IL-1 ANTAGONIST FORMULATIONS

BACKGROUND OF INVENTION

Field of the Invention

[0001] The present invention is directed to pharmaceutical formulations comprising agents capable of inhibiting interleukin-1 (IL-1), and to methods for making and using such formulations.

Statement of Related Art

[0002] Interleukin-1 (IL-1) antagonists capable of blocking or inhibiting the biological action of IL-1, have been described. An example IL-1 antagonist, an IL-1 trap, is described in U.S. Patent Publication No. 2003/0143697, published 31 July 2003. An IL-1 trap is an IL-1-specific fusion protein comprising two IL-1 receptor components and a multimerizing component.

[0003] Lyophilization (freeze drying under controlled conditions) is commonly used for long term storage of proteins. The lyophilized protein is substantially resistant to degradation, aggregation, oxidation, and other degenerative processes while in the freeze dried state (see, for example, U.S. 6,436,897).

BRIEF SUMMARY OF THE INVENTION

[0004] Stable formulations of an interleukin-1 (IL-1) antagonist are herein provided. The pharmaceutically acceptable formulations of the invention comprise an IL-1 trap with a pharmaceutically acceptable carrier. In specific embodiments, liquid and freeze-dried, or lyophilized formulations are provided.

[0005] In a first example aspect, the invention features a pre-lyophilization formulation of an interleukin-1 (IL-1) antagonist, comprising an IL-1 protein antagonist capable of binding to and inhibiting the biological action of IL-1, a buffer, an organic co-solvent or bulking agent, and one or more lyoprotectants. In a specific embodiment, the IL-1 antagonist is a fusion protein capable of binding to IL-1, the buffer is histidine, the organic co-solvent or bulking agent is PEG, and the lyoprotectant(s) is at least one of glycine, arginine, and sucrose. In one embodiment, the pre-lyophilized formulation of the invention does not contain a preservative.

[0006] In one embodiment of the pre-lyophilization formulation of the invention, the formulation comprises 5-100 mM histidine, 0.5-3.0% PEG, 0.25-3.0% glycine, 5-50 mM arginine, 0.5-30.0% sucrose, and 5-50 mg/ml of an IL-1 antagonist, at a pH of about 6.5. In one embodiment, the pre-lyophilization formulation may further comprise up to 5 mM citrate and/or 0.003-0.005% polysorbate. The polysorbate present may be, for example, polysorbate 20 or 80.

[0007] In a more specific embodiment, the pre-lyophilization formulation of an IL-1 antagonist comprises about 20 mM histidine, about 1.5% PEG 3350, about 0.5% glycine, about 25 mM

arginine, about 1.0% sucrose, and about 40 mg/ml IL-1 trap, at a pH of about 6.5. In a specific embodiment, the IL-1 antagonist is an IL-1 trap fusion protein as shown in SEQ ID NO:2, 4, 6, 8, 10, 12,14, 16, 18, 20, 22, 24, 26. More preferably, the IL-1 trap is the trap shown in SEQ ID NO:10.

[0008] In a preferred embodiment, the pre-lyophilization IL-1 antagonist formulation consists essentially of about 20 mM histidine, about 1.5% PEG 3350, about 0.5% glycine, about 25 mM arginine, about 1.0% sucrose, and about 40 mg/ml of the IL-1 fusion protein having the sequence of SEQ ID NO:10, at a pH of about 6.5. Citrate (less than or equal to about 0.15 mM) and polysorbate (less than or equal to about 0.005%) may be present.

[0009] In a second aspect, the invention features a pre-lyophilization IL-1 antagonist formulation that consists essentially of about 20 mM histidine, about 1.5% PEG 3350, about 0.5% glycine, about 25 mM arginine, about 1.0% sucrose, and about 40 mg/ml of the IL-1 fusion protein having the sequence of SEQ ID NO:10, at a pH of about 6.5, wherein the pre-lyophilization formulation does not contain a preservative, a phosphate buffer, more than trace amounts of NaCl, and/or more than 1.5% sucrose. Citrate may be present in amounts of less than about 0.15 mM and up to about 0.005-0.01% polysorbate 20 may also be present.

[0010] In a third aspect, the invention features a method of producing a lyophilized formulation of an IL-1 antagonist, comprising subjecting the pre-lyophilization IL-1 antagonist formulation of the invention to lyophilization to generate a lyophilized IL-1 antagonist formulation. The lyophilized formulation may be lyophilized by any method known in the art for lyophilizing a liquid.

[0011] In a fourth related aspect, the invention features a method of producing a reconstituted lyophilized formulation of an IL-1 antagonist, comprising reconstituting the lyophilized formulation of the invention to a reconstituted formulation. In one embodiment, the reconstituted formulation is twice the concentration of the pre-lyophilized formulation, e.g., the method of the invention comprises: (a) producing a pre-lyophilization formulation of an IL-1 antagonist consisting of about 20 mM histidine, about 1.5% PEG 3350, about 0.5% glycine, about 25 mM arginine, about 1.0% sucrose, and about 40 mg/ml of an IL-1 protein antagonist, at a pH of about 6.5; (b) subjecting the pre-lyophilized formulation of step (a) to lyophilization; and (c) reconstituting the lyophilized formulation of step (b) to a composition consisting of about 40 mM histidine, about 3% PEG 3350, about 1% glycine, about 50 mM arginine, about 2.0% sucrose, and about 80 mg/ml of the IL-1 protein antagonist, wherein the reconstituted formulation may further contain about 0.2 mM citrate and/or about 0.008% polysorbate 20. In a specific embodiment, the IL-1 antagonist is an IL-1 trap fusion protein as shown in SEQ ID NO:2, 4, 6, 8, 10, 12,14, 16, 18, 20, 22, 24, 26. More preferably, the IL-1 trap is the trap shown in SEQ ID NO:10. In separate embodiments, the reconstituted formulation is 3 times the concentration of the pre-lyophilized formulation, e.g., a 20 mg IL-1 antagonist protein/ml pre-lyophilization

formulation is reconstituted to a final formulation of 60 mg IL-1 antagonist protein/ml. Generally, the lyophilized formulation is reconstituted with sterile water suitable for injection. In one embodiment, the reconstitution liquid may be bacteriostatic water.

[0012] In specific embodiments of the method of producing a reconstituted lyophilized formulation, a pre-lyophilization solution is present in a vial as a 40 mg IL-1 antagonist protein per ml solution of pre-lyophilization formulation, which is lyophilized and reconstituted to an 80 mg/ml solution. In another embodiment, a 20 mg/ml pre-lyophilization solution is lyophilized and reconstituted to a 40 mg/ml solution. In another embodiment, a 25 mg/ml pre-lyophilization solution is lyophilized and reconstituted to a 50 mg/ml solution. In another embodiment, a 12.5 mg/ml pre-lyophilization solution is lyophilized and reconstituted to a 25 mg/ml solution. In another embodiment, a 12.5 mg/ml pre-lyophilization solution is lyophilized and reconstituted to a 50 mg/ml solution. In another embodiment, a 25 mg/ml pre-lyophilization solution is lyophilized and reconstituted to a 75 mg/ml solution. In another embodiment, a 40 mg/ml pre-lyophilization solution is lyophilized and reconstituted to a 120 mg/ml solution. In another embodiment, a 40 mg/ml pre-lyophilization solution is lyophilized and reconstituted to a 20 mg/ml solution. Preferably, the reconstituted lyophilized formulation does not contain a preservative. In another embodiment, the reconstituted formulation includes up to 30% sucrose and one or more preservatives.

[0013] In a fifth aspect, the invention features a stable liquid formulation of an IL-1 antagonist, comprising an IL-1 antagonist protein capable of binding to and inhibiting the biological action of IL-1, a buffer, an organic co-solvent, and one or more thermal stabilizers. In a specific embodiment, the IL-1 antagonist is an IL-1 trap fusion protein as shown in SEQ ID NO:2, 4, 6, 8, 10, 12,14, 16, 18, 20, 22, 24, 26. More preferably, the IL-1 trap is the trap shown in SEQ ID NO:10. In one embodiment, the buffer is a phosphate buffer. In one embodiment, the organic co-solvent agent is PEG, preferably PEG 3350. In one embodiment, the thermal stabilizers are NaCl and/or sucrose. More preferably, the thermal stabilizers are both NaCl and sucrose.

[0014] In a specific embodiment, the stable liquid formulation of an IL-1 antagonist comprises 5-100 mM phosphate buffer, 0.5-3% PEG, 25-150 mM NaCl, 5-30% sucrose, 10-500 mg/ml of an IL-1 trap protein, at a pH of about 6-6.5. In a more specific embodiment, the stable liquid formulation of an IL-1 antagonist comprises 10 mM phosphate buffer, 3% PEG 3350, 50 mM NaCl, 5-20% sucrose, 12.5-50 mg/ml of an IL-1 trap protein, at a pH of about 6-6.5. Additionally, low or trace amounts of a citrate buffer or polysorbate may be present. The stable liquid formulation of the IL-1 antagonist of the invention exhibits little or no precipitation as determined by visual inspection after storage of a 50 mg/ml IL-1 trap formulation for up to about 29 months at 5°C. Further, little or no aggregation is observed as determine by size-exclusion chromatography, e.g., HPLC, after storage of a 50 mg/ml IL-1 trap formulation for up to about 24 months at 5°C.

[0015] Other objects and advantages will become apparent from a review of the ensuing detailed description.

DETAILED DESCRIPTION OF THE INVENTION

[0016] The present invention is not limited to particular methods, and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting unless indicated, since the scope of the present invention will be limited only by the appended claims.

[0017] As used in this specification and the appended claims, the singular forms "a", "an", and "the" include plural references unless the context clearly dictates otherwise. Thus for example, references to "a method" include one or more methods, and/or steps of the type described herein and/or which will become apparent to those persons skilled in the art upon reading this disclosure.

[0018] Unless stated otherwise, all technical and scientific terms and phrases used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described.

General Description

[0019] Safe handling and administration of formulations comprising proteins represent significant challenges to pharmaceutical formulators. Proteins possess unique chemical and physical properties that present stability problems: a variety of degradation pathways exist for proteins, implicating both chemical and physical instability. Chemical instability includes deamination, aggregation, clipping of the peptide backbone, and oxidation of methionine residues. Physical instability encompasses many phenomena, including, for example, aggregation.

[0020] Chemical and physical stability can be promoted by removing water from the protein. Lyophilization (freeze-drying under controlled conditions) is commonly used for long-term storage of proteins. The lyophilized protein is substantially resistant to degradation, aggregation, oxidation, and other degenerative processes while in the freeze-dried state. The lyophilized protein is normally reconstituted with water optionally containing a bacteriostatic preservative (e.g., benzyl alcohol) prior to administration.

Definitions

[0021] By the term "therapeutically or pharmaceutically effective dose" is meant a dose that produces the desired effect for which it is administered. The exact dose will depend on the

purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, for example, Lloyd (1999) The Art, Science and Technology of Pharmaceutical Compounding).

[0022] By the term "blocker", "inhibitor", or "antagonist" is meant a substance that retards or prevents a chemical or physiological reaction or response. Common blockers or inhibitors include, but are not limited to, antisense molecules, antibodies, antagonists and their derivatives.

[0023] The term "pharmaceutically acceptable" includes approval by a regulatory agency of the federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans.

[0024] The term "carrier" includes a diluent, adjuvant, excipient, or vehicle with which a composition is administered. Carriers can include sterile liquids, such as, for example, water and oils, including oils of petroleum, animal, vegetable or synthetic origin, such as, for example, peanut oil, soybean oil, mineral oil, sesame oil and the like.

[0025] The term "excipient" includes a non-therapeutic agent added to a pharmaceutical composition to provide a desired consistency or stabilizing effect. Suitable pharmaceutical excipients include, for example, 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.

[0026] The term "lyophilized" or "freeze-dried" includes a state of a substance that has been subjected to a drying procedure such as lyophilization, where at least 50% of moisture has been removed.

[0027] The phrase "bulking agent" includes a compound that is pharmaceutically acceptable and that adds bulk to a lyo cake. Generally, acceptable bulking agents known to the art include, for example, carbohydrates, including simple sugars such as dextrose, ribose, fructose and the like, alcohol sugars such as mannitol, inositol and sorbitol, disaccharides including trehalose, sucrose and lactose, naturally occurring polymers such as starch, dextrans, chitosan, hyaluronate, proteins (e.g., gelatin and serum albumin), glycogen, and synthetic monomers and polymers. In the formulations of the invention, PEG 3350 is an organic co-solvent which is used to stabilize the IL-1 protein antagonist when agitated, mixed, or handled, and as a bulking agent to help produce an acceptable bulk.

[0028] The term "lyoprotectant" includes a substance that may be added to a freeze-dried or lyophilized formulation to help maintain protein structure when freeze-dried or lyophilized.

[0029] A "preservative" includes a bacteriostatic, bacteriocidal, fungistatic or fungicidal compound that is generally added to formulations to retard or eliminate growth of bacteria or other contaminating microorganisms in the formulations. Preservatives include, for example, benzyl alcohol, phenol, benzalkonium chloride, m-cresol, thimerosol, chlorobutanol,

methylparaben, propylparaben and the like. Other examples of pharmaceutically acceptable preservatives can be found in the USP.

