggg gcggaggctt gatgcaatcc cgataagaaa    240

tgctcgggtg tcttgggcac ctacccgtgg ggcccgtaag gcgctactat ataaggctgc    300

cggcccggag ccgccgcgcc gtcagagcag gagcgctgcg tccaggatct agggccacga    360

ccatcccaac ccggcactca cagccccgca gcgcatcccg gtcgccgccc agcctcccgc    420

acccccatcg ccggagctgc gccgagagcc ccagggaggt gccatgcgga gcgggtgtgt    480

ggtggtccac gtatggatcc tggccggcct ctggctggcc gtggccgggc gccccctcgc    540
```

cttctcggac gcggggcccc acgtgcacta cggctggggc gaccccatcc gcctgcggca 600

cctgtacacc tccggccccc acgggctctc cagctgcttc ctgcgcatcc gtgccgacgg 660

cgtcgtggac tgcgcgcggg gccagagcgc gcacagtttg ctggagatca aggcagtcgc 720

tctgcggacc gtggccatca agggcgtgca cagcgtgcgg tacctctgca tgggcgccga 780

cggcaagatg caggggctgc ttcagtactc ggaggaagac tgtgctttcg aggaggagat 840

ccgcccagat ggctacaatg tgtaccgatc cgagaagcac cgcctcccgg tctccctgag 900

cagtgccaaa cagcggcagc tgtacaagaa cagaggcttt cttccactct ctcatttcct 960

gcccatgctg cccatggtcc cagaggagcc tgaggacctc aggggccact tggaatctga 1020

catgttctct tcgcccctgg agaccgacag catggaccca tttgggcttg tcaccggact 1080

ggaggccgtg aggagtccca gctttgagaa gtaactgaga ccatgcccgg gcctcttcac 1140

tgctgccagg ggctgtggta cctgcagcgt gggggacgtg cttctacaag aacagtcctg 1200

agtccacgtt ctgtttagct ttaggaagaa acatctagaa gttgtacata ttcagagttt 1260

tccattggca gtgccagttt ctagccaata gacttgtctg atcataacat tgtaagcctg 1320

tagcttgccc agctgctgcc tgggccccca ttctgctccc tcgaggttgc tggacaagct 1380

gctgcactgt ctcagttctg cttgaatacc tccatcgatg gggaactcac ttcctttgga 1440

aaaattctta tgtcaagctg aaattctcta atttttttctc atcacttccc caggagcagc 1500

cagaagacag gcagtagttt taatttcagg aacaggtgat ccactctgta aaacagcagg 1560

taaatttcac tcaaccccat gtgggaattg atctatatct ctacttccag ggaccatttg 1620

cccttcccaa atccctccag gccagaactg actggagcag gcatggccca ccaggcttca 1680

ggagtagggg aagcctggag ccccactcca gccctgggac aacttgagaa ttccccctga 1740

ggccagttct gtcatggatg ctgtcctgag aataacttgc tgtcccggtg tcacctgctt 1800

ccatctccca gcccaccagc cctctgccca cctcacatgc ctccccatgg attggggcct 1860

cccaggcccc ccaccttatg tcaacctgca cttcttgttc aaaaatcagg aaaagaaaag 1920

atttgaagac cccaagtctt gtcaataact tgctgtgtgg aagcagcggg ggaagaccta 1980

gaaccctttc cccagcactt ggttttccaa catgatattt atgagtaatt tattttgata 2040

tgtacatctc ttatttttctt acattattta tgcccccaaa ttatatttat gtatgtaagt 2100

gaggtttgtt ttgtatatta aaatggagtt tgtttgtaaa aaaaaaaaaa aaaaaaa 2157

<210> 31
<211> 216
<212> PRT
<213> Homo Sapiens

<400> 31

```
Met Arg Ser Gly Cys Val Val Val His Val Trp Ile Leu Ala Gly Leu
1               5                   10                  15

Trp Leu Ala Val Ala Gly Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro
            20                  25                  30

His Val His Tyr Gly Trp Gly Asp Pro Ile Arg Leu Arg His Leu Tyr
        35                  40                  45

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

Asp Gly Val Val Asp Cys Ala Arg Gly Gln Ser Ala His Ser Leu Leu
65                  70                  75                  80

Glu Ile Lys Ala Val Ala Leu Arg Thr Val Ala Ile Lys Gly Val His
                85                  90                  95

Ser Val Arg Tyr Leu Cys Met Gly Ala Asp Gly Lys Met Gln Gly Leu
            100                 105                 110

Leu Gln Tyr Ser Glu Glu Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro
        115                 120                 125

Asp Gly Tyr Asn Val Tyr Arg Ser Glu Lys His Arg Leu Pro Val Ser
    130                 135                 140

Leu Ser Ser Ala Lys Gln Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu
145                 150                 155                 160

Pro Leu Ser His Phe Leu Pro Met Leu Pro Met Val Pro Glu Glu Pro
                165                 170                 175

Glu Asp Leu Arg Gly His Leu Glu Ser Asp Met Phe Ser Ser Pro Leu
            180                 185                 190

Glu Thr Asp Ser Met Asp Pro Phe Gly Leu Val Thr Gly Leu Glu Ala
        195                 200                 205

Val Arg Ser Pro Ser Phe Glu Lys
    210                 215
```

<210> 32
<211> 940
<212> PRT
<213> Homo Sapiens

<400> 32

```
Cys Thr Gly Thr Cys Ala Gly Cys Thr Gly Ala Gly Gly Ala Thr Cys
1               5                   10                  15

Cys Ala Gly Cys Cys Gly Ala Ala Ala Gly Ala Gly Gly Ala Gly Cys
            20                  25                  30

Cys Ala Gly Gly Cys Ala Cys Thr Cys Ala Gly Gly Cys Cys Ala Cys
        35                  40                  45

Cys Thr Gly Ala Gly Thr Cys Thr Ala Cys Thr Cys Ala Cys Cys Thr
    50                  55                  60

Gly Gly Ala Cys Ala Ala Cys Thr Gly Gly Ala Ala Thr Cys Thr Gly
65                  70                  75                  80

Gly Cys Ala Cys Cys Ala Ala Thr Thr Cys Thr Ala Ala Ala Cys Cys
                85                  90                  95

Ala Cys Thr Cys Ala Gly Cys Thr Thr Cys Thr Cys Cys Gly Ala Gly
            100                 105                 110

Cys Thr Cys Ala Cys Ala Cys Cys Cys Cys Gly Gly Ala Gly Ala Thr
        115                 120                 125

Cys Ala Cys Cys Thr Gly Ala Gly Gly Ala Cys Cys Cys Gly Ala Gly
    130                 135                 140

Cys Cys Ala Thr Thr Gly Ala Thr Gly Gly Ala Cys Thr Cys Gly Gly
145                 150                 155                 160

Ala Cys Gly Ala Gly Ala Cys Cys Gly Gly Gly Thr Thr Cys Gly Ala
                165                 170                 175

Gly Cys Ala Cys Thr Cys Ala Gly Gly Ala Cys Thr Gly Thr Gly Gly
            180                 185                 190

Gly Thr Thr Thr Cys Thr Gly Thr Gly Cys Thr Gly Gly Cys Thr Gly
        195                 200                 205

Gly Thr Cys Thr Thr Cys Thr Gly Cys Thr Gly Gly Gly Ala Gly Cys
    210                 215                 220

Cys Thr Gly Cys Cys Ala Gly Gly Cys Ala Cys Ala Cys Cys Cys Cys
225                 230                 235                 240

Ala Thr Cys Cys Cys Thr Gly Ala Cys Thr Cys Cys Ala Gly Thr Cys
                245                 250                 255
```

```
Cys Thr Cys Thr Cys Cys Thr Gly Cys Ala Ala Thr Thr Cys Gly Gly
            260                 265                 270

Gly Gly Gly Cys Cys Ala Ala Gly Thr Cys Cys Gly Gly Cys Ala Gly
        275                 280                 285

Cys Gly Gly Thr Ala Cys Cys Thr Cys Thr Ala Cys Ala Cys Ala Gly
    290                 295                 300

Ala Thr Gly Ala Thr Gly Cys Cys Cys Ala Gly Cys Ala Gly Ala Cys
305                 310                 315                 320

Ala Gly Ala Ala Gly Cys Cys Cys Ala Cys Cys Thr Gly Gly Ala Gly
                325                 330                 335

Ala Thr Cys Ala Gly Gly Gly Ala Gly Gly Ala Thr Gly Gly Gly Ala
            340                 345                 350

Cys Gly Gly Thr Gly Gly Gly Gly Gly Gly Cys Gly Cys Thr Gly Cys
        355                 360                 365

Thr Gly Ala Cys Cys Ala Gly Ala Gly Cys Cys Cys Cys Gly Ala Ala
    370                 375                 380

Ala Gly Thr Cys Thr Cys Cys Thr Gly Cys Ala Gly Cys Thr Gly Ala
385                 390                 395                 400

Ala Ala Gly Cys Cys Thr Thr Gly Ala Ala Gly Cys Cys Gly Gly Gly
                405                 410                 415

Ala Gly Thr Thr Ala Thr Thr Cys Ala Ala Ala Thr Cys Thr Thr Gly
            420                 425                 430

Gly Gly Ala Gly Thr Cys Ala Ala Gly Ala Cys Ala Thr Cys Cys Ala
        435                 440                 445

Gly Gly Thr Thr Cys Cys Thr Gly Thr Gly Cys Cys Ala Gly Cys Gly
    450                 455                 460

Gly Cys Cys Ala Gly Ala Thr Gly Gly Gly Gly Cys Cys Cys Thr Gly
465                 470                 475                 480

Thr Ala Thr Gly Gly Ala Thr Cys Gly Cys Thr Cys Cys Ala Cys Thr
                485                 490                 495

Thr Thr Gly Ala Cys Cys Cys Thr Gly Ala Gly Gly Cys Cys Thr Gly
            500                 505                 510
```

```
Cys Ala Gly Cys Thr Thr Cys Cys Gly Gly Gly Ala Gly Cys Thr Gly
        515                 520                 525

Cys Thr Thr Cys Thr Thr Gly Ala Gly Gly Ala Cys Gly Gly Ala Thr
    530                 535                 540

Ala Cys Ala Ala Thr Gly Thr Thr Thr Ala Cys Cys Ala Gly Thr Cys
545                 550                 555                 560

Cys Gly Ala Ala Gly Cys Cys Cys Ala Cys Gly Gly Cys Cys Thr Cys
                565                 570                 575

Cys Cys Gly Cys Thr Gly Cys Ala Cys Cys Thr Gly Cys Cys Ala Gly
            580                 585                 590

Gly Gly Ala Ala Cys Ala Ala Gly Thr Cys Cys Cys Cys Ala Cys Ala
        595                 600                 605

Cys Cys Gly Gly Gly Ala Cys Cys Cys Thr Gly Cys Ala Cys Cys Cys
    610                 615                 620

Cys Gly Ala Gly Gly Ala Cys Cys Ala Gly Cys Thr Cys Gly Cys Thr
625                 630                 635                 640

Thr Cys Cys Thr Gly Cys Cys Ala Cys Thr Ala Cys Cys Ala Gly Gly
                645                 650                 655

Cys Cys Thr Gly Cys Cys Cys Cys Cys Cys Gly Cys Ala Cys Thr Cys
            660                 665                 670

Cys Cys Gly Gly Ala Gly Cys Cys Ala Cys Cys Cys Gly Gly Ala Ala
        675                 680                 685

Thr Cys Cys Thr Gly Gly Cys Cys Cys Cys Cys Cys Ala Gly Cys Cys
    690                 695                 700

Cys Cys Cys Cys Gly Ala Thr Gly Thr Gly Gly Gly Cys Thr Cys Cys
705                 710                 715                 720

Thr Cys Gly Gly Ala Cys Cys Cys Thr Cys Thr Gly Ala Gly Cys Ala
                725                 730                 735

Thr Gly Gly Thr Gly Gly Gly Ala Cys Cys Thr Thr Cys Cys Cys Ala
            740                 745                 750

Gly Gly Gly Cys Cys Gly Ala Ala Gly Cys Cys Cys Cys Ala Gly Cys
```

```
        755                 760                 765

Thr Ala Cys Gly Cys Thr Thr Cys Cys Thr Gly Ala Ala Gly Cys Cys
    770                 775                 780

Ala Gly Ala Gly Gly Cys Thr Gly Thr Thr Thr Ala Cys Thr Ala Thr
785                 790                 795                 800

Gly Ala Cys Ala Thr Cys Thr Cys Cys Thr Cys Thr Thr Thr Ala Thr
                805                 810                 815

Thr Thr Ala Thr Thr Ala Gly Gly Thr Thr Ala Thr Thr Thr Ala Thr
            820                 825                 830

Cys Thr Thr Ala Thr Thr Thr Ala Thr Thr Thr Thr Thr Thr Thr Ala
        835                 840                 845

Thr Thr Thr Thr Thr Cys Thr Thr Ala Cys Thr Thr Gly Ala Gly Ala
    850                 855                 860

Thr Ala Ala Thr Ala Ala Ala Gly Ala Gly Thr Thr Cys Cys Ala Gly
865                 870                 875                 880

Ala Gly Gly Ala Gly Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala
                885                 890                 895

Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala
            900                 905                 910

Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala
        915                 920                 925

Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala
    930                 935                 940


<210>  33
<211>  209
<212>  PRT
<213>  Homo Sapiens

<400>  33

Met Asp Ser Asp Glu Thr Gly Phe Glu His Ser Gly Leu Trp Val Ser
1               5                   10                  15

Val Leu Ala Gly Leu Leu Leu Gly Ala Cys Gln Ala His Pro Ile Pro
            20                  25                  30

