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(54) Title: METHODS OF USING IL-1 ANTAGONISTS TO TREAT NEOINTIMAL HYPERPLASIA

(57) Abstract: Methods of using interleukin-1 (IL-1) antagonists to prevent or treat restenosis and other neointimal hyperplasia conditions, including atherosclerosis, vascular access dysfunction, hypertension and related vascular diseases are provided.

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METHODS OF USING IL-1 ANTAGONISTS TO TREAT NEOINTIMAL HYPERPLASIA

BACKGROUND

Field of the Invention

[0001] The invention relates to methods of using interleukin-1 (IL-1) antagonists to treat neointimal hyperplasia. In particular, the field of the invention is methods of treating restenosis and other neointimal hyperplasia conditions, including atherosclerosis, venous grafts of fistulae for hemodialysis, also known as vascular access dysfunction, bypass vein grafts, balloon angioplasty, hypertension, and related vascular diseases, using antagonists of IL-1-mediated biological activity.

Description of Related Art

[0002] Neointimal hyperplasia is the major complication associated with the progression of atherosclerotic plaques, chronic hypertension, and the injury response caused by surgical procedures treating vascular diseases, such as angioplasty and stenting. The activation of smooth muscle cells residing in the vessel wall stimulates their proliferation and migration into the intima area where they narrow the blood vessel and limit blood supply to the affected region. Surgical procedures to remove the neointima (endarterectomy) or to insert a solid support (stenting) have been the most effective treatments to correct the deficiency. Nonetheless, physical injury during these surgical procedures tends to accelerate neointima formation and cause the re-narrowing of the vessel, a process termed restenosis.

[0003] Tumor necrosis factor-α (TNFα) and interleukin-1 (IL-1) are inflammatory cytokines that stimulate expression of adhesion molecules and induce the synthesis of other pro-inflammatory cytokines. TNFα and IL-1 are also known to influence vascular smooth muscle cell migration and proliferation *in vitro*. Rectenwald et al. (2000) Circulation 102:1697-1702, have shown that TNFα and IL-1 modulate low shear stress-induced neointimal hyperplasia (NIH).

BRIEF SUMMARY OF THE INVENTION

[0004] In a first aspect, the invention features a method of treating, inhibiting, or ameliorating restenosis and other neointimal hyperplasia conditions, including atherosclerosis, vascular access dysfunction, hypertension and related vascular diseases, comprising administering to a subject in need an interleukin 1 (IL-1) antagonist. 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, interleukin-1 antagonist (IL-1ra), an anti-IL-1 antibody or fragment thereof, an anti-IL-1 receptor antibody or fragment thereof, a small molecule, or a nucleic acid capable of interfering with the expression of IL-1.

[0005] In a preferred embodiment, the IL-1 antagonist 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, herein specifically incorporated by reference in its entirety. In a specific embodiment, the IL-1 trap is the fusion protein shown in SEQ ID NO:2, 4, 6, 8, 10, 12,1 4, 16, 18, 20, 22, 24, 26. A preferred IL-1 trap is shown in SEQ ID NO:10. In another embodiment, the IL-1 antagonist is an antibody or antibody fragment capable of binding IL-1α and/or IL-1β. In another embodiment, the IL-1 antagonist is an anti-IL-1 receptor (IL-1R1 or IL-1RAcp), or a fragment thereof. 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. In another embodiment, the IL-1 antagonist is IL-1ra (SEQ ID NO:27 (full-length molecule); SEQ ID NO:28 (mature protein). In yet another embodiment, the IL-1 antagonist is a nucleic acid capable of interfering with the expression of IL-1. Examples of IL-1 antagonist nucleic acids include, for example, antisense molecules, inhibitory ribozymes designed to catalytically cleave gene mRNA transcripts encoding IL-1α, IL-1β, IL-1R1, IL-1RAcp, or short interfering RNA (siRNA) molecules.

[0006] The subject being treated is most preferably a human suffering from or at risk for the development of restenosis and other neointimal hyperplasia conditions, including atherosclerosis, vascular access dysfunction, hypertension and related vascular diseases.

[0007] The method of the invention includes administration of the IL-1 antagonist by any means

known to the art, for example, subcutaneous, intramuscular , intranasal, intraarterial, intravenous, topical, transvaginal, transdermal, transanal administration or oral routes of administration.

[0008] In a second aspect, the invention features a method of preventing or inhibiting the development of restenosis in a subject in need thereof, comprising administering an IL-1 antagonist to a subject at risk for or suffering from restenosis, such that development of restenosis or the progression of the disease is inhibited.

[0009] In a third aspect, the invention features a method of preventing or inhibiting the development of atherosclerosis in a subject in need thereof, comprising administering an IL-1 antagonist to a subject at risk for or suffering from atherosclerosis, such that development of atherosclerosis or the progression of the disease is inhibited.

[0010] In a fourth aspect, the invention features a method of preventing or inhibiting the development of vascular access dysfunction in a subject in need thereof, comprising administering an IL-1 antagonist to a subject at risk for or suffering from vascular access dysfunction, such that development of vascular access dysfunction or the progression of the disease is inhibited.

[0011] In a fifth aspect, the invention features a method of inhibiting or ameliorating neointimal hyperplasia caused by hypertension and related vascular diseases, in a subject in need thereof, comprising administering an IL-1 antagonist to a subject at risk for or suffering from neointimal hyperplasia, such that development of neointimal hyperplasia or the progression of the disease is inhibited.

[0012] Accordingly, in a sixth aspect, the invention features pharmaceutical compositions comprising IL-1 antagonists with a pharmaceutically acceptable carrier. Such pharmaceutical compositions may comprise IL-1 traps or anti-IL-1 antibodies, antisense molecules, or siRNAs. The therapeutic methods of the invention may be treated with a combination of one or more IL-1 antagonists and a second therapeutic agent.

[0013] Other objects and advantages will become apparent from a review of the ensuing detailed description.

Brief Description of the Figures

[0014] Fig. 1 shows the inhibitory effect of the IL-1 trap IL-1RAcp-IL-R1-Fc on neointima proliferation. IEL= internal elastic lamina; EEL= external elastic lamina.

[0015] Fig.2 compares wildtype and IL-1R knockout (KO) animals on neointima proliferation.

[0016] Figs. 3-4 shows the effect of APOE KO mice transfected with IL-1 trap (Fig. 3) or an Fc control and IL-1R2 trap (Fig. 4).

DETAILED DESCRIPTION

[0017] Before the present methods are described, it is to be understood that this 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, since the scope of the present invention will be limited only the appended claims.

[0018] 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, a reference to "a method" includes 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 and so forth.

[0019] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this 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. All publications mentioned herein are incorporated herein by reference in their entirety.

General Description

[0020] The invention is based in part on the finding that administration of an agent capable of blocking or inhibiting IL-1-mediated biological activity is capable of decreasing , treating or preventing restenosis and other neointimal hyperplasia conditions, including atherosclerosis, vascular access dysfunction, hypertension and related vascular diseases. Thus, the invention provides for methods of decreasing, treating or preventing restenosis and other neointimal hyperplasia conditions in a mammal by administering an IL-1 antagonist, in particular, an IL-1 trap, IL-1ra or anti-IL-1 antibodies.

Definitions

[0021] 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. More specifically, an example of an IL-1 blocker or inhibitor is an IL-1 antagonist including, but not limited to, IL-1 trap.

[0022] By the term "therapeutically 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).

IL-1 Trap Antagonists

[0023] Interleukin-1 (IL-1) traps are multimers of fusion proteins containing IL-1 receptor components and a multimerizing component capable of interacting with the multimerizing component present in another fusion protein to form a higher order structure, such as a dimer. Cytokine traps are a novel extension of the receptor-Fc fusion concept in that they include two distinct receptor components that bind a single cytokine, resulting in the generation of antagonists with dramatically increased affinity over that offered by single component reagents. In fact, the cytokine traps that are described herein are among the most potent cytokine blockers ever described. Briefly, the cytokine traps called IL-1 traps are comprised of the extracellular domain of human IL-1R Type I (IL-1RI) or Type II (IL-1RII) followed by the extracellular domain of human IL-1 Accessory protein (IL-1AcP), followed by a multimerizing component. In a preferred embodiment, the multimerizing component is an immunoglobulin-derived domain, such as, for example, the Fc region of human IgG, including part of the hinge region, the CH2 and CH3 domains. Alternatively, the IL-1 traps are comprised of the extracellular domain of human IL-1AcP, followed by the extracellular domain of human IL-1RI or IL-1RII, followed by a multimerizing component. For a more detailed description of the IL-1 traps, see WO 00/18932, which publication is herein specifically incorporated by reference in its entirety. Preferred IL-1 traps have the amino acid sequence shown in SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, and 26.

