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CA 2518101 A1 2005/06/09

(21) **2 518 101**

(12) **DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION**

(13) **A1**

(86) Date de dépôt PCT/PCT Filing Date: 2004/03/02
(87) Date publication PCT/PCT Publication Date: 2005/06/09
(85) Entrée phase nationale/National Entry: 2005/09/02
(86) N° demande PCT/PCT Application No.: US 2004/006460
(87) N° publication PCT/PCT Publication No.: 2005/051988
(30) Priorité/Priority: 2003/03/03 (60/451,884) US

(51) Cl.Int.⁷/Int.Cl.⁷ C07K 14/435, A61K 38/17, A61P 37/00,
C12N 15/12, C12Q 1/68

(71) Demandeur/Applicant:
GENENTECH, INC., US

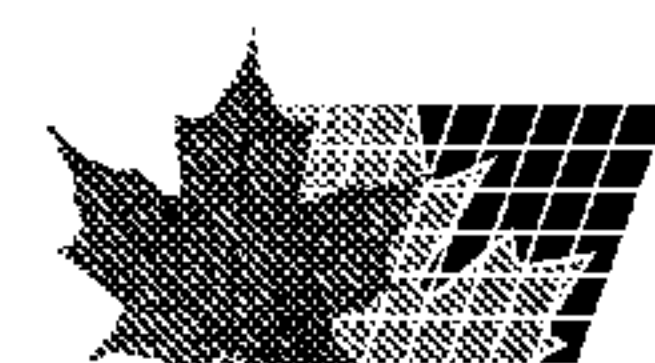
(72) Inventeurs/Inventors:
ABBAS, ALEXANDER, US;
BODARY, SARAH, US;
CLARK, HILARY, US;
SCHOENFELD, JILL, US;
WILLIAMS, P. MICKEY, US;
WOOD, WILLIAM I., US;
WU, THOMAS D., US

(74) Agent: SMART & BIGGAR

(54) Titre : COMPOSITIONS ET PROCEDES PERMETTANT DE TRAITER UN LUPUS ERYTHEMATEUX SYSTEMIQUE
(54) Title: COMPOSITIONS AND METHODS FOR THE TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSIS

(57) **Abrégé/Abstract:**

The present invention relates to compositions containing novel proteins and methods of using those compositions for the diagnosis and treatment of immune related diseases



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
9 June 2005 (09.06.2005)

PCT

(10) International Publication Number
WO 2005/051988 A3

(51) International Patent Classification⁷: **C07K 14/435**,
C12N 15/12, A61K 38/17, C12Q 1/68, A61P 37/00

(21) International Application Number:
PCT/US2004/006460

(22) International Filing Date: 2 March 2004 (02.03.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/451,884 3 March 2003 (03.03.2003) US

(71) Applicant (for all designated States except US): **GENEN-TECH, INC.** [US/US]; 1 DNA Way, South San Francisco, California 94080-4990 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **ABBAS, Alexander** [US/US]; 6087 Ocean View Drive, Oakland, California 94618-1844 (US). **BODARY, Sarah** [US/US]; 1951 Camino de los Robles, Menlo Park, California 94025 (US). **CLARK, Hilary** [US/US]; 1504 Noe St., San Francisco, California 94131 (US). **SCHOENFELD, Jill** [US/US]; 680 Spring Creek Drive, Ashland, Oregon 97520 (US). **WILLIAMS, P. Mickey** [US/US]; 509 Alto Avenue, Half Moon Bay, California 94019 (US). **WOOD, William I.** [US/US]; 15060 Montebello Rd., Cupertino, California 95014 (US). **WU, Thomas D.** [US/US]; 41 Nevada Street, San Francisco, California 94110 (US).

(74) Agent: **CARPENTER, David A.**; MS 49, 1 DNA Way, South San Francisco, CA 94080 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- with sequence listing part of description published separately in electronic form and available upon request from the International Bureau

(88) Date of publication of the international search report:
28 July 2005

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMPOSITIONS AND METHODS FOR THE TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSIS

(57) Abstract: The present invention relates to compositions containing novel proteins and methods of using those compositions for the diagnosis and treatment of immune related diseases

WO 2005/051988 A3

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 3
CONTENANT LES PAGES 1 À 304

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

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NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

COMPOSITIONS AND METHODS FOR THE TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSIS

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Field of the Invention

The present invention relates to compositions and methods useful for the diagnosis and treatment of systemic lupus erythematosus.

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Background of the Invention

Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

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Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

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Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases, non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, *etc.*

Immune related diseases could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

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Systemic Lupus Erythematosus (SLE) is an autoimmune diseases characterized by chronic relapsing inflammation of various tissue sites, primarily kidney, which result in tissue destruction. SLE is more common in women and genetic susceptibility is thought to contribute to the dysregulation of the immune system. Animal studies as well as human clinical experience have also demonstrated that environmental factors also contribute to these diseases. While the etiology and pathogenesis of SLE is still poorly understood, B cells, T cells and monocytes have all been implicated as playing critical roles in disease progression. Therapeutics know to target these cell types have been shown to impact disease pregression in human as well as animal studies. Analysis of the gene expression patterns of white blood cells from healthy individuals compared to SLE patients was carried out using Affymetrix® GeneChips®. The identification of genes that are differentially expressed in disease vs healthy cells is likely to provide important information as to the role of these gene products in the pathogenesis of disease. These disease associated genes may be used as targets or therapies for the treatment of SLE and other autoimmune

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mediated inflammatory diseases and may include the gene products themselves as well as antibody, peptide or small molecule antagonists. The identification of genes that are differentially expressed in disease vs healthy cells is likely to provide important information as to the role of these gene products in the pathogenesis of disease. These disease associated genes may be used as targets or therapies for the treatment of SLE and other autoimmune mediated inflammatory diseases and may include the gene products themselves as well as antibody, peptide or small molecule antagonists.

Summary of the Invention

A. Embodiments

The present invention concerns compositions and methods useful for the diagnosis and treatment of SLE in mammals, including humans. The present invention is based on the identification of proteins (including agonist and antagonist antibodies) which are a result of stimulation of the immune response in mammals, resulting in autoimmunity. Immune related diseases can be treated by suppressing or enhancing the immune response. Molecules that enhance the immune response stimulate or potentiate the immune response to an antigen. Molecules which stimulate the immune response can be used therapeutically where enhancement of the immune response would be beneficial. Alternatively, molecules that suppress the immune response attenuate or reduce the immune response to an antigen (*e.g.*, neutralizing antibodies) can be used therapeutically where attenuation of the immune response would be beneficial (*e.g.*, inflammation). Accordingly, the PRO polypeptides, agonists and antagonists thereof are also useful to prepare medicines and medicaments for the treatment of SLE. In a specific aspect, such medicines and medicaments comprise a therapeutically effective amount of a PRO polypeptide, agonist or antagonist thereof with a pharmaceutically acceptable carrier. Preferably, the admixture is sterile.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists to a PRO polypeptide which comprises contacting the PRO polypeptide with a candidate molecule and monitoring a biological activity mediated by said PRO polypeptide. Preferably, the PRO polypeptide is a native sequence PRO polypeptide. In a specific aspect, the PRO agonist or antagonist is an anti-PRO antibody.

In another embodiment, the invention concerns a composition of matter comprising a PRO polypeptide or an agonist or antagonist antibody which binds the polypeptide in admixture with a carrier or excipient. In one aspect, the composition comprises a therapeutically effective amount of the polypeptide or antibody.

In a further aspect, when the composition comprises an immune inhibiting molecule, the composition is useful for: (a) inhibiting or reducing SLE in a mammal in need thereof, (b) decreasing the activity of immune cells or (c) decreasing the proliferation of immune cells in a mammal in need thereof in response to an antigen. In another aspect, the composition comprises a further active ingredient, which may, for example, be a further antibody or a cytotoxic or chemotherapeutic agent. Preferably, the composition is sterile.

In another embodiment, the invention concerns a method of treating an immune related disorder in a mammal in need thereof, comprising administering to the mammal an effective amount of a PRO polypeptide, an agonist thereof, or an antagonist thereto. In a preferred aspect, the immune related disorder

is selected from the group consisting of: SLE rheumatoid arthritis, osteoarthritis, juvenile chronic arthritis, spondyloarthropathies, systemic sclerosis, idiopathic inflammatory myopathies, Sjögren's syndrome, systemic vasculitis, sarcoidosis, autoimmune hemolytic anemia, autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis, lymphadenopathy, splenomegaly and leukopenia. In another embodiment, the invention provides an antibody which specifically binds to any of the above or below described polypeptides. Optionally, the antibody is a monoclonal antibody, humanized antibody, antibody fragment or single-chain antibody. In one aspect, the present invention concerns an isolated antibody which binds a PRO polypeptide. In another aspect, the antibody mimics the activity of a PRO polypeptide (an agonist antibody) or conversely the antibody inhibits or neutralizes the activity of a PRO polypeptide (an antagonist antibody). In another aspect, the antibody is a monoclonal antibody, which preferably has nonhuman complementarity determining region (CDR) residues and human framework region (FR) residues. The antibody may be labeled and may be immobilized on a solid support. In a further aspect, the antibody is an antibody fragment, a monoclonal antibody, a single-chain antibody, or an anti-idiotypic antibody.

In yet another embodiment, the present invention provides a composition comprising an anti-PRO antibody in admixture with a pharmaceutically acceptable carrier. In one aspect, the composition comprises a therapeutically effective amount of the antibody. Preferably, the composition is sterile. The composition may be administered in the form of a liquid pharmaceutical formulation, which may be preserved to achieve extended storage stability. Alternatively, the antibody is a monoclonal antibody, an antibody fragment, a humanized antibody, or a single-chain antibody.

In a further embodiment, the invention concerns an article of manufacture, comprising:

- (a) a composition of matter comprising a PRO polypeptide or agonist or antagonist thereof;
- (b) a container containing said composition; and
- (c) a label affixed to said container, or a package insert included in said container referring to

the use of said PRO polypeptide or agonist or antagonist thereof in the treatment of an immune related disease. The composition may comprise a therapeutically effective amount of the PRO polypeptide or the agonist or antagonist thereof.

In yet another embodiment, the present invention concerns a method of diagnosing SLE in a mammal, comprising detecting the level of expression of a gene encoding a PRO polypeptide (a) in a test sample of tissue cells obtained from the mammal, and (b) in a control sample of known normal tissue cells of the same cell type, wherein a higher or lower expression level in the test sample as compared to the control sample indicates the presence of immune related disease in the mammal from which the test tissue cells were obtained.

In another embodiment, the present invention concerns a method of diagnosing SLE in a mammal, comprising (a) contacting an anti-PRO antibody with a test sample of tissue cells obtained from the mammal, and (b) detecting the formation of a complex between the antibody and a PRO polypeptide, in the test sample; wherein the formation of said complex is indicative of the presence or absence of said disease. The detection may be qualitative or quantitative, and may be performed in comparison with monitoring the complex formation in a control sample of known normal tissue cells of the same cell type. A larger quantity of complexes formed in the test sample indicates the presence or absence of an immune disease in the

mammal from which the test tissue cells were obtained. The antibody preferably carries a detectable label. Complex formation can be monitored, for example, by light microscopy, flow cytometry, fluorimetry, or other techniques known in the art. The test sample is usually obtained from an individual suspected of having SLE.

5 In another embodiment, the invention provides a method for determining the presence of a PRO polypeptide in a sample comprising exposing a test sample of cells suspected of containing the PRO polypeptide to an anti-PRO antibody and determining the binding of said antibody to said cell sample. In a specific aspect, the sample comprises a cell suspected of containing the PRO polypeptide and the antibody binds to the cell. The antibody is preferably detectably labeled and/or bound to a solid support.

10 In another embodiment, the present invention concerns an immune-related disease diagnostic kit, comprising an anti-PRO antibody and a carrier in suitable packaging. The kit preferably contains instructions for using the antibody to detect the presence of the PRO polypeptide. Preferably the carrier is pharmaceutically acceptable.

15 In another embodiment, the present invention concerns a diagnostic kit, containing an anti-PRO antibody in suitable packaging. The kit preferably contains instructions for using the antibody to detect the PRO polypeptide.

20 In another embodiment, the invention provides a method of diagnosing SLE in a mammal which comprises detecting the presence or absence of a PRO polypeptide in a test sample of tissue cells obtained from said mammal, wherein the presence or absence of the PRO polypeptide in said test sample is indicative of the presence of SLE in said mammal.

In another embodiment, the present invention concerns a method for identifying an agonist of a PRO polypeptide comprising:

(a) contacting cells and a test compound to be screened under conditions suitable for the induction of a cellular response normally induced by a PRO polypeptide; and

25 (b) determining the induction of said cellular response to determine if the test compound is an effective agonist, wherein the induction of said cellular response is indicative of said test compound being an effective agonist.

In another embodiment, the invention concerns a method for identifying a compound capable of inhibiting the activity of a PRO polypeptide comprising contacting a candidate compound with a PRO polypeptide under conditions and for a time sufficient to allow these two components to interact and determining whether the activity of the PRO polypeptide is inhibited. In a specific aspect, either the candidate compound or the PRO polypeptide is immobilized on a solid support. In another aspect, the non-immobilized component carries a detectable label. In a preferred aspect, this method comprises the steps of:

35 (a) contacting cells and a test compound to be screened in the presence of a PRO polypeptide under conditions suitable for the induction of a cellular response normally induced by a PRO polypeptide; and

(b) determining the induction of said cellular response to determine if the test compound is an effective antagonist.

40 In another embodiment, the invention provides a method for identifying a compound that inhibits the expression of a PRO polypeptide in cells that normally express the polypeptide, wherein the method comprises contacting the cells with a test compound and determining whether the expression of the PRO

polypeptide is inhibited. In a preferred aspect, this method comprises the steps of:

- (a) contacting cells and a test compound to be screened under conditions suitable for allowing expression of the PRO polypeptide; and
- (b) determining the inhibition of expression of said polypeptide.

5 In yet another embodiment, the present invention concerns a method for treating SLE in a mammal that suffers therefrom comprising administering to the mammal a nucleic acid molecule that codes for either (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide or (c) an antagonist of a PRO polypeptide, wherein said agonist or antagonist may be an anti-PRO antibody. In a preferred embodiment, the mammal is human. In another preferred embodiment, the nucleic acid is administered via *ex vivo* gene therapy. In a further preferred embodiment, the nucleic acid is comprised within a vector, more preferably an adenoviral, adeno-associated viral, lentiviral or retroviral vector.

15 In yet another aspect, the invention provides a recombinant viral particle comprising a viral vector consisting essentially of a promoter, nucleic acid encoding (a) a PRO polypeptide, (b) an agonist polypeptide of a PRO polypeptide, or (c) an antagonist polypeptide of a PRO polypeptide, and a signal sequence for cellular secretion of the polypeptide, wherein the viral vector is in association with viral structural proteins. Preferably, the signal sequence is from a mammal, such as from a native PRO polypeptide.

In a still further embodiment, the invention concerns an *ex vivo* producer cell comprising a nucleic acid construct that expresses retroviral structural proteins and also comprises a retroviral vector consisting essentially of a promoter, nucleic acid encoding (a) a PRO polypeptide, (b) an agonist polypeptide of a PRO polypeptide or (c) an antagonist polypeptide of a PRO polypeptide, and a signal sequence for cellular secretion of the polypeptide, wherein said producer cell packages the retroviral vector in association with the structural proteins to produce recombinant retroviral particles.

25 In a still further embodiment, the invention provides a method of alleviating SLE in a mammal comprising administering to said mammal (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide, or (c) an antagonist of a PRO polypeptide, wherein SLE in the mammal is alleviated.

B. Additional Embodiments

30 In other embodiments of the present invention, the invention provides vectors comprising DNA encoding any of the herein described polypeptides. Host cell comprising any such vector are also provided. By way of example, the host cells may be CHO cells, *E. coli*, or yeast. A process for producing any of the herein described polypeptides is further provided and comprises culturing host cells under conditions suitable for expression of the desired polypeptide and recovering the desired polypeptide from the cell culture.

35 In other embodiments, the invention provides chimeric molecules comprising any of the herein described polypeptides fused to a heterologous polypeptide or amino acid sequence. Example of such chimeric molecules comprise any of the herein described polypeptides fused to an epitope tag sequence or a Fc region of an immunoglobulin.

In another embodiment, the invention provides an antibody which specifically binds to any of the above or below described polypeptides. Optionally, the antibody is a monoclonal antibody, humanized antibody, antibody fragment or single-chain antibody.

In yet other embodiments, the invention provides oligonucleotide probes useful for isolating genomic and cDNA nucleotide sequences or as antisense probes, wherein those probes may be derived from any of the above or below described nucleotide sequences.

In other embodiments, the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence that encodes a PRO polypeptide.

In one aspect, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule encoding a PRO polypeptide having a full-length amino acid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

In other aspects, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule comprising the coding sequence of a full-length PRO polypeptide cDNA as disclosed herein, the coding sequence of a PRO polypeptide lacking the signal peptide as disclosed herein, the coding sequence of an extracellular domain of a transmembrane PRO polypeptide, with or without the signal peptide, as disclosed herein or the coding sequence of any other specifically defined fragment of the full-length amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule that encodes the same mature polypeptide encoded by any of the human protein cDNAs as disclosed herein, or (b) the complement of the DNA molecule of (a).

Another aspect the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence encoding a PRO polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated, or is complementary to such encoding nucleotide sequence, wherein the transmembrane domain(s) of such polypeptide are disclosed herein. Therefore, soluble extracellular domains of the herein described PRO polypeptides are contemplated.

Another embodiment is directed to fragments of a PRO polypeptide coding sequence, or the complement thereof, that may find use as, for example, hybridization probes, for encoding fragments of a PRO polypeptide that may optionally encode a polypeptide comprising a binding site for an anti-PRO antibody or as antisense oligonucleotide probes. Such nucleic acid fragments are usually at least about 20 nucleotides in length, alternatively at least about 30 nucleotides in length, alternatively at least about 40 nucleotides in length, alternatively at least about 50 nucleotides in length, alternatively at least about 60 nucleotides in length, alternatively at least about 70 nucleotides in length, alternatively at least about 80 nucleotides in length, alternatively at least about 90 nucleotides in length, alternatively at least about 100 nucleotides in length, alternatively at least about 110 nucleotides in length, alternatively at least about 120 nucleotides in length, alternatively at least about 130 nucleotides in length, alternatively at least about 140 nucleotides in length, alternatively at least about 150 nucleotides in length, alternatively at least about 160 nucleotides in length, alternatively at least about 170 nucleotides in length, alternatively at least about 180 nucleotides in length, alternatively at least about 190 nucleotides in length, alternatively at least about 200 nucleotides in length, alternatively at least about 250 nucleotides in length, alternatively at least about 300 nucleotides in length, alternatively at least about 350 nucleotides in length, alternatively at least about 400 nucleotides in length, alternatively at least about 450 nucleotides in length, alternatively at least about 500 nucleotides in length, alternatively at least about 600 nucleotides in length, alternatively at least about 700 nucleotides in length, alternatively at least about 800 nucleotides in length, alternatively at least about 900 nucleotides in length and alternatively at least about 1000 nucleotides in length, wherein in this context the term "about" means the referenced nucleotide sequence length plus-or minus 10% of that referenced length.

It is noted that novel fragments of a PRO polypeptide-encoding nucleotide sequence may be determined in a routine manner by aligning the PRO polypeptide-encoding nucleotide sequence with other known nucleotide sequences using any of a number of well known sequence alignment programs and determining which PRO polypeptide-encoding nucleotide sequence fragment(s) are novel. All of such PRO polypeptide-encoding nucleotide sequences are contemplated herein. Also contemplated are the PRO polypeptide fragments encoded by these nucleotide molecule fragments, preferably those PRO polypeptide fragments that comprise a binding site for an anti-PRO antibody.

In another embodiment, the invention provides isolated PRO polypeptide encoded by any of the isolated nucleic acid sequences herein above identified.

In a certain aspect, the invention concerns an isolated PRO polypeptide, comprising an amino acid sequence having at least about 80% amino acid sequence identity, alternatively at least about 81% amino acid sequence identity, alternatively at least about 82% amino acid sequence identity, alternatively at least about 83% amino acid sequence identity, alternatively at least about 84% amino acid sequence identity, alternatively at least about 85% amino acid sequence identity, alternatively at least about 86% amino acid sequence identity, alternatively at least about 87% amino acid sequence identity, alternatively at least about 88% amino acid sequence identity, alternatively at least about 89% amino acid sequence identity, alternatively at least about 90% amino acid sequence identity, alternatively at least about 91% amino acid sequence identity, alternatively at least about 92% amino acid sequence identity, alternatively at least about 93% amino acid sequence identity, alternatively at least about 94% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 96% amino acid sequence identity, alternatively at least about 97% amino acid sequence identity, alternatively at least about 98% amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to a PRO polypeptide having a full-length amino acid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein.

In a further aspect, the invention concerns an isolated PRO polypeptide comprising an amino acid sequence having at least about 80% amino acid sequence identity, alternatively at least about 81% amino acid sequence identity, alternatively at least about 82% amino acid sequence identity, alternatively at least about 83% amino acid sequence identity, alternatively at least about 84% amino acid sequence identity, alternatively at least about 85% amino acid sequence identity, alternatively at least about 86% amino acid sequence identity, alternatively at least about 87% amino acid sequence identity, alternatively at least about 88% amino acid sequence identity, alternatively at least about 89% amino acid sequence identity, alternatively at least about 90% amino acid sequence identity, alternatively at least about 91% amino acid sequence identity, alternatively at least about 92% amino acid sequence identity, alternatively at least about 93% amino acid sequence identity, alternatively at least about 94% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 96% amino acid sequence identity, alternatively at least about 97% amino acid sequence identity, alternatively at least about 98% amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to an amino acid sequence encoded by any of the human protein cDNAs as disclosed herein.

In a specific aspect, the invention provides an isolated PRO polypeptide without the N-terminal signal sequence and/or the initiating methionine and is encoded by a nucleotide sequence that encodes such an amino acid sequence as herein before described. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the PRO polypeptide from the cell culture.

Another aspect the invention provides an isolated PRO polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the PRO polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO polypeptide as defined herein. In a particular embodiment, the agonist or antagonist is an anti-PRO antibody or a small molecule.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists to a PRO polypeptide which comprise contacting the PRO polypeptide with a candidate molecule and monitoring a biological activity mediated by said PRO polypeptide. Preferably, the PRO polypeptide is a native PRO polypeptide.

In a still further embodiment, the invention concerns a composition of matter comprising a PRO polypeptide, or an agonist or antagonist of a PRO polypeptide as herein described, or an anti-PRO antibody, in combination with a carrier. Optionally, the carrier is a pharmaceutically acceptable carrier.

Another embodiment of the present invention is directed to the use of a PRO polypeptide, or an agonist or antagonist thereof as herein before described, or an anti-PRO antibody, for the preparation of a medicament useful in the treatment of a condition which is responsive to the PRO polypeptide, an agonist or antagonist thereof or an anti-PRO antibody.

BRIEF DESCRIPTION OF THE DRAWINGS

The Figures 1-596 show the nucleic acids of the invention and their encoded PRO polypeptides. Also included, for convenience is a List of Figures attached hereto as Appendix A.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

I. Definitions

The terms "PRO polypeptide" and "PRO" as used herein and when immediately followed by a numerical designation refer to various polypeptides, wherein the complete designation (i.e., PRO/number) refers to specific polypeptide sequences as described herein. The terms "PRO/number polypeptide" and "PRO/number" wherein the term "number" is provided as an actual numerical designation as used herein encompass native sequence polypeptides and polypeptide variants (which are further defined herein). The PRO polypeptides described herein may be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods. The term "PRO polypeptide" refers to each individual PRO/number polypeptide disclosed herein. All disclosures in this specification which refer to the "PRO polypeptide" refer to each of the polypeptides individually as well as

jointly. For example, descriptions of the preparation of, purification of, derivation of, formation of antibodies to or against, administration of, compositions containing, treatment of a disease with, etc., pertain to each polypeptide of the invention individually. The term "PRO polypeptide" also includes variants of the PRO/number polypeptides disclosed herein.

5 A "native sequence PRO polypeptide" comprises a polypeptide having the same amino acid sequence as the corresponding PRO polypeptide derived from nature. Such native sequence PRO polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term "native sequence PRO polypeptide" specifically encompasses naturally-occurring truncated or secreted forms of the specific PRO polypeptide (*e.g.*, an extracellular domain sequence), naturally-occurring variant
10 forms (*e.g.*, alternatively spliced forms) and naturally-occurring allelic variants of the polypeptide. In various embodiments of the invention, the native sequence PRO polypeptides disclosed herein are mature or full-length native sequence polypeptides comprising the full-length amino acids sequences shown in the accompanying figures. Start and stop codons are shown in bold font and underlined in the figures. However, while the PRO polypeptide disclosed in the accompanying figures are shown to begin with
15 methionine residues designated herein as amino acid position 1 in the figures, it is conceivable and possible that other methionine residues located either upstream or downstream from the amino acid position 1 in the figures may be employed as the starting amino acid residue for the PRO polypeptides.

The PRO polypeptide "extracellular domain" or "ECD" refers to a form of the PRO polypeptide which is essentially free of the transmembrane and cytoplasmic domains. Ordinarily, a PRO polypeptide
20 ECD will have less than 1% of such transmembrane and/or cytoplasmic domains and preferably, will have less than 0.5% of such domains. It will be understood that any transmembrane domains identified for the PRO polypeptides of the present invention are identified pursuant to criteria routinely employed in the art for identifying that type of hydrophobic domain. The exact boundaries of a transmembrane domain may vary but most likely by no more than about 5 amino acids at either end of the domain as initially identified herein.

25 Optionally, therefore, an extracellular domain of a PRO polypeptide may contain from about 5 or fewer amino acids on either side of the transmembrane domain/extracellular domain boundary as identified in the Examples or specification and such polypeptides, with or without the associated signal peptide, and nucleic acid encoding them, are contemplated by the present invention.

The approximate location of the "signal peptides" of the various PRO polypeptides disclosed herein
30 are shown in the present specification and/or the accompanying figures. It is noted, however, that the C-terminal boundary of a signal peptide may vary, but most likely by no more than about 5 amino acids on either side of the signal peptide C-terminal boundary as initially identified herein, wherein the C-terminal boundary of the signal peptide may be identified pursuant to criteria routinely employed in the art for identifying that type of amino acid sequence element (*e.g.*, Nielsen et al., Prot. Eng. 10:1-6 (1997) and von
35 Heinje et al., Nucl. Acids. Res. 14:4683-4690 (1986)). Moreover, it is also recognized that, in some cases, cleavage of a signal sequence from a secreted polypeptide is not entirely uniform, resulting in more than one secreted species. These mature polypeptides, where the signal peptide is cleaved within no more than about 5 amino acids on either side of the C-terminal boundary of the signal peptide as identified herein, and the polynucleotides encoding them, are contemplated by the present invention.

"PRO polypeptide variant" means an active PRO polypeptide as defined above or below having at least about 80% amino acid sequence identity with a full-length native sequence PRO polypeptide sequence as disclosed herein, a PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Such PRO polypeptide variants include, for instance, PRO polypeptides wherein one or more amino acid residues are added, or deleted, at the N- or C-terminus of the full-length native amino acid sequence. Ordinarily, a PRO polypeptide variant will have at least about 80% amino acid sequence identity, alternatively at least about 81% amino acid sequence identity, alternatively at least about 82% amino acid sequence identity, alternatively at least about 83% amino acid sequence identity, alternatively at least about 84% amino acid sequence identity, alternatively at least about 85% amino acid sequence identity, alternatively at least about 86% amino acid sequence identity, alternatively at least about 87% amino acid sequence identity, alternatively at least about 88% amino acid sequence identity, alternatively at least about 89% amino acid sequence identity, alternatively at least about 90% amino acid sequence identity, alternatively at least about 91% amino acid sequence identity, alternatively at least about 92% amino acid sequence identity, alternatively at least about 93% amino acid sequence identity, alternatively at least about 94% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 96% amino acid sequence identity, alternatively at least about 97% amino acid sequence identity, alternatively at least about 98% amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to a full-length native sequence PRO polypeptide sequence as disclosed herein, a PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of a full-length PRO polypeptide sequence as disclosed herein. Ordinarily, PRO variant polypeptides are at least about 10 amino acids in length, alternatively at least about 20 amino acids in length, alternatively at least about 30 amino acids in length, alternatively at least about 40 amino acids in length, alternatively at least about 50 amino acids in length, alternatively at least about 60 amino acids in length, alternatively at least about 70 amino acids in length, alternatively at least about 80 amino acids in length, alternatively at least about 90 amino acids in length, alternatively at least about 100 amino acids in length, alternatively at least about 150 amino acids in length, alternatively at least about 200 amino acids in length, alternatively at least about 300 amino acids in length, or more.

"Percent (%) amino acid sequence identity" with respect to the PRO polypeptide sequences identified herein is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific PRO polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are

generated using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1 below. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. and the source code shown in Table 1 below has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1 below. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

In situations where ALIGN-2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

$$100 \text{ times the fraction } X/Y$$

where X is the number of amino acid residues scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. As examples of % amino acid sequence identity calculations using this method, Tables 2 and 3 demonstrate how to calculate the % amino acid sequence identity of the amino acid sequence designated "Comparison Protein" to the amino acid sequence designated "PRO", wherein "PRO" represents the amino acid sequence of a hypothetical PRO polypeptide of interest, "Comparison Protein" represents the amino acid sequence of a polypeptide against which the "PRO" polypeptide of interest is being compared, and "X", "Y" and "Z" each represent different hypothetical amino acid residues.

Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program. However, % amino acid sequence identity values may also be obtained as described below by using the WU-BLAST-2 computer program (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Most of the WU-BLAST-2 search parameters are set to the default values. Those not set to default values, i.e., the adjustable parameters, are set with the following values: overlap span = 1, overlap fraction = 0.125, word threshold (T) = 11, and scoring matrix = BLOSUM62. When WU-BLAST-2 is employed, a % amino acid sequence identity value is determined by dividing (a) the number of matching identical amino acid residues between the amino acid sequence of the PRO polypeptide of interest having a sequence derived from the native PRO polypeptide and the comparison amino acid sequence of interest (i.e., the sequence against which the PRO polypeptide of interest is being compared which may be a PRO variant polypeptide) as determined by WU-BLAST-2 by (b) the total number of amino acid residues of the PRO polypeptide of interest. For example, in the statement "a polypeptide comprising an the amino acid sequence A which has or having at least 80% amino acid sequence identity to the amino acid sequence B", the amino acid sequence

A is the comparison amino acid sequence of interest and the amino acid sequence B is the amino acid sequence of the PRO polypeptide of interest.

Percent amino acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul et al., Nucleic Acids Res. 25:3389-3402 (1997)). The NCBI-BLAST2 sequence comparison program may be downloaded from <http://www.ncbi.nlm.nih.gov> or otherwise obtained from the National Institute of Health, Bethesda, MD. NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.

In situations where NCBI-BLAST2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

$$100 \text{ times the fraction } X/Y$$

where X is the number of amino acid residues scored as identical matches by the sequence alignment program NCBI-BLAST2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A.

"PRO variant polynucleotide" or "PRO variant nucleic acid sequence" means a nucleic acid molecule which encodes an active PRO polypeptide as defined below and which has at least about 80% nucleic acid sequence identity with a nucleotide acid sequence encoding a full-length native sequence PRO polypeptide sequence as disclosed herein, a full-length native sequence PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Ordinarily, a PRO variant polynucleotide will have at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and

alternatively at least about 99% nucleic acid sequence identity with a nucleic acid sequence encoding a full-length native sequence PRO polypeptide sequence as disclosed herein, a full-length native sequence PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal sequence, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Variants do not encompass the native nucleotide sequence.

Ordinarily, PRO variant polynucleotides are at least about 30 nucleotides in length, alternatively at least about 60 nucleotides in length, alternatively at least about 90 nucleotides in length, alternatively at least about 120 nucleotides in length, alternatively at least about 150 nucleotides in length, alternatively at least about 180 nucleotides in length, alternatively at least about 210 nucleotides in length, alternatively at least about 240 nucleotides in length, alternatively at least about 270 nucleotides in length, alternatively at least about 300 nucleotides in length, alternatively at least about 450 nucleotides in length, alternatively at least about 600 nucleotides in length, alternatively at least about 900 nucleotides in length, or more.

"Percent (%) nucleic acid sequence identity" with respect to PRO-encoding nucleic acid sequences identified herein is defined as the percentage of nucleotides in a candidate sequence that are identical with the nucleotides in the PRO nucleic acid sequence of interest, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Alignment for purposes of determining percent nucleic acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. For purposes herein, however, % nucleic acid sequence identity values are generated using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1 below. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. and the source code shown in Table 1 below has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1 below. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

In situations where ALIGN-2 is employed for nucleic acid sequence comparisons, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence D (which can alternatively be phrased as a given nucleic acid sequence C that has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D) is calculated as follows:

$$100 \text{ times the fraction } W/Z$$

where W is the number of nucleotides scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of C and D, and where Z is the total number of nucleotides in D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of nucleic acid sequence D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence identity of D to C. As examples of % nucleic acid sequence identity calculations, Tables 4 and 5, demonstrate how to calculate the % nucleic acid sequence identity of the nucleic acid sequence designated

"Comparison DNA" to the nucleic acid sequence designated "PRO-DNA", wherein "PRO-DNA" represents a hypothetical PRO-encoding nucleic acid sequence of interest, "Comparison DNA" represents the nucleotide sequence of a nucleic acid molecule against which the "PRO-DNA" nucleic acid molecule of interest is being compared, and "N", "L" and "V" each represent different hypothetical nucleotides.

5 Unless specifically stated otherwise, all % nucleic acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program. However, % nucleic acid sequence identity values may also be obtained as described below by using the WU-BLAST-2 computer program (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Most of the WU-BLAST-2 search parameters are set to the default values. Those not set to default values, i.e., the
10 adjustable parameters, are set with the following values: overlap span = 1, overlap fraction = 0.125, word threshold (T) = 11, and scoring matrix = BLOSUM62. When WU-BLAST-2 is employed, a % nucleic acid sequence identity value is determined by dividing (a) the number of matching identical nucleotides between the nucleic acid sequence of the PRO polypeptide-encoding nucleic acid molecule of interest having a sequence derived from the native sequence PRO polypeptide-encoding nucleic acid and the comparison
15 nucleic acid molecule of interest (i.e., the sequence against which the PRO polypeptide-encoding nucleic acid molecule of interest is being compared which may be a variant PRO polynucleotide) as determined by WU-BLAST-2 by (b) the total number of nucleotides of the PRO polypeptide-encoding nucleic acid molecule of interest. For example, in the statement "an isolated nucleic acid molecule comprising a nucleic acid sequence A which has or having at least 80% nucleic acid sequence identity to the nucleic acid
20 sequence B", the nucleic acid sequence A is the comparison nucleic acid molecule of interest and the nucleic acid sequence B is the nucleic acid sequence of the PRO polypeptide-encoding nucleic acid molecule of interest.

