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(54) **Title:** METHODS OF USING IL-1 ANTAGONISTS TO TREAT AUTOINFLAMMATORY DISEASE

(57) **Abstract:** Methods of treating, inhibiting, or ameliorating an autoinflammatory disorder, disease, or condition in a subject in need thereof, comprising administering to a subject in need a therapeutic amount of an interleukin 1 (IL-1) antagonist, wherein the autoinflammatory disorder, disease, or condition is treated, inhibited, or ameliorated. The IL-1 antagonist is a molecule capable of binding and inhibiting IL-1. The therapeutic methods are useful for treating a human adult or child suffering from Neonatal Onset Multisystem Inflammatory Disorder (NOM ID/CINCA), Muckle-Wells Syndrome (MWS), Familial Cold Autoinflammatory Syndrome (FCAS), familial mediterranean fever (FMF), tumor necrosis factor receptor-associated periodic fever syndrome (TRAPS), or systemic onset juvenile idiopathic arthritis (Still's Disease).

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METHODS OF USING IL-1 ANTAGONISTS TO TREAT AUTOINFLAMMATORY DISEASE

BACKGROUND

Field of the Invention

[0001] The invention relates to methods of using interleukin-1 (IL-1) antagonists to treat autoinflammatory diseases, such as, for example, including familial mediterranean fever (FMF), NOMID/CINCA, Muckle-Wells Syndrome, FCAS, and tumour necrosis factor receptor-associated periodic fever syndrome (TRAPS).

Description of Related Art

[0002] One important group of autoinflammatory disorders encompasses autosomal dominant conditions associated with mutations in CIAS-1, a gene that encodes a pyrin-related protein called "cryopyrin" (Feldmann et al. (2002) Am. J. Hum. Genet. 71:198-203; Hoffman et al. (2001) Nat. Genet. 29:301-305). These disorders include Neonatal Onset Multisystem Inflammatory Disorder (NOMID/CINCA), Muckle-Wells Syndrome (MWS), and Familial Cold Autoinflammatory Syndrome (FCAS). These disorders present a spectrum of clinical manifestations ranging from FCAS being the mildest to the seriously disabling disease of NOMID/CINCA. An urticaria-like skin rash is common to the entire spectrum of these diseases. In patients with FCAS, this rash is inducible by cold exposure while most patients with MWS or NOMID present with daily rashes that are consistently provoked by a number of different stimuli. Conjunctivitis is present in all forms of disease expression, however, hearing loss, aseptic meningitis and arthritis are mainly seen in patients with MWS and NOMID/ CINCA. The disfiguring and disabling body overgrowth at the epiphyses and patellae is only seen in patients with NOMID/CINCA.

[0003] FMF is a recessively inherited condition characterized by episodes of fever and serositis or synovitis; some subjects also develop systemic amyloidosis (Balow et al. (1997) Genomics 44:280-291). The FMF gene encodes a novel protein called pyrin that is the prototype of a family of molecules involved in the regulation of apoptosis (cell-death) and inflammation. The precise biochemical mechanism by which these proteins function, and by which mutations cause disease, is still unknown.

[0004] Still's Disease (systemic onset juvenile idiopathic arthritis), is manifest by spiking fevers, evanescent salmon color rash, arthritis, arthralgia, and hepatosplenomegaly (Masson et al. (1995) Rev. Rhum. Engl. Ed. 62:748-757; Spiegel et al. (2000) Arthritis Rheum. 43:2402-2409). There are as yet no definitive genetic associations with Still's Disease and the pathogenesis is poorly understood. Interestingly, many of the signs and symptoms of Still's disease are similar to those with autoinflammatory disease. Still's Disease typically first occurs during childhood, but can also have its onset in adulthood.

[0005] Similarly, Kawasaki disease is a disease affecting children that is accompanied by fevers, swelling and arthritic joints, and rash, as well as vascular inflammation that can cause permanent coronary damage in approximately 15-25% of affected children. Two other similar

diseases are Blau's syndrome and Early Onset Sarcoidosis (EOS), both of which are caused by a gain of function mutations in NOD2, a protein similar to Pyrin, and cause rash, granulomatosis, arthritis and uveitis. Other diseases that have also been considered autoinflammatory include, Hidradenitis suppurativa, Behcet's, hyperimmunoglobulinemia D with periodic fever syndrome (HIDS), tumour necrosis factor receptor-associated periodic fever syndrome (TRAPS), and Pyogenic sterile arthritis, pyoderma gangrenosum and acne (PAPA syndrome).

[0006] The pathogenesis of autoinflammatory disease is not completely understood. There is a growing body of evidence that interleukin-1 (IL-1) plays a role in a number of these conditions and that targeting of this cytokine can provide important benefits (Hoffman et al. (2004) Arthritis. Rheum. 50:345-349). There is clearly a need to develop improved therapeutic treatment of these autoinflammatory diseases.

BRIEF SUMMARY OF THE INVENTION

[0007] In a first aspect, the invention features a method of treating, inhibiting, or ameliorating an autoinflammatory disorder, 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 IL-1-binding fusion proteins. 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 fusion protein trap antagonist (an "IL-1 trap") described in U.S. patent publication No. 2003/0143697, published 31 July 2003. In a specific embodiment, the IL-1 antagonist is the fusion protein shown in SEQ ID NO: 4, 6, 8, 10, 12,14, 16, 18, 20, 22, 24, 26. A preferred fusion protein is shown in SEQ ID NO:10. The invention encompasses the use of an IL-1-binding fusion protein substantially identical to the protein of SEQ ID NO: 4, 6, 8, 10, 12,14, 16, 18, 20, 22, 24, 26, that is, a protein having at least 95% identity, at least 97% identity, at least 98% identity to the protein of SEQ ID NO: 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 and capable of binding and inhibiting IL-1. Further, in specific embodiments, the IL-1 antagonist is a fusion protein comprising one or more immunoglobulin-derived components in place of one or more receptor components. In specific embodiments, the IL-1 antagonist comprises one or more immunoglobulin-derived components specific for IL-1 and/or an IL-1 receptor.

[0008] The subject being treated is most preferably a human diagnosed as suffering from an autoinflammatory disorder. More specifically, the subject is a human adult or child diagnosed with an autoinflammatory disorder associated with mutations in CIAS-1, such as Neonatal Onset Multisystem Inflammatory Disorder (NOMID/CINCA), Muckle-Wells Syndrome (MWS), Familial Cold Autoinflammatory Syndrome (FCAS); familial mediterranean fever (FMF); systemic onset juvenile idiopathic arthritis (Still's Disease), tumour necrosis factor receptor-associated periodic fever syndrome (TRAPS), or Kawasaki Disease.

[0009] The method of the invention includes administration of the IL-1 antagonist by any means known to the art, for example, subcutaneous, intramuscular, intranasal, intravenous, transdermal administration or oral routes of administration. Preferably, administration is subcutaneous or

intravenous.

[0010] In a second aspect, the invention features a method of treating, inhibiting, or ameliorating a disease or condition selected from the group consisting of NOMID/CINCA, MWS, FCAS, FMP, Still's Disease, TRAPS, and Kawasaki Disease, the method comprising administering to a subject in need an interleukin 1 (IL-1) antagonist. In a preferred embodiment, the IL-1 antagonist is a fusion protein capable of trapping IL-1. In a specific embodiment, the IL-1 antagonist is the fusion protein shown in SEQ ID NO: 4, 6, 8, 10, 12,14, 16, 18, 20, 22, 24, 26, or a substantially identical protein capable of binding and inhibiting IL-1. A preferred IL-1 antagonist is shown in SEQ ID NO:10. Preferably, the subject treated is a child or adult human diagnosed with the disease or condition.

[0011] In a third aspect, the invention features a method of treating, inhibiting, or ameliorating Neonatal Onset Multisystem Inflammatory Disorder (NOMID/CINCA), comprising administering to a subject in need an interleukin 1 (IL-1) antagonist. In a preferred embodiment, the IL-1 antagonist is a fusion protein capable of trapping IL-1. In a specific embodiment, the IL-1 antagonist is the fusion protein shown in SEQ ID NO: 4, 6, 8, 10, 12,14, 16, 18, 20, 22, 24, 26, or a substantially identical protein capable of binding and inhibiting IL-1. A preferred IL-1 antagonist is shown in SEQ ID NO:10.

[0012] In a fourth aspect, the invention features a method of treating, inhibiting, or ameliorating Muckle-Wells Syndrome (MWS), the method comprising administering to a subject in need an interleukin 1 (IL-1) antagonist. In a preferred embodiment, the IL-1 antagonist is a fusion protein capable of trapping IL-1. In a specific embodiment, the IL-1 antagonist is the fusion protein shown in SEQ ID NO: 4, 6, 8, 10, 12,14, 16, 18, 20, 22, 24, 26, or a substantially identical protein capable of binding and inhibiting IL-1. A preferred IL-1 antagonist is shown in SEQ ID NO:10.