[0024] In specific embodiments, the IL-1 antagonist comprises an antibody fragment capable of

binding IL-1α, IL-1β, IL-1R1 and/or IL-1RAcp, or a fragment thereof. One embodiment of an IL-1 antagonist comprising one or more antibody fragments, for example, single chain Fv (scFv), is described in U.S. 6,472,179, which publication is herein specifically incorporated by reference in its entirety. In all of the IL-1 antagonist embodiments comprising one or more antibody-derived components specific for IL-1 or an IL-1 receptor, the components may be arranged in a variety of configurations, e.g., a IL-1 receptor component(s)-scFv(s)-multimerizing component; IL-1 receptor component(s)-multimerizing component-scFv(s); scFv(s)-IL-1 receptor component(s)-multimerizing component, etc., so long as the molecule or multimer is capable of inhibiting the biological activity of IL-1. In another embodiment, the IL-1 antagonist is IL-1ra, including the full length protein of SEQ ID NO:27 or the mature protein of SEQ ID NO:28.

Anti-IL-1 Human Antibodies and Antibody Fragments

[0025] In another embodiment of the IL-1 antagonist useful in the method of the invention, examples of anti-IL-1 antibodies are disclosed in US 4,935,343; US 5,681,933; WO 95/01997; EP 0267611, US 6,419,944; WO 02/16436 and WO 01/53353. The IL-1 antagonist of the invention may include an antibody or antibody fragment specific for an IL-1 ligand (e.g., IL-1α or IL-1β) and/or an IL-1 receptor (e.g., IL-1R1 and/or IL-1RAcp). Antibody fragments include any fragment having the required target specificity, e.g. antibody fragments either produced by the modification of whole antibodies (e.g. enzymatic digestion), or those synthesized *de novo* using recombinant DNA methodologies (scFv, single domain antibodies or dAbs, single variable domain antibodies) or those identified using human phase display libraries (see, for example, McCafferty et al. (1990) Nature 348:552-554). Alternatively, antibodies can be isolated from mice producing human or human-mouse chimeric antibodies using standard immunization and antibody isolation methods, including but not limited to making hybridomas, or using B cell screening technologies, such as SLAM. Immunoglobulin binding domains also include, but are not limited to, the variable regions of the heavy (V_H) or the light (V_L) chains of immunoglobulins.

[0026] The term "antibody" as used herein refers to a polypeptide comprising a framework region from an immunoglobulin gene or fragments thereof that specifically binds and recognizes an antigen. The recognized immunoglobulin genes include the kappa, lambda , alpha, gamma, delta, epsilon, and mu constant regions, as well as the myriad immunoglobulin variable region genes. Light chains are classified as either kappa or lambda. Heavy chains are classified as gamma, mu,

alpha, delta, or epsilon, which in turn define the immunoglobulin classes, IgG, IgM, IgA, IgD, and IgE, respectively. Within each IgG class, there are different isotypes (eg. IgG_1, IgG_2, IgG_3, IgG_4). Typically, the antigen-binding region of an antibody will be the most critical in determining specificity and affinity of binding.

[0027] An exemplary immunoglobulin (antibody) structural unit comprises a tetramer. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one light chain (about 25 kD) and one heavy chain (about 50-70 kD). The N-terminus of each chain defines a variable region of about 100-110 or more amino acids primarily responsible for antigen recognition. The terms "variable light chain" (V_L) and variable heavy chain (V_H) refer to these light and heavy chains respectively.

[0028] Antibodies exist as intact immunoglobulins, or as a number of well-characterized fragments produced by digestion with various peptidases. For example, pepsin digests an antibody below the disulfide linkages in the hinge region to produce $F(ab)'_2$, a dimer of Fab which itself is a light chain joined to V_H-C_H1 by a disulfide bond. The $F(ab)'_2$ may be reduced under mild conditions to break the disulfide linkage in the hinge region, thereby converting the $F(ab)'_2$ dimer into an Fab' monomer. The Fab' monomer is essentially Fab with part of the hinge region. While various antibody fragments are defined in terms of the digestion of an intact antibody, one of skill will appreciate that such fragments may be synthesized *de novo* either chemically or by using recombinant DNA methodology.

[0029] Methods for preparing antibodies are known to the art. See, for example, Kohler & Milstein (1975) Nature 256:495-497; Harlow & Lane (1988) Antibodies: a Laboratory Manual, Cold Spring Harbor Lab., Cold Spring Harbor, NY). The genes encoding the heavy and light chains of an antibody of interest can be cloned from a cell, e.g., the genes encoding a monoclonal antibody can be cloned from a hybridoma and used to produce a recombinant monoclonal antibody. Monoclonal antibodies can be humanized using standard cloning of the CDR regions into a human scaffold. Gene libraries encoding human heavy and light chains of monoclonal antibodies can also be made from hybridoma or plasma cells. Random combinations of the heavy and light chain gene products generate a large pool of antibodies with different antigenic specificity. Techniques for the production of single chain antibodies or recombinant antibodies (US 4,946,778; US 4,816,567) can be adapted to produce antibodies used in the fusion proteins and methods of the instant invention. Also, transgenic mice, or other organisms such as other

mammals, may be used to express human, human-mouse chimeric, or humanized antibodies. Alternatively, phage display technology can be used to identify human antibodies and heteromeric Fab fragments that specifically bind to selected antigens.

Antibody Screening and Selection

[0030] Screening and selection of preferred antibodies can be conducted by a variety of methods known to the art. Initial screening for the presence of monoclonal antibodies specific to a target antigen may be conducted through the use of ELISA-based methods, for example. A secondary screen is preferably conducted to identify and select a desired monoclonal antibody for use in construction of the multi-specific fusion proteins of the invention. Secondary screening may be conducted with any suitable method known to the art. One preferred method, termed "Biosensor Modification-Assisted Profiling" ("BiaMAP") is described in co-pending USSN 60/423,017 filed 01 Nov 2002, herein specifically incorporated by reference in its entirety. BiaMAP allows rapid identification of hybridoma clones producing monoclonal antibodies with desired characteristics. More specifically, monoclonal antibodies are sorted into distinct epitope-related groups based on evaluation of antibody:antigen interactions. Antibodies capable of blocking either a ligand or a receptor may be identified by a cell based assay, such as a luciferase assay utilizing a luciferase gene under the control of an NFKB driven promoter. Stimulation of the IL-1 receptors by IL-1 ligands leads to a signal through NFKB thus increasing luciferase levels in the cell. Blocking antibodies are identified as those antibodies that blocked IL-1 induction of luciferase activity.

Antisense Nucleic Acids

[0031] In a further embodiment, IL-1-mediated biological activity is blocked or inhibited by the use of IL-1 antisense nucleic acids. The present invention provides the therapeutic or prophylactic use of nucleic acids comprising at least six nucleotides that are antisense to the gene or cDNA encoding IL-1α, IL-1β, IL-1R1, or IL-1RAcp or portions thereof. As used herein, IL-1 "antisense" nucleic acids refers to nucleic acids capable of hybridizing by virtue of some sequence complementarity to a portion of an RNA (preferably mRNA) encoding IL-1α, IL-1β, IL-1R1, or IL-1RAcp. The antisense nucleic acids may be complementary to a coding and/or noncoding region of an mRNA encoding IL-1α, IL-1β, IL-1R1, or IL-1RAcp. Such antisense nucleic acids have utility as compounds that prevent IL-1α, IL-1β, IL-1R1, or IL-1RAcp expression, and can

be used in the prevention or treatment of restenosis and other neointimal hyperplasia conditions, including atherosclerosis, vascular access dysfunction, hypertension and related vascular diseases. The antisense nucleic acids of the invention are double-stranded or single-stranded oligonucleotides, RNA or DNA or a modification or derivative thereof, and can be directly administered to a cell or produced intracellularly by transcription of exogenous, introduced sequences.