IL-1 Antagonists

[0030] An IL-1 antagonist is a compound capable of blocking or inhibiting the biological action of IL-1, including fusion proteins capable of trapping IL-1, such as an IL-1 trap. In a preferred embodiment, the IL-1 trap is an IL-1-specific fusion protein comprising two IL-1 receptor components and a multimerizing component, for example, an IL-1 trap described in U.S. Patent Publication No. 2003/0143697, published 31 July 2003. In a specific embodiment, the IL-1 trap is the fusion protein shown in SEQ ID NO:2, 4, 6, 8, 10, 12,14, 16, 18, 20, 22, 24, 26. A preferred IL-1 trap is shown in SEQ ID NO:10. The invention encompasses the use of an IL-1 trap substantially identical to the protein of SEQ ID NO: 2, 4, 6, 8, 10, 12,14, 16, 18, 20, 22, 24, 26, that is, a protein having at least 95% identity, preferably at least 97% identity, and more preferably at least 98% identity to the protein of SEQ ID NO: 2, 4, 6, 8, 10, 12,14, 16, 18, 20, 22, 24, 26 and capable of binding and inhibiting IL-1. Further, in specific embodiments, the IL-1 antagonist is a modified IL-1 trap comprising one or more receptor components and one or more immunoglobulin-derived components specific for IL-1 and/or an IL-1 receptor. In another embodiment, the IL-1 antagonist is a modified IL-1 trap comprising one or more immunoglobulin-derived components specific for IL-1 and/or an IL-1 receptor.

[0031] The IL-1 trap of the methods and formulations of the invention can be prepared by any suitable method known in the art, or that comes to be known, that is useful in preparing an IL-1 trap. The IL-1 trap is preferably substantially free of protein contaminants at the time it is used to prepare the pharmaceutically acceptable formulation. By "substantially free of protein contaminants" is meant, preferably, that at least 90 % of the weight of protein of an IL-1 trap preparation used for making a formulation comprising an IL-1 trap is IL-1 trap protein, more preferably at least 95%, most preferably at least 99%. The IL-1 trap is preferably substantially free of aggregates. "Substantially free of aggregates" means that at least 90% of the weight of IL-1 trap protein is not present in an aggregate at the time the IL-1 trap is used to prepare the pharmaceutically effective formulation. The IL-1 trap of the methods and formulations of the invention may contain low or trace amounts of compounds as a results of the purification process, for example, low or trace amounts of citrate and/or polysorbate. In one embodiment of the pre-lyophilization formulation of the invention containing about 40 mg of IL-1 trap/ml, citrate may be present at a concentration of about 0.1 mM and/or polysorbate may be present at a concentration of about 0.004%. If the pre-lyophilization formulation is reconstituted after lyophilization to half of the original volume (e.g., 80 mg/ml of IL-1 trap), the resulting concentrations may be 0.2 mM citrate and/or 0.008% polysorbate. If the pre-lyophilization

formulation is reconstituted after lyophilization to a third of the original volume (e.g., 120 mg/ml of IL-1 trap), the resulting concentrations may be 0.6 mM citrate and/or 0.012% polysorbate.

Lyophilization and Lyophilized Formulations

[0032] In one aspect of the invention, a pharmaceutically acceptable formulation comprising an IL-1 trap is provided, wherein the formulation is a freeze-dried or lyophilized formulation. Preferably, the freeze-dried or lyophilized formulation comprises a pharmaceutically effective amount of an IL-1 trap. Lyophilized formulations can be reconstituted into solutions, suspensions, emulsions, or any other suitable form for administration or use. Lyophilized formulations are typically first prepared as liquids, then frozen and lyophilized. The total liquid volume before lyophilization can be less, equal to, or more than, the final reconstituted volume of the lyophilized formulation. The lyophilization process is well known to those of ordinary skill in the art, and typically includes sublimation of water from a frozen formulation under controlled conditions.

[0033] Lyophilized formulations can be stored at a wide range of temperatures. Lyophilized formulations may be stored at or below 30°C, for example, refrigerated at 4°C, or at room temperature (e.g., approximately 25°C). Preferably, lyophilized formulations are stored below about 25°C, more preferably, at about 4-20°C; below about 4°C; below about -20°C; about -40°C; or about -70°C.

[0034] Lyophilized formulations are typically reconstituted for use by addition of an aqueous solution to dissolve the lyophilized formulation. A wide variety of aqueous solutions can be used to reconstitute a lyophilized formulation. Preferably, lyophilized formulations are reconstituted using water. Lyophilized formulations are preferably reconstituted with a solution consisting essentially of water (e.g., USP WFI, or water for injection) or bacteriostatic water (e.g., USP WFI with 0.9% benzyl alcohol). However, solutions comprising buffers and/or excipients and/or one or more pharmacetically acceptable carries can also be used.

[0035] Freeze-dried or lyophilized formulations are typically prepared from liquids, that is, from solutions, suspensions, emulsions, and the like. Thus, the liquid that is to undergo freeze-drying or lyophilization preferably comprises all components desired in a final reconstituted liquid formulation. As a result, when reconstituted, the freeze-dried or lyophilized formulation will render a desired liquid formulation upon reconstitution. A preferred liquid formulation used to generate a freeze-dried or lyophilized formulation comprises an IL-1 trap in a pharmaceutically effective amount, a buffer, a stabilizer, and a bulking agent. Freeze-dried or lyophilized formulations preferably comprise histidine, since histidine, in comparison to phosphate, is more effective at stabilizing the IL-1 trap when the IL-1 trap is lyophilized. Organic cosolvents, such as PEG 3350, are used to stabilize the IL-1 trap when agitated, mixed, or handled. A lyoprotectant is preferably used in freeze-dried or lyophilized formulations. Lyoprotectants help

to maintain the secondary structure of proteins when freeze-dried or lyophilized. Three preferred example lyoprotectants are glycine, arginine, and sucrose, which are preferably used together.

Stable Liquid Formulations

[0036] In one aspect, the invention provides a stable pharmaceutically acceptable formulation comprising an IL-1 trap, wherein the formulation is a liquid formulation. Preferably, the liquid formulation comprises a pharmaceutically effective amount of an IL-1 trap. The formulation can also comprise one or more pharmaceutically acceptable carriers, buffers, bulking agents, stabilizers, preservatives, and/or excipients. An example of a pharmaceutically acceptable liquid formulation comprising an IL-1 trap comprises an IL-1 trap in a pharmaceutically effective amount, a buffer, a co-solvent, and one or more stabilizers.

[0037] A preferred liquid formulation comprises phosphate buffer, an organic co-solvent, and one or more thermal stabilizers to minimize formation of aggregates and low molecular weight products when stored, and about 12.5 mg/ml to about 50 mg/ml IL-1 trap, wherein the formulation is from about pH 6.0 to about pH 6.75. A more preferred liquid formulation comprises 10 mM phosphate buffer, 3% PEG, 50 mM NaCl, 5-20% sucrose, and 10-100 mg/ml IL-1 trap, wherein the formulation is at a pH of about 6.0 to about 6.5. Although either NaCl or sucrose can be used as a stabilizer, a combination of NaCl and sucrose has been established to stabilize the IL-1 trap more effectively than either individual stabilizer alone. Preferably, PEG is PEG 3350, which has been established to enhance IL-1 trap stability.

[0038] Table 1 shows the percent of native IL-1 trap or percent aggregated IL-1 trap in samples containing either 5 or 20% sucrose as determined over a period of up to 24 months when incubated at 5°C. In the presence of 20% sucrose, the native (non-aggregated) form of IL-1 trap dropped from 92.6% at day 0 to 88.9% at 24 months and the percentage aggregate increased from 2.3% to 3.4% over the same time period. The 5% sucrose formulation had a native (non-aggregated) form of IL-1 trap dropped from 92.4% at day 0 to 86.9% at 24 months and the percentage aggregate increased from 2.6% to 3.6% over the same time period.

TABLE 1

Incubation time at 5 °C (months)	% Native (20% sucrose)	% Aggregate (20% sucrose)	% Native (5% sucrose)	% Aggregate (5% sucrose)
0	92.6	2.3	92.4	2.6
1.0	92.6	2.4	92.5	2.5
2.0	91.9	2.6	91.5	2.9
6.0	91.6	2.8	91.0	2.9
18	91.8	3.2	90.7	3.6
21.0	91.3	2.9	89.5	3.6
24.0	88.9	3.4	86.9	3.6

[0039] Table 2 shows the percent of native IL-1 trap in samples containing either 0, 5 or 20% sucrose as determined over a period of up to 2.9 months when incubated at 5°C (50 mg/ml IL-1 trap, 10 mM Phosphate, 0.2% polysorbate-20, 50 or 135 (with 0% sucrose) mM NaCl, pH 6.5. In the presence of 0% sucrose, the native (non-aggregated) form of IL-1 trap dropped from 96.4% at day 0 to 0.5% at 2.9 months. The 5% sucrose formulation had a native (non-aggregated) form of IL-1 trap which dropped from 96.5% at day 0 to 39.2% at 2.9 months. The 20% sucrose formulation had a native (non-aggregated) form of IL-1 trap which dropped from 96.4% at day 0 to 95.3% at 2.9 months.

TABLE 2

Incubation Time (months)	% Native (0% Sucrose)	% Native (5% sucrose)	% Native (20% sucrose)
0	96.4	96.5	96.4
1	96.7	89.3	96.2
2.9	0.5	39.2	95.3

[0040] Formulations, whether liquid or freeze-dried and lyophilized, can be stored in an oxygen-deprived environment. Oxygen-deprived environments can be generated by storing the formulations under an inert gas such as, for example, argon, nitrogen, or helium.

[0041] The stability of pre-lyophilized and lyophilized formulations was determined. A pre-lyophilized formulation containing 40 mg/ml IL-1 trap (SEQ ID NO:10), 20 mM histidine, 1.5% PEG-3350, 1% sucrose, 0.5% glycine, 25 mM arginine-HCl, pH 6.5 was incubated at 5°C for 0-52 weeks. As shown in Table 3, the native (non-aggregated) form of IL-1 decreased from 94.9 (0 weeks) to 92.3 (52 weeks), and the percent aggregate increased from 1% to 1.8% in the same time period.

TABLE 3

Incubation time (weeks at 5°C)	% Native	% Aggregate
0	94.9	1.0
4	94.3	1.3
12	93.5	1.7
24	93.3	1.5
36	92.6	1.5
52	92.3	1.8

[0042] The stability of a lyophilized formulation containing 40 mg/ml IL-1 trap (SEQ ID NO:10), 20 mM histidine, 1.5% PEG-3350, 1% sucrose, 0.5% glycine, 25 mM arginine-hcl, pH 6.5 (pre-lyophilized concentrations) was incubated at 25°C for 0-56 weeks. As shown in Table 4, the native (non-aggregated) form of IL-1 decreased from 97.0 (0 weeks) to 94.0 (56 weeks), and the

percent aggregate increased from 0.8% to 3.6% in the same time period.

TABLE 4

Incubation time (weeks at 25°C)	% Native	% Aggregate
0	97.0	0.8
3.9	96.3	1.4
6.1	95.5	1.5
12.3	95.4	1.9
25.7	94.7	2.2
39.3	94.4	2.9
56	94.0	3.6

[0043] Although the foregoing invention has been described in some detail by way of illustration and examples, it will be readily apparent to those of ordinary skill in the art that certain changes and modifications may be made to the teachings of the invention without departing from the spirit or scope of the appended claims.

CLAIMS

1. A stable formulation of an interleukin-1 (IL-1) antagonist suitable for lyophilization, comprising an IL-1 protein antagonist capable of binding and inhibiting the biological action of IL-1, wherein the IL-1 protein antagonist comprises the amino acid sequence of SEQ ID NO:10, and the formulation comprises 5 to 100 mM histidine, 0.5 to 3.0% PEG, 0.25 to 3% glycine, 5 to 50 mM arginine, and 0.5 to 30% sucrose.

2. The formulation of claim 1, wherein the IL-1 antagonist is a dimer (trap) comprising two fusion proteins, wherein the dimer is capable of binding IL-1.

3. The formulation of claim 1 comprising 5-50 mg/ml of the IL-1 protein antagonist.

4. The formulation of claim 3, comprising about 20 mM histidine, about 1.5% PEG 3350, about 0.5% glycine, about 25 mM arginine, about 1.0% sucrose, and about 40 mg/ml IL-1 dimer (trap).

5. A formulation of an interleukin-1 (IL-1) antagonist suitable for lyophilization, comprising an IL-1 protein antagonist capable of binding and inhibiting the biological action of IL-1, about 20 mM histidine, about 1.5% PEG 3350, about 0.5% glycine, about 25 mM arginine, about 1.0% sucrose, and about 5 to 50 mg/ml of an IL-1 antagonist, wherein the IL-1 antagonist is a dimer comprising two fusion proteins comprising an amino acid sequence of SEQ ID NO:10.

6. A method of producing a reconstituted formulation solution of an IL-1 antagonist, comprising: (a) subjecting the formulation of claim 1 to lyophilization to form a lyophilized formulation; and (b) reconstituting the lyophilized formulation of step (a) to a reconstituted formulation solution comprising about 20-120 mg/ml of the IL-1 antagonist.

7. The method of claim 6, wherein the IL-1 antagonist is an IL-1 trap comprising two fusion proteins each having the amino acid sequence SEQ ID NO:10.

8. The method of claim 6, wherein the formulation suitable for lyophilization comprises about 20 mM histidine, about 1.5% PEG 3350, about 0.5% glycine, about 25 mM arginine, and about 1.0% sucrose, pH about 6.5.

9. The method of claim 6, wherein the formulation suitable for lyophilization comprises 40 mg IL-1 antagonist/ml and the reconstituted lyophilized formulation solution comprises 80 to 120 mg IL-1 antagonist/ml.

10. A stable liquid formulation of an IL-1 antagonist, comprising an IL-1 protein antagonist capable of binding and inhibiting the biological action of IL-1 comprising the amino acid sequence of SEQ ID NO:10, 5-100 mM phosphate buffer, 0-3% PEG 3350, 25-150 mM NaCl, and 5-30% sucrose.

11. The stable liquid formulation of claim 10, wherein the IL-1 antagonist is an IL-1 trap comprising two fusion proteins, each fusion protein comprising the amino acid sequence of SEQ ID NO:10.