[0013] In a fifth aspect, the invention features a method of treating, inhibiting, or ameliorating Familial Cold Autoinflammatory Syndrome (FCAS) the method comprising administering to a subject in need an interleukin 1 (IL-1) antagonist. In a preferred embodiment, the IL-1 antagonist is a fusion protein capable of trapping IL-1. In a specific embodiment, the IL-1 antagonist is the fusion protein shown in SEQ ID NO: 4, 6, 8, 10, 12,14, 16, 18, 20, 22, 24, 26, or a substantially identical protein capable of binding and inhibiting IL-1. A preferred IL-1 antagonist is shown in SEQ ID NO:10.

[0014] In a sixth aspect, the invention features a method of treating, inhibiting, or ameliorating familial mediterranean fever (FMF), the method comprising administering to a subject in need an interleukin 1 (IL-1) antagonist. In a preferred embodiment, the IL-1 antagonist is a fusion protein capable of trapping IL-1. In a specific embodiment, the IL-1 trap is the fusion protein shown in SEQ ID NO:4, 6, 8, 10, 12,14, 16, 18, 20, 22, 24, 26, or a substantially identical protein capable of binding and inhibiting IL-1. A preferred IL-1 trap is shown in SEQ ID NO:10.

[0015] In a seventh aspect, the invention features a method of treating, inhibiting, or ameliorating systemic onset juvenile idiopathic arthritis (Still's Disease), the method comprising administering to a subject in need an interleukin 1 (IL-1) antagonist. In a preferred embodiment, the IL-1 antagonist is a fusion protein capable of trapping IL-1. In a specific embodiment, the IL-1

antagonist is the fusion protein shown in SEQ ID NO: 4, 6, 8, 10, 12,14, 16, 18, 20, 22, 24, 26, or a substantially identical protein capable of binding and inhibiting IL-1. A preferred IL-1 trap is shown in SEQ ID NO:10.

[0016] In an eighth aspect, the invention features a method of treating, inhibiting, or ameliorating tumour necrosis factor receptor-associated periodic fever syndrome (TRAPS), the method comprising administering to a subject in need an IL-1 antagonist. In a preferred embodiment, the IL-1 antagonist is a fusion protein capable of trapping IL-1. In a specific embodiment, the IL-1 antagonist is the fusion protein shown in SEQ ID NO: 4, 6, 8, 10, 12,14, 16, 18, 20, 22, 24, 26, or a substantially identical protein capable of binding and inhibiting IL-1. A preferred IL-1 trap is shown in SEQ ID NO:10.

[0017] In specific embodiments of the therapeutic method of the invention, the subject is treated with a combination of a first IL-1-binding fusion protein trap molecule and a second therapeutic agent. The second therapeutic agent may be a second IL-1 antagonist, such as, for example, a second IL-1-binding fusion protein trap, anakinra (Kineret®, Amgen), a recombinant, nonglycosylated form of the human IL-1 receptor antagonist (IL1Ra), or an anti-IL-18 drug such as IL-18BP or a derivative, an IL-18-binding fusion protein trap (an "IL-18 trap"), anti-IL-18, anti-IL-18R1, or anti-IL-18Racp antibodies or antibody fragments. Other co- therapies include low dose colchine for FMF, aspirin or other NSAIDs, steroids such as prednisolone, methotrexate, low dose cyclosporine A, TNF inhibitors such as Enbrel®, or Humira®,, other inflammatory inhibitors such as inhibitors of caspase-1, p38, IKK1/2, CTLA-4Ig, anti-IL-6 or anti-IL6Ra, etc.

[0018] In a ninth aspect, the invention features a therapeutic method of treating an autoinflammatory disease or condition, comprising administering a pharmaceutical composition comprising an IL-1-binding fusion protein trap and a pharmaceutically acceptable carrier. In one embodiment, the IL-1-binding fusion protein trap is administered in a dose range of 1-20 mg/kg on a weekly basis for a treatment period of between 1 week to one year or more. In another embodiment, a total IL-1-binding fusion protein is administered in the range of 50-2000 mg, which may be provided in a single dose or in sequential doses over a period of time such as a period of weeks or months.

[0019] Other objects and advantages will become apparent from a review of the ensuing detailed description.

DETAILED DESCRIPTION

[0020] 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 to the appended claims.

[0021] 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.

[0022] 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.

General Description

[0023] Mutations in the gene *CIAS1* are now recognized as being responsible for three rare genetic syndromes: Neonatal Onset Multisystem Inflammatory Disorder (NOMID), Muckle-Wells Syndrome (MWS), and Familial Cold Autoinflammatory Syndrome (FCAS). (Hoffman et al. 2001 Naure 29:301-305; Feldmann et al. 2002 Am J Hum Genet 71:198-203; Aksentijevich et al. 2002 Arthritis Rheum 46:3340-3348). In aggregate, these conditions are known as "CAPS", an acronym for "*CIAS1* Associated Periodic Syndromes". CAPS disorders are exceedingly rare; with approximately 200-300 adults and children in the U.S. with FCAS and significantly fewer adults with NOMID or MWS known to have these conditions. The rarity of these conditions, particularly NOMID and MWS, are probably due to effects of disease severity on survival or reproductive fitness.

[0024] CAPS are inherited in an autosomal dominant manner, with a sporadic or familial pattern. *CIAS1* encodes a protein called NALP3 that is a component of the "inflammasome", a subcellular enzyme complex that regulates the activity of caspase 1. Caspase 1 is the enzyme that cleaves the inactive pro-form of the proinflammatory cytokine, IL-1, into its biologically active form (Agostini et al. 2004 *supra*). Mutations in *CIAS1* lead to increased production of IL-1 and numerous pathological consequences (Aksentijevich et al. 2002 *supra*). IL-1 strongly induces the production of acute phase reactants in the liver, such as C-reactive protein (CRP) and serum amyloid A (SAA).

[0025] The genetics of CAPS are interesting in that there can be a number of different point mutations in *CIAS1* associated with these syndromes (Sarrauste de Menthiere et al. 2003 Nucleic Acids Res 31:282-285; Aksentijevich et al. 2002 *supra*). Some of these mutations are associated with only one syndrome; others two. For example, some mutations may be associated with FCAS as well as MWS; other mutations may be associated with MWS and NOMID. Approximately 50% of patients with NOMID do not have a recognized mutation in the coding region of *CIAS1*. In these patients, the disease may be due to an as-yet-unrecognized mutation in a regulatory region or protein of CIAS1, or in another gene encoding a closely-related protein in this pathway. FCAS is more genetically homogeneous than NOMID; almost all patients with FCAS share a common mutation (Sarrauste de Menthiere et al. 2003 *supra*; Hoffman et al. 2001 *supra*).

[0026] CAPS disorders share common clinical features and present as a spectrum of clinical severity. NOMID is the most seriously disabling, MWS somewhat less so and FCAS is the least severe. CAPS disorders have overlapping features and there are individuals and kindred with

unique constellations of signs and symptoms. Features common to all these conditions include fevers, urticaria-like rash, arthritis or arthralgia, myalgia, malaise, and conjunctivitis. However, the spectrum of symptoms for any patient with a CAPS disorder may differ from that of another patient with the same disorder. A universal feature of active CAPS disease is laboratory test elevation of acute phase reactants, such as CRP, SAA, and/or erythrocyte sedimentation rate (ESR).

[0027] In NOMID, chronic aseptic meningitis may lead to mental retardation and these patients may also suffer disfiguring and disabling bony overgrowth at the epiphyses and patellae. These patients may also suffer blindness due to optic nerve atrophy that results from increased intracranial pressure. MWS and NOMID are commonly associated with severe inflammation that may include the auditory system, meninges, and joints. These patients may suffer daily high spiking fevers and a chronic rash that frequently changes in distribution and intensity. Patients may suffer hearing loss or deafness. Conjunctivitis and papilledema are frequently observed. Amyloidosis may develop and lead to renal failure due to chronic inflammation and overproduction of acute phase reactants (particularly SAA). MWS is also known as "amyloidosis-deafness syndrome".

[0028] The clinical signs and symptoms of FCAS are induced by exposure to modestly cold air (e.g., seasonal temperature changes, air conditioning). Patients may have frequent (sometimes daily) episodes of a painful or pruritic rash, fever, fatigue, malaise, headache, nausea, and thirst during cold months or in locations where air conditioning is prevalent. In many locales, this may include most work places. FCAS is a source of frequent pain to patients and may restrict their employment, social, and recreational opportunities. Up to 2% of patients with FCAS develop amyloidosis, a life-threatening condition. This frequency is substantially higher than the rate of amyloidosis in the general community. The genetics and natural history of FCAS are described in detail Hoffman et al. 2001 Nature 29:301-305 and Hoffman et al. 2001 J Allergy clin Immunol 108:615-620.