Asp Ser Ser Pro Leu Leu Gln Phe Gly Gly Gln Val Arg Gln Arg Tyr
```

35 40 45

Leu Tyr Thr Asp Asp Ala Gln Gln Thr Glu Ala His Leu Glu Ile Arg
50 55 60

Glu Asp Gly Thr Val Gly Gly Ala Ala Asp Gln Ser Pro Glu Ser Leu
65 70 75 80

Leu Gln Leu Lys Ala Leu Lys Pro Gly Val Ile Gln Ile Leu Gly Val
85 90 95

Lys Thr Ser Arg Phe Leu Cys Gln Arg Pro Asp Gly Ala Leu Tyr Gly
100 105 110

Ser Leu His Phe Asp Pro Glu Ala Cys Ser Phe Arg Glu Leu Leu Leu
115 120 125

Glu Asp Gly Tyr Asn Val Tyr Gln Ser Glu Ala His Gly Leu Pro Leu
130 135 140

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

Pro Ala Arg Phe Leu Pro Leu Pro Gly Leu Pro Pro Ala Leu Pro Glu
165 170 175

Pro Pro Gly Ile Leu Ala Pro Gln Pro Pro Asp Val Gly Ser Ser Asp
180 185 190

Pro Leu Ser Met Val Gly Pro Ser Gln Gly Arg Ser Pro Ser Tyr Ala
195 200 205

Ser

<210> 34
<211> 3018
<212> DNA
<213> Homo Sapiens

<400> 34
cggcaaaaag gagggaatcc agtctaggat cctcacacca gctacttgca agggagaagg 60

aaaaggccag taaggcctgg gccaggagag tcccgacagg agtgtcaggt ttcaatctca 120

gcaccagcca ctcagagcag ggcacgatgt tgggggcccg cctcaggctc tgggtctgtg 180

ccttgtgcag cgtctgcagc atgagcgtcc tcagagccta tcccaatgcc tccccactgc 240

tcggctccag ctggggtggc ctgatccacc tgtacacagc cacagccagg aacagctacc 300

acctgcagat ccacaagaat ggccatgtgg atggcgcacc ccatcagacc atctacagtg 360

ccctgatgat cagatcagag gatgctggct ttgtggtgat tacaggtgtg atgagcagaa 420

gatacctctg catggatttc agaggcaaca tttttggatc acactatttc gacccggaga 480

actgcaggtt ccaacaccag acgctggaaa acgggtacga cgtctaccac tctcctcagt 540

atcacttcct ggtcagtctg ggccgggcga agagagcctt cctgccaggc atgaacccac 600

ccccgtactc ccagttcctg tcccggagga acgagatccc cctaattcac ttcaacaccc 660

ccataccacg gcggcacacc cggagcgccg aggacgactc ggagcgggac cccctgaacg 720

tgctgaagcc ccgggcccgg atgaccccgg ccccggcctc ctgttcacag gagctcccga 780

gcgccgagga caacagcccg atggccagtg acccattagg ggtggtcagg ggcggtcgag 840

tgaacacgca cgctgggggа acgggcccgg aaggctgccg ccccttcgcc aagttcatct 900

agggtcgctg gaagggcacc ctctttaacc catccctcag caaacgcagc tcttcccaag 960

gaccaggtcc cttgacgttc cgaggatggg aaaggtgaca ggggcatgta tggaatttgc 1020

tgcttctctg gggtcccttc cacaggaggt cctgtgagaa ccaacctttg aggcccaagt 1080

catggggttt caccgccttc ctcactccat atagaacacc tttcccaata ggaaacccca 1140

acaggtaaac tagaaatttc cccttcatga aggtagagag aaggggtctc tcccaacata 1200

tttctcttcc ttgtgcctct cctctttatc acttttaagc ataaaaaaaa aaaaaaaaaa 1260

aaaaaaaaaa aaaagcagtg ggttcctgag ctcaagactt tgaaggtgta gggaagagga 1320

aatcggagat cccagaagct tctccactgc cctatgcatt tatgttagat gccccgatcc 1380

cactggcatt tgagtgtgca aaccttgaca ttaacagctg aatggggcaa gttgatgaaa 1440

acactacttt caagccttcg ttcttccttg agcatctctg gggaagagct gtcaaaagac 1500

tggtggtagg ctggtgaaaa cttgacagct agacttgatg cttgctgaaa tgaggcagga 1560

atcataatag aaaactcagc ctccctacag ggtgagcacc ttctgtctcg ctgtctccct 1620

ctgtgcagcc acagccagag ggcccagaat ggccccactc tgttcccaag cagttcatga 1680

tacagcctca ccttttggcc ccatctctgg tttttgaaaa tttggtctaa ggaataaata 1740

gcttttacac tggctcacga aaatctgccc tgctagaatt tgcttttcaa aatggaaata 1800

aattccaact ctcctaagag gcatttaatt aaggctctac ttccaggttg agtaggaatc 1860

cattctgaac aaactacaaa aatgtgactg ggaagggggc tttgagagac tgggactgct 1920

ctgggttagg ttttctgtgg actgaaaaat cgtgtccttt tctctaaatg aagtggcatc 1980

aaggactcag ggggaaagaa atcaggggac atgttataga agttatgaaa agacaaccac 2040

atggtcaggc tcttgtctgt ggtctctagg gctctgcagc agcagtggct cttcgattag 2100

ttaaaactct cctaggctga cacatctggg tctcaatccc cttggaaatt cttggtgcat 2160

taaatgaagc cttaccccat tactgcggtt cttcctgtaa gggggctcca ttttcctccc 2220

tctctttaaa tgaccaccta aaggacagta tattaacaag caaagtcgat tcaacaacag 2280

cttcttccca gtcacttttt tttttctcac tgccatcaca tactaacctt atactttgat 2340

ctattctttt tggttatgag agaaatgttg ggcaactgtt tttacctgat ggttttaagc 2400

tgaacttgaa ggactggttc ctattctgaa acagtaaaac tatgtataat agtatatagc 2460

catgcatggc aaatatttta atatttctgt tttcatttcc tgttggaaat attatcctgc 2520

ataatagcta ttggaggctc ctcagtgaaa gatcccaaaa ggattttggt ggaaaactag 2580

ttgtaatctc acaaactcaa cactaccatc aggggttttc tttatggcaa agccaaaata 2640

gctcctacaa tttcttatat ccctcgtcat gtggcagtat ttatttattt atttggaagt 2700

ttgcctatcc ttctatattt atagatattt ataaaaatgt aacccctttt tcctttcttc 2760

tgtttaaaat aaaaataaaa tttatctcag cttctgttag cttatcctct ttgtagtact 2820

acttaaaagc atgtcggaat ataagaataa aaaggattat gggaggggaa cattagggaa 2880

atccagagaa ggcaaaattg aaaaaaagat tttagaattt taaaattttc aaagatttct 2940

tccattcata aggagactca atgattttaa ttgatctaga cagaattatt taagttttat 3000

caatattgga tttctggt 3018

<210> 35
<211> 251
<212> PRT
<213> Homo Sapiens

<400> 35

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

Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
20 25 30

Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
35 40 45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
50 55 60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65 70 75 80

Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
85 90 95

Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
100 105 110

```
Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
        115                 120                 125

Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
    130                 135                 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
145                 150                 155                 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
                165                 170                 175

His Thr Arg Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
            180                 185                 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
        195                 200                 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
    210                 215                 220

Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225                 230                 235                 240

Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile
                245                 250
```

<210> 36
<211> 251
<212> PRT
<213> Homo Sapiens

<400> 36

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

Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
            20                  25                  30

Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
        35                  40                  45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
    50                  55                  60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65                  70                  75                  80
```

```
Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
                85                  90                  95

Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
            100                 105                 110

Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
        115                 120                 125

Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
    130                 135                 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
145                 150                 155                 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
                165                 170                 175

His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
            180                 185                 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
        195                 200                 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
    210                 215                 220

Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225                 230                 235                 240

Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile
                245                 250


<210>  37
<211>  431
<212>  PRT
<213>  Homo Sapiens

<400>  37

Tyr Asp Thr Phe Pro Lys Asn Phe Phe Trp Gly Ile Gly Thr Gly Ala
1               5                   10                  15

Leu Gln Val Glu Gly Ser Trp Lys Lys Asp Gly Lys Gly Pro Ser Ile
            20                  25                  30

Trp Asp His Phe Ile His Thr His Leu Lys Asn Val Ser Ser Thr Asn
        35                  40                  45
```

```
Gly Ser Ser Asp Ser Tyr Ile Phe Leu Glu Lys Asp Leu Ser Ala Leu
    50                  55                  60

Asp Phe Ile Gly Val Ser Phe Tyr Gln Phe Ser Ile Ser Trp Pro Arg
65                  70                  75                  80

Leu Phe Pro Asp Gly Ile Val Thr Val Ala Asn Ala Lys Gly Leu Gln
                85                  90                  95

Tyr Tyr Ser Thr Leu Leu Asp Ala Leu Val Leu Arg Asn Ile Glu Pro
            100                 105                 110

Ile Val Thr Leu Tyr His Trp Asp Leu Pro Leu Ala Leu Gln Glu Lys
        115                 120                 125

Tyr Gly Gly Trp Lys Asn Asp Thr Ile Ile Asp Ile Phe Asn Asp Tyr
    130                 135                 140

Ala Thr Tyr Cys Phe Gln Met Phe Gly Asp Arg Val Lys Tyr Trp Ile
145                 150                 155                 160

Thr Ile His Asn Pro Tyr Leu Val Ala Trp His Gly Tyr Gly Thr Gly
                165                 170                 175

Met His Ala Pro Gly Glu Lys Gly Asn Leu Ala Ala Val Tyr Thr Val
            180                 185                 190

Gly His Asn Leu Ile Lys Ala His Ser Lys Val Trp His Asn Tyr Asn
        195                 200                 205

Thr His Phe Arg Pro His Gln Lys Gly Trp Leu Ser Ile Thr Leu Gly
    210                 215                 220

Ser His Trp Ile Glu Pro Asn Arg Ser Glu Asn Thr Met Asp Ile Phe
225                 230                 235                 240

Lys Cys Gln Gln Ser Met Val Ser Val Leu Gly Trp Phe Ala Asn Pro
                245                 250                 255

Ile His Gly Asp Gly Asp Tyr Pro Glu Gly Met Arg Lys Lys Leu Phe
            260                 265                 270

Ser Val Leu Pro Ile Phe Ser Glu Ala Glu Lys His Glu Met Arg Gly
        275                 280                 285

Thr Ala Asp Phe Phe Ala Phe Ser Phe Gly Pro Asn Asn Phe Lys Pro
```

290 295 300

Leu Asn Thr Met Ala Lys Met Gly Gln Asn Val Ser Leu Asn Leu Arg
305 310 315 320

Glu Ala Leu Asn Trp Ile Lys Leu Glu Tyr Asn Asn Pro Arg Ile Leu
325 330 335

Ile Ala Glu Asn Gly Trp Phe Thr Asp Ser Arg Val Lys Thr Glu Asp
340 345 350

Thr Thr Ala Ile Tyr Met Met Lys Asn Phe Leu Ser Gln Val Leu Gln
355 360 365

Ala Ile Arg Leu Asp Glu Ile Arg Val Phe Gly Tyr Thr Ala Trp Ser
370 375 380

Leu Leu Asp Gly Phe Glu Trp Gln Asp Ala Tyr Thr Ile Arg Arg Gly
385 390 395 400

Leu Phe Tyr Val Asp Phe Asn Ser Lys Gln Lys Glu Arg Lys Pro Lys
405 410 415

Ser Ser Ala His Tyr Tyr Lys Gln Ile Ile Arg Glu Asn Gly Phe
420 425 430

<210> 38
<211> 397
<212> PRT
<213> Homo Sapiens

<400> 38

Thr Arg Pro Ala Gln Cys Thr Asp Phe Val Asn Ile Lys Lys Gln Leu
1 5 10 15

Glu Met Leu Ala Arg Met Lys Val Thr His Tyr Arg Phe Ala Leu Asp
20 25 30

Trp Ala Ser Val Leu Pro Thr Gly Asn Leu Ser Ala Val Asn Arg Gln
35 40 45

Ala Leu Arg Tyr Tyr Arg Cys Val Val Ser Glu Gly Leu Lys Leu Gly
50 55 60

Ile Ser Ala Met Val Thr Leu Tyr Tyr Pro Thr His Ala His Leu Gly
65 70 75 80

Leu Pro Glu Pro Leu Leu His Ala Asp Gly Trp Leu Asn Pro Ser Thr

```
                85                  90                  95

Ala Glu Ala Phe Gln Ala Tyr Ala Gly Leu Cys Phe Gln Glu Leu Gly
            100                 105                 110

Asp Leu Val Lys Leu Trp Ile Thr Ile Asn Glu Pro Asn Arg Leu Ser
        115                 120                 125

Asp Ile Tyr Asn Arg Ser Gly Asn Asp Thr Tyr Gly Ala Ala His Asn
    130                 135                 140

Leu Leu Val Ala His Ala Leu Ala Trp Arg Leu Tyr Asp Arg Gln Phe
145                 150                 155                 160

Arg Pro Ser Gln Arg Gly Ala Val Ser Leu Ser Leu His Ala Asp Trp
                165                 170                 175

Ala Glu Pro Ala Asn Pro Tyr Ala Asp Ser His Trp Arg Ala Ala Glu
            180                 185                 190

Arg Phe Leu Gln Phe Glu Ile Ala Trp Phe Ala Glu Pro Leu Phe Lys
        195                 200                 205

Thr Gly Asp Tyr Pro Ala Ala Met Arg Glu Tyr Ile Ala Ser Lys His
    210                 215                 220

Arg Arg Gly Leu Ser Ser Ser Ala Leu Pro Arg Leu Thr Glu Ala Glu
225                 230                 235                 240

Arg Arg Leu Leu Lys Gly Thr Val Asp Phe Cys Ala Leu Asn His Phe
                245                 250                 255

Thr Thr Arg Phe Val Met His Glu Gln Leu Ala Gly Ser Arg Tyr Asp
            260                 265                 270

Ser Asp Arg Asp Ile Gln Phe Leu Gln Asp Ile Thr Arg Leu Ser Ser
        275                 280                 285

Pro Thr Arg Leu Ala Val Ile Pro Trp Gly Val Arg Lys Leu Leu Arg
    290                 295                 300

Trp Val Arg Arg Asn Tyr Gly Asp Met Asp Ile Tyr Ile Thr Ala Ser
305                 310                 315                 320

Gly Ile Asp Asp Gln Ala Leu Glu Asp Asp Arg Leu Arg Lys Tyr Tyr
                325                 330                 335
```