12. The stable liquid formulation of claim 10, comprising 10-120 mg/ml of the IL-1 protein antagonist.

13. The stable liquid formulation of claim 12, wherein the IL-1 antagonist exhibits little or no precipitation upon visual inspection after storage of a 50 mg/ml IL-1 trap formulation for 29 months at 5° C.

SEQUENCE LISTING

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<213> Homo sapiens

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        35                  40                  45
Leu Phe Glu His Phe Leu Lys Phe Asn Tyr Ser Thr Ala His Ser Ala
    50                  55                  60
Gly Leu Thr Leu Ile Trp Tyr Trp Thr Arg Gln Asp Arg Asp Leu Glu
65                  70                  75                  80
Glu Pro Ile Asn Phe Arg Leu Pro Glu Asn Arg Ile Ser Lys Glu Lys
                85                  90                  95
Asp Val Leu Trp Phe Arg Pro Thr Leu Leu Asn Asp Thr Gly Asn Tyr
            100                 105                 110
Thr Cys Met Leu Arg Asn Thr Thr Tyr Cys Ser Lys Val Ala Phe Pro
        115                 120                 125
Leu Glu Val Val Gln Lys Asp Ser Cys Phe Asn Ser Pro Met Lys Leu
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Pro Val His Lys Leu Tyr Ile Glu Tyr Gly Ile Gln Arg Ile Thr Cys
145                 150                 155                 160
Pro Asn Val Asp Gly Tyr Phe Pro Ser Ser Val Lys Pro Thr Ile Thr
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Trp Tyr Met Gly Cys Tyr Lys Ile Gln Asn Phe Asn Asn Val Ile Pro
            180                 185                 190
Glu Gly Met Asn Leu Ser Phe Leu Ile Ala Leu Ile Ser Asn Asn Gly
        195                 200                 205
Asn Tyr Thr Cys Val Val Thr Tyr Pro Glu Asn Gly Arg Thr Phe His
    210                 215                 220
Leu Thr Arg Thr Leu Thr Val Lys Val Val Gly Ser Pro Lys Asn Ala
225                 230                 235                 240
Val Pro Pro Val Ile His Ser Pro Asn Asp His Val Val Tyr Glu Lys
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Glu Pro Gly Glu Glu Leu Leu Ile Pro Cys Thr Val Tyr Phe Ser Phe
            260                 265                 270
Leu Met Asp Ser Arg Asn Glu Val Trp Trp Thr Ile Asp Gly Lys Lys
        275                 280                 285
Pro Asp Asp Ile Thr Ile Asp Val Thr Ile Asn Glu Ser Ile Ser His
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Ser Arg Thr Glu Asp Glu Thr Arg Thr Gln Ile Leu Ser Ile Lys Lys
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Val Thr Ser Glu Asp Leu Lys Arg Ser Tyr Val Cys His Ala Arg Ser
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Ala Lys Gly Glu Val Ala Lys Ala Ala Lys Val Lys Gln Lys Val Pro
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            340                 345                 350
Ala Pro Arg Tyr Thr Val Ser Gly Gly Ala Pro Met Leu Ser Glu Ala
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Asn Glu Ile Asp Val Arg Pro Cys Pro Leu Asn Pro Asn Glu His Lys
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Glu Gln Ala Ser Arg Ile His Gln His Lys Glu Lys Leu Trp Phe Val
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Pro Ala Lys Val Glu Asp Ser Gly His Tyr Tyr Cys Val Val Arg Asn
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Ser Ser Tyr Cys Leu Arg Ile Lys Ile Ser Ala Lys Phe Val Glu Asn
    450                 455                 460
Glu Pro Asn Leu Cys Tyr Asn Ala Gln Ala Ile Phe Lys Gln Lys Leu
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Pro Val Ala Gly Asp Gly Gly Leu Val Cys Pro Tyr Met Glu Phe Phe
                485                 490                 495
Lys Asn Glu Asn Asn Glu Leu Pro Lys Leu Gln Trp Tyr Lys Asp Cys
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Lys Pro Leu Leu Leu Asp Asn Ile His Phe Ser Gly Val Lys Asp Arg
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Leu Ile Val Met Asn Val Ala Glu Lys His Arg Gly Asn Tyr Thr Cys
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His Ala Ser Tyr Thr Tyr Leu Gly Lys Gln Tyr Pro Ile Thr Arg Val
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Ile Glu Phe Ile Thr Leu Glu Glu Asn Lys Pro Thr Arg Pro Val Ile
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Val Ser Pro Ala Asn Glu Thr Met Glu Val Asp Leu Gly Ser Gln Ile
            580                 585                 590
Gln Leu Ile Cys Asn Val Thr Gly Gln Leu Ser Asp Ile Ala Tyr Trp
        595                 600                 605
Lys Trp Asn Gly Ser Val Ile Asp Glu Asp Asp Pro Val Leu Gly Glu
    610                 615                 620
Asp Tyr Tyr Ser Val Glu Asn Pro Ala Asn Lys Arg Arg Ser Thr Leu
625                 630                 635                 640
Ile Thr Val Leu Asn Ile Ser Glu Ile Glu Ser Arg Phe Tyr Lys His
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Pro Phe Thr Cys Phe Ala Lys Asn Thr His Gly Ile Asp Ala Ala Tyr
            660                 665                 670
Ile Gln Leu Ile Tyr Pro Val Thr Asn Ser Gly Asp Lys Thr His Thr
        675                 680                 685
Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
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Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
705                 710                 715                 720
Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
                725                 730                 735
Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
            740                 745                 750
Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
        755                 760                 765
Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
    770                 775                 780
Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
785                 790                 795                 800
Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
                805                 810                 815
Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
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Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
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Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
    850                 855                 860
Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
865                 870                 875                 880
Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
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Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
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<211> 2703
<212> DNA
<213> Homo sapiens

<400> 3

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tataatgcac aagccatatt taagcagaaa ctacccgttg caggagacgg aggacttgtg 420
tgcccttata tggagttttt taaaaatgaa aataatgagt tacctaaatt acagtggtat 480
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<213> Homo sapiens

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

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Leu Leu Asn Asp Thr Gly Asn Tyr Thr Cys Met Leu Arg Asn Thr Thr
            420                 425                 430
Tyr Cys Ser Lys Val Ala Phe Pro Leu Glu Val Val Gln Lys Asp Ser
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Cys Phe Asn Ser Pro Met Lys Leu Pro Val His Lys Leu Tyr Ile Glu
    450                 455                 460
Tyr Gly Ile Gln Arg Ile Thr Cys Pro Asn Val Asp Gly Tyr Phe Pro
465                 470                 475                 480
Ser Ser Val Lys Pro Thr Ile Thr Trp Tyr Met Gly Cys Tyr Lys Ile
                485                 490                 495
Gln Asn Phe Asn Asn Val Ile Pro Glu Gly Met Asn Leu Ser Phe Leu
            500                 505                 510
Ile Ala Leu Ile Ser Asn Asn Gly Asn Tyr Thr Cys Val Val Thr Tyr
        515                 520                 525
Pro Glu Asn Gly Arg Thr Phe His Leu Thr Arg Thr Leu Thr Val Lys
    530                 535                 540
Val Val Gly Ser Pro Lys Asn Ala Val Pro Pro Val Ile His Ser Pro
545                 550                 555                 560
Asn Asp His Val Val Tyr Glu Lys Glu Pro Gly Glu Glu Leu Leu Ile
                565                 570                 575
Pro Cys Thr Val Tyr Phe Ser Phe Leu Met Asp Ser Arg Asn Glu Val
            580                 585                 590
Trp Trp Thr Ile Asp Gly Lys Lys Pro Asp Asp Ile Thr Ile Asp Val
        595                 600                 605
Thr Ile Asn Glu Ser Ile Ser His Ser Arg Thr Glu Asp Glu Thr Arg
    610                 615                 620
Thr Gln Ile Leu Ser Ile Lys Lys Val Thr Ser Glu Asp Leu Lys Arg
625                 630                 635                 640
Ser Tyr Val Cys His Ala Arg Ser Ala Lys Gly Glu Val Ala Lys Ala
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Ala Lys Val Lys Gln Lys Val Pro Ala Pro Arg Tyr Thr Val Glu Ser
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Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
        675                 680                 685
Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
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Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
705                 710                 715                 720
His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
                725                 730                 735
Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
            740                 745                 750
Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
        755                 760                 765
Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
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Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
785                 790                 795                 800
Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
                805                 810                 815
Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
            820                 825                 830
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
        835                 840                 845
Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
    850                 855                 860
Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
865                 870                 875                 880
Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
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<212> DNA
<213> Homo sapiens

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<211> 902
<212> PRT
<213> Homo sapiens

<400> 6

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

Asn Tyr Ser Thr Ala His Ser Ala Gly Leu Thr Leu Ile Trp Tyr Trp
    370                 375                 380
Thr Arg Gln Asp Arg Asp Leu Glu Glu Pro Ile Asn Phe Arg Leu Pro
385                 390                 395                 400
Glu Asn Arg Ile Ser Lys Glu Lys Asp Val Leu Trp Phe Arg Pro Thr
                405                 410                 415
Leu Leu Asn Asp Thr Gly Asn Tyr Thr Cys Met Leu Arg Asn Thr Thr
            420                 425                 430
Tyr Cys Ser Lys Val Ala Phe Pro Leu Glu Val Val Gln Lys Asp Ser
        435                 440                 445
Cys Phe Asn Ser Pro Met Lys Leu Pro Val His Lys Leu Tyr Ile Glu
    450                 455                 460
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Tyr Gly Ile Gln Arg Ile Thr Cys Pro Asn Val Asp Gly Tyr Phe Pro
465                 470                 475                 480
Ser Ser Val Lys Pro Thr Ile Thr Trp Tyr Met Gly Cys Tyr Lys Ile
                485                 490                 495
Gln Asn Phe Asn Asn Val Ile Pro Glu Gly Met Asn Leu Ser Phe Leu
            500                 505                 510
Ile Ala Leu Ile Ser Asn Asn Gly Asn Tyr Thr Cys Val Val Thr Tyr
        515                 520                 525
Pro Glu Asn Gly Arg Thr Phe His Leu Thr Arg Thr Leu Thr Val Lys
    530                 535                 540
Val Val Gly Ser Pro Lys Asn Ala Val Pro Pro Val Ile His Ser Pro
545                 550                 555                 560
Asn Asp His Val Val Tyr Glu Lys Glu Pro Gly Glu Glu Leu Leu Ile
                565                 570                 575
Pro Cys Thr Val Tyr Phe Ser Phe Leu Met Asp Ser Arg Asn Glu Val
            580                 585                 590
Trp Trp Thr Ile Asp Gly Lys Lys Pro Asp Asp Ile Thr Ile Asp Val
        595                 600                 605
Thr Ile Asn Glu Ser Ile Ser His Ser Arg Thr Glu Asp Glu Thr Arg
    610                 615                 620
Thr Gln Ile Leu Ser Ile Lys Lys Val Thr Ser Glu Asp Leu Lys Arg
625                 630                 635                 640
Ser Tyr Val Cys His Ala Arg Ser Ala Lys Gly Glu Val Ala Lys Ala
                645                 650                 655
Ala Lys Val Lys Gln Lys Val Pro Ala Pro Arg Tyr Thr Val Glu Ser
            660                 665                 670
Gly Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu
        675                 680                 685
Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
    690                 695                 700
Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp

705                 710                 715                 720
Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
                725                 730                 735
Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
            740                 745                 750
Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
        755                 760                 765
Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
    770                 775                 780
Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
785                 790                 795                 800
Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn
                805                 810                 815
Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
            820                 825                 830
Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
        835                 840                 845
Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg
    850                 855                 860
Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys
865                 870                 875                 880
Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
                885                 890                 895
Ser Leu Ser Leu Gly Lys
            900
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<211> 2709

<212> DNA
<213> Homo sapiens

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aaatgcaagg aacgtgaaga aaaaataatt ttagtgtcat ctgcaaatga aattgatgtt 120
cgtccctgtc ctcttaaccc aaatgaacac aaaggcacta taacttggta taaggatgac 180
agcaagacac ctgtatctac agaacaagcc tccaggattc atcaacacaa agagaaactt 240
tggtttgttc ctgctaaggt ggaggattca ggacattact attgcgtggt aagaaattca 300
tcttactgcc tcagaattaa aataagtgca aaatttgtgg agaatgagcc taacttatgt 360
tataatgcac aagccatatt taagcagaaa ctacccgttg caggagacgg aggacttgtg 420
tgcccttata tggagttttt taaaaatgaa aataatgagt tacctaaatt acagtggtat 480
aaggattgca aacctctact tcttgacaat atacacttta gtggagtcaa agataggctc 540
atcgtgatga atgtggctga aaagcataga gggaactata cttgtcatgc atcctacaca 600
tacttgggca agcaatatcc tattacccgg gtaatagaat ttattactct agaggaaaac 660
aaacccacaa ggcctgtgat tgtgagccca gctaatgaga caatggaagt agacttggga 720
tcccagatac aattgatctg taatgtcacc ggccagttga gtgacattgc ttactggaag 780
tggaatgggt cagtaattga tgaagatgac ccagtgctag gggaagacta ttacagtgtg 840
gaaaatcctg caaacaaaag aaggagtacc ctcatcacag tgcttaatat atcggaaatt 900
gagagtagat tttataaaca tccatttacc tgttttgcca agaatacaca tggtatagat 960
gcagcatata tccagttaat atatccagtc actaattcag aacgctgcga tgactgggga 1020
ctagacacca tgaggcaaat ccaagtgttt gaagatgagc cagctcgcat caagtgccca 1080
ctctttgaac acttcttgaa attcaactac agcacagccc attcagctgg ccttactctg 1140
atctggtatt ggactaggca ggaccgggac cttgaggagc caattaactt ccgcctcccc 1200
gagaaccgca ttagtaagga gaaagatgtg ctgtggttcc ggcccactct cctcaatgac 1260
actggcaact atacctgcat gttaaggaac actacatatt gcagcaaagt tgcatttccc 1320
ttggaagttg ttcaaaaaga cagctgtttc aattccccca tgaaactccc agtgcataaa 1380
ctgtatatag aatatggcat tcagaggatc acttgtccaa atgtagatgg atattttcct 1440
tccagtgtca aaccgactat cacttggtat atgggctgtt ataaaataca gaattttaat 1500
aatgtaatac ccgaaggtat gaacttgagt ttcctcattg ccttaatttc aaataatgga 1560
aattacacat gtgttgttac atatccagaa aatggacgta cgtttcatct caccaggact 1620
ctgactgtaa aggtagtagg ctctccaaaa aatgcagtgc cccctgtgat ccattcacct 1680
aatgatcatg tggtctatga gaaagaacca ggagaggagc tactcattcc ctgtacggtc 1740
tattttagtt ttctgatgga ttctcgcaat gaggtttggt ggaccattga tggaaaaaaa 1800
cctgatgaca tcactattga tgtcaccatt aacgaaagta taagtcatag tagaacagaa 1860