[0032] The invention further provides pharmaceutical compositions comprising a therapeutically effective amount of IL-1α, IL-1β, IL-1R1, or IL-1RAcp antisense nucleic acids, and a pharmaceutically acceptable carrier, vehicle or diluent.

[0033] The IL-1α, IL-1β, IL-1R1, or IL-1RAcp antisense nucleic acids are of at least six nucleotides and are preferably oligonucleotides ranging from 6 to about 50 oligonucleotides. In specific aspects, the oligonucleotide is at least 10 nucleotides, at least 15 nucleotides, at least 100 nucleotides, or at least 200 nucleotides. The oligonucleotides can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof and can be single-stranded or double-stranded.

Short interfering RNAs

[0034] In another embodiment, IL-1α, IL-1β, IL-1R1, or IL-1RAcp expression is inhibited by a short interfering RNA (siRNA) through RNA interference (RNAi) or post-transcriptional gene silencing (PTGS) (see, for example, Ketting et al. (2001) Genes Develop. 15:2654-2659). siRNA molecules can target homologous mRNA molecules for destruction by cleaving the mRNA molecule within the region spanned by the siRNA molecule. Accordingly, siRNAs capable of targeting and cleaving homologous IL-1α, IL-1β, IL-1R1, or IL-1RAcp mRNA are useful for preventing or treating restenosis and other neointimal hyperplasia conditions, including atherosclerosis, vascular access dysfunction, hypertension and related vascular diseases.

Inhibitory Ribozymes

[0035] In another embodiment, restenosis and other neointimal hyperplasia conditions, including atherosclerosis, vascular access dysfunction, hypertension and related vascular diseases may be treated in a subject suffering from such diseases or disorders by decreasing the level of IL-1-mediated biological activity by using ribozyme molecules designed to catalytically cleave gene

mRNA transcripts encoding IL-1α, IL-1β, IL-1R1, or IL-1RAcp, preventing translation of target gene mRNA and, therefore, expression of the gene product.

[0036] Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme molecule to complementary target RNA, followed by an endonucleolytic cleavage event. The composition of ribozyme molecules must include one or more sequences complementary to the target gene mRNA, and must include the well known catalytic sequence responsible for mRNA cleavage. For this sequence, see, *e.g.*, U.S. Patent No. 5,093,246. While ribozymes that cleave mRNA at site-specific recognition sequences can be used to destroy mRNAs encoding IL-1α, IL-1β, IL-1R1, or IL-1RAcp, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA has the following sequence of two bases: 5'-UG-3'. The construction and production of hammerhead ribozymes is well known in the art. The ribozymes of the present invention also include RNA endoribonucleases (hereinafter "Cech-type ribozymes") such as the one that occurs naturally in *Tetrahymena thermophila* (known as the IVS, or L-19 IVS RNA). The Cech-type ribozymes have an eight base pair active site that hybridizes to a target RNA sequence where after cleavage of the target RNA takes place. The invention encompasses those Cech-type ribozymes that target eight base-pair active site sequences that are present in the genes encoding IL-1α, IL-1β, IL-1R1, or IL-1RAcp.

[0037] Standard methods for assessing cardiovascular health can be used to determine whether a subject is positively responding to treatment with the IL-1 antagonists. For example, after treatment with a IL-1 cytokine antagonist of the invention, a physician may choose to administer a stress test to determine that the subject is benefiting from administration of the cytokine antagonist. Generally the physician will monitor the patients activity level and general health to assess whether the subject is benefiting from administration of the cytokine antagonist. Thus, these as well as other methods known to the art, may be used to determine the extent to which the methods of the present invention are effective at treating neointimal hyperplasia including restenosis.

Treatment Population

[0038] Treatment population would include those people with vascular diseases being treated with coronary bypass surgery, angioplasty treatment, treatment with stents or drug coated stents; hemodialysis patients requiring grafts or fistulae; patients with elevated CRP levels with a history of vascular disease or atherosclerosis; patients diagnosed with peripheral vascular disease or hypertension; patients diagnosed with Buerger's disease, critical limb ischemia or thromboangiitis obliterans; patients undergoing vascular surgery for example, varicose veins, aneurysms, or arotic dissection.

Methods of Administration

[0039] The invention provides methods of treatment comprising administering to a subject an effective amount of an agent of the invention. In a preferred aspect, the agent is substantially purified (*e.g.*, substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, *e.g.,* such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably human.

[0040] Various delivery systems are known and can be used to administer an agent of the invention, *e.g.*, encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, *e.g.*, Wu and Wu, 1987, J. Biol. Chem. 262:4429-4432), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction can be enteral or parenteral and include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, *e.g.*, by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

[0041] In a specific embodiment, it may be desirable to administer the pharmaceutical

compositions of the invention locally to the area in need of treatment; this may be achieved, for example, and not by way of limitation, by local infusion during surgery, topical application, *e.g.*, by injection, by means of a catheter, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, fibers, commercial skin substitutes or angioplasty balloons or stents.

[0042] In another embodiment, the active agent can be delivered in a vesicle, in particular a liposome (see Langer (1990) Science 249:1527-1533). In yet another embodiment, the active agent can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer (1990) *supra*). In another embodiment, polymeric materials can be used (see Howard et al. (1989) J. Neurosurg. 71:105). In another embodiment where the active agent of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered *in vivo* to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, *e.g.*, by use of a retroviral vector (see, for example, U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (*e.g.*, a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox-like peptide which is known to enter the nucleus (see *e.g.*, Joliot et al., 1991, Proc. Natl. Acad. Sci. USA 88:1864-1868), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

Cellular Transfection and Gene Therapy

[0043] The present invention encompasses the use of nucleic acids encoding the IL-1-specific fusion proteins of the invention for transfection of cells *in vitro* and *in vivo*. These nucleic acids can be inserted into any of a number of well-known vectors for transfection of target cells and organisms. The nucleic acids are transfected into cells *ex vivo* and *in vivo*, through the interaction of the vector and the target cell. Reintroduction of transfected cells may be accomplished by any method known to the art, including re-implantation of encapsulated cells. The compositions are administered (e.g., by injection into a muscle) to a subject in an amount sufficient to elicit a therapeutic response. An amount adequate to accomplish this is defined as "a therapeutically effective dose or amount."

[0044] In another aspect, the invention provides a method of treating or preventing neointimal

hyperplasia in a human comprising transfecting a cell with a nucleic acid encoding an IL-1-specific fusion protein of the invention, antibody or IL-1ra, wherein the nucleic acid comprises an inducible promoter operably linked to the nucleic acid encoding the IL-1-specific fusion protein antibody or IL-1ra. For gene therapy procedures in the treatment or prevention of human disease, see for example, Van Brunt (1998) Biotechnology 6:1149-1154.

Combination Therapies

[0045] In numerous embodiments, the IL-1 antagonists of the present invention may be administered in combination with one or more additional compounds or therapies or surgical procedures. For example, a suitable therapeutic agent for use in combination, either alternating or simultaneously, with the IL-1 antagonists may include anti-platelet therapy such as aspirin, Reopro™ (Lilly), anti-p-selectin antibodies; antithrombolic and blood thinning agents, such as Retavse™ (Centocor); Streptase™ (AstraZeneca), TNKase™ (Genentech), Ticlid™ (Roche) and Plavix™ (Bristol-Myers Squibb) and heparin; HMG-CoA reductase inhibitors, such as Baycol™ (Bayer), Lescol™ (Noavartis), Lipitor™ (Pfizer), Mevacor™ (Merck), Pravachol™ (Bristol Myers Squibb, Zocor™ (Merck) or antilipidemic agents such as, Colestid™ (Pfizer), WelChol™ (Sankyo), Atromid-S™ (Wyeth), Lopid™ (Pfizer), Tricor™ (Abbott); agents effective to treat or prevent restenosis such as Sirolimus ™ (Wyeth, Johnson & Johnson), dexamethasone (Merck), Predisolone™ (Muro, Mylan, Watson, We), Tacrolimus™ (Fujisawa), Pimecrolimus ™ (Novartis) Taxol/Paclitaxel (Bristol-Myers Squibb), or Methotrexate (Baxter, Mylan, Roxane) ; anti-fibrolytic agents such as antibodies against TGFß PDGF, or CTGF; PDGF inhibitors such as Gleevec™ (Novartis); anti-inflammatory agents such as antibodies, peptides and other inhibitors of CD11a/CD8 (Mac1) [Raptiva™ (Genentech)], ICAM, C5a and TNFa [Humira™ (Abbott), Enbrel™ (Amgen), Remicade™ (Centocor)], Thalidomide™ (Celltech); hypertension drugs, such as ACE inhibitors [Accupril™ (Parke-Davis); Altace™ (Monarch); Captopril™ (Mylan); Enalaprilate™ (Baxter); Lotensin™ (Novartis); Mavik™ (Bristol-Myers Squibb); Prinivil™ (Merck); Univasc™ (Schwarz), Vasotec™ (Merck)]. In addition the IL-1 antagonists may be used in combination, either alternating or simultaneously, with surgical procedures including but not limited to surgical stenting and balloon angioplasty.