Definitions

[0029] 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, an IL-1 fusion protein trap antagonist, which binds and inhibits IL-1.

[0030] 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).

[0031] By the term "substantially identical" is meant a protein sequence having at least 95% identity to an amino acid sequence selected from the group consisting of the amino acid sequences SEQ ID NOs: 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, and 26, and capable of binding IL-

1 and inhibiting the biological activity of IL-1.

[0032] The term "identity" or "homology" is construed to mean the percentage of amino acid residues in the candidate sequence that are identical with the residue of a corresponding sequence to which it is compared, after aligning the sequences and introducing gaps, if necessary to achieve the maximum percent identity for the entire sequence, and not considering any conservative substitutions as part of the sequence identity. Neither N- or C-terminal extensions nor insertions will be construed as reducing identity or homology. Methods and computer programs for the alignment are well known in the art. Sequence identity may be measured using sequence analysis software (e.g., Sequence Analysis Software Package, Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Ave., Madison, Wis. 53705). This software matches similar sequences by assigning degrees of homology to various substitutions, deletions, and other modifications.

IL-1-Binding Fusion Protein Trap Antagonists

[0033] 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. The IL-1-binding fusion proteins useful in the methods of the invention 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. The IL-1-binding fusion protein 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. An immunoglobulin-derived domain may be selected from any of the major classes of immunoglobulins, including IgA, IgD, IgE, IgG and IgM, and any subclass or isotype, e.g. IgG1, IgG2, IgG3 and IgG4; IgA-1 and IgA-2. Alternatively, the IL-1-binding fusion proteins useful in the method of the invention 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-binding fusion protein traps, see WO 00/18932. Preferred IL-1 antagonists have the amino acid sequence shown in SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, and 26, or a substantially identical protein at least 95% identity to a sequence of SEQ ID NO: 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, or 26, and capable of binding and inhibiting IL1.

Treatment Population

[0034] The therapeutic methods of the invention are useful for treating individuals affected with *CIAS-1* mutation disorders (NOMID, MWS, FCAS), FMF, TRAPS, or Still's Disease. Commonly accepted diagnostic criteria for *CIAS-1* mutation associated disease (NOMID, MWS, FCAS), Familial Mediterranean Fever, or Still's Disease (adult- or juvenile- onset) are know to those skilled

in the art. In the case of patients diagnosed with FMF, the therapeutic method of the invention may be particularly useful for those with disease refractory to therapy with colchicine.

Methods of Administration

[0035] 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).

[0036] 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.

[0037] 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.

[0038] 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.

Combination Therapies

[0039] In numerous embodiments, the IL-1 antagonists useful in the methods of the present invention may be administered in combination with one or more additional compounds or therapies. Combination therapy may be simultaneous or sequential. The IL-1-binding fusion proteins of the invention may be combined with, for example, TNF-inhibiting agents such as etanercept (Enbrel®, Amgen), infliximab (Remicade®, Centocor), Humira® (Abbott), thalidomide, steroids, anakinra (Kinaret®, Amgen), or colchicine. Colchicine is a mainstay of therapy for subjects with FMF; in this study, subjects will not be removed from treatment with this medication. For Still's Disease (and classical autoinflammatory diseases), compounds such as methotrexate, cyclosporine, chlorambucil, cyclophosphamide (DMARDs) have been used as monotherapy or in combination with no consistent response. Some subjects respond to high doses of steroids. DMARDs, and more recently anti-TNF agents have been used with variable success. The IL-1-binding fusion proteins of the invention may also be combined with anti-IL-18 drugs, such as for example, IL-18BP or a derivative, an IL-18-binding fusion protein, anti-IL-18, anti-IL-18R1, or anti-IL-18Racp. Other co-therapies include low dose colchine for FMF, aspirin or other NSAIDs, steroids such as prednisolone, methotrexate, low dose cyclosporine A, TNF inhibitors such as Enbrel®, or Humira®, other inflammatory inhibitors such as inhibitors of caspase-1, p38, IKK1/2, CTLA-4Ig, anti-IL-6 or anti-IL6Ra, etc.

Pharmaceutical Compositions

[0040] 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.

[0041] 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.

[0042] 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.

[0043] 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 up to about 2 grams of active compound. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

[0044] 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.

[0045] 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.

[0046] 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, the frequency 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

[0047] 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 an autoinflammatory disease or condition.

[0048] 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

[0049] 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. Effect of IL-1 Trap on Human Autoinflammatory Disease.

[0050] An initial study is conducted with 15 adult subjects suffering from diseases known to respond to IL-1 blockade (NOMID/MWS/FCAS) as well as subjects with Adult Still's disease and colchicine-resistant FMF. Subjects are screened for eligibility, clinical symptoms determined, active disease confirmed and baseline blood is drawn on approximately 3 occasions one week apart to determine baseline levels of inflammation. A careful, complete standardized history and physical exam is performed, appropriate for the disease under study to assure uniform data collection on every subject. Vital signs and weight is obtained at each visit. The clinical data is based on a detailed questionnaire including all the reported clinical manifestations. The following evaluation procedures pertain specifically to *CIAS-1* mutation associated disorders and are performed as clinically indicated: dermatological evaluation; ophthalmologic evaluation; ear/nose/throat evaluation; neurology evaluation; lumbar puncture; head MRI; radiographs, joint MRI; and pharmacokinetic profiling.

[0051] All study subjects receive IL-1-binding fusion protein (SEQ ID NO:10) with a dosing regimen of 100 mg once a day for 3 consecutive days, a regimen expected to provide 2-4 weeks of significant IL-1 inhibitory activity. The primary outcomes are measured during this period and include drug safety, clinical efficacy analysis, and the change in selected biomarkers of

inflammation (e.g., acute phase reactants such as CRP, serum amyloid A, and ESR) at Day 10 following initiation of treatment with IL-1 trap. If a favorable response is observed at Day 10, subjects are monitored at predefined timepoints (with no further treatment) until return of signs and symptoms (flare). Upon flare, subjects are eligible for entry into an extension phase that entails re-treatment with the loading regimen (100 mg/day IL-1 trap for three consecutive days) followed by once-weekly dosing with 100 mg IL-1 trap for up to one year.

[0052] Based on the Investigator's clinical judgment, an IL-1 trap dose escalation regimen may be implemented if, after 4 weeks of dosing in the extension phase at 100 mg/week, a subject's Month 1 acute phase reactant levels have not normalized (CRP > 0.5 mg/dL and/or SAA> 10 mg/L) or escalation is warranted based on persistent signs and/or symptoms of disease. The first dose escalation level may be 160 s.c. once weekly. Subjects will be observed for 4 weeks; if criteria for dose escalation are still met, then the dose may be raised to 320 mg s.c. once-weekly.

[0053] Preliminary Results. Four subjects with CAPS were initially enrolled. Results indicated that all subjects experienced rapid and extensive improvement in inflammatory signs and symptoms upon treatment with IL-1 trap (SEQ ID NO:10), including improvement in both patient- and physician- reported disease manifestation. Major declines in inflammatory biomarkers, such as CRP and SAA were also observed. Signs and symptoms returned within a median of 21 days (range 9-26) of initial dosing and then responded promptly to re-treatment. Table 1 provides a summary of the daily diary scores, acute phase reactants and clinical assessments (‡ Performed on 3 patients; * statistically significant difference from previous time point at $p < 0.1$ level; ** statistically significant difference from previous time point at $p < 0.05$ level). The Physician and Patient global assessment VAS scores mirrored the changes in the acute phase reactants (SAA, CRP and ESR) at baseline, at the time of flare, and at a time point designated as reflecting maximal efficacy.

Table 1

	Baseline median (range)	**Maximal Efficacy** median (range)	**Flare** median (range)
Daily Diary Score	6.06 (2.2-7.56)	1.67 (0-3.3)*	4.5 (2-7.33)
Acute phase reactants			
SAA (mg/L)	96 (16.1-468)	8.25 (2-19)	84 (50-236)‡
CRP (mg/dL)	7.28 (2.32-8.65)	0.72 (0.07-1.15)**	2.93 (0.076-6.21)
ESR (mm/hr)	56.67 (22-92)	24 (7-45)**	34 (11-70)*
Blood Count			
WBC	15.28 (9.33-19.4)	7.58 (7.21-9.9)**	8.48 (6.34-11.47)
Hgb	12.95 (8.1-14.7)	13.3 (8.2-15.6)*	13.1 (7.9-14.57)
Plt	356.5 (291-445.5)	303.25 (240-377)**	291 (257-359.3)
Questionnaires‡			
Physician global VAS (cm)	6.85 (4.1-6.95)	0.2 (0.2-2.6)	3.3 (3.1-3.5)
Patient global VAS (cm)	5.2 (3.95-6.9)	1.1 (0.95-3.05)**	3.6 (3.1-6.45)**
Fatigue VAS (cm)	5.55 (3.25-8)	1.15 (0.5-3.9)	6.6 (3.15-6.9)
Pain VAS (cm)	7.55 (3.6-7.7)	0.95 (0.2-1.05)*	4.1 (0.5-6.55)
SF-36 Physical Health	44.38 (42.5-47.5)	50.63 (33.75-92.5)	41.56 (35-69.4)
SF-36 Mental Health	41.625 (28.5-57.8)	75.88 (55-96)	39.6 (37-57)

CLAIMS

1. Use of an interleukin 1 (IL-1) fusion protein antagonist comprising two IL-1 receptor components and a multimerizing component in the manufacture of a medicament for treating, inhibiting, or ameliorating an autoinflammatory disorder, disease, or condition.