gatgaaacaa gaactcagat tttgagcatc aagaaagtta cctctgagga tctcaagcgc 1920
agctatgtct gtcatgctag aagtgccaaa ggcgaagttg ccaaagcagc caaggtgaag 1980
cagaaagtgc cagctccaag atacacagtg gaatccggag agtccaaata cggtccgcca 2040
tgcccaccat gcccagcacc tgagttcctg gggggaccat cagtcttcct gttcccccca 2100
aaacccaagg acactctcat gatctcccgg acccctgagg tcacgtgcgt ggtggtggac 2160
gtgagccagg aagaccccga ggtccagttc aactggtacg tggatggcgt ggaggtgcat 2220
aatgccaaga caaagccgcg ggaggagcag ttcaacagca cgtaccgtgt ggtcagcgtc 2280
ctcaccgtcc tgcaccagga ctggctgaac ggcaaggagt acaagtgcaa ggtctccaac 2340
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ccacaggtgt acaccctgcc cccatcccag gaggagatga ccaagaacca ggtcagcctg 2460
acctgcctgg tcaaaggctt ctaccccagc gacatcgccg tggagtggga gagcaatggg 2520
cagccggaga acaactacaa gaccacgcct cccgtgctgg actccgacgg ctccttcttc 2580
ctctacagca ggctaaccgt ggacaagagc aggtggcagg aggggaatgt cttctcatgc 2640
tccgtgatgc atgaggctct gcacaaccac tacacacaga agagcctctc cctgtctctg 2700
ggtaaatga 2709

<210> 8
<211> 902
<212> PRT
<213> Homo sapiens

<400> 8
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 1   5   10   15
Leu Glu Ala Asp Lys Cys Lys Glu Arg Glu Glu Lys Ile Ile Leu Val

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                20                  25                  30
Ser Ser Ala Asn Glu Ile Asp Val Arg Pro Cys Pro Leu Asn Pro Asn
        35                  40                  45
Glu His Lys Gly Thr Ile Thr Trp Tyr Lys Asp Asp Ser Lys Thr Pro
    50                  55                  60
Val Ser Thr Glu Gln Ala Ser Arg Ile His Gln His Lys Glu Lys Leu
65                  70                  75                  80
Trp Phe Val Pro Ala Lys Val Glu Asp Ser Gly His Tyr Tyr Cys Val
                85                  90                  95
Val Arg Asn Ser Ser Tyr Cys Leu Arg Ile Lys Ile Ser Ala Lys Phe
            100                 105                 110
Val Glu Asn Glu Pro Asn Leu Cys Tyr Asn Ala Gln Ala Ile Phe Lys
        115                 120                 125
Gln Lys Leu Pro Val Ala Gly Asp Gly Gly Leu Val Cys Pro Tyr Met
    130                 135                 140
Glu Phe Phe Lys Asn Glu Asn Asn Glu Leu Pro Lys Leu Gln Trp Tyr
145                 150                 155                 160
Lys Asp Cys Lys Pro Leu Leu Leu Asp Asn Ile His Phe Ser Gly Val
                165                 170                 175
Lys Asp Arg Leu Ile Val Met Asn Val Ala Glu Lys His Arg Gly Asn
            180                 185                 190
Tyr Thr Cys His Ala Ser Tyr Thr Tyr Leu Gly Lys Gln Tyr Pro Ile
        195                 200                 205
Thr Arg Val Ile Glu Phe Ile Thr Leu Glu Glu Asn Lys Pro Thr Arg
    210                 215                 220
Pro Val Ile Val Ser Pro Ala Asn Glu Thr Met Glu Val Asp Leu Gly
225                 230                 235                 240
Ser Gln Ile Gln Leu Ile Cys Asn Val Thr Gly Gln Leu Ser Asp Ile
                245                 250                 255
Ala Tyr Trp Lys Trp Asn Gly Ser Val Ile Asp Glu Asp Asp Pro Val
            260                 265                 270
Leu Gly Glu Asp Tyr Tyr Ser Val Glu Asn Pro Ala Asn Lys Arg Arg
        275                 280                 285
Ser Thr Leu Ile Thr Val Leu Asn Ile Ser Glu Ile Glu Ser Arg Phe
    290                 295                 300
Tyr Lys His Pro Phe Thr Cys Phe Ala Lys Asn Thr His Gly Ile Asp
305                 310                 315                 320
Ala Ala Tyr Ile Gln Leu Ile Tyr Pro Val Thr Asn Ser Glu Arg Cys
                325                 330                 335
Asp Asp Trp Gly Leu Asp Thr Met Arg Gln Ile Gln Val Phe Glu Asp
            340                 345                 350
Glu Pro Ala Arg Ile Lys Cys Pro Leu Phe Glu His Phe Leu Lys Phe
        355                 360                 365
Asn Tyr Ser Thr Ala His Ser Ala Gly Leu Thr Leu Ile Trp Tyr Trp
    370                 375                 380
Thr Arg Gln Asp Arg Asp Leu Glu Glu Pro Ile Asn Phe Arg Leu Pro
385                 390                 395                 400
Glu Asn Arg Ile Ser Lys Glu Lys Asp Val Leu Trp Phe Arg Pro Thr
                405                 410                 415
Leu Leu Asn Asp Thr Gly Asn Tyr Thr Cys Met Leu Arg Asn Thr Thr
            420                 425                 430
Tyr Cys Ser Lys Val Ala Phe Pro Leu Glu Val Val Gln Lys Asp Ser
        435                 440                 445
Cys Phe Asn Ser Pro Met Lys Leu Pro Val His Lys Leu Tyr Ile Glu
    450                 455                 460
Tyr Gly Ile Gln Arg Ile Thr Cys Pro Asn Val Asp Gly Tyr Phe Pro
465                 470                 475                 480
Ser Ser Val Lys Pro Thr Ile Thr Trp Tyr Met Gly Cys Tyr Lys Ile
                485                 490                 495
Gln Asn Phe Asn Asn Val Ile Pro Glu Gly Met Asn Leu Ser Phe Leu
            500                 505                 510
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Ile Ala Leu Ile Ser Asn Asn Gly Asn Tyr Thr Cys Val Val Thr Tyr
        515                 520                 525
Pro Glu Asn Gly Arg Thr Phe His Leu Thr Arg Thr Leu Thr Val Lys
    530                 535                 540
Val Val Gly Ser Pro Lys Asn Ala Val Pro Pro Val Ile His Ser Pro
545                 550                 555                 560
Asn Asp His Val Val Tyr Glu Lys Glu Pro Gly Glu Glu Leu Leu Ile
                565                 570                 575
Pro Cys Thr Val Tyr Phe Ser Phe Leu Met Asp Ser Arg Asn Glu Val
            580                 585                 590
Trp Trp Thr Ile Asp Gly Lys Lys Pro Asp Asp Ile Thr Ile Asp Val
        595                 600                 605
Thr Ile Asn Glu Ser Ile Ser His Ser Arg Thr Glu Asp Glu Thr Arg
    610                 615                 620
Thr Gln Ile Leu Ser Ile Lys Lys Val Thr Ser Glu Asp Leu Lys Arg
625                 630                 635                 640
Ser Tyr Val Cys His Ala Arg Ser Ala Lys Gly Glu Val Ala Lys Ala
                645                 650                 655
Ala Lys Val Lys Gln Lys Val Pro Ala Pro Arg Tyr Thr Val Glu Ser
            660                 665                 670
Gly Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu
        675                 680                 685
Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
    690                 695                 700
Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
705                 710                 715                 720
Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
                725                 730                 735
Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
            740                 745                 750
Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
        755                 760                 765
Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
    770                 775                 780
Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
785                 790                 795                 800
Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn
                805                 810                 815
Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
            820                 825                 830
Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
        835                 840                 845
Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg
    850                 855                 860
Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys
865                 870                 875                 880
Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
                885                 890                 895
Ser Leu Ser Leu Gly Lys
            900
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<210> 9
<211> 2703
<212> DNA
<213> Homo sapiens

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tcagaacgct gcgatgactg gggactagac accatgaggc aaatccaagt gtttgaagat 120
gagccagctc gcatcaagtg cccactcttt gaacacttct tgaaattcaa ctacagcaca 180

gcccattcag ctggccttac tctgatctgg tattggacta ggcaggaccg ggaccttgag 240
gagccaatta acttccgcct ccccgagaac cgcattagta aggagaaaga tgtgctgtgg 300
ttccggccca ctctcctcaa tgacactggc aactatacct gcatgttaag gaacactaca 360
tattgcagca aagttgcatt tcccttggaa gttgttcaaa aagacagctg tttcaattcc 420
cccatgaaac tcccagtgca taaactgtat atagaatatg gcattcagag gatcacttgt 480
ccaaatgtag atggatattt tccttccagt gtcaaaccga ctatcacttg gtatatgggc 540
tgttataaaa tacagaattt taataatgta atacccgaag gtatgaactt gagtttcctc 600
attgccttaa tttcaaataa tggaaattac acatgtgttg ttacatatcc agaaaatgga 660
cgtacgtttc atctcaccag gactctgact gtaaaggtag taggctctcc aaaaaatgca 720
gtgccccctg tgatccattc acctaatgat catgtggtct atgagaaaga accaggagag 780
gagctactca ttccctgtac ggtctatttt agttttctga tggattctcg caatgaggtt 840
tggtggacca ttgatggaaa aaaacctgat gacatcacta ttgatgtcac cattaacgaa 900
agtataagtc atagtagaac agaagatgaa acaagaactc agattttgag catcaagaaa 960
gttacctctg aggatctcaa gcgcagctat gtctgtcatg ctagaagtgc caaaggcgaa 1020
gttgccaaag cagccaaggt gaagcagaaa gtgccagctc caagatacac agtggaaaaa 1080
tgcaaggaac gtgaagaaaa aataatttta gtgagctcag caaatgaaat cgatgttcgt 1140
ccctgtcctc ttaacccaaa tgaacacaaa ggcactataa cttggtataa ggatgacagc 1200
aagacacctg tatctacaga acaagcctcc aggattcatc aacacaaaga gaaactttgg 1260
tttgttcctg ctaaggtgga ggattcagga cattactatt gcgtggtaag aaattcatct 1320
tactgcctca gaattaaaat aagtgcaaaa tttgtggaga atgagcctaa cttatgttat 1380
aatgcacaag ccatatttaa gcagaaacta cccgttgcag gagacggagg acttgtgtgc 1440
ccttatatgg agtttttaa aaatgaaaat aatgagttac ctaaattaca gtggtataag 1500
gattgcaaac ctctacttct tgacaatata cactttagtg gagtcaaaga taggctcatc 1560
gtgatgaatg tggctgaaaa gcatagaggg aactatactt gtcatgcatc ctacacatac 1620
ttgggcaagc aatatcctat tacccgggta atagaattta ttactctaga ggaaaacaaa 1680
cccacaaggc ctgtgattgt gagcccagct aatgagacaa tggaagtaga cttgggatcc 1740
cagatacaat tgatctgtaa tgtcaccggc cagttgagtg acattgctta ctggaagtgg 1800
aatgggtcag taattgatga agatgaccca gtgctagggg aagactatta cagtgtggaa 1860
aatcctgcaa acaaaagaag gagtaccctc atcacagtgc ttaatatatc ggaaattgag 1920
agtagatttt ataaacatcc atttacctgt tttgccaaga atacacatgg tatagatgca 1980
gcatatatcc agttaatata tccagtcact aattccggag acaaaactca cacatgccca 2040
ccgtgcccag cacctgaact cctgggggga ccgtcagtct tcctcttccc cccaaaaccc 2100
aaggacaccc tcatgatctc ccggacccct gaggtcacat gcgtggtggt ggacgtgagc 2160
cacgaagacc ctgaggtcaa gttcaactgg tacgtggacg gcgtggaggt gcataatgcc 2220
aagacaaagc cgcgggagga gcagtacaac agcacgtacc gtgtggtcag cgtcctcacc 2280
gtcctgcacc aggactggct gaatggcaag gagtacaagt gcaaggtctc caacaaagcc 2340
ctcccagccc ccatcgagaa aaccatctcc aaagccaaag ggcagccccg agaaccacag 2400
gtgtacaccc tgcccccatc ccgggatgag ctgaccaaga accaggtcag cctgacctgc 2460
ctggtcaaag gcttctatcc cagcgacatc gccgtggagt gggagagcaa tgggcagccg 2520
gagaacaact acaagaccac gcctcccgtg ctggactccg acggctcctt cttcctctac 2580
agcaagctca ccgtggacaa gagcaggtgg cagcagggga acgtcttctc atgctccgtg 2640
atgcatgagg ctctgcacaa ccactacacg cagaagagcc tctccctgtc tccgggtaaa 2700
tga 2703