Pharmaceutical Compositions

[0046] The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of an active agent, and a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable" means approved 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. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin.

[0047] In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lidocaine to ease pain at the site of the injection. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[0048] The active agents of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with free amino groups such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with

free carboxyl groups such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

[0049] The amount of the active agent of the invention which will be effective in the treatment of delayed-type hypersensitivity can be determined by standard clinical techniques based on the present description. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the condition, and should be decided according to the judgment of the practitioner and each subject's circumstances. However, suitable dosage ranges for intravenous administration are generally about 20 micrograms to 2 grams of active compound per kilogram body weight. Suitable dosage ranges for intra-nasal administration are generally about 0.01 pg/kg body weight to 1 mg/kg body weight. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

[0050] For systemic administration, a therapeutically effective dose can be estimated initially from *in vitro* assays. For example, a dose can be formulated in animal models to achieve a circulating concentration range that includes the IC_{50} as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Initial dosages can also be estimated from *in vivo* data, e.g., animal models, using techniques that are well known in the art. One having ordinary skill in the art could readily optimize administration to humans based on animal data.

[0051] Dosage amount and interval may be adjusted individually to provide plasma levels of the compounds that are sufficient to maintain therapeutic effect. In cases of local administration or selective uptake, the effective local concentration of the compounds may not be related to plasma concentration. One having skill in the art will be able to optimize therapeutically effective local dosages without undue experimentation.

[0052] The amount of compound administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration, and the judgment of the prescribing physician. The therapy may be repeated intermittently while symptoms are detectable or even when they are not detectable. The therapy may be provided alone or in combination with other drugs.

Kits

[0053] The invention also provides an article of manufacturing comprising packaging material and a pharmaceutical agent contained within the packaging material, wherein the pharmaceutical agent comprises at least one IL-1-specific fusion protein of the invention and wherein the packaging material comprises a label or package insert which indicates that the IL-1-specific fusion protein can be used for treating neointimal hyperplasia.

[0054] Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

EXAMPLES

[0055] The following example is put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the methods and compositions of the invention, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1. Experimental protocol and surgical procedures

[0056] Animals: C57Bl6 mice, interleukin-1 receptor type I deficient (IL-1RI -/-) mice and apolipoprotein E deficient (APOE -/-) mice at the age of 8 to 12 weeks were used in this study to assess vascular response to injury. Both of the genetically modified mice are congenic to the C57Bl6 background. All animals were purchased from Jackson Laboratories (Bar Harbor, ME). Mice were housed in individual cages after surgery and were allowed *ad libitum* access to regular chow and water.

[0057] Vascular injury model: Vascular injury was induced by surgical ligation of the left common carotid artery before bifurcation. Mice were anesthetized by intraperitoneal injection of a Ketamine/xylazine solution. After anesthesia was attained, a midline incision was made at the tracheal area from the caudal end of the larynx to the suprasternal notch. After separating the

sternothyroideus muscle on the left side, the pulsating carotid artery was identified and ligated with sterile 6-0 silk sutures. The skin was closed with sterile sutures.

[0058] Delivery of murine IL-1 trap: Expression of murine IL-1 trap was introduced using a hydrodynamics-based administration of plasmid DNA via tail vein injection. Four days prior to surgery, animals were divided equally into two groups. One group of mice received 50-100 μg/animal plasmid DNA carrying the murine IL-1 trap expression vector. The other group of mice received an equal amount of empty control vector DNA. Mice were anesthetized using Isoflurane™. Plasmid DNA diluted in sterile saline in an amount equivalent to 10% (V/W) of the mouse body weight was injected promptly into tail vein.

[0059] Tissue harvesting and preparation: Twenty-eight days after carotid artery ligation, the mice were anesthetized and whole blood was collected from each mouse through cardiac puncture. Subsequently, mice were perfused with saline followed by 10% neutral buffered formalin through the left cardiac ventricle. The entire neck section was collected from each mouse and post-fixed in 10% formalin for an additional 48 hours. Fixed neck tissue was decalcified in 10% EDTA solution for 8 days with frequent changes of fresh solution. Decalcified neck tissue were embedded in gelatin by sequential incubation in 5%, 10% and 25% gelatin solution and prepared for cryosection. Ligation sites were identified by suture position. Seven successive 10 mm sections at 500 mm intervals proximal to the ligation site were used for morphometric analysis per mouse.

[0060] Morphometry: Cryosections were stained with standard hematoxylin and eosin methodology. The images of injured arteries and contra-lateral uninjured arteries were captured using a Nikon Microphot microscope and SPOT software and a SPOT RT COLOR camera. The length encircling the lumen, the internal elastic lamina (IEL) and the external elastic lamina (EEL) was determined by digitally tracing the perimeter of each layer using Bersoft Image Measurement 2.01 software. The length was then converted to circumference assuming the native artery formed a circular structure to calculate the area. The neointima area was defined as the difference between the areas of lumen and IEL. The thickness of media was calculated as the difference of radius between IEL and EEL.

[0061] Results. A mouse vascular injury model was used to investigate factors mediating the formation of neointima. The left common carotid artery of C57Bl/6 mouse was surgically ligated at the position before the bifurcation. The occlusion of the common carotid artery stimulates

significant neointima formation proximal to the ligation site over a four week period. Interleukin-1b appears to play an important role in this response because (1) the expression of interleukin-1b is substantially increased under the injury condition and (2) the neointima formation is suppressed in a genetically engineered mouse lacking the signal transducing receptor of interleukin-1 (IL-1RI knockout mouse) (Rectenwald (2000) Circulation 102:1967-1702). However, IL-1α may also play a role, thus the IL-1 traps are a superior method of blocking the response over those that block only a single IL-1 ligand.

[0062] To examine if the interleukin-1 antagonist IL-1 trap can inhibit neointima formation, IL-1 trap IL-1RAcp-IL-1R1-Fc trap expressed *in vivo* using a hydrodynamic-based transfection method with plasmid DNA vector four days prior to the surgery. Half of C57Bl/6 mice (N=10) received plasmid DNA carrying an IL-1 trap expression vectors. Others were injected with empty control vector DNA. Four weeks after surgical injury, mice were sacrificed for subsequent analyses. Histological examination of the injured vessels revealed that the neointima formation was completely blocked in IL-1 trap-expressing animals, whereas the arteries from the vector control group revealed a significant accumulation of cells under the endothelial cell layer. Morphometric quantitation of the common carotid arteries over a 3.5 mm length demonstrated the inhibitory effect of the IL-1Racp-IL-1R1-Fc trap in neointima proliferation (Fig. 1). The neointimal growth is determined as the area between the IEL, and the lumen and thus is the difference between the IEL and Lumen radii. The effect of the lack of IL-1R1 in knockout mice is shown in Fig. 2. Similar reductions on neointimal growth were seen in the trap-treated mice as were seen in the IL-1R1 knockout indicating the IL-1 trap has an effect similar to a complete blockade of IL-1 signaling.

[0063] APOE is a surface protein of serum lipoprotein particles whose deficiency results in hypercholesterolemia and spontaneous atherosclerotic plaque formation in APOE knockout mice. APOE deficiency also exacerbates arterial injury causing increased neointima formation with necrotic cores similar to advanced fibroatheroma. To test if the IL-1 trap could prevent the neointima formation under APOE-deficient conditions, APOE knockout mice were transfected with either an IL-1RAcp-IL-1R1-Fc or IL-1Acrp-IL-1R2-Fc trap expression vector or an Fc control vector before surgical injury. At 28 days after surgical injury, IL-1 trap treatments caused a 85% reduction of neointima area including the fibrous cap (Figs. 3 and 4). This confirms that the IL-1 Traps are potent blockers of neointima formation under hypercholesterolemia condition.