Percent nucleic acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul et al., Nucleic Acids Res. 25:3389-3402 (1997)). The NCBI-BLAST2
25 sequence comparison program may be downloaded from <http://www.ncbi.nlm.nih.gov> or otherwise obtained from the National Institute of Health, Bethesda, MD. NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.

30 In situations where NCBI-BLAST2 is employed for sequence comparisons, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence D (which can alternatively be phrased as a given nucleic acid sequence C that has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D) is calculated as follows:

35
$$100 \text{ times the fraction } W/Z$$

where W is the number of nucleotides scored as identical matches by the sequence alignment program NCBI-BLAST2 in that program's alignment of C and D, and where Z is the total number of nucleotides in D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of

nucleic acid sequence D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence identity of D to C.

In other embodiments, PRO variant polynucleotides are nucleic acid molecules that encode an active PRO polypeptide and which are capable of hybridizing, preferably under stringent hybridization and wash conditions, to nucleotide sequences encoding a full-length PRO polypeptide as disclosed herein. PRO variant polypeptides may be those that are encoded by a PRO variant polynucleotide.

"Isolated," when used to describe the various polypeptides disclosed herein, means polypeptide that has been identified and separated and/or recovered from a component of its natural environment.

Contaminant components of its natural environment are materials that would typically interfere with

diagnostic or therapeutic uses for the polypeptide, and may include enzymes, hormones, and other

proteinaceous or non-proteinaceous solutes. In preferred embodiments, the polypeptide will be purified (1)

to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (2) to homogeneity by SDS-PAGE under non-reducing or reducing conditions

using Coomassie blue or, preferably, silver stain. Isolated polypeptide includes polypeptide *in situ* within

recombinant cells, since at least one component of the PRO polypeptide natural environment will not be

present. Ordinarily, however, isolated polypeptide will be prepared by at least one purification step.

An "isolated" PRO polypeptide-encoding nucleic acid or other polypeptide-encoding nucleic acid is a nucleic acid molecule that is identified and separated from at least one contaminant nucleic acid molecule with which it is ordinarily associated in the natural source of the polypeptide-encoding nucleic acid. An

isolated polypeptide-encoding nucleic acid molecule is other than in the form or setting in which it is found in nature. Isolated polypeptide-encoding nucleic acid molecules therefore are distinguished from the

specific polypeptide-encoding nucleic acid molecule as it exists in natural cells. However, an isolated

polypeptide-encoding nucleic acid molecule includes polypeptide-encoding nucleic acid molecules

contained in cells that ordinarily express the polypeptide where, for example, the nucleic acid molecule is in

a chromosomal location different from that of natural cells.

The term "control sequences" refers to DNA sequences necessary for the expression of an operably linked coding sequence in a particular host organism. The control sequences that are suitable for

prokaryotes, for example, include a promoter, optionally an operator sequence, and a ribosome binding site.

Eukaryotic cells are known to utilize promoters, polyadenylation signals, and enhancers.

Nucleic acid is "operably linked" when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence;

or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to facilitate

translation. Generally, "operably linked" means that the DNA sequences being linked are contiguous, and,

in the case of a secretory leader, contiguous and in reading phase. However, enhancers do not have to be

contiguous. Linking is accomplished by ligation at convenient restriction sites. If such sites do not exist, the synthetic oligonucleotide adaptors or linkers are used in accordance with conventional practice.

The term "antibody" is used in the broadest sense and specifically covers, for example, single anti-

PRO monoclonal antibodies (including agonist, antagonist, and neutralizing antibodies), anti-PRO antibody

compositions with polypeptidic specificity, single chain anti-PRO antibodies, and fragments of anti-PRO antibodies (see below). The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally-occurring mutations that may be present in minor amounts.

"Stringency" of hybridization reactions is readily determinable by one of ordinary skill in the art, and generally is an empirical calculation dependent upon probe length, washing temperature, and salt concentration. In general, longer probes require higher temperatures for proper annealing, while shorter probes need lower temperatures. Hybridization generally depends on the ability of denatured DNA to reanneal when complementary strands are present in an environment below their melting temperature. The higher the degree of desired homology between the probe and hybridizable sequence, the higher the relative temperature which can be used. As a result, it follows that higher relative temperatures would tend to make the reaction conditions more stringent, while lower temperatures less so. For additional details and explanation of stringency of hybridization reactions, see Ausubel et al., Current Protocols in Molecular Biology, Wiley Interscience Publishers, (1995).

"Stringent conditions" or "high stringency conditions", as defined herein, may be identified by those that: (1) employ low ionic strength and high temperature for washing, for example 0.015 M sodium chloride/0.0015 M sodium citrate/0.1% sodium dodecyl sulfate at 50°C; (2) employ during hybridization a denaturing agent, such as formamide, for example, 50% (v/v) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50mM sodium phosphate buffer at pH 6.5 with 750 mM sodium chloride, 75 mM sodium citrate at 42°C; or (3) employ 50% formamide, 5 x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with washes at 42°C in 0.2 x SSC (sodium chloride/sodium citrate) and 50% formamide at 55°C, followed by a high-stringency wash consisting of 0.1 x SSC containing EDTA at 55°C.

"Moderately stringent conditions" may be identified as described by Sambrook et al., Molecular Cloning: A Laboratory Manual, New York: Cold Spring Harbor Press, 1989, and include the use of washing solution and hybridization conditions (e.g., temperature, ionic strength and %SDS) less stringent than those described above. An example of moderately stringent conditions is overnight incubation at 37°C in a solution comprising: 20% formamide, 5 x SSC (150 mM NaCl, 15 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5 x Denhardt's solution, 10% dextran sulfate, and 20 mg/ml denatured sheared salmon sperm DNA, followed by washing the filters in 1 x SSC at about 37-50°C. The skilled artisan will recognize how to adjust the temperature, ionic strength, etc. as necessary to accommodate factors such as probe length and the like.

The term "epitope tagged" when used herein refers to a chimeric polypeptide comprising a PRO polypeptide fused to a "tag polypeptide". The tag polypeptide has enough residues to provide an epitope against which an antibody can be made, yet is short enough such that it does not interfere with activity of the polypeptide to which it is fused. The tag polypeptide preferably also is fairly unique so that the antibody does not substantially cross-react with other epitopes. Suitable tag polypeptides generally have at least six

amino acid residues and usually between about 8 and 50 amino acid residues (preferably, between about 10 and 20 amino acid residues).

As used herein, the term "immunoadhesin" designates antibody-like molecules which combine the binding specificity of a heterologous protein (an "adhesin") with the effector functions of immunoglobulin constant domains. Structurally, the immunoadhesins comprise a fusion of an amino acid sequence with the desired binding specificity which is other than the antigen recognition and binding site of an antibody (i.e., is "heterologous"), and an immunoglobulin constant domain sequence. The adhesin part of an immunoadhesin molecule typically is a contiguous amino acid sequence comprising at least the binding site of a receptor or a ligand. The immunoglobulin constant domain sequence in the immunoadhesin may be obtained from any immunoglobulin, such as IgG-1, IgG-2, IgG-3, or IgG-4 subtypes, IgA (including IgA-1 and IgA-2), IgE, IgD or IgM.

"Active" or "activity" for the purposes herein refers to form(s) of a PRO polypeptide which retain a biological and/or an immunological activity of native or naturally-occurring PRO, wherein "biological" activity refers to a biological function (either inhibitory or stimulatory) caused by a native or naturally-occurring PRO other than the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO and an "immunological" activity refers to the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO.

The term "antagonist" is used in the broadest sense, and includes any molecule that partially or fully blocks, inhibits, or neutralizes a biological activity of a native PRO polypeptide disclosed herein. In a similar manner, the term "agonist" is used in the broadest sense and includes any molecule that mimics a biological activity of a native PRO polypeptide disclosed herein. Suitable agonist or antagonist molecules specifically include agonist or antagonist antibodies or antibody fragments, fragments or amino acid sequence variants of native PRO polypeptides, peptides, antisense oligonucleotides, small organic molecules, etc. Methods for identifying agonists or antagonists of a PRO polypeptide may comprise contacting a PRO polypeptide with a candidate agonist or antagonist molecule and measuring a detectable change in one or more biological activities normally associated with the PRO polypeptide.

"Treatment" refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) the targeted pathologic condition or disorder. Those in need of treatment include those already with the disorder as well as those prone to have the disorder or those in whom the disorder is to be prevented.

"Chronic" administration refers to administration of the agent(s) in a continuous mode as opposed to an acute mode, so as to maintain the initial therapeutic effect (activity) for an extended period of time. "Intermittent" administration is treatment that is not consecutively done without interruption, but rather is cyclic in nature.

"Mammal" for purposes of treatment refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, cats, cattle, horses, sheep, pigs, goats, rabbits, etc. Preferably, the mammal is human.

Administration "in combination with" one or more further therapeutic agents includes simultaneous (concurrent) and consecutive administration in any order.

"Carriers" as used herein include pharmaceutically acceptable carriers, excipients, or stabilizers which are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the physiologically acceptable carrier is an aqueous pH buffered solution. Examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptide; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEENTM, polyethylene glycol (PEG), and PLURONICSTM.

"Antibody fragments" comprise a portion of an intact antibody, preferably the antigen binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', F(ab')₂, and Fv fragments; diabodies; linear antibodies (Zapata et al., Protein Eng. 8(10): 1057-1062 [1995]); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment, a designation reflecting the ability to crystallize readily. Pepsin treatment yields an F(ab')₂ fragment that has two antigen-combining sites and is still capable of cross-linking antigen.

"Fv" is the minimum antibody fragment which contains a complete antigen-recognition and -binding site. This region consists of a dimer of one heavy- and one light-chain variable domain in tight, non-covalent association. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the V_H-V_L dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

The Fab fragment also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab fragments differ from Fab' fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. F(ab')₂ antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

The "light chains" of antibodies (immunoglobulins) from any vertebrate species can be assigned to one of two clearly distinct types, called kappa and lambda, based on the amino acid sequences of their constant domains.

Depending on the amino acid sequence of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA, and IgA2.

"Single-chain Fv" or "sFv" antibody fragments comprise the V_H and V_L domains of antibody, wherein these domains are present in a single polypeptide chain. Preferably, the Fv polypeptide further comprises a polypeptide linker between the V_H and V_L domains which enables the sFv to form the desired structure for antigen binding. For a review of sFv, see Pluckthun in The Pharmacology of Monoclonal
5 Antibodies, vol. 113, Rosenberg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994).

The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) in the same polypeptide chain (V_H-V_L). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain
10 and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger et al., Proc. Natl. Acad. Sci. USA, 90:6444-6448 (1993).

An "isolated" antibody is one which has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials which would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes,
15 hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the antibody will be purified (1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or nonreducing conditions using Coomassie blue or, preferably, silver stain. Isolated
20 antibody includes the antibody in situ within recombinant cells since at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

An antibody that "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide is one that binds to that particular polypeptide or epitope on a particular polypeptide
25 without substantially binding to any other polypeptide or polypeptide epitope.

The word "label" when used herein refers to a detectable compound or composition which is conjugated directly or indirectly to the antibody so as to generate a "labeled" antibody. The label may be detectable by itself (e.g. radioisotope labels or fluorescent labels) or, in the case of an enzymatic label, may catalyze chemical alteration of a substrate compound or composition which is detectable.

By "solid phase" is meant a non-aqueous matrix to which the antibody of the present invention can adhere. Examples of solid phases encompassed herein include those formed partially or entirely of glass (e.g., controlled pore glass), polysaccharides (e.g., agarose), polyacrylamides, polystyrene, polyvinyl alcohol and silicones. In certain embodiments, depending on the context, the solid phase can comprise the well of an assay plate; in others it is a purification column (e.g., an affinity chromatography column). This term also
35 includes a discontinuous solid phase of discrete particles, such as those described in U.S. Patent No. 4,275,149.

A "liposome" is a small vesicle composed of various types of lipids, phospholipids and/or surfactant which is useful for delivery of a drug (such as a PRO polypeptide or antibody thereto) to a

mammal. The components of the liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes.

A "small molecule" is defined herein to have a molecular weight below about 500 Daltons.

5 The term "immune related disease" means a disease in which a component of the immune system of a mammal causes, mediates or otherwise contributes to a morbidity in the mammal. Also included are diseases in which stimulation or intervention of the immune response has an ameliorative effect on progression of the disease. Included within this term are immune-mediated inflammatory diseases, non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, *etc.*

10 The term "T cell mediated disease" means a disease in which T cells directly or indirectly mediate or otherwise contribute to a morbidity in a mammal. The T cell mediated disease may be associated with cell mediated effects, lymphokine mediated effects, *etc.*, and even effects associated with B cells if the B cells are stimulated, for example, by the lymphokines secreted by T cells.

15 Examples of immune-related and inflammatory diseases, include: systemic lupus erythematosus, (SLE), rheumatoid arthritis, osteoarthritis, juvenile chronic arthritis, spondyloarthropathies, systemic sclerosis, idiopathic inflammatory myopathies, Sjögren's syndrome, systemic vasculitis, sarcoidosis, autoimmune hemolytic anemia, autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis, lymphadenopathy, splenomegaly and leukopenia.

20 The term "effective amount" is a concentration or amount of a PRO polypeptide and/or agonist/antagonist which results in achieving a particular stated purpose. An "effective amount" of a PRO polypeptide or agonist or antagonist thereof may be determined empirically. Furthermore, a "therapeutically effective amount" is a concentration or amount of a PRO polypeptide and/or agonist/antagonist which is effective for achieving a stated therapeutic effect. This amount may also be determined empirically.

25 The term "cytotoxic agent" as used herein refers to a substance that inhibits or prevents the function of cells and/or causes destruction of cells. The term is intended to include radioactive isotopes (*e.g.*, I^{131} , I^{125} , Y^{90} and Re^{186}), chemotherapeutic agents, and toxins such as enzymatically active toxins of bacterial, fungal, plant or animal origin, or fragments thereof.

30 A "chemotherapeutic agent" is a chemical compound useful in the treatment of cancer. Examples of chemotherapeutic agents include adriamycin, doxorubicin, epirubicin, 5-fluorouracil, cytosine arabinoside ("Ara-C"), cyclophosphamide, thiotepa, busulfan, cytoxan, taxoids, *e.g.*, paclitaxel (Taxol, Bristol-Myers Squibb Oncology, Princeton, NJ), and doxetaxel (Taxotere, Rhône-Poulenc Rorer, Antony, France), toxotere, methotrexate, cisplatin, melphalan, vinblastine, bleomycin, etoposide, ifosfamide, mitomycin C, mitoxantrone, vincristine, vinorelbine, carboplatin, teniposide, daunomycin, carminomycin, aminopterin, dactinomycin, mitomycins, esperamicins (see U.S. Pat. No. 4,675,187), melphalan and other related nitrogen
35 mustards. Also included in this definition are hormonal agents that act to regulate or inhibit hormone action on tumors such as tamoxifen and onapristone.

A "growth inhibitory agent" when used herein refers to a compound or composition which inhibits growth of a cell, especially cancer cell overexpressing any of the genes identified herein, either *in vitro* or *in vivo*. Thus, the growth inhibitory agent is one which significantly reduces the percentage of cells
40 overexpressing such genes in S phase. Examples of growth inhibitory agents include agents that block cell

cycle progression (at a place other than S phase), such as agents that induce G1 arrest and M-phase arrest. Classical M-phase blockers include the vincas (vincristine and vinblastine), taxol, and topo II inhibitors such as doxorubicin, epirubicin, daunorubicin, etoposide, and bleomycin. Those agents that arrest G1 also spill over into S-phase arrest, for example, DNA alkylating agents such as tamoxifen, prednisone, dacarbazine, mechlorethamine, cisplatin, methotrexate, 5-fluorouracil, and ara-C. Further information can be found in *The Molecular Basis of Cancer*, Mendelsohn and Israel, eds., Chapter 1, entitled "Cell cycle regulation, oncogens, and antineoplastic drugs" by Murakami *et al.* (WB Saunders: Philadelphia, 1995), especially p. 13.

The term "cytokine" is a generic term for proteins released by one cell population which act on another cell as intercellular mediators. Examples of such cytokines are lymphokines, monokines, and traditional polypeptide hormones. Included among the cytokines are growth hormone such as human growth hormone, N-methionyl human growth hormone, and bovine growth hormone; parathyroid hormone; thyroxine; insulin; proinsulin; relaxin; prorelaxin; glycoprotein hormones such as follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and luteinizing hormone (LH); hepatic growth factor; fibroblast growth factor; prolactin; placental lactogen; tumor necrosis factor- α and - β ; mullerian-inhibiting substance; mouse gonadotropin-associated peptide; inhibin; activin; vascular endothelial growth factor; integrin; thrombopoietin (TPO); nerve growth factors such as NGF- β ; platelet-growth factor; transforming growth factors (TGFs) such as TGF- α and TGF- β ; insulin-like growth factor-I and -II; erythropoietin (EPO); osteoinductive factors; interferons such as interferon- α , - β , and - γ ; colony stimulating factors (CSFs) such as macrophage-CSF (M-CSF); granulocyte-macrophage-CSF (GM-CSF); and granulocyte-CSF (G-CSF); interleukins (ILs) such as IL-1, IL-1 α , IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-11, IL-12; a tumor necrosis factor such as TNF- α or TNF- β ; and other polypeptide factors including LIF and kit ligand (KL). As used herein, the term cytokine includes proteins from natural sources or from recombinant cell culture and biologically active equivalents of the native sequence cytokines.

As used herein, the term "immunoadhesin" designates antibody-like molecules which combine the binding specificity of a heterologous protein (an "adhesin") with the effector functions of immunoglobulin constant domains. Structurally, the immunoadhesins comprise a fusion of an amino acid sequence with the desired binding specificity which is other than the antigen recognition and binding site of an antibody (*i.e.*, is "heterologous"), and an immunoglobulin constant domain sequence. The adhesin part of an immunoadhesin molecule typically is a contiguous amino acid sequence comprising at least the binding site of a receptor or a ligand. The immunoglobulin constant domain sequence in the immunoadhesin may be obtained from any immunoglobulin, such as IgG-1, IgG-2, IgG-3, or IgG-4 subtypes, IgA (including IgA-1 and IgA-2), IgE, IgD or IgM.

As used herein, the term "inflammatory cells" designates cells that enhance the inflammatory response such as mononuclear cells, eosinophils, macrophages, and polymorphonuclear neutrophils (PMN).

Table 1

```

/*
5  *
  * C-C increased from 12 to 15
  * Z is average of EQ
  * B is average of ND
  * match with stop is _M; stop-stop = 0; J (joker) match = 0
10 */
#define _M      -8      /* value of a match with a stop */

int  _day[26][26] = {
/*  A B C D E F G H I J K L M N O P Q R S T U V W X Y Z */
15 /* A */ { 2, 0, -2, 0, 0, -4, 1, -1, -1, 0, -1, -2, -1, 0, _M, 1, 0, -2, 1, 1, 0, 0, -6, 0, -3, 0},
/* B */ { 0, 3, -4, 3, 2, -5, 0, 1, -2, 0, 0, -3, -2, 2, _M, -1, 1, 0, 0, 0, 0, -2, -5, 0, -3, 1},
/* C */ {-2, -4, 15, -5, -5, -4, -3, -3, -2, 0, -5, -6, -5, -4, _M, -3, -5, -4, 0, -2, 0, -2, -8, 0, 0, -5},
/* D */ { 0, 3, -5, 4, 3, -6, 1, 1, -2, 0, 0, -4, -3, 2, _M, -1, 2, -1, 0, 0, 0, -2, -7, 0, -4, 2},
/* E */ { 0, 2, -5, 3, 4, -5, 0, 1, -2, 0, 0, -3, -2, 1, _M, -1, 2, -1, 0, 0, 0, -2, -7, 0, -4, 3},
20 /* F */ {-4, -5, -4, -6, -5, 9, -5, -2, 1, 0, -5, 2, 0, -4, _M, -5, -5, -4, -3, -3, 0, -1, 0, 0, 7, -5},
/* G */ { 1, 0, -3, 1, 0, -5, 5, -2, -3, 0, -2, -4, -3, 0, _M, -1, -1, -3, 1, 0, 0, -1, -7, 0, -5, 0},
/* H */ {-1, 1, -3, 1, 1, -2, -2, 6, -2, 0, 0, -2, -2, 2, _M, 0, 3, 2, -1, -1, 0, -2, -3, 0, 0, 2},
/* I */ {-1, -2, -2, -2, -2, 1, -3, -2, 5, 0, -2, 2, 2, -2, _M, -2, -2, -2, -1, 0, 0, 4, -5, 0, -1, -2},
/* J */ { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0},
25 /* K */ {-1, 0, -5, 0, 0, -5, -2, 0, -2, 0, 5, -3, 0, 1, _M, -1, 1, 3, 0, 0, 0, -2, -3, 0, -4, 0},
/* L */ {-2, -3, -6, -4, -3, 2, -4, -2, 2, 0, -3, 6, 4, -3, _M, -3, -2, -3, -3, -1, 0, 2, -2, 0, -1, -2},
/* M */ {-1, -2, -5, -3, -2, 0, -3, -2, 2, 0, 0, 4, 6, -2, _M, -2, -1, 0, -2, -1, 0, 2, -4, 0, -2, -1},
/* N */ { 0, 2, -4, 2, 1, -4, 0, 2, -2, 0, 1, -3, -2, 2, _M, -1, 1, 0, 1, 0, 0, -2, -4, 0, -2, 1},
/* O */ { _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M,
30 0, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M},
/* P */ { 1, -1, -3, -1, -1, -5, -1, 0, -2, 0, -1, -3, -2, -1, _M, 6, 0, 0, 1, 0, 0, -1, -6, 0, -5, 0},
/* Q */ { 0, 1, -5, 2, 2, -5, -1, 3, -2, 0, 1, -2, -1, 1, _M, 0, 4, 1, -1, -1, 0, -2, -5, 0, -4, 3},
/* R */ {-2, 0, -4, -1, -1, -4, -3, 2, -2, 0, 3, -3, 0, 0, _M, 0, 1, 6, 0, -1, 0, -2, 2, 0, -4, 0},
/* S */ { 1, 0, 0, 0, 0, -3, 1, -1, -1, 0, 0, -3, -2, 1, _M, 1, -1, 0, 2, 1, 0, -1, -2, 0, -3, 0},
35 /* T */ { 1, 0, -2, 0, 0, -3, 0, -1, 0, 0, 0, -1, -1, 0, _M, 0, -1, -1, 1, 3, 0, 0, -5, 0, -3, 0},
/* U */ { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* V */ { 0, -2, -2, -2, -2, -1, -1, -2, 4, 0, -2, 2, 2, -2, _M, -1, -2, -2, -1, 0, 0, 4, -6, 0, -2, -2},
/* W */ {-6, -5, -8, -7, -7, 0, -7, -3, -5, 0, -3, -2, -4, -4, _M, -6, -5, 2, -2, -5, 0, -6, 17, 0, 0, -6},
/* X */ { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0},
40 /* Y */ {-3, -3, 0, -4, -4, 7, -5, 0, -1, 0, -4, -1, -2, -2, _M, -5, -4, -4, -3, -3, 0, -2, 0, 0, 10, -4},
/* Z */ { 0, 1, -5, 2, 3, -5, 0, 2, -2, 0, 0, -2, -1, 1, _M, 0, 3, 0, 0, 0, 0, -2, -6, 0, -4, 4}
};

```

45

50

55

Table 1 (cont')

```

/*
*/
#include <stdio.h>
5  #include <ctype.h>

#define MAXJMP      16      /* max jumps in a diag */
#define MAXGAP      24      /* don't continue to penalize gaps larger than this */
#define JMPS        1024    /* max jmps in an path */
10  #define MX        4      /* save if there's at least MX-1 bases since last jmp */

#define DMAT         3      /* value of matching bases */
#define DMIS         0      /* penalty for mismatched bases */
#define DINS0        8      /* penalty for a gap */
15  #define DINS1        1    /* penalty per base */
#define PINS0        8      /* penalty for a gap */
#define PINS1        4      /* penalty per residue */

struct jmp {
20     short          n[MAXJMP];    /* size of jmp (neg for dely) */
     unsigned short x[MAXJMP];    /* base no. of jmp in seq x */
};                                /* limits seq to 2^16 -1 */

struct diag {
25     int            score;        /* score at last jmp */
     long            offset;       /* offset of prev block */
     short           ijmp;         /* current jmp index */
     struct jmp      jp;          /* list of jmps */
};

30  struct path {
     int             spc;          /* number of leading spaces */
     short           n[JMPS];     /* size of jmp (gap) */
     int             x[JMPS];     /* loc of jmp (last elem before gap) */
35  };

char      *ofile;                /* output file name */
char      *namex[2];             /* seq names: getseqs() */
char      *prog;                 /* prog name for err msgs */
40  char      *seqx[2];           /* seqs: getseqs() */
int        dmax;                 /* best diag: nw() */
int        dmax0;               /* final diag */
int        dna;                 /* set if dna: main() */
int        endgaps;             /* set if penalizing end gaps */
45  int        gapx, gapy;        /* total gaps in seqs */
int        len0, len1;          /* seq lens */
int        ngapx, ngapy;        /* total size of gaps */
int        smax;                /* max score: nw() */
int        *xbm;                /* bitmap for matching */
50  long       offset;           /* current offset in jmp file */
struct     diag    *dx;         /* holds diagonals */
struct     path    pp[2];       /* holds path for seqs */

char      *calloc(), *malloc(), *index(), *strcpy();
55  char      *getseq(), *g_calloc();

```


Table 1 (cont')

```

/* Needleman-Wunsch alignment program
*
* usage: progs file1 file2
5  * where file1 and file2 are two dna or two protein sequences.
* The sequences can be in upper- or lower-case and may contain ambiguity
* Any lines beginning with ';', '>' or '<' are ignored
* Max file length is 65535 (limited by unsigned short x in the jmp struct)
* A sequence with 1/3 or more of its elements ACGTU is assumed to be DNA
10 * Output is in the file "align.out"
*
* The program may create a tmp file in /tmp to hold info about traceback.
* Original version developed under BSD 4.3 on a vax 8650
*/
15 #include "nw.h"
#include "day.h"

static _dbval[26] = {
20     1,14,2,13,0,0,4,11,0,0,12,0,3,15,0,0,0,5,6,8,8,7,9,0,10,0
};

static _pbval[26] = {
25     1, 2|(1<<('D'-'A'))|(1<<('N'-'A')), 4, 8, 16, 32, 64,
    128, 256, 0xFFFFFFFF, 1<<10, 1<<11, 1<<12, 1<<13, 1<<14,
    1<<15, 1<<16, 1<<17, 1<<18, 1<<19, 1<<20, 1<<21, 1<<22,
    1<<23, 1<<24, 1<<25|(1<<('E'-'A'))|(1<<('Q'-'A'))
};

main(ac, av)
30     main
    int     ac;
    char    *av[ ];
{
    prog = av[0];
35     if (ac != 3) {
        fprintf(stderr, "usage: %s file1 file2\n", prog);
        fprintf(stderr, "where file1 and file2 are two dna or two protein sequences.\n");
        fprintf(stderr, "The sequences can be in upper- or lower-case\n");
        fprintf(stderr, "Any lines beginning with ';' or '<' are ignored\n");
40         fprintf(stderr, "Output is in the file \"align.out\"\n");
        exit(1);
    }
    namex[0] = av[1];
    namex[1] = av[2];
45     seqx[0] = getseq(namex[0], &len0);
    seqx[1] = getseq(namex[1], &len1);
    xbm = (dna)? _dbval : _pbval;

    endgaps = 0;                                /* 1 to penalize endgaps */
50     ofile = "align.out";                       /* output file */

    nw();                                         /* fill in the matrix, get the possible jumps */
    readjumps();                                /* get the actual jumps */
    print();                                    /* print stats, alignment */
55     cleanup(0);                                /* unlink any tmp files */
}

```


Table 1 (cont')

```

/* do the alignment, return best score: main()
* dna: values in Fitch and Smith, PNAS, 80, 1382-1386, 1983
* pro: PAM 250 values
5  * When scores are equal, we prefer mismatches to any gap, prefer
* a new gap to extending an ongoing gap, and prefer a gap in seqx
* to a gap in seq y.
*/
nw()
10  nw
{
    char          *px, *py;          /* seqs and ptrs */
    int           *ndely, *dely;      /* keep track of dely */
    int           ndelx, delx;        /* keep track of delx */
15  int           *tmp;              /* for swapping row0, row1 */
    int           mis;               /* score for each type */
    int           ins0, ins1;         /* insertion penalties */
    register       id;               /* diagonal index */
    register       ij;              /* jmp index */
20  register       *col0, *col1;      /* score for curr, last row */
    register       xx, yy;           /* index into seqs */

    dx = (struct diag *)g_calloc("to get diags", len0+len1+1, sizeof(struct diag));

25  ndely = (int *)g_calloc("to get ndely", len1+1, sizeof(int));
    dely = (int *)g_calloc("to get dely", len1+1, sizeof(int));
    col0 = (int *)g_calloc("to get col0", len1+1, sizeof(int));
    col1 = (int *)g_calloc("to get col1", len1+1, sizeof(int));
    ins0 = (dna)? DINS0 : PINS0;
30  ins1 = (dna)? DINS1 : PINS1;

    smax = -10000;
    if (endgaps) {
        for (col0[0] = dely[0] = -ins0, yy = 1; yy <= len1; yy++) {
35  col0[yy] = dely[yy] = col0[yy-1] - ins1;
            ndely[yy] = yy;
        }
        col0[0] = 0;          /* Waterman Bull Math Biol 84 */
    }
40  else
        for (yy = 1; yy <= len1; yy++)
            dely[yy] = -ins0;

    /* fill in match matrix
    */
45  for (px = seqx[0], xx = 1; xx <= len0; px++, xx++) {
        /* initialize first entry in col
        */
        if (endgaps) {
50  if (xx == 1)
            col1[0] = delx = -(ins0+ins1);
            else
            col1[0] = delx = col0[0] - ins1;
            ndelx = xx;
55  }
        else {
            col1[0] = 0;
            delx = -ins0;
            ndelx = 0;
60  }
    }

```


Table 1 (cont')**...nw**

```

for (py = seqx[1], yy = 1; yy <= len1; py++, yy++) {
    mis = col0[yy-1];
5    if (dna)
        mis += (xbm[*px-'A']&xbm[*py-'A'])? DMAT : DMIS;
    else
        mis += _day[*px-'A'][*py-'A'];

10    /* update penalty for del in x seq;
        * favor new del over ongoing del
        * ignore MAXGAP if weighting endgaps
        */
    if (endgaps || ndely[yy] < MAXGAP) {
15        if (col0[yy] - ins0 >= dely[yy]) {
            dely[yy] = col0[yy] - (ins0+ins1);
            ndely[yy] = 1;
        } else {
            dely[yy] -= ins1;
20            ndely[yy]++;
        }
    } else {
        if (col0[yy] - (ins0+ins1) >= dely[yy]) {
25            dely[yy] = col0[yy] - (ins0+ins1);
            ndely[yy] = 1;
        } else
            ndely[yy]++;
    }

30    /* update penalty for del in y seq;
        * favor new del over ongoing del
        */
    if (endgaps || ndelx < MAXGAP) {
        if (col1[yy-1] - ins0 >= delx) {
35            delx = col1[yy-1] - (ins0+ins1);
            ndelx = 1;
        } else {
            delx -= ins1;
            ndelx++;
40        }
    } else {
        if (col1[yy-1] - (ins0+ins1) >= delx) {
            delx = col1[yy-1] - (ins0+ins1);
            ndelx = 1;
45        } else
            ndelx++;
    }

50    /* pick the maximum score; we're favoring
        * mis over any del and delx over dely
        */

```

55

60

Table 1 (cont')**...nw**

```

id = xx - yy + len1 - 1;
if (mis >= delx && mis >= dely[yy])
5   col1[yy] = mis;
else if (delx >= dely[yy]) {
    col1[yy] = delx;
    ij = dx[id].ijmp;
    if (dx[id].jp.n[0] && (!dna || (ndelx >= MAXJMP
10   && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
        dx[id].ijmp++;
        if (++ij >= MAXJMP) {
            writejumps(id);
            ij = dx[id].ijmp = 0;
            dx[id].offset = offset;
            offset += sizeof(struct jmp) + sizeof(offset);
        }
    }
    dx[id].jp.n[ij] = ndelx;
    dx[id].jp.x[ij] = xx;
    dx[id].score = delx;
}
else {
25   col1[yy] = dely[yy];
    ij = dx[id].ijmp;
    if (dx[id].jp.n[0] && (!dna || (ndely[yy] >= MAXJMP
        && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
        dx[id].ijmp++;
        if (++ij >= MAXJMP) {
30   writejumps(id);
            ij = dx[id].ijmp = 0;
            dx[id].offset = offset;
            offset += sizeof(struct jmp) + sizeof(offset);
        }
    }
    dx[id].jp.n[ij] = -ndely[yy];
    dx[id].jp.x[ij] = xx;
    dx[id].score = dely[yy];
}
40   if (xx == len0 && yy < len1) {
        /* last col
        */
        if (endgaps)
            col1[yy] -= ins0+ins1*(len1-yy);
        if (col1[yy] > smax) {
45   smax = col1[yy];
            dmax = id;
        }
    }
}
50   if (endgaps && xx < len0)
        col1[yy-1] -= ins0+ins1*(len0-xx);
    if (col1[yy-1] > smax) {
        smax = col1[yy-1];
55   dmax = id;
    }
}
tmp = col0; col0 = col1; col1 = tmp;
}
(void) free((char *)ndely);
(void) free((char *)dely);
60   (void) free((char *)col0);
    (void) free((char *)col1);
}

```


Table 1 (cont')

```

/*
*
* print() -- only routine visible outside this module
5  *
* static:
* getmat() -- trace back best path, count matches: print()
* pr_align() -- print alignment of described in array p[ ]: print()
* dumpblock() -- dump a block of lines with numbers, stars: pr_align()
10 * nums() -- put out a number line: dumpblock()
* putline() -- put out a line (name, [num], seq, [num]): dumpblock()
* stars() -- put a line of stars: dumpblock()
* stripname() -- strip any path and prefix from a seqname
*/
15
#include "nw.h"

#define SPC      3
#define P_LINE   256    /* maximum output line */
20 #define P_SPC   3      /* space between name or num and seq */

extern  _day[26][26];
int     olen;           /* set output line length */
FILE    *fx;            /* output file */
25

print()

    print
{
    int     lx, ly, firstgap, lastgap;    /* overlap */
30
    if ((fx = fopen(ofile, "w")) == 0) {
        fprintf(stderr, "%s: can't write %s\n", prog, ofile);
        cleanup(1);
    }
35
    fprintf(fx, "<first sequence: %s (length = %d)\n", namex[0], len0);
    fprintf(fx, "<second sequence: %s (length = %d)\n", namex[1], len1);
    olen = 60;
    lx = len0;
    ly = len1;
40
    firstgap = lastgap = 0;
    if (dmax < len1 - 1) {    /* leading gap in x */
        pp[0].spc = firstgap = len1 - dmax - 1;
        ly -= pp[0].spc;
    }
45
    else if (dmax > len1 - 1) { /* leading gap in y */
        pp[1].spc = firstgap = dmax - (len1 - 1);
        lx -= pp[1].spc;
    }
    if (dmax0 < len0 - 1) {    /* trailing gap in x */
50
        lastgap = len0 - dmax0 - 1;
        lx -= lastgap;
    }
    else if (dmax0 > len0 - 1) { /* trailing gap in y */
        lastgap = dmax0 - (len0 - 1);
55
        ly -= lastgap;
    }
    getmat(lx, ly, firstgap, lastgap);
    pr_align();
}
60