Leu Gly Lys Tyr Leu Gln Glu Val Leu Lys Ala Tyr Leu Ile Asp Lys
340 345 350

Val Arg Ile Lys Gly Tyr Tyr Ala Phe Lys Leu Ala Glu Glu Lys Ser
355 360 365

Lys Pro Arg Phe Gly Phe Phe Thr Ser Asp Phe Lys Ala Lys Ser Ser
370 375 380

Ile Gln Phe Tyr Asn Lys Val Ile Ser Ser Arg Gly Phe
385 390 395

<210> 39
<211> 946
<212> PRT
<213> Homo Sapiens

<400> 39

Gly Phe Ser Gly Asp Gly Arg Ala Ile Trp Ser Lys Asn Pro Asn Phe
1 5 10 15

Thr Pro Val Asn Glu Ser Gln Leu Phe Leu Tyr Asp Thr Phe Pro Lys
20 25 30

Asn Phe Phe Trp Gly Ile Gly Thr Gly Ala Leu Gln Val Glu Gly Ser
35 40 45

Trp Lys Lys Asp Gly Lys Gly Pro Ser Ile Trp Asp His Phe Ile His
50 55 60

Thr His Leu Lys Asn Val Ser Ser Thr Asn Gly Ser Ser Asp Ser Tyr
65 70 75 80

Ile Phe Leu Glu Lys Asp Leu Ser Ala Leu Asp Phe Ile Gly Val Ser
85 90 95

Phe Tyr Gln Phe Ser Ile Ser Trp Pro Arg Leu Phe Pro Asp Gly Ile
100 105 110

Val Thr Val Ala Asn Ala Lys Gly Leu Gln Tyr Tyr Ser Thr Leu Leu
115 120 125

Asp Ala Leu Val Leu Arg Asn Ile Glu Pro Ile Val Thr Leu Tyr His
130 135 140

Trp Asp Leu Pro Leu Ala Leu Gln Glu Lys Tyr Gly Gly Trp Lys Asn
145 150 155 160

```
Asp Thr Ile Ile Asp Ile Phe Asn Asp Tyr Ala Thr Tyr Cys Phe Gln
                165                 170                 175

Met Phe Gly Asp Arg Val Lys Tyr Trp Ile Thr Ile His Asn Pro Tyr
            180                 185                 190

Leu Val Ala Trp His Gly Tyr Gly Thr Gly Met His Ala Pro Gly Glu
        195                 200                 205

Lys Gly Asn Leu Ala Ala Val Tyr Thr Val Gly His Asn Leu Ile Lys
    210                 215                 220

Ala His Ser Lys Val Trp His Asn Tyr Asn Thr His Phe Arg Pro His
225                 230                 235                 240

Gln Lys Gly Trp Leu Ser Ile Thr Leu Gly Ser His Trp Ile Glu Pro
                245                 250                 255

Asn Arg Ser Glu Asn Thr Met Asp Ile Phe Lys Cys Gln Gln Ser Met
            260                 265                 270

Val Ser Val Leu Gly Trp Phe Ala Asn Pro Ile His Gly Asp Gly Asp
        275                 280                 285

Tyr Pro Glu Gly Met Arg Lys Lys Leu Phe Ser Val Leu Pro Ile Phe
    290                 295                 300

Ser Glu Ala Glu Lys His Glu Met Arg Gly Thr Ala Asp Phe Phe Ala
305                 310                 315                 320

Phe Ser Phe Gly Pro Asn Asn Phe Lys Pro Leu Asn Thr Met Ala Lys
                325                 330                 335

Met Gly Gln Asn Val Ser Leu Asn Leu Arg Glu Ala Leu Asn Trp Ile
            340                 345                 350

Lys Leu Glu Tyr Asn Asn Pro Arg Ile Leu Ile Ala Glu Asn Gly Trp
        355                 360                 365

Phe Thr Asp Ser Arg Val Lys Thr Glu Asp Thr Thr Ala Ile Tyr Met
    370                 375                 380

Met Lys Asn Phe Leu Ser Gln Val Leu Gln Ala Ile Arg Leu Asp Glu
385                 390                 395                 400

Ile Arg Val Phe Gly Tyr Thr Ala Trp Ser Leu Leu Asp Gly Phe Glu
                405                 410                 415
```

```
Trp Gln Asp Ala Tyr Thr Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe
            420                 425                 430

Asn Ser Lys Gln Lys Glu Arg Lys Pro Lys Ser Ser Ala His Tyr Tyr
        435                 440                 445

Lys Gln Ile Ile Arg Glu Asn Gly Phe Ser Leu Lys Glu Ser Thr Pro
    450                 455                 460

Asp Val Gln Gly Gln Phe Pro Cys Asp Phe Ser Trp Gly Val Thr Glu
465                 470                 475                 480

Ser Val Leu Lys Pro Glu Ser Val Ala Ser Ser Pro Gln Phe Ser Asp
                485                 490                 495

Pro His Leu Tyr Val Trp Asn Ala Thr Gly Asn Arg Leu Leu His Arg
            500                 505                 510

Val Glu Gly Val Arg Leu Lys Thr Arg Pro Ala Gln Cys Thr Asp Phe
        515                 520                 525

Val Asn Ile Lys Lys Gln Leu Glu Met Leu Ala Arg Met Lys Val Thr
    530                 535                 540

His Tyr Arg Phe Ala Leu Asp Trp Ala Ser Val Leu Pro Thr Gly Asn
545                 550                 555                 560

Leu Ser Ala Val Asn Arg Gln Ala Leu Arg Tyr Tyr Arg Cys Val Val
                565                 570                 575

Ser Glu Gly Leu Lys Leu Gly Ile Ser Ala Met Val Thr Leu Tyr Tyr
            580                 585                 590

Pro Thr His Ala His Leu Gly Leu Pro Glu Pro Leu Leu His Ala Asp
        595                 600                 605

Gly Trp Leu Asn Pro Ser Thr Ala Glu Ala Phe Gln Ala Tyr Ala Gly
    610                 615                 620

Leu Cys Phe Gln Glu Leu Gly Asp Leu Val Lys Leu Trp Ile Thr Ile
625                 630                 635                 640

Asn Glu Pro Asn Arg Leu Ser Asp Ile Tyr Asn Arg Ser Gly Asn Asp
                645                 650                 655

Thr Tyr Gly Ala Ala His Asn Leu Leu Val Ala His Ala Leu Ala Trp
            660                 665                 670
```

```
Arg Leu Tyr Asp Arg Gln Phe Arg Pro Ser Gln Arg Gly Ala Val Ser
        675                 680                 685

Leu Ser Leu His Ala Asp Trp Ala Glu Pro Ala Asn Pro Tyr Ala Asp
    690                 695                 700

Ser His Trp Arg Ala Ala Glu Arg Phe Leu Gln Phe Glu Ile Ala Trp
705                 710                 715                 720

Phe Ala Glu Pro Leu Phe Lys Thr Gly Asp Tyr Pro Ala Ala Met Arg
                725                 730                 735

Glu Tyr Ile Ala Ser Lys His Arg Arg Gly Leu Ser Ser Ser Ala Leu
            740                 745                 750

Pro Arg Leu Thr Glu Ala Glu Arg Arg Leu Leu Lys Gly Thr Val Asp
        755                 760                 765

Phe Cys Ala Leu Asn His Phe Thr Thr Arg Phe Val Met His Glu Gln
    770                 775                 780

Leu Ala Gly Ser Arg Tyr Asp Ser Asp Arg Asp Ile Gln Phe Leu Gln
785                 790                 795                 800

Asp Ile Thr Arg Leu Ser Ser Pro Thr Arg Leu Ala Val Ile Pro Trp
                805                 810                 815

Gly Val Arg Lys Leu Leu Arg Trp Val Arg Arg Asn Tyr Gly Asp Met
            820                 825                 830

Asp Ile Tyr Ile Thr Ala Ser Gly Ile Asp Asp Gln Ala Leu Glu Asp
        835                 840                 845

Asp Arg Leu Arg Lys Tyr Tyr Leu Gly Lys Tyr Leu Gln Glu Val Leu
    850                 855                 860

Lys Ala Tyr Leu Ile Asp Lys Val Arg Ile Lys Gly Tyr Tyr Ala Phe
865                 870                 875                 880

Lys Leu Ala Glu Glu Lys Ser Lys Pro Arg Phe Gly Phe Phe Thr Ser
                885                 890                 895

Asp Phe Lys Ala Lys Ser Ser Ile Gln Phe Tyr Asn Lys Val Ile Ser
            900                 905                 910

Ser Arg Gly Phe Pro Phe Glu Asn Ser Ser Ser Arg Cys Ser Gln Thr
```

915 920 925

Gln Glu Asn Thr Glu Cys Thr Val Cys Leu Phe Leu Val Gln Lys Lys
930 935 940

Pro Leu
945

<210> 40
<211> 1195
<212> PRT
<213> Homo Sapiens

<400> 40

Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro Pro
1 5 10 15

Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly Phe
20 25 30

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

Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro
50 55 60

Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala
65 70 75 80

Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr
85 90 95

Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr
100 105 110

His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser
115 120 125

Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu
130 135 140

Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His
145 150 155 160

Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn
165 170 175

Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg

```
            180                 185                 190

His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr
        195                 200                 205

Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile
    210                 215                 220

Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu
225                 230                 235                 240

Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr
                245                 250                 255

Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro
            260                 265                 270

Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp
        275                 280                 285

Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr
    290                 295                 300

Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr
305                 310                 315                 320

Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu
                325                 330                 335

Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys
            340                 345                 350

Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile
        355                 360                 365

Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp
    370                 375                 380

Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr
385                 390                 395                 400

Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly
                405                 410                 415

Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu
            420                 425                 430
```

```
Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe
        435                 440                 445

Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr
    450                 455                 460

Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln
465                 470                 475                 480

Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp
                485                 490                 495

Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn
            500                 505                 510

Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp
        515                 520                 525

Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala
    530                 535                 540

Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe
545                 550                 555                 560

Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser
                565                 570                 575

Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu
            580                 585                 590

Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met
        595                 600                 605

Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp
    610                 615                 620

Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys
625                 630                 635                 640

Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu
                645                 650                 655

Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys
            660                 665                 670

Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala
        675                 680                 685
```

```
Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro
    690                 695                 700

Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu
705                 710                 715                 720

Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp
                725                 730                 735

Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu
            740                 745                 750

Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe
        755                 760                 765

Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu
    770                 775                 780

Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met
785                 790                 795                 800

Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro
                805                 810                 815

Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly Asp
            820                 825                 830

Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His Ala
        835                 840                 845

Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn Glu
    850                 855                 860

Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr Phe
865                 870                 875                 880

Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr Arg
                885                 890                 895

Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr Arg
            900                 905                 910

Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu Arg
        915                 920                 925

Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe His
    930                 935                 940
```

```
Thr Arg Lys Ser Leu Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
945                 950                 955                 960

Ser Gly Gly Gly Gly Ser Leu Lys Tyr Pro Asn Ala Ser Pro Leu Leu
                965                 970                 975

Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
            980                 985                 990

Asn Ser Tyr His Leu Gln Ile His  Lys Asn Gly His Val  Asp Gly Ala
        995                 1000                1005

Pro His  Gln Thr Ile Tyr Ser  Ala Leu Met Ile Arg  Ser Glu Asp
    1010                1015                1020

Ala Gly  Phe Val Val Ile Thr  Gly Val Met Ser Arg  Arg Tyr Leu
    1025                1030                1035

Cys Met  Asp Phe Arg Gly Asn  Ile Phe Gly Ser His  Tyr Phe Asp
    1040                1045                1050

Pro Glu  Asn Cys Arg Phe Gln  His Gln Thr Leu Glu  Asn Gly Tyr
    1055                1060                1065

Asp Val  Tyr His Ser Pro Gln  Tyr His Phe Leu Val  Ser Leu Gly
    1070                1075                1080

Arg Ala  Lys Arg Ala Phe Leu  Pro Gly Met Asn Pro  Pro Pro Tyr
    1085                1090                1095

Ser Gln  Phe Leu Ser Arg Arg  Asn Glu Ile Pro Leu  Ile His Phe
    1100                1105                1110

Asn Thr  Pro Ile Pro Arg Arg  His Thr Arg Ser Ala  Glu Asp Asp
    1115                1120                1125

Ser Glu  Arg Asp Pro Leu Asn  Val Leu Lys Pro Arg  Ala Arg Met
    1130                1135                1140

Thr Pro  Ala Pro Ala Ser Cys  Ser Gln Glu Leu Pro  Ser Ala Glu
    1145                1150                1155

Asp Asn  Ser Pro Met Ala Ser  Asp Pro Leu Gly Val  Val Arg Gly
    1160                1165                1170

Gly Arg  Val Asn Thr His Ala  Gly Gly Thr Gly Pro  Glu Gly Cys
```

1175 1180 1185

Arg Pro Phe Ala Lys Phe Ile
1190 1195

<210> 41
<211> 1195
<212> PRT
<213> Homo Sapiens

<400> 41

Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro Pro
1 5 10 15

Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly Phe
20 25 30

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

Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro
50 55 60

Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala
65 70 75 80

Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr
85 90 95

Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr
100 105 110

His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser
115 120 125

Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu
130 135 140

Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His
145 150 155 160

Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn
165 170 175

Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg
180 185 190

His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr

```
        195                 200                 205

Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile
    210                 215                 220

Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu
225                 230                 235                 240

Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr
                245                 250                 255

Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro
            260                 265                 270

Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp
        275                 280                 285

Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr
    290                 295                 300

Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr
305                 310                 315                 320

Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu
                325                 330                 335

Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys
            340                 345                 350

Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile
        355                 360                 365

Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp
    370                 375                 380

Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr
385                 390                 395                 400

Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly
                405                 410                 415

Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu
            420                 425                 430

Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe
        435                 440                 445
```

```
Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr
    450                 455                 460

Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln
465                 470                 475                 480

Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp
                485                 490                 495

Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn
            500                 505                 510

Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp
        515                 520                 525

Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala
    530                 535                 540

Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe
545                 550                 555                 560

Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser
                565                 570                 575

Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu
            580                 585                 590

Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met
        595                 600                 605

Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp
    610                 615                 620

Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys
625                 630                 635                 640

Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu
                645                 650                 655

Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys
            660                 665                 670

Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala
        675                 680                 685

Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro
    690                 695                 700
```

```
Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu
705                 710                 715                 720

Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp
                725                 730                 735

Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu
            740                 745                 750

Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe
        755                 760                 765

Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu
    770                 775                 780

Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met
785                 790                 795                 800

Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro
                805                 810                 815

Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly Asp
            820                 825                 830

Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His Ala
        835                 840                 845

Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn Glu
    850                 855                 860

Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr Phe
865                 870                 875                 880

Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr Arg
                885                 890                 895

Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr Arg
            900                 905                 910

Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu Arg
        915                 920                 925

Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe His
    930                 935                 940

Thr Arg Lys Ser Leu Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
945                 950                 955                 960
```

```
Ser Gly Gly Gly Gly Ser Leu Lys Tyr Pro Asn Ala Ser Pro Leu Leu
                965                 970                 975

Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
            980                 985                 990

Asn Ser Tyr His Leu Gln Ile His  Lys Asn Gly His Val  Asp Gly Ala
        995                 1000                1005

Pro His  Gln Thr Ile Tyr Ser  Ala Leu Met Ile Arg  Ser Glu Asp
    1010                1015                1020

Ala Gly  Phe Val Val Ile Thr  Gly Val Met Ser Arg  Arg Tyr Leu
    1025                1030                1035

Cys Met  Asp Phe Arg Gly Asn  Ile Phe Gly Ser His  Tyr Phe Asp
    1040                1045                1050

Pro Glu  Asn Cys Arg Phe Gln  His Gln Thr Leu Glu  Asn Gly Tyr
    1055                1060                1065

Asp Val  Tyr His Ser Pro Gln  Tyr His Phe Leu Val  Ser Leu Gly
    1070                1075                1080

Arg Ala  Lys Arg Ala Phe Leu  Pro Gly Met Asn Pro  Pro Pro Tyr
    1085                1090                1095

Ser Gln  Phe Leu Ser Arg Arg  Asn Glu Ile Pro Leu  Ile His Phe
    1100                1105                1110

Asn Thr  Pro Ile Pro Arg Arg  His Thr Gln Ser Ala  Glu Asp Asp
    1115                1120                1125

Ser Glu  Arg Asp Pro Leu Asn  Val Leu Lys Pro Arg  Ala Arg Met
    1130                1135                1140

Thr Pro  Ala Pro Ala Ser Cys  Ser Gln Glu Leu Pro  Ser Ala Glu
    1145                1150                1155

Asp Asn  Ser Pro Met Ala Ser  Asp Pro Leu Gly Val  Val Arg Gly
    1160                1165                1170

Gly Arg  Val Asn Thr His Ala  Gly Gly Thr Gly Pro  Glu Gly Cys
    1175                1180                1185

Arg Pro  Phe Ala Lys Phe Ile
```