2. Use according to claim 1, wherein the fusion protein antagonist comprises:

an amino acid sequence selected from amino acid sequences shown in SEQ ID NO: 4, 6, 8, 10, 12,14, 16, 18, 20, 22, 24 and 26; or

an amino acid sequence which exhibits at least 95% sequence identity to said sequence of SEQ ID NO: 4, 6, 8, 10, 12,14, 16, 18, 20, 22, 24 or 26 and is capable of binding and inhibiting IL-1.

3. Use according to claim 1 or 2, wherein the fusion protein antagonist comprises SEQ ID NO:10.

4. Use of an interleukin-1 (IL-1) fusion protein antagonist as defined in claim 1, 2 or 3 as a first therapeutic agent,

and of one or more further therapeutic agents selected from an IL-1 fusion protein which is different from the first therapeutic agent, etanercept (Enbrel®, Amgen), infliximab (Remicade®, Centocor), Humira® (Abbott), thalidomide, a steroid, anakinra (Kinaret®, Amgen), colchicine, IL-18BP or a derivative, an IL-18-binding fusion protein, anti-IL-18, anti-IL-18R1, anti-IL-18Racp, aspirin, prednisolone, methotrexate, cyclosporine A, caspase-1, p38, IKK1/2, CTLA-4Ig, anti-IL-6 and anti-IL6Ra

in the manufacture of a medicament for treating, inhibiting, or ameliorating an autoinflammatory disorder, disease or condition.

5. Use according to any one of the preceding claims, wherein the autoinflammatory disorder, disease, or condition is Neonatal Onset Multisystem Inflammatory Disorder (NOMID/CINCA), Muckle-Wells Syndrome (MWS), Familial Cold Autoinflammatory Syndrome (FCAS), familial mediterranean fever (FMF), tumor necrosis factor receptor-associated periodic fever syndrome (TRAPS), or systemic onset juvenile idiopathic arthritis (Still's Disease); and/or the autoinflammatory disorder, disease, or condition is associated with mutations in *CIAS-1*.

6. A pharmaceutical composition comprising:

as a first therapeutic agent, an interleukin-1 (IL-1) fusion protein antagonist as defined in claim 1, 2 or 3;

one or more further therapeutic agents selected from an IL-1 fusion protein which is different from the first therapeutic agent, etanercept (Enbrel®, Amgen), infliximab (Remicade®, Centocor), Humira® (Abbott), thalidomide, a steroid, anakinra (Kinaret®, Amgen), colchicine, IL-

18BP or a derivative, an IL-18-binding fusion protein, anti-IL-18, anti-IL-18R1, anti-IL-18Racp, aspirin, prednisolone, methotrexate, cyclosporine A, caspase-1, p38, IKK1/2, CTLA-4Ig, anti-IL-6 and anti-IL6Ra; and

a pharmaceutically acceptable carrier or excipient.

7. A product comprising:

as a first therapeutic agent, an interleukin 1 (IL-1) fusion protein antagonist as defined in claim 1, 2 or 3, and

one or more further therapeutic agents:

for separate, simultaneous or sequential use in the treatment of an autoinflammatory disorder, disease or condition of the human or animal body.

8. A product according to claim 7, wherein the further therapeutic agent or agents are as defined in claim 4.

9. A product according to claim 7 or 8, wherein the autoinflammatory disorder, disease or condition is as defined in claim 5.

10. Use of an interleukin-1 (IL-1) fusion protein antagonist as defined in claim 1, 2 or 3 in the manufacture of a medicament for treating, inhibiting or ameliorating an autoinflammatory disorder, disease or condition, by co-administration with a further therapeutic agent as defined in claim 4.

11. Use of a further therapeutic agent as defined in claim 4 in the manufacture of a medicament for treating, inhibiting or ameliorating an autoinflammatory disorder, disease or condition, by co-administration with an interleukin-1 (IL-1) fusion protein antagonist as defined in claim 1, 2 or 3.

12. Use according to any one of claims 1 to 5, 10 or 11, wherein said medicament is for subcutaneous, intramuscular, intravenous, topical, transdermal or oral administration.

13. Use according to any one of claims 1 to 5, 10 to 12, wherein said medicament is for the administration of a therapeutically effective amount of said fusion protein antagonist at a dose of from 1 to 20 mg/kg.

14. A method of treating, inhibiting, or ameliorating an autoinflammatory disorder, disease or condition, comprising administering to a subject in need thereof a therapeutic amount of an interleukin 1 (IL-1) antagonist as defined in claim 1, 2 or 3.

15. A method according to claim 14 wherein said autoinflammatory disorder, disease or condition is as defined in claim 5.

16. A method according to claim 14 or 15 further comprising administering to said subject one or more further therapeutic agents as defined in claim 4.

17. A method according to claim 14, 15 or 16 wherein said autoinflammatory disorder, disease or condition is associated with mutations in *CIAS-1* and said IL-1 antagonist comprises the amino acid sequence of SEQ ID NO:10.

18. A method according to claim 15, 16, 17 or 18 wherein said medicament fusion protein antagonist is administered at a dose of from 1 to 20 mg/kg.

SEQUENCE LISTING

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<120> Methods of Using IL-1 Antagonists to Treat Autoinflammatory Disease

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tacttgggca agcaatatcc tattacccgg gtaatagaat ttattactct agaggaaaac     660
aaacccacaa ggcctgtgat tgtgagccca gctaatgaga caatggaagt agacttggga     720
tcccagatac aattgatctg taatgtcacc ggccagttga gtgacattgc ttactggaag     780
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tggaatgggt cagtaattga tgaagatgac ccagtgctag gggaagacta ttacagtgtg     840
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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
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gagaaccgca ttagtaagga gaaagatgtg ctgtggttcc ggcccactct cctcaatgac    1260
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ttggaagttg ttcaaaaaga cagctgtttc aattccccca tgaaactccc agtgcataaa    1380
ctgtatatag aatatggcat tcagaggatc acttgtccaa atgtagatgg atattttcct    1440
tccagtgtca aaccgactat cacttggtat atgggctgtt ataaaataca gaattttaat    1500
aatgtaatac ccgaaggtat gaacttgagt ttcctcattg ccttaatttc aaataatgga    1560
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cctgatgaca tcactattga tgtcaccatt aacgaaagta taagtcatag tagaacagaa    1860
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agctatgtct gtcatgctag aagtgccaaa ggcgaagttg ccaaagcagc caaggtgaag    1980
cagaaagtgc cagctccaag atacacagtg gaatccggag acaaaactca cacatgccca    2040
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aaggacaccc tcatgatctc ccggacccct gaggtcacat gcgtggtggt ggacgtgagc    2160
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<210> 4
<211> 900
<212> PRT
<213> Homo sapiens