```


Table 1 (cont')

```

/*
 * trace back the best path, count matches
 */
5  static
   getmat(lx, ly, firstgap, lastgap)                                getmat
       int      lx, ly;                                           /* "core" (minus endgaps) */
       int      firstgap, lastgap;                                /* leading trailing overlap */
   {
10      int      nm, i0, i1, siz0, siz1;
       char      outx[32];
       double    pct;
       register  n0, n1;
       register char *p0, *p1;

15      /* get total matches, score
       */
       i0 = i1 = siz0 = siz1 = 0;
       p0 = seqx[0] + pp[1].spc;
20      p1 = seqx[1] + pp[0].spc;
       n0 = pp[1].spc + 1;
       n1 = pp[0].spc + 1;

       nm = 0;
25      while ( *p0 && *p1 ) {
           if (siz0) {
               p1++;
               n1++;
               siz0--;
30           }
           else if (siz1) {
               p0++;
               n0++;
               siz1--;
35           }
           else {
               if (xbm[*p0-'A']&xbm[*p1-'A'])
                   nm++;
               if (n0++ == pp[0].x[i0])
                   siz0 = pp[0].n[i0++];
40               if (n1++ == pp[1].x[i1])
                   siz1 = pp[1].n[i1++];
               p0++;
               p1++;
45           }
       }

       /* pct homology:
       * if penalizing endgaps, base is the shorter seq
50      * else, knock off overhangs and take shorter core
       */
       if (endgaps)
           lx = (len0 < len1)? len0 : len1;
       else
55           lx = (lx < ly)? lx : ly;
       pct = 100.*(double)nm/(double)lx;
       fprintf(fx, "\n");
       fprintf(fx, "< %d match%s in an overlap of %d: %.2f percent similarity\n",
           nm, (nm == 1)? "" : "es", lx, pct);
60

```


Table 1 (cont')

```

fprintf(fx, "< gaps in first sequence: %d", gapx);
...getmat
5  if (gapx) {
    (void) sprintf(outx, " (%d %s%s)",
        ngapx, (dna)? "base":"residue", (ngapx == 1)? ":" : "s");
    fprintf(fx, "%s", outx);

10  fprintf(fx, ", gaps in second sequence: %d", gapy);
    if (gapy) {
        (void) sprintf(outx, " (%d %s%s)",
            ngapy, (dna)? "base":"residue", (ngapy == 1)? ":" : "s");
        fprintf(fx, "%s", outx);

15  }
    if (dna)
        fprintf(fx,
            "\n< score: %d (match = %d, mismatch = %d, gap penalty = %d + %d per base)\n",
            smax, DMAT, DMIS, DINS0, DINS1);

20  else
        fprintf(fx,
            "\n< score: %d (Dayhoff PAM 250 matrix, gap penalty = %d + %d per residue)\n",
            smax, PINS0, PINS1);
    if (endgaps)
25  fprintf(fx,
        "<endgaps penalized. left endgap: %d %s%s, right endgap: %d %s%s\n",
        firstgap, (dna)? "base" : "residue", (firstgap == 1)? "" : "s",
        lastgap, (dna)? "base" : "residue", (lastgap == 1)? "" : "s");
    else
30  fprintf(fx, "<endgaps not penalized\n");
}
static nm; /* matches in core -- for checking */
static lmax; /* lengths of stripped file names */
static ij[2]; /* jmp index for a path */
35 static nc[2]; /* number at start of current line */
static ni[2]; /* current elem number -- for gapping */
static siz[2];
static char *ps[2]; /* ptr to current element */
static char *po[2]; /* ptr to next output char slot */
40 static char out[2][P_LINE]; /* output line */
static char star[P_LINE]; /* set by stars() */

/*
* print alignment of described in struct path pp[ ]
*/
45 static
pr_align()
    pr_align
{
50  int nm; /* char count */
    int more;
    register i;

    for (i = 0, lmax = 0; i < 2; i++) {
55  nm = stripname(nameex[i]);
        if (nm > lmax)
            lmax = nm;

        nc[i] = 1;
60  ni[i] = 1;
        siz[i] = ij[i] = 0;
        ps[i] = seqx[i];
        po[i] = out[i];
    }

```


Table 1 (cont')

```

for (nm = nm = 0, more = 1; more; ) {
...pr_align
    for (i = more = 0; i < 2; i++) {
5         /*
           * do we have more of this sequence?
           */
           if (!*ps[i])
10                continue;

           more++;

           if (pp[i].spc) { /* leading space */
               *po[i]++ = ' ';
15               pp[i].spc--;
           }
           else if (siz[i]) { /* in a gap */
               *po[i]++ = '-';
               siz[i]--;
20           }
           else { /* we're putting a seq element
                  */
               *po[i] = *ps[i];
               if (islower(*ps[i]))
25                   *ps[i] = toupper(*ps[i]);
               po[i]++;
               ps[i]++;

               /*
30              * are we at next gap for this seq?
              */
               if (ni[i] == pp[i].x[ij[i]]) {
                   /*
                   * we need to merge all gaps
                   * at this location
                   */
35                   siz[i] = pp[i].n[ij[i]++];
                   while (ni[i] == pp[i].x[ij[i]])
                       siz[i] += pp[i].n[ij[i]++];
                   }
                   ni[i]++;
               }
           }
           }
45         if (++nm == olen || !more && nm) {
            dumpblock();
            for (i = 0; i < 2; i++)
                po[i] = out[i];
            nm = 0;
        }
50     }
}

/*
 * dump a block of lines, including numbers, stars: pr_align()
55 */
static
dumpblock()
    dumpblock
{
60     register i;
    for (i = 0; i < 2; i++)
        *po[i]-- = '\0';

```


Table 1 (cont')**...dumpblock**

```

5      (void) putc('\n', fx);
      for (i = 0; i < 2; i++) {
          if (*out[i] && (*out[i] != ' ' || *(po[i]) != ' ')) {
              if (i == 0)
                  nums(i);
              if (i == 0 && *out[1])
10                 stars();
              putline(i);
              if (i == 0 && *out[1])
                  fprintf(fx, star);
              if (i == 1)
15                 nums(i);
          }
      }
  }

20  /*
   * put out a number line: dumpblock()
   */
  static
  nums(ix)
25      int      ix;      /* index in out[ ] holding seq line */
  {
      char      nline[P_LINE];
      register  i, j;
      register char *pn, *px, *py;
30
      for (pn = nline, i = 0; i < lmax+P_SPC; i++, pn++)
          *pn = ' ';
      for (i = nc[ix], py = out[ix]; *py; py++, pn++) {
          if (*py == ' ' || *py == '-')
35              *pn = ' ';
          else {
              if (i%10 == 0 || (i == 1 && nc[ix] != 1)) {
                  j = (i < 0)? -i : i;
                  for (px = pn; j; j /= 10, px--)
40                      *px = j%10 + '0';
                  if (i < 0)
                      *px = '-';
              }
              else
45                  *pn = ' ';
              i++;
          }
      }
      *pn = '\0';
50      nc[ix] = i;
      for (pn = nline; *pn; pn++)
          (void) putc(*pn, fx);
      (void) putc('\n', fx);
  }
55
  /*
   * put out a line (name, [num], seq, [num]): dumpblock()
   */
  static
60  putline(ix)
      int      ix;
      {

```

nums**putline**

Table 1 (cont')**...putline**

```

5      int          i;
      register char *px;

      for (px = namex[ix], i = 0; *px && *px != ':'; px++, i++)
          (void) putc(*px, fx);
      for (; i < lmax+P_SPC; i++)
10         (void) putc(' ', fx);

      /* these count from 1:
      * ni[ ] is current element (from 1)
      * nc[ ] is number at start of current line
      */
15     for (px = out[ix]; *px; px++)
          (void) putc(*px&0x7F, fx);
      (void) putc('\n', fx);
20 }

/*
 * put a line of stars (seqs always in out[0], out[1]): dumpblock()
 */
25 static
stars()
{
    stars
    {
30         int          i;
        register char *p0, *p1, cx, *px;

        if (!*out[0] || (*out[0] == ' ' && *(po[0]) == ' ') ||
            !*out[1] || (*out[1] == ' ' && *(po[1]) == ' '))
            return;
35         px = star;
        for (i = lmax+P_SPC; i; i--)
            *px++ = ' ';

        for (p0 = out[0], p1 = out[1]; *p0 && *p1; p0++, p1++) {
40             if (isalpha(*p0) && isalpha(*p1)) {

                    if (xbm[*p0-'A']&xbm[*p1-'A']) {
                        cx = '*';
                        nm++;
45                     }
                    else if (!dna && _day[*p0-'A'][*p1-'A'] > 0)
                        cx = '.';
                    else
                        cx = ' ';
50                 }
                else
                    cx = ' ';
                *px++ = cx;
            }
55         *px++ = '\n';
        *px = '\0';
    }
60

```


Table 1 (cont')

```
/*
 * strip path or prefix from pn, return len: pr_align()
 */
5 static
  stripname(pn)
      stripname
      char    *pn;    /* file name (may be path) */
10 {
      register char    *px, *py;

      py = 0;
      for (px = pn; *px; px++)
          if (*px == '/')
15             py = px + 1;
      if (py)
          (void) strcpy(pn, py);
      return(strlen(pn));
20 }

25

30

35

40

45

50

55

60
```


Table 1 (cont')

```

/*
 * cleanup() -- cleanup any tmp file
 * getseq() -- read in seq, set dna, len, maxlen
5  * g_calloc() -- calloc() with error checkin
 * readjumps() -- get the good jumps, from tmp file if necessary
 * writejumps() -- write a filled array of jumps to a tmp file: nw()
 */
#include "nw.h"
10 #include <sys/file.h>

char    *jname = "/tmp/homgXXXXXX";          /* tmp file for jumps */
FILE    *fj;

15 int    cleanup();                          /* cleanup tmp file */
long    lseek();

/*
20 * remove any tmp file if we blow
 */
cleanup(i)
    int    i;
{
    if (fj)
25         (void) unlink(jname);
    exit(i);
}

/*
30 * read, return ptr to seq, set dna, len, maxlen
 * skip lines starting with ';', '<', or '>'
 * seq in upper or lower case
 */
char    *
35 getseq(file, len)
    char    *file;    /* file name */
    int     *len;     /* seq len */
{
    char    line[1024], *pseq;
40     register char    *px, *py;
    int     natgc, tlen;
    FILE    *fp;

    if ((fp = fopen(file, "r")) == 0) {
45         fprintf(stderr, "%s: can't read %s\n", prog, file);
        exit(1);
    }
    tlen = natgc = 0;
    while (fgets(line, 1024, fp)) {
50         if (*line == ';' || *line == '<' || *line == '>')
            continue;
        for (px = line; *px != '\n'; px++)
            if (isupper(*px) || islower(*px))
                tlen++;
55     }
    if ((pseq = malloc((unsigned)(tlen+6))) == 0) {
        fprintf(stderr, "%s: malloc() failed to get %d bytes for %s\n", prog, tlen+6, file);
        exit(1);
    }
60     pseq[0] = pseq[1] = pseq[2] = pseq[3] = '\0';

```

cleanup

getseq

Table 1 (cont')

...getseq

```

py = pseq + 4;
*len = tlen;
5  rewind(fp);

while (fgets(line, 1024, fp)) {
    if (*line == ';' || *line == '<' || *line == '>')
        continue;
10    for (px = line; *px != '\n'; px++) {
        if (isupper(*px))
            *py++ = *px;
        else if (islower(*px))
            *py++ = toupper(*px);
15    if (index("ATGCU",*(py-1)))
        natgc++;
    }
}
*py++ = '\0';
20 *py = '\0';
(void) fclose(fp);
dna = natgc > (tlen/3);
return(pseq+4);
}
25 char *
g_alloc(msg, nx, sz)
    char *msg;          /* program, calling routine */
    int nx, sz;          /* number and size of elements */
30 {
    char *px, *calloc();

    if ((px = calloc((unsigned)nx, (unsigned)sz)) == 0) {
        if (*msg) {
35            fprintf(stderr, "%s: g_alloc() failed %s (n=%d, sz=%d)\n", prog, msg, nx, sz);
            exit(1);
        }
    }
    return(px);
40 }

/*
 * get final jmps from dx[ ] or tmp file, set pp[ ], reset dmax: main()
 */
45 readjmps()
    readjmps
{
    int fd = -1;
    int siz, i0, i1;
50 register i, j, xx;

    if (fj) {
        (void) fclose(fj);
        if ((fd = open(jname, O_RDONLY, 0)) < 0) {
55            fprintf(stderr, "%s: can't open() %s\n", prog, jname);
            cleanup(1);
        }
    }
    for (i = i0 = i1 = 0, dmax0 = dmax, xx = len0; ; i++) {
60        while (1) {
            for (j = dx[dmax].ijmp; j >= 0 && dx[dmax].jp.x[j] >= xx; j--)
                ;

```

g_alloc

Table 1 (cont')**...readjumps**

```

5         if (j < 0 && dx[dmax].offset && fj) {
            (void) lseek(fd, dx[dmax].offset, 0);
            (void) read(fd, (char *)&dx[dmax].jp, sizeof(struct jmp));
            (void) read(fd, (char *)&dx[dmax].offset, sizeof(dx[dmax].offset));
            dx[dmax].ijmp = MAXJMP-1;
        }
10        else
            break;
    }
    if (i >= JMPS) {
        fprintf(stderr, "%s: too many gaps in alignment\n", prog);
        cleanup(1);
    }
15    if (j >= 0) {
        siz = dx[dmax].jp.n[j];
        xx = dx[dmax].jp.x[j];
        dmax += siz;
20        if (siz < 0) { /* gap in second seq */
            pp[1].n[i1] = -siz;
            xx += siz;
            /* id = xx - yy + len1 - 1
            */
25            pp[1].x[i1] = xx - dmax + len1 - 1;
            gapy++;
            ngapy -= siz;
        /* ignore MAXGAP when doing endgaps */
            siz = (-siz < MAXGAP || endgaps)? -siz : MAXGAP;
30            i1++;
        }
        else if (siz > 0) { /* gap in first seq */
            pp[0].n[i0] = siz;
            pp[0].x[i0] = xx;
35            gapx++;
            ngapx += siz;
        /* ignore MAXGAP when doing endgaps */
            siz = (siz < MAXGAP || endgaps)? siz : MAXGAP;
            i0++;
40        }
    }
    else
        break;
}

45    /* reverse the order of jumps
    */
    for (j = 0, i0--; j < i0; j++, i0--) {
        i = pp[0].n[j]; pp[0].n[j] = pp[0].n[i0]; pp[0].n[i0] = i;
50        i = pp[0].x[j]; pp[0].x[j] = pp[0].x[i0]; pp[0].x[i0] = i;
    }
    for (j = 0, i1--; j < i1; j++, i1--) {
        i = pp[1].n[j]; pp[1].n[j] = pp[1].n[i1]; pp[1].n[i1] = i;
        i = pp[1].x[j]; pp[1].x[j] = pp[1].x[i1]; pp[1].x[i1] = i;
55    }
    if (fd >= 0)
        (void) close(fd);
    if (fj) {
        (void) unlink(jname);
60        fj = 0;
        offset = 0;
    }
}

```


Table 1 (cont')

```

/*
 * write a filled jmp struct offset of the prev one (if any): nw()
 */
5 writejumps(ix)
    writejumps
    int    ix;
10 {
    char    *mktemp();

    if (!fj) {
        if (mktemp(jname) < 0) {
            fprintf(stderr, "%s: can't mktemp() %s\n", prog, jname);
            cleanup(1);
        }
        if ((fj = fopen(jname, "w")) == 0) {
            fprintf(stderr, "%s: can't write %s\n", prog, jname);
            exit(1);
        }
    }
    (void) fwrite((char *)&dx[ix].jp, sizeof(struct jmp), 1, fj);
    (void) fwrite((char *)&dx[ix].offset, sizeof(dx[ix].offset), 1, fj);
    }
25

```


Table 2

5	PRO	XXXXXXXXXXXXXXXXXX	(Length = 15 amino acids)
	Comparison Protein	XXXXXXYYYYYYY	(Length = 12 amino acids)
	% amino acid sequence identity =		

(the number of identically matching amino acid residues between the two polypeptide sequences as
 10 determined by ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) =
 5 divided by 15 = 33.3%

Table 3

15	PRO	XXXXXXXXXXXX	(Length = 10 amino acids)
	Comparison Protein	XXXXXXYYYYYYYZZYZ	(Length = 15 amino acids)
	% amino acid sequence identity =		

(the number of identically matching amino acid residues between the two polypeptide sequences as
 20 determined by ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) =
 5 divided by 10 = 50%

Table 4

25	PRO-DNA	NNNNNNNNNNNNNN	(Length = 14 nucleotides)
	Comparison DNA	NNNNNNLLLLLLLLLL	(Length = 16 nucleotides)
	% nucleic acid sequence identity =		

(the number of identically matching nucleotides between the two nucleic acid sequences as determined by
 30 ALIGN-2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) =
 6 divided by 14 = 42.9%

Table 5

35	PRO-DNA	NNNNNNNNNNNNNN	(Length = 12 nucleotides)
	Comparison DNA	NNNNLLLLVV	(Length = 9 nucleotides)

% nucleic acid sequence identity =

(the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) =

5 4 divided by 12 = 33.3 %

II. Compositions and Methods of the Invention

A. Full-Length PRO Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding
10 polypeptides referred to in the present application as PRO polypeptides. In particular, cDNAs encoding various PRO polypeptides have been identified and isolated, as disclosed in further detail in the Examples below. However, for sake of simplicity, in the present specification the protein encoded by the full length native nucleic acid molecules disclosed herein as well as all further native homologues and variants included in the foregoing definition of PRO, will be referred to as "PRO/number", regardless of their
15 origin or mode of preparation.

As disclosed in the Examples below, various cDNA clones have been disclosed. The predicted amino acid sequence can be determined from the nucleotide sequence using routine skill. For the PRO polypeptides and encoding nucleic acids described herein, Applicants have identified what is believed to be the reading frame best identifiable with the sequence information available at the time.

20 B. PRO Polypeptide Variants

In addition to the full-length native sequence PRO polypeptides described herein, it is contemplated that PRO variants can be prepared. PRO variants can be prepared by introducing appropriate nucleotide changes into the PRO DNA, and/or by synthesis of the desired PRO polypeptide. Those skilled in the art will appreciate that amino acid changes may alter post-translational processes of
25 the PRO, such as changing the number or position of glycosylation sites or altering the membrane anchoring characteristics.

Variations in the native full-length sequence PRO or in various domains of the PRO described herein, can be made, for example, using any of the techniques and guidelines for conservative and non-conservative mutations set forth, for instance, in U.S. Patent No. 5,364,934. Variations may be a
30 substitution, deletion or insertion of one or more codons encoding the PRO that results in a change in the amino acid sequence of the PRO as compared with the native sequence PRO. Optionally, the variation is by substitution of at least one amino acid with any other amino acid in one or more of the domains of the PRO. Guidance in determining which amino acid residue may be inserted, substituted or deleted without adversely affecting the desired activity may be found by comparing the sequence of the PRO with that of
35 homologous known protein molecules and minimizing the number of amino acid sequence changes made in regions of high homology. Amino acid substitutions can be the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, such as the replacement of a leucine with a serine, i.e., conservative amino acid replacements. Insertions or deletions may optionally

be in the range of about 1 to 5 amino acids. The variation allowed may be determined by systematically making insertions, deletions or substitutions of amino acids in the sequence and testing the resulting variants for activity exhibited by the full-length or mature native sequence.

PRO polypeptide fragments are provided herein. Such fragments may be truncated at the N-terminus or C-terminus, or may lack internal residues, for example, when compared with a full length native protein. Certain fragments lack amino acid residues that are not essential for a desired biological activity of the PRO polypeptide.

PRO fragments may be prepared by any of a number of conventional techniques. Desired peptide fragments may be chemically synthesized. An alternative approach involves generating PRO fragments by enzymatic digestion, e.g., by treating the protein with an enzyme known to cleave proteins at sites defined by particular amino acid residues, or by digesting the DNA with suitable restriction enzymes and isolating the desired fragment. Yet another suitable technique involves isolating and amplifying a DNA fragment encoding a desired polypeptide fragment, by polymerase chain reaction (PCR). Oligonucleotides that define the desired termini of the DNA fragment are employed at the 5' and 3' primers in the PCR.

Preferably, PRO polypeptide fragments share at least one biological and/or immunological activity with the native PRO polypeptide disclosed herein.

In particular embodiments, conservative substitutions of interest are shown in Table 6 under the heading of preferred substitutions. If such substitutions result in a change in biological activity, then more substantial changes, denominated exemplary substitutions in Table 6, or as further described below in reference to amino acid classes, are introduced and the products screened.

Table 6

	<u>Original Residue</u>	<u>Exemplary Substitutions</u>	<u>Preferred Substitutions</u>
25	Ala (A)	val; leu; ile	val
	Arg (R)	lys; gln; asn	lys
	Asn (N)	gln; his; lys; arg	gln
	Asp (D)	glu	glu
	Cys (C)	ser	ser
30	Gln (Q)	asn	asn
	Glu (E)	asp	asp
	Gly (G)	pro; ala	ala
	His (H)	asn; gln; lys; arg	arg
	Ile (I)	leu; val; met; ala; phe;	
35		norleucine	leu
	Leu (L)	norleucine; ile; val;	
		met; ala; phe	ile
	Lys (K)	arg; gln; asn	arg
	Met (M)	leu; phe; ile	leu
40	Phe (F)	leu; val; ile; ala; tyr	leu
	Pro (P)	ala	ala
	Ser (S)	thr	thr
	Thr (T)	ser	ser
	Trp (W)	tyr; phe	tyr
45	Tyr (Y)	trp; phe; thr; ser	phe
	Val (V)	ile; leu; met; phe;	
		ala; norleucine	leu

Substantial modifications in function or immunological identity of the PRO polypeptide are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side-chain properties:

- (1) hydrophobic: norleucine, met, ala, val, leu, ile;
- (2) neutral hydrophilic: cys, ser, thr;
- (3) acidic: asp, glu;
- (4) basic: asn, gln, his, lys, arg;
- (5) residues that influence chain orientation: gly, pro; and
- (6) aromatic: trp, tyr, phe.

Non-conservative substitutions will entail exchanging a member of one of these classes for another class. Such substituted residues also may be introduced into the conservative substitution sites or, more preferably, into the remaining (non-conserved) sites.

The variations can be made using methods known in the art such as oligonucleotide-mediated (site-directed) mutagenesis, alanine scanning, and PCR mutagenesis. Site-directed mutagenesis [Carter et al., Nucl. Acids Res., 13:4331 (1986); Zoller et al., Nucl. Acids Res., 10:6487 (1987)], cassette mutagenesis [Wells et al., Gene, 34:315 (1985)], restriction selection mutagenesis [Wells et al., Philos. Trans. R. Soc. London SerA, 317:415 (1986)] or other known techniques can be performed on the cloned DNA to produce the PRO variant DNA.

Scanning amino acid analysis can also be employed to identify one or more amino acids along a contiguous sequence. Among the preferred scanning amino acids are relatively small, neutral amino acids. Such amino acids include alanine, glycine, serine, and cysteine. Alanine is typically a preferred scanning amino acid among this group because it eliminates the side-chain beyond the beta-carbon and is less likely to alter the main-chain conformation of the variant [Cunningham and Wells, Science, 244:1081-1085 (1989)]. Alanine is also typically preferred because it is the most common amino acid. Further, it is frequently found in both buried and exposed positions [Creighton, The Proteins, (W.H. Freeman & Co., N.Y.); Chothia, J. Mol. Biol., 150:1 (1976)]. If alanine substitution does not yield adequate amounts of variant, an isoteric amino acid can be used.

C. Modifications of PRO

Covalent modifications of PRO are included within the scope of this invention. One type of covalent modification includes reacting targeted amino acid residues of a PRO polypeptide with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C- terminal residues of the PRO. Derivatization with bifunctional agents is useful, for instance, for crosslinking PRO to a water-insoluble support matrix or surface for use in the method for purifying anti-PRO antibodies, and vice-versa. Commonly used crosslinking agents include, e.g., 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-

dithiobis(succinimidylpropionate), bifunctional maleimides such as bis-N-maleimido-1,8-octane and agents such as methyl-3-[(p-azidophenyl)dithio]propioimide.

Other modifications include deamidation of glutamyl and asparaginy residues to the corresponding glutamyl and aspartyl residues, respectively, hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the α -amino groups of lysine, arginine, and histidine side chains [T.E. Creighton, Proteins: Structure and Molecular Properties, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)], acetylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

Another type of covalent modification of the PRO polypeptide included within the scope of this invention comprises altering the native glycosylation pattern of the polypeptide. "Altering the native glycosylation pattern" is intended for purposes herein to mean deleting one or more carbohydrate moieties found in native sequence PRO (either by removing the underlying glycosylation site or by deleting the glycosylation by chemical and/or enzymatic means), and/or adding one or more glycosylation sites that are not present in the native sequence PRO. In addition, the phrase includes qualitative changes in the glycosylation of the native proteins, involving a change in the nature and proportions of the various carbohydrate moieties present.

Addition of glycosylation sites to the PRO polypeptide may be accomplished by altering the amino acid sequence. The alteration may be made, for example, by the addition of, or substitution by, one or more serine or threonine residues to the native sequence PRO (for O-linked glycosylation sites). The PRO amino acid sequence may optionally be altered through changes at the DNA level, particularly by mutating the DNA encoding the PRO polypeptide at preselected bases such that codons are generated that will translate into the desired amino acids.

Another means of increasing the number of carbohydrate moieties on the PRO polypeptide is by chemical or enzymatic coupling of glycosides to the polypeptide. Such methods are described in the art, e.g., in WO 87/05330 published 11 September 1987, and in Aplin and Wriston, CRC Crit. Rev. Biochem., pp. 259-306 (1981).

Removal of carbohydrate moieties present on the PRO polypeptide may be accomplished chemically or enzymatically or by mutational substitution of codons encoding for amino acid residues that serve as targets for glycosylation. Chemical deglycosylation techniques are known in the art and described, for instance, by Hakimuddin, et al., Arch. Biochem. Biophys., 259:52 (1987) and by Edge et al., Anal. Biochem., 118:131 (1981). Enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety of endo- and exo-glycosidases as described by Thotakura et al., Meth. Enzymol., 138:350 (1987).

Another type of covalent modification of PRO comprises linking the PRO polypeptide to one of a variety of nonproteinaceous polymers, e.g., polyethylene glycol (PEG), polypropylene glycol, or polyoxyalkylenes, in the manner set forth in U.S. Patent Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337.

The PRO of the present invention may also be modified in a way to form a chimeric molecule comprising PRO fused to another, heterologous polypeptide or amino acid sequence.

In one embodiment, such a chimeric molecule comprises a fusion of the PRO with a tag polypeptide which provides an epitope to which an anti-tag antibody can selectively bind. The epitope tag is generally placed at the amino- or carboxyl- terminus of the PRO. The presence of such epitope-tagged forms of the PRO can be detected using an antibody against the tag polypeptide. Also, provision of the epitope tag enables the PRO to be readily purified by affinity purification using an anti-tag antibody or another type of affinity matrix that binds to the epitope tag. Various tag polypeptides and their respective antibodies are well known in the art. Examples include poly-histidine (poly-his) or poly-histidine-glycine (poly-his-gly) tags; the flu HA tag polypeptide and its antibody 12CA5 [Field et al., Mol. Cell. Biol., 8:2159-2165 (1988)]; the c-myc tag and the 8F9, 3C7, 6E10, G4, B7 and 9E10 antibodies thereto [Evan et al., Molecular and Cellular Biology, 5:3610-3616 (1985)]; and the Herpes Simplex virus glycoprotein D (gD) tag and its antibody [Paborsky et al., Protein Engineering, 3(6):547-553 (1990)]. Other tag polypeptides include the Flag-peptide [Hopp et al., BioTechnology, 6:1204-1210 (1988)]; the KT3 epitope peptide [Martin et al., Science, 255:192-194 (1992)]; an alpha-tubulin epitope peptide [Skinner et al., J. Biol. Chem., 266:15163-15166 (1991)]; and the T7 gene 10 protein peptide tag [Lutz-Freyermuth et al., Proc. Natl. Acad. Sci. USA, 87:6393-6397 (1990)].

In an alternative embodiment, the chimeric molecule may comprise a fusion of the PRO with an immunoglobulin or a particular region of an immunoglobulin. For a bivalent form of the chimeric molecule (also referred to as an "immunoadhesin"), such a fusion could be to the Fc region of an IgG molecule. The Ig fusions preferably include the substitution of a soluble (transmembrane domain deleted or inactivated) form of a PRO polypeptide in place of at least one variable region within an Ig molecule. In a particularly preferred embodiment, the immunoglobulin fusion includes the hinge, CH2 and CH3, or the hinge, CH1, CH2 and CH3 regions of an IgG1 molecule. For the production of immunoglobulin fusions see also US Patent No. 5,428,130 issued June 27, 1995.

D. Preparation of PRO

The description below relates primarily to production of PRO by culturing cells transformed or transfected with a vector containing PRO nucleic acid. It is, of course, contemplated that alternative methods, which are well known in the art, may be employed to prepare PRO. For instance, the PRO sequence, or portions thereof, may be produced by direct peptide synthesis using solid-phase techniques [see, e.g., Stewart et al., Solid-Phase Peptide Synthesis, W.H. Freeman Co., San Francisco, CA (1969); Merrifield, J. Am. Chem. Soc., 85:2149-2154 (1963)]. *In vitro* protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be accomplished, for instance, using an Applied Biosystems Peptide Synthesizer (Foster City, CA) using manufacturer's instructions. Various portions of the PRO may be chemically synthesized separately and combined using chemical or enzymatic methods to produce the full-length PRO.

1. Isolation of DNA Encoding PRO

DNA encoding PRO may be obtained from a cDNA library prepared from tissue believed to possess the PRO mRNA and to express it at a detectable level. Accordingly, human PRO DNA can be conveniently obtained from a cDNA library prepared from human tissue, such as described in the Examples. The PRO-encoding gene may also be obtained from a genomic library or by known synthetic procedures (e.g., automated nucleic acid synthesis).

Libraries can be screened with probes (such as antibodies to the PRO or oligonucleotides of at least about 20-80 bases) designed to identify the gene of interest or the protein encoded by it. Screening the cDNA or genomic library with the selected probe may be conducted using standard procedures, such as described in Sambrook et al., Molecular Cloning: A Laboratory Manual (New York: Cold Spring Harbor Laboratory Press, 1989). An alternative means to isolate the gene encoding PRO is to use PCR methodology [Sambrook et al., supra; Dieffenbach et al., PCR Primer: A Laboratory Manual (Cold Spring Harbor Laboratory Press, 1995)].

The Examples below describe techniques for screening a cDNA library. The oligonucleotide sequences selected as probes should be of sufficient length and sufficiently unambiguous that false positives are minimized. The oligonucleotide is preferably labeled such that it can be detected upon hybridization to DNA in the library being screened. Methods of labeling are well known in the art, and include the use of radiolabels like ³²P-labeled ATP, biotinylation or enzyme labeling. Hybridization conditions, including moderate stringency and high stringency, are provided in Sambrook et al., supra.

Sequences identified in such library screening methods can be compared and aligned to other known sequences deposited and available in public databases such as GenBank or other private sequence databases. Sequence identity (at either the amino acid or nucleotide level) within defined regions of the molecule or across the full-length sequence can be determined using methods known in the art and as described herein.

Nucleic acid having protein coding sequence may be obtained by screening selected cDNA or genomic libraries using the deduced amino acid sequence disclosed herein for the first time, and, if necessary, using conventional primer extension procedures as described in Sambrook et al., supra, to detect precursors and processing intermediates of mRNA that may not have been reverse-transcribed into cDNA.

2. Selection and Transformation of Host Cells

Host cells are transfected or transformed with expression or cloning vectors described herein for PRO production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences. The culture conditions, such as media, temperature, pH and the like, can be selected by the skilled artisan without undue experimentation. In general, principles, protocols, and practical techniques for maximizing the productivity of cell cultures can be found in Mammalian Cell Biotechnology: a Practical Approach, M. Butler, ed. (IRL Press, 1991) and Sambrook et al., supra.

Methods of eukaryotic cell transfection and prokaryotic cell transformation are known to the ordinarily skilled artisan, for example, CaCl_2 , CaPO_4 , liposome-mediated and electroporation. Depending on the host cell used, transformation is performed using standard techniques appropriate to such cells. The calcium treatment employing calcium chloride, as described in Sambrook et al., *supra*, or electroporation is generally used for prokaryotes. Infection with *Agrobacterium tumefaciens* is used for transformation of certain plant cells, as described by Shaw et al., *Gene*, 23:315 (1983) and WO 89/05859 published 29 June 1989. For mammalian cells without such cell walls, the calcium phosphate precipitation method of Graham and van der Eb, *Virology*, 52:456-457 (1978) can be employed. General aspects of mammalian cell host system transfections have been described in U.S. Patent No. 4,399,216. Transformations into yeast are typically carried out according to the method of Van Solingen et al., *J. Bact.*, 130:946 (1977) and Hsiao et al., *Proc. Natl. Acad. Sci. (USA)*, 76:3829 (1979). However, other methods for introducing DNA into cells, such as by nuclear microinjection, electroporation, bacterial protoplast fusion with intact cells, or polycations, e.g., polybrene, polyornithine, may also be used. For various techniques for transforming mammalian cells, see Keown et al., *Methods in Enzymology*, 185:527-537 (1990) and Mansour et al., *Nature*, 336:348-352 (1988).