1190 1195

<210> 42
<211> 227
<212> PRT
<213> Homo Sapiens

<400> 42

Tyr Pro Asn Ala Ser Pro Leu Leu Gly Ser Ser Trp Gly Gly Leu Ile
1 5 10 15

His Leu Tyr Thr Ala Thr Ala Arg Asn Ser Tyr His Leu Gln Ile His
20 25 30

Lys Asn Gly His Val Asp Gly Ala Pro His Gln Thr Ile Tyr Ser Ala
35 40 45

Leu Met Ile Arg Ser Glu Asp Ala Gly Phe Val Val Ile Thr Gly Val
50 55 60

Met Ser Arg Arg Tyr Leu Cys Met Asp Phe Arg Gly Asn Ile Phe Gly
65 70 75 80

Ser His Tyr Phe Asp Pro Glu Asn Cys Arg Phe Gln His Gln Thr Leu
85 90 95

Glu Asn Gly Tyr Asp Val Tyr His Ser Pro Gln Tyr His Phe Leu Val
100 105 110

Ser Leu Gly Arg Ala Lys Arg Ala Phe Leu Pro Gly Met Asn Pro Pro
115 120 125

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

Phe Asn Thr Pro Ile Pro Arg Arg His Thr Arg Ser Ala Glu Asp Asp
145 150 155 160

Ser Glu Arg Asp Pro Leu Asn Val Leu Lys Pro Arg Ala Arg Met Thr
165 170 175

Pro Ala Pro Ala Ser Cys Ser Gln Glu Leu Pro Ser Ala Glu Asp Asn
180 185 190

Ser Pro Met Ala Ser Asp Pro Leu Gly Val Val Arg Gly Gly Arg Val
195 200 205

Asn Thr His Ala Gly Gly Thr Gly Pro Glu Gly Cys Arg Pro Phe Ala

210 215 220

Lys Phe Ile
225

<210> 43
<211> 227
<212> PRT
<213> Homo Sapiens

<400> 43

Tyr Pro Asn Ala Ser Pro Leu Leu Gly Ser Ser Trp Gly Gly Leu Ile
1 5 10 15

His Leu Tyr Thr Ala Thr Ala Arg Asn Ser Tyr His Leu Gln Ile His
20 25 30

Lys Asn Gly His Val Asp Gly Ala Pro His Gln Thr Ile Tyr Ser Ala
35 40 45

Leu Met Ile Arg Ser Glu Asp Ala Gly Phe Val Val Ile Thr Gly Val
50 55 60

Met Ser Arg Arg Tyr Leu Cys Met Asp Phe Arg Gly Asn Ile Phe Gly
65 70 75 80

Ser His Tyr Phe Asp Pro Glu Asn Cys Arg Phe Gln His Gln Thr Leu
85 90 95

Glu Asn Gly Tyr Asp Val Tyr His Ser Pro Gln Tyr His Phe Leu Val
100 105 110

Ser Leu Gly Arg Ala Lys Arg Ala Phe Leu Pro Gly Met Asn Pro Pro
115 120 125

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

Phe Asn Thr Pro Ile Pro Arg Arg His Thr Gln Ser Ala Glu Asp Asp
145 150 155 160

Ser Glu Arg Asp Pro Leu Asn Val Leu Lys Pro Arg Ala Arg Met Thr
165 170 175

Pro Ala Pro Ala Ser Cys Ser Gln Glu Leu Pro Ser Ala Glu Asp Asn
180 185 190

Ser Pro Met Ala Ser Asp Pro Leu Gly Val Val Arg Gly Gly Arg Val

195 200 205

Asn Thr His Ala Gly Gly Thr Gly Pro Glu Gly Cys Arg Pro Phe Ala
210 215 220

Lys Phe Ile
225

<210> 44
<211> 982
<212> PRT
<213> Homo Sapiens

<400> 44

Met Pro Ala Ser Ala Pro Pro Arg Arg Pro Arg Pro Pro Pro Pro Ser
1 5 10 15

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

Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro
35 40 45

Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly
50 55 60

Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp
65 70 75 80

Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His
85 90 95

Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly
100 105 110

Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser
115 120 125

Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val
130 135 140

Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly
145 150 155 160

Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu
165 170 175

Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr

```
            180                 185                 190

His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala
        195                 200                 205

Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe
    210                 215                 220

Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro
225                 230                 235                 240

Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly
                245                 250                 255

Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu
            260                 265                 270

Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro
        275                 280                 285

Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn
    290                 295                 300

Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu
305                 310                 315                 320

Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp
                325                 330                 335

Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe
            340                 345                 350

Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala
        355                 360                 365

Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met
    370                 375                 380

Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp
385                 390                 395                 400

Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly
                405                 410                 415

Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr
            420                 425                 430
```

```
Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp
        435                 440                 445

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

Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp
465                 470                 475                 480

Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe
                485                 490                 495

Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn
            500                 505                 510

Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val
        515                 520                 525

Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu
    530                 535                 540

Asn Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val
545                 550                 555                 560

Asp Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala
                565                 570                 575

Ala Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His
            580                 585                 590

Phe Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln
        595                 600                 605

Ser Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser
    610                 615                 620

Glu Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro
625                 630                 635                 640

Met Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala
                645                 650                 655

Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu
            660                 665                 670

Cys Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn
        675                 680                 685
```

```
Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu
    690                 695                 700

Lys Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His
705                 710                 715                 720

Ala Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu
                725                 730                 735

Pro Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val
            740                 745                 750

Leu Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly
        755                 760                 765

Asp Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe
    770                 775                 780

Leu Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr
785                 790                 795                 800

Phe Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser
                805                 810                 815

Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu
            820                 825                 830

Met Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val
        835                 840                 845

Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly
    850                 855                 860

Asp Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His
865                 870                 875                 880

Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn
                885                 890                 895

Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr
            900                 905                 910

Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr
        915                 920                 925

Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr
    930                 935                 940
```

```
Arg Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu
945                 950                 955                 960

Arg Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe
                965                 970                 975

His Thr Arg Lys Ser Leu
            980
```

<210> 45
<211> 974
<212> PRT
<213> Homo Sapiens

<400> 45

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Met Ser Val Leu Thr Gln Val Leu Ala Leu Leu Leu Leu Trp Leu Thr
1               5                   10                  15

Gly Leu Gly Gly Arg Arg Leu Arg Ala Glu Pro Gly Asp Gly Ala Gln
            20                  25                  30

Thr Trp Ala Arg Phe Ser Arg Pro Pro Ala Pro Glu Ala Ala Gly Leu
        35                  40                  45

Phe Gln Gly Thr Phe Pro Asp Gly Phe Leu Trp Ala Val Gly Ser Ala
    50                  55                  60

Ala Tyr Gln Thr Glu Gly Gly Trp Gln Gln His Gly Lys Gly Ala Ser
65                  70                  75                  80

Ile Trp Asp Thr Phe Thr His His Pro Leu Ala Pro Pro Gly Asp Ser
                85                  90                  95

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

Thr Gly Asp Val Ala Ser Asp Ser Tyr Asn Asn Val Phe Arg Asp Thr
        115                 120                 125

Glu Ala Leu Arg Glu Leu Gly Val Thr His Tyr Arg Phe Ser Ile Ser
    130                 135                 140

Trp Ala Arg Val Leu Pro Asn Gly Ser Ala Gly Val Pro Asn Arg Glu
145                 150                 155                 160

Gly Leu Arg Tyr Tyr Arg Arg Leu Leu Glu Arg Leu Arg Glu Leu Gly
                165                 170                 175
```

```
Val Gln Pro Val Val Thr Leu Tyr His Trp Asp Leu Pro Gln Arg Leu
            180                 185                 190

Gln Asp Ala Tyr Gly Gly Trp Ala Asn Arg Ala Leu Ala Asp His Phe
        195                 200                 205

Arg Asp Tyr Ala Glu Leu Cys Phe Arg His Phe Gly Gly Gln Val Lys
    210                 215                 220

Tyr Trp Ile Thr Ile Asp Asn Pro Tyr Val Val Ala Trp His Gly Tyr
225                 230                 235                 240

Ala Thr Gly Arg Leu Ala Pro Gly Ile Arg Gly Ser Pro Arg Leu Gly
                245                 250                 255

Tyr Leu Val Ala His Asn Leu Leu Leu Ala His Ala Lys Val Trp His
            260                 265                 270

Leu Tyr Asn Thr Ser Phe Arg Pro Thr Gln Gly Gly Gln Val Ser Ile
        275                 280                 285

Ala Leu Ser Ser His Trp Ile Asn Pro Arg Arg Met Thr Asp His Ser
    290                 295                 300

Ile Lys Glu Cys Gln Lys Ser Leu Asp Phe Val Leu Gly Trp Phe Ala
305                 310                 315                 320

Lys Pro Val Phe Ile Asp Gly Asp Tyr Pro Glu Ser Met Lys Asn Asn
                325                 330                 335

Leu Ser Ser Ile Leu Pro Asp Phe Thr Glu Ser Glu Lys Lys Phe Ile
            340                 345                 350

Lys Gly Thr Ala Asp Phe Phe Ala Leu Cys Phe Gly Pro Thr Leu Ser
        355                 360                 365

Phe Gln Leu Leu Asp Pro His Met Lys Phe Arg Gln Leu Glu Ser Pro
    370                 375                 380

Asn Leu Arg Gln Leu Leu Ser Trp Ile Asp Leu Glu Phe Asn His Pro
385                 390                 395                 400

Gln Ile Phe Ile Val Glu Asn Gly Trp Phe Val Ser Gly Thr Thr Lys
                405                 410                 415

Arg Asp Asp Ala Lys Tyr Met Tyr Tyr Leu Lys Lys Phe Ile Met Glu
```

```
            420                 425                 430

Thr Leu Lys Ala Ile Lys Leu Asp Gly Val Asp Val Ile Gly Tyr Thr
        435                 440                 445

Ala Trp Ser Leu Met Asp Gly Phe Glu Trp His Arg Gly Tyr Ser Ile
    450                 455                 460

Arg Arg Gly Leu Phe Tyr Val Asp Phe Leu Ser Gln Asp Lys Met Leu
465                 470                 475                 480

Leu Pro Lys Ser Ser Ala Leu Phe Tyr Gln Lys Leu Ile Glu Lys Asn
                485                 490                 495

Gly Phe Pro Pro Leu Pro Glu Asn Gln Pro Leu Glu Gly Thr Phe Pro
            500                 505                 510

Cys Asp Phe Ala Trp Gly Val Val Asp Asn Tyr Ile Gln Val Asp Thr
        515                 520                 525

Thr Leu Ser Gln Phe Thr Asp Leu Asn Val Tyr Leu Trp Asp Val His
    530                 535                 540

His Ser Lys Arg Leu Ile Lys Val Asp Gly Val Val Thr Lys Lys Arg
545                 550                 555                 560

Lys Ser Tyr Cys Val Asp Phe Ala Ala Ile Gln Pro Gln Ile Ala Leu
                565                 570                 575

Leu Gln Glu Met His Val Thr His Phe Arg Phe Ser Leu Asp Trp Ala
            580                 585                 590

Leu Ile Leu Pro Leu Gly Asn Gln Ser Gln Val Asn His Thr Ile Leu
        595                 600                 605

Gln Tyr Tyr Arg Cys Met Ala Ser Glu Leu Val Arg Val Asn Ile Thr
    610                 615                 620

Pro Val Val Ala Leu Trp Gln Pro Met Ala Pro Asn Gln Gly Leu Pro
625                 630                 635                 640

Arg Leu Leu Ala Arg Gln Gly Ala Trp Glu Asn Pro Tyr Thr Ala Leu
                645                 650                 655

Ala Phe Ala Glu Tyr Ala Arg Leu Cys Phe Gln Glu Leu Gly His His
            660                 665                 670
```

```
Val Lys Leu Trp Ile Thr Met Asn Glu Pro Tyr Thr Arg Asn Met Thr
        675                 680                 685

Tyr Ser Ala Gly His Asn Leu Leu Lys Ala His Ala Leu Ala Trp His
    690                 695                 700

Val Tyr Asn Glu Lys Phe Arg His Ala Gln Asn Gly Lys Ile Ser Ile
705                 710                 715                 720

Ala Leu Gln Ala Asp Trp Ile Glu Pro Ala Cys Pro Phe Ser Gln Lys
                725                 730                 735

Asp Lys Glu Val Ala Glu Arg Val Leu Glu Phe Asp Ile Gly Trp Leu
            740                 745                 750

Ala Glu Pro Ile Phe Gly Ser Gly Asp Tyr Pro Trp Val Met Arg Asp
        755                 760                 765