<400> 4

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

```
Gln Lys Leu Pro Val Ala Gly Asp Gly Gly Leu Val Cys Pro Tyr Met
    130                 135                 140
Glu Phe Phe Lys Asn Glu Asn Asn Glu Leu Pro Lys Leu Gln Trp Tyr
145                 150                 155                 160
Lys Asp Cys Lys Pro Leu Leu Leu Asp Asn Ile His Phe Ser Gly Val
                165                 170                 175
Lys Asp Arg Leu Ile Val Met Asn Val Ala Glu Lys His Arg Gly Asn
            180                 185                 190
Tyr Thr Cys His Ala Ser Tyr Thr Tyr Leu Gly Lys Gln Tyr Pro Ile
        195                 200                 205
Thr Arg Val Ile Glu Phe Ile Thr Leu Glu Glu Asn Lys Pro Thr Arg
    210                 215                 220
Pro Val Ile Val Ser Pro Ala Asn Glu Thr Met Glu Val Asp Leu Gly
225                 230                 235                 240
Ser Gln Ile Gln Leu Ile Cys Asn Val Thr Gly Gln Leu Ser Asp Ile
                245                 250                 255
Ala Tyr Trp Lys Trp Asn Gly Ser Val Ile Asp Glu Asp Asp Pro Val
            260                 265                 270
Leu Gly Glu Asp Tyr Tyr Ser Val Glu Asn Pro Ala Asn Lys Arg Arg
        275                 280                 285
Ser Thr Leu Ile Thr Val Leu Asn Ile Ser Glu Ile Glu Ser Arg Phe
    290                 295                 300
Tyr Lys His Pro Phe Thr Cys Phe Ala Lys Asn Thr His Gly Ile Asp
305                 310                 315                 320
Ala Ala Tyr Ile Gln Leu Ile Tyr Pro Val Thr Asn Ser Glu Arg Cys
                325                 330                 335
Asp Asp Trp Gly Leu Asp Thr Met Arg Gln Ile Gln Val Phe Glu Asp
            340                 345                 350
Glu Pro Ala Arg Ile Lys Cys Pro Leu Phe Glu His Phe Leu Lys Phe
        355                 360                 365
Asn Tyr Ser Thr Ala His Ser Ala Gly Leu Thr Leu Ile Trp Tyr Trp
    370                 375                 380
Thr Arg Gln Asp Arg Asp Leu Glu Glu Pro Ile Asn Phe Arg Leu Pro
385                 390                 395                 400
Glu Asn Arg Ile Ser Lys Glu Lys Asp Val Leu Trp Phe Arg Pro Thr
                405                 410                 415
Leu Leu Asn Asp Thr Gly Asn Tyr Thr Cys Met Leu Arg Asn Thr Thr
            420                 425                 430
Tyr Cys Ser Lys Val Ala Phe Pro Leu Glu Val Val Gln Lys Asp Ser
        435                 440                 445
Cys Phe Asn Ser Pro Met Lys Leu Pro Val His Lys Leu Tyr Ile Glu
    450                 455                 460
Tyr Gly Ile Gln Arg Ile Thr Cys Pro Asn Val Asp Gly Tyr Phe Pro
465                 470                 475                 480
Ser Ser Val Lys Pro Thr Ile Thr Trp Tyr Met Gly Cys Tyr Lys Ile
                485                 490                 495
Gln Asn Phe Asn Asn Val Ile Pro Glu Gly Met Asn Leu Ser Phe Leu
            500                 505                 510
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 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
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> 5
<211> 2709
<212> DNA
<213> Homo sapiens

<400> 5

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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
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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
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gcagcatata tccagttaat atatccagtc actaattcag aacgctgcga tgactgggga    1020
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gagaaccgca ttagtaagga gaaagatgtg ctgtggttcc ggcccactct cctcaatgac    1260
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aatgtaatac ccgaaggtat gaacttgagt ttcctcattg ccttaatttc aaataatgga    1560
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gtgagccagg aagaccccga ggtccagttc aactggtacg tggatggcgt ggaggtgcat    2220
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<210> 6
<211> 902
<212> PRT
<213> Homo sapiens

<400> 6

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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
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
580 585 590
Trp Trp Thr Ile Asp Gly Lys Lys Pro Asp Asp Ile Thr Ile Asp Val
595 600 605
Thr Ile Asn Glu Ser Ile Ser His Ser Arg Thr Glu Asp Glu Thr Arg
610 615 620
Thr Gln Ile Leu Ser Ile Lys Lys Val Thr Ser Glu Asp Leu Lys Arg
625 630 635 640
Ser Tyr Val Cys His Ala Arg Ser Ala Lys Gly Glu Val Ala Lys Ala
645 650 655
Ala Lys Val Lys Gln Lys Val Pro Ala Pro Arg Tyr Thr Val Glu Ser
660 665 670
Gly Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu
675 680 685
Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
690 695 700
Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
705 710 715 720
Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
725 730 735
Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
740 745 750
Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
755 760 765
Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
770 775 780
Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
785 790 795 800
Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn
805 810 815
Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
820 825 830
Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
835 840 845
Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg
850 855 860
Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys
865 870 875 880
Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
885 890 895
Ser Leu Ser Leu Gly Lys
900

<210> 7
<211> 2709
<212> DNA
<213> Homo sapiens

<400> 7
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agcaagacac ctgtatctac agaacaagcc tccaggattc atcaacacaa agagaaactt 240
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ggtaaatga 2709

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

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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

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

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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 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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gcatatatcc agttaatata tccagtcact aattccggag acaaaactca cacatgccca 2040
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gtcctgcacc aggactggct gaatggcaag gagtacaagt gcaaggtctc caacaaagcc 2340
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ctggtcaaag gcttctatcc cagcgacatc gccgtggagt gggagagcaa tgggcagccg 2520
gagaacaact acaagaccac gcctcccgtg ctggactccg acggctcctt cttcctctac 2580
agcaagctca ccgtggacaa gagcaggtgg cagcagggga acgtcttctc atgctccgtg 2640
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tga 2703

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

<400> 10
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Gln Ser Asp Ala Ser Glu Arg Cys Asp Asp Trp Gly Leu Asp Thr Met
20 25 30

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

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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 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 agttttttaa 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
aatgggtcag taattgatga agatgaccca gtgctagggg aagactatta cagtgtggaa 1860
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agtagatttt ataaacatcc atttacctgt tttgccaaga atacacatgg tatagatgca 1980
gcatatatcc agttaatata tccagtcact aattccggag agtccaaata cggtccgcca 2040
tgcccatcat gcccagcacc tgagttcctg gggggaccat cagtcttcct gttcccccca 2100
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ggtaaatga 2709

<210> 12
<211> 902
<212> PRT
<213> Homo sapiens

<400> 12

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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 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
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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 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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900

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<211> 2709
<212> DNA
<213> Homo sapiens

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gagccagctc gcatcaagtg cccactcttt gaacacttct tgaaattcaa ctacagcaca 180
gcccattcag ctggccttac tctgatctgg tattggacta ggcaggaccg ggaccttgag 240
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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
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gagctactca ttccctgtac ggtctatttt agttttctga tggattctcg caatgaggtt 840
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<210> 14
<211> 902

<212> PRT
<213> Homo sapiens

<400> 14

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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 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
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                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
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Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
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Ser Leu Ser Leu Gly Lys
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<211> 2748
<212> DNA
<213> Homo sapiens

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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
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tccccccctca agaccatatc agcttctctg gggtcaagac tgacaatccc atgtaaggtg 780
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gacaagagca ggtggcagca ggggaacgtc ttctcatgct ccgtgatgca tgaggctctg 2700
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<210> 16
<211> 915
<212> PRT
<213> Homo sapiens

<400> 16

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            20                  25                  30
Arg His Tyr Lys Arg Glu Phe Arg Leu Glu Gly Glu Pro Val Ala Leu
        35                  40                  45
Arg Cys Pro Gln Val Pro Tyr Trp Leu Trp Ala Ser Val Ser Pro Arg
    50                  55                  60
Ile Asn Leu Thr Trp His Lys Asn Asp Ser Ala Arg Thr Val Pro Gly
65                  70                  75                  80
Glu Glu Glu Thr Arg Met Trp Ala Gln Asp Gly Ala Leu Trp Leu Leu
                85                  90                  95
Pro Ala Leu Gln Glu Asp Ser Gly Thr Tyr Val Cys Thr Thr Arg Asn
            100                 105                 110
Ala Ser Tyr Cys Asp Lys Met Ser Ile Glu Leu Arg Val Phe Glu Asn
        115                 120                 125
Thr Asp Ala Phe Leu Pro Phe Ile Ser Tyr Pro Gln Ile Leu Thr Leu
    130                 135                 140
Ser Thr Ser Gly Val Leu Val Cys Pro Asp Leu Ser Glu Phe Thr Arg
145                 150                 155                 160
Asp Lys Thr Asp Val Lys Ile Gln Trp Tyr Lys Asp Ser Leu Leu Leu
                165                 170                 175
Asp Lys Asp Asn Glu Lys Phe Leu Ser Val Arg Gly Thr Thr His Leu
            180                 185                 190
Leu Val His Asp Val Ala Leu Glu Asp Ala Gly Tyr Tyr Arg Cys Val
        195                 200                 205
Leu Thr Phe Ala His Glu Gly Gln Gln Tyr Asn Ile Thr Arg Ser Ile
    210                 215                 220
Glu Leu Arg Ile Lys Lys Lys Lys Glu Glu Thr Ile Pro Val Ile Ile
225                 230                 235                 240
Ser Pro Leu Lys Thr Ile Ser Ala Ser Leu Gly Ser Arg Leu Thr Ile
                245                 250                 255
Pro Cys Lys Val Phe Leu Gly Thr Gly Thr Pro Leu Thr Thr Met Leu
            260                 265                 270
Trp Trp Thr Ala Asn Asp Thr His Ile Glu Ser Ala Tyr Pro Gly Gly
        275                 280                 285
Arg Val Thr Glu Gly Pro Arg Gln Glu Tyr Ser Glu Asn Asn Glu Asn
    290                 295                 300