Suitable host cells for cloning or expressing the DNA in the vectors herein include prokaryote, yeast, or higher eukaryote cells. Suitable prokaryotes include but are not limited to eubacteria, such as Gram-negative or Gram-positive organisms, for example, Enterobacteriaceae such as *E. coli*. Various *E. coli* strains are publicly available, such as *E. coli* K12 strain MM294 (ATCC 31,446); *E. coli* X1776 (ATCC 31,537); *E. coli* strain W3110 (ATCC 27,325) and K5 772 (ATCC 53,635). Other suitable prokaryotic host cells include Enterobacteriaceae such as *Escherichia*, e.g., *E. coli*, *Enterobacter*, *Erwinia*, *Klebsiella*, *Proteus*, *Salmonella*, e.g., *Salmonella typhimurium*, *Serratia*, e.g., *Serratia marcescans*, and *Shigella*, as well as *Bacilli* such as *B. subtilis* and *B. licheniformis* (e.g., *B. licheniformis* 41P disclosed in DD 266,710 published 12 April 1989), *Pseudomonas* such as *P. aeruginosa*, and *Streptomyces*. These examples are illustrative rather than limiting. Strain W3110 is one particularly preferred host or parent host because it is a common host strain for recombinant DNA product fermentations. Preferably, the host cell secretes minimal amounts of proteolytic enzymes. For example, strain W3110 may be modified to effect a genetic mutation in the genes encoding proteins endogenous to the host, with examples of such hosts including *E. coli* W3110 strain 1A2, which has the complete genotype *tonA*; *E. coli* W3110 strain 9E4, which has the complete genotype *tonA ptr3*; *E. coli* W3110 strain 27C7 (ATCC 55,244), which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT kan'*; *E. coli* W3110 strain 37D6, which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT rbs7 ilvG kan'*; *E. coli* W3110 strain 40B4, which is strain 37D6 with a non-kanamycin resistant *degP* deletion mutation; and an *E. coli* strain having mutant periplasmic protease disclosed in U.S. Patent No. 4,946,783 issued 7 August 1990. Alternatively, *in vitro* methods of cloning, e.g., PCR or other nucleic acid polymerase reactions, are suitable.

In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for PRO-encoding vectors. *Saccharomyces cerevisiae* is a commonly used

lower eukaryotic host microorganism. Others include *Schizosaccharomyces pombe* (Beach and Nurse, Nature, 290: 140 [1981]; EP 139,383 published 2 May 1985); *Kluyveromyces* hosts (U.S. Patent No. 4,943,529; Fleer et al., Bio/Technology, 9:968-975 (1991)) such as, e.g., *K. lactis* (MW98-8C, CBS683, CBS4574; Louvencourt et al., J. Bacteriol., 154(2):737-742 [1983]), *K. fragilis* (ATCC 12,424), *K. bulgaricus* (ATCC 16,045), *K. wickerhamii* (ATCC 24,178), *K. waltii* (ATCC 56,500), *K. drosophilae* (ATCC 36,906; Van den Berg et al., Bio/Technology, 8:135 (1990)), *K. thermotolerans*, and *K. marxianus*; *Yarrowia* (EP 402,226); *Pichia pastoris* (EP 183,070; Sreekrishna et al., J. Basic Microbiol., 28:265-278 [1988]); *Candida*; *Trichoderma reesei* (EP 244,234); *Neurospora crassa* (Case et al., Proc. Natl. Acad. Sci. USA, 76:5259-5263 [1979]); *Schwanniomyces* such as *Schwanniomyces occidentalis* (EP 394,538 published 31 October 1990); and filamentous fungi such as, e.g., *Neurospora*, *Penicillium*, *Tolypocladium* (WO 91/00357 published 10 January 1991), and *Aspergillus* hosts such as *A. nidulans* (Ballance et al., Biochem. Biophys. Res. Commun., 112:284-289 [1983]; Tilburn et al., Gene, 26:205-221 [1983]; Yelton et al., Proc. Natl. Acad. Sci. USA, 81: 1470-1474 [1984]) and *A. niger* (Kelly and Hynes, EMBO J., 4:475-479 [1985]). Methylotropic yeasts are suitable herein and include, but are not limited to, yeast capable of growth on methanol selected from the genera consisting of *Hansenula*, *Candida*, *Kloeckera*, *Pichia*, *Saccharomyces*, *Torulopsis*, and *Rhodotorula*. A list of specific species that are exemplary of this class of yeasts may be found in C. Anthony, The Biochemistry of Methylotrophs, 269 (1982).

Suitable host cells for the expression of glycosylated PRO are derived from multicellular organisms. Examples of invertebrate cells include insect cells such as *Drosophila* S2 and *Spodoptera* Sf9, as well as plant cells. Examples of useful mammalian host cell lines include Chinese hamster ovary (CHO) and COS cells. More specific examples include monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, Graham et al., J. Gen Virol., 36:59 (1977)); Chinese hamster ovary cells/-DHFR (CHO, Urlaub and Chasin, Proc. Natl. Acad. Sci. USA, 77:4216 (1980)); mouse sertoli cells (TM4, Mather, Biol. Reprod., 23:243-251 (1980)); human lung cells (W138, ATCC CCL 75); human liver cells (Hep G2, HB 8065); and mouse mammary tumor (MMT 060562, ATCC CCL51). The selection of the appropriate host cell is deemed to be within the skill in the art.

3. Selection and Use of a Replicable Vector

The nucleic acid (e.g., cDNA or genomic DNA) encoding PRO may be inserted into a replicable vector for cloning (amplification of the DNA) or for expression. Various vectors are publicly available. The vector may, for example, be in the form of a plasmid, cosmid, viral particle, or phage. The appropriate nucleic acid sequence may be inserted into the vector by a variety of procedures. In general, DNA is inserted into an appropriate restriction endonuclease site(s) using techniques known in the art. Vector components generally include, but are not limited to, one or more of a signal sequence, an origin of replication, one or more marker genes, an enhancer element, a promoter, and a transcription termination sequence. Construction of suitable vectors containing one or more of these components employs standard ligation techniques which are known to the skilled artisan.

The PRO may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous polypeptide, which may be a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. In general, the signal sequence may be a component of the vector, or it may be a part of the PRO-encoding DNA that is inserted into the vector. The signal sequence may be a prokaryotic signal sequence selected, for example, from the group of the alkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II leaders. For yeast secretion the signal sequence may be, e.g., the yeast invertase leader, alpha factor leader (including *Saccharomyces* and *Kluyveromyces* α -factor leaders, the latter described in U.S. Patent No. 5,010,182), or acid phosphatase leader, the *C. albicans* glucoamylase leader (EP 362,179 published 4 April 1990), or the signal described in WO 90/13646 published 15 November 1990. In mammalian cell expression, mammalian signal sequences may be used to direct secretion of the protein, such as signal sequences from secreted polypeptides of the same or related species, as well as viral secretory leaders.

Both expression and cloning vectors contain a nucleic acid sequence that enables the vector to replicate in one or more selected host cells. Such sequences are well known for a variety of bacteria, yeast, and viruses. The origin of replication from the plasmid pBR322 is suitable for most Gram-negative bacteria, the 2μ plasmid origin is suitable for yeast, and various viral origins (SV40, polyoma, adenovirus, VSV or BPV) are useful for cloning vectors in mammalian cells.

Expression and cloning vectors will typically contain a selection gene, also termed a selectable marker. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, e.g., ampicillin, neomycin, methotrexate, or tetracycline, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not available from complex media, e.g., the gene encoding D-alanine racemase for *Bacilli*.

An example of suitable selectable markers for mammalian cells are those that enable the identification of cells competent to take up the PRO-encoding nucleic acid, such as DHFR or thymidine kinase. An appropriate host cell when wild-type DHFR is employed is the CHO cell line deficient in DHFR activity, prepared and propagated as described by Urlaub et al., Proc. Natl. Acad. Sci. USA, 77:4216 (1980). A suitable selection gene for use in yeast is the *trp1* gene present in the yeast plasmid YRp7 [Stinchcomb et al., Nature, 282:39 (1979); Kingsman et al., Gene, 7:141 (1979); Tschemper et al., Gene, 10:157 (1980)]. The *trp1* gene provides a selection marker for a mutant strain of yeast lacking the ability to grow in tryptophan, for example, ATCC No. 44076 or PEP4-1 [Jones, Genetics, 85:12 (1977)].

Expression and cloning vectors usually contain a promoter operably linked to the PRO-encoding nucleic acid sequence to direct mRNA synthesis. Promoters recognized by a variety of potential host cells are well known. Promoters suitable for use with prokaryotic hosts include the β -lactamase and lactose promoter systems [Chang et al., Nature, 275:615 (1978); Goeddel et al., Nature, 281:544 (1979)], alkaline phosphatase, a tryptophan (*trp*) promoter system [Goeddel, Nucleic Acids Res., 8:4057 (1980); EP 36,776], and hybrid promoters such as the tac promoter [deBoer et al., Proc. Natl. Acad. Sci. USA, 80:21-25 (1983)]. Promoters for use in bacterial systems also will contain a Shine-Dalgarno (S.D.) sequence operably linked to the DNA encoding PRO.

Examples of suitable promoting sequences for use with yeast hosts include the promoters for 3-phosphoglycerate kinase [Hitzeman et al., *J. Biol. Chem.*, 255:2073 (1980)] or other glycolytic enzymes [Hess et al., *J. Adv. Enzyme Reg.*, 7:149 (1968); Holland, *Biochemistry*, 17:4900 (1978)], such as enolase, glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose isomerase, and glucokinase.

Other yeast promoters, which are inducible promoters having the additional advantage of transcription controlled by growth conditions, are the promoter regions for alcohol dehydrogenase 2, isocytochrome C, acid phosphatase, degradative enzymes associated with nitrogen metabolism, metallothionein, glyceraldehyde-3-phosphate dehydrogenase, and enzymes responsible for maltose and galactose utilization. Suitable vectors and promoters for use in yeast expression are further described in EP 73,657.

PRO transcription from vectors in mammalian host cells is controlled, for example, by promoters obtained from the genomes of viruses such as polyoma virus, fowlpox virus (UK 2,211,504 published 5 July 1989), adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, a retrovirus, hepatitis-B virus and Simian Virus 40 (SV40), from heterologous mammalian promoters, e.g., the actin promoter or an immunoglobulin promoter, and from heat-shock promoters, provided such promoters are compatible with the host cell systems.

Transcription of a DNA encoding the PRO by higher eukaryotes may be increased by inserting an enhancer sequence into the vector. Enhancers are cis-acting elements of DNA, usually about from 10 to 300 bp, that act on a promoter to increase its transcription. Many enhancer sequences are now known from mammalian genes (globin, elastase, albumin, α -fetoprotein, and insulin). Typically, however, one will use an enhancer from a eukaryotic cell virus. Examples include the SV40 enhancer on the late side of the replication origin (bp 100-270), the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers. The enhancer may be spliced into the vector at a position 5' or 3' to the PRO coding sequence, but is preferably located at a site 5' from the promoter.

Expression vectors used in eukaryotic host cells (yeast, fungi, insect, plant, animal, human, or nucleated cells from other multicellular organisms) will also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from the 5' and, occasionally 3', untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA encoding PRO.

Still other methods, vectors, and host cells suitable for adaptation to the synthesis of PRO in recombinant vertebrate cell culture are described in Gething et al., *Nature*, 293:620-625 (1981); Mantei et al., *Nature*, 281:40-46 (1979); EP 117,060; and EP 117,058.

4. Detecting Gene Amplification/Expression

Gene amplification and/or expression may be measured in a sample directly, for example, by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA [Thomas, Proc. Natl. Acad. Sci. USA, 77:5201-5205 (1980)], dot blotting (DNA analysis), or *in situ* hybridization, using an appropriately labeled probe, based on the sequences provided herein. Alternatively, antibodies may be employed that can recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes. The antibodies in turn may be labeled and the assay may be carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of antibody bound to the duplex can be detected.

Gene expression, alternatively, may be measured by immunological methods, such as immunohistochemical staining of cells or tissue sections and assay of cell culture or body fluids, to quantitate directly the expression of gene product. Antibodies useful for immunohistochemical staining and/or assay of sample fluids may be either monoclonal or polyclonal, and may be prepared in any mammal. Conveniently, the antibodies may be prepared against a native sequence PRO polypeptide or against a synthetic peptide based on the DNA sequences provided herein or against exogenous sequence fused to PRO DNA and encoding a specific antibody epitope.

5. Purification of Polypeptide

Forms of PRO may be recovered from culture medium or from host cell lysates. If membrane-bound, it can be released from the membrane using a suitable detergent solution (e.g. Triton-X 100) or by enzymatic cleavage. Cells employed in expression of PRO can be disrupted by various physical or chemical means, such as freeze-thaw cycling, sonication, mechanical disruption, or cell lysing agents.

It may be desired to purify PRO from recombinant cell proteins or polypeptides. The following procedures are exemplary of suitable purification procedures: by fractionation on an ion-exchange column; ethanol precipitation; reverse phase HPLC; chromatography on silica or on a cation-exchange resin such as DEAE; chromatofocusing; SDS-PAGE; ammonium sulfate precipitation; gel filtration using, for example, Sephadex G-75; protein A Sepharose columns to remove contaminants such as IgG; and metal chelating columns to bind epitope-tagged forms of the PRO. Various methods of protein purification may be employed and such methods are known in the art and described for example in Deutscher, Methods in Enzymology, 182 (1990); Scopes, Protein Purification: Principles and Practice, Springer-Verlag, New York (1982). The purification step(s) selected will depend, for example, on the nature of the production process used and the particular PRO produced.

E. Tissue Distribution

The location of tissues expressing the PRO can be identified by determining mRNA expression in various human tissues. The location of such genes provides information about which tissues are most likely to be affected by the stimulating and inhibiting activities of the PRO polypeptides. The location of a gene in a specific tissue also provides sample tissue for the activity blocking assays discussed below.

As noted before, gene expression in various tissues may be measured by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA (Thomas, *Proc. Natl. Acad. Sci. USA*,

77:5201-5205 [1980]), dot blotting (DNA analysis), or *in situ* hybridization, using an appropriately labeled probe, based on the sequences provided herein. Alternatively, antibodies may be employed that can recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes.

5 Gene expression in various tissues, alternatively, may be measured by immunological methods, such as immunohistochemical staining of tissue sections and assay of cell culture or body fluids, to quantitate directly the expression of gene product. Antibodies useful for immunohistochemical staining and/or assay of sample fluids may be either monoclonal or polyclonal, and may be prepared in any mammal. Conveniently, the antibodies may be prepared against a native sequence of a PRO polypeptide
10 or against a synthetic peptide based on the DNA sequences encoding the PRO polypeptide or against an exogenous sequence fused to a DNA encoding a PRO polypeptide and encoding a specific antibody epitope. General techniques for generating antibodies, and special protocols for Northern blotting and *in situ* hybridization are provided below.

F. Antibody Binding Studies

15 The activity of the PRO polypeptides can be further verified by antibody binding studies, in which the ability of anti-PRO antibodies to inhibit the effect of the PRO polypeptides, respectively, on tissue cells is tested. Exemplary antibodies include polyclonal, monoclonal, humanized, bispecific, and heteroconjugate antibodies, the preparation of which will be described hereinbelow.

 Antibody binding studies may be carried out in any known assay method, such as competitive
20 binding assays, direct and indirect sandwich assays, and immunoprecipitation assays. Zola, *Monoclonal Antibodies: A Manual of Techniques*, pp.147-158 (CRC Press, Inc., 1987).

 Competitive binding assays rely on the ability of a labeled standard to compete with the test
sample analyte for binding with a limited amount of antibody. The amount of target protein in the test sample is inversely proportional to the amount of standard that becomes bound to the antibodies. To
25 facilitate determining the amount of standard that becomes bound, the antibodies preferably are insolubilized before or after the competition, so that the standard and analyte that are bound to the antibodies may conveniently be separated from the standard and analyte which remain unbound.

 Sandwich assays involve the use of two antibodies, each capable of binding to a different immunogenic portion, or epitope, of the protein to be detected. In a sandwich assay, the test sample
30 analyte is bound by a first antibody which is immobilized on a solid support, and thereafter a second antibody binds to the analyte, thus forming an insoluble three-part complex. See, *e.g.*, US Pat No. 4,376,110. The second antibody may itself be labeled with a detectable moiety (direct sandwich assays) or may be measured using an anti-immunoglobulin antibody that is labeled with a detectable moiety (indirect sandwich assay). For example, one type of sandwich assay is an ELISA assay, in which case the
35 detectable moiety is an enzyme.

 For immunohistochemistry, the tissue sample may be fresh or frozen or may be embedded in paraffin and fixed with a preservative such as formalin, for example.

G. Cell-Based Assays

Cell-based assays and animal models for immune related diseases can be used to further understand the relationship between the genes and polypeptides identified herein and the development and pathogenesis of immune related disease.

5 In a different approach, cells of a cell type known to be involved in a particular immune related disease are transfected with the cDNAs described herein, and the ability of these cDNAs to stimulate or inhibit immune function is analyzed. Suitable cells can be transfected with the desired gene, and monitored for immune function activity. Such transfected cell lines can then be used to test the ability of poly- or monoclonal antibodies or antibody compositions to inhibit or stimulate immune function, for
10 example to modulate T-cell proliferation or inflammatory cell infiltration. Cells transfected with the coding sequences of the genes identified herein can further be used to identify drug candidates for the treatment of immune related diseases.

In addition, primary cultures derived from transgenic animals (as described below) can be used in the cell-based assays herein, although stable cell lines are preferred. Techniques to derive continuous cell
15 lines from transgenic animals are well known in the art (see, *e.g.*, Small *et al.*, *Mol. Cell. Biol.* 5: 642-648 [1985])

An example of one suitable cell based assay is the mixed lymphocyte reaction (MLR). *Current Protocols in Immunology*, unit 3.12; edited by J E Coligan, A M Kruisbeek, D H Marglies, E M Shevach, W Strober, National Institutes of Health, Published by John Wiley & Sons, Inc. In this assay, the ability
20 of a test compound to stimulate or inhibit the proliferation of activated T cells is assayed. A suspension of responder T cells is cultured with allogeneic stimulator cells and the proliferation of T cells is measured by uptake of tritiated thymidine. This assay is a general measure of T cell reactivity. Since the majority of T cells respond to and produce IL-2 upon activation, differences in responsiveness in this assay in part reflect differences in IL-2 production by the responding cells. The MLR results can be verified by a
25 standard lymphokine (IL-2) detection assay. *Current Protocols in Immunology*, above, 3.15, 6.3.

Direct use of a stimulating compound as in the invention has been validated in experiments with 4-1BB glycoprotein, a member of the tumor necrosis factor receptor family, which binds to a ligand (4-1BBL) expressed on primed T cells and signals T cell activation and growth. Alderson, M. E. *et al.*, *J. Immunol.* (1994) 24:2219.

30 The use of an agonist stimulating compound has also been validated experimentally. Activation of 4-1BB by treatment with an agonist anti-4-1BB antibody enhances eradication of tumors. Hellstrom, I. and Hellstrom, K. E., *Crit. Rev. Immunol.* (1998) 18:1. Immunoadjuvant therapy for treatment of tumors, described in more detail below, is another example of the use of the stimulating compounds of the invention.

35 Alternatively, an immune stimulating or enhancing effect can also be achieved by administration of a PRO which has vascular permeability enhancing properties. Enhanced vascular permeability would be beneficial to disorders which can be attenuated by local infiltration of immune cells (*e.g.*, monocytes, eosinophils, PMNs) and inflammation.

On the other hand, PRO polypeptides, as well as other compounds of the invention, which are direct inhibitors of immune cell proliferation/activation, lymphokine secretion, and/or vascular permeability can be directly used to suppress the immune response. These compounds are useful to reduce the degree of the immune response and to treat immune related diseases characterized by a hyperactive, superoptimal, or autoimmune response such as RA. This use of the compounds of the invention has been validated by the experiments described above in which CTLA-4 binding to receptor B7 deactivates T cells. The direct inhibitory compounds of the invention function in an analogous manner. The use of compound which suppress vascular permeability would be expected to reduce inflammation. Such uses would be beneficial in treating conditions associated with excessive inflammation.

Alternatively, compounds, *e.g.*, antibodies, which bind to stimulating PRO polypeptides and block the stimulating effect of these molecules produce a net inhibitory effect and can be used to suppress the cell mediated immune response by inhibiting immune cell proliferation/activation and/or lymphokine secretion. Blocking the stimulating effect of the polypeptides suppresses the immune response of the mammal. This use has been validated in experiments using an anti-IL2 antibody. In these experiments, the antibody binds to IL-2 and blocks binding of IL-2 to its receptor thereby achieving a T cell inhibitory effect.

H. Animal Models

The results of the cell based *in vitro* assays can be further verified using *in vivo* animal models and assays for immune cell function. A variety of well known animal models can be used to further understand the role of the genes identified herein in the development and pathogenesis of immune related disease, and to test the efficacy of candidate therapeutic agents, including antibodies, and other antagonists of the native polypeptides, including small molecule antagonists. The *in vivo* nature of such models makes them predictive of responses in human patients. Animal models of immune related diseases include both non-recombinant and recombinant (transgenic) animals. Non-recombinant animal models include, for example, rodent, *e.g.*, murine models. Such models can be generated by introducing cells into syngeneic mice using standard techniques, *e.g.*, subcutaneous injection, tail vein injection, spleen implantation, intraperitoneal implantation, implantation under the renal capsule, *etc.*

Graft-versus-host disease occurs when immunocompetent cells are transplanted into immunosuppressed or tolerant patients. The donor cells recognize and respond to host antigens. The response can vary from life threatening severe inflammation to mild cases of diarrhea and weight loss. Graft-versus-host disease models provide a means of assessing immune cell reactivity against MHC antigens and minor transplant antigens. A suitable procedure is described in detail in Current Protocols in Immunology, above, unit 4.3.

An animal model for skin allograft rejection is a means of testing the ability of T cells to mediate *in vivo* tissue destruction and a measure of their role in transplant rejection. The most common and accepted models use murine tail-skin grafts. Repeated experiments have shown that skin allograft rejection is mediated by T cells, helper T cells and killer-effector T cells, and not antibodies. Auchincloss, H. Jr. and Sachs, D. H., *Fundamental Immunology*, 2nd ed., W. E. Paul ed., Raven Press,

NY, 1989, 889-992. A suitable procedure is described in detail in *Current Protocols in Immunology*, above, unit 4.4. Other transplant rejection models which can be used to test the compounds of the invention are the allogeneic heart transplant models described by Tanabe, M. *et al*, *Transplantation* (1994) 58:23 and Tinubu, S. A. *et al*, *J. Immunol.* (1994) 4330-4338.

5 An animal model for arthritis is collagen-induced arthritis. This model shares clinical, histological and immunological characteristics of human autoimmune rheumatoid arthritis and is an acceptable model for human autoimmune arthritis. Mouse and rat models are characterized by synovitis, erosion of cartilage and subchondral bone. The compounds of the invention can be tested for activity against autoimmune arthritis using the protocols described in *Current Protocols in Immunology*, above,
10 units 15.5. See also the model using a monoclonal antibody to CD18 and VLA-4 integrins described in Issekutz, A.C. *et al.*, *Immunology* (1996) 88:569.

Recombinant (transgenic) animal models can be engineered by introducing the coding portion of the genes identified herein into the genome of animals of interest, using standard techniques for producing transgenic animals. Animals that can serve as a target for transgenic manipulation include, without
15 limitation, mice, rats, rabbits, guinea pigs, sheep, goats, pigs, and non-human primates, *e.g.*, baboons, chimpanzees and monkeys. Techniques known in the art to introduce a transgene into such animals include pronucleic microinjection (Hoppe and Wanger, U.S. Patent No. 4,873,191); retrovirus-mediated gene transfer into germ lines (*e.g.*, Van der Putten *et al.*, *Proc. Natl. Acad. Sci. USA* 82, 6148-615 [1985]); gene targeting in embryonic stem cells (Thompson *et al.*, *Cell* 56, 313-321 [1989]);
20 electroporation of embryos (Lo, *Mol. Cel. Biol.* 3, 1803-1814 [1983]); sperm-mediated gene transfer (Lavitrano *et al.*, *Cell* 57, 717-73 [1989]). For review, see, for example, U.S. Patent No. 4,736,866.

For the purpose of the present invention, transgenic animals include those that carry the transgene only in part of their cells ("mosaic animals"). The transgene can be integrated either as a single transgene, or in concatamers, *e.g.*, head-to-head or head-to-tail tandems. Selective introduction of a transgene into a
25 particular cell type is also possible by following, for example, the technique of Lasko *et al.*, *Proc. Natl. Acad. Sci. USA* 89, 6232-636 (1992).

The expression of the transgene in transgenic animals can be monitored by standard techniques. For example, Southern blot analysis or PCR amplification can be used to verify the integration of the transgene. The level of mRNA expression can then be analyzed using techniques such as *in situ*
30 hybridization, Northern blot analysis, PCR, or immunocytochemistry.

The animals may be further examined for signs of immune disease pathology, for example by histological examination to determine infiltration of immune cells into specific tissues. Blocking experiments can also be performed in which the transgenic animals are treated with the compounds of the invention to determine the extent of the immune cell proliferation/stimulation or inhibition of the
35 compounds. In these experiments, blocking antibodies which bind to the PRO polypeptide, prepared as described above, are administered to the animal and the effect on immune function is determined.

Alternatively, "knock out" animals can be constructed which have a defective or altered gene encoding a polypeptide identified herein, as a result of homologous recombination between the endogenous

gene encoding the polypeptide and altered genomic DNA encoding the same polypeptide introduced into an embryonic cell of the animal. For example, cDNA encoding a particular polypeptide can be used to clone genomic DNA encoding that polypeptide in accordance with established techniques. A portion of the genomic DNA encoding a particular polypeptide can be deleted or replaced with another gene, such as a gene encoding a selectable marker which can be used to monitor integration. Typically, several kilobases of unaltered flanking DNA (both at the 5' and 3' ends) are included in the vector [see *e.g.*, Thomas and Capecchi, *Cell*, 51:503 (1987) for a description of homologous recombination vectors]. The vector is introduced into an embryonic stem cell line (*e.g.*, by electroporation) and cells in which the introduced DNA has homologously recombined with the endogenous DNA are selected [see *e.g.*, Li *et al.*, *Cell*, 69:915 (1992)]. The selected cells are then injected into a blastocyst of an animal (*e.g.*, a mouse or rat) to form aggregation chimeras [see *e.g.*, Bradley, in *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, E. J. Robertson, ed. (IRL, Oxford, 1987), pp. 113-152]. A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term to create a "knock out" animal. Progeny harboring the homologously recombined DNA in their germ cells can be identified by standard techniques and used to breed animals in which all cells of the animal contain the homologously recombined DNA. Knockout animals can be characterized for instance, for their ability to defend against certain pathological conditions and for their development of pathological conditions due to absence of the polypeptide.

I. ImmunoAdjuvant Therapy

In one embodiment, the immunostimulating compounds of the invention can be used in immunoadjuvant therapy for the treatment of tumors (cancer). It is now well established that immune cells recognize human tumor specific antigens. One group of tumor antigens, encoded by the MAGE, BAGE and GAGE families of genes, are silent in all adult normal tissues, but are expressed in significant amounts in tumors, such as melanomas, lung tumors, head and neck tumors, and bladder carcinomas. DeSmet, C. *et al.*, (1996) *Proc. Natl. Acad. Sci. USA*, 93:7149. It has been shown that costimulation of T cells induces tumor regression and an antitumor response both *in vitro* and *in vivo*. Melero, I. *et al.*, *Nature Medicine* (1997) 3:682; Kwon, E. D. *et al.*, *Proc. Natl. Acad. Sci. USA* (1997) 94: 8099; Lynch, D. H. *et al.*, *Nature Medicine* (1997) 3:625; Finn, O. J. and Lotze, M. T., *J. Immunol.* (1998) 21:114. The stimulatory compounds of the invention can be administered as adjuvants, alone or together with a growth regulating agent, cytotoxic agent or chemotherapeutic agent, to stimulate immune cell proliferation/activation and an antitumor response to tumor antigens. The growth regulating, cytotoxic, or chemotherapeutic agent may be administered in conventional amounts using known administration regimes. Immunostimulating activity by the compounds of the invention allows reduced amounts of the growth regulating, cytotoxic, or chemotherapeutic agents thereby potentially lowering the toxicity to the patient.

J. Screening Assays for Drug Candidates

Screening assays for drug candidates are designed to identify compounds that bind to or complex with the polypeptides encoded by the genes identified herein or a biologically active fragment thereof, or

otherwise interfere with the interaction of the encoded polypeptides with other cellular proteins. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates. Small molecules contemplated include synthetic organic or inorganic compounds, including peptides, preferably soluble peptides, (poly)peptide-immunoglobulin fusions, and, in particular, antibodies including, without limitation, poly- and monoclonal antibodies and antibody fragments, single-chain antibodies, anti-idiotypic antibodies, and chimeric or humanized versions of such antibodies or fragments, as well as human antibodies and antibody fragments. The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays and cell based assays, which are well characterized in the art. All assays are common in that they call for contacting the drug candidate with a polypeptide encoded by a nucleic acid identified herein under conditions and for a time sufficient to allow these two components to interact.

In binding assays, the interaction is binding and the complex formed can be isolated or detected in the reaction mixture. In a particular embodiment, the polypeptide encoded by the gene identified herein or the drug candidate is immobilized on a solid phase, *e.g.*, on a microtiter plate, by covalent or non-covalent attachments. Non-covalent attachment generally is accomplished by coating the solid surface with a solution of the polypeptide and drying. Alternatively, an immobilized antibody, *e.g.*, a monoclonal antibody, specific for the polypeptide to be immobilized can be used to anchor it to a solid surface. The assay is performed by adding the non-immobilized component, which may be labeled by a detectable label, to the immobilized component, *e.g.*, the coated surface containing the anchored component. When the reaction is complete, the non-reacted components are removed, *e.g.*, by washing, and complexes anchored on the solid surface are detected. When the originally non-immobilized component carries a detectable label, the detection of label immobilized on the surface indicates that complexing occurred. Where the originally non-immobilized component does not carry a label, complexing can be detected, for example, by using a labelled antibody specifically binding the immobilized complex.

If the candidate compound interacts with but does not bind to a particular protein encoded by a gene identified herein, its interaction with that protein can be assayed by methods well known for detecting protein-protein interactions. Such assays include traditional approaches, such as, cross-linking, co-immunoprecipitation, and co-purification through gradients or chromatographic columns. In addition, protein-protein interactions can be monitored by using a yeast-based genetic system described by Fields and co-workers [Fields and Song, *Nature (London)* 340, 245-246 (1989); Chien *et al.*, *Proc. Natl. Acad. Sci. USA* 88, 9578-9582 (1991)] as disclosed by Chevray and Nathans, *Proc. Natl. Acad. Sci. USA* 89, 5789-5793 (1991). Many transcriptional activators, such as yeast GAL4, consist of two physically discrete modular domains, one acting as the DNA-binding domain, while the other one functioning as the transcription activation domain. The yeast expression system described in the foregoing publications (generally referred to as the "two-hybrid system") takes advantage of this property, and employs two hybrid proteins, one in which the target protein is fused to the DNA-binding domain of GAL4, and another, in which candidate activating proteins are fused to the activation domain. The expression of a

GAL1-*lacZ* reporter gene under control of a GAL4-activated promoter depends on reconstitution of GAL4 activity via protein-protein interaction. Colonies containing interacting polypeptides are detected with a chromogenic substrate for β -galactosidase. A complete kit (MATCHMAKER™) for identifying protein-protein interactions between two specific proteins using the two-hybrid technique is commercially available from Clontech. This system can also be extended to map protein domains involved in specific protein interactions as well as to pinpoint amino acid residues that are crucial for these interactions.

In order to find compounds that interfere with the interaction of a gene identified herein and other intra- or extracellular components can be tested, a reaction mixture is usually prepared containing the product of the gene and the intra- or extracellular component under conditions and for a time allowing for the interaction and binding of the two products. To test the ability of a test compound to inhibit binding, the reaction is run in the absence and in the presence of the test compound. In addition, a placebo may be added to a third reaction mixture, to serve as positive control. The binding (complex formation) between the test compound and the intra- or extracellular component present in the mixture is monitored as described above. The formation of a complex in the control reaction(s) but not in the reaction mixture containing the test compound indicates that the test compound interferes with the interaction of the test compound and its reaction partner.

K. Compositions and Methods for the Treatment of Immune Related Diseases

The compositions useful in the treatment of immune related diseases include, without limitation, proteins, antibodies, small organic molecules, peptides, phosphopeptides, antisense and ribozyme molecules, triple helix molecules, *etc.* that inhibit or stimulate immune function, for example, immune cell proliferation/activation, lymphokine release, or immune cell infiltration.

For example, antisense RNA and RNA molecules act to directly block the translation of mRNA by hybridizing to targeted mRNA and preventing protein translation. When antisense DNA is used, oligodeoxyribonucleotides derived from the translation initiation site, *e.g.*, between about -10 and +10 positions of the target gene nucleotide sequence, are preferred.

Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. Ribozymes act by sequence-specific hybridization to the complementary target RNA, followed by endonucleolytic cleavage. Specific ribozyme cleavage sites within a potential RNA target can be identified by known techniques. For further details see, *e.g.*, Rossi, *Current Biology* 4, 469-471 (1994), and PCT publication No. WO 97/33551 (published September 18, 1997).

Nucleic acid molecules in triple helix formation used to inhibit transcription should be single-stranded and composed of deoxynucleotides. The base composition of these oligonucleotides is designed such that it promotes triple helix formation via Hoogsteen base pairing rules, which generally require sizeable stretches of purines or pyrimidines on one strand of a duplex. For further details see, *e.g.*, PCT publication No. WO 97/33551, *supra*.

These molecules can be identified by any or any combination of the screening assays discussed above and/or by any other screening techniques well known for those skilled in the art.

L. Anti-PRO Antibodies

The present invention further provides anti-PRO antibodies. Exemplary antibodies include polyclonal, monoclonal, humanized, bispecific, and heteroconjugate antibodies.

1. Polyclonal Antibodies

5 The anti-PRO antibodies may comprise polyclonal antibodies. Methods of preparing polyclonal antibodies are known to the skilled artisan. Polyclonal antibodies can be raised in a mammal, for example, by one or more injections of an immunizing agent and, if desired, an adjuvant. Typically, the immunizing agent and/or adjuvant will be injected in the mammal by multiple subcutaneous or intraperitoneal injections. The immunizing agent may include the PRO polypeptide or a fusion protein
10 thereof. It may be useful to conjugate the immunizing agent to a protein known to be immunogenic in the mammal being immunized. Examples of such immunogenic proteins include but are not limited to keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, and soybean trypsin inhibitor. Examples of adjuvants which may be employed include Freund's complete adjuvant and MPL-TDM adjuvant (monophosphoryl Lipid A, synthetic trehalose dicorynomycolate). The immunization protocol
15 may be selected by one skilled in the art without undue experimentation.

2. Monoclonal Antibodies

The anti-PRO antibodies may, alternatively, be monoclonal antibodies. Monoclonal antibodies may be prepared using hybridoma methods, such as those described by Kohler and Milstein, Nature, 256:495 (1975). In a hybridoma method, a mouse, hamster, or other appropriate host animal, is typically
20 immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes may be immunized *in vitro*.

The immunizing agent will typically include the PRO polypeptide or a fusion protein thereof. Generally, either peripheral blood lymphocytes ("PBLs") are used if cells of human origin are desired, or
25 spleen cells or lymph node cells are used if non-human mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell [Goding, Monoclonal Antibodies: Principles and Practice, Academic Press, (1986) pp. 59-103]. Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine and human origin. Usually, rat or mouse myeloma cell lines are employed. The
30 hybridoma cells may be cultured in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine ("HAT medium"), which substances prevent the growth of HGPRT-deficient cells.