Trp Leu Asn Gln Arg Asn Asn Phe Leu Leu Pro Tyr Phe Thr Glu Asp
    770                 775                 780

Glu Lys Lys Leu Ile Gln Gly Thr Phe Asp Phe Leu Ala Leu Ser His
785                 790                 795                 800

Tyr Thr Thr Ile Leu Val Asp Ser Glu Lys Glu Asp Pro Ile Lys Tyr
                805                 810                 815

Asn Asp Tyr Leu Glu Val Gln Glu Met Thr Asp Ile Thr Trp Leu Asn
            820                 825                 830

Ser Pro Ser Gln Val Ala Val Val Pro Trp Gly Leu Arg Lys Val Leu
        835                 840                 845

Asn Trp Leu Lys Phe Lys Tyr Gly Asp Leu Pro Met Tyr Ile Ile Ser
    850                 855                 860

Asn Gly Ile Asp Asp Gly Leu His Ala Glu Asp Asp Gln Leu Arg Val
865                 870                 875                 880

Tyr Tyr Met Gln Asn Tyr Ile Asn Glu Ala Leu Lys Ala His Ile Leu
                885                 890                 895

Asp Gly Ile Asn Leu Cys Gly Tyr Phe Ala Tyr Ser Phe Asn Asp Arg
            900                 905                 910

Thr Ala Pro Arg Phe Gly Leu Tyr Arg Tyr Ala Ala Asp Gln Phe Glu
        915                 920                 925
```

Pro Lys Ala Ser Met Lys His Tyr Arg Lys Ile Ile Asp Ser Asn Gly
930 935 940

Phe Pro Gly Pro Glu Thr Leu Glu Arg Phe Cys Pro Glu Glu Phe Thr
945 950 955 960

Val Cys Thr Glu Cys Ser Phe Phe His Thr Arg Lys Ser Leu
965 970

<210> 46
<211> 4380
<212> DNA
<213> Homo Sapiens

<400> 46
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acctgggccc gtttctcgcg gcctcctgcc cccgaggccg cgggcctctt ccagggcacc 180

ttccccgacg gcttcctctg ggccgtgggc agcgccgcct accagaccga gggcggctgg 240

cagcagcacg gcaagggtgc gtccatctgg gatacgttca cccaccaccc cctggcaccc 300

ccgggagact cccggaacgc cagtctgccg ttgggcgccc cgtcgccgct gcagcccgcc 360

accggggacg tagccagcga cagctacaac aacgtcttcc gcgacacgga ggcgctgcgc 420

gagctcgggg tcactcacta ccgcttctcc atctcgtggg cgcgagtgct ccccaatggc 480

agcgcgggcg tccccaaccg cgaggggctg cgctactacc ggcgcctgct ggagcggctg 540

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gctcagaatg ggaaaatatc catagccttg caggctgatt ggatagaacc tgcctgccct 2220

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aacaactaca agacaacacc cccggtgctg gatagtgacg gatctttctt tctctactca 4260

aagctgaccg tggataagtc caggtggcag cagggaaacg tgttttcctg ctctgtcatg 4320

catgaagcgc tgcataatca ctatacccag aagtctctga gcttgagccc aggcaagtaa 4380

<210> 47
<211> 1459
<212> PRT
<213> Homo Sapiens

<400> 47

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

Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro
35 40 45

Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly
50 55 60

```
Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp
65                  70                  75                  80

Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His
                85                  90                  95

Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly
            100                 105                 110

Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser
        115                 120                 125

Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val
    130                 135                 140

Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly
145                 150                 155                 160

Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu
                165                 170                 175

Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr
            180                 185                 190

His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala
        195                 200                 205

Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe
    210                 215                 220

Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro
225                 230                 235                 240

Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly
                245                 250                 255

Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu
            260                 265                 270

Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro
        275                 280                 285

Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn
    290                 295                 300

Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu
305                 310                 315                 320
```

```
Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp
                325                 330                 335

Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe
            340                 345                 350

Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala
        355                 360                 365

Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met
    370                 375                 380

Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp
385                 390                 395                 400

Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly
                405                 410                 415

Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr
            420                 425                 430

Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp
        435                 440                 445

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

Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp
465                 470                 475                 480

Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe
                485                 490                 495

Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn
            500                 505                 510

Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val
        515                 520                 525

Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu
    530                 535                 540

Asn Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val
545                 550                 555                 560

Asp Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala
                565                 570                 575
```

```
Ala Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His
            580                 585                 590

Phe Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln
        595                 600                 605

Ser Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser
    610                 615                 620

Glu Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro
625                 630                 635                 640

Met Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala
                645                 650                 655

Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu
            660                 665                 670

Cys Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn
        675                 680                 685

Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu
    690                 695                 700

Lys Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His
705                 710                 715                 720

Ala Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu
                725                 730                 735

Pro Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val
            740                 745                 750

Leu Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly
        755                 760                 765

Asp Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe
    770                 775                 780

Leu Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr
785                 790                 795                 800

Phe Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser
                805                 810                 815

Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu
```

```
            820                 825                 830

Met Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val
        835                 840                 845

Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly
    850                 855                 860

Asp Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His
865                 870                 875                 880

Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn
                885                 890                 895

Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr
            900                 905                 910

Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr
        915                 920                 925

Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr
    930                 935                 940

Arg Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu
945                 950                 955                 960

Arg Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe
                965                 970                 975

His Thr Arg Lys Ser Leu Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
            980                 985                 990

Gly Ser Gly Gly Gly Gly Ser Leu  Lys Tyr Pro Asn Ala  Ser Pro Leu
        995                 1000                1005

Leu Gly  Ser Ser Trp Gly Gly  Leu Ile His Leu Tyr  Thr Ala Thr
    1010                1015                1020

Ala Arg  Asn Ser Tyr His Leu  Gln Ile His Lys Asn  Gly His Val
    1025                1030                1035

Asp Gly  Ala Pro His Gln Thr  Ile Tyr Ser Ala Leu  Met Ile Arg
    1040                1045                1050

Ser Glu  Asp Ala Gly Phe Val  Val Ile Thr Gly Val  Met Ser Arg
    1055                1060                1065
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```
Arg Tyr  Leu Cys Met Asp Phe  Arg Gly Asn Ile Phe  Gly Ser His
    1070                1075                1080

Tyr Phe  Asp Pro Glu Asn Cys  Arg Phe Gln His Gln  Thr Leu Glu
    1085                1090                1095

Asn Gly  Tyr Asp Val Tyr His  Ser Pro Gln Tyr His  Phe Leu Val
    1100                1105                1110

Ser Leu  Gly Arg Ala Lys Arg  Ala Phe Leu Pro Gly  Met Asn Pro
    1115                1120                1125

Pro Pro  Tyr Ser Gln Phe Leu  Ser Arg Arg Asn Glu  Ile Pro Leu
    1130                1135                1140

Ile His  Phe Asn Thr Pro Ile  Pro Arg Arg His Thr  Gln Ser Ala
    1145                1150                1155

Glu Asp  Asp Ser Glu Arg Asp  Pro Leu Asn Val Leu  Lys Pro Arg
    1160                1165                1170

Ala Arg  Met Thr Pro Ala Pro  Ala Ser Cys Ser Gln  Glu Leu Pro
    1175                1180                1185

Ser Ala  Glu Asp Asn Ser Pro  Met Ala Ser Asp Pro  Leu Gly Val
    1190                1195                1200

Val Arg  Gly Gly Arg Val Asn  Thr His Ala Gly Gly  Thr Gly Pro
    1205                1210                1215

Glu Gly  Cys Arg Pro Phe Ala  Lys Phe Ile Gly Gly  Gly Gly Ser
    1220                1225                1230

Lys Thr  His Thr Cys Pro Pro  Cys Pro Ala Pro Glu  Ala Ala Gly
    1235                1240                1245

Gly Pro  Ser Val Phe Leu Phe  Pro Pro Lys Pro Lys  Asp Thr Leu
    1250                1255                1260

Met Ile  Ser Arg Thr Pro Glu  Val Thr Cys Val Val  Val Asp Val
    1265                1270                1275

Ser His  Glu Asp Pro Glu Val  Lys Phe Asn Trp Tyr  Val Asp Gly
    1280                1285                1290

Val Glu  Val His Asn Ala Lys  Thr Lys Pro Arg Glu  Glu Gln Tyr
    1295                1300                1305
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Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
1310 1315 1320

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
1325 1330 1335

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
1340 1345 1350

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
1355 1360 1365

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
1370 1375 1380

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
1385 1390 1395

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
1400 1405 1410

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
1415 1420 1425

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
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Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
1445 1450 1455

Lys

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<212> PRT
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<400> 49

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35 40 45

Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly
50 55 60

Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp
65 70 75 80

Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His
85 90 95

Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly
100 105 110

Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser
115 120 125

Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val
130 135 140

Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly
145 150 155 160

Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu
165 170 175

Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr
180 185 190

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His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala
        195                 200                 205

Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe
    210                 215                 220

Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro
225                 230                 235                 240

Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly
                245                 250                 255

Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu
            260                 265                 270

Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro
        275                 280                 285

Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn
    290                 295                 300

Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu
305                 310                 315                 320

Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp
                325                 330                 335

Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe
            340                 345                 350

Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala
        355                 360                 365

Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met
    370                 375                 380

Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp
385                 390                 395                 400

Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly
                405                 410                 415

Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr
            420                 425                 430

Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp
        435                 440                 445
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Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe
    450                 455                 460

Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp
465                 470                 475                 480

Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe
                485                 490                 495

Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn
            500                 505                 510

Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val
        515                 520                 525

Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu
    530                 535                 540

Asn Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val
545                 550                 555                 560

Asp Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala
                565                 570                 575

Ala Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His
            580                 585                 590

Phe Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln
        595                 600                 605

Ser Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser
    610                 615                 620

Glu Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro
625                 630                 635                 640

Met Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala
                645                 650                 655

Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu
            660                 665                 670

Cys Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn
        675                 680                 685

Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu
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690 695 700

Lys Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His
705 710 715 720

Ala Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu
725 730 735

Pro Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val
740 745 750

Leu Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly
755 760 765

Asp Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe
770 775 780

Leu Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr
785 790 795 800

Phe Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser
805 810 815

Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu
820 825 830

Met Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val
835 840 845

Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly
850 855 860

Asp Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His
865 870 875 880

Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn
885 890 895

Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr
900 905 910

Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr
915 920 925

Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr
930 935 940

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Arg Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu
945                 950                 955                 960

Arg Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe
                965                 970                 975

His Thr Arg Lys Ser Leu Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
            980                 985                 990

Gly Ser Gly Gly Gly Gly Ser Leu  Lys Tyr Pro Asn Ala  Ser Pro Leu
        995                 1000                1005

Leu Gly  Ser Ser Trp Gly Gly  Leu Ile His Leu Tyr  Thr Ala Thr
    1010                1015                1020

Ala Arg  Asn Ser Tyr His Leu  Gln Ile His Lys Asn  Gly His Val
    1025                1030                1035

Asp Gly  Ala Pro His Gln Thr  Ile Tyr Ser Ala Leu  Met Ile Arg
    1040                1045                1050

Ser Glu  Asp Ala Gly Phe Val  Val Ile Thr Gly Val  Met Ser Arg
    1055                1060                1065

Arg Tyr  Leu Cys Met Asp Phe  Arg Gly Asn Ile Phe  Gly Ser His
    1070                1075                1080

Tyr Phe  Asp Pro Glu Asn Cys  Arg Phe Gln His Gln  Thr Leu Glu
    1085                1090                1095

Asn Gly  Tyr Asp Val Tyr His  Ser Pro Gln Tyr His  Phe Leu Val
    1100                1105                1110

Ser Leu  Gly Arg Ala Lys Arg  Ala Phe Leu Pro Gly  Met Asn Pro
    1115                1120                1125

Pro Pro  Tyr Ser Gln Phe Leu  Ser Arg Arg Asn Glu  Ile Pro Leu
    1130                1135                1140

Ile His  Phe Asn Thr Pro Ile  Pro Arg Arg His Thr  Gln Ser Ala
    1145                1150                1155

Glu Asp  Asp Ser Glu Arg Asp  Pro Leu Asn Val Leu  Lys Pro Arg
    1160                1165                1170

Ala Arg  Met Thr Pro Ala Pro  Ala Ser Cys Ser Gln  Glu Leu Pro
    1175                1180                1185
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Ser Ala  Glu Asp Asn Ser Pro  Met Ala Ser Asp Pro  Leu Gly Val
    1190                 1195                 1200

Val Arg  Gly Gly Arg Val Asn  Thr His Ala Gly Gly  Thr Gly Pro
    1205                 1210                 1215

Glu Gly  Cys Arg Pro Phe Ala  Lys Phe Ile Gly Gly  Gly Gly Ser
    1220                 1225                 1230

Ala Pro  Glu Ala Ala Gly Gly  Pro Ser Val Phe Leu  Phe Pro Pro
    1235                 1240                 1245

Lys Pro  Lys Asp Thr Leu Met  Ile Ser Arg Thr Pro  Glu Val Thr
    1250                 1255                 1260

Cys Val  Val Val Asp Val Ser  His Glu Asp Pro Glu  Val Lys Phe
    1265                 1270                 1275

Asn Trp  Tyr Val Asp Gly Val  Glu Val His Asn Ala  Lys Thr Lys
    1280                 1285                 1290

Pro Arg  Glu Glu Gln Tyr Asn  Ser Thr Tyr Arg Val  Val Ser Val
    1295                 1300                 1305

Leu Thr  Val Leu His Gln Asp  Trp Leu Asn Gly Lys  Glu Tyr Lys
    1310                 1315                 1320

Cys Lys  Val Ser Asn Lys Ala  Leu Pro Ala Pro Ile  Glu Lys Thr
    1325                 1330                 1335

Ile Ser  Lys Ala Lys Gly Gln  Pro Arg Glu Pro Gln  Val Tyr Thr
    1340                 1345                 1350

Leu Pro  Pro Ser Arg Glu Glu  Met Thr Lys Asn Gln  Val Ser Leu
    1355                 1360                 1365

Thr Cys  Leu Val Lys Gly Phe  Tyr Pro Ser Asp Ile  Ala Val Glu
    1370                 1375                 1380

Trp Glu  Ser Asn Gly Gln Pro  Glu Asn Asn Tyr Lys  Thr Thr Pro
    1385                 1390                 1395

Pro Val  Leu Asp Ser Asp Gly  Ser Phe Phe Leu Tyr  Ser Lys Leu
    1400                 1405                 1410