CLAIMS

We claim,

1. Use of an interleukin-1 (IL-1) antagonist in the preparation of a medicament for the treatment of neointimal hyperplasia in a mammal.

2. The use of claim 1, wherein the neointinal hyperplasia is restenosis.

3. The use of claim 1, wherein the neointimal hyperplasia is atherosclerosis.

4. The use of claim 1, wherein the neointimal hyperplasia is vascular access dysfunction.

5. The use of claim 1, wherein the neointimal hyperplasia is caused by surgical stenting, angioplasty, or vascular grafting.

6. The use of any of claims 1 to 5, wherein the IL-1 antagonist blocks IL-1 activity or expression.

7. The use of claim 6, wherein the IL-1 antagonist is selected from the group consisting of an anti-IL-1 antibody or antibody fragment, an anti-IL-1R1 antibody or antibody fragment, an antiIL-1RAcp antibody or antibody fragment, an IL-1 trap, IL-1Ra, an antisense molecule, an inhibitory ribozyme designed to catalytically cleave gene mRNA transcripts encoding IL-1α, IL-1β, IL-1R1, IL-1RAcp, and a short interfering RNA (siRNA) molecule.

8. The use of claim 7, wherein the IL-1 trap comprises (i) one or more IL-1 receptor components or fragments thereof, (ii) one or more antibody or antibody fragments specific to an IL-1 ligand or an IL-1 receptor, or fragments thereof, or a combination of receptor components and antibody fragments, and (iii) a multimerizing component.

9. The use of claim 8, wherein the multimerizing component is an immunoglobulin-derived domain.

10. The use of claim 1, wherein the subject is a human.

11. The use of claim 1, wherein the administration is subcutaneous, intramuscular, intranasal, intraarterial, intravenous, topical, transvaginal, transdermal, transanal administration or oral routes of administration.

12. A pharmaceutical composition comprising an IL-1 antagonist and a pharmaceutically acceptable carrier.

13. The pharmaceutical composition of claim 12, wherein the IL-1 antagonist blocks IL-1 activity or expression.

14. The pharmaceutical composition of claim 13, wherein the IL-1 antagonist is selected from the group consisting of an anti-IL-1 antibody or antibody fragment, an anti-IL-1R1 antibody or antibody fragment, an antiIL-1RAcp antibody or antibodyfragment, an IL-1 trap, IL-1Ra, an antisense molecule, an inhibitory ribozyme designed to catalytically cleave gene mRNA transcripts encoding IL-1α, IL-1β, IL-1R1, IL-1RAcp, and a short interfering RNA (siRNA) molecule.

15. The pharmaceutical composition of claim 14, wherein the IL-1 trap comprises (i) one or more IL-1 receptor components or fragments thereof, (ii) one or more antibody or antibody fragments specific to an IL-1 ligand or an IL-1 receptor, or fragments thereof, or a combination of receptor components and antibody fragments, and (iii) a multimerizing component.

16. The pharmaceutical composition of claim 15, wherein the multimerizing component is an immunoglobulin-derived domain.

17. Use of a cytokine antagonist in the preparation of a medicament for the treatment or prevention of neointimal hyperplasia in a mammal.

18. The use of claim 17, wherein the neointinal hyperplasia is restenosis, atherosclerosis, or vascular access dysfunction.

19. The use of claim 18, wherein the neointimal hyperplasia is caused by surgical stenting, angioplasty, or vascular grafting.

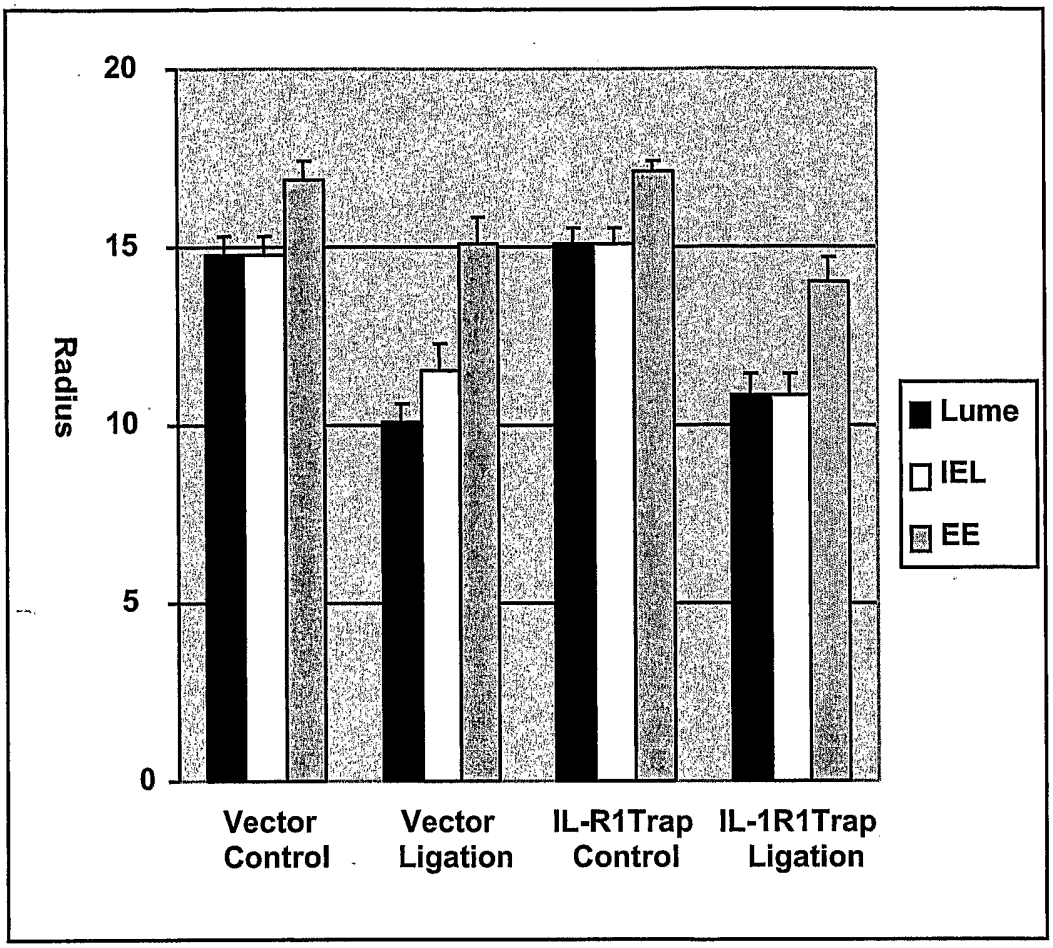
20. An article of manufacturing, comprising:

(a) packaging material; and

(b) a pharmaceutical gent contained within the packaging materi9al;

wherein the pharmaceutical agent comprises at least one interleuking-1 (IL-1) trap of the invention and wherein the packaging material comprises a label or package insert which indicates the IL-1 trap can be used for the treatment of neointimal hyperplasia.