<210> 10
<211> 900
<212> PRT
<213> Homo sapiens

<400> 10
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Gln Ser Asp Ala Ser Glu Arg Cys Asp Asp Trp Gly Leu Asp Thr Met
            20   25   30
Arg Gln Ile Gln Val Phe Glu Asp Glu Pro Ala Arg Ile Lys Cys Pro
        35   40   45
Leu Phe Glu His Phe Leu Lys Phe Asn Tyr Ser Thr Ala His Ser Ala
    50   55   60
Gly Leu Thr Leu Ile Trp Tyr Trp Thr Arg Gln Asp Arg Asp Leu Glu
65   70   75   80
Glu Pro Ile Asn Phe Arg Leu Pro Glu Asn Arg Ile Ser Lys Glu Lys

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                    85                  90                  95
Asp Val Leu Trp Phe Arg Pro Thr Leu Leu Asn Asp Thr Gly Asn Tyr
                100                 105                 110
Thr Cys Met Leu Arg Asn Thr Thr Tyr Cys Ser Lys Val Ala Phe Pro
            115                 120                 125
Leu Glu Val Val Gln Lys Asp Ser Cys Phe Asn Ser Pro Met Lys Leu
        130                 135                 140
Pro Val His Lys Leu Tyr Ile Glu Tyr Gly Ile Gln Arg Ile Thr Cys
145                 150                 155                 160
Pro Asn Val Asp Gly Tyr Phe Pro Ser Ser Val Lys Pro Thr Ile Thr
                165                 170                 175
Trp Tyr Met Gly Cys Tyr Lys Ile Gln Asn Phe Asn Asn Val Ile Pro
            180                 185                 190
Glu Gly Met Asn Leu Ser Phe Leu Ile Ala Leu Ile Ser Asn Asn Gly
        195                 200                 205
Asn Tyr Thr Cys Val Val Thr Tyr Pro Glu Asn Gly Arg Thr Phe His
    210                 215                 220
Leu Thr Arg Thr Leu Thr Val Lys Val Val Gly Ser Pro Lys Asn Ala
225                 230                 235                 240
Val Pro Pro Val Ile His Ser Pro Asn Asp His Val Val Tyr Glu Lys
                245                 250                 255
Glu Pro Gly Glu Glu Leu Leu Ile Pro Cys Thr Val Tyr Phe Ser Phe
            260                 265                 270
Leu Met Asp Ser Arg Asn Glu Val Trp Trp Thr Ile Asp Gly Lys Lys
        275                 280                 285
Pro Asp Asp Ile Thr Ile Asp Val Thr Ile Asn Glu Ser Ile Ser His
    290                 295                 300
Ser Arg Thr Glu Asp Glu Thr Arg Thr Gln Ile Leu Ser Ile Lys Lys
305                 310                 315                 320
Val Thr Ser Glu Asp Leu Lys Arg Ser Tyr Val Cys His Ala Arg Ser
                325                 330                 335
Ala Lys Gly Glu Val Ala Lys Ala Ala Lys Val Lys Gln Lys Val Pro
            340                 345                 350
Ala Pro Arg Tyr Thr Val Glu Lys Cys Lys Glu Arg Glu Glu Lys Ile
        355                 360                 365
Ile Leu Val Ser Ser Ala Asn Glu Ile Asp Val Arg Pro Cys Pro Leu
    370                 375                 380
Asn Pro Asn Glu His Lys Gly Thr Ile Thr Trp Tyr Lys Asp Asp Ser
385                 390                 395                 400
Lys Thr Pro Val Ser Thr Glu Gln Ala Ser Arg Ile His Gln His Lys
                405                 410                 415
Glu Lys Leu Trp Phe Val Pro Ala Lys Val Glu Asp Ser Gly His Tyr
            420                 425                 430
Tyr Cys Val Val Arg Asn Ser Ser Tyr Cys Leu Arg Ile Lys Ile Ser
        435                 440                 445
Ala Lys Phe Val Glu Asn Glu Pro Asn Leu Cys Tyr Asn Ala Gln Ala
    450                 455                 460
Ile Phe Lys Gln Lys Leu Pro Val Ala Gly Asp Gly Gly Leu Val Cys
465                 470                 475                 480
Pro Tyr Met Glu Phe Phe Lys Asn Glu Asn Asn Glu Leu Pro Lys Leu
                485                 490                 495
Gln Trp Tyr Lys Asp Cys Lys Pro Leu Leu Leu Asp Asn Ile His Phe
            500                 505                 510
Ser Gly Val Lys Asp Arg Leu Ile Val Met Asn Val Ala Glu Lys His
        515                 520                 525
Arg Gly Asn Tyr Thr Cys His Ala Ser Tyr Thr Tyr Leu Gly Lys Gln
    530                 535                 540
Tyr Pro Ile Thr Arg Val Ile Glu Phe Ile Thr Leu Glu Glu Asn Lys
545                 550                 555                 560
Pro Thr Arg Pro Val Ile Val Ser Pro Ala Asn Glu Thr Met Glu Val
                565                 570                 575
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Asp Leu Gly Ser Gln Ile Gln Leu Ile Cys Asn Val Thr Gly Gln Leu
            580                 585                 590
Ser Asp Ile Ala Tyr Trp Lys Trp Asn Gly Ser Val Ile Asp Glu Asp
        595                 600                 605
Asp Pro Val Leu Gly Glu Asp Tyr Tyr Ser Val Glu Asn Pro Ala Asn
    610                 615                 620
Lys Arg Arg Ser Thr Leu Ile Thr Val Leu Asn Ile Ser Glu Ile Glu
625                 630                 635                 640
Ser Arg Phe Tyr Lys His Pro Phe Thr Cys Phe Ala Lys Asn Thr His
                645                 650                 655
Gly Ile Asp Ala Ala Tyr Ile Gln Leu Ile Tyr Pro Val Thr Asn Ser
            660                 665                 670
Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
        675                 680                 685
Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
    690                 695                 700
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
705                 710                 715                 720
His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
                725                 730                 735
Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
            740                 745                 750
Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
        755                 760                 765
Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
    770                 775                 780
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
785                 790                 795                 800
Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
                805                 810                 815
Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
            820                 825                 830
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
        835                 840                 845
Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
    850                 855                 860
Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
865                 870                 875                 880
Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
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Ser Pro Gly Lys
            900
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<210> 11
<211> 2709
<212> DNA
<213> Homo sapiens

<400> 11

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gagccagctc gcatcaagtg cccactcttt gaacacttct tgaaattcaa ctacagcaca 180
gcccattcag ctggccttac tctgatctgg tattggacta ggcaggaccg ggaccttgag 240
gagccaatta acttccgcct ccccgagaac cgcattagta aggagaaaga tgtgctgtgg 300
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tattgcagca aagttgcatt tcccttggaa gttgttcaaa aagacagctg tttcaattcc 420
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<210> 12
<211> 902
<212> PRT
<213> Homo sapiens

<400> 12

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

Leu Glu Val Val Gln Lys Asp Ser Cys Phe Asn Ser Pro Met Lys Leu
    130                 135                 140
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Pro Val His Lys Leu Tyr Ile Glu Tyr Gly Ile Gln Arg Ile Thr Cys
145                 150                 155                 160
Pro Asn Val Asp Gly Tyr Phe Pro Ser Ser Val Lys Pro Thr Ile Thr
                165                 170                 175
Trp Tyr Met Gly Cys Tyr Lys Ile Gln Asn Phe Asn Asn Val Ile Pro
            180                 185                 190
Glu Gly Met Asn Leu Ser Phe Leu Ile Ala Leu Ile Ser Asn Asn Gly
        195                 200                 205
Asn Tyr Thr Cys Val Val Thr Tyr Pro Glu Asn Gly Arg Thr Phe His
    210                 215                 220
Leu Thr Arg Thr Leu Thr Val Lys Val Val Gly Ser Pro Lys Asn Ala
225                 230                 235                 240
Val Pro Pro Val Ile His Ser Pro Asn Asp His Val Val Tyr Glu Lys
                245                 250                 255
Glu Pro Gly Glu Glu Leu Leu Ile Pro Cys Thr Val Tyr Phe Ser Phe
            260                 265                 270
Leu Met Asp Ser Arg Asn Glu Val Trp Trp Thr Ile Asp Gly Lys Lys
        275                 280                 285
Pro Asp Asp Ile Thr Ile Asp Val Thr Ile Asn Glu Ser Ile Ser His
    290                 295                 300
Ser Arg Thr Glu Asp Glu Thr Arg Thr Gln Ile Leu Ser Ile Lys Lys
305                 310                 315                 320
Val Thr Ser Glu Asp Leu Lys Arg Ser Tyr Val Cys His Ala Arg Ser
                325                 330                 335
Ala Lys Gly Glu Val Ala Lys Ala Ala Lys Val Lys Gln Lys Val Pro
            340                 345                 350
Ala Pro Arg Tyr Thr Val Glu Lys Cys Lys Glu Arg Glu Glu Lys Ile
        355                 360                 365
Ile Leu Val Ser Ser Ala Asn Glu Ile Asp Val Arg Pro Cys Pro Leu
    370                 375                 380
Asn Pro Asn Glu His Lys Gly Thr Ile Thr Trp Tyr Lys Asp Asp Ser
385                 390                 395                 400
Lys Thr Pro Val Ser Thr Glu Gln Ala Ser Arg Ile His Gln His Lys
                405                 410                 415
Glu Lys Leu Trp Phe Val Pro Ala Lys Val Glu Asp Ser Gly His Tyr
            420                 425                 430
Tyr Cys Val Val Arg Asn Ser Ser Tyr Cys Leu Arg Ile Lys Ile Ser
        435                 440                 445
Ala Lys Phe Val Glu Asn Glu Pro Asn Leu Cys Tyr Asn Ala Gln Ala
    450                 455                 460
Ile Phe Lys Gln Lys Leu Pro Val Ala Gly Asp Gly Gly Leu Val Cys

465                 470                 475                 480
Pro Tyr Met Glu Phe Phe Lys Asn Glu Asn Asn Glu Leu Pro Lys Leu
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Gln Trp Tyr Lys Asp Cys Lys Pro Leu Leu Leu Asp Asn Ile His Phe
            500                 505                 510
Ser Gly Val Lys Asp Arg Leu Ile Val Met Asn Val Ala Glu Lys His
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    530                 535                 540
Tyr Pro Ile Thr Arg Val Ile Glu Phe Ile Thr Leu Glu Glu Asn Lys
545                 550                 555                 560
Pro Thr Arg Pro Val Ile Val Ser Pro Ala Asn Glu Thr Met Glu Val
                565                 570                 575
Asp Leu Gly Ser Gln Ile Gln Leu Ile Cys Asn Val Thr Gly Gln Leu
            580                 585                 590
Ser Asp Ile Ala Tyr Trp Lys Trp Asn Gly Ser Val Ile Asp Glu Asp
        595                 600                 605
Asp Pro Val Leu Gly Glu Asp Tyr Tyr Ser Val Glu Asn Pro Ala Asn
    610                 615                 620
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Lys Arg Arg Ser Thr Leu Ile Thr Val Leu Asn Ile Ser Glu Ile Glu
625                 630                 635                 640
Ser Arg Phe Tyr Lys His Pro Phe Thr Cys Phe Ala Lys Asn Thr His
                645                 650                 655
Gly Ile Asp Ala Ala Tyr Ile Gln Leu Ile Tyr Pro Val Thr Asn Ser
            660                 665                 670
Gly Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu
        675                 680                 685
Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
    690                 695                 700
Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
705                 710                 715                 720
Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
                725                 730                 735
Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
            740                 745                 750
Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
        755                 760                 765
Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
    770                 775                 780
Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
785                 790                 795                 800
Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn
                805                 810                 815
Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
            820                 825                 830
Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
        835                 840                 845
Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg
    850                 855                 860
Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys
865                 870                 875                 880
Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
                885                 890                 895
Ser Leu Ser Leu Gly Lys
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<211> 2709
<212> DNA
<213> Homo sapiens

<400> 13

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gagccagctc gcatcaagtg cccactcttt gaacacttct tgaaattcaa ctacagcaca 180
gcccattcag ctggccttac tctgatctgg tattggacta ggcaggaccg ggaccttgag 240
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tattgcagca aagttgcatt tcccttggaa gttgttcaaa aagacagctg tttcaattcc 420
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ccaaatgtag atggatattt tccttccagt gtcaaaccga ctatcacttg gtatatgggc 540
tgttataaaa tacagaattt taataatgta atacccgaag gtatgaactt gagtttcctc 600
attgccttaa tttcaaataa tggaaattac acatgtgttg ttacatatcc agaaaatgga 660
cgtacgtttc atctcaccag gactctgact gtaaaggtag taggctctcc aaaaaatgca 720
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<212> PRT
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Arg Gln Ile Gln Val Phe Glu Asp Glu Pro Ala Arg Ile Lys Cys Pro
        35   40   45
Leu Phe Glu His Phe Leu Lys Phe Asn Tyr Ser Thr Ala His Ser Ala
    50   55   60
Gly Leu Thr Leu Ile Trp Tyr Trp Thr Arg Gln Asp Arg Asp Leu Glu
65   70   75   80
Glu Pro Ile Asn Phe Arg Leu Pro Glu Asn Arg Ile Ser Lys Glu Lys
                85   90   95
Asp Val Leu Trp Phe Arg Pro Thr Leu Leu Asn Asp Thr Gly Asn Tyr
            100   105   110
Thr Cys Met Leu Arg Asn Thr Thr Tyr Cys Ser Lys Val Ala Phe Pro
        115   120   125
Leu Glu Val Val Gln Lys Asp Ser Cys Phe Asn Ser Pro Met Lys Leu
    130   135   140
Pro Val His Lys Leu Tyr Ile Glu Tyr Gly Ile Gln Arg Ile Thr Cys
145   150   155   160
Pro Asn Val Asp Gly Tyr Phe Pro Ser Ser Val Lys Pro Thr Ile Thr
                165   170   175
Trp Tyr Met Gly Cys Tyr Lys Ile Gln Asn Phe Asn Asn Val Ile Pro
            180   185   190
Glu Gly Met Asn Leu Ser Phe Leu Ile Ala Leu Ile Ser Asn Asn Gly