Thr Val  Asp Lys Ser Arg Trp  Gln Gln Gly Asn Val  Phe Ser Cys
    1415                 1420                 1425
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Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
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Leu Ser Leu Ser Pro Gly Lys
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<213> Homo Sapiens

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gtggatggcg caccccatca gaccatctac agtgccctga tgatcagatc agaggatgct 240

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<400> 51

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            20                  25                  30

Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
        35                  40                  45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
    50                  55                  60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65                  70                  75                  80

Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
                85                  90                  95

Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
            100                 105                 110

Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
        115                 120                 125

Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
    130                 135                 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
145                 150                 155                 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
                165                 170                 175

His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
            180                 185                 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
        195                 200                 205
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Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
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Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225                 230                 235                 240

Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile Gly Gly Gly Gly Ser
                245                 250                 255

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
            260                 265                 270

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

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

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

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

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

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

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
    370                 375                 380

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
385                 390                 395                 400

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
                405                 410                 415

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

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

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
    450                 455                 460
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Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
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Gly Lys

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<212> DNA
<213> Homo Sapiens

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cacctgtaca cagccacagc caggaacagc taccacctgc agatccacaa gaatggccat 180

gtggatggcg caccccatca gaccatctac agtgccctga tgatcagatc agaggatgct 240

ggctttgtgg tgattacagg tgtgatgagc agaagatacc tctgcatgga tttcagaggc 300

aacatttttg gatcacacta tttcgacccg gagaactgca ggttccaaca ccagacgctg 360

gaaaacgggt acgacgtcta ccactctcct cagtatcact tcctggtcag tctgggccgg 420

gcgaagagag ccttcctgcc aggcatgaac ccacccccgt actcccagtt cctgtcccgg 480

aggaacgaga tccccctaat tcacttcaac acccccatac cacggcggca cacccagagc 540

gccgaggacg actcggagcg ggacccccctg aacgtgctga agccccgggc ccggatgacc 600

ccggccccgg cctcctgttc acaggagctc ccgagcgccg aggacaacag cccgatggcc 660

agtgacccat taggggtggt caggggcggt cgagtgaaca cgcacgctgg gggaacgggc 720

ccggaaggct gccgcccctt cgccaagttc atcggaggtg gaggttcagc cccagaagca 780

gcaggtggtc catcagtttt tcttttccct cccaaaccca aggatacgct gatgatctct 840

cgcacgcctg aggtgacatg cgtcgtagta gacgtgagcc acgaagatcc cgaggtgaag 900

ttcaattggt atgtggacgg agtagaagtg cataacgcga aaactaagcc gcgcgaggaa 960

caatataaca gtacttacag ggtggtatcc gtgctcacag tcctgcacca ggactggctg 1020

aacggtaagg aatacaagtg caaagtaagc aacaaggcac ttcccgcgcc tattgagaaa 1080

acaatctcca aggcgaaggg acaaccaaga gaacctcagg tttacactct cccgccttcc 1140

agggaagaga tgaccaaaaa tcaagtttcc ctgacttgcc tcgtcaaagg attctaccct 1200

tccgacattg ctgttgaatg ggaaagcaat ggacaaccag agaacaacta caagacaaca 1260

cccccggtgc tggatagtga cggatctttc tttctctact caaagctgac cgtggataag 1320

tccaggtggc agcagggaaa cgtgttttcc tgctctgtca tgcatgaagc gctgcataat 1380

cactataccc agaagtctct gagcttgagc ccaggcaagt aa 1422

<210> 53
<211> 473
<212> PRT
<213> Homo Sapiens

<400> 53

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

Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
            20                  25                  30

Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
        35                  40                  45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
    50                  55                  60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65                  70                  75                  80

Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
                85                  90                  95

Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
            100                 105                 110

Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
        115                 120                 125

Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
    130                 135                 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
145                 150                 155                 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
                165                 170                 175

His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
            180                 185                 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
        195                 200                 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
    210                 215                 220
```

```
Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225                 230                 235                 240

Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile Gly Gly Gly Gly Ser
                245                 250                 255

Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
            260                 265                 270

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
        275                 280                 285

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
    290                 295                 300

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
305                 310                 315                 320

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
                325                 330                 335

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
            340                 345                 350

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
        355                 360                 365

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
    370                 375                 380

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
385                 390                 395                 400

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
                405                 410                 415

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
            420                 425                 430

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
        435                 440                 445

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
    450                 455                 460

Lys Ser Leu Ser Leu Ser Pro Gly Lys
465                 470
```

<210> 54
<211> 1228
<212> PRT
<213> Homo Sapiens

<400> 54

```
Met Pro Ala Ser Ala Pro Pro Arg Arg Pro Arg Pro Pro Pro Pro Ser
1               5                   10                  15

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

Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro
        35                  40                  45

Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly
    50                  55                  60

Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp
65                  70                  75                  80

Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His
                85                  90                  95

Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly
            100                 105                 110

Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser
        115                 120                 125

Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val
    130                 135                 140

Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly
145                 150                 155                 160

Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu
                165                 170                 175

Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr
            180                 185                 190

His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala
        195                 200                 205

Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe
    210                 215                 220
```

```
Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro
225                 230                 235                 240

Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly
                245                 250                 255

Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu
            260                 265                 270

Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro
        275                 280                 285

Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn
    290                 295                 300

Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu
305                 310                 315                 320

Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp
                325                 330                 335

Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe
            340                 345                 350

Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala
        355                 360                 365

Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met
    370                 375                 380

Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp
385                 390                 395                 400

Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly
                405                 410                 415

Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr
            420                 425                 430

Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp
        435                 440                 445

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

Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp
```

465 470 475 480

Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe
485 490 495

Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn
500 505 510

Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val
515 520 525

Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu
530 535 540

Asn Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val
545 550 555 560

Asp Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala
565 570 575

Ala Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His
580 585 590

Phe Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln
595 600 605

Ser Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser
610 615 620

Glu Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro
625 630 635 640

Met Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala
645 650 655

Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu
660 665 670

Cys Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn
675 680 685

Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu
690 695 700

Lys Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His
705 710 715 720

```
Ala Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu
                725                 730                 735

Pro Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val
            740                 745                 750

Leu Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly
        755                 760                 765

Asp Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe
    770                 775                 780

Leu Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr
785                 790                 795                 800

Phe Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser
                805                 810                 815

Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu
            820                 825                 830

Met Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val
        835                 840                 845

Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly
    850                 855                 860

Asp Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His
865                 870                 875                 880

Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn
                885                 890                 895

Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr
            900                 905                 910

Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr
        915                 920                 925

Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr
    930                 935                 940

Arg Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu
945                 950                 955                 960

Arg Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe
                965                 970                 975
```

```
His Thr Arg Lys Ser Leu Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
            980                 985                 990

Gly Ser Gly Gly Gly Gly Ser Leu  Lys Tyr Pro Asn Ala  Ser Pro Leu
        995                 1000                1005

Leu Gly  Ser Ser Trp Gly Gly  Leu Ile His Leu Tyr  Thr Ala Thr
    1010                1015                1020

Ala Arg  Asn Ser Tyr His Leu  Gln Ile His Lys Asn  Gly His Val
    1025                1030                1035

Asp Gly  Ala Pro His Gln Thr  Ile Tyr Ser Ala Leu  Met Ile Arg
    1040                1045                1050

Ser Glu  Asp Ala Gly Phe Val  Val Ile Thr Gly Val  Met Ser Arg
    1055                1060                1065

Arg Tyr  Leu Cys Met Asp Phe  Arg Gly Asn Ile Phe  Gly Ser His
    1070                1075                1080

Tyr Phe  Asp Pro Glu Asn Cys  Arg Phe Gln His Gln  Thr Leu Glu
    1085                1090                1095

Asn Gly  Tyr Asp Val Tyr His  Ser Pro Gln Tyr His  Phe Leu Val
    1100                1105                1110

Ser Leu  Gly Arg Ala Lys Arg  Ala Phe Leu Pro Gly  Met Asn Pro
    1115                1120                1125

Pro Pro  Tyr Ser Gln Phe Leu  Ser Arg Arg Asn Glu  Ile Pro Leu
    1130                1135                1140

Ile His  Phe Asn Thr Pro Ile  Pro Arg Arg His Thr  Gln Ser Ala
    1145                1150                1155

Glu Asp  Asp Ser Glu Arg Asp  Pro Leu Asn Val Leu  Lys Pro Arg
    1160                1165                1170

Ala Arg  Met Thr Pro Ala Pro  Ala Ser Ser Ser Gln  Glu Leu Pro
    1175                1180                1185

Ser Ala  Glu Asp Asn Ser Pro  Met Ala Ser Asp Pro  Leu Gly Val
    1190                1195                1200

Val Arg  Gly Gly Arg Val Asn  Thr His Ala Gly Gly  Thr Gly Pro
    1205                1210                1215
```

```
Glu Gly  Cys Arg Pro Phe Ala  Lys Phe Ile
    1220                1225


<210>  55
<211>  1228
<212>  PRT
<213>  Homo Sapiens

<400>  55

Met Pro Ala Ser Ala Pro Pro Arg Arg Pro Arg Pro Pro Pro Pro Ser
1               5                   10                  15


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


Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro
        35                  40                  45


Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly
    50                  55                  60


Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp
65                  70                  75                  80


Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His
                85                  90                  95


Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly
            100                 105                 110


Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser
        115                 120                 125


Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val
    130                 135                 140


Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly
145                 150                 155                 160


Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu
                165                 170                 175


Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr
            180                 185                 190


His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala
        195                 200                 205
```

```
Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe
    210                 215                 220

Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro
225                 230                 235                 240

Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly
                245                 250                 255

Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu
            260                 265                 270

Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro
        275                 280                 285

Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn
    290                 295                 300

Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu
305                 310                 315                 320

Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp
                325                 330                 335

Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe
            340                 345                 350

Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala
        355                 360                 365

Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met
    370                 375                 380

Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp
385                 390                 395                 400

Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly
                405                 410                 415

Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr
            420                 425                 430

Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp
        435                 440                 445

Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe
```

450 455 460

Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp
465 470 475 480

Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe
485 490 495

Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn
500 505 510

Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val
515 520 525

Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu
530 535 540

Asn Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val
545 550 555 560

Asp Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala
565 570 575

Ala Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His
580 585 590

Phe Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln
595 600 605

Ser Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser
610 615 620

Glu Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro
625 630 635 640

Met Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala
645 650 655

Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu
660 665 670

Cys Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn
675 680 685

Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu
690 695 700

```
Lys Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His
705                 710                 715                 720

Ala Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu
                725                 730                 735

Pro Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val
            740                 745                 750

Leu Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly
        755                 760                 765

Asp Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe
    770                 775                 780

Leu Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr
785                 790                 795                 800

Phe Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser
                805                 810                 815

Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu
            820                 825                 830

Met Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val
        835                 840                 845

Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly
    850                 855                 860

Asp Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His
865                 870                 875                 880

Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn
                885                 890                 895

Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr
            900                 905                 910

Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr
        915                 920                 925

Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr
    930                 935                 940

Arg Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu
945                 950                 955                 960
```

```
Arg Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe
                965                 970                 975

His Thr Arg Lys Ser Leu Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
            980                 985                 990

Gly Ser Gly Gly Gly Gly Ser Leu  Lys Tyr Pro Asn Ala  Ser Pro Leu
        995                 1000                1005

Leu Gly  Ser Ser Trp Gly Gly  Leu Ile His Leu Tyr  Thr Ala Thr
    1010                1015                1020

Ala Arg  Asn Ser Tyr His Leu  Gln Ile His Lys Asn  Gly His Val
    1025                1030                1035

Asp Gly  Ala Pro His Gln Thr  Ile Tyr Ser Ala Leu  Met Ile Arg
    1040                1045                1050

Ser Glu  Asp Ala Gly Phe Val  Val Ile Thr Gly Val  Met Ser Arg
    1055                1060                1065

Arg Tyr  Leu Cys Met Asp Phe  Arg Gly Asn Ile Phe  Gly Ser His
    1070                1075                1080

Tyr Phe  Asp Pro Glu Asn Cys  Arg Phe Gln His Gln  Thr Leu Glu
    1085                1090                1095

Asn Gly  Tyr Asp Val Tyr His  Ser Pro Gln Tyr His  Phe Leu Val
    1100                1105                1110

Ser Leu  Gly Arg Ala Lys Arg  Ala Phe Leu Pro Gly  Met Asn Pro
    1115                1120                1125

Pro Pro  Tyr Ser Gln Phe Leu  Ser Arg Arg Asn Glu  Ile Pro Leu
    1130                1135                1140

Ile His  Phe Asn Thr Pro Ile  Pro Arg Arg His Thr  Gln Ser Ala
    1145                1150                1155

Glu Asp  Asp Ser Glu Arg Asp  Pro Leu Asn Val Leu  Lys Pro Arg
    1160                1165                1170

Ala Arg  Met Thr Pro Ala Pro  Ala Ser Cys Ser Gln  Glu Leu Pro
    1175                1180                1185

Ser Ala  Glu Asp Asn Ser Pro  Met Ala Ser Asp Pro  Leu Gly Val
    1190                1195                1200
```

```
Val Arg  Gly Gly Arg Val Asn  Thr His Ala Gly Gly  Thr Gly Pro
    1205                 1210                 1215


Glu Gly  Ser Arg Pro Phe Ala  Lys Phe Ile
    1220                 1225


<210>  56
<211>  1228
<212>  PRT
<213>  Homo Sapiens

<400>  56

Met Pro Ala Ser Ala Pro Pro Arg Arg Pro Arg Pro Pro Pro Pro Ser
1               5                  10                  15


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


Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro
        35                  40                  45


Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly
    50                  55                  60


Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp
65                  70                  75                  80


Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His
                85                  90                  95


Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly
            100                 105                 110


Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser
        115                 120                 125


Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val
    130                 135                 140


Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly
145                 150                 155                 160


Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu
                165                 170                 175


Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr
            180                 185                 190
```

```
His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala
        195                 200                 205

Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe
    210                 215                 220

Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro
225                 230                 235                 240

Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly
                245                 250                 255

Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu
            260                 265                 270

Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro
        275                 280                 285

Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn
    290                 295                 300

Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu
305                 310                 315                 320

Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp
                325                 330                 335

Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe
            340                 345                 350

Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala
        355                 360                 365

Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met
    370                 375                 380

Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp
385                 390                 395                 400

Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly
                405                 410                 415

Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr
            420                 425                 430

Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp
```

435 440 445

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

Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp
465 470 475 480

Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe
485 490 495

Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn
500 505 510

Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val
515 520 525

Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu
530 535 540

Asn Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val
545 550 555 560

Asp Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala
565 570 575

Ala Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His
580 585 590

Phe Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln
595 600 605

Ser Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser
610 615 620

Glu Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro
625 630 635 640

Met Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala
645 650 655

Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu
660 665 670

Cys Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn
675 680 685