35 Preferred immortalized cell lines are those that fuse efficiently, support stable high level expression of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. More preferred immortalized cell lines are murine myeloma lines, which can be obtained, for instance, from the Salk Institute Cell Distribution Center, San Diego, California and the American

Type Culture Collection, Manassas, Virginia. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies [Kozbor, J. Immunol., 133:3001 (1984); Brodeur et al., Monoclonal Antibody Production Techniques and Applications, Marcel Dekker, Inc., New York, (1987) pp. 51-63].

5 The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of monoclonal antibodies directed against PRO. Preferably, the binding specificity of monoclonal antibodies produced by the hybridoma cells is determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA).

Such techniques and assays are known in the art. The binding affinity of the monoclonal antibody can, 10 for example, be determined by the Scatchard analysis of Munson and Pollard, Anal. Biochem., 107:220 (1980).

After the desired hybridoma cells are identified, the clones may be subcloned by limiting dilution procedures and grown by standard methods [Goding, supra]. Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the 15 hybridoma cells may be grown *in vivo* as ascites in a mammal.

The monoclonal antibodies secreted by the subclones may be isolated or purified from the culture medium or ascites fluid by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

20 The monoclonal antibodies may also be made by recombinant DNA methods, such as those described in U.S. Patent No. 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies).

The hybridoma cells of the invention serve as a preferred source of such DNA. Once isolated, the DNA 25 may be placed into expression vectors, which are then transfected into host cells such as simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also may be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains in place of the homologous murine sequences [U.S. Patent No. 4,816,567; Morrison et al., supra] or by covalently joining to the immunoglobulin coding sequence all or part of the coding 30 sequence for a non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of an antibody of the invention, or can be substituted for the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent antibody.

35 The antibodies may be monovalent antibodies. Methods for preparing monovalent antibodies are well known in the art. For example, one method involves recombinant expression of immunoglobulin light chain and modified heavy chain. The heavy chain is truncated generally at any point in the Fc region

so as to prevent heavy chain crosslinking. Alternatively, the relevant cysteine residues are substituted with another amino acid residue or are deleted so as to prevent crosslinking.

In vitro methods are also suitable for preparing monovalent antibodies. Digestion of antibodies to produce fragments thereof, particularly, Fab fragments, can be accomplished using routine techniques

known in the art.

3. Human and Humanized Antibodies

The anti-PRO antibodies of the invention may further comprise humanized antibodies or human antibodies. Humanized forms of non-human (e.g., murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')₂ or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin [Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-329 (1988); and Presta, Curr. Op. Struct. Biol., 2:593-596 (1992)].

Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers [Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-327 (1988); Verhoeyen et al., Science, 239:1534-1536 (1988)], by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Patent No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

Human antibodies can also be produced using various techniques known in the art, including phage display libraries [Hoogenboom and Winter, J. Mol. Biol., 227:381 (1991); Marks et al., J. Mol. Biol., 222:581 (1991)]. The techniques of Cole et al. and Boerner et al. are also available for the preparation of human monoclonal antibodies (Cole et al., Monoclonal Antibodies and Cancer Therapy,

Alan R. Liss, p. 77 (1985) and Boerner et al., *J. Immunol.*, 147(1):86-95 (1991)]. Similarly, human antibodies can be made by introducing of human immunoglobulin loci into transgenic animals, e.g., mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed, which closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach is described, for example, in U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, and in the following scientific publications: Marks *et al.*, *Bio/Technology* 10, 779-783 (1992); Lonberg *et al.*, *Nature* 368 856-859 (1994); Morrison, *Nature* 368, 812-13 (1994); Fishwild *et al.*, *Nature Biotechnology* 14, 845-51 (1996); Neuberger, *Nature Biotechnology* 14, 826 (1996); Lonberg and Huszar, *Intern. Rev. Immunol.* 13 65-93 (1995).

The antibodies may also be affinity matured using known selection and/or mutagenesis methods as described above. Preferred affinity matured antibodies have an affinity which is five times, more preferably 10 times, even more preferably 20 or 30 times greater than the starting antibody (generally murine, humanized or human) from which the matured antibody is prepared.

4. Bispecific Antibodies

Bispecific antibodies are monoclonal, preferably human or humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for the PRO, the other one is for any other antigen, and preferably for a cell-surface protein or receptor or receptor subunit.

Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy-chain/light-chain pairs, where the two heavy chains have different specificities [Milstein and Cuello, *Nature*, 305:537-539 (1983)]. Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of ten different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule is usually accomplished by affinity chromatography steps. Similar procedures are disclosed in WO 93/08829, published 13 May 1993, and in Traunecker et al., *EMBO J.*, 10:3655-3659 (1991).

Antibody variable domains with the desired binding specificities (antibody-antigen combining sites) can be fused to immunoglobulin constant domain sequences. The fusion preferably is with an immunoglobulin heavy-chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It is preferred to have the first heavy-chain constant region (CH1) containing the site necessary for light-chain binding present in at least one of the fusions. DNAs encoding the immunoglobulin heavy-chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism. For further details of generating bispecific antibodies see, for example, Suresh et al., *Methods in Enzymology*, 121:210 (1986).

According to another approach described in WO 96/27011, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant cell culture. The preferred interface comprises at least a part of the CH3 region of an

antibody constant domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (e.g. tyrosine or tryptophan).

Compensatory "cavities" of identical or similar size to the large side chain(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (e.g. alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

Bispecific antibodies can be prepared as full length antibodies or antibody fragments (e.g. F(ab')₂ bispecific antibodies). Techniques for generating bispecific antibodies from antibody fragments have been described in the literature. For example, bispecific antibodies can be prepared using chemical linkage. Brennan *et al.*, Science 229:81 (1985) describe a procedure wherein intact antibodies are proteolytically cleaved to generate F(ab')₂ fragments. These fragments are reduced in the presence of the dithiol complexing agent sodium arsenite to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

Fab' fragments may be directly recovered from *E. coli* and chemically coupled to form bispecific antibodies. Shalaby *et al.*, J. Exp. Med. 175:217-225 (1992) describe the production of a fully humanized bispecific antibody F(ab')₂ molecule. Each Fab' fragment was separately secreted from *E. coli* and subjected to directed chemical coupling *in vitro* to form the bispecific antibody. The bispecific antibody thus formed was able to bind to cells overexpressing the ErbB2 receptor and normal human T cells, as well as trigger the lytic activity of human cytotoxic lymphocytes against human breast tumor targets.

Various technique for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. Kostelny *et al.*, J. Immunol. 148(5):1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody homodimers. The "diabody" technology described by Hollinger *et al.*, Proc. Natl. Acad. Sci. USA 90:6444-6448 (1993) has provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the V_H and V_L domains of one fragment are forced to pair with the complementary V_L and V_H domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. See, Gruber *et al.*, J. Immunol. 152:5368 (1994).

Antibodies with more than two valencies are contemplated. For example, trispecific antibodies can be prepared. Tutt *et al.*, J. Immunol. 147:60 (1991).

Exemplary bispecific antibodies may bind to two different epitopes on a given PRO polypeptide herein. Alternatively, an anti-PRO polypeptide arm may be combined with an arm which binds to a triggering molecule on a leukocyte such as a T-cell receptor molecule (e.g. CD2, CD3, CD28, or B7), or Fc receptors for IgG (FcγR), such as FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16) so as to focus cellular defense mechanisms to the cell expressing the particular PRO polypeptide. Bispecific antibodies may also be used to localize cytotoxic agents to cells which express a particular PRO polypeptide. These antibodies possess a PRO-binding arm and an arm which binds a cytotoxic agent or a radionuclide chelator, such as EOTUBE, DPTA, DOTA, or TETA. Another bispecific antibody of interest binds the PRO polypeptide and further binds tissue factor (TF).

5. Heteroconjugate Antibodies

Heteroconjugate antibodies are also within the scope of the present invention. Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells [U.S. Patent No. 4,676,980], and for treatment of HIV infection [WO 91/00360; WO 92/200373; EP 03089]. It is contemplated that the antibodies may be prepared *in vitro* using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins may be constructed using a disulfide exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptobutyrimidate and those disclosed, for example, in U.S. Patent No. 4,676,980.

6. Effector Function Engineering

It may be desirable to modify the antibody of the invention with respect to effector function, so as to enhance, *e.g.*, the effectiveness of the antibody in treating cancer. For example, cysteine residue(s) may be introduced into the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated may have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). See Caron *et al.*, J. Exp Med., 176: 1191-1195 (1992) and Shopes, J. Immunol., 148: 2918-2922 (1992). Homodimeric antibodies with enhanced anti-tumor activity may also be prepared using heterobifunctional cross-linkers as described in Wolff *et al.* Cancer Research, 53: 2560-2565 (1993). Alternatively, an antibody can be engineered that has dual Fc regions and may thereby have enhanced complement lysis and ADCC capabilities. See Stevenson *et al.*, Anti-Cancer Drug Design, 3: 219-230 (1989).

7. Immunoconjugates

The invention also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a chemotherapeutic agent, toxin (*e.g.*, an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (*i.e.*, a radioconjugate).

Chemotherapeutic agents useful in the generation of such immunoconjugates have been described above. Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin

A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolacca americana* proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes. A variety of radionuclides are available for the production of radioconjugated antibodies.

5 Examples include ^{212}Bi , ^{131}I , ^{131}In , ^{90}Y , and ^{186}Re .

Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-
10 ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta *et al.*, *Science*, 238: 1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of
15 radionucleotide to the antibody. See WO94/11026.

In another embodiment, the antibody may be conjugated to a "receptor" (such streptavidin) for utilization in tumor pretargeting wherein the antibody-receptor conjugate is administered to the patient, followed by removal of unbound conjugate from the circulation using a clearing agent and then administration of a "ligand" (*e.g.*, avidin) that is conjugated to a cytotoxic agent (*e.g.*, a radionucleotide).

20 8. Immunoliposomes

The antibodies disclosed herein may also be formulated as immunoliposomes. Liposomes containing the antibody are prepared by methods known in the art, such as described in Epstein *et al.*, *Proc. Natl. Acad. Sci. USA*, 82: 3688 (1985); Hwang *et al.*, *Proc. Natl. Acad. Sci. USA*, 77: 4030 (1980); and U.S. Pat. Nos. 4,485,045 and 4,544,545. Liposomes with enhanced circulation time are
25 disclosed in U.S. Patent No. 5,013,556.

Particularly useful liposomes can be generated by the reverse-phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol, and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of the antibody of the present invention can be
30 conjugated to the liposomes as described in Martin *et al.*, *J. Biol. Chem.*, 257: 286-288 (1982) via a disulfide-interchange reaction. A chemotherapeutic agent (such as Doxorubicin) is optionally contained within the liposome. See Gabizon *et al.*, *J. National Cancer Inst.*, 81(19): 1484 (1989).

M. Pharmaceutical Compositions

The active PRO molecules of the invention (*e.g.*, PRO polypeptides, anti-PRO antibodies, and/or
35 variants of each) as well as other molecules identified by the screening assays disclosed above, can be administered for the treatment of immune related diseases, in the form of pharmaceutical compositions.

Therapeutic formulations of the active PRO molecule, preferably a polypeptide or antibody of the invention, are prepared for storage by mixing the active molecule having the desired degree of purity with

optional pharmaceutically acceptable carriers, excipients or stabilizers (*Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. [1980]), in the form of lyophilized formulations or aqueous solutions.

Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (*e.g.*, Zn-protein complexes); and/or non-ionic surfactants such as TWEENTM, PLURONICSTM or polyethylene glycol (PEG).

Compounds identified by the screening assays disclosed herein can be formulated in an analogous manner, using standard techniques well known in the art.

Lipofections or liposomes can also be used to deliver the PRO molecule into cells. Where antibody fragments are used, the smallest inhibitory fragment which specifically binds to the binding domain of the target protein is preferred. For example, based upon the variable region sequences of an antibody, peptide molecules can be designed which retain the ability to bind the target protein sequence. Such peptides can be synthesized chemically and/or produced by recombinant DNA technology (see, *e.g.*, Marasco *et al.*, *Proc. Natl. Acad. Sci. USA* 90, 7889-7893 [1993]).

The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Alternatively, or in addition, the composition may comprise a cytotoxic agent, cytokine or growth inhibitory agent. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

The active PRO molecules may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in *Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980).

The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

Sustained-release preparations of the PRO molecules may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, *e.g.*, films, or microcapsules. Examples

of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and γ -ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOTTM (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated antibodies remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37°C, resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for stabilization depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond formation through thio-disulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

N. Methods of Treatment

It is contemplated that the polypeptides, antibodies and other active compounds of the present invention may be used to treat various immune related diseases and conditions, such as immune cell mediated diseases, including those characterized by infiltration of inflammatory cells into a tissue, stimulation of immune cell proliferation, inhibition of immune-cell proliferation, increased or decreased vascular permeability or the inhibition thereof.

Exemplary conditions or disorders to be treated with the polypeptides, antibodies and other compounds of the invention, include, but are not limited to: systemic lupus erythematosus, rheumatoid arthritis, osteoarthritis, juvenile chronic arthritis, spondyloarthropathies, systemic sclerosis, idiopathic inflammatory myopathies, Sjögren's syndrome, systemic vasculitis, sarcoidosis, autoimmune hemolytic anemia, autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis, lymphadenopathy, splenomegaly and leukopenia.

Systemic Lupus erythematosus (SLE) is an autoimmune inflammatory connective tissue disease with variable symptomatology including fever, joint pains or arthritis resembling rheumatoid arthritis, erythematous skin lesions on the face, neck and upper torso. Cases that are more severe may include liquefaction degeneration of the basal layer and epidermal atrophy. For the past 30 years, cyclophosphamide has been used to treat SLE. Cyclophosphamide however, generally inhibits inflammation and has many side effects. Improvements in the understanding of the molecular events involved in the progression of SLE have lead to the trial of new therapeutic agents with less side effects and more efficacy due to the specific targeting of identified components of SLE. Therapeutics that are immunosuppressive are Mycophenolate mofetilTM (MMF), LeflunomideTM and TacrolimusTM (FK506). These molecules have a suppressive effect on the immune system, and in limited trials, have had fewer and less severe side effects than cyclophosphamide. Biological therapies such as RituxanTM, anti-C5b, anti-CD40L, anti-BLYS and anti-IL10, are all antibody therapies that have few side effects and target one specific molecule or pathway that is believed to be significant in the progression of SLE. Rituxan, for

example, has been used to deplete B cells in SLE patients, and this correlated with improvements in arthritis, rash and fatigue. The biological therapies also have the advantage of being well tolerated, and can be used in combination with established agents such as cyclophosphamide. In the most severe cases of SLE, hematopoietic stem cell replacement has caused remission in SLE patients, but the long-term results of these cell transplantations has not yet been determined. While cyclophosphamide has remained the major drug treatment of choice for SLE, the new therapies discussed herein that target specific aspects of SLE which may be the major affliction for that particular patient show great promise. The wider range of treatments now in development may mean improved control of this disease.

Transplantation associated diseases, including Graft rejection and Graft-Versus-Host-Disease (GVHD) are immune cell dependent; inhibition of immune cell function is ameliorative.

Other diseases in which intervention of the immune and/or inflammatory response have benefit are infectious disease including but not limited to viral infection (including but not limited to AIDS, hepatitis A, B, C, D, E and herpes) bacterial infection, fungal infections, and protozoal and parasitic infections. Molecules (or derivatives/agonists) which stimulate the immune cell can be utilized therapeutically to enhance the immune response to infectious agents, diseases of immunodeficiency (molecules/derivatives/agonists) which stimulate the immune cell can be utilized therapeutically to enhance the immune response for conditions of inherited, acquired, infectious induced (as in HIV infection), or iatrogenic (*i.e.*, as from chemotherapy) immunodeficiency, and neoplasia.

It has been demonstrated that some human cancer patients develop an antibody and/or immune cell response to antigens on neoplastic cells. It has also been shown in animal models of neoplasia that enhancement of the immune response can result in rejection or regression of that particular neoplasm. Molecules that enhance the immune cell response have utility *in vivo* in enhancing the immune response against neoplasia. Molecules which enhance the immune cell proliferative response (or small molecule agonists or antibodies that affected the same receptor in an agonistic fashion) can be used therapeutically to treat cancer. Molecules that inhibit the immune response also function *in vivo* during neoplasia to suppress the immune response to a neoplasm; such molecules can either be expressed by the neoplastic cells themselves or their expression can be induced by the neoplasm in other cells. Antagonism of such inhibitory molecules (either with antibody, small molecule antagonists or other means) enhances immune-mediated tumor rejection.

Additionally, inhibition of molecules with proinflammatory properties may have therapeutic benefit in reperfusion injury; stroke; myocardial infarction; atherosclerosis; acute lung injury; hemorrhagic shock; burn; sepsis/septic shock; acute tubular necrosis; endometriosis; degenerative joint disease and pancreatitis.

The compounds of the present invention, *e.g.*, polypeptides or antibodies, are administered to a mammal, preferably a human, in accord with known methods, such as intravenous administration as a bolus or by continuous infusion over a period of time, by intramuscular, intraperitoneal, intracerebrospinal, subcutaneous, intra-articular, intrasynovial, intrathecal, oral, topical, or inhalation (intranasal, intrapulmonary) routes. Intravenous or inhaled administration of polypeptides and antibodies

is preferred.

In immunoadjuvant therapy, other therapeutic regimens, such administration of an anti-cancer agent, may be combined with the administration of the proteins, antibodies or compounds of the instant invention. For example, the patient to be treated with a the immunoadjuvant of the invention may also
5 receive an anti-cancer agent (chemotherapeutic agent) or radiation therapy. Preparation and dosing schedules for such chemotherapeutic agents may be used according to manufacturers' instructions or as determined empirically by the skilled practitioner. Preparation and dosing schedules for such chemotherapy are also described in *Chemotherapy Service* Ed., M.C. Perry, Williams & Wilkins, Baltimore, MD (1992). The chemotherapeutic agent may precede, or follow administration of the
10 immunoadjuvant or may be given simultaneously therewith. Additionally, an anti-estrogen compound such as tamoxifen or an anti-progesterone such as onapristone (see, EP 616812) may be given in dosages known for such molecules.

It may be desirable to also administer antibodies against other immune disease associated or tumor associated antigens, such as antibodies which bind to CD20, CD11a, CD18, ErbB2, EGFR, ErbB3,
15 ErbB4, or vascular endothelial factor (VEGF). Alternatively, or in addition, two or more antibodies binding the same or two or more different antigens disclosed herein may be coadministered to the patient. Sometimes, it may be beneficial to also administer one or more cytokines to the patient. In one embodiment, the PRO polypeptides are coadministered with a growth inhibitory agent. For example, the growth inhibitory agent may be administered first, followed by a PRO polypeptide. However,
20 simultaneous administration or administration first is also contemplated. Suitable dosages for the growth inhibitory agent are those presently used and may be lowered due to the combined action (synergy) of the growth inhibitory agent and the PRO polypeptide.

For the treatment or reduction in the severity of immune related disease, the appropriate dosage of an a compound of the invention will depend on the type of disease to be treated, as defined above, the
25 severity and course of the disease, whether the agent is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the compound, and the discretion of the attending physician. The compound is suitably administered to the patient at one time or over a series of treatments.

For example, depending on the type and severity of the disease, about 1 µg/kg to 15 mg/kg (*e.g.*,
30 0.1-20 mg/kg) of polypeptide or antibody is an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. A typical daily dosage might range from about 1 µg/kg to 100 mg/kg or more, depending on the factors mentioned above. For repeated administrations over several days or longer, depending on the condition, the treatment is sustained until a desired suppression of disease symptoms occurs. However, other dosage regimens may
35 be useful. The progress of this therapy is easily monitored by conventional techniques and assays.

O. Articles of Manufacture

In another embodiment of the invention, an article of manufacture containing materials (*e.g.*, comprising a PRO molecule) useful for the diagnosis or treatment of the disorders described above is

provided. The article of manufacture comprises a container and an instruction. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is effective for diagnosing or treating the condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The active agent in the composition is usually a polypeptide or an antibody of the invention. An instruction or label on, or associated with, the container indicates that the composition is used for diagnosing or treating the condition of choice. The article of manufacture may further comprise a second container comprising a pharmaceutically-acceptable buffer, such as phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, syringes, and package inserts with instructions for use.

P. Diagnosis and Prognosis of Immune Related Disease

Cell surface proteins, such as proteins which are overexpressed in certain immune related diseases, are excellent targets for drug candidates or disease treatment. The same proteins along with secreted proteins encoded by the genes amplified in immune related disease states find additional use in the diagnosis and prognosis of these diseases. For example, antibodies directed against the protein products of genes amplified in rheumatoid arthritis, or another immune related disease, can be used as diagnostics or prognostics.

For example, antibodies, including antibody fragments, can be used to qualitatively or quantitatively detect the expression of proteins encoded by amplified or overexpressed genes ("marker gene products"). The antibody preferably is equipped with a detectable, *e.g.*, fluorescent label, and binding can be monitored by light microscopy, flow cytometry, fluorimetry, or other techniques known in the art. These techniques are particularly suitable, if the overexpressed gene encodes a cell surface protein. Such binding assays are performed essentially as described above.

In situ detection of antibody binding to the marker gene products can be performed, for example, by immunofluorescence or immunoelectron microscopy. For this purpose, a histological specimen is removed from the patient, and a labeled antibody is applied to it, preferably by overlaying the antibody on a biological sample. This procedure also allows for determining the distribution of the marker gene product in the tissue examined. It will be apparent for those skilled in the art that a wide variety of histological methods are readily available for *in situ* detection.

The following examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way.

All patent and literature references cited in the present specification are hereby incorporated by reference in their entirety.

EXAMPLES

Commercially available reagents referred to in the examples were used according to manufacturer's instructions unless otherwise indicated. The source of those cells identified in the

following examples, and throughout the specification, by ATCC accession numbers is the American Type Culture Collection, Manassas, VA.

EXAMPLE 1: Microarray analysis of Systemic Lupus Erythematosus (SLE)

5 Nucleic acid microarrays, often containing thousands of gene sequences, are useful for identifying differentially expressed genes in diseased tissues as compared to their normal counterparts. Using nucleic acid microarrays, test and control mRNA samples from test and control tissue samples are reverse transcribed and labeled to generate cDNA probes. The cDNA probes are then hybridized to an array of nucleic acids immobilized on a solid support. The array is configured such that the sequence and position
10 of each member of the array is known. For example, a selection of genes known to be expressed in certain disease states may be arrayed on a solid support. Hybridization of a labeled probe with a particular array member indicates that the sample from which the probe was derived expresses that gene. If the hybridization signal of a probe from a test (in this instance, Peripheral Blood Mononuclear cells (PBMC) taken from whole blood of SLE patients) sample is greater than hybridization signal of a probe
15 from a control (in this instance, normal PBMC) sample, the gene or genes overexpressed in the test tissue are identified. The implication of this result is that an overexpressed protein in a test tissue is useful not only as a diagnostic marker for the presence of the disease condition, but also as a therapeutic target for treatment of the disease condition.

The methodology of hybridization of nucleic acids and microarray technology is well known in
20 the art. In one example, the specific preparation of nucleic acids for hybridization and probes, slides, and hybridization conditions are all detailed in PCT Patent Application Serial No. PCT/US01/10482, filed on March 30, 2001 and which is herein incorporated by reference.

A proprietary database containing gene expression information (GeneExpress®, Gene Logic Inc., Gaithersburg, MD) was analyzed in an attempt to identify polypeptides (and their encoding
25 nucleic acids) whose expression is significantly upregulated in SLE as compared to normal tissues. Specifically, analysis of the GeneExpress® database was conducted using either software available through Gene Logic Inc., Gaithersburg, MD, for use with the GeneExpress® database or with proprietary software written and developed at Genentech, Inc. for use with the GeneExpress® database. The rating of positive hits in the analysis is based upon several criteria including, for example; expression level,
30 tissue specificity, and expression level in normal essential and/or normal proliferating tissues. The following is a list of molecules whose tissue expression profile as determined from an analysis of the GeneExpress® database evidences high tissue expression and significant upregulation of expression in PBMC from SLE patients as compared to normal PBMC taken from twenty-five healthy individuals and optionally relatively low expression in normal essential and/or normal proliferating tissues. As such, the
35 molecules listed below are excellent polypeptide targets for the diagnosis and therapy for SLE in mammals.

The results of these experiments, are that Figures 1-596 are PRO polypeptides of the present invention significantly overexpressed in PBMC isolated from patients with SLE as compared to normal PBMC.

EXAMPLE 2: Use of PRO as a hybridization probe

The following method describes use of a nucleotide sequence encoding PRO as a hybridization probe.

5 DNA comprising the coding sequence of full-length or mature PRO as disclosed herein is employed as a probe to screen for homologous DNAs (such as those encoding naturally-occurring variants of PRO) in human tissue cDNA libraries or human tissue genomic libraries.

Hybridization and washing of filters containing either library DNAs is performed under the following high stringency conditions. Hybridization of radiolabeled PRO-derived probe to the filters is
10 performed in a solution of 50% formamide, 5x SSC, 0.1% SDS, 0.1% sodium pyrophosphate, 50 mM sodium phosphate, pH 6.8, 2x Denhardt's solution, and 10% dextran sulfate at 42°C for 20 hours. Washing of the filters is performed in an aqueous solution of 0.1x SSC and 0.1% SDS at 42°C.

DNAs having a desired sequence identity with the DNA encoding full-length native sequence PRO can then be identified using standard techniques known in the art.

15

EXAMPLE 3: Expression of PRO in *E. coli*

This example illustrates preparation of an unglycosylated form of PRO by recombinant expression in *E. coli*.

The DNA sequence encoding PRO is initially amplified using selected PCR primers. The
20 primers should contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector. A variety of expression vectors may be employed. An example of a suitable vector is pBR322 (derived from *E. coli*; see Bolivar et al., Gene, 2:95 (1977)) which contains genes for ampicillin and tetracycline resistance. The vector is digested with restriction enzyme and dephosphorylated. The PCR amplified sequences are then ligated into the vector. The vector will
25 preferably include sequences which encode for an antibiotic resistance gene, a trp promoter, a polyhis leader (including the first six STII codons, polyhis sequence, and enterokinase cleavage site), the PRO coding region, lambda transcriptional terminator, and an argU gene.

The ligation mixture is then used to transform a selected *E. coli* strain using the methods described in Sambrook et al., supra. Transformants are identified by their ability to grow on LB plates
30 and antibiotic resistant colonies are then selected. Plasmid DNA can be isolated and confirmed by restriction analysis and DNA sequencing.

Selected clones can be grown overnight in liquid culture medium such as LB broth supplemented with antibiotics. The overnight culture may subsequently be used to inoculate a larger scale culture. The cells are then grown to a desired optical density, during which the expression promoter is turned on.

35 After culturing the cells for several more hours, the cells can be harvested by centrifugation. The cell pellet obtained by the centrifugation can be solubilized using various agents known in the art, and the solubilized PRO protein can then be purified using a metal chelating column under conditions that allow tight binding of the protein.

PRO may be expressed in *E. coli* in a poly-His tagged form, using the following procedure. The DNA encoding PRO is initially amplified using selected PCR primers. The primers will contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector, and other useful sequences providing for efficient and reliable translation initiation, rapid purification on a metal chelation column, and proteolytic removal with enterokinase. The PCR-amplified, poly-His tagged sequences are then ligated into an expression vector, which is used to transform an *E. coli* host based on strain 52 (W3110 fuhA(tonA) lon galE rpoHts(htpRts) clpP(lacIq). Transformants are first grown in LB containing 50 mg/ml carbenicillin at 30°C with shaking until an O.D.600 of 3-5 is reached. Cultures are then diluted 50-100 fold into CRAP media (prepared by mixing 3.57 g (NH₄)₂SO₄, 0.71 g sodium citrate•2H₂O, 1.07 g KCl, 5.36 g Difco yeast extract, 5.36 g Sheffield hycase SF in 500 mL water, as well as 110 mM MPOS, pH 7.3, 0.55% (w/v) glucose and 7 mM MgSO₄) and grown for approximately 20-30 hours at 30°C with shaking. Samples are removed to verify expression by SDS-PAGE analysis, and the bulk culture is centrifuged to pellet the cells. Cell pellets are frozen until purification and refolding.

E. coli paste from 0.5 to 1 L fermentations (6-10 g pellets) is resuspended in 10 volumes (w/v) in 7 M guanidine, 20 mM Tris, pH 8 buffer. Solid sodium sulfite and sodium tetrathionate is added to make final concentrations of 0.1M and 0.02 M, respectively, and the solution is stirred overnight at 4°C. This step results in a denatured protein with all cysteine residues blocked by sulfitolization. The solution is centrifuged at 40,000 rpm in a Beckman Ultracentrifuge for 30 min. The supernatant is diluted with 3-5 volumes of metal chelate column buffer (6 M guanidine, 20 mM Tris, pH 7.4) and filtered through 0.22 micron filters to clarify. The clarified extract is loaded onto a 5 ml Qiagen Ni-NTA metal chelate column equilibrated in the metal chelate column buffer. The column is washed with additional buffer containing 50 mM imidazole (Calbiochem, Utrol grade), pH 7.4. The protein is eluted with buffer containing 250 mM imidazole. Fractions containing the desired protein are pooled and stored at 4°C. Protein concentration is estimated by its absorbance at 280 nm using the calculated extinction coefficient based on its amino acid sequence.

The proteins are refolded by diluting the sample slowly into freshly prepared refolding buffer consisting of: 20 mM Tris, pH 8.6, 0.3 M NaCl, 2.5 M urea, 5 mM cysteine, 20 mM glycine and 1 mM EDTA. Refolding volumes are chosen so that the final protein concentration is between 50 to 100 micrograms/ml. The refolding solution is stirred gently at 4°C for 12-36 hours. The refolding reaction is quenched by the addition of TFA to a final concentration of 0.4% (pH of approximately 3). Before further purification of the protein, the solution is filtered through a 0.22 micron filter and acetonitrile is added to 2-10% final concentration. The refolded protein is chromatographed on a Poros R1/H reversed phase column using a mobile buffer of 0.1% TFA with elution with a gradient of acetonitrile from 10 to 80%. Aliquots of fractions with A280 absorbance are analyzed on SDS polyacrylamide gels and fractions containing homogeneous refolded protein are pooled. Generally, the properly refolded species of most proteins are eluted at the lowest concentrations of acetonitrile since those species are the most compact with their hydrophobic interiors shielded from interaction with the reversed phase resin. Aggregated

species are usually eluted at higher acetonitrile concentrations. In addition to resolving misfolded forms of proteins from the desired form, the reversed phase step also removes endotoxin from the samples.

Fractions containing the desired folded PRO polypeptide are pooled and the acetonitrile removed using a gentle stream of nitrogen directed at the solution. Proteins are formulated into 20 mM Hepes, pH 6.8 with 0.14 M sodium chloride and 4% mannitol by dialysis or by gel filtration using G25 Superfine (Pharmacia) resins equilibrated in the formulation buffer and sterile filtered.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

EXAMPLE 4: Expression of PRO in mammalian cells

This example illustrates preparation of a potentially glycosylated form of PRO by recombinant expression in mammalian cells.

The vector, pRK5 (see EP 307,247, published March 15, 1989), is employed as the expression vector. Optionally, the PRO DNA is ligated into pRK5 with selected restriction enzymes to allow insertion of the PRO DNA using ligation methods such as described in Sambrook et al., *supra*. The resulting vector is called pRK5-PRO.

In one embodiment, the selected host cells may be 293 cells. Human 293 cells (ATCC CCL 1573) are grown to confluence in tissue culture plates in medium such as DMEM supplemented with fetal calf serum and optionally, nutrient components and/or antibiotics. About 10 μ g pRK5-PRO DNA is mixed with about 1 μ g DNA encoding the VA RNA gene [Thimmappaya et al., *Cell*, 31:543 (1982)] and dissolved in 500 μ l of 1 mM Tris-HCl, 0.1 mM EDTA, 0.227 M CaCl_2 . To this mixture is added, dropwise, 500 μ l of 50 mM HEPES (pH 7.35), 280 mM NaCl, 1.5 mM NaPO_4 , and a precipitate is allowed to form for 10 minutes at 25°C. The precipitate is suspended and added to the 293 cells and allowed to settle for about four hours at 37°C. The culture medium is aspirated off and 2 ml of 20% glycerol in PBS is added for 30 seconds. The 293 cells are then washed with serum free medium, fresh medium is added and the cells are incubated for about 5 days.

Approximately 24 hours after the transfections, the culture medium is removed and replaced with culture medium (alone) or culture medium containing 200 μ Ci/ml ^{35}S -cysteine and 200 μ Ci/ml ^{35}S -methionine. After a 12 hour incubation, the conditioned medium is collected, concentrated on a spin filter, and loaded onto a 15% SDS gel. The processed gel may be dried and exposed to film for a selected period of time to reveal the presence of PRO polypeptide. The cultures containing transfected cells may undergo further incubation (in serum free medium) and the medium is tested in selected bioassays.

In an alternative technique, PRO may be introduced into 293 cells transiently using the dextran sulfate method described by Sompayrac et al., *Proc. Natl. Acad. Sci.*, 12:7575 (1981). 293 cells are grown to maximal density in a spinner flask and 700 μ g pRK5-PRO DNA is added. The cells are first concentrated from the spinner flask by centrifugation and washed with PBS. The DNA-dextran precipitate is incubated on the cell pellet for four hours. The cells are treated with 20% glycerol for 90 seconds, washed with tissue culture medium, and re-introduced into the spinner flask containing tissue culture medium, 5 μ g/ml bovine insulin and 0.1 μ g/ml bovine transferrin. After about four days, the conditioned

media is centrifuged and filtered to remove cells and debris. The sample containing expressed PRO can then be concentrated and purified by any selected method, such as dialysis and/or column chromatography.

In another embodiment, PRO can be expressed in CHO cells. The pRK5-PRO can be transfected
5 into CHO cells using known reagents such as CaPO_4 or DEAE-dextran. As described above, the cell cultures can be incubated, and the medium replaced with culture medium (alone) or medium containing a radiolabel such as ^{35}S -methionine. After determining the presence of PRO polypeptide, the culture medium may be replaced with serum free medium. Preferably, the cultures are incubated for about 6 days, and then the conditioned medium is harvested. The medium containing the expressed PRO can then
10 be concentrated and purified by any selected method.

Epitope-tagged PRO may also be expressed in host CHO cells. The PRO may be subcloned out of the pRK5 vector. The subclone insert can undergo PCR to fuse in frame with a selected epitope tag such as a poly-his tag into a Baculovirus expression vector. The poly-his tagged PRO insert can then be subcloned into a SV40 promoter/enhancer containing vector containing a selection marker such as DHFR
15 for selection of stable clones. Finally, the CHO cells can be transfected (as described above) with the SV40 promoter/enhancer containing vector. Labeling may be performed, as described above, to verify expression. The culture medium containing the expressed poly-His tagged PRO can then be concentrated and purified by any selected method, such as by Ni^{2+} -chelate affinity chromatography.

PRO may also be expressed in CHO and/or COS cells by a transient expression procedure or in
20 CHO cells by another stable expression procedure.