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Asn Tyr Thr Cys Val Val Thr Tyr Pro Glu Asn Gly Arg Thr Phe His
    210                 215                 220
Leu Thr Arg Thr Leu Thr Val Lys Val Val Gly Ser Pro Lys Asn Ala
225                 230                 235                 240
Val Pro Pro Val Ile His Ser Pro Asn Asp His Val Val Tyr Glu Lys
                245                 250                 255
Glu Pro Gly Glu Glu Leu Leu Ile Pro Cys Thr Val Tyr Phe Ser Phe
            260                 265                 270
Leu Met Asp Ser Arg Asn Glu Val Trp Trp Thr Ile Asp Gly Lys Lys
        275                 280                 285
Pro Asp Asp Ile Thr Ile Asp Val Thr Ile Asn Glu Ser Ile Ser His
    290                 295                 300
Ser Arg Thr Glu Asp Glu Thr Arg Thr Gln Ile Leu Ser Ile Lys Lys
305                 310                 315                 320
Val Thr Ser Glu Asp Leu Lys Arg Ser Tyr Val Cys His Ala Arg Ser
                325                 330                 335
Ala Lys Gly Glu Val Ala Lys Ala Ala Lys Val Lys Gln Lys Val Pro
            340                 345                 350
Ala Pro Arg Tyr Thr Val Glu Lys Cys Lys Glu Arg Glu Glu Lys Ile
        355                 360                 365
Ile Leu Val Ser Ser Ala Asn Glu Ile Asp Val Arg Pro Cys Pro Leu
    370                 375                 380
Asn Pro Asn Glu His Lys Gly Thr Ile Thr Trp Tyr Lys Asp Asp Ser
385                 390                 395                 400
Lys Thr Pro Val Ser Thr Glu Gln Ala Ser Arg Ile His Gln His Lys
                405                 410                 415
Glu Lys Leu Trp Phe Val Pro Ala Lys Val Glu Asp Ser Gly His Tyr
            420                 425                 430
Tyr Cys Val Val Arg Asn Ser Ser Tyr Cys Leu Arg Ile Lys Ile Ser
        435                 440                 445
Ala Lys Phe Val Glu Asn Glu Pro Asn Leu Cys Tyr Asn Ala Gln Ala
    450                 455                 460

Ile Phe Lys Gln Lys Leu Pro Val Ala Gly Asp Gly Gly Leu Val Cys
465                 470                 475                 480
Pro Tyr Met Glu Phe Phe Lys Asn Glu Asn Asn Glu Leu Pro Lys Leu
                485                 490                 495
Gln Trp Tyr Lys Asp Cys Lys Pro Leu Leu Leu Asp Asn Ile His Phe
            500                 505                 510
Ser Gly Val Lys Asp Arg Leu Ile Val Met Asn Val Ala Glu Lys His
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Tyr Pro Ile Thr Arg Val Ile Glu Phe Ile Thr Leu Glu Glu Asn Lys
545                 550                 555                 560
Pro Thr Arg Pro Val Ile Val Ser Pro Ala Asn Glu Thr Met Glu Val
                565                 570                 575
Asp Leu Gly Ser Gln Ile Gln Leu Ile Cys Asn Val Thr Gly Gln Leu
            580                 585                 590
Ser Asp Ile Ala Tyr Trp Lys Trp Asn Gly Ser Val Ile Asp Glu Asp
        595                 600                 605
Asp Pro Val Leu Gly Glu Asp Tyr Tyr Ser Val Glu Asn Pro Ala Asn
    610                 615                 620
Lys Arg Arg Ser Thr Leu Ile Thr Val Leu Asn Ile Ser Glu Ile Glu
625                 630                 635                 640
Ser Arg Phe Tyr Lys His Pro Phe Thr Cys Phe Ala Lys Asn Thr His
                645                 650                 655
Gly Ile Asp Ala Ala Tyr Ile Gln Leu Ile Tyr Pro Val Thr Asn Ser
            660                 665                 670
Gly Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu
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        675                 680                 685
Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
    690                 695                 700
Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
705                 710                 715                 720
Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
                725                 730                 735
Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
            740                 745                 750
Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
        755                 760                 765
Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
    770                 775                 780
Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
785                 790                 795                 800
Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn

                805                 810                 815
Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
            820                 825                 830
Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
        835                 840                 845
Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg
    850                 855                 860
Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys
865                 870                 875                 880
Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
                885                 890                 895
Ser Leu Ser Leu Gly Lys
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<211> 2748
<212> DNA
<213> Homo sapiens

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actcagattt tgagcatcaa gaaagttacc tctgaggatc tcaagcgcag ctatgtctgt 1980
catgctagaa gtgccaaagg cgaagttgcc aaagcagcca aggtgaagca gaaagtgcca 2040
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gaactcctgg ggggaccgtc agtcttcctc ttcccccaa aacccaagga caccctcatg 2160
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gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac 2340
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gagaaaacca tctccaaagc caaagggcag ccccgagaac cacaggtgta caccctgccc 2460
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<210> 16
<211> 915
<212> PRT
<213> Homo sapiens

<400> 16

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

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Ser Pro Leu Lys Thr Ile Ser Ala Ser Leu Gly Ser Arg Leu Thr Ile
                  245                 250                 255
Pro Cys Lys Val Phe Leu Gly Thr Gly Thr Pro Leu Thr Thr Met Leu
             260                 265                 270
Trp Trp Thr Ala Asn Asp Thr His Ile Glu Ser Ala Tyr Pro Gly Gly
         275                 280                 285
Arg Val Thr Glu Gly Pro Arg Gln Glu Tyr Ser Glu Asn Asn Glu Asn
     290                 295                 300
Tyr Ile Glu Val Pro Leu Ile Phe Asp Pro Val Thr Arg Glu Asp Leu
305                 310                 315                 320
His Met Asp Phe Lys Cys Val Val His Asn Thr Leu Ser Phe Gln Thr
                  325                 330                 335
Leu Arg Thr Thr Val Lys Glu Ala Ser Ser Thr Phe Ser Glu Arg Cys
             340                 345                 350
Asp Asp Trp Gly Leu Asp Thr Met Arg Gln Ile Gln Val Phe Glu Asp
         355                 360                 365
Glu Pro Ala Arg Ile Lys Cys Pro Leu Phe Glu His Phe Leu Lys Phe
     370                 375                 380
Asn Tyr Ser Thr Ala His Ser Ala Gly Leu Thr Leu Ile Trp Tyr Trp
385                 390                 395                 400
Thr Arg Gln Asp Arg Asp Leu Glu Glu Pro Ile Asn Phe Arg Leu Pro
                  405                 410                 415
Glu Asn Arg Ile Ser Lys Glu Lys Asp Val Leu Trp Phe Arg Pro Thr
             420                 425                 430
Leu Leu Asn Asp Thr Gly Asn Tyr Thr Cys Met Leu Arg Asn Thr Thr
         435                 440                 445
Tyr Cys Ser Lys Val Ala Phe Pro Leu Glu Val Val Gln Lys Asp Ser
     450                 455                 460
Cys Phe Asn Ser Pro Met Lys Leu Pro Val His Lys Leu Tyr Ile Glu
465                 470                 475                 480
Tyr Gly Ile Gln Arg Ile Thr Cys Pro Asn Val Asp Gly Tyr Phe Pro
                  485                 490                 495
Ser Ser Val Lys Pro Thr Ile Thr Trp Tyr Met Gly Cys Tyr Lys Ile
             500                 505                 510
Gln Asn Phe Asn Asn Val Ile Pro Glu Gly Met Asn Leu Ser Phe Leu
         515                 520                 525
Ile Ala Leu Ile Ser Asn Asn Gly Asn Tyr Thr Cys Val Val Thr Tyr
     530                 535                 540
Pro Glu Asn Gly Arg Thr Phe His Leu Thr Arg Thr Leu Thr Val Lys
545                 550                 555                 560
Val Val Gly Ser Pro Lys Asn Ala Val Pro Pro Val Ile His Ser Pro
                  565                 570                 575
Asn Asp His Val Val Tyr Glu Lys Glu Pro Gly Glu Glu Leu Leu Ile
             580                 585                 590
Pro Cys Thr Val Tyr Phe Ser Phe Leu Met Asp Ser Arg Asn Glu Val
         595                 600                 605
Trp Trp Thr Ile Asp Gly Lys Lys Pro Asp Asp Ile Thr Ile Asp Val
     610                 615                 620
Thr Ile Asn Glu Ser Ile Ser His Ser Arg Thr Glu Asp Glu Thr Arg
625                 630                 635                 640
Thr Gln Ile Leu Ser Ile Lys Lys Val Thr Ser Glu Asp Leu Lys Arg
                  645                 650                 655
Ser Tyr Val Cys His Ala Arg Ser Ala Lys Gly Glu Val Ala Lys Ala
             660                 665                 670
Ala Lys Val Lys Gln Lys Val Pro Ala Pro Arg Tyr Thr Val Ser Gly
         675                 680                 685
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
     690                 695                 700
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
705                 710                 715                 720
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
```

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                725                 730                 735
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
            740                 745                 750
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
        755                 760                 765
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
    770                 775                 780
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
785                 790                 795                 800

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
                805                 810                 815
Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
            820                 825                 830
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
        835                 840                 845
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
    850                 855                 860
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
865                 870                 875                 880
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
                885                 890                 895
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
            900                 905                 910
Pro Gly Lys
        915
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<210> 17
<211> 2754
<212> DNA
<213> Homo sapiens

<400> 17

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ctggaagggg agcctgtagc cctgaggtgc ccccaggtgc cctactggtt gtgggcctct 180
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gaagaagaga cacggatgtg ggcccaggac ggtgctctgt ggcttctgcc agccttgcag 300
gaggactctg gcacctacgt ctgcactact agaaatgctt cttactgtga caaaatgtcc 360
attgagctca gagtttttga gaatacagat gctttcctgc cgttcatctc atacccgcaa 420
attttaacct tgtcaacctc tggggtatta gtatgccctg acctgagtga attcacccgt 480
gacaaaactg acgtgaagat tcaatggtac aaggattctc ttcttttgga taaagacaat 540
gagaaatttc taagtgtgag ggggaccact cacttactcg tacacgatgt ggccctggaa 600
gatgctggct attaccgctg tgtcctgaca tttgcccatg aaggccagca atacaaacatc 660
actaggagta ttgagctacg catcaagaaa aaaaaagaag agaccattcc tgtgatcatt 720
tccccccctca agaccatatc agcttctctg gggtcaagac tgacaatccc atgtaaggtg 780
tttctgggaa ccggcacacc cttaaccacc atgctgtggt ggacggccaa tgacacccac 840
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aataatgaga actacattga agtgccattg atttttgatc ctgtcacaag agaggatttg 960
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ccgactatca cttggtatat gggctgttat aaaatacaga attttaataa tgtaataccc 1560
gaaggtatga acttgagttt cctcattgcc ttaatttcaa ataatggaaa ttacacatgt 1620
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actattgatg tcaccattaa cgaaagtata agtcatagta gaacagaaga tgaaacaaga 1920
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<210> 18
<211> 917
<212> PRT
<213> Homo sapiens

<400> 18
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            20   25   30
Arg His Tyr Lys Arg Glu Phe Arg Leu Glu Gly Glu Pro Val Ala Leu
        35   40   45
Arg Cys Pro Gln Val Pro Tyr Trp Leu Trp Ala Ser Val Ser Pro Arg
    50   55   60
Ile Asn Leu Thr Trp His Lys Asn Asp Ser Ala Arg Thr Val Pro Gly
65   70   75   80
Glu Glu Glu Thr Arg Met Trp Ala Gln Asp Gly Ala Leu Trp Leu Leu
                85   90   95
Pro Ala Leu Gln Glu Asp Ser Gly Thr Tyr Val Cys Thr Thr Arg Asn
            100   105   110
Ala Ser Tyr Cys Asp Lys Met Ser Ile Glu Leu Arg Val Phe Glu Asn
        115   120   125
Thr Asp Ala Phe Leu Pro Phe Ile Ser Tyr Pro Gln Ile Leu Thr Leu
    130   135   140
Ser Thr Ser Gly Val Leu Val Cys Pro Asp Leu Ser Glu Phe Thr Arg
145   150   155   160
Asp Lys Thr Asp Val Lys Ile Gln Trp Tyr Lys Asp Ser Leu Leu Leu
                165   170   175
Asp Lys Asp Asn Glu Lys Phe Leu Ser Val Arg Gly Thr Thr His Leu
            180   185   190
Leu Val His Asp Val Ala Leu Glu Asp Ala Gly Tyr Tyr Arg Cys Val
        195   200   205
Leu Thr Phe Ala His Glu Gly Gln Gln Tyr Asn Ile Thr Arg Ser Ile
    210   215   220
Glu Leu Arg Ile Lys Lys Lys Lys Glu Glu Thr Ile Pro Val Ile Ile
225   230   235   240
Ser Pro Leu Lys Thr Ile Ser Ala Ser Leu Gly Ser Arg Leu Thr Ile
                245   250   255
Pro Cys Lys Val Phe Leu Gly Thr Gly Thr Pro Leu Thr Thr Met Leu
            260   265   270
Trp Trp Thr Ala Asn Asp Thr His Ile Glu Ser Ala Tyr Pro Gly Gly

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        275                 280                 285
Arg Val Thr Glu Gly Pro Arg Gln Glu Tyr Ser Glu Asn Asn Glu Asn
    290                 295                 300
Tyr Ile Glu Val Pro Leu Ile Phe Asp Pro Val Thr Arg Glu Asp Leu
305                 310                 315                 320
His Met Asp Phe Lys Cys Val Val His Asn Thr Leu Ser Phe Gln Thr
                325                 330                 335
Leu Arg Thr Thr Val Lys Glu Ala Ser Ser Thr Phe Ser Glu Arg Cys
            340                 345                 350
Asp Asp Trp Gly Leu Asp Thr Met Arg Gln Ile Gln Val Phe Glu Asp
        355                 360                 365
Glu Pro Ala Arg Ile Lys Cys Pro Leu Phe Glu His Phe Leu Lys Phe
    370                 375                 380
Asn Tyr Ser Thr Ala His Ser Ala Gly Leu Thr Leu Ile Trp Tyr Trp
385                 390                 395                 400
Thr Arg Gln Asp Arg Asp Leu Glu Glu Pro Ile Asn Phe Arg Leu Pro
                405                 410                 415
Glu Asn Arg Ile Ser Lys Glu Lys Asp Val Leu Trp Phe Arg Pro Thr
            420                 425                 430
Leu Leu Asn Asp Thr Gly Asn Tyr Thr Cys Met Leu Arg Asn Thr Thr
        435                 440                 445
Tyr Cys Ser Lys Val Ala Phe Pro Leu Glu Val Val Gln Lys Asp Ser
    450                 455                 460
Cys Phe Asn Ser Pro Met Lys Leu Pro Val His Lys Leu Tyr Ile Glu
465                 470                 475                 480
Tyr Gly Ile Gln Arg Ile Thr Cys Pro Asn Val Asp Gly Tyr Phe Pro
                485                 490                 495
Ser Ser Val Lys Pro Thr Ile Thr Trp Tyr Met Gly Cys Tyr Lys Ile
            500                 505                 510
Gln Asn Phe Asn Asn Val Ile Pro Glu Gly Met Asn Leu Ser Phe Leu
        515                 520                 525
Ile Ala Leu Ile Ser Asn Asn Gly Asn Tyr Thr Cys Val Val Thr Tyr
    530                 535                 540
Pro Glu Asn Gly Arg Thr Phe His Leu Thr Arg Thr Leu Thr Val Lys
545                 550                 555                 560
Val Val Gly Ser Pro Lys Asn Ala Val Pro Pro Val Ile His Ser Pro
                565                 570                 575
Asn Asp His Val Val Tyr Glu Lys Glu Pro Gly Glu Glu Leu Leu Ile
            580                 585                 590
Pro Cys Thr Val Tyr Phe Ser Phe Leu Met Asp Ser Arg Asn Glu Val
        595                 600                 605
Trp Trp Thr Ile Asp Gly Lys Lys Pro Asp Asp Ile Thr Ile Asp Val
    610                 615                 620
Thr Ile Asn Glu Ser Ile Ser His Ser Arg Thr Glu Asp Glu Thr Arg
625                 630                 635                 640
Thr Gln Ile Leu Ser Ile Lys Lys Val Thr Ser Glu Asp Leu Lys Arg
                645                 650                 655
Ser Tyr Val Cys His Ala Arg Ser Ala Lys Gly Glu Val Ala Lys Ala
            660                 665                 670
Ala Lys Val Lys Gln Lys Val Pro Ala Pro Arg Tyr Thr Val Ser Gly
        675                 680                 685
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu Phe
    690                 695                 700
Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
705                 710                 715                 720
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                725                 730                 735
Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
            740                 745                 750
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
        755                 760                 765
```