Tyr Ile Glu Val Pro Leu Ile Phe Asp Pro Val Thr Arg Glu Asp Leu
305                 310                 315                 320
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
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                405                 410                 415
Glu Asn Arg Ile Ser Lys Glu Lys Asp Val Leu Trp Phe Arg Pro Thr
            420                 425                 430
Leu Leu Asn Asp Thr Gly Asn Tyr Thr Cys Met Leu Arg Asn Thr Thr
        435                 440                 445
Tyr Cys Ser Lys Val Ala Phe Pro Leu Glu Val Val Gln Lys Asp Ser
    450                 455                 460
Cys Phe Asn Ser Pro Met Lys Leu Pro Val His Lys Leu Tyr Ile Glu
465                 470                 475                 480
Tyr Gly Ile Gln Arg Ile Thr Cys Pro Asn Val Asp Gly Tyr Phe Pro
                485                 490                 495
Ser Ser Val Lys Pro Thr Ile Thr Trp Tyr Met Gly Cys Tyr Lys Ile
            500                 505                 510
Gln Asn Phe Asn Asn Val Ile Pro Glu Gly Met Asn Leu Ser Phe Leu
        515                 520                 525
Ile Ala Leu Ile Ser Asn Asn Gly Asn Tyr Thr Cys Val Val Thr Tyr
    530                 535                 540
Pro Glu Asn Gly Arg Thr Phe His Leu Thr Arg Thr Leu Thr Val Lys
545                 550                 555                 560
Val Val Gly Ser Pro Lys Asn Ala Val Pro Pro Val Ile His Ser Pro
                565                 570                 575
Asn Asp His Val Val Tyr Glu Lys Glu Pro Gly Glu Glu Leu Leu Ile
            580                 585                 590
Pro Cys Thr Val Tyr Phe Ser Phe Leu Met Asp Ser Arg Asn Glu Val
        595                 600                 605
Trp Trp Thr Ile Asp Gly Lys Lys Pro Asp Asp Ile Thr Ile Asp Val
    610                 615                 620
Thr Ile Asn Glu Ser Ile Ser His Ser Arg Thr Glu Asp Glu Thr Arg
625                 630                 635                 640
Thr Gln Ile Leu Ser Ile Lys Lys Val Thr Ser Glu Asp Leu Lys Arg
                645                 650                 655
Ser Tyr Val Cys His Ala Arg Ser Ala Lys Gly Glu Val Ala Lys Ala
            660                 665                 670
Ala Lys Val Lys Gln Lys Val Pro Ala Pro Arg Tyr Thr Val Ser Gly
        675                 680                 685
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
    690                 695                 700
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
705                 710                 715                 720
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
                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
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    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
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<210> 17
<211> 2754
<212> DNA
<213> Homo sapiens

<400> 17

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agtaaggaga aagatgtgct gtggttccgg cccactctcc tcaatgacac tggcaactat    1320
acctgcatgt taaggaacac tacatattgc agcaaagttg catttccctt ggaagttgtt    1380
caaaaagaca gctgtttcaa ttccccccatg 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 cggagagtcc aaatacggtc cgccatgccc atcatgccca    2100
gcacctgagt tcctgggggg accatcagtc ttcctgttcc ccccaaaacc caaggacact    2160
ctcatgatct cccggacccc tgaggtcacg tgcgtggtgg tggacgtgag ccaggaagac    2220
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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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ctgcccccat cccaggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 2520
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tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaggcta 2640
accgtggaca agagcaggtg gcaggagggg aatgtcttct catgctccgt gatgcatgag 2700
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<210> 18
<211> 917
<212> PRT
<213> Homo sapiens

<400> 18
Met Val Arg Leu Tyr Val Leu Val Met Gly Val Ser Ala Phe Thr Leu
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Gln Pro Ala Ala His Thr Gly Ala Ala Arg Ser Cys Arg Phe Arg Gly
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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
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

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        355                 360                 365
Glu Pro Ala Arg Ile Lys Cys Pro Leu Phe Glu His Phe Leu Lys Phe
    370                 375                 380
Asn Tyr Ser Thr Ala His Ser Ala Gly Leu Thr Leu Ile Trp Tyr Trp
385                 390                 395                 400
Thr Arg Gln Asp Arg Asp Leu Glu Glu Pro Ile Asn Phe Arg Leu Pro
                405                 410                 415
Glu Asn Arg Ile Ser Lys Glu Lys Asp Val Leu Trp Phe Arg Pro Thr
            420                 425                 430
Leu Leu Asn Asp Thr Gly Asn Tyr Thr Cys Met Leu Arg Asn Thr Thr
        435                 440                 445
Tyr Cys Ser Lys Val Ala Phe Pro Leu Glu Val Val Gln Lys Asp Ser
    450                 455                 460
Cys Phe Asn Ser Pro Met Lys Leu Pro Val His Lys Leu Tyr Ile Glu
465                 470                 475                 480
Tyr Gly Ile Gln Arg Ile Thr Cys Pro Asn Val Asp Gly Tyr Phe Pro
                485                 490                 495
Ser Ser Val Lys Pro Thr Ile Thr Trp Tyr Met Gly Cys Tyr Lys Ile
            500                 505                 510
Gln Asn Phe Asn Asn Val Ile Pro Glu Gly Met Asn Leu Ser Phe Leu
        515                 520                 525
Ile Ala Leu Ile Ser Asn Asn Gly Asn Tyr Thr Cys Val Val Thr Tyr
    530                 535                 540
Pro Glu Asn Gly Arg Thr Phe His Leu Thr Arg Thr Leu Thr Val Lys
545                 550                 555                 560
Val Val Gly Ser Pro Lys Asn Ala Val Pro Pro Val Ile His Ser Pro
                565                 570                 575
Asn Asp His Val Val Tyr Glu Lys Glu Pro Gly Glu Glu Leu Leu Ile
            580                 585                 590
Pro Cys Thr Val Tyr Phe Ser Phe Leu Met Asp Ser Arg Asn Glu Val
        595                 600                 605
Trp Trp Thr Ile Asp Gly Lys Lys Pro Asp Asp Ile Thr Ile Asp Val
    610                 615                 620
Thr Ile Asn Glu Ser Ile Ser His Ser Arg Thr Glu Asp Glu Thr Arg
625                 630                 635                 640
Thr Gln Ile Leu Ser Ile Lys Lys Val Thr Ser Glu Asp Leu Lys Arg
                645                 650                 655
Ser Tyr Val Cys His Ala Arg Ser Ala Lys Gly Glu Val Ala Lys Ala
            660                 665                 670
Ala Lys Val Lys Gln Lys Val Pro Ala Pro Arg Tyr Thr Val Ser Gly
        675                 680                 685
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu Phe
    690                 695                 700
Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
705                 710                 715                 720
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                725                 730                 735
Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
            740                 745                 750
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
        755                 760                 765
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
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Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
            820                 825                 830
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        835                 840                 845
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
    850                 855                 860
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
865                 870                 875                 880
Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
                885                 890                 895
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
            900                 905                 910
Leu Ser Leu Gly Lys
        915
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<210> 19
<211> 2754
<212> DNA
<213> Homo sapiens

<400> 19

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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
tccccctca 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
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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 cggagagtcc aaatacggtc cgccatgccc accatgccca    2100
gcacctgagt tcctgggggg accatcagtc ttcctgttcc ccccaaaacc caaggacact    2160
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ctcatgatct cccggacccc tgaggtcacg tgcgtggtgg tggacgtgag ccaggaagac    2220
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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
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<210> 20
<211> 917
<212> PRT
<213> Homo sapiens

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

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    770                 775                 780
Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
785                 790                 795                 800
Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
                805                 810                 815
Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
            820                 825                 830
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        835                 840                 845
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
    850                 855                 860
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
865                 870                 875                 880
Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
                885                 890                 895
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
            900                 905                 910
Leu Ser Leu Gly Lys
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<210> 21
<211> 2748
<212> DNA
<213> Homo sapiens

<400> 21

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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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ccccgcatca acctgacatg gcataaaaat gactctgcta ggacggtccc aggagaagaa   1260
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tttctaagtg tgagggggac cactcactta ctcgtacacg atgtggccct ggaagatgct   1620
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agtattgagc tacgcatcaa gaaaaaaaaa gaagagacca ttcctgtgat catttccccc   1740
ctcaagacca tatcagcttc tctggggtca agactgacaa tcccatgtaa ggtgtttctg   1800
ggaaccggca cacccttaac caccatgctg tggtggacgg ccaatgacac ccacatagag   1860
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agcgcctacc cgggaggccg cgtgaccgag gggccacgcc aggaatattc agaaaataat    1920
gagaactaca ttgaagtgcc attgattttt gatcctgtca caagagagga tttgcacatg    1980
gattttaaat gtgttgtcca taataccctg agttttcaga cactacgcac cacagtcaag    2040
gaagcctcct ccacgttctc cggagacaaa actcacacat gcccaccgtg cccagcacct    2100
gaactcctgg ggggaccgtc agtcttcctc ttcccccaa aacccaagga caccctcatg    2160
atctcccgga cccctgaggt cacatgcgtg gtggtggacg tgagccacga agaccctgag    2220
gtcaagttca actggtacgt ggacggcgtg gaggtgcata atgccaagac aaagccgcgg    2280
gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac    2340
tggctgaatg gcaaggagta caagtgcaag gtctccaaca aagccctccc agcccccatc    2400
gagaaaacca tctccaaagc caaagggcag ccccgagaac cacaggtgta caccctgccc    2460
ccatcccggg atgagctgac caagaaccag gtcagcctga cctgcctggt caaaggcttc    2520
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<210> 22
<211> 915
<212> PRT
<213> Homo sapiens

<400> 22

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