Figure 1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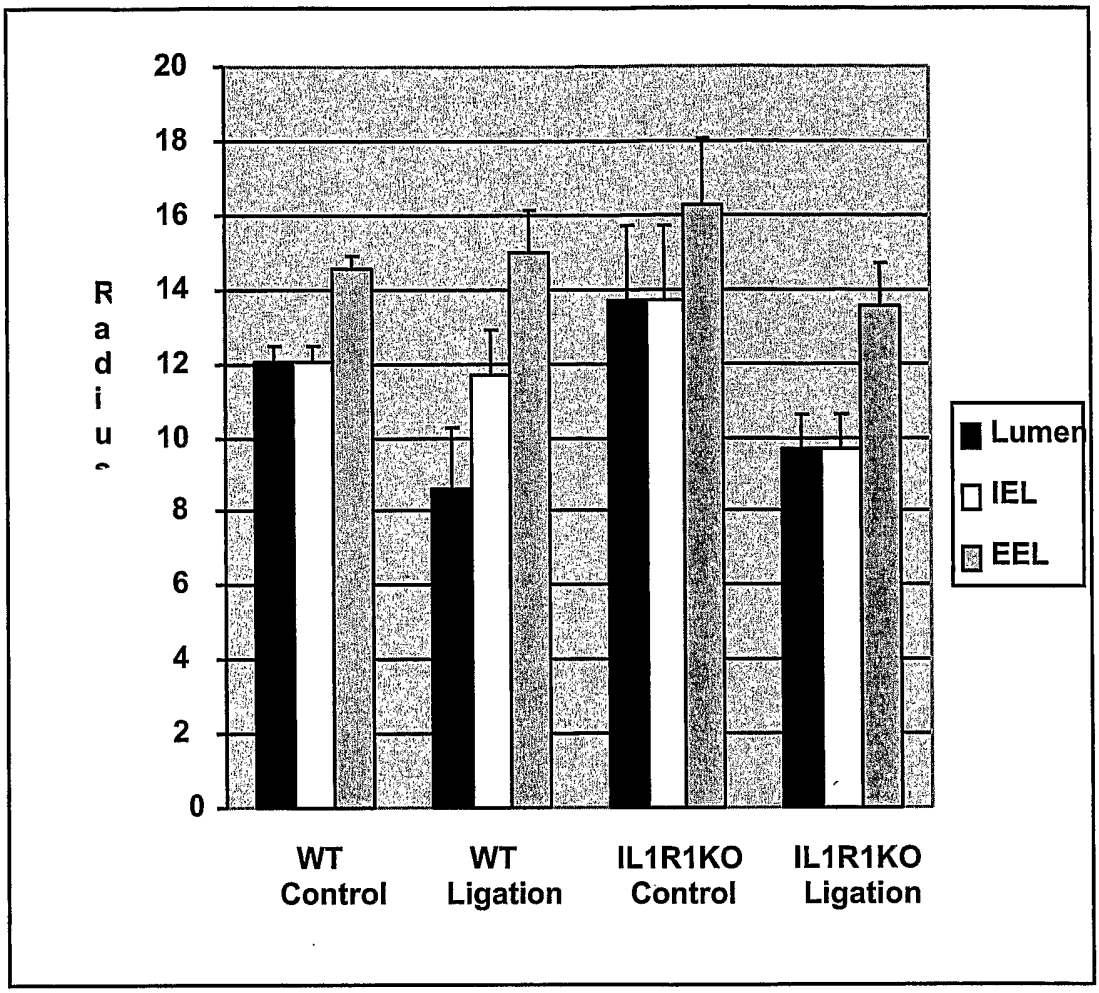
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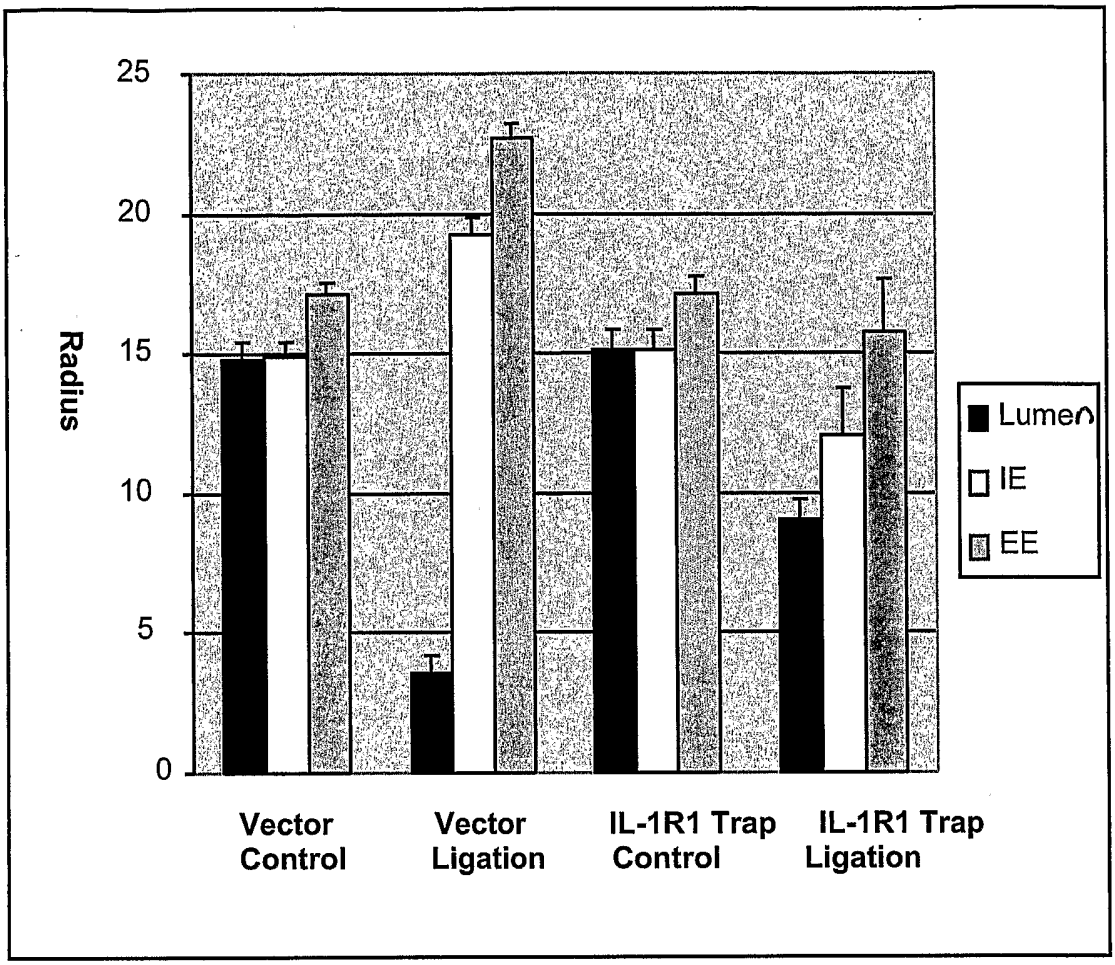
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IL-1R1 Trap Ligation

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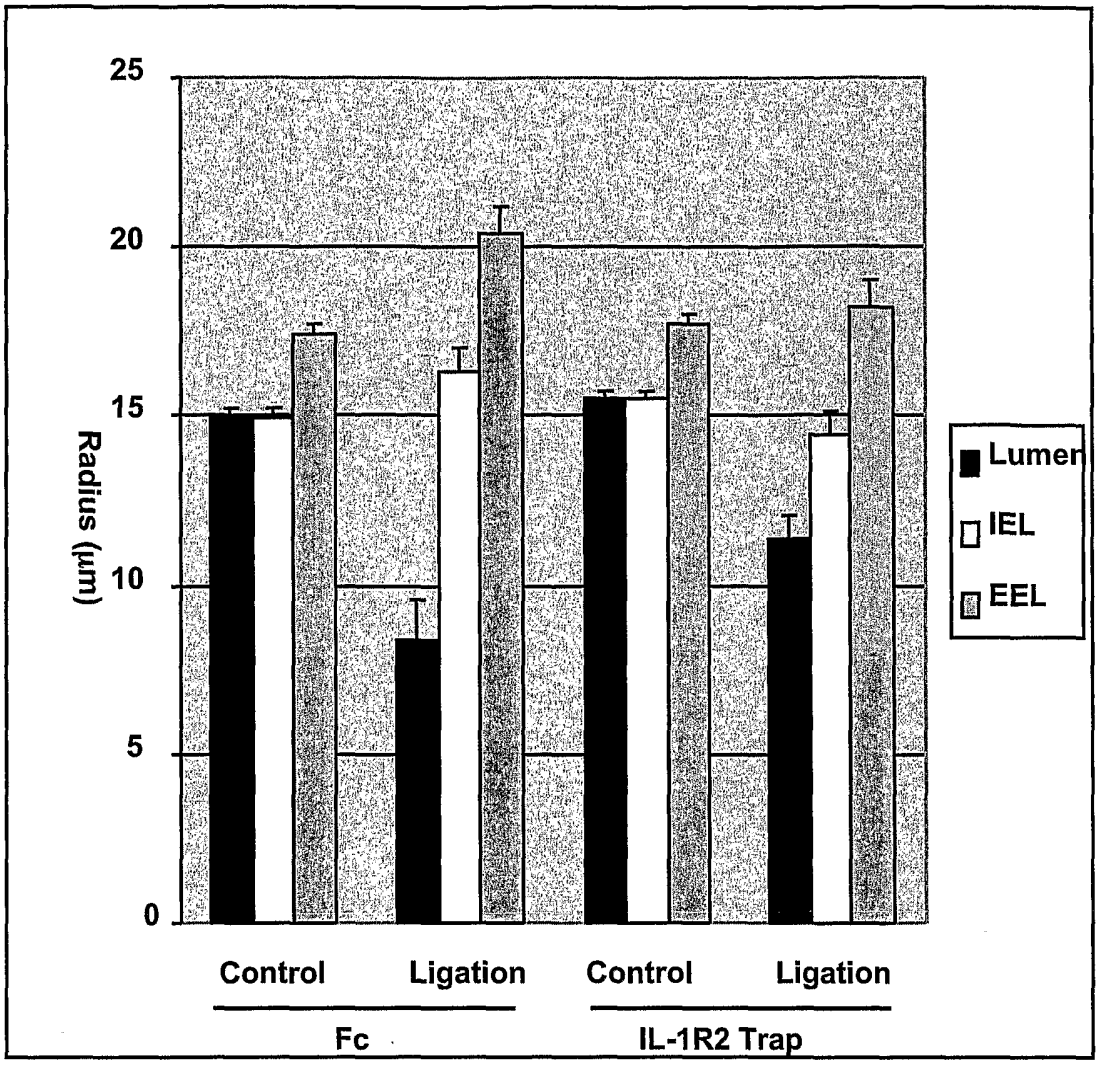
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Radius (μm)
Lumen
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Fc
IL-1R2 Trap