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Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    770                 775                 780
Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
785                 790                 795                 800
Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
                805                 810                 815
Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
            820                 825                 830
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        835                 840                 845
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
    850                 855                 860
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
865                 870                 875                 880
Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
                885                 890                 895
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
            900                 905                 910
Leu Ser Leu Gly Lys
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<210> 19
<211> 2754
<212> DNA
<213> Homo sapiens

<400> 19

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ctggaagggg agcctgtagc cctgaggtgc ccccaggtgc cctactggtt gtgggcctct 180
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gaagaagaga cacggatgtg ggcccaggac ggtgctctgt ggcttctgcc agccttgcag 300
gaggactctg gcacctacgt ctgcactact agaaatgctt cttactgtga caaaatgtcc 360
attgagctca gagtttttga gaatacagat gctttcctgc cgttcatctc atacccgcaa 420
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gacaaaactg acgtgaagat tcaatggtac aaggattctc ttcttttgga taaagacaat 540
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actcagattt tgagcatcaa gaaagttacc tctgaggatc tcaagcgcag ctatgtctgt 1980
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<210> 20
<211> 917
<212> PRT
<213> Homo sapiens

<400> 20

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

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His Met Asp Phe Lys Cys Val Val His Asn Thr Leu Ser Phe Gln Thr
                  325                 330                 335
Leu Arg Thr Thr Val Lys Glu Ala Ser Ser Thr Phe Ser Glu Arg Cys
              340                 345                 350
Asp Asp Trp Gly Leu Asp Thr Met Arg Gln Ile Gln Val Phe Glu Asp
          355                 360                 365
Glu Pro Ala Arg Ile Lys Cys Pro Leu Phe Glu His Phe Leu Lys Phe
      370                 375                 380
Asn Tyr Ser Thr Ala His Ser Ala Gly Leu Thr Leu Ile Trp Tyr Trp
385                 390                 395                 400
Thr Arg Gln Asp Arg Asp Leu Glu Glu Pro Ile Asn Phe Arg Leu Pro
                  405                 410                 415
Glu Asn Arg Ile Ser Lys Glu Lys Asp Val Leu Trp Phe Arg Pro Thr
              420                 425                 430
Leu Leu Asn Asp Thr Gly Asn Tyr Thr Cys Met Leu Arg Asn Thr Thr
          435                 440                 445
Tyr Cys Ser Lys Val Ala Phe Pro Leu Glu Val Val Gln Lys Asp Ser
      450                 455                 460
Cys Phe Asn Ser Pro Met Lys Leu Pro Val His Lys Leu Tyr Ile Glu
465                 470                 475                 480
Tyr Gly Ile Gln Arg Ile Thr Cys Pro Asn Val Asp Gly Tyr Phe Pro
                  485                 490                 495
Ser Ser Val Lys Pro Thr Ile Thr Trp Tyr Met Gly Cys Tyr Lys Ile
              500                 505                 510
Gln Asn Phe Asn Asn Val Ile Pro Glu Gly Met Asn Leu Ser Phe Leu
          515                 520                 525
Ile Ala Leu Ile Ser Asn Asn Gly Asn Tyr Thr Cys Val Val Thr Tyr
      530                 535                 540
Pro Glu Asn Gly Arg Thr Phe His Leu Thr Arg Thr Leu Thr Val Lys
545                 550                 555                 560
Val Val Gly Ser Pro Lys Asn Ala Val Pro Pro Val Ile His Ser Pro
                  565                 570                 575
Asn Asp His Val Val Tyr Glu Lys Glu Pro Gly Glu Glu Leu Leu Ile
              580                 585                 590
Pro Cys Thr Val Tyr Phe Ser Phe Leu Met Asp Ser Arg Asn Glu Val
          595                 600                 605
Trp Trp Thr Ile Asp Gly Lys Lys Pro Asp Asp Ile Thr Ile Asp Val
      610                 615                 620
Thr Ile Asn Glu Ser Ile Ser His Ser Arg Thr Glu Asp Glu Thr Arg
625                 630                 635                 640
Thr Gln Ile Leu Ser Ile Lys Lys Val Thr Ser Glu Asp Leu Lys Arg
                  645                 650                 655
Ser Tyr Val Cys His Ala Arg Ser Ala Lys Gly Glu Val Ala Lys Ala
              660                 665                 670
Ala Lys Val Lys Gln Lys Val Pro Ala Pro Arg Tyr Thr Val Ser Gly
          675                 680                 685
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
      690                 695                 700
Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
705                 710                 715                 720
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                  725                 730                 735
Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
              740                 745                 750
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
          755                 760                 765
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
      770                 775                 780
Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
785                 790                 795                 800
Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
```

```
                805                 810                 815
Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
            820                 825                 830
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        835                 840                 845
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
    850                 855                 860
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
865                 870                 875                 880
Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
                885                 890                 895
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
            900                 905                 910
Leu Ser Leu Gly Lys
        915
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<210> 21
<211> 2748
<212> DNA
<213> Homo sapiens

<400> 21

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atggtgcttc tgtggtgtgt agtgagtctc tacttttatg gaatcctgca aagtgatgcc 60
tcagaacgct gcgatgactg gggactagac accatgaggc aaatccaagt gtttgaagat 120
gagccagctc gcatcaagtg cccactcttt gaacacttct tgaaattcaa ctacagcaca 180
gcccattcag ctggccttac tctgatctgg tattggacta ggcaggaccg ggaccttgag 240
gagccaatta acttccgcct ccccgagaac cgcattagta aggagaaaga tgtgctgtgg 300
ttccggccca ctctcctcaa tgacactggc aactatacct gcatgttaag gaacactaca 360
tattgcagca aagttgcatt tcccttggaa gttgttcaaa aagacagctg tttcaattcc 420
cccatgaaac tcccagtgca taaactgtat atagaatatg gcattcagag gatcacttgt 480
ccaaatgtag atggatattt tccttccagt gtcaaaccga ctatcacttg gtatatgggc 540
tgttataaaa tacagaattt taataatgta atacccgaag gtatgaactt gagtttcctc 600
attgccttaa tttcaaataa tggaaattac acatgtgttg ttacatatcc agaaaatgga 660
cgtacgtttc atctcaccag gactctgact gtaaaggtag taggctctcc aaaaaatgca 720
gtgccccctg tgatccattc acctaatgat catgtggtct atgagaaaga accaggagag 780
gagctactca ttccctgtac ggtctatttt agttttctga tggattctcg caatgaggtt 840
tggtggacca ttgatggaaa aaaacctgat gacatcacta ttgatgtcac cattaacgaa 900
agtataagtc atagtagaac agaagatgaa acaagaactc agattttgag catcaagaaa 960
gttacctctg aggatctcaa gcgcagctat gtctgtcatg ctagaagtgc caaaggcgaa 1020
gttgccaaag cagccaaggt gaagcagaaa gtgccagctc caagatacac agtgcacaca 1080
ggggctgcca gaagctgccg gtttcgtggg aggcattaca agcgggagtt caggctggaa 1140
ggggagcctg tagccctgag gtgcccccag gtgccctact ggttgtgggc ctctgtcagc 1200
ccccgcatca acctgacatg gcataaaaat gactctgcta ggacggtccc aggagaagaa 1260
gagacacgga tgtgggccca ggacggtgct ctgtggcttc tgccagcctt gcaggaggac 1320
tctggcacct acgtctgcac tactagaaat gcttcttact gtgacaaaat gtccattgag 1380
ctcagagttt ttgagaatac agatgctttc ctgccgttca tctcataccc gcaaatttta 1440
accttgtcaa cctctggggt attagtatgc cctgacctga gtgaattcac ccgtgacaaa 1500
actgacgtga agattcaatg gtacaaggat tctcttcttt tggataaaga caatgagaaa 1560
tttctaagtg tgaggggggac cactcactta ctcgtacacg atgtggccct ggaagatgct 1620
ggctattacc gctgtgtcct gacatttgcc catgaaggcc agcaatacaa catcactagg 1680
agtattgagc tacgcatcaa gaaaaaaaaa gaagagacca ttcctgtgat catttccccc 1740
ctcaagacca tatcagcttc tctggggtca agactgacaa tcccatgtaa ggtgtttctg 1800
ggaaccggca cacccttaac caccatgctg tggtggacgg ccaatgacac ccacatagag 1860
agcgcctacc cgggaggccg cgtgaccgag gggccacgcc aggaatattc agaaaataat 1920
gagaactaca ttgaagtgcc attgattttt gatcctgtca caagagagga tttgcacatg 1980
gattttaaat gtgttgtcca taataccctg agttttcaga cactacgcac cacagtcaag 2040
gaagcctcct ccacgttctc cggagacaaa actcacacat gcccaccgtg cccagcacct 2100
gaactcctgg ggggaccgtc agtcttcctc ttcccccaa aacccaagga caccctcatg 2160
atctcccgga cccctgaggt cacatgcgtg gtggtggacg tgagccacga agaccctgag 2220
gtcaagttca actggtacgt ggacggcgtg gaggtgcata atgccaagac aaagccgcgg 2280
```

```
gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac 2340
tggctgaatg gcaaggagta caagtgcaag gtctccaaca aagccctccc agccccatc 2400
gagaaaacca tctccaaagc caaagggcag ccccgagaac cacaggtgta caccctgccc 2460
ccatcccggg atgagctgac caagaaccag gtcagcctga cctgcctggt caaaggcttc 2520
tatcccagcg acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacaag 2580
accacgcctc ccgtgctgga ctccgacggc tccttcttcc tctatagcaa gctcaccgtg 2640
gacaagagca ggtggcagca ggggaacgtc ttctcatgct ccgtgatgca tgaggctctg 2700
cacaaccact acacgcagaa gagcctctcc ctgtctccgg gtaaatga              2748
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<210> 22
<211> 915
<212> PRT
<213> Homo sapiens