Stable expression in CHO cells is performed using the following procedure. The proteins are expressed as an IgG construct (immunoadhesin), in which the coding sequences for the soluble forms (e.g. extracellular domains) of the respective proteins are fused to an IgG1 constant region sequence containing the hinge, CH2 and CH2 domains and/or is a poly-His tagged form.

25 Following PCR amplification, the respective DNAs are subcloned in a CHO expression vector using standard techniques as described in Ausubel et al., Current Protocols of Molecular Biology, Unit 3.16, John Wiley and Sons (1997). CHO expression vectors are constructed to have compatible restriction sites 5' and 3' of the DNA of interest to allow the convenient shuttling of cDNA's. The vector used expression in CHO cells is as described in Lucas et al., Nucl. Acids Res. 24:9 (1774-1779 (1996), and
30 uses the SV40 early promoter/enhancer to drive expression of the cDNA of interest and dihydrofolate reductase (DHFR). DHFR expression permits selection for stable maintenance of the plasmid following transfection.

Twelve micrograms of the desired plasmid DNA is introduced into approximately 10 million CHO cells using commercially available transfection reagents Superfect[®] (Quiagen), Dosper[®] or Eugene[®]
35 (Boehringer Mannheim). The cells are grown as described in Lucas et al., supra. Approximately 3×10^7 cells are frozen in an ampule for further growth and production as described below.

The ampules containing the plasmid DNA are thawed by placement into water bath and mixed by vortexing. The contents are pipetted into a centrifuge tube containing 10 mL of media and centrifuged at

1000 rpm for 5 minutes. The supernatant is aspirated and the cells are resuspended in 10 mL of selective media (0.2 μ m filtered PS20 with 5% 0.2 μ m diafiltered fetal bovine serum). The cells are then aliquoted into a 100 mL spinner containing 90 mL of selective media. After 1-2 days, the cells are transferred into a 250 mL spinner filled with 150 mL selective growth medium and incubated at 37°C. After another 2-3
 5 days, 250 mL, 500 mL and 2000 mL spinners are seeded with 3×10^5 cells/mL. The cell media is exchanged with fresh media by centrifugation and resuspension in production medium. Although any suitable CHO media may be employed, a production medium described in U.S. Patent No. 5,122,469, issued June 16, 1992 may actually be used. A 3L production spinner is seeded at 1.2×10^6 cells/mL. On day 0, pH is determined. On day 1, the spinner is sampled and sparging with filtered air is commenced.
 10 On day 2, the spinner is sampled, the temperature shifted to 33°C, and 30 mL of 500 g/L glucose and 0.6 mL of 10% antifoam (e.g., 35% polydimethylsiloxane emulsion, Dow Corning 365 Medical Grade Emulsion) taken. Throughout the production, the pH is adjusted as necessary to keep it at around 7.2. After 10 days, or until the viability dropped below 70%, the cell culture is harvested by centrifugation and filtering through a 0.22 μ m filter. The filtrate was either stored at 4°C or immediately loaded onto
 15 columns for purification.

For the poly-His tagged constructs, the proteins are purified using a Ni-NTA column (Qiagen). Before purification, imidazole is added to the conditioned media to a concentration of 5 mM. The conditioned media is pumped onto a 6 ml Ni-NTA column equilibrated in 20 mM Hepes, pH 7.4, buffer containing 0.3 M NaCl and 5 mM imidazole at a flow rate of 4-5 ml/min. at 4°C. After loading, the
 20 column is washed with additional equilibration buffer and the protein eluted with equilibration buffer containing 0.25 M imidazole. The highly purified protein is subsequently desalted into a storage buffer containing 10 mM Hepes, 0.14 M NaCl and 4% mannitol, pH 6.8, with a 25 ml G25 Superfine (Pharmacia) column and stored at -80°C.

Immunoadhesin (Fc-containing) constructs are purified from the conditioned media as follows.
 25 The conditioned medium is pumped onto a 5 ml Protein A column (Pharmacia) which had been equilibrated in 20 mM Na phosphate buffer, pH 6.8. After loading, the column is washed extensively with equilibration buffer before elution with 100 mM citric acid, pH 3.5. The eluted protein is immediately neutralized by collecting 1 ml fractions into tubes containing 275 μ l of 1 M Tris buffer, pH 9. The highly purified protein is subsequently desalted into storage buffer as described above for the poly-
 30 His tagged proteins. The homogeneity is assessed by SDS polyacrylamide gels and by N-terminal amino acid sequencing by Edman degradation.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

EXAMPLE 5: Expression of PRO in Yeast

35 The following method describes recombinant expression of PRO in yeast.

First, yeast expression vectors are constructed for intracellular production or secretion of PRO from the ADH2/GAPDH promoter. DNA encoding PRO and the promoter is inserted into suitable restriction enzyme sites in the selected plasmid to direct intracellular expression of PRO. For secretion,

DNA encoding PRO can be cloned into the selected plasmid, together with DNA encoding the ADH2/GAPDH promoter, a native PRO signal peptide or other mammalian signal peptide, or, for example, a yeast alpha-factor or invertase secretory signal/leader sequence, and linker sequences (if needed) for expression of PRO.

5 Yeast cells, such as yeast strain AB110, can then be transformed with the expression plasmids described above and cultured in selected fermentation media. The transformed yeast supernatants can be analyzed by precipitation with 10% trichloroacetic acid and separation by SDS-PAGE, followed by staining of the gels with Coomassie Blue stain.

Recombinant PRO can subsequently be isolated and purified by removing the yeast cells from the fermentation medium by centrifugation and then concentrating the medium using selected cartridge filters. The concentrate containing PRO may further be purified using selected column chromatography resins.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

EXAMPLE 6: Expression of PRO in Baculovirus-Infected Insect Cells

15 The following method describes recombinant expression of PRO in Baculovirus-infected insect cells.

The sequence coding for PRO is fused upstream of an epitope tag contained within a baculovirus expression vector. Such epitope tags include poly-his tags and immunoglobulin tags (like Fc regions of IgG). A variety of plasmids may be employed, including plasmids derived from commercially available plasmids such as pVL1393 (Novagen). Briefly, the sequence encoding PRO or the desired portion of the coding sequence of PRO such as the sequence encoding the extracellular domain of a transmembrane protein or the sequence encoding the mature protein if the protein is extracellular is amplified by PCR with primers complementary to the 5' and 3' regions. The 5' primer may incorporate flanking (selected) restriction enzyme sites. The product is then digested with those selected restriction enzymes and subcloned into the expression vector.

Recombinant baculovirus is generated by co-transfecting the above plasmid and BaculoGold™ virus DNA (PharMingen) into *Spodoptera frugiperda* ("Sf9") cells (ATCC CRL 1711) using lipofectin (commercially available from GIBCO-BRL). After 4 - 5 days of incubation at 28°C, the released viruses are harvested and used for further amplifications. Viral infection and protein expression are performed as described by O'Reilley et al., Baculovirus expression vectors: A Laboratory Manual, Oxford: Oxford University Press (1994).

Expressed poly-his tagged PRO can then be purified, for example, by Ni²⁺-chelate affinity chromatography as follows. Extracts are prepared from recombinant virus-infected Sf9 cells as described by Rupert et al., Nature, 362:175-179 (1993). Briefly, Sf9 cells are washed, resuspended in sonication buffer (25 mL Hepes, pH 7.9; 12.5 mM MgCl₂; 0.1 mM EDTA; 10% glycerol; 0.1% NP-40; 0.4 M KCl), and sonicated twice for 20 seconds on ice. The sonicates are cleared by centrifugation, and the supernatant is diluted 50-fold in loading buffer (50 mM phosphate, 300 mM NaCl, 10% glycerol, pH 7.8) and filtered through a 0.45 µm filter. A Ni²⁺-NTA agarose column (commercially available from Qiagen)

is prepared with a bed volume of 5 mL, washed with 25 mL of water and equilibrated with 25 mL of loading buffer. The filtered cell extract is loaded onto the column at 0.5 mL per minute. The column is washed to baseline A_{280} with loading buffer, at which point fraction collection is started. Next, the column is washed with a secondary wash buffer (50 mM phosphate; 300 mM NaCl, 10% glycerol, pH 6.0), which elutes nonspecifically bound protein. After reaching A_{280} baseline again, the column is developed with a 0 to 500 mM Imidazole gradient in the secondary wash buffer. One mL fractions are collected and analyzed by SDS-PAGE and silver staining or Western blot with Ni^{2+} -NTA-conjugated to alkaline phosphatase (Qiagen). Fractions containing the eluted His₁₀-tagged PRO are pooled and dialyzed against loading buffer.

Alternatively, purification of the IgG tagged (or Fc tagged) PRO can be performed using known chromatography techniques, including for instance, Protein A or protein G column chromatography.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

EXAMPLE 7: Preparation of Antibodies that Bind PRO

This example illustrates preparation of monoclonal antibodies which can specifically bind PRO.

Techniques for producing the monoclonal antibodies are known in the art and are described, for instance, in Goding, *supra*. Immunogens that may be employed include purified PRO, fusion proteins containing PRO, and cells expressing recombinant PRO on the cell surface. Selection of the immunogen can be made by the skilled artisan without undue experimentation.

Mice, such as Balb/c, are immunized with the PRO immunogen emulsified in complete Freund's adjuvant and injected subcutaneously or intraperitoneally in an amount from 1-100 micrograms.

Alternatively, the immunogen is emulsified in MPL-TDM adjuvant (Ribi Immunochemical Research, Hamilton, MT) and injected into the animal's hind foot pads. The immunized mice are then boosted 10 to 12 days later with additional immunogen emulsified in the selected adjuvant. Thereafter, for several weeks, the mice may also be boosted with additional immunization injections. Serum samples may be periodically obtained from the mice by retro-orbital bleeding for testing in ELISA assays to detect anti-PRO antibodies.

After a suitable antibody titer has been detected, the animals "positive" for antibodies can be injected with a final intravenous injection of PRO. Three to four days later, the mice are sacrificed and the spleen cells are harvested. The spleen cells are then fused (using 35% polyethylene glycol) to a selected murine myeloma cell line such as P3X63AgU.1, available from ATCC, No. CRL 1597. The fusions generate hybridoma cells which can then be plated in 96 well tissue culture plates containing HAT (hypoxanthine, aminopterin, and thymidine) medium to inhibit proliferation of non-fused cells, myeloma hybrids, and spleen cell hybrids.

The hybridoma cells will be screened in an ELISA for reactivity against PRO. Determination of "positive" hybridoma cells secreting the desired monoclonal antibodies against PRO is within the skill in the art.

The positive hybridoma cells can be injected intraperitoneally into syngeneic Balb/c mice to produce ascites containing the anti-PRO monoclonal antibodies. Alternatively, the hybridoma cells can be grown in tissue culture flasks or roller bottles. Purification of the monoclonal antibodies produced in the ascites can be accomplished using ammonium sulfate precipitation, followed by gel exclusion chromatography. Alternatively, affinity chromatography based upon binding of antibody to protein A or protein G can be employed.

EXAMPLE 8: Purification of PRO Polypeptides Using Specific Antibodies

Native or recombinant PRO polypeptides may be purified by a variety of standard techniques in the art of protein purification. For example, pro-PRO polypeptide, mature PRO polypeptide, or pre-PRO polypeptide is purified by immunoaffinity chromatography using antibodies specific for the PRO polypeptide of interest. In general, an immunoaffinity column is constructed by covalently coupling the anti-PRO polypeptide antibody to an activated chromatographic resin.

Polyclonal immunoglobulins are prepared from immune sera either by precipitation with ammonium sulfate or by purification on immobilized Protein A (Pharmacia LKB Biotechnology, Piscataway, N.J.). Likewise, monoclonal antibodies are prepared from mouse ascites fluid by ammonium sulfate precipitation or chromatography on immobilized Protein A. Partially purified immunoglobulin is covalently attached to a chromatographic resin such as CnBr-activated SEPHAROSE™ (Pharmacia LKB Biotechnology). The antibody is coupled to the resin, the resin is blocked, and the derivative resin is washed according to the manufacturer's instructions.

Such an immunoaffinity column is utilized in the purification of PRO polypeptide by preparing a fraction from cells containing PRO polypeptide in a soluble form. This preparation is derived by solubilization of the whole cell or of a subcellular fraction obtained via differential centrifugation by the addition of detergent or by other methods well known in the art. Alternatively, soluble PRO polypeptide containing a signal sequence may be secreted in useful quantity into the medium in which the cells are grown.

A soluble PRO polypeptide-containing preparation is passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of PRO polypeptide (*e.g.*, high ionic strength buffers in the presence of detergent). Then, the column is eluted under conditions that disrupt antibody/PRO polypeptide binding (*e.g.*, a low pH buffer such as approximately pH 2-3, or a high concentration of a chaotrope such as urea or thiocyanate ion), and PRO polypeptide is collected.

EXAMPLE 9: Drug Screening

This invention is particularly useful for screening compounds by using PRO polypeptides or binding fragment thereof in any of a variety of drug screening techniques. The PRO polypeptide or fragment employed in such a test may either be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the PRO polypeptide or

fragment. Drugs are screened against such transformed cells in competitive binding assays. Such cells, either in viable or fixed form, can be used for standard binding assays. One may measure, for example, the formation of complexes between PRO polypeptide or a fragment and the agent being tested. Alternatively, one can examine the diminution in complex formation between the PRO polypeptide and its target cell or target receptors caused by the agent being tested.

Thus, the present invention provides methods of screening for drugs or any other agents which can affect a PRO polypeptide-associated disease or disorder. These methods comprise contacting such an agent with an PRO polypeptide or fragment thereof and assaying (i) for the presence of a complex between the agent and the PRO polypeptide or fragment, or (ii) for the presence of a complex between the PRO polypeptide or fragment and the cell, by methods well known in the art. In such competitive binding assays, the PRO polypeptide or fragment is typically labeled. After suitable incubation, free PRO polypeptide or fragment is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of the particular agent to bind to PRO polypeptide or to interfere with the PRO polypeptide/cell complex.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to a polypeptide and is described in detail in WO 84/03564, published on September 13, 1984. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. As applied to a PRO polypeptide, the peptide test compounds are reacted with PRO polypeptide and washed. Bound PRO polypeptide is detected by methods well known in the art. Purified PRO polypeptide can also be coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies can be used to capture the peptide and immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding PRO polypeptide specifically compete with a test compound for binding to PRO polypeptide or fragments thereof. In this manner, the antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with PRO polypeptide.

EXAMPLE 10: Rational Drug Design

The goal of rational drug design is to produce structural analogs of biologically active polypeptide of interest (*i.e.*, a PRO polypeptide) or of small molecules with which they interact, *e.g.*, agonists, antagonists, or inhibitors. Any of these examples can be used to fashion drugs which are more active or stable forms of the PRO polypeptide or which enhance or interfere with the function of the PRO polypeptide *in vivo* (*c.f.*, Hodgson, Bio/Technology, 9: 19-21 (1991)).

In one approach, the three-dimensional structure of the PRO polypeptide, or of a PRO polypeptide-inhibitor complex, is determined by x-ray crystallography, by computer modeling or, most typically, by a combination of the two approaches. Both the shape and charges of the PRO polypeptide must be ascertained to elucidate the structure and to determine active site(s) of the molecule. Less often, useful information regarding the structure of the PRO polypeptide may be gained by modeling based on

the structure of homologous proteins. In both cases, relevant structural information is used to design analogous PRO polypeptide-like molecules or to identify efficient inhibitors. Useful examples of rational drug design may include molecules which have improved activity or stability as shown by Braxton and Wells, Biochemistry, 31:7796-7801 (1992) or which act as inhibitors, agonists, or antagonists of native peptides as shown by Athauda *et al.*, J. Biochem., 113:742-746 (1993).

It is also possible to isolate a target-specific antibody, selected by functional assay, as described above, and then to solve its crystal structure. This approach, in principle, yields a pharmacore upon which subsequent drug design can be based. It is possible to bypass protein crystallography altogether by generating anti-idiotypic antibodies (anti-ids) to a functional, pharmacologically active antibody. As a mirror image of a mirror image, the binding site of the anti-ids would be expected to be an analog of the original receptor. The anti-id could then be used to identify and isolate peptides from banks of chemically or biologically produced peptides. The isolated peptides would then act as the pharmacore.

By virtue of the present invention, sufficient amounts of the PRO polypeptide may be made available to perform such analytical studies as X-ray crystallography. In addition, knowledge of the PRO polypeptide amino acid sequence provided herein will provide guidance to those employing computer modeling techniques in place of or in addition to x-ray crystallography.

The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by the construct deposited, since the deposited embodiment is intended as a single illustration of certain aspects of the invention and any constructs that are functionally equivalent are within the scope of this invention. The deposit of material herein does not constitute an admission that the written description herein contained is inadequate to enable the practice of any aspect of the invention, including the best mode thereof, nor is it to be construed as limiting the scope of the claims to the specific illustrations that it represents. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims.

Sequence Listing

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 <212> PRT
 <213> Homo sapien

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

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Val Ser Cys Leu	Val Pro Glu Ser Asn Gln Lys Met Lys Asp Ser				
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Tyr Leu Ile Leu	Asp Glu Tyr Met Arg Phe Leu Asn Cys Arg Lys				
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Gly Arg Lys Asp	Pro Ser Lys Ser Ile Leu Asp Val Gly Val Glu				
	320		325		330
Glu Ala Ile Lys	Phe Ser Gly Phe Asp Glu Lys Met Phe Leu Lys				
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 <212> DNA
 <213> Homo sapien

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<211> 361

<212> PRT

<213> Homo sapien

<400> 4

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

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Arg Phe Asn Val	Glu Glu Asp Met Thr	Glu Gln Ile Lys Ala Leu			
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	245	250			255
Glu Asn Cys Gly	Glu Asp Ala Leu Arg	Glu Ala Glu Arg Phe Val			
	260	265			270
Ile Gly Asp Glu	Glu Phe Glu Arg Phe	Leu Glu Arg His Lys Glu			
	275	280			285
Val Ser Cys Leu	Val Pro Glu Ser Asn	Gln Lys Met Lys Asp Ser			
	290	295			300
Tyr Leu Ile Leu	Asp Glu Tyr Met Arg	Phe Leu Asn Cys Arg Lys			
	305	310			315
Gly Arg Lys Asp	Pro Ser Lys Ser Ile	Leu Asp Val Gly Val Glu			
	320	325			330
Glu Ala Ile Lys	Phe Ser Gly Phe Asp	Glu Lys Met Phe Leu Lys			
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Arg Gly Gly Lys	Tyr Ile Trp Ser Lys	Ala Asp Leu Lys Leu Asp			
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Trp

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<211> 413

<212> PRT

<213> Homo sapien

<400> 6

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				20					25					30

Ile	Asn	Leu	Arg	Glu	Ser	Ser	Thr	Glu	Pro	Asn	Asp	Ser	Leu	Trp

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

Asp Ile Leu Ile Leu Ser Ala Leu Arg Gln Met Leu Arg Ala Ala
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Glu Arg Ala Leu Gln Pro Cys Ile
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 <211> 2498
 <212> DNA
 <213> Homo sapien

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 <212> DNA
 <213> Homo sapien

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 <212> PRT
 <213> Homo sapien

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

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Ser Ala Asp Asp	Asn Leu Lys Thr	Pro Pro Glu Cys Leu	Leu Thr		
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Pro					

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 <211> 1709
 <212> PRT
 <213> Homo sapien

<400> 12
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 Gly Val Lys Gly Ser Cys Leu Leu Ile Pro Cys Ile Phe Ser Phe
 35 40 45
 Pro Ala Asp Val Glu Val Pro Asp Gly Ile Thr Ala Ile Trp Tyr
 50 55 60
 Tyr Asp Tyr Ser Gly Gln Arg Gln Val Val Ser His Ser Ala Asp
 65 70 75
 Pro Lys Leu Val Glu Ala Arg Phe Arg Gly Arg Thr Glu Phe Met
 80 85 90
 Gly Asn Pro Glu His Arg Val Cys Asn Leu Leu Leu Lys Asp Leu
 95 100 105
 Gln Pro Glu Asp Ser Gly Ser Tyr Asn Phe Arg Phe Glu Ile Ser
 110 115 120
 Glu Val Asn Arg Trp Ser Asp Val Lys Gly Thr Leu Val Thr Val
 125 130 135
 Thr Glu Glu Pro Arg Val Pro Thr Ile Ala Ser Pro Val Glu Leu
 140 145 150
 Leu Glu Gly Thr Glu Val Asp Phe Asn Cys Ser Thr Pro Tyr Val
 155 160 165
 Cys Leu Gln Glu Gln Val Arg Leu Gln Trp Gln Gly Gln Asp Pro
 170 175 180
 Ala Arg Ser Val Thr Phe Asn Ser Gln Lys Phe Glu Pro Thr Gly
 185 190 195
 Val Gly His Leu Glu Thr Leu His Met Ala Met Ser Trp Gln Asp
 200 205 210

His Gly Arg Ile	Leu Arg Cys Gln Leu Ser Val Ala Asn His Arg	215	220	225
Ala Gln Ser Glu	Ile His Leu Gln Val Lys Tyr Ala Pro Lys Gly	230	235	240
Val Lys Ile Leu	Leu Ser Pro Ser Gly Arg Asn Ile Leu Pro Gly	245	250	255
Glu Leu Val Thr	Leu Thr Cys Gln Val Asn Ser Ser Tyr Pro Ala	260	265	270
Val Ser Ser Ile	Lys Trp Leu Lys Asp Gly Val Arg Leu Gln Thr	275	280	285
Lys Thr Gly Val	Leu His Leu Pro Gln Ala Ala Trp Ser Asp Ala	290	295	300
Gly Val Tyr Thr	Cys Gln Ala Glu Asn Gly Val Gly Ser Leu Val	305	310	315
Ser Pro Pro Ile	Ser Leu His Ile Phe Met Ala Glu Val Gln Val	320	325	330
Ser Pro Ala Gly	Pro Ile Leu Glu Asn Gln Thr Val Thr Leu Val	335	340	345
Cys Asn Thr Pro	Asn Glu Ala Pro Ser Asp Leu Arg Tyr Ser Trp	350	355	360
Tyr Lys Asn His	Val Leu Leu Glu Asp Ala His Ser His Thr Leu	365	370	375
Arg Leu His Leu	Ala Thr Arg Ala Asp Thr Gly Phe Tyr Phe Cys	380	385	390
Glu Val Gln Asn	Val His Gly Ser Glu Arg Ser Gly Pro Val Ser	395	400	405
Val Val Val Asn	His Pro Pro Leu Thr Pro Val Leu Thr Ala Phe	410	415	420
Leu Glu Thr Gln	Ala Gly Leu Val Gly Ile Leu His Cys Ser Val	425	430	435
Val Ser Glu Pro	Leu Ala Thr Leu Val Leu Ser His Gly Gly His	440	445	450
Ile Leu Ala Ser	Thr Ser Gly Asp Ser Asp His Ser Pro Arg Phe	455	460	465
Ser Gly Thr Ser	Gly Pro Asn Ser Leu Arg Leu Glu Ile Arg Asp	470	475	480
Leu Glu Glu Thr	Asp Ser Gly Glu Tyr Lys Cys Ser Ala Thr Asn	485	490	495
Ser Leu Gly Asn	Ala Thr Ser Thr Leu Asp Phe His Ala Asn Ala	500	505	510
Ala Arg Leu Leu	Ile Ser Pro Ala Ala Glu Val Val Glu Gly Gln	515	520	525
Ala Val Thr Leu	Ser Cys Arg Ser Gly Leu Ser Pro Thr Pro Asp	530	535	540
Ala Arg Phe Ser	Trp Tyr Leu Asn Gly Ala Leu Leu His Glu Gly			

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Pro	Gly	Ser	Ser	Leu	Leu	Leu	Pro	Ala	Ala	Ser	Ser	Thr	Asp	Ala	
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Gly	Ser	Tyr	His	Cys	Arg	Ala	Arg	Asp	Gly	His	Ser	Ala	Ser	Gly	
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Pro	Ser	Ser	Pro	Ala	Val	Leu	Thr	Val	Leu	Tyr	Pro	Pro	Arg	Gln	
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Pro	Thr	Phe	Thr	Thr	Arg	Leu	Asp	Leu	Asp	Ala	Ala	Gly	Ala	Gly	
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Ala	Gly	Arg	Arg	Gly	Leu	Leu	Leu	Cys	Arg	Val	Asp	Ser	Asp	Pro	
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Pro	Ala	Arg	Leu	Gln	Leu	Leu	His	Lys	Asp	Arg	Val	Val	Ala	Thr	
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Ser	Leu	Pro	Ser	Gly	Gly	Gly	Cys	Ser	Thr	Cys	Gly	Gly	Cys	Ser	
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Pro	Arg	Met	Lys	Val	Thr	Lys	Ala	Pro	Asn	Leu	Leu	Arg	Val	Glu	
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Ile	His	Asn	Pro	Leu	Leu	Glu	Glu	Glu	Gly	Leu	Tyr	Leu	Cys	Glu	
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Ala	Ser	Asn	Ala	Leu	Gly	Asn	Ala	Ser	Thr	Ser	Ala	Thr	Phe	Asn	
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Glu	Gly	Thr	Glu	Ala	Asn	Leu	Thr	Cys	Asn	Val	Ser	Arg	Glu	Ala	
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Ala	Gly	Ser	Pro	Ala	Asn	Phe	Ser	Trp	Phe	Arg	Asn	Gly	Val	Leu	
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Trp	Ala	Gln	Gly	Pro	Leu	Glu	Thr	Val	Thr	Leu	Leu	Pro	Val	Ala	
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Arg	Thr	Asp	Ala	Ala	Leu	Tyr	Ala	Cys	Arg	Ile	Leu	Thr	Glu	Ala	
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Pro	Asp	Arg	Pro	Lys	Leu	Ser	Ala	Leu	Leu	Asp	Met	Gly	Gln	Gly	
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His	Met	Ala	Leu	Phe	Ile	Cys	Thr	Val	Asp	Ser	Arg	Pro	Leu	Ala	
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Leu	Leu	Ala	Leu	Phe	His	Gly	Glu	His	Leu	Leu	Ala	Thr	Ser	Leu	
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Gly	Pro	Gln	Val	Pro	Ser	His	Gly	Arg	Phe	Gln	Ala	Lys	Ala	Glu	
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Ala	Asn	Ser	Leu	Lys	Leu	Glu	Val	Arg	Glu	Leu	Gly	Leu	Gly	Asp	
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Ser	Gly	Ser	Tyr	Arg	Cys	Glu	Ala	Thr	Asn	Val	Leu	Gly	Ser	Ser	
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Ser	Pro	Ser	Pro	Glu	Leu	Gln	Glu	Gly	Gln	Ala	Val	Val	Leu	Ser	
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Tyr	Arg	Asp	Gly	Gln	Pro	Leu	Gln	Glu	Ser	Thr	Ser	Ala	Thr	Leu	
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Arg	Phe	Ala	Ala	Ile	Thr	Leu	Thr	Gln	Ala	Gly	Ala	Tyr	His	Cys	
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Gln	Ala	Gln	Ala	Pro	Gly	Ser	Ala	Thr	Thr	Ser	Leu	Ala	Ala	Pro	
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Ile	Ser	Leu	His	Val	Ser	Tyr	Ala	Pro	Arg	His	Val	Thr	Leu	Thr	
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Thr	Leu	Met	Asp	Thr	Gly	Pro	Gly	Arg	Leu	Gly	Leu	Leu	Leu	Cys	
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Thr	Val	Arg	Glu	Gly	Gln	Leu	Val	Asn	Leu	Thr	Cys	Leu	Val	Trp	
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Pro Leu Gly Gln Ala Asn Thr Ser Leu Glu Leu Arg Leu Glu Gly		
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Val Arg Val Ile Leu Ala Pro Glu Ala Ala Val Pro Glu Gly Ala		
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Pro Ile Thr Val Thr Cys Ala Asp Pro Ala Ala His Ala Pro Thr		
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Leu Tyr Thr Trp Tyr His Asn Gly Arg Trp Leu Gln Glu Gly Pro		
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Gln Cys Thr Val Asp Ser Glu Pro Pro Ala Glu Leu Ala Leu Ser		
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His Asp Gly Lys Val Leu Ala Thr Ser Ser Gly Val His Ser Leu		
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Ala Ser Gly Thr Gly His Val Gln Val Ala Arg Asn Ala Leu Arg		
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Leu Gln Val Gln Asp Val Pro Ala Gly Asp Asp Thr Tyr Val Cys		
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Thr Ala Gln Asn Leu Leu Gly Ser Ile Ser Thr Ile Gly Arg Leu		
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Gln Val Glu Gly Ala Arg Val Val Ala Glu Pro Gly Leu Asp Val		
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Pro Glu Gly Ala Ala Leu Asn Leu Ser Cys Arg Leu Leu Gly Gly		
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Pro Gly Pro Val Gly Asn Ser Thr Phe Ala Trp Phe Trp Asn Asp		
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Arg Arg Leu His Ala Glu Pro Val Pro Thr Leu Ala Phe Thr His		
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Val Ala Arg Ala Gln Ala Gly Met Tyr His Cys Leu Ala Glu Leu		
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Pro Thr Gly Ala Ala Ala Ser Ala Pro Val Met Leu Arg Val Leu		
1520	1525	1530
Tyr Pro Pro Lys Thr Pro Thr Met Met Val Phe Val Glu Pro Glu		
1535	1540	1545
Gly Gly Leu Arg Gly Ile Leu Asp Cys Arg Val Asp Ser Glu Pro		
1550	1555	1560

Leu Ala Ser Leu Thr Leu His Leu Gly Ser Arg Leu Val Ala Ser
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 Ser Gln Pro Gln Gly Ala Pro Ala Glu Pro His Ile His Val Leu
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 Ala Ser Pro Asn Ala Leu Arg Val Asp Ile Glu Ala Leu Arg Pro
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 Ser Ala Ser Thr Ser Thr Tyr Phe Gly Val Arg Ala Leu His Arg
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 Arg Arg Arg Arg Val Cys Lys Gln Ser Met Gly Glu Asn Ser Val
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 <212> DNA
 <213> Homo sapien

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 <213> Homo sapien

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caagggccgg aaataaaggc tggtgtaaga gaat 634

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 <211> 165
 <212> PRT
 <213> Homo sapien

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

<210> 16
 <211> 1642
 <212> DNA
 <213> Homo sapien

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 cgatgaaatg cctgatttag aaaacagagt cttggatcag attgaattcc 200
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 tgtaatgatg taattcttga ataataaatc tgacaaaata tt 1642

<210> 17
 <211> 478
 <212> PRT
 <213> Homo sapien

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 35 40 45
 Leu Asp Thr Lys Tyr Ser Val Gly Ile His Asn Leu Leu Ala Tyr
 50 55 60
 Val Lys His Leu Lys Gly Gln Asn Glu Glu Ala Leu Lys Ser Leu
 65 70 75

Lys	Glu	Ala	Glu	Asn	Leu	Met	Gln	Glu	Glu	His	Asp	Asn	Gln	Ala	
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Asn	Val	Arg	Ser	Leu	Val	Thr	Trp	Gly	Asn	Phe	Ala	Trp	Met	Tyr	
				95					100					105	
Tyr	His	Met	Gly	Arg	Leu	Ala	Glu	Ala	Gln	Thr	Tyr	Leu	Asp	Lys	
				110					115					120	
Val	Glu	Asn	Ile	Cys	Lys	Lys	Leu	Ser	Asn	Pro	Phe	Arg	Tyr	Arg	
				125					130					135	
Met	Glu	Cys	Pro	Glu	Ile	Asp	Cys	Glu	Glu	Gly	Trp	Ala	Leu	Leu	
				140					145					150	
Lys	Cys	Gly	Gly	Lys	Asn	Tyr	Glu	Arg	Ala	Lys	Ala	Cys	Phe	Glu	
				155					160					165	
Lys	Val	Leu	Glu	Val	Asp	Pro	Glu	Asn	Pro	Glu	Ser	Ser	Ala	Gly	
				170					175					180	
Tyr	Ala	Ile	Ser	Ala	Tyr	Arg	Leu	Asp	Gly	Phe	Lys	Leu	Ala	Thr	
				185					190					195	
Lys	Asn	His	Lys	Pro	Phe	Ser	Leu	Leu	Pro	Leu	Arg	Gln	Ala	Val	
				200					205					210	
Arg	Leu	Asn	Pro	Asp	Asn	Gly	Tyr	Ile	Lys	Val	Leu	Leu	Ala	Leu	
				215					220					225	
Lys	Leu	Gln	Asp	Glu	Gly	Gln	Glu	Ala	Glu	Gly	Glu	Lys	Tyr	Ile	
				230					235					240	
Glu	Glu	Ala	Leu	Ala	Asn	Met	Ser	Ser	Gln	Thr	Tyr	Val	Phe	Arg	
				245					250					255	
Tyr	Ala	Ala	Lys	Phe	Tyr	Arg	Arg	Lys	Gly	Ser	Val	Asp	Lys	Ala	
				260					265					270	
Leu	Glu	Leu	Leu	Lys	Lys	Ala	Leu	Gln	Glu	Thr	Pro	Thr	Ser	Val	
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Leu	Leu	His	His	Gln	Ile	Gly	Leu	Cys	Tyr	Lys	Ala	Gln	Met	Ile	
				290					295					300	
Gln	Ile	Lys	Glu	Ala	Thr	Lys	Gly	Gln	Pro	Arg	Gly	Gln	Asn	Arg	
				305					310					315	
Glu	Lys	Leu	Asp	Lys	Met	Ile	Arg	Ser	Ala	Ile	Phe	His	Phe	Glu	
				320					325					330	
Ser	Ala	Val	Glu	Lys	Lys	Pro	Thr	Phe	Glu	Val	Ala	His	Leu	Asp	
				335					340					345	
Leu	Ala	Arg	Met	Tyr	Ile	Glu	Ala	Gly	Asn	His	Arg	Lys	Ala	Glu	
				350					355					360	
Glu	Asn	Phe	Gln	Lys	Leu	Leu	Cys	Met	Lys	Pro	Val	Val	Glu	Glu	
				365					370					375	
Thr	Met	Gln	Asp	Ile	His	Phe	Tyr	Tyr	Gly	Arg	Phe	Gln	Glu	Phe	
				380					385					390	
Gln	Lys	Lys	Ser	Asp	Val	Asn	Ala	Ile	Ile	His	Tyr	Leu	Lys	Ala	
				395					400					405	
Ile	Lys	Ile	Glu	Gln	Ala	Ser	Leu	Thr	Arg	Asp	Lys	Ser	Ile	Asn	

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Ser Leu Lys Lys	Leu Val Leu Arg Lys	Leu Arg Arg Lys Ala	Leu		
	425		430		435
Asp Leu Glu Ser	Leu Ser Leu Leu Gly	Phe Val Tyr Lys Leu	Glu		
	440		445		450
Gly Asn Met Asn	Glu Ala Leu Glu Tyr	Tyr Glu Arg Ala Leu	Arg		
	455		460		465
Leu Ala Ala Asp	Phe Glu Asn Ser Val	Arg Gln Gly Pro			
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 <211> 4579
 <212> DNA
 <213> Homo sapien

<400> 18
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 <211> 191
 <212> PRT
 <213> Homo sapien