```
Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu
    690                 695                 700

Lys Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His
705                 710                 715                 720

Ala Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu
                725                 730                 735

Pro Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val
            740                 745                 750

Leu Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly
        755                 760                 765

Asp Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe
    770                 775                 780

Leu Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr
785                 790                 795                 800

Phe Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser
                805                 810                 815

Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu
            820                 825                 830

Met Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val
        835                 840                 845

Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly
    850                 855                 860

Asp Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His
865                 870                 875                 880

Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn
                885                 890                 895

Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr
            900                 905                 910

Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr
        915                 920                 925

Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr
    930                 935                 940
```

```
Arg Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu
945                 950                 955                 960

Arg Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe
                965                 970                 975

His Thr Arg Lys Ser Leu Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
            980                 985                 990

Gly Ser Gly Gly Gly Gly Ser Leu  Lys Tyr Pro Asn Ala  Ser Pro Leu
        995                 1000                1005

Leu Gly  Ser Ser Trp Gly Gly  Leu Ile His Leu Tyr  Thr Ala Thr
    1010                1015                1020

Ala Arg  Asn Ser Tyr His Leu  Gln Ile His Lys Asn  Gly His Val
    1025                1030                1035

Asp Gly  Ala Pro His Gln Thr  Ile Tyr Ser Ala Leu  Met Ile Arg
    1040                1045                1050

Ser Glu  Asp Ala Gly Phe Val  Val Ile Thr Gly Val  Met Ser Arg
    1055                1060                1065

Arg Tyr  Leu Cys Met Asp Phe  Arg Gly Asn Ile Phe  Gly Ser His
    1070                1075                1080

Tyr Phe  Asp Pro Glu Asn Cys  Arg Phe Gln His Gln  Thr Leu Glu
    1085                1090                1095

Asn Gly  Tyr Asp Val Tyr His  Ser Pro Gln Tyr His  Phe Leu Val
    1100                1105                1110

Ser Leu  Gly Arg Ala Lys Arg  Ala Phe Leu Pro Gly  Met Asn Pro
    1115                1120                1125

Pro Pro  Tyr Ser Ala Phe Leu  Ser Arg Arg Asn Glu  Ile Pro Leu
    1130                1135                1140

Ile His  Phe Asn Thr Pro Ile  Pro Arg Arg His Thr  Gln Ser Ala
    1145                1150                1155

Glu Asp  Asp Ser Glu Arg Asp  Pro Leu Asn Val Leu  Lys Pro Arg
    1160                1165                1170

Ala Arg  Met Thr Pro Ala Pro  Ala Ser Cys Ser Gln  Glu Leu Pro
    1175                1180                1185
```

```
Ser Ala  Glu Asp Asn Ser Pro  Met Ala Ser Asp Pro  Leu Gly Val
    1190                 1195                 1200


Val Arg  Gly Gly Arg Val Asn  Thr His Ala Gly Gly  Thr Gly Pro
    1205                 1210                 1215


Glu Gly  Cys Arg Pro Phe Ala  Lys Phe Ile
    1220                 1225


<210>  57
<211>  1228
<212>  PRT
<213>  Homo Sapiens

<400>  57

Met Pro Ala Ser Ala Pro Pro Arg Arg Pro Arg Pro Pro Pro Pro Ser
1               5                   10                  15


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


Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro
        35                  40                  45


Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly
    50                  55                  60


Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp
65                  70                  75                  80


Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His
                85                  90                  95


Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly
            100                 105                 110


Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser
        115                 120                 125


Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val
    130                 135                 140


Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly
145                 150                 155                 160


Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu
                165                 170                 175
```

```
Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr
            180                 185                 190

His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala
        195                 200                 205

Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe
    210                 215                 220

Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro
225                 230                 235                 240

Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly
                245                 250                 255

Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu
            260                 265                 270

Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro
        275                 280                 285

Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn
    290                 295                 300

Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu
305                 310                 315                 320

Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp
                325                 330                 335

Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe
            340                 345                 350

Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala
        355                 360                 365

Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met
    370                 375                 380

Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp
385                 390                 395                 400

Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly
                405                 410                 415

Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr
```

```
            420                 425                 430

Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp
        435                 440                 445

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

Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp
465                 470                 475                 480

Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe
                485                 490                 495

Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn
            500                 505                 510

Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val
        515                 520                 525

Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu
    530                 535                 540

Asn Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val
545                 550                 555                 560

Asp Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala
                565                 570                 575

Ala Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His
            580                 585                 590

Phe Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln
        595                 600                 605

Ser Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser
    610                 615                 620

Glu Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro
625                 630                 635                 640

Met Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala
                645                 650                 655

Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu
            660                 665                 670
```

```
Cys Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn
        675                 680                 685

Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu
    690                 695                 700

Lys Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His
705                 710                 715                 720

Ala Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu
                725                 730                 735

Pro Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val
            740                 745                 750

Leu Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly
        755                 760                 765

Asp Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe
    770                 775                 780

Leu Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr
785                 790                 795                 800

Phe Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser
                805                 810                 815

Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu
            820                 825                 830

Met Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val
        835                 840                 845

Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly
    850                 855                 860

Asp Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His
865                 870                 875                 880

Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn
                885                 890                 895

Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr
            900                 905                 910

Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr
        915                 920                 925
```

```
Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr
    930                 935                 940

Arg Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu
945                 950                 955                 960

Arg Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe
                965                 970                 975

His Thr Arg Lys Ser Leu Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
            980                 985                 990

Gly Ser Gly Gly Gly Gly Ser Leu  Lys Tyr Pro Asn Ala  Ser Pro Leu
        995                 1000                1005

Leu Gly  Ser Ser Trp Gly Gly  Leu Ile His Leu Tyr  Thr Ala Thr
    1010                1015                1020

Ala Arg  Asn Ser Tyr His Leu  Gln Ile His Lys Asn  Gly His Val
    1025                1030                1035

Asp Gly  Ala Pro His Gln Thr  Ile Tyr Ser Ala Leu  Met Ile Arg
    1040                1045                1050

Ser Glu  Asp Ala Gly Phe Val  Val Ile Thr Gly Val  Met Ser Arg
    1055                1060                1065

Arg Tyr  Leu Cys Met Asp Phe  Arg Gly Asn Ile Phe  Gly Ser His
    1070                1075                1080

Tyr Phe  Asp Pro Glu Asn Cys  Arg Phe Gln His Gln  Thr Leu Glu
    1085                1090                1095

Asn Gly  Tyr Asp Val Tyr His  Ser Pro Gln Tyr His  Phe Leu Val
    1100                1105                1110

Ser Leu  Gly Arg Ala Lys Arg  Ala Phe Leu Pro Gly  Met Asn Pro
    1115                1120                1125

Pro Pro  Tyr Ser Gln Phe Leu  Ser Arg Arg Asn Glu  Ile Pro Leu
    1130                1135                1140

Ile His  Phe Asn Thr Pro Ile  Pro Arg Arg His Thr  Gln Ser Ala
    1145                1150                1155

Glu Asp  Asp Ser Glu Arg Asp  Pro Leu Asn Val Leu  Lys Pro Arg
    1160                1165                1170
```

```
Ala Arg  Met Thr Pro Ala Pro  Ala Ser Ser Ser Gln  Glu Leu Pro
    1175                1180                1185


Ser Ala  Glu Asp Asn Ser Pro  Met Ala Ser Asp Pro  Leu Gly Val
    1190                1195                1200


Val Arg  Gly Gly Arg Val Asn  Thr His Ala Gly Gly  Thr Gly Pro
    1205                1210                1215


Glu Gly  Ser Arg Pro Phe Ala  Lys Phe Ile
    1220                1225


<210>  58
<211>  1228
<212>  PRT
<213>  Homo Sapiens

<400>  58

Met Pro Ala Ser Ala Pro Pro Arg Arg Pro Arg Pro Pro Pro Pro Ser
1               5                   10                  15


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


Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro
        35                  40                  45


Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly
    50                  55                  60


Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp
65                  70                  75                  80


Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His
                85                  90                  95


Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly
            100                 105                 110


Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser
        115                 120                 125


Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val
    130                 135                 140


Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly
145                 150                 155                 160
```

```
Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu
                165                 170                 175

Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr
            180                 185                 190

His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala
        195                 200                 205

Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe
    210                 215                 220

Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro
225                 230                 235                 240

Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly
                245                 250                 255

Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu
            260                 265                 270

Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro
        275                 280                 285

Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn
    290                 295                 300

Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu
305                 310                 315                 320

Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp
                325                 330                 335

Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe
            340                 345                 350

Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala
        355                 360                 365

Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met
    370                 375                 380

Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp
385                 390                 395                 400

Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly
```

405 410 415

Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr
420 425 430

Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp
435 440 445

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

Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp
465 470 475 480

Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe
485 490 495

Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn
500 505 510

Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val
515 520 525

Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu
530 535 540

Asn Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val
545 550 555 560

Asp Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala
565 570 575

Ala Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His
580 585 590

Phe Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln
595 600 605

Ser Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser
610 615 620

Glu Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro
625 630 635 640

Met Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala
645 650 655

```
Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu
            660                 665                 670

Cys Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn
        675                 680                 685

Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu
    690                 695                 700

Lys Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His
705                 710                 715                 720

Ala Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu
                725                 730                 735

Pro Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val
            740                 745                 750

Leu Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly
        755                 760                 765

Asp Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe
    770                 775                 780

Leu Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr
785                 790                 795                 800

Phe Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser
                805                 810                 815

Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu
            820                 825                 830

Met Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val
        835                 840                 845

Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly
    850                 855                 860

Asp Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His
865                 870                 875                 880

Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn
                885                 890                 895

Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr
            900                 905                 910
```

```
Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr
        915                 920                 925

Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr
    930                 935                 940

Arg Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu
945                 950                 955                 960

Arg Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe
                965                 970                 975

His Thr Arg Lys Ser Leu Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
            980                 985                 990

Gly Ser Gly Gly Gly Gly Ser Leu  Lys Tyr Pro Asn Ala  Ser Pro Leu
        995                 1000                1005

Leu Gly  Ser Ser Trp Gly Gly  Leu Ile His Leu Tyr  Thr Ala Thr
    1010                1015                1020

Ala Arg  Asn Ser Tyr His Leu  Gln Ile His Lys Asn  Gly His Val
    1025                1030                1035

Asp Gly  Ala Pro His Gln Thr  Ile Tyr Ser Ala Leu  Met Ile Arg
    1040                1045                1050

Ser Glu  Asp Ala Gly Phe Val  Val Ile Thr Gly Val  Met Ser Arg
    1055                1060                1065

Arg Tyr  Leu Cys Met Asp Phe  Arg Gly Asn Ile Phe  Gly Ser His
    1070                1075                1080

Tyr Phe  Asp Pro Glu Asn Cys  Arg Phe Gln His Gln  Thr Leu Glu
    1085                1090                1095

Asn Gly  Tyr Asp Val Tyr His  Ser Pro Gln Tyr His  Phe Leu Val
    1100                1105                1110

Ser Leu  Gly Arg Ala Lys Arg  Ala Phe Leu Pro Gly  Met Asn Pro
    1115                1120                1125

Pro Pro  Tyr Ser Ala Phe Leu  Ser Arg Arg Asn Glu  Ile Pro Leu
    1130                1135                1140

Ile His  Phe Asn Thr Pro Ile  Pro Arg Arg His Thr  Gln Ser Ala
    1145                1150                1155
```

```
Glu Asp  Asp Ser Glu Arg Asp  Pro Leu Asn Val Leu  Lys Pro Arg
    1160                1165                1170


Ala Arg  Met Thr Pro Ala Pro  Ala Ser Ser Ser Gln  Glu Leu Pro
    1175                1180                1185


Ser Ala  Glu Asp Asn Ser Pro  Met Ala Ser Asp Pro  Leu Gly Val
    1190                1195                1200


Val Arg  Gly Gly Arg Val Asn  Thr His Ala Gly Gly  Thr Gly Pro
    1205                1210                1215


Glu Gly  Ser Arg Pro Phe Ala  Lys Phe Ile
    1220                1225


<210>  59
<211>  482
<212>  PRT
<213>  Homo Sapiens

<400>  59

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


Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
            20                  25                  30


Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
        35                  40                  45


Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
    50                  55                  60


Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65                  70                  75                  80


Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
                85                  90                  95


Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
            100                 105                 110


Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
        115                 120                 125


Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
    130                 135                 140
```

```
Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
145                 150                 155                 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
                165                 170                 175

His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
            180                 185                 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Ser Ser Gln
        195                 200                 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
    210                 215                 220

Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225                 230                 235                 240

Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile Gly Gly Gly Gly Ser
                245                 250                 255

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
            260                 265                 270

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

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

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

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

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

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

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
    370                 375                 380

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
```

385 390 395 400

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
405 410 415

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

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

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
450 455 460

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
465 470 475 480

Gly Lys

<210> 60
<211> 482
<212> PRT
<213> Homo Sapiens

<400> 60

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

Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
20 25 30

Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
35 40 45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
50 55 60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65 70 75 80

Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
85 90 95

Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
100 105 110

Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His

```
        115                 120                 125

Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
    130                 135                 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
145                 150                 155                 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
                165                 170                 175

His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
            180                 185                 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
        195                 200                 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
    210                 215                 220

Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225                 230                 235                 240

Pro Glu Gly Ser Arg Pro Phe Ala Lys Phe Ile Gly Gly Gly Gly Ser
                245                 250                 255

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
            260                 265                 270

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

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

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

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

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

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

```
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
    370                 375                 380

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
385                 390                 395                 400

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
                405                 410                 415

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

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

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
    450                 455                 460

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
465                 470                 475                 480

Gly Lys
```

<210> 61
<211> 482
<212> PRT
<213> Homo Sapiens

<400> 61

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

Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
            20                  25                  30

Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
        35                  40                  45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
    50                  55                  60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65                  70                  75                  80

Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
                85                  90                  95
```

```
Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
            100                 105                 110

Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
        115                 120                 125

Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
    130                 135                 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Ala Phe Leu Ser Arg
145                 150                 155                 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
                165                 170                 175

His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
            180                 185                 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
        195                 200                 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
    210                 215                 220

Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225                 230                 235                 240

Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile Gly Gly Gly Gly Ser
                245                 250                 255

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
            260                 265                 270

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

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

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

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

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
            340                 345                 350
```

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

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
    370                 375                 380

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
385                 390                 395                 400

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
                405                 410                 415

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

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

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
    450                 455                 460

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
465                 470                 475                 480

Gly Lys
```