```
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
            740                 745                 750
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
        755                 760                 765
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
    770                 775                 780
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
785                 790                 795                 800
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
                805                 810                 815
Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
            820                 825                 830
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
        835                 840                 845
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
    850                 855                 860
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
865                 870                 875                 880
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
                885                 890                 895
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
            900                 905                 910
Pro Gly Lys
        915
```

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

<400> 23

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atggtgcttc tgtggtgtgt agtgagtctc tacttttatg gaatcctgca aagtgatgcc     60
tcagaacgct gcgatgactg gggactagac accatgaggc aaatccaagt gtttgaagat    120
gagccagctc gcatcaagtg cccactcttt gaacacttct tgaaattcaa ctacagcaca    180
gcccattcag ctggccttac tctgatctgg tattggacta ggcaggaccg ggaccttgag    240
gagccaatta acttccgcct ccccgagaac cgcattagta aggagaaaga tgtgctgtgg    300
ttccggccca ctctcctcaa tgacactggc aactatacct gcatgttaag gaacactaca    360
tattgcagca aagttgcatt tcccttggaa gttgttcaaa aagacagctg tttcaattcc    420
cccatgaaac tcccagtgca taaactgtat atagaatatg gcattcagag gatcacttgt    480
ccaaatgtag atggatattt tccttccagt gtcaaaccga ctatcacttg gtatatgggc    540
tgttataaaa tacagaattt taataatgta atacccgaag gtatgaactt gagtttcctc    600
attgccttaa tttcaaataa tggaaattac acatgtgttg ttacatatcc agaaaatgga    660
cgtacgtttc atctcaccag gactctgact gtaaaggtag taggctctcc aaaaaatgca    720
gtgccccctg tgatccattc acctaatgat catgtggtct atgagaaaga accaggagag    780
gagctactca ttccctgtac ggtctatttt agttttctga tggattctcg caatgaggtt    840
tggtggacca ttgatggaaa aaaacctgat gacatcacta ttgatgtcac cattaacgaa    900
agtataagtc atagtagaac agaagatgaa acaagaactc agattttgag catcaagaaa    960
gttacctctg aggatctcaa gcgcagctat gtctgtcatg ctagaagtgc caaaggcgaa   1020
gttgccaaag cagccaaggt gaagcagaaa gtgccagctc caagatacac agtgcacaca   1080
ggggctgcca gaagctgccg gtttcgtggg aggcattaca agcgggagtt caggctggaa   1140
ggggagcctg tagccctgag gtgcccccag gtgccctact ggttgtgggc ctctgtcagc   1200
ccccgcatca acctgacatg gcataaaaat gactctgcta ggacggtccc aggagaagaa   1260
gagacacgga tgtgggccca ggacggtgct ctgtggcttc tgccagcctt gcaggaggac   1320
tctggcacct acgtctgcac tactagaaat gcttcttact gtgacaaaat gtccattgag   1380
ctcagagttt ttgagaatac agatgctttc ctgccgttca tctcataccc gcaaatttta   1440
accttgtcaa cctctggggt attagtatgc cctgacctga gtgaattcac ccgtgacaaa   1500
actgacgtga agattcaatg gtacaaggat tctcttcttt tggataaaga caatgagaaa   1560
```

```
tttctaagtg tgaggggac 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 cggagagtcc aaatacggtc cgccatgccc atcatgccca   2100
gcacctgagt tcctgggggg accatcagtc ttcctgttcc ccccaaaacc caaggacact   2160
ctcatgatct cccggacccc tgaggtcacg tgcgtggtgg tggacgtgag ccaggaagac   2220
cccgaggtcc agttcaactg gtacgtggat ggcgtggagg tgcataatgc caagacaaag   2280
ccgcgggagg agcagttcaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac   2340
caggactggc tgaacggcaa ggagtacaag tgcaaggtct ccaacaaagg cctcccgtcc   2400
tccatcgaga aaaccatctc caaagccaaa gggcagcccc gagagccaca ggtgtacacc   2460
ctgccccat cccaggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa   2520
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

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

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