<400> 19
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 35 40 45
 Leu Gln Glu Asn Leu Arg Arg Glu Ala Phe Arg Glu His Gln Gln
 50 55 60
 Tyr Lys Thr Ala Glu Phe Leu Ser Lys Leu Asn Thr Glu Ser Pro
 65 70 75
 Asp Arg Ser Ala Cys Gln Ser Ala Val Cys Gly Pro Gln Ser Ser
 80 85 90
 Thr Trp Lys Leu Pro Ile Leu Pro Arg Asp His Ser Trp Ala Arg
 95 100 105
 Ser Trp Ala Tyr Arg Asp Ser Leu Lys Ala Glu Glu Asn Arg Lys
 110 115 120
 Leu Gln Lys Met Lys Asp Glu Gln His Gln Lys Ser Glu Leu Leu
 125 130 135
 Glu Leu Lys Arg Gln Gln Gln Glu Gln Glu Arg Ala Lys Ile His
 140 145 150
 Gln Thr Glu His Arg Arg Val Asn Asn Ala Phe Leu Asp Arg Leu
 155 160 165
 Gln Gly Lys Ser Gln Pro Gly Gly Leu Glu Gln Ser Gly Gly Cys
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 Trp Asn Met Asn Ser Gly Asn Ser Trp Gly Ile
 185 190

<210> 20
 <211> 2787
 <212> DNA
 <213> Homo sapien

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 Glu Glu Lys Val Arg Pro Cys Ile Asp Leu Ile Asp Ser Leu Arg
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 Ala Leu Gly Val Glu Gln Asp Leu Ala Leu Pro Ala Ile Ala Val
 65 70 75
 Ile Gly Asp Gln Ser Ser Gly Lys Ser Ser Val Leu Glu Ala Leu
 80 85 90
 Ser Gly Val Ala Leu Pro Arg Gly Ser Gly Ile Val Thr Arg Cys
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 Pro Leu Val Leu Lys Leu Lys Lys Leu Val Asn Glu Asp Lys Trp
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 Arg Gly Lys Val Ser Tyr Gln Asp Tyr Glu Ile Glu Ile Ser Asp
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 Ala Ser Glu Val Glu Lys Glu Ile Asn Lys Ala Gln Asn Ala Ile
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 Ala Gly Glu Gly Met Gly Ile Ser His Glu Leu Ile Thr Leu Glu
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Ile	Ser	Ser	Arg	Asp	Val	Pro	Asp	Leu	Thr	Leu	Ile	Asp	Leu	Pro	170	175	180
Gly	Ile	Thr	Arg	Val	Ala	Val	Gly	Asn	Gln	Pro	Ala	Asp	Ile	Gly	185	190	195
Tyr	Lys	Ile	Lys	Thr	Leu	Ile	Lys	Lys	Tyr	Ile	Gln	Arg	Gln	Glu	200	205	210
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Thr	Glu	Asp	Lys	Val	Val	Asp	Val	Val	Arg	Asn	Leu	Val	Phe	His	260	265	270
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Asn	Phe	Gln	Glu	Gly	His	Lys	Ile	Leu	Ser	Arg	Lys	Ile	Gln	Lys	425	430	435
Phe	Glu	Asn	Gln	Tyr	Arg	Gly	Arg	Glu	Leu	Pro	Gly	Phe	Val	Asn	440	445	450
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Glu	Glu	Pro	Ala	Val	Asp	Met	Leu	His	Thr	Val	Thr	Asp	Met	Val	470	475	480
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Lys Lys Ser Trp Asp Phe Gly Ala Phe Gln Ser Ser Ser Ala Thr	560		565		570
Asp Ser Ser Met Glu Glu Ile Phe Gln His Leu Met Ala Tyr His	575		580		585
Gln Glu Ala Ser Lys Arg Ile Ser Ser His Ile Pro Leu Ile Ile	590		595		600
Gln Phe Phe Met Leu Gln Thr Tyr Gly Gln Gln Leu Gln Lys Ala	605		610		615
Met Leu Gln Leu Leu Gln Asp Lys Asp Thr Tyr Ser Trp Leu Leu	620		625		630
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 <213> Homo sapien

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 Pro Thr Pro Gly Ser Cys Gly His Gly Gly Val Val Asn Ile Ser
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 Lys Pro Ser Val Val Gln Leu Asn Trp Arg Gly Phe Ser Tyr Leu
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<210> 24

<211> 1919

<212> DNA

<213> Homo sapien

<400> 24

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 Lys His Leu Asp Gly Asn Asn Glu Ala Ala Leu Glu Cys Leu Arg
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Lys	Ala	Lys	Val	Arg	Gln	Met	Gln	Asn	Thr	Gly	Glu	Ser	Glu	Ala	290	295	300
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Gly	Ser	Glu	Glu	Met	Gly	Gln	Gly	Ala	Val	Ser	Ser	Ser	Pro	Arg	470	475	480
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WO 2005/051988

PCT/US2004/006460

<211> 444
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 <213> Homo sapien

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 Asn Gln Gly Pro Thr Leu Thr Val Ile Tyr Ser Glu Asp His Ile
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 Ile Gly Ala Tyr Ala Glu Glu Ser Tyr Gln Glu Gly Lys Tyr Ala
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 Ser Ile Ile Leu Phe Ala Leu Gln Asp Thr Lys Ile Ser Glu Trp
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 Lys Leu Gly Leu Cys Thr Pro Glu Thr Leu Phe Cys Cys Asp Val
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 Thr Lys Tyr Asn Ser Pro Thr Asn Phe Gln Ile Asp Gly Arg Asn
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 Arg Lys Val Ile Met Asp Leu Lys Thr Met Glu Asn Leu Gly Leu
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 Ala Gln Asn Cys Thr Ile Ser Ile Gln Asp Tyr Glu Val Phe Arg
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 Cys Glu Asp Ser Leu Asp Glu Arg Lys Ile Lys Gly Val Ile Glu
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 Leu Arg Lys Ser Leu Leu Ser Ala Leu Arg Thr Tyr Glu Pro Tyr
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 Gly Ser Leu Val Gln Gln Ile Arg Ile Leu Leu Leu Gly Pro Ile
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 Gly Ala Gly Lys Ser Ser Phe Phe Asn Ser Val Arg Ser Val Phe
 200 205 210
 Gln Gly His Val Thr His Gln Ala Leu Val Gly Thr Asn Thr Thr
 215 220 225
 Gly Ile Ser Glu Lys Tyr Arg Thr Tyr Ser Ile Arg Asp Gly Lys
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 Asp Gly Lys Tyr Leu Pro Phe Ile Leu Cys Asp Ser Leu Gly Leu
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 Ser Glu Lys Glu Gly Gly Leu Cys Arg Asp Asp Ile Phe Tyr Ile
 260 265 270
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				335					340					345
Thr	His	Val	Asp	Ser	Met	Asp	Leu	Ile	Thr	Lys	Gly	Asp	Leu	Ile
				350					355					360
Glu	Ile	Glu	Arg	Cys	Glu	Pro	Val	Arg	Ser	Lys	Leu	Glu	Glu	Val
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Gln	Arg	Lys	Leu	Gly	Phe	Ala	Leu	Ser	Asp	Ile	Ser	Val	Val	Ser
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Asn	Tyr	Ser	Ser	Glu	Trp	Glu	Leu	Asp	Pro	Val	Lys	Asp	Val	Leu
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Ile	Leu	Ser	Ala	Leu	Arg	Arg	Met	Leu	Trp	Ala	Ala	Asp	Asp	Phe
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Leu	Glu	Asp	Leu	Pro	Phe	Glu	Gln	Ile	Gly	Asn	Leu	Arg	Glu	Glu
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Asn Tyr Cys Val Thr Val Ser Ala Ser Ala Gly Ile Gly Asn Leu
50 55 60
Val Thr Phe Gly His Ser Leu Ser Lys Thr Cys Ser Pro Ala Cys
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Pro Ile Pro Glu Gly Val Asn Val Gly Val Ala Ser Met Gly Ile
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Ser Cys Cys Gln Ser Phe Leu Cys Asn Phe Ser Ala Ala Asp Gly
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<210> 31

<211> 1024

<212> PRT

<213> Homo sapien

<400> 31

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Ala	Gln	Leu	Trp	Leu	Phe	Pro	Ser	Ala	Ala	Gly	Leu	His	Arg	Ala	35	40	45
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His	Gln	Leu	Leu	Ala	Gly	Ser	Gly	Gly	Ala	Arg	Thr	Pro	Lys	Cys	80	85	90
Ile	Lys	Leu	Gly	Lys	Asn	Met	Lys	Ile	His	Ser	Val	Asp	Gln	Gly	95	100	105
Ala	Glu	His	Met	Leu	Ile	Leu	Ser	Ser	Asp	Gly	Lys	Pro	Phe	Glu	110	115	120
Tyr	Asp	Asn	Tyr	Ser	Met	Lys	His	Leu	Arg	Phe	Glu	Ser	Ile	Leu	125	130	135
Gln	Glu	Lys	Lys	Ile	Ile	Gln	Ile	Thr	Cys	Gly	Asp	Tyr	His	Ser	140	145	150
Leu	Ala	Leu	Ser	Lys	Gly	Gly	Glu	Leu	Phe	Ala	Trp	Gly	Gln	Asn	155	160	165
Leu	His	Gly	Gln	Leu	Gly	Val	Gly	Arg	Lys	Phe	Pro	Ser	Thr	Thr	170	175	180
Thr	Pro	Gln	Ile	Val	Glu	His	Leu	Ala	Gly	Val	Pro	Leu	Ala	Gln	185	190	195
Ile	Ser	Ala	Gly	Glu	Ala	His	Ser	Met	Ala	Leu	Ser	Met	Ser	Gly	200	205	210
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Lys	His	Gly	Gln	Leu	Gly	His	Asn	Ser	Thr	Gln	Asn	Glu	Leu	Arg	275	280	285
Pro	Cys	Leu	Val	Ala	Glu	Leu	Val	Gly	Tyr	Arg	Val	Thr	Gln	Ile	290	295	300
Ala	Cys	Gly	Arg	Trp	His	Thr	Leu	Ala	Tyr	Val	Ser	Asp	Leu	Gly	305	310	315
Lys	Val	Phe	Ser	Phe	Gly	Ser	Gly	Lys	Asp	Gly	Gln	Leu	Gly	Asn	320	325	330
Gly	Gly	Thr	Arg	Asp	Gln	Leu	Met	Pro	Leu	Pro	Val	Lys	Val	Ser	335	340	345
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Lys	Arg	Trp	Gln	Ser	Thr	Lys	Arg	Glu	Ile	Gln	Glu	Ile	Phe	Ser	
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Ser	Pro	Ala	Cys	Leu	Thr	Gly	Ser	Phe	Leu	Arg	Lys	Arg	Arg	Thr	
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Thr	Glu	Met	Met	Pro	Val	Tyr	Leu	Asp	Leu	Asn	Lys	Ala	Arg	Asn	
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Ile	Phe	Arg	Glu	Leu	Thr	Gln	Lys	Asp	Trp	Ile	Thr	Asn	Met	Ile	
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Thr	Thr	Cys	Leu	Lys	Asp	Asn	Leu	Leu	Lys	Arg	Leu	Pro	Phe	His	
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Cys	Pro	Val	Met	His	Ile	Ser	Asn	Asn	Trp	Glu	Ser	Leu	Val	Val	
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Pro	Phe	Ala	Lys	Val	Val	Cys	Lys	Met	Ser	Asp	Gln	Ser	Ser	Leu	
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Lys	Leu	Val	Gln	Met	Phe	Lys	Thr	Ala	Val	Ile	Cys	Gln	Leu	Asp	
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Gln	Leu	Pro	Glu	Ser	Ile	Phe	Gln	Val	Asp	Glu	Leu	Leu	His	Arg	
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Thr	Val	Asp	Ala	Ser	Glu	Asn	Val	Gln	Cys	Cys	Val	Ile	Phe	Ser	
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His	Phe	Pro	Phe	Ile	Phe	Asn	Asn	Leu	Ser	Lys	Ile	Lys	Leu	Leu	
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His	Thr	Asp	Thr	Leu	Leu	Lys	Ile	Glu	Ser	Lys	Lys	His	Lys	Ala	
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Tyr	Leu	Arg	Ser	Ala	Ala	Ile	Glu	Glu	Glu	Arg	Glu	Ser	Glu	Phe	
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Ala	Leu	Arg	Pro	Thr	Phe	Asp	Leu	Thr	Val	Arg	Arg	Asn	His	Leu	
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Asp	Leu	Gly	Gly	Val	Lys	Lys	Glu	Phe	Phe	Tyr	Cys	Leu	Phe	Ala	725	730	735
Glu	Met	Ile	Gln	Pro	Glu	Tyr	Gly	Met	Phe	Met	Tyr	Pro	Glu	Gly	740	745	750
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Arg	Tyr	Phe	Phe	Phe	Gly	Val	Leu	Cys	Gly	Leu	Ser	Leu	Phe	Asn	770	775	780
Cys	Asn	Val	Ala	Asn	Leu	Pro	Phe	Pro	Leu	Ala	Leu	Phe	Lys	Lys	785	790	795
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His	Pro	Glu	Glu	Leu	Lys	Asp	Val	Ile	Val	Gly	Asn	Thr	Asp	Tyr	905	910	915
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Thr	Phe	Cys	Cys	Pro	Glu	Ser	Trp	Asn	Glu	Arg	Asp	Pro	Ile	Arg	980	985	990
Ala	Leu	Thr	Cys	Phe	Ser	Val	Leu	Phe	Leu	Pro	Lys	Tyr	Ser	Thr	995	1000	1005
Met	Glu	Thr	Val	Glu	Glu	Ala	Leu	Gln	Glu	Ala	Ile	Asn	Asn	Asn	1010	1015	1020
Arg	Gly	Phe	Gly														

<210> 32
 <211> 579
 <212> DNA
 <213> Homo sapien

<220>
 <221> Unsure
 <222> 80-119
 <223> Unknown base

<400> 32
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 nnnnnnnnnn nnnnnnnnnc atgttcatta tagttcatta cagttacata 150
 gtccgaaggt cttacaacta atcactggta gcaataaatg cttcaggccc 200
 acatgatgct gattagttct cagttttcat tcagttcaca atataaccac 250
 cattcctgcc ctccctgcc agggtcataa atggtgactg cctaacaaca 300
 aaatttgcag tctcatctca ttttcatcca gacttctgga actcaaagat 350
 taacttttga ctaaccctgg aatatctctt atctcactta tagcttcagg 400
 catgtattta tatgtattct tgatagcaat accataatca atgtgtattc 450
 ctgatagtaa tgctacaata aatccaaaca tttcaactct gttagaatag 500
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 aaaatttctc ctactaggaa cagtgggta 579

<210> 33
 <211> 56
 <212> PRT
 <213> Homo sapien

<220>
 <221> unsure
 <222> 27-40
 <223> unknown amino acid

<220>
 <221> Unsure
 <222> 80-119
 <223> Unknown amino acid

<400> 33
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 1 5 10 15
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 20 25 30
 Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Met Phe Ile Ile Val
 35 40 45
 His Tyr Ser Tyr Ile Val Arg Arg Ser Tyr Asn
 50 55

<210> 34
 <211> 347
 <212> DNA

<213> Homo sapien

<400> 34

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 aagcctacac atgtgcccct gaacctaata aaaaagttaa aagaaaaacg 150
 tttggattat tttccctctt tcgaacaaag acattgggtt gcccaaggac 200
 tacaaataaa ccaacgggaa aaaagaaagg ttccagtttt gtctgaaaat 250
 tctgattaag cctctggggc ctacagcctg gagaacctgg agaatcctac 300
 acccacagaa cccggctttg tccccaaaga ataaaaacac ctctctg 347

<210> 35

<211> 39

<212> PRT

<213> Homo sapien

<400> 35

Arg	Ile	Lys	Lys	Leu	Pro	Ile	Trp	Tyr	Tyr	Ala	Phe	Tyr	Leu	Asp
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Asp	Glu	Ile	Ile	Cys	Thr	Thr	Asn	Pro	Gly	Asp	Met	Gln	Phe	Thr
				20					25					30
Tyr	Ile	Ala	Ser	Leu	His	Met	Cys	Pro						
				35										

<210> 36

<211> 3554

<212> DNA

<213> Homo sapien

<400> 36

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 gtaaataaat ttgagataca tattctagag gtagaatgtg caatactttt 200
 tgtatgtcca tatacagaaa ttggttgcat tttccttaaa taaaaagatt 250
 ttttaaaagt tagtgagctg ttatgttttc ttccctctga cttcaattcc 300
 ttgattcttt caattttttt aatataaatt tactgtctaa aagctggatc 350
 agcttatgct cctttgttga gagaagttgg catgctgtca agtgggctgg 400
 gcacactgag tttcagtttc ctttctctga gtctttgaag cttcaaggct 450
 gctgaataat ttccttctcc cattttgtgc ctgcctagct atccagacag 500
 agcagctacc ctcagctcta gctgatacta cagacagtac aacagatcaa 550
 gaagtatggc agtgacaact cgtttgacat gggtgcacga aaagatcctg 600
 caaatcatt ttggagggaa gcggcttagc cttctctata agggtagtgt 650
 ccatggattc cgtaatggag ttttgcttga cagatgttgt aatcaagggc 700
 ctactctaac agtgatttat agtgaagatc atattattgg agcatatgca 750

gaagagagtt accaggaagg aaagtatgct tccatcatcc tttttgcact 800
 tcaagatact aaaatttcag aatggaaact aggactatgt acaccagaaa 850
 cactgttttg ttgtgatggt acaaaatata actccccaac taatttccag 900
 atagatggaa gaaatagaaa agtgattatg gacttaaaga caatggaaaa 950
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 tcccatggaa tcaatcaa taaatcatca tgactacatt gattcccat 1450
 cgctgaagga cagaattcat tgtgtggcat ttgtatttga tgccagctct 1500
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 aataaaatct acttatccag agaatgtttt ttaaaagaaa caggaaatat 1900
 atggactgta ggataggtgt cataaaaatt ttgtttctaa atcatttaga 1950
 atccactgca tgtattccaa attacaatta tcagtgcacat tagaacttga 2000
 tatgtgaagt tcttcaagag tactttgtga gaccagatct ccattttttt 2050
 ccaatgggaa attattgcaa gttcctacat cttgatattg ctttcgtaat 2100
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<210> 37
 <211> 392
 <212> PRT
 <213> Homo sapien

<400> 37
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 Ser Val His Gly Phe Arg Asn Gly Val Leu Leu Asp Arg Cys Cys
 35 40 45
 Asn Gln Gly Pro Thr Leu Thr Val Ile Tyr Ser Glu Asp His Ile
 50 55 60
 Ile Gly Ala Tyr Ala Glu Glu Ser Tyr Gln Glu Gly Lys Tyr Ala
 65 70 75

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

Thr Glu

<210> 38

<211> 2952

<212> DNA

<213> Homo sapien

<400> 38

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 ctccaagatc taaaccgaga atcgaaacta agctggggtc catggagcct 150
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 gccacccatg cctccccccg agaccccctc tgaaggccgc cagcccagcc 250
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 gctgctcaat aaacacttgt tgaaccatca aaaaaaaaaa aaaaaaaaaa 2950
 aa 2952

<210> 39

<211> 781

<212> PRT

<213> Homo sapien

<400> 39

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

				350					355					360
Gln	Glu	Glu	Pro	Gln	Ser	Leu	Gln	Ala	Ala	Val	Arg	Thr	Asp	Gly
				365					370					375
Phe	Asp	Glu	Phe	Lys	Val	Arg	Leu	Gln	Asp	Leu	Ser	Ser	Cys	Ile
				380					385					390
Thr	Gln	Gly	Lys	Asp	Ala	Ala	Val	Ser	Lys	Lys	Ala	Ser	Pro	Glu
				395					400					405
Ala	Ala	Ser	Thr	Pro	Arg	Asp	Pro	Ile	Asp	Val	Asp	Leu	Asp	Val
				410					415					420
Ser	Asn	Thr	Thr	Thr	Ala	Gln	Lys	Arg	Lys	Cys	Ser	Gln	Thr	Gln
				425					430					435
Cys	Pro	Arg	Lys	Val	Ile	Lys	Met	Glu	Ser	Glu	Glu	Gly	Lys	Glu
				440					445					450
Ala	Arg	Leu	Ala	Arg	Ser	Ser	Pro	Glu	Gln	Pro	Arg	Pro	Ser	Thr
				455					460					465
Ser	Lys	Ala	Val	Ser	Pro	Pro	His	Leu	Asp	Gly	Pro	Pro	Ser	Pro
				470					475					480
Arg	Ser	Pro	Val	Ile	Gly	Ser	Glu	Val	Phe	Leu	Pro	Asn	Ser	Asn
				485					490					495
His	Val	Ala	Ser	Gly	Ala	Gly	Glu	Ala	Glu	Glu	Arg	Val	Val	Val
				500					505					510
Ile	Ser	Ser	Ser	Glu	Asp	Ser	Asp	Ala	Glu	Asn	Ser	Cys	Met	Glu
				515					520					525
Pro	Met	Glu	Thr	Ala	Glu	Pro	Gln	Ser	Ser	Pro	Ala	His	Ser	Ser
				530					535					540
Pro	Ala	His	Ser	Ser	Pro	Ala	His	Ser	Ser	Pro	Val	Gln	Ser	Leu
				545					550					555
Leu	Arg	Ala	Gln	Gly	Ala	Ser	Ser	Leu	Pro	Cys	Gly	Thr	Tyr	His
				560					565					570
Pro	Pro	Ala	Trp	Pro	Pro	His	Gln	Pro	Ala	Glu	Gln	Ala	Ala	Thr
				575					580					585
Pro	Asp	Ala	Glu	Pro	His	Ser	Glu	Pro	Pro	Asp	His	Gln	Glu	Arg
				590					595					600
Pro	Ala	Val	His	Arg	Gly	Ile	Arg	Tyr	Leu	Leu	Tyr	Arg	Ala	Gln
				605					610					615
Arg	Ala	Ile	Arg	Leu	Arg	His	Ala	Leu	Arg	Leu	His	Pro	Gln	Leu
				620					625					630
His	Arg	Ala	Pro	Ile	Arg	Thr	Trp	Ser	Pro	His	Val	Val	Gln	Ala
				635					640					645
Ser	Thr	Pro	Ala	Ile	Thr	Gly	Pro	Leu	Asn	His	Pro	Ala	Asn	Ala
				650					655					660
Gln	Glu	His	Pro	Ala	Gln	Leu	Gln	Arg	Gly	Ile	Ser	Pro	Pro	His
				665					670					675
Arg	Ile	Arg	Gly	Ala	Val	Arg	Ser	Arg	Ser	Arg	Ser	Leu	Arg	Gly
				680					685					690

Ser Ser His Leu Ser Gln Trp Leu Asn Asn Phe Phe Ala Leu Pro
 695 700 705
 Phe Ser Ser Met Ala Ser Gln Leu Asp Met Ser Ser Val Val Gly
 710 715 720
 Ala Gly Glu Gly Arg Ala Gln Thr Leu Gly Ala Val Val Pro Pro
 725 730 735
 Gly Asp Ser Val Arg Gly Ser Met Glu Ala Ser Gln Val Gln Val
 740 745 750
 Pro Leu Glu Ala Ser Pro Ile Thr Phe Pro Pro Pro Cys Ala Pro
 755 760 765
 Glu Arg Pro Pro Ile Ser Pro Val Pro Gly Ala Arg Gln Ala Gly
 770 775 780
 Leu

<210> 40
 <211> 1924
 <212> DNA
 <213> Homo sapien

<400> 40
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 gacgtggaac tcagcagcgg aggctggacg cttgcatggc gcttgagaga 100
 ttccatcgtg cctggctcac ataagcgctt cctggaagtg aagtcgtgct 150
 gtcctgaacg cgggccaggc agctgcggcc tggggggttt ggagtgatca 200
 cgaatgagca aggcgtttgg gctcctgagg caaatctgtc agtccatcct 250
 ggctgagtcc tcgcagtccc cggcagatct tgaagaaaag aaggaagaag 300
 acagcaacat gaagagagag cagcccagag agcgtcccag ggccctgggac 350
 taccctcatg gcctgggttg tttacacaac attggacaga cctgctgcct 400
 taactccttg attcaggtgt tcgtaatgaa tgtggacttc accaggatat 450
 tgaagaggat cacggtgccc aggggagctg acgagcagag gagaagcgtc 500
 cctttccaga tgcttctgct gctggagaag atgcaggaca gccggcagaa 550
 agcagtgcgg cccctggagc tggcctactg cctgcagaag tgcaacgtgc 600
 ccttgtttgt ccaacatgat gctgcccac tgtacctcaa actctggaac 650
 ctgattaagg accagatcac tgatgtgcac ttggtggaga gactgcaggc 700
 cctgtatacg atccgggtga aggactcctt gatttgcgtt gactgtgcca 750
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 gatgtggact caaagcccct gaagacactg gaggacgccc tgcactgctt 850
 cttccagccc aggagttat caagcaaaag caagtgcttc tgtgagaact 900
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gagaaagatc tgccactccc tgtacttccc ccagagcttg gatttcagcc 1050
 agatccttcc aatgaagcga gagtcttggt atgctgagga gcagtctgga 1100
 gggcagtatg agcttttttgc tgtgattgcg cacgtgggaa tggcagactc 1150
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 acctacggaa atcctaacta cactggcag gaaactgcat atcttctggt 1300
 ttacatgaag atggagtgt aatggaaatg cccaaaacct tcagagattg 1350
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 tgtaactgct attcatttat tcagcaaata tttattgagc atctcttctc 1850
 cataagatag tgtgataaac acggtcatga ataaagttat tttccccgaa 1900
 aaaaaaaaaa aaaaaaaaaa aaaa 1924

<210> 41
 <211> 372
 <212> PRT
 <213> Homo sapien

<400> 41
 Met Ser Lys Ala Phe Gly Leu Leu Arg Gln Ile Cys Gln Ser Ile
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 Glu Glu Asp Ser Asn Met Lys Arg Glu Gln Pro Arg Glu Arg Pro
 35 40 45
 Arg Ala Trp Asp Tyr Pro His Gly Leu Val Gly Leu His Asn Ile
 50 55 60
 Gly Gln Thr Cys Cys Leu Asn Ser Leu Ile Gln Val Phe Val Met
 65 70 75
 Asn Val Asp Phe Thr Arg Ile Leu Lys Arg Ile Thr Val Pro Arg
 80 85 90
 Gly Ala Asp Glu Gln Arg Arg Ser Val Pro Phe Gln Met Leu Leu
 95 100 105
 Leu Leu Glu Lys Met Gln Asp Ser Arg Gln Lys Ala Val Arg Pro
 110 115 120

Leu Glu Leu Ala Tyr Cys Leu Gln Lys Cys Asn Val Pro Leu Phe
 125 130 135
 Val Gln His Asp Ala Ala Gln Leu Tyr Leu Lys Leu Trp Asn Leu
 140 145 150
 Ile Lys Asp Gln Ile Thr Asp Val His Leu Val Glu Arg Leu Gln
 155 160 165
 Ala Leu Tyr Thr Ile Arg Val Lys Asp Ser Leu Ile Cys Val Asp
 170 175 180
 Cys Ala Met Glu Ser Ser Arg Asn Ser Ser Met Leu Thr Leu Pro
 185 190 195
 Leu Ser Leu Phe Asp Val Asp Ser Lys Pro Leu Lys Thr Leu Glu
 200 205 210
 Asp Ala Leu His Cys Phe Phe Gln Pro Arg Glu Leu Ser Ser Lys
 215 220 225
 Ser Lys Cys Phe Cys Glu Asn Cys Gly Lys Lys Thr Arg Gly Lys
 230 235 240
 Gln Val Leu Lys Leu Thr His Leu Pro Gln Thr Leu Thr Ile His
 245 250 255
 Leu Met Arg Phe Ser Ile Arg Asn Ser Gln Thr Arg Lys Ile Cys
 260 265 270
 His Ser Leu Tyr Phe Pro Gln Ser Leu Asp Phe Ser Gln Ile Leu
 275 280 285
 Pro Met Lys Arg Glu Ser Cys Asp Ala Glu Glu Gln Ser Gly Gly
 290 295 300
 Gln Tyr Glu Leu Phe Ala Val Ile Ala His Val Gly Met Ala Asp
 305 310 315
 Ser Gly His Tyr Cys Val Tyr Ile Arg Asn Ala Val Asp Gly Lys
 320 325 330
 Trp Ser Cys Phe Asn Asp Ser Asn Ile Cys Leu Val Ser Trp Glu
 335 340 345
 Asp Ile Gln Cys Thr Tyr Gly Asn Pro Asn Tyr His Trp Gln Glu
 350 355 360
 Thr Ala Tyr Leu Leu Val Tyr Met Lys Met Glu Cys
 365 370

<210> 42

<211> 1508

<212> DNA

<213> Homo sapien

<400> 42

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ggcggcaagg ggagctgagc cccgtggaag accagagaga gggtttggag 200

gcagccccta agggcccttc gcgggagagc gtcgtgcacg cgggccagag 250

gcgcacaagt gcatacacct tgatagcacc aaatataaac cggagaaatg 300
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 gagcagaaca gagctaaacc gggtcacctg gtgcccagac ggctaggtgg 400
 aagccagtca gaaactgaag tcagacagaa acaacaactc cagctgatgc 450
 aatctaaata caagcaaaag ctaaaaagag aagaatctgt aagaatcaag 500
 aaggaagctg aagaagctga actccaaaaa atgaaggcaa ttcagagaga 550
 gaagagcaat aaactggagg agaaaaaaag acttcaagaa aaccttagaa 600
 gagaagcatt tagagagcat cagcaatata aaaccgctga gttcttgagc 650
 aaactgaaca cagaatcgcc agacagaagt gcctgtcaaa gtgctgtttg 700
 tggcccacaa tcctcaacat gggccagaag ctgggcttac agagattctc 750
 taaaggcaga agaaaacaga aaattgcaaa agatgaagga tgaacaacat 800
 caaaagagtg aattactgga actgaaacgg cagcagcaag agcaagaaag 850
 agccaaaatc caccagactg aacacaggag ggtaaataat gcttttctgg 900
 accgactcca aggcaaaagt caaccaggtg gcctcgagca atctggaggc 950
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 tactgccagg gaaatgctac attatttttc taattggaag tataattaga 1250
 gtgatgttgg tagggtagaa aaagaggag tcacttgatg ctttcagggtt 1300
 aatcagagct atgggtgcta caggcttgct tttctaagt acatattctt 1350
 atctaattct cagatcaggt tttgaaagct ttgggggtct ttttagattt 1400
 taatccctac tttctttatg gtacaaatat gtacaaaaga aaaaggctctt 1450
 atattctttt acacaaattt ataaataaat tttgaactcc ttctgtaaaa 1500
 aaaaaaaa 1508

<210> 43
 <211> 307
 <212> PRT
 <213> Homo sapien

<400> 43
 Met Asn Thr Arg Asn Arg Val Val Asn Ser Gly Leu Gly Ala Ser
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 Pro Ala Ser Arg Pro Thr Arg Asp Pro Gln Asp Pro Ser Gly Arg
 20 25 30
 Gln Gly Glu Leu Ser Pro Val Glu Asp Gln Arg Glu Gly Leu Glu
 35 40 45

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

<210> 44
 <211> 1590
 <212> DNA
 <213> Homo sapien

<400> 44
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 ttctgaagg aaaggtgctt ccgaggtagc tctaccctg tgtgtgtgtc 200

caaggtggta aaggggtggct cctcaggcaa gggcaccacc ctcagaggcc 250
 gatctgacgc tgacctgggt gtcttcctca gtcctctcac cacttttcag 300
 gatcagttaa atcgccgggg agagttcatc caggaaatta ggagacagct 350
 ggaagcctgt caaagagaga gagcactttc cgtgaagttt gaggtccagg 400
 ctccacgctg gggcaacccc cgtgcgctca gcttcgtact gagttcgctc 450
 cagctcgggg aggggggtgga gttcgatgtg ctgcctgcct ttgatgccct 500
 gggtcagttg actggcagct ataaacctaa cccccaatc tatgtcaagc 550
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 ttgggaagct gccacctcag tatgccttgg agctcctgac ggtctatgct 750
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 caaagtatta tgactttaaa aaccccatta ttgaaaagta cctgagaagg 900
 cagctcacga aaccaggcc tgtgatcctg gaccggcgg accctacagg 950
 aaacttgggt ggtggagacc caaagggttg gaggcagctg gcacaagagg 1000
 ctgaggcctg gctgaattac ccatgcttta agaattggga tgggtcccca 1050
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 cgacgatccc aggacgtatc agaaatatgg ttacattgga acacatgagt 1150
 accctcattt ctctcataga cccagcacgc tccaggcagc atccaccca 1200
 caggcagaag aggactggac ctgcaccatc ctctgaatgc cagtgcattc 1250
 tgggggaaag ggctccagtg ttatctggac cagttccttc attttcagg 1300
 gggactcttg atccagagaa gacaaagctc ctcagtgagc tgggtgtataa 1350
 tccaagacag aaccaagtc tcctgactcc tggccttcta tgcctctat 1400
 cctatcatag ataacattct ccacagctc acttcattcc acctattctc 1450
 tgaaaatatt ccctgagaga gaacagagag atttagataa gagaatgaaa 1500
 ttccagcctt gactttcttc tgtgcacctg atgggagggg aatgtcta 1550
 gtattatcaa taacaataaa aataaagcaa ataccaaaa 1590

<210> 45

<211> 400

<212> PRT

<213> Homo sapien

<400> 45

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

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

	365		370		375
Phe Ser His Arg	Pro Ser Thr Leu Gln Ala Ala Ser Thr Pro Gln				
	380		385		390
Ala Glu Glu Asp	Trp Thr Cys Thr Ile Leu				
	395		400		

<210> 46
 <211> 1590
 <212> DNA
 <213> Homo sapien

<400> 46
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 ttcctgaagg aaaggtgctt ccgaggtagc tcctaccctg tgtgtgtgtc 200
 caaggtggta aaggggtggct cctcaggcaa gggcaccacc ctcagaggcc 250
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 gatcagttaa atcgccgggg agagttcatc caggaaatta ggagacagct 350
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 tgaaaatatt ccctgagaga gaacagagag atttagataa gagaatgaaa 1500
 ttccagcctt gactttcttc tgtgcacctg atgggagggt aatgtctaata 1550
 gtattatcaa taacaataaa aataaagcaa ataccaaaaa 1590