SEQUENCE LISTING

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<120> Methods of Using IL-1 Antagonists to Treat Neointimal Hyperplasia

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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
    530                 535                 540
His Ala Ser Tyr Thr Tyr Leu Gly Lys Gln Tyr Pro Ile Thr Arg Val
545                 550                 555                 560
Ile Glu Phe Ile Thr Leu Glu Glu Asn Lys Pro Thr Arg Pro Val Ile
                565                 570                 575
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
                645                 650                 655
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Pro Phe Thr Cys Phe Ala Lys Asn Thr His Gly Ile Asp Ala Ala Tyr
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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
    690                 695                 700
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
            820                 825                 830
Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
        835                 840                 845
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
                885                 890                 895
Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
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<213> Homo sapiens

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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
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gagaaccgca ttagtaagga gaaagatgtg ctgtggttcc ggcccactct cctcaatgac    1260
actggcaact atacctgcat gttaaggaac actacatatt gcagcaaagt tgcatttccc    1320
ttggaagttg ttcaaaaaga cagctgtttc aattccccca tgaaactccc agtgcataaa    1380
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gagaacaact acaagaccac gcctcccgtg ctggactccg acggctcctt cttcctctat    2580
agcaagctca ccgtggacaa gagcaggtgg cagcagggga acgtcttctc atgctccgtg    2640
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tga                                                                  2703

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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
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Lys Asp Arg Leu Ile Val Met Asn Val Ala Glu Lys His Arg Gly Asn
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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
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
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Val Val Gly Ser Pro Lys Asn Ala Val Pro Pro Val Ile His Ser Pro
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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
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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
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 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
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Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
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Ser Pro Gly Lys
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<213> Homo sapiens

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agcaagacac ctgtatctac agaacaagcc tccaggattc atcaacacaa agagaaactt 240
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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
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tggaatgggt cagtaattga tgaagatgac ccagtgctag gggaagacta ttacagtgtg 840
gaaaatcctg caaacaaaag aaggagtacc ctcatcacag tgcttaatat atcggaaatt 900

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ctagacacca tgaggcaaat ccaagtgttt gaagatgagc cagctcgcat caagtgccca    1080
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<212> PRT
<213> Homo sapiens

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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
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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
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
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Thr Ile Asn Glu Ser Ile Ser His Ser Arg Thr Glu Asp Glu Thr Arg
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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
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<212> DNA
<213> Homo sapiens

<400> 7

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cgtccctgtc ctcttaaccc aaatgaacac aaaggcacta taacttggta taaggatgac     180
agcaagacac ctgtatctac agaacaagcc tccaggattc atcaacacaa agagaaactt     240
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tcttactgcc tcagaattaa aataagtgca aaatttgtgg agaatgagcc taacttatgt     360
tataatgcac aagccatatt taagcagaaa ctacccgttg caggagacgg aggacttgtg     420
tgcccttata tggagttttt taaaaatgaa aataatgagt tacctaaatt acagtggtat     480
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atcgtgatga atgtggctga aaagcataga gggaactata cttgtcatgc atcctacaca     600
tacttgggca agcaatatcc tattacccgg gtaatagaat ttattactct agaggaaaac     660
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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
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ttggaagttg ttcaaaaaga cagctgtttc aattccccca tgaaactccc agtgcataaa    1380
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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
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aatgccaaga caaagccgcg ggaggagcag ttcaacagca cgtaccgtgt ggtcagcgtc    2280
ctcaccgtcc tgcaccagga ctggctgaac ggcaaggagt acaagtgcaa ggtctccaac    2340
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<210> 8
<211> 902
<212> PRT
<213> Homo sapiens

<400> 8
Met Val Leu Leu Arg Leu Ile Cys Phe Ile Ala Leu Leu Ile Ser Ser
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Leu Glu Ala Asp Lys Cys Lys Glu Arg Glu Glu Lys Ile Ile Leu Val
            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
```

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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
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
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            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

<400> 9

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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
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
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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
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cagatacaat tgatctgtaa tgtcaccggc cagttgagtg acattgctta ctggaagtgg    1800
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aatcctgcaa acaaaagaag gagtaccctc atcacagtgc ttaatatatc ggaaattgag    1920
agtagatttt ataaacatcc atttacctgt tttgccaaga atacacatgg tatagatgca    1980
gcatatatcc agttaatata tccagtcact aattccggag acaaaactca cacatgccca    2040
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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
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agcaagctca ccgtggacaa gagcaggtgg cagcagggga acgtcttctc atgctccgtg    2640
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tga                                                                 2703
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<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
                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
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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 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
                885                 890                 895
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
ttccggccca ctctcctcaa tgacactggc aactatacct gcatgttaag gaacactaca     360
```

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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
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ccctgtcctc ttaacccaaa tgaacacaaa ggcactataa cttggtataa ggatgacagc    1200
aagacacctg tatctacaga acaagcctcc aggattcatc aacacaaaga gaaactttgg    1260
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ccttatatgg agtttttaa aaatgaaaat aatgagttac ctaaattaca gtggtataag    1500
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gtgatgaatg tggctgaaaa gcatagaggg aactatactt gtcatgcatc ctacacatac    1620
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cagatacaat tgatctgtaa tgtcaccggc cagttgagtg acattgctta ctggaagtgg    1800
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gcatatatcc agttaatata tccagtcact aattccggag agtccaaata cggtccgcca    2040
tgcccatcat gcccagcacc tgagttcctg gggggaccat cagtcttcct gttcccccca    2100
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ctctacagca ggctaaccgt ggacaagagc aggtggcagg aggggaatgt cttctcatgc    2640
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<210> 12
<211> 902
<212> PRT
<213> Homo sapiens

<400> 12
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
```

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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 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
```

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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
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
            900
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<210> 13
<211> 2709
<212> DNA
<213> Homo sapiens

<400> 13
atggtgcttc tgtggtgtgt agtgagtctc tacttttatg gaatcctgca aagtgatgcc 60
tcagaacgct gcgatgactg gggactagac accatgaggc aaatccaagt gtttgaagat 120
gagccagctc gcatcaagtg cccactcttt gaacacttct tgaaattcaa ctacagcaca 180

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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 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
aaaggcctcc cgtcctccat cgagaaaacc atctccaaag ccaaagggca gccccgagag    2400
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
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<210> 14
<211> 902
<212> PRT
<213> Homo sapiens