<400> 22

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

```
Arg Gly Arg His Tyr Lys Arg Glu Phe Arg Leu Glu Gly Glu Pro Val
    370                 375                 380
Ala Leu Arg Cys Pro Gln Val Pro Tyr Trp Leu Trp Ala Ser Val Ser
385                 390                 395                 400
Pro Arg Ile Asn Leu Thr Trp His Lys Asn Asp Ser Ala Arg Thr Val
                405                 410                 415
Pro Gly Glu Glu Glu Thr Arg Met Trp Ala Gln Asp Gly Ala Leu Trp
            420                 425                 430
Leu Leu Pro Ala Leu Gln Glu Asp Ser Gly Thr Tyr Val Cys Thr Thr
        435                 440                 445
Arg Asn Ala Ser Tyr Cys Asp Lys Met Ser Ile Glu Leu Arg Val Phe
    450                 455                 460
Glu Asn Thr Asp Ala Phe Leu Pro Phe Ile Ser Tyr Pro Gln Ile Leu
465                 470                 475                 480
Thr Leu Ser Thr Ser Gly Val Leu Val Cys Pro Asp Leu Ser Glu Phe
                485                 490                 495
Thr Arg Asp Lys Thr Asp Val Lys Ile Gln Trp Tyr Lys Asp Ser Leu
            500                 505                 510
Leu Leu Asp Lys Asp Asn Glu Lys Phe Leu Ser Val Arg Gly Thr Thr
        515                 520                 525
His Leu Leu Val His Asp Val Ala Leu Glu Asp Ala Gly Tyr Tyr Arg
    530                 535                 540
Cys Val Leu Thr Phe Ala His Glu Gly Gln Gln Tyr Asn Ile Thr Arg
545                 550                 555                 560
Ser Ile Glu Leu Arg Ile Lys Lys Lys Lys Glu Glu Thr Ile Pro Val
                565                 570                 575
Ile Ile Ser Pro Leu Lys Thr Ile Ser Ala Ser Leu Gly Ser Arg Leu
            580                 585                 590
Thr Ile Pro Cys Lys Val Phe Leu Gly Thr Gly Thr Pro Leu Thr Thr
        595                 600                 605

Met Leu Trp Trp Thr Ala Asn Asp Thr His Ile Glu Ser Ala Tyr Pro
    610                 615                 620
Gly Gly Arg Val Thr Glu Gly Pro Arg Gln Glu Tyr Ser Glu Asn Asn
625                 630                 635                 640
Glu Asn Tyr Ile Glu Val Pro Leu Ile Phe Asp Pro Val Thr Arg Glu
                645                 650                 655
Asp Leu His Met Asp Phe Lys Cys Val Val His Asn Thr Leu Ser Phe
            660                 665                 670
Gln Thr Leu Arg Thr Thr Val Lys Glu Ala Ser Ser Thr Phe Ser Gly
        675                 680                 685
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
    690                 695                 700
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
705                 710                 715                 720
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
                725                 730                 735
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
            740                 745                 750
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
        755                 760                 765
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
    770                 775                 780
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
785                 790                 795                 800
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
                805                 810                 815
Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
            820                 825                 830
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
        835                 840                 845
```

```
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
    850                 855                 860
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
865                 870                 875                 880
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
                885                 890                 895
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
            900                 905                 910
Pro Gly Lys
        915
```

<210> 23
<211> 2754
<212> DNA
<213> Homo sapiens

<400> 23

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tcagaacgct gcgatgactg gggactagac accatgaggc aaatccaagt gtttgaagat 120
gagccagctc gcatcaagtg cccactcttt gaacacttct tgaaattcaa ctacagcaca 180
gcccattcag ctggccttac tctgatctgg tattggacta ggcaggaccg ggaccttgag 240
gagccaatta acttccgcct ccccgagaac cgcattagta aggagaaaga tgtgctgtgg 300
ttccggccca ctctcctcaa tgacactggc aactatacct gcatgttaag gaacactaca 360
tattgcagca aagttgcatt tcccttggaa gttgttcaaa aagacagctg tttcaattcc 420
cccatgaaac tcccagtgca taaactgtat atagaatatg gcattcagag gatcacttgt 480
ccaaatgtag atggatattt tccttccagt gtcaaaccga ctatcacttg gtatatgggc 540
tgttataaaa tacagaattt taataatgta atacccgaag gtatgaactt gagtttcctc 600
attgccttaa tttcaaataa tggaaattac acatgtgttg ttacatatcc agaaaatgga 660
cgtacgtttc atctcaccag gactctgact gtaaaggtag taggctctcc aaaaaatgca 720
gtgccccctg tgatccattc acctaatgat catgtggtct atgagaaaga accaggagag 780
gagctactca ttccctgtac ggtctatttt agttttctga tggattctcg caatgaggtt 840
tggtggacca ttgatggaaa aaaacctgat gacatcacta ttgatgtcac cattaacgaa 900
agtataagtc atagtagaac agaagatgaa acaagaactc agattttgag catcaagaaa 960
gttacctctg aggatctcaa gcgcagctat gtctgtcatg ctagaagtgc caaaggcgaa 1020
gttgccaaag cagccaaggt gaagcagaaa gtgccagctc caagatacac agtgcacaca 1080
ggggctgcca gaagctgccg gtttcgtggg aggcattaca agcgggagtt caggctggaa 1140
ggggagcctg tagccctgag gtgcccccag gtgccctact ggttgtgggc ctctgtcagc 1200
ccccgcatca acctgacatg gcataaaaat gactctgcta ggacggtccc aggagaagaa 1260
gagacacgga tgtgggccca ggacggtgct ctgtggcttc tgccagcctt gcaggaggac 1320
tctggcacct acgtctgcac tactagaaat gcttcttact gtgacaaaat gtccattgag 1380
ctcagagttt ttgagaatac agatgctttc ctgccgttca tctcataccc gcaaatttta 1440
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tttctaagtg tgagggggac cactcactta ctcgtacacg atgtggccct ggaagatgct 1620
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agtattgagc tacgcatcaa gaaaaaaaaa gaagagacca ttcctgtgat catttccccc 1740
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ggaaccggca cacccttaac caccatgctg tggtggacgg ccaatgacac ccacatagag 1860
agcgcctacc cgggaggccg cgtgaccgag gggccacgcc aggaatattc agaaaataat 1920
gagaactaca ttgaagtgcc attgattttt gatcctgtca caagagagga tttgcacatg 1980
gattttaaat gtgttgtcca taataccctg agttttcaga cactacgcac cacagtcaag 2040
gaagcctcct ccacgttctc cggagagtcc aaatacggtc cgccatgccc atcatgccca 2100
gcacctgagt tcctgggggg accatcagtc ttcctgttcc ccccaaaacc caaggacact 2160
ctcatgatct cccggacccc tgaggtcacg tgcgtggtgg tggacgtgag ccaggaagac 2220
cccgaggtcc agttcaactg gtacgtggat ggcgtggagg tgcataatgc caagacaaag 2280
ccgcgggagg agcagttcaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 2340

caggactggc tgaacggcaa ggagtacaag tgcaaggtct ccaacaaagg cctcccgtcc 2400
tccatcgaga aaaccatctc caaagccaaa gggcagcccc gagagccaca ggtgtacacc 2460
ctgccccat cccaggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 2520
```

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tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaggcta 2640
accgtggaca agagcaggtg gcaggagggg aatgtcttct catgctccgt gatgcatgag 2700
gctctgcaca accactacac acagaagagc ctctccctgt ctctgggtaa atga       2754
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<210> 24
<211> 917
<212> PRT
<213> Homo sapiens

<400> 24

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

Pro Arg Ile Asn Leu Thr Trp His Lys Asn Asp Ser Ala Arg Thr Val
405 410 415
Pro Gly Glu Glu Glu Thr Arg Met Trp Ala Gln Asp Gly Ala Leu Trp
420 425 430
Leu Leu Pro Ala Leu Gln Glu Asp Ser Gly Thr Tyr Val Cys Thr Thr
435 440 445
Arg Asn Ala Ser Tyr Cys Asp Lys Met Ser Ile Glu Leu Arg Val Phe
450 455 460
Glu Asn Thr Asp Ala Phe Leu Pro Phe Ile Ser Tyr Pro Gln Ile Leu
465 470 475 480
Thr Leu Ser Thr Ser Gly Val Leu Val Cys Pro Asp Leu Ser Glu Phe
485 490 495
Thr Arg Asp Lys Thr Asp Val Lys Ile Gln Trp Tyr Lys Asp Ser Leu
500 505 510
Leu Leu Asp Lys Asp Asn Glu Lys Phe Leu Ser Val Arg Gly Thr Thr
515 520 525
His Leu Leu Val His Asp Val Ala Leu Glu Asp Ala Gly Tyr Tyr Arg
530 535 540
Cys Val Leu Thr Phe Ala His Glu Gly Gln Gln Tyr Asn Ile Thr Arg
545 550 555 560
Ser Ile Glu Leu Arg Ile Lys Lys Lys Lys Glu Glu Thr Ile Pro Val
565 570 575
Ile Ile Ser Pro Leu Lys Thr Ile Ser Ala Ser Leu Gly Ser Arg Leu
580 585 590
Thr Ile Pro Cys Lys Val Phe Leu Gly Thr Gly Thr Pro Leu Thr Thr
595 600 605
Met Leu Trp Trp Thr Ala Asn Asp Thr His Ile Glu Ser Ala Tyr Pro
610 615 620
Gly Gly Arg Val Thr Glu Gly Pro Arg Gln Glu Tyr Ser Glu Asn Asn
625 630 635 640
Glu Asn Tyr Ile Glu Val Pro Leu Ile Phe Asp Pro Val Thr Arg Glu
645 650 655
Asp Leu His Met Asp Phe Lys Cys Val Val His Asn Thr Leu Ser Phe
660 665 670
Gln Thr Leu Arg Thr Thr Val Lys Glu Ala Ser Ser Thr Phe Ser Gly
675 680 685
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu Phe
690 695 700
Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
705 710 715 720
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
725 730 735
Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
740 745 750
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
755 760 765
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
770 775 780
Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
785 790 795 800
Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
805 810 815
Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
820 825 830
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
835 840 845
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
850 855 860
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
865 870 875 880
Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser

```
                885                 890                 895
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
            900                 905                 910
Leu Ser Leu Gly Lys
        915
```

<210> 25
<211> 2754
<212> DNA
<213> Homo sapiens

<400> 25

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Leu Phe Glu His Phe Leu Lys Phe Asn Tyr Ser Thr Ala His Ser Ala
    50   55   60
Gly Leu Thr Leu Ile Trp Tyr Trp Thr Arg Gln Asp Arg Asp Leu Glu
65   70   75   80
Glu Pro Ile Asn Phe Arg Leu Pro Glu Asn Arg Ile Ser Lys Glu Lys
                85   90   95
Asp Val Leu Trp Phe Arg Pro Thr Leu Leu Asn Asp Thr Gly Asn Tyr
            100   105   110
Thr Cys Met Leu Arg Asn Thr Thr Tyr Cys Ser Lys Val Ala Phe Pro
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Leu Glu Val Val Gln Lys Asp Ser Cys Phe Asn Ser Pro Met Lys Leu
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Pro Val His Lys Leu Tyr Ile Glu Tyr Gly Ile Gln Arg Ile Thr Cys
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Pro Asn Val Asp Gly Tyr Phe Pro Ser Ser Val Lys Pro Thr Ile Thr
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Trp Tyr Met Gly Cys Tyr Lys Ile Gln Asn Phe Asn Asn Val Ile Pro
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Glu Gly Met Asn Leu Ser Phe Leu Ile Ala Leu Ile Ser Asn Asn Gly
        195   200   205
Asn Tyr Thr Cys Val Val Thr Tyr Pro Glu Asn Gly Arg Thr Phe His
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Leu Thr Arg Thr Leu Thr Val Lys Val Val Gly Ser Pro Lys Asn Ala
225   230   235   240
Val Pro Pro Val Ile His Ser Pro Asn Asp His Val Val Tyr Glu Lys
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Glu Pro Gly Glu Glu Leu Leu Ile Pro Cys Thr Val Tyr Phe Ser Phe
            260   265   270
Leu Met Asp Ser Arg Asn Glu Val Trp Trp Thr Ile Asp Gly Lys Lys
        275   280   285
Pro Asp Asp Ile Thr Ile Asp Val Thr Ile Asn Glu Ser Ile Ser His
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Ser Arg Thr Glu Asp Glu Thr Arg Thr Gln Ile Leu Ser Ile Lys Lys
305   310   315   320
Val Thr Ser Glu Asp Leu Lys Arg Ser Tyr Val Cys His Ala Arg Ser
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Ala Lys Gly Glu Val Ala Lys Ala Ala Lys Val Lys Gln Lys Val Pro
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Ala Leu Arg Cys Pro Gln Val Pro Tyr Trp Leu Trp Ala Ser Val Ser
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Pro Arg Ile Asn Leu Thr Trp His Lys Asn Asp Ser Ala Arg Thr Val
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Leu Leu Asp Lys Asp Asn Glu Lys Phe Leu Ser Val Arg Gly Thr Thr
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His Leu Leu Val His Asp Val Ala Leu Glu Asp Ala Gly Tyr Tyr Arg
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Cys Val Leu Thr Phe Ala His Glu Gly Gln Gln Tyr Asn Ile Thr Arg
545                 550                 555                 560
Ser Ile Glu Leu Arg Ile Lys Lys Lys Lys Glu Glu Thr Ile Pro Val
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Ile Ile Ser Pro Leu Lys Thr Ile Ser Ala Ser Leu Gly Ser Arg Leu
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Glu Asn Tyr Ile Glu Val Pro Leu Ile Phe Asp Pro Val Thr Arg Glu
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Asp Leu His Met Asp Phe Lys Cys Val Val His Asn Thr Leu Ser Phe
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Gln Thr Leu Arg Thr Thr Val Lys Glu Ala Ser Ser Thr Phe Ser Gly
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Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
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Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
705                 710                 715                 720
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
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            740                 745                 750
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
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Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
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Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
785                 790                 795                 800
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Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        835                 840                 845
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
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Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
865                 870                 875                 880
Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
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Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
            900                 905                 910
Leu Ser Leu Gly Lys
        915
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