<210> 47

<211> 400

<212> PRT

<213> Homo sapien

<400> 47

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

Arg	Thr	Val	Leu	Glu	Leu	Val	Ile	Asn	Tyr	Gln	Gln	Leu	Cys	Ile
				260					265					270
Tyr	Trp	Thr	Lys	Tyr	Tyr	Asp	Phe	Lys	Asn	Pro	Ile	Ile	Glu	Lys
				275					280					285
Tyr	Leu	Arg	Arg	Gln	Leu	Thr	Lys	Pro	Arg	Pro	Val	Ile	Leu	Asp
				290					295					300
Pro	Ala	Asp	Pro	Thr	Gly	Asn	Leu	Gly	Gly	Gly	Asp	Pro	Lys	Gly
				305					310					315
Trp	Arg	Gln	Leu	Ala	Gln	Glu	Ala	Glu	Ala	Trp	Leu	Asn	Tyr	Pro
				320					325					330
Cys	Phe	Lys	Asn	Trp	Asp	Gly	Ser	Pro	Val	Ser	Ser	Trp	Ile	Leu
				335					340					345
Leu	Ala	Glu	Ser	Asn	Ser	Thr	Asp	Asp	Glu	Thr	Asp	Asp	Pro	Arg
				350					355					360
Thr	Tyr	Gln	Lys	Tyr	Gly	Tyr	Ile	Gly	Thr	His	Glu	Tyr	Pro	His
				365					370					375
Phe	Ser	His	Arg	Pro	Ser	Thr	Leu	Gln	Ala	Ala	Ser	Thr	Pro	Gln
				380					385					390
Ala	Glu	Glu	Asp	Trp	Thr	Cys	Thr	Ile	Leu					
				395					400					

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 <211> 2355
 <212> DNA
 <213> Homo sapien

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 aaaaa 2355

<210> 49
 <211> 558
 <212> PRT

<213> Homo sapien

<400> 49

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

				320						325					330
Leu	Gly	Lys	Ala	Ala	Arg	Phe	Ser	Cys	Asp	Ile	Glu	Gln	Leu	Lys	
				335					340					345	
Ala	Gln	Ile	Met	Leu	Cys	Gly	Glu	Ile	Thr	His	Pro	Lys	Asn	Asn	
				350					355					360	
Tyr	Ser	Ser	Arg	Thr	Pro	Cys	Ser	Ser	Leu	Leu	Pro	Leu	Leu	Asn	
				365					370					375	
Ala	His	Ala	Ala	Thr	Ser	Gly	Lys	Gln	Ser	Asn	Phe	Ser	Arg	Lys	
				380					385					390	
Ser	Ser	Thr	His	Asn	Lys	Pro	Ser	Glu	Gly	Lys	Ala	Ala	Asn	Pro	
				395					400					405	
Lys	Met	Val	Ser	Ser	Leu	Pro	Ser	Thr	Ala	Asp	Pro	Ser	His	Gln	
				410					415					420	
Thr	Met	Pro	Ala	Asn	Lys	Gln	Asn	Gly	Ser	Ser	Asn	Gln	Arg	Arg	
				425					430					435	
Arg	Phe	Asn	Pro	Gln	Tyr	His	Asn	Asn	Arg	Leu	Asn	Gly	Pro	Ala	
				440					445					450	
Lys	Ser	Gln	Gly	Ser	Gly	Asn	Glu	Ala	Glu	Pro	Leu	Gly	Lys	Gly	
				455					460					465	
Asn	Ser	Arg	His	Glu	His	Arg	Arg	Gln	Pro	His	Asn	Gly	Phe	Arg	
				470					475					480	
Pro	Lys	Asn	Lys	Gly	Gly	Ala	Lys	Asn	Gln	Glu	Ala	Ser	Leu	Gly	
				485					490					495	
Met	Lys	Thr	Pro	Glu	Ala	Pro	Ala	His	Ser	Glu	Lys	Pro	Arg	Arg	
				500					505					510	
Arg	Gln	His	Ala	Ala	Asp	Thr	Ser	Glu	Ala	Arg	Pro	Phe	Arg	Gly	
				515					520					525	
Ser	Val	Gly	Arg	Val	Ser	Gln	Cys	Asn	Leu	Cys	Pro	Thr	Arg	Ile	
				530					535					540	
Glu	Val	Ser	Thr	Asp	Ala	Ala	Val	Leu	Ser	Val	Pro	Ala	Val	Thr	
				545					550					555	

Leu Val Ala

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 <211> 3468
 <212> DNA
 <213> Homo sapien

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 tgagtgagaa caataagaat tccttggaga gcagcctacg gcaactaaaa 200
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 tgaagacaaa gtattttacc ggactgagtt tcagaatcgt gaattcaaag 300

ccacaatgtg caacctactg gcctatctaa agcacctcaa agggcaaaac 350
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<210> 51

<211> 521

<212> PRT

<213> Homo sapien

<400> 51

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

Gln Val Met Asn Leu Arg Glu Asn Gly Met Tyr Gly Lys Arg Lys
 350 355 360
 Leu Leu Glu Leu Ile Gly His Ala Val Ala His Leu Lys Lys Ala
 365 370 375
 Asp Glu Ala Asn Asp Asn Leu Phe Arg Val Cys Ser Ile Leu Ala
 380 385 390
 Ser Leu His Ala Leu Ala Asp Gln Tyr Glu Glu Ala Glu Tyr Tyr
 395 400 405
 Phe Gln Lys Glu Phe Ser Lys Glu Leu Thr Pro Val Ala Lys Gln
 410 415 420
 Leu Leu His Leu Arg Tyr Gly Asn Phe Gln Leu Tyr Gln Met Lys
 425 430 435
 Cys Glu Asp Lys Ala Ile His His Phe Ile Glu Gly Val Lys Ile
 440 445 450
 Asn Gln Lys Ser Arg Glu Lys Glu Lys Met Lys Asp Lys Leu Gln
 455 460 465
 Lys Ile Ala Lys Met Arg Leu Ser Lys Asn Gly Ala Asp Ser Glu
 470 475 480
 Ala Leu His Val Leu Ala Phe Leu Gln Glu Leu Asn Glu Lys Met
 485 490 495
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 500 505 510
 Leu Ile Pro Ser Ala Ser Ser Trp Asn Gly Glu
 515 520

<210> 52
 <211> 6270
 <212> DNA
 <213> Homo sapien

<400> 52
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 Glu Leu Val Ile Phe Leu Asp Cys Phe Lys Ser Tyr Val Asp Gln
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 Pro Glu Gln Ser Val Pro Gly Ala Leu Gln Phe Arg Leu Thr Ser
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 Asn Val Leu Gly Gln Ala Gly Ser Ala Val Lys Pro Lys Pro Gln
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His	Gln	Val	Cys	Leu	Gln	Gly	Leu	Trp	Lys	Glu	Thr	Leu	Pro	Pro	
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Cys	Lys	Lys	Asp	Ala	Phe	Ser	Leu	Gly	Glu	Gly	Leu	Arg	Thr	Val	
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Val	Asn	Tyr	Gly	Phe	Glu	Asp	Pro	Ala	Val	Gly	Gln	Phe	Leu	Gln	
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Leu	Asp	Leu	Ser	Gln	Ile	Pro	Thr	Lys	Glu	Leu	Asp	Arg	Phe	Ile	
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His	Lys	Ala	Ser	Arg	Val	Ser	Lys	Gly	Gly	Ser	Phe	Gly	Arg	Gly	
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Thr	Asp	Leu	Arg	Asp	Gly	Cys	Asp	Val	Glu	Leu	Ile	Ile	Phe	Leu	
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Asn	Cys	Phe	Thr	Asp	Tyr	Lys	Asp	Gln	Gly	Pro	Arg	Arg	Ala	Glu	
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Ile	Leu	Asp	Glu	Met	Arg	Ala	His	Val	Glu	Ser	Trp	Trp	Gln	Asp	
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Gln	Val	Pro	Ser	Leu	Ser	Leu	Gln	Phe	Pro	Glu	Gln	Asn	Val	Pro	
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Leu	Arg	Arg	Asn	Phe	Met	Asn	Ile	Arg	Pro	Val	Lys	Leu	Lys	Asn
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Leu	Ile	Leu	Leu	Val	Lys	His	Trp	Tyr	Arg	Gln	Val	Ala	Ala	Gln
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Asn	Lys	Gly	Lys	Gly	Pro	Ala	Pro	Ala	Ser	Leu	Pro	Pro	Ala	Tyr
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Ala	Leu	Glu	Leu	Leu	Thr	Ile	Phe	Ala	Trp	Glu	Gln	Gly	Cys	Arg
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Gln	Asp	Cys	Phe	Asn	Met	Ala	Gln	Gly	Phe	Arg	Thr	Val	Leu	Gly
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Trp	Asn	Val	Gly	His	Gly	Ser	Trp	Glu	Leu	Leu	Ala	Gln	Glu	Ala
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Ala	Ala	Leu	Gly	Met	Gln	Ala	Cys	Phe	Leu	Ser	Arg	Asp	Gly	Thr
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Ser	Val	Gln	Pro	Trp	Asp	Val	Met	Pro	Ala	Leu	Leu	Tyr	Gln	Thr
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Pro	Ala	Gly	Asp	Leu	Asp	Lys	Phe	Ile	Ser	Glu	Phe	Leu	Gln	Pro
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Cys	Ser	Phe	Leu	Lys	Glu	Asn	Cys	Phe	Arg	Asn	Ser	Pro	Ile	Lys
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 Gln Asp Ile Lys Lys Pro Val Gln Gln Pro Ala Lys Gln Ala Pro
 50 55 60
 His Gln Thr Leu Ala Ala Arg Phe Met Asp Gly His Ile Thr Phe
 65 70 75
 Gln Thr Ala Ala Thr Val Lys Ile Pro Thr Thr Thr Pro Ala Thr
 80 85 90

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Thr	Thr	Gln	Ala	Thr	Pro	Asn	Asn	Ser	His	Thr	Ala	Pro	Pro	Val
				110					115					120
Thr	Glu	Val	Thr	Val	Gly	Pro	Ser	Leu	Ala	Pro	Tyr	Ser	Leu	Pro
				125					130					135
Pro	Thr	Ile	Thr	Pro	Pro	Ala	His	Thr	Ala	Gly	Thr	Ser	Ser	Ser
				140					145					150
Thr	Val	Ser	His	Thr	Thr	Gly	Asn	Thr	Thr	Gln	Pro	Ser	Asn	Gln
				155					160					165
Thr	Thr	Leu	Pro	Ala	Thr	Leu	Ser	Ile	Ala	Leu	His	Lys	Ser	Thr
				170					175					180
Thr	Gly	Gln	Lys	Pro	Asp	Gln	Pro	Thr	His	Ala	Pro	Gly	Thr	Thr
				185					190					195
Ala	Ala	Ala	His	Asn	Thr	Thr	Arg	Thr	Ala	Ala	Pro	Ala	Ser	Thr
				200					205					210
Val	Pro	Gly	Pro	Thr	Leu	Ala	Pro	Gln	Pro	Ser	Ser	Val	Lys	Thr
				215					220					225
Gly	Ile	Tyr	Gln	Val	Leu	Asn	Gly	Ser	Arg	Leu	Cys	Ile	Lys	Ala
				230					235					240
Glu	Met	Gly	Ile	Gln	Leu	Ile	Val	Gln	Asp	Lys	Glu	Ser	Val	Phe
				245					250					255
Ser	Pro	Arg	Arg	Tyr	Phe	Asn	Ile	Asp	Pro	Asn	Ala	Thr	Gln	Ala
				260					265					270
Ser	Gly	Asn	Cys	Gly	Thr	Arg	Lys	Ser	Asn	Leu	Leu	Leu	Asn	Phe
				275					280					285
Gln	Gly	Gly	Phe	Val	Asn	Leu	Thr	Phe	Thr	Lys	Asp	Glu	Glu	Ser
				290					295					300
Tyr	Tyr	Ile	Ser	Glu	Val	Gly	Ala	Tyr	Leu	Thr	Val	Ser	Asp	Pro
				305					310					315
Glu	Thr	Val	Tyr	Gln	Gly	Ile	Lys	His	Ala	Val	Val	Met	Phe	Gln
				320					325					330
Thr	Ala	Val	Gly	His	Ser	Phe	Lys	Cys	Val	Ser	Glu	Gln	Ser	Leu
				335					340					345
Gln	Leu	Ser	Ala	His	Leu	Gln	Val	Lys	Thr	Thr	Asp	Val	Gln	Leu
				350					355					360
Gln	Ala	Phe	Asp	Phe	Glu	Asp	Asp	His	Phe	Gly	Asn	Val	Asp	Glu
				365					370					375
Cys	Ser	Ser	Asp	Tyr	Thr	Ile	Val	Leu	Pro	Val	Ile	Gly	Ala	Ile
				380					385					390
Val	Val	Gly	Leu	Cys	Leu	Met	Gly	Met	Gly	Val	Tyr	Lys	Ile	Arg
				395					400					405
Leu	Arg	Cys	Gln	Ser	Ser	Gly	Tyr	Gln	Arg	Ile				
				410					415					

<210> 56

<211> 1820

<212> DNA

<213> Homo sapien

<400> 56

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 caaggtgggc tccttcggga atggcacggt tctcaggagc accagagagg 250
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 aggactgttg ctatgacaac agggagaacc ccactctccag ctggaacgtg 1050
 aagagggcac gagacatcca cttgacagtg gagcagaggg gttaccacaga 1100
 tttcaacctc atcgtgaacc cttatgagcc cataaggaag gttaaagaga 1150
 aaatccggag gaccaggggc tactctggcc tgcagcgtct gtccttccag 1200
 gttcctggca gtgagaggca gcttctcagc agcaggtgct ccttagccaa 1250
 atatgggatc ttctcccaca ctcacatcta tctgctggag accatcccct 1300
 ccgagatcca ggtcttcgtg aagaatcctg atgggtgggag ctacgcctat 1350
 gccatcaacc ccaacagctt catcctgggt ctgaagcagc agattgaaga 1400
 ccagcagggg cttcctaaaa agcagcagca gctggaattc caaggccaag 1450
 tcctgcagga ctggttgggt ctggggatct atggcatcca agacagtgac 1500
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gttttctctg ggagacttct ctgtacattt ctgccatgta ctccagaact 1600
 catcctgtca atcactctgt cccattgtct actgggaagg tcccaggtct 1650
 tcaccagttt tacaatgagt tatcccaggc cagacgtggt agctcacacc 1700
 tgtaatccca gaactttggg aggccgaggt gggaggagcg cttgagccga 1750
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 taaaaaaata attcactggg 1820

<210> 57

<211> 514

<212> PRT

<213> Homo sapien

<400> 57

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

	245		250		255
Leu Asp Glu Gly	Phe Thr Thr Val Met	Asp Leu Leu Leu Glu Tyr			
	260	265			270
Glu Val Ile Cys	Ile Tyr Trp Thr Lys	Tyr Tyr Thr Leu His Asn			
	275	280			285
Ala Ile Ile Glu	Asp Cys Val Arg Lys	Gln Leu Lys Lys Glu Arg			
	290	295			300
Pro Ile Ile Leu	Asp Pro Ala Asp Pro	Thr Leu Asn Val Ala Glu			
	305	310			315
Gly Tyr Arg Trp	Asp Ile Val Ala Gln	Arg Ala Ser Gln Cys Leu			
	320	325			330
Lys Gln Asp Cys	Cys Tyr Asp Asn Arg	Glu Asn Pro Ile Ser Ser			
	335	340			345
Trp Asn Val Lys	Arg Ala Arg Asp Ile	His Leu Thr Val Glu Gln			
	350	355			360
Arg Gly Tyr Pro	Asp Phe Asn Leu Ile	Val Asn Pro Tyr Glu Pro			
	365	370			375
Ile Arg Lys Val	Lys Glu Lys Ile Arg	Arg Thr Arg Gly Tyr Ser			
	380	385			390
Gly Leu Gln Arg	Leu Ser Phe Gln Val	Pro Gly Ser Glu Arg Gln			
	395	400			405
Leu Leu Ser Ser	Arg Cys Ser Leu Ala	Lys Tyr Gly Ile Phe Ser			
	410	415			420
His Thr His Ile	Tyr Leu Leu Glu Thr	Ile Pro Ser Glu Ile Gln			
	425	430			435
Val Phe Val Lys	Asn Pro Asp Gly Gly	Ser Tyr Ala Tyr Ala Ile			
	440	445			450
Asn Pro Asn Ser	Phe Ile Leu Gly Leu	Lys Gln Gln Ile Glu Asp			
	455	460			465
Gln Gln Gly Leu	Pro Lys Lys Gln Gln	Gln Leu Glu Phe Gln Gly			
	470	475			480
Gln Val Leu Gln	Asp Trp Leu Gly Leu	Gly Ile Tyr Gly Ile Gln			
	485	490			495
Asp Ser Asp Thr	Leu Ile Leu Ser Lys	Lys Lys Gly Glu Ala Leu			
	500	505			510

Phe Pro Ala Ser

<210> 58
 <211> 597
 <212> DNA
 <213> Homo sapien

<400> 58
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 aggcattggag gcctctgctc tcacctcatc agcagtgacc agtgtggcca 100
 aagtggtcag ggtggcctct ggctctgccg tagttttgcc cctggccagg 150

attgctacag ttgtgattgg aggagttgtg gccatggcgg ctgtgccccat 200
 ggtgctcagt gccatgggct tcactgcggc gggaatcgcc tcgtcctcca 250
 tagcagccaa gatgatgtcc gcggcggcca ttgccaatgg ggggtggagtt 300
 gcctcgggca gccttgtggg tactctgcag tcactgggag caactggact 350
 ctccggattg accaagttca tcctgggctc cattgggtct gccattgcgg 400
 ctgtcattgc gaggttctac tagctccctg cccctcgccc tgcagagaag 450
 agaaccatgc caggggagaa ggcacccagc catcctgacc cagcgaggag 500
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 agaggaaaat aagaaataaa gatgaattgt tgcaactctt aaaaaaa 597

<210> 59
 <211> 122
 <212> PRT
 <213> Homo sapien

<400> 59
 Met Glu Ala Ser Ala Leu Thr Ser Ser Ala Val Thr Ser Val Ala
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 Lys Val Val Arg Val Ala Ser Gly Ser Ala Val Val Leu Pro Leu
 20 25 30
 Ala Arg Ile Ala Thr Val Val Ile Gly Gly Val Val Ala Met Ala
 35 40 45
 Ala Val Pro Met Val Leu Ser Ala Met Gly Phe Thr Ala Ala Gly
 50 55 60
 Ile Ala Ser Ser Ser Ile Ala Ala Lys Met Met Ser Ala Ala Ala
 65 70 75
 Ile Ala Asn Gly Gly Gly Val Ala Ser Gly Ser Leu Val Gly Thr
 80 85 90
 Leu Gln Ser Leu Gly Ala Thr Gly Leu Ser Gly Leu Thr Lys Phe
 95 100 105
 Ile Leu Gly Ser Ile Gly Ser Ala Ile Ala Ala Val Ile Ala Arg
 110 115 120

Phe Tyr

<210> 60
 <211> 3328
 <212> DNA
 <213> Homo sapien

<400> 60
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 gggccgcagc cgccgccgcg atgccagta agttcagctg ccggcagctc 100
 cgggaggcgg gccagtgttt cgagagtttc ctggtcgttc ggggactgga 150
 catggagaca gatcgcgagc ggctgcggac catttataac cgcgacttca 200
 agatcagctt tgggaccccc gccctgggt tctcctccat gctgtatgga 250

atgaagattg caaatctggc ctacgtcacc aagactcggg tcaggttctt 300
 cagactcgac cgctgggccc acgtgcggtt cccagaaaag aggagaatga 350
 agctgggggtc agatatcagc aaacaccaca agtcactgct agccaagatc 400
 ttttatgaca gggctgagta tcttcatggg aaacatggtg tggatgtgga 450
 agtccagggg ccccatgaag cccgagatgg gcagctcctt atccgcctgg 500
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 cagtctgtta ccctcactca cctcttccca ctctgccgga caccctcagtt 600
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 aatgctatga actccatgtc cattgtaaga ccagctttgt gggctacttc 700
 ccagccacag tgctctggga gctgctggga cctggggagt cgggttcaga 750
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 actaccacc tccccgcctc aggcagctgc tccccatgct tcttcaggga 1000
 acaagtatct tctactgccc taaggagatc gcagagatca aggccagct 1050
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 gagcttttcc atgagcctcc tgagccgctt tgtggatggg ctgaccttca 1400
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 ataccgggtg tcccttcctt gccaaactgg acctgcaaca gggacagaat 2950
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 ccatgactac ctcccccagg agcgggaggg tgaagggggc ctgtctctgc 3050
 aagtggagcc agagtggagg aatgagctct gaagacacag caccagcct 3100
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 tgttctatgc aaaaaaaaaa aaaaaaaaaa 3328

<210> 61
 <211> 1003
 <212> PRT
 <213> Homo sapien

<400> 61
 Met Pro Ser Lys Phe Ser Cys Arg Gln Leu Arg Glu Ala Gly Gln
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 Cys Phe Glu Ser Phe Leu Val Val Arg Gly Leu Asp Met Glu Thr
 20 25 30

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

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

Leu	Leu	Thr	Tyr	Asn	Ser	Leu	Tyr	Lys	Lys	Gly	Pro	Asp	Gly	Tyr	710	715	720
Asp	Pro	Gln	Phe	Ile	Thr	Lys	Leu	Leu	Arg	Asn	Tyr	Arg	Ser	His	725	730	735
Pro	Thr	Ile	Leu	Asp	Ile	Pro	Asn	Gln	Leu	Tyr	Tyr	Glu	Gly	Glu	740	745	750
Leu	Gln	Ala	Cys	Ala	Asp	Val	Val	Asp	Arg	Glu	Arg	Phe	Cys	Arg	755	760	765
Trp	Ala	Gly	Leu	Pro	Arg	Gln	Gly	Phe	Pro	Ile	Ile	Phe	His	Gly	770	775	780
Val	Met	Gly	Lys	Asp	Glu	Arg	Glu	Gly	Asn	Ser	Pro	Ser	Phe	Phe	785	790	795
Asn	Pro	Glu	Glu	Ala	Ala	Thr	Val	Thr	Ser	Tyr	Leu	Lys	Leu	Leu	800	805	810
Leu	Ala	Pro	Ser	Ser	Lys	Lys	Gly	Lys	Ala	Arg	Leu	Ser	Pro	Arg	815	820	825
Ser	Val	Gly	Val	Ile	Ser	Pro	Tyr	Arg	Lys	Gln	Val	Glu	Lys	Ile	830	835	840
Arg	Tyr	Cys	Ile	Thr	Lys	Leu	Asp	Arg	Glu	Leu	Arg	Gly	Leu	Asp	845	850	855
Asp	Ile	Lys	Asp	Leu	Lys	Val	Gly	Ser	Val	Glu	Glu	Phe	Gln	Gly	860	865	870
Gln	Glu	Arg	Ser	Val	Ile	Leu	Ile	Ser	Thr	Val	Arg	Ser	Ser	Gln	875	880	885
Ser	Phe	Val	Gln	Leu	Asp	Leu	Asp	Phe	Asn	Leu	Gly	Phe	Leu	Lys	890	895	900
Asn	Pro	Lys	Arg	Phe	Asn	Val	Ala	Val	Thr	Arg	Ala	Lys	Ala	Leu	905	910	915
Leu	Ile	Ile	Val	Gly	Asn	Pro	Leu	Leu	Leu	Gly	His	Asp	Pro	Asp	920	925	930
Trp	Lys	Val	Phe	Leu	Glu	Phe	Cys	Lys	Glu	Asn	Gly	Gly	Tyr	Thr	935	940	945
Gly	Cys	Pro	Phe	Pro	Ala	Lys	Leu	Asp	Leu	Gln	Gln	Gly	Gln	Asn	950	955	960
Leu	Leu	Gln	Gly	Leu	Ser	Lys	Leu	Ser	Pro	Ser	Thr	Ser	Gly	Pro	965	970	975
His	Ser	His	Asp	Tyr	Leu	Pro	Gln	Glu	Arg	Glu	Gly	Glu	Gly	Gly	980	985	990
Leu	Ser	Leu	Gln	Val	Glu	Pro	Glu	Trp	Arg	Asn	Glu	Leu			995	1000	

<210> 62

<211> 3667

<212> DNA

<213> Homo sapien

<400> 62

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<210> 63
 <211> 751
 <212> PRT
 <213> Homo sapien

<400> 63
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 35 40 45
 Asp Leu Thr Leu Thr Pro Gln Glu Ser Ile Gln Leu Tyr Asp Thr
 50 55 60
 Met Ala Gln Val Trp Glu Thr Trp Pro Arg Ala Gln Glu Leu Cys
 65 70 75
 Pro Glu Glu Phe Ile Leu Phe Lys Asn Lys Ile Val Ile Lys Lys
 80 85 90
 Leu Asp Ala Arg Lys Tyr Glu Glu Asn Leu Lys Ala Glu Leu Thr
 95 100 105
 Asn Trp Ile Lys Asn Gly Gln Val Lys Lys Val Lys Arg Val Leu
 110 115 120
 Lys Asn Leu Ser Pro Asp Ser Leu Ser Ser Ser Lys Asp Met Val
 125 130 135
 Lys Met Phe Pro Leu Leu Val Glu Lys Leu Arg Gln Met Asp Lys
 140 145 150
 Leu Pro Ala Ile Phe Phe Leu Phe Lys Asn Asp Asp Val Gly Lys
 155 160 165
 Arg Ala Gly Ser Val Cys Thr Phe Leu Glu Lys Thr Glu Thr Lys
 170 175 180
 Ser His Pro His Thr Glu Ser His Ser Tyr Val Phe Ala Ile Asp
 185 190 195
 Glu Val Leu Glu Lys Val Arg Lys Thr Gln Lys Arg Ile Thr Lys
 200 205 210
 Lys Lys Pro Lys Glu Gly Glu Lys Leu Glu Arg Lys Lys Val Tyr
 215 220 225
 Arg Ala Glu Tyr Ile Asn Phe Leu Glu Asn Leu Lys Ile Leu Glu
 230 235 240
 Ile Ser Glu Asp Cys Thr Tyr Ala Asp Val Lys Ala Leu His Thr
 245 250 255

Glu	Ile	Thr	Arg	Asn	Lys	Asp	Ser	Thr	Leu	Asp	Arg	Val	Leu	Pro	260	265	270
Arg	Val	Arg	Phe	Thr	Arg	His	Gly	Lys	Glu	Leu	Lys	Ala	Leu	Ala	275	280	285
Gln	Arg	Gly	Ile	Gly	Tyr	His	His	Ser	Ser	Met	Tyr	Phe	Lys	Glu	290	295	300
Lys	Glu	Phe	Val	Glu	Ile	Leu	Phe	Val	Lys	Gly	Leu	Ile	Arg	Val	305	310	315
Val	Thr	Ala	Thr	Glu	Thr	Leu	Ala	Leu	Gly	Ile	His	Met	Pro	Cys	320	325	330
Lys	Ser	Ile	Val	Phe	Ala	Gln	Asp	Ser	Val	Tyr	Leu	Asp	Ala	Leu	335	340	345
Asn	Tyr	Arg	Gln	Met	Ser	Gly	Arg	Ala	Gly	Arg	Arg	Gly	Gln	Asp	350	355	360
Leu	Leu	Gly	Asn	Val	Tyr	Phe	Phe	Asp	Ile	Pro	Leu	Pro	Lys	Ile	365	370	375
Lys	Lys	Arg	Leu	Leu	Ala	Ser	Ser	Val	Pro	Glu	Leu	Arg	Gly	Gln	380	385	390
Phe	Pro	Leu	Ser	Ile	Thr	Leu	Val	Leu	Arg	Leu	Met	Leu	Leu	Ala	395	400	405
Ser	Lys	Gly	Asp	Asp	Pro	Glu	Asp	Ala	Lys	Ala	Lys	Val	Leu	Ser	410	415	420
Val	Leu	Lys	His	Ser	Leu	Leu	Ser	Phe	Lys	Arg	Arg	Arg	Ala	Met	425	430	435
Glu	Thr	Leu	Lys	Leu	Tyr	Phe	Leu	Phe	Ser	Leu	Gln	Leu	Leu	Ile	440	445	450
Lys	Glu	Asp	Tyr	Leu	Asn	Lys	Lys	Gly	Asn	Pro	Lys	Lys	Phe	Ala	455	460	465
Gly	Leu	Ala	Ser	Tyr	Leu	His	Gly	His	Glu	Pro	Ser	Asn	Leu	Val	470	475	480
Phe	Val	Asn	Phe	Leu	Lys	Arg	Gly	Leu	Phe	His	Asn	Leu	Cys	Lys	485	490	495
Pro	Ala	Trp	Lys	Gly	Ser	Gln	Gln	Phe	Ser	Gln	Asp	Val	Met	Glu	500	505	510
Lys	Leu	Val	Leu	Val	Leu	Ala	Asn	Leu	Phe	Gly	Arg	Lys	Tyr	Ile	515	520	525
Pro	Ala	Lys	Phe	Gln	Asn	Ala	Asp	Leu	Ser	Phe	Ser	Gln	Ser	Lys	530	535	540
Val	Ile	Leu	Ala	Glu	Leu	Pro	Glu	Asp	Phe	Lys	Ala	Ala	Leu	Tyr	545	550	555
Glu	Tyr	Asn	Leu	Ala	Val	Met	Lys	Asp	Phe	Ala	Ser	Phe	Leu	Leu	560	565	570
Ile	Ala	Ser	Lys	Ser	Val	Asn	Met	Lys	Lys	Glu	His	Gln	Leu	Pro	575	580	585
Leu	Ser	Arg	Ile	Lys	Phe	Thr	Gly	Lys	Glu	Cys	Glu	Asp	Ser	Gln			

	590		595		600
Leu Val Ser His	Leu Met Ser Cys Lys	Lys Gly Arg Val Ala	Ile		
	605		610		615
Ser Pro Phe Val	Cys Leu Ser Gly Asn	Thr Asp Asn Asp Leu	Leu		
	620		625		630
Arg Pro Glu Thr	Ile Asn Gln Val Ile	Leu Arg Thr Val Gly	Val		
	635		640		645
Ser Gly Thr Gln	Ala Pro Leu Leu Trp	Pro Trp Lys Leu Asp	Asn		
	650		655		660
Arg Gly Arg Arg	Met Pro Leu Asn Ala	Tyr Val Leu Asn Phe	Tyr		
	665		670		675
Lys His Asn Cys	Leu Thr Arg Leu Asp	Gln Lys Asn Gly Met	Arg		
	680		685		690
Val Gly Gln Leu	Leu Lys Cys Leu Lys	Asp Phe Ala Phe Asn	Ile		
	695		700		705
Gln Ala Ile Ser	Asp Ser Leu Ser Glu	Leu Cys Glu Asn Lys	Arg		
	710		715		720
Asp Asn Val Val	Leu Ala Phe Lys Gln	Leu Ser Gln Thr Phe	Tyr		
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Glu Lys Leu Gln	Glu Met Gln Ile Gln	Met Ser Gln Asn His	Leu		
	740		745		750

Glu

<210> 64
 <211> 2984
 <212> DNA
 <213> Homo sapien

<400> 64
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 aaaacagcaa cttgtttgct actttttatct ctgttgattt ttttttcttg 200
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 ctattctaac gcaaaaccac taactgaagt tcagatataa tggatgggtt 2950
 gtgactatag tgtaaataaa tacttttcaa caat 2984

<210> 65
 <211> 476
 <212> PRT
 <213> Homo sapien

<400> 65
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 Leu Ala Ala Thr Ser Val Thr Ile Phe Pro Asn Ala Glu Leu Gly
 35 40 45
 Gly Pro Phe Asp Gln Met Asn Gly Val Ala Gly Asp Gly Met Ile
 50 55 60
 Asn Ile Asp Met Thr Gly Glu Lys Arg Ser Leu Asp Leu Pro Tyr
 65 70 75
 Pro Ser Ser Phe Ala Pro Val Ser Ala Pro Arg Asn Gln Thr Phe
 80 85 90
 Thr Tyr Met Gly Lys Phe Ser Ile Asp Pro Gln Tyr Pro Gly Ala
 95 100 105
 Ser Cys Tyr Pro Glu Gly Ile Ile Asn Ile Val Ser Ala Gly Ile
 110 115 120
 Leu Gln Gly Val Thr Ser Pro Ala Ser Thr Thr Ala Ser Ser Ser
 125 130 135
 Val Thr Ser Ala Ser Pro Asn Pro Leu Ala Thr Gly Pro Leu Gly
 140 145 150
 Val Cys Thr Met Ser Gln Thr Gln Pro Asp Leu Asp His Leu Tyr
 155 160 165
 Ser Pro Pro Pro Pro Pro Pro Tyr Ser Gly Cys Ala Gly Asp
 170 175 180

Leu	Tyr	Gln	Asp	Pro	Ser	Ala	Phe	Leu	Ser	Ala	Ala	Thr	Thr	Ser	185	190	195
Thr	Ser	Ser	Ser	Leu	Ala	Tyr	Pro	Pro	Pro	Pro	Ser	Tyr	Pro	Ser	200	205	210
Pro	Lys	Pro	Ala	Thr	Asp	Pro	Gly	Leu	Phe	Pro	Met	Ile	Pro	Asp	215	220	225
Tyr	Pro	Gly	Phe	Phe	Pro	Ser	Gln	Cys	Gln	Arg	Asp	Leu	His	Gly	230	235	240
Thr	Ala	Gly	Pro	Asp	Arg	Lys	Pro	Phe	Pro	Cys	Pro	Leu	Asp	Thr	245	250	255
Leu	Arg	Val	Pro	Pro	Pro	Leu	Thr	Pro	Leu	Ser	Thr	Ile	Arg	Asn	260	265	270
Phe	Thr	Leu	Gly	Gly	Pro	Ser	Ala	Gly	Val	Thr	Gly	Pro	Gly	Ala	275	280	285
Ser	Gly	Gly	Ser	Glu	Gly	Pro	Arg	Leu	Pro	Gly	Ser	Ser	Ser	Ala	290	295	300
Ala	Ala	Ala	Ala	Ala	Ala	Ala	Ala	Ala	Tyr	Asn	Pro	His	His	Leu	305	310	315
Pro	Leu	Arg	Pro	Ile	Leu	Arg	Pro	Arg	Lys	Tyr	Pro	Asn	Arg	Pro	320	325	330
Ser	Lys	Thr	Pro	Val	His	Glu	Arg	Pro	Tyr	Pro	Cys	Pro	Ala	Glu	335	340	345
Gly	Cys	Asp	Arg	Arg	Phe	Ser	Arg	Ser	Asp	Glu	Leu	Thr	Arg	His	350	355	360
Ile	Arg	Ile	His	Thr	Gly	His	Lys	Pro	Phe	Gln	Cys	Arg	Ile	Cys	365	370	375
Met	Arg	Asn	Phe	Ser	Arg	Ser	Asp	His	Leu	Thr	Thr	His	Ile	Arg	380	385	390
Thr	His	Thr	Gly	Glu	Lys	Pro	Phe	Ala	Cys	Asp	Tyr	Cys	Gly	Arg	395	400	405
Lys	Phe	Ala	Arg	Ser	Asp	Glu	Arg	Lys	Arg	His	Thr	Lys	Ile	His	410	415	420
Leu	Arg	Gln	Lys	Glu	Arg	Lys	Ser	Ser	Ala	Pro	Ser	Ala	Ser	Val	425	430	435
Pro	Ala	Pro	Ser	Thr	Ala	Ser	Cys	Ser	