<210> 62
<211> 482
<212> PRT
<213> Homo Sapiens

<400> 62

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

Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
            20                  25                  30

Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
        35                  40                  45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
    50                  55                  60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65                  70                  75                  80
```

```
Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
                85                  90                  95

Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
            100                 105                 110

Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
        115                 120                 125

Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
    130                 135                 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
145                 150                 155                 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
                165                 170                 175

His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
            180                 185                 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Ser Ser Gln
        195                 200                 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
    210                 215                 220

Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225                 230                 235                 240

Pro Glu Gly Ser Arg Pro Phe Ala Lys Phe Ile Gly Gly Gly Gly Ser
                245                 250                 255

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
            260                 265                 270

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

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

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

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

```
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
            340                 345                 350

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

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
    370                 375                 380

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
385                 390                 395                 400

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
                405                 410                 415

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

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

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
    450                 455                 460

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
465                 470                 475                 480

Gly Lys
```

<210> 63
<211> 482
<212> PRT
<213> Homo Sapiens

<400> 63

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

Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
            20                  25                  30

Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
        35                  40                  45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
    50                  55                  60
```

```
Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65                  70                  75                  80

Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
                85                  90                  95

Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
            100                 105                 110

Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
        115                 120                 125

Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
    130                 135                 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Ala Phe Leu Ser Arg
145                 150                 155                 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
                165                 170                 175

His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
            180                 185                 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Ser Ser Gln
        195                 200                 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
    210                 215                 220

Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225                 230                 235                 240

Pro Glu Gly Ser Arg Pro Phe Ala Lys Phe Ile Gly Gly Gly Gly Ser
                245                 250                 255

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
            260                 265                 270

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

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

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
```

305 310 315 320

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

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

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

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
370 375 380

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
385 390 395 400

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
405 410 415

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

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

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
450 455 460

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
465 470 475 480

Gly Lys

<210> 64
<211> 473
<212> PRT
<213> Homo Sapiens

<400> 64

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

Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
20 25 30

Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg

```
        35                  40                  45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
    50                  55                  60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65                  70                  75                  80

Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
                85                  90                  95

Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
            100                 105                 110

Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
        115                 120                 125

Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
    130                 135                 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
145                 150                 155                 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
                165                 170                 175

His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
            180                 185                 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Ser Ser Gln
        195                 200                 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
    210                 215                 220

Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225                 230                 235                 240

Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile Gly Gly Gly Gly Ser
                245                 250                 255

Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
            260                 265                 270

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
        275                 280                 285
```

```
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
    290                 295                 300

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
305                 310                 315                 320

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
                325                 330                 335

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
            340                 345                 350

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
        355                 360                 365

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
    370                 375                 380

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
385                 390                 395                 400

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
                405                 410                 415

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
            420                 425                 430

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
        435                 440                 445

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
    450                 455                 460

Lys Ser Leu Ser Leu Ser Pro Gly Lys
465                 470
```

<210> 65
<211> 473
<212> PRT
<213> Homo Sapiens

<400> 65

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

Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
            20                  25                  30
```

```
Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
        35                  40                  45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
    50                  55                  60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65                  70                  75                  80

Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
                85                  90                  95

Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
            100                 105                 110

Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
        115                 120                 125

Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
    130                 135                 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
145                 150                 155                 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
                165                 170                 175

His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
            180                 185                 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
        195                 200                 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
    210                 215                 220

Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225                 230                 235                 240

Pro Glu Gly Ser Arg Pro Phe Ala Lys Phe Ile Gly Gly Gly Gly Ser
                245                 250                 255

Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
            260                 265                 270

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
        275                 280                 285
```

```
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
    290                 295                 300

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
305                 310                 315                 320

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
                325                 330                 335

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
            340                 345                 350

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
        355                 360                 365

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
    370                 375                 380

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
385                 390                 395                 400

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
                405                 410                 415

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
            420                 425                 430

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
        435                 440                 445

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
    450                 455                 460

Lys Ser Leu Ser Leu Ser Pro Gly Lys
465                 470
```

<210> 66
<211> 473
<212> PRT
<213> Homo Sapiens

<400> 66

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

Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
            20                  25                  30
```

```
Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
        35                  40                  45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
    50                  55                  60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65                  70                  75                  80

Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
                85                  90                  95

Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
            100                 105                 110

Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
        115                 120                 125

Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
    130                 135                 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Ala Phe Leu Ser Arg
145                 150                 155                 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
                165                 170                 175

His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
            180                 185                 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
        195                 200                 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
    210                 215                 220

Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225                 230                 235                 240

Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile Gly Gly Gly Gly Ser
                245                 250                 255

Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
            260                 265                 270

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
        275                 280                 285
```

```
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
    290                 295                 300

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
305                 310                 315                 320

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
                325                 330                 335

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
            340                 345                 350

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
        355                 360                 365

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
    370                 375                 380

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
385                 390                 395                 400

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
                405                 410                 415

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
            420                 425                 430

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
        435                 440                 445

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
    450                 455                 460

Lys Ser Leu Ser Leu Ser Pro Gly Lys
465                 470
```

<210> 67
<211> 473
<212> PRT
<213> Homo Sapiens

<400> 67

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

Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
            20                  25                  30
```

```
Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
        35                  40                  45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
    50                  55                  60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65                  70                  75                  80

Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
                85                  90                  95

Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
            100                 105                 110

Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
        115                 120                 125

Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
    130                 135                 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
145                 150                 155                 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
                165                 170                 175

His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
            180                 185                 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Ser Ser Gln
        195                 200                 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
    210                 215                 220

Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225                 230                 235                 240

Pro Glu Gly Ser Arg Pro Phe Ala Lys Phe Ile Gly Gly Gly Gly Ser
                245                 250                 255

Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
            260                 265                 270

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
```

275 280 285

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
290 295 300

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
305 310 315 320

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
325 330 335

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
340 345 350

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
355 360 365

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
370 375 380

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
385 390 395 400

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
405 410 415

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
420 425 430

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
435 440 445

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
450 455 460

Lys Ser Leu Ser Leu Ser Pro Gly Lys
465 470

<210> 68
<211> 473
<212> PRT
<213> Homo Sapiens

<400> 68

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

Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu

```
            20                  25                  30

Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
        35                  40                  45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
    50                  55                  60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65                  70                  75                  80

Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
                85                  90                  95

Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
            100                 105                 110

Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
        115                 120                 125

Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
    130                 135                 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Ala Phe Leu Ser Arg
145                 150                 155                 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
                165                 170                 175

His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
            180                 185                 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Ser Ser Gln
        195                 200                 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
    210                 215                 220

Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225                 230                 235                 240

Pro Glu Gly Ser Arg Pro Phe Ala Lys Phe Ile Gly Gly Gly Gly Ser
                245                 250                 255

Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
            260                 265                 270
```

```
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
        275                 280                 285


Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
    290                 295                 300


Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
305                 310                 315                 320


Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
                325                 330                 335


Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
            340                 345                 350


Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
        355                 360                 365


Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
    370                 375                 380


Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
385                 390                 395                 400


Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
                405                 410                 415


Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
            420                 425                 430


Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
        435                 440                 445


Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
    450                 455                 460


Lys Ser Leu Ser Leu Ser Pro Gly Lys
465                 470


<210>  69
<211>  251
<212>  PRT
<213>  Homo Sapiens

<400>  69

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

```
Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
            20                  25                  30

Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
        35                  40                  45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
    50                  55                  60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65                  70                  75                  80

Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
                85                  90                  95

Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
            100                 105                 110

Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
        115                 120                 125

Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
    130                 135                 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
145                 150                 155                 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
                165                 170                 175

His Thr Arg Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
            180                 185                 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
        195                 200                 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
    210                 215                 220

Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225                 230                 235                 240

Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile
                245                 250
```

<210> 70
<211> 251
<212> PRT

<213> Macaca mulatta

<400> 70

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

Cys Ser Met Ser Val Ile Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
            20                  25                  30

Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
        35                  40                  45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
    50                  55                  60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65                  70                  75                  80

Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
                85                  90                  95

Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asn Pro Glu Asn
            100                 105                 110

Cys Arg Phe Arg His Trp Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
        115                 120                 125

Ser Pro Gln His His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
    130                 135                 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
145                 150                 155                 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Arg Pro Arg Arg
                165                 170                 175

His Thr Arg Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
            180                 185                 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
        195                 200                 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Val Ala Ser Asp Pro Leu
    210                 215                 220

Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225                 230                 235                 240
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Pro Glu Ala Cys Arg Pro Phe Pro Lys Phe Ile
245 250

<210> 71
<211> 245
<212> PRT
<213> Bos taurus

<400> 71

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

Val Gln Ala Tyr Pro Asn Ser Ser Pro Leu Leu Gly Ser Ser Trp Gly
20 25 30

Gly Leu Thr His Leu Tyr Thr Ala Thr Ala Arg Asn Ser Tyr His Leu
35 40 45

Gln Ile His Gly Asp Gly His Val Asp Gly Ser Pro Gln Gln Thr Val
50 55 60

Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala Gly Phe Val Val Ile
65 70 75 80

Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met Asp Phe Thr Gly Asn
85 90 95

Ile Phe Gly Ser His His Phe Ser Pro Glu Ser Cys Arg Phe Arg Gln
100 105 110

Arg Thr Leu Glu Asn Gly Tyr Asp Val Tyr His Ser Pro Gln His Arg
115 120 125

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

Asn Pro Pro Pro Tyr Ala Gln Phe Leu Ser Arg Arg Asn Glu Ile Pro
145 150 155 160

Leu Pro His Phe Ala Ala Thr Ala Arg Pro Arg Arg His Thr Arg Ser
165 170 175

Ala His Asp Ser Gly Asp Pro Leu Ser Val Leu Lys Pro Arg Ala Arg
180 185 190

Ala Thr Pro Val Pro Ala Ala Cys Ser Gln Glu Leu Pro Ser Ala Glu
195 200 205

```
Asp Ser Gly Pro Ala Ala Ser Asp Pro Leu Gly Val Leu Arg Gly His
    210                 215                 220

Arg Leu Asp Val Arg Ala Gly Ser Ala Gly Ala Glu Arg Cys Arg Pro
225                 230                 235                 240

Phe Pro Gly Phe Ala
                245
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<210> 72
<211> 251
<212> PRT
<213> Mus musculus

<400> 72

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Met Leu Gly Thr Cys Leu Arg Leu Leu Val Gly Val Leu Cys Thr Val
1               5                   10                  15

Cys Ser Leu Gly Thr Ala Arg Ala Tyr Pro Asp Thr Ser Pro Leu Leu
            20                  25                  30

Gly Ser Asn Trp Gly Ser Leu Thr His Leu Tyr Thr Ala Thr Ala Arg
        35                  40                  45

Thr Ser Tyr His Leu Gln Ile His Arg Asp Gly His Val Asp Gly Thr
    50                  55                  60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Thr Ser Glu Asp Ala
65                  70                  75                  80

Gly Ser Val Val Ile Thr Gly Ala Met Thr Arg Arg Phe Leu Cys Met
                85                  90                  95

Asp Leu His Gly Asn Ile Phe Gly Ser Leu His Phe Ser Pro Glu Asn
            100                 105                 110

Cys Lys Phe Arg Gln Trp Thr Leu Glu Asn Gly Tyr Asp Val Tyr Leu
        115                 120                 125

Ser Gln Lys His His Tyr Leu Val Ser Leu Gly Arg Ala Lys Arg Ile
    130                 135                 140

Phe Gln Pro Gly Thr Asn Pro Pro Pro Phe Ser Gln Phe Leu Ala Arg
145                 150                 155                 160

Arg Asn Glu Val Pro Leu Leu His Phe Tyr Thr Val Arg Pro Arg Arg
                165                 170                 175
```

```
His Thr Arg Ser Ala Glu Asp Pro Pro Glu Arg Asp Pro Leu Asn Val
            180                 185                 190


Leu Lys Pro Arg Pro Arg Ala Thr Pro Val Pro Val Ser Cys Ser Arg
        195                 200                 205


Glu Leu Pro Ser Ala Glu Glu Gly Gly Pro Ala Ala Ser Asp Pro Leu
    210                 215                 220


Gly Val Leu Arg Arg Gly Arg Gly Asp Ala Arg Gly Gly Ala Gly Gly
225                 230                 235                 240


Ala Asp Arg Cys Arg Pro Phe Pro Arg Phe Val
                245                 250


<210>  73
<211>  251
<212>  PRT
<213>  Rattus norvegicus

<400>  73

Met Leu Gly Ala Cys Leu Arg Leu Leu Val Gly Ala Leu Cys Thr Val
1               5                   10                  15


Cys Ser Leu Gly Thr Ala Arg Ala Tyr Ser Asp Thr Ser Pro Leu Leu
            20                  25                  30


Gly Ser Asn Trp Gly Ser Leu Thr His Leu Tyr Thr Ala Thr Ala Arg
        35                  40                  45


Asn Ser Tyr His Leu Gln Ile His Arg Asp Gly His Val Asp Gly Thr
    50                  55                  60


Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Thr Ser Glu Asp Ala
65                  70                  75                  80


Gly Ser Val Val Ile Ile Gly Ala Met Thr Arg Arg Phe Leu Cys Met
                85                  90                  95


Asp Leu Arg Gly Asn Ile Phe Gly Ser Tyr His Phe Ser Pro Glu Asn
            100                 105                 110


Cys Arg Phe Arg Gln Trp Thr Leu Glu Asn Gly Tyr Asp Val Tyr Leu
        115                 120                 125


Ser Pro Lys His His Tyr Leu Val Ser Leu Gly Arg Ser Lys Arg Ile
    130                 135                 140
```

```
Phe Gln Pro Gly Thr Asn Pro Pro Pro Phe Ser Gln Phe Leu Ala Arg
145                 150                 155                 160

Arg Asn Glu Val Pro Leu Leu His Phe Tyr Thr Ala Arg Pro Arg Arg
                165                 170                 175

His Thr Arg Ser Ala Glu Asp Pro Pro Glu Arg Asp Pro Leu Asn Val
            180                 185                 190

Leu Lys Pro Arg Pro Arg Ala Thr Pro Ile Pro Val Ser Cys Ser Arg
        195                 200                 205

Glu Leu Pro Ser Ala Glu Glu Gly Gly Pro Ala Ala Ser Asp Pro Leu
    210                 215                 220

Gly Val Leu Arg Arg Gly Arg Gly Asp Ala Arg Arg Gly Ala Gly Gly
225                 230                 235                 240

Thr Asp Arg Cys Arg Pro Phe Pro Arg Phe Val
                245                 250
```