<400> 14

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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 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
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
        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
```

<210> 15
<211> 2748
<212> DNA
<213> Homo sapiens

<400> 15

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cacacagggg ctgccagaag ctgccggttt cgtgggaggc attacaagcg ggagttcagg     120
ctggaagggg agcctgtagc cctgaggtgc ccccaggtgc cctactggtt gtgggcctct     180
gtcagccccc gcatcaacct gacatggcat aaaaatgact ctgctaggac ggtcccagga     240
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 atacaacatc     660
actaggagta ttgagctacg catcaagaaa aaaaaagaag agaccattcc tgtgatcatt     720
tccccccctca agaccatatc agcttctctg gggtcaagac tgacaatccc atgtaaggtg     780
tttctgggaa ccggcacacc cttaaccacc atgctgtggt ggacggccaa tgacacccac     840
atagagagcg cctacccggg aggccgcgtg accgaggggc cacgccagga atattcagaa     900
aataatgaga actacattga agtgccattg atttttgatc ctgtcacaag agaggatttg     960
cacatggatt ttaaatgtgt tgtccataat accctgagtt ttcagacact acgcaccaca    1020
gtcaaggaag cctcctccac gttctcagaa cgctgcgatg actggggact agacaccatg    1080
aggcaaatcc aagtgtttga agatgagcca gctcgcatca agtgcccact ctttgaacac    1140
ttcttgaaat tcaactacag cacagcccat tcagctggcc ttactctgat ctggtattgg    1200
actaggcagg accgggacct tgaggagcca attaacttcc gcctccccga gaaccgcatt    1260
agtaaggaga aagatgtgct gtggttccgg cccactctcc tcaatgacac tggcaactat    1320
acctgcatgt taaggaacac tacatattgc agcaaagttg catttccctt ggaagttgtt    1380
caaaaagaca gctgtttcaa ttcccccatg aaactcccag tgcataaact gtatatagaa    1440
tatggcattc agaggatcac ttgtccaaat gtagatggat attttccttc cagtgtcaaa    1500
ccgactatca cttggtatat gggctgttat aaaatacaga attttaataa tgtaataccc    1560
gaaggtatga acttgagttt cctcattgcc ttaatttcaa ataatggaaa ttacacatgt    1620
gttgttacat atccagaaaa tggacgtacg tttcatctca ccaggactct gactgtaaag    1680
gtagtaggct ctccaaaaaa tgcagtgccc cctgtgatcc attcacctaa tgatcatgtg    1740
gtctatgaga aagaaccagg agaggagcta ctcattccct gtacggtcta ttttagtttt    1800
ctgatggatt ctcgcaatga ggtttggtgg accattgatg gaaaaaaacc tgatgacatc    1860
actattgatg tcaccattaa cgaaagtata agtcatagta gaacagaaga tgaaacaaga    1920
actcagattt tgagcatcaa gaaagttacc tctgaggatc tcaagcgcag ctatgtctgt    1980
catgctagaa gtgccaaagg cgaagttgcc aaagcagcca aggtgaagca gaaagtgcca    2040
gctccaagat acacagtgtc 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 agcccccatc    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

<210> 16
<211> 915
<212> PRT
<213> Homo sapiens

<400> 16
Met Val Arg Leu Tyr Val Leu Val Met Gly Val Ser Ala Phe Thr Leu
 1               5                  10                  15
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
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
```

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                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
                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
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Pro Gly Lys
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<211> 2754
<212> DNA
<213> Homo sapiens

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ctggaagggg agcctgtagc cctgaggtgc ccccaggtgc cctactggtt gtgggcctct 180
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gaagaagaga cacggatgtg ggcccaggac ggtgctctgt ggcttctgcc agccttgcag 300
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aataatgaga actacattga agtgccattg atttttgatc ctgtcacaag agaggatttg 960
cacatggatt ttaaatgtgt tgtccataat accctgagtt ttcagacact acgcaccaca 1020
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<210> 18
<211> 917
<212> PRT
<213> Homo sapiens

<400> 18

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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
His Met Asp Phe Lys Cys Val Val His Asn Thr Leu Ser Phe Gln Thr
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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
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Thr Arg Gln Asp Arg Asp Leu Glu Glu Pro Ile Asn Phe Arg Leu Pro
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Leu Leu Asn Asp Thr Gly Asn Tyr Thr Cys Met Leu Arg Asn Thr Thr
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Tyr Cys Ser Lys Val Ala Phe Pro Leu Glu Val Val Gln Lys Asp Ser
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485 490 495
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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
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Asn Asp His Val Val Tyr Glu Lys Glu Pro Gly Glu Glu Leu Leu Ile
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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
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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
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

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Leu Ser Leu Gly Lys
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<213> Homo sapiens

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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
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
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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
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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
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625 630 635 640
Thr Gln Ile Leu Ser Ile Lys Lys Val Thr Ser Glu Asp Leu Lys Arg
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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

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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
                885                 890                 895
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
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<213> Homo sapiens

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accttgtcaa cctctggggt attagtatgc cctgacctga gtgaattcac ccgtgacaaa    1500
actgacgtga agattcaatg gtacaaggat tctcttcttt tggataaaga caatgagaaa    1560
tttctaagtg tgagggggac 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
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gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac    2340
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gagaaaacca tctccaaagc caaagggcag ccccgagaac cacaggtgta caccctgccc    2460
ccatcccggg atgagctgac caagaaccag gtcagcctga cctgcctggt caaaggcttc    2520
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tatcccagcg acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacaag 2580
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gacaagagca ggtggcagca ggggaacgtc ttctcatgct ccgtgatgca tgaggctctg 2700
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<210> 22
<211> 915
<212> PRT
<213> Homo sapiens

<400> 22
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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
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

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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
```

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

<400> 23

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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
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
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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
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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 cggagagtcc aaatacggtc cgccatgccc atcatgccca    2100
gcacctgagt tcctgggggg accatcagtc ttcctgttcc ccccaaaacc caaggacact    2160
ctcatgatct cccggacccc tgaggtcacg tgcgtggtgg tggacgtgag ccaggaagac    2220
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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
ggcttctacc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac    2580
tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaggcta    2640
accgtggaca agagcaggtg gcaggagggg aatgtcttct catgctccgt gatgcatgag    2700
gctctgcaca accactacac acagaagagc ctctccctgt ctctgggtaa atga          2754

<210> 24
<211> 917
<212> PRT
<213> Homo sapiens

<400> 24
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            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
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                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
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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> 25
<211> 2754
<212> DNA
<213> Homo sapiens

<400> 25

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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
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
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ccccgcatca acctgacatg gcataaaaat gactctgcta ggacggtccc aggagaagaa    1260
gagacacgga tgtgggccca ggacggtgct ctgtggcttc tgccagcctt gcaggaggac    1320
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ctcagagttt ttgagaatac agatgctttc ctgccgttca tctcataccc gcaaatttta    1440
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actgacgtga agattcaatg gtacaaggat tctcttcttt tggataaaga caatgagaaa    1560
tttctaagtg tgagggggac 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
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gagaactaca ttgaagtgcc attgattttt gatcctgtca caagagagga tttgcacatg    1980
gattttaaat gtgttgtcca taataccctg agttttcaga cactacgcac cacagtcaag    2040
gaagcctcct ccacgttctc cggagagtcc aaatacggtc cgccatgccc accatgccca    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
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ggcttctacc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac    2580
tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaggcta    2640
accgtggaca agagcaggtg gcaggagggg aatgtcttct catgctccgt gatgcatgag    2700
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<210> 26
<211> 917
<212> PRT
<213> Homo sapiens

<400> 26
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            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 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
```

<210> 27
<211> 177
<212> PRT
<213> Homo sapiens

<400> 27

```
Met Glu Ile Cys Arg Gly Leu Arg Ser His Leu Ile Thr Leu Leu Leu
 1               5                  10                  15
Phe Leu Phe His Ser Glu Thr Ile Cys Arg Pro Ser Gly Arg Lys Ser
            20                  25                  30
Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe
        35                  40                  45
Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn
    50                  55                  60
Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His Ala
65                  70                  75                  80
Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val Lys
                85                  90                  95
Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp
            100                 105                 110
Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser
        115                 120                 125
Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Cys Pro Gly Trp
    130                 135                 140
Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn
145                 150                 155                 160
Met Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp
                165                 170                 175
Glu
```

<210> 28

<211> 152
<212> PRT
<213> Homo sapiens

<400> 28

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

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