```
    690                 695                 700
Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
705                 710                 715                 720
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                725                 730                 735
Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
            740                 745                 750
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
        755                 760                 765
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    770                 775                 780
Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
785                 790                 795                 800
Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
                805                 810                 815
Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
            820                 825                 830
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        835                 840                 845
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
    850                 855                 860
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
865                 870                 875                 880
Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
                885                 890                 895
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
            900                 905                 910
Leu Ser Leu Gly Lys
        915
```

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

<400> 25

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atggtgcttc tgtggtgtgt agtgagtctc tacttttatg gaatcctgca aagtgatgcc     60
tcagaacgct gcgatgactg gggactagac accatgaggc aaatccaagt gtttgaagat    120
gagccagctc gcatcaagtg cccactcttt gaacacttct tgaaattcaa ctacagcaca    180
gcccattcag ctggccttac tctgatctgg tattggacta ggcaggaccg ggaccttgag    240
gagccaatta acttccgcct ccccgagaac cgcattagta aggagaaaga tgtgctgtgg    300
ttccggccca ctctcctcaa tgacactggc aactatacct gcatgttaag gaacactaca    360
tattgcagca aagttgcatt tcccttggaa gttgttcaaa aagacagctg tttcaattcc    420
cccatgaaac tcccagtgca taaactgtat atagaatatg gcattcagag gatcacttgt    480
ccaaatgtag atggatattt tccttccagt gtcaaaccga ctatcacttg gtatatgggc    540
tgttataaaa tacagaattt taataatgta atacccgaag gtatgaactt gagtttcctc    600
attgccttaa tttcaaataa tggaaattac acatgtgttg ttacatatcc agaaaatgga    660
cgtacgtttc atctcaccag gactctgact gtaaaggtag taggctctcc aaaaaatgca    720
gtgccccctg tgatccattc acctaatgat catgtggtct atgagaaaga accaggagag    780
gagctactca ttccctgtac ggtctatttt agttttctga tggattctcg caatgaggtt    840
tggtggacca ttgatggaaa aaaacctgat gacatcacta ttgatgtcac cattaacgaa    900
agtataagtc atagtagaac agaagatgaa acaagaactc agattttgag catcaagaaa    960
gttacctctg aggatctcaa gcgcagctat gtctgtcatg ctagaagtgc caaaggcgaa   1020
gttgccaaag cagccaaggt gaagcagaaa gtgccagctc caagatacac agtgcacaca   1080
ggggctgcca gaagctgccg gtttcgtggg aggcattaca agcgggagtt caggctggaa   1140
ggggagcctg tagccctgag gtgcccccag gtgccctact ggttgtgggc ctctgtcagc   1200
ccccgcatca acctgacatg gcataaaaat gactctgcta ggacggtccc aggagaagaa   1260
```

```
gagacacgga tgtgggccca ggacggtgct ctgtggcttc tgccagcctt gcaggaggac    1320
tctggcacct acgtctgcac tactagaaat gcttcttact gtgacaaaat gtccattgag    1380
ctcagagttt ttgagaatac agatgctttc ctgccgttca tctcataccc gcaaatttta    1440
accttgtcaa cctctggggt attagtatgc cctgacctga gtgaattcac ccgtgacaaa    1500
actgacgtga agattcaatg gtacaaggat tctcttcttt tggataaaga caatgagaaa    1560
tttctaagtg tgaggggggac cactcactta ctcgtacacg atgtggccct ggaagatgct    1620
ggctattacc gctgtgtcct gacatttgcc catgaaggcc agcaatacaa catcactagg    1680
agtattgagc tacgcatcaa gaaaaaaaaa gaagagacca ttcctgtgat catttccccc    1740
ctcaagacca tatcagcttc tctggggtca agactgacaa tcccatgtaa ggtgtttctg    1800
ggaaccggca cacccttaac caccatgctg tggtggacgg ccaatgacac ccacatagag    1860
agcgcctacc cgggaggccg cgtgaccgag gggccacgcc aggaatattc agaaaataat    1920
gagaactaca ttgaagtgcc attgattttt gatcctgtca caagagagga tttgcacatg    1980
gattttaaat gtgttgtcca taataccctg agttttcaga cactacgcac cacagtcaag    2040
gaagcctcct ccacgttctc 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
ctgcccccat 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> 26
<211> 917
<212> PRT
<213> Homo sapiens

<400> 26

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Met Val Leu Leu Trp Cys Val Val Ser Leu Tyr Phe Tyr Gly Ile Leu
 1               5                  10                  15
Gln Ser Asp Ala Ser Glu Arg Cys Asp Asp Trp Gly Leu Asp Thr Met
            20                  25                  30
Arg Gln Ile Gln Val Phe Glu Asp Glu Pro Ala Arg Ile Lys Cys Pro
        35                  40                  45
Leu Phe Glu His Phe Leu Lys Phe Asn Tyr Ser Thr Ala His Ser Ala
    50                  55                  60
Gly Leu Thr Leu Ile Trp Tyr Trp Thr Arg Gln Asp Arg Asp Leu Glu
65                  70                  75                  80
Glu Pro Ile Asn Phe Arg Leu Pro Glu Asn Arg Ile Ser Lys Glu Lys
                85                  90                  95
Asp Val Leu Trp Phe Arg Pro Thr Leu Leu Asn Asp Thr Gly Asn Tyr
            100                 105                 110
Thr Cys Met Leu Arg Asn Thr Thr Tyr Cys Ser Lys Val Ala Phe Pro
        115                 120                 125
Leu Glu Val Val Gln Lys Asp Ser Cys Phe Asn Ser Pro Met Lys Leu
    130                 135                 140
Pro Val His Lys Leu Tyr Ile Glu Tyr Gly Ile Gln Arg Ile Thr Cys
145                 150                 155                 160
Pro Asn Val Asp Gly Tyr Phe Pro Ser Ser Val Lys Pro Thr Ile Thr
                165                 170                 175
Trp Tyr Met Gly Cys Tyr Lys Ile Gln Asn Phe Asn Asn Val Ile Pro
            180                 185                 190
Glu Gly Met Asn Leu Ser Phe Leu Ile Ala Leu Ile Ser Asn Asn Gly
```

```
        195                 200                 205
Asn Tyr Thr Cys Val Val Thr Tyr Pro Glu Asn Gly Arg Thr Phe His
    210                 215                 220
Leu Thr Arg Thr Leu Thr Val Lys Val Val Gly Ser Pro Lys Asn Ala
225                 230                 235                 240
Val Pro Pro Val Ile His Ser Pro Asn Asp His Val Val Tyr Glu Lys
                245                 250                 255
Glu Pro Gly Glu Glu Leu Leu Ile Pro Cys Thr Val Tyr Phe Ser Phe
            260                 265                 270
Leu Met Asp Ser Arg Asn Glu Val Trp Trp Thr Ile Asp Gly Lys Lys
        275                 280                 285
Pro Asp Asp Ile Thr Ile Asp Val Thr Ile Asn Glu Ser Ile Ser His
    290                 295                 300
Ser Arg Thr Glu Asp Glu Thr Arg Thr Gln Ile Leu Ser Ile Lys Lys
305                 310                 315                 320
Val Thr Ser Glu Asp Leu Lys Arg Ser Tyr Val Cys His Ala Arg Ser
                325                 330                 335
Ala Lys Gly Glu Val Ala Lys Ala Ala Lys Val Lys Gln Lys Val Pro
            340                 345                 350
Ala Pro Arg Tyr Thr Val His Thr Gly Ala Ala Arg Ser Cys Arg Phe
        355                 360                 365
Arg Gly Arg His Tyr Lys Arg Glu Phe Arg Leu Glu Gly Glu Pro Val
    370                 375                 380
Ala Leu Arg Cys Pro Gln Val Pro Tyr Trp Leu Trp Ala Ser Val Ser
385                 390                 395                 400
Pro Arg Ile Asn Leu Thr Trp His Lys Asn Asp Ser Ala Arg Thr Val
                405                 410                 415
Pro Gly Glu Glu Glu Thr Arg Met Trp Ala Gln Asp Gly Ala Leu Trp
            420                 425                 430
Leu Leu Pro Ala Leu Gln Glu Asp Ser Gly Thr Tyr Val Cys Thr Thr
        435                 440                 445
Arg Asn Ala Ser Tyr Cys Asp Lys Met Ser Ile Glu Leu Arg Val Phe
    450                 455                 460
Glu Asn Thr Asp Ala Phe Leu Pro Phe Ile Ser Tyr Pro Gln Ile Leu
465                 470                 475                 480
Thr Leu Ser Thr Ser Gly Val Leu Val Cys Pro Asp Leu Ser Glu Phe
                485                 490                 495
Thr Arg Asp Lys Thr Asp Val Lys Ile Gln Trp Tyr Lys Asp Ser Leu
            500                 505                 510
Leu Leu Asp Lys Asp Asn Glu Lys Phe Leu Ser Val Arg Gly Thr Thr
        515                 520                 525
His Leu Leu Val His Asp Val Ala Leu Glu Asp Ala Gly Tyr Tyr Arg
    530                 535                 540
Cys Val Leu Thr Phe Ala His Glu Gly Gln Gln Tyr Asn Ile Thr Arg
545                 550                 555                 560
Ser Ile Glu Leu Arg Ile Lys Lys Lys Lys Glu Glu Thr Ile Pro Val
                565                 570                 575
Ile Ile Ser Pro Leu Lys Thr Ile Ser Ala Ser Leu Gly Ser Arg Leu
            580                 585                 590
Thr Ile Pro Cys Lys Val Phe Leu Gly Thr Gly Thr Pro Leu Thr Thr
        595                 600                 605
Met Leu Trp Trp Thr Ala Asn Asp Thr His Ile Glu Ser Ala Tyr Pro
    610                 615                 620
Gly Gly Arg Val Thr Glu Gly Pro Arg Gln Glu Tyr Ser Glu Asn Asn
625                 630                 635                 640
Glu Asn Tyr Ile Glu Val Pro Leu Ile Phe Asp Pro Val Thr Arg Glu
                645                 650                 655
```

```
Asp Leu His Met Asp Phe Lys Cys Val Val His Asn Thr Leu Ser Phe
            660                 665                 670
Gln Thr Leu Arg Thr Thr Val Lys Glu Ala Ser Ser Thr Phe Ser Gly
        675                 680                 685
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
    690                 695                 700
Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
705                 710                 715                 720
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                725                 730                 735
Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
            740                 745                 750
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
        755                 760                 765
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    770                 775                 780
Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
785                 790                 795                 800
Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
                805                 810                 815
Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
            820                 825                 830
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        835                 840                 845
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
    850                 855                 860
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
865                 870                 875                 880
Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
                885                 890                 895
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
            900                 905                 910
Leu Ser Leu Gly Lys
        915
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INTERNATIONAL SEARCH REPORT

Internat[redacted] Application No
PCT/US2005/019674

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/17 A61K39/395 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data, PAJ, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HAWKINS PHILIP N ET AL: "Spectrum of clinical features in Muckle-Wells syndrome and response to anakinra." ARTHRITIS AND RHEUMATISM. FEB 2004, vol. 50, no. 2, February 2004 (2004-02), pages 607-612, XP002345728 ISSN: 0004-3591 page 307	1-18
Y	US 2001/053764 A1 (SIMS JOHN E ET AL) 20 December 2001 (2001-12-20) paragraph '0054!	1-18
Y	WO 2004/022718 A (AMGEN, INC; VARNUM, BRIAN; VEZINA, CHRIS; WITTE, ALISON; QIAN, XUEMING) 18 March 2004 (2004-03-18) page 4 page 60	1-18

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 September 2005	29/09/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Wagner, R

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

Internat[redacted] Application No
PCT/US2005/019674

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2003/143697 A1 (STAHL NEIL ET AL) 31 July 2003 (2003-07-31) figure 41	1-18
A	ECONOMIDES A N ET AL: "Cytokine traps: multi-component, high-affinity blockers of cytokine action" NATURE MEDICINE, NATURE PUBLISHING, CO, US, vol. 9, no. 1, January 2003 (2003-01), pages 47-52, XP002256034 ISSN: 1078-8956 the whole document	1-18
A	WO 2004/039951 A (REGENERON PHARMA 'US!; STAHL NEIL 'US!; YANCOPOULOS GEORGE D 'US!) 13 May 2004 (2004-05-13) the whole document	1-18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/019674

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 14-18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Internat[redacted] Application No
PCT/US2005/019674

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2001053764 A1	20-12-2001	US 2004023869 A1	05-02-2004
WO 2004022718 A	18-03-2004	AU 2003270370 A1	29-03-2004
		BR 0314038 A	19-07-2005
		CA 2497884 A1	18-03-2004
		EP 1572946 A2	14-09-2005
US 2003143697 A1	31-07-2003	US 2005074855 A1	07-04-2005
WO 2004039951 A	13-05-2004	AU 2003284895 A1	25-05-2004
		BR 0315652 A	30-08-2005
		CA 2502385 A1	13-05-2004
		EP 1572967 A2	14-09-2005
		US 2005197293 A1	08-09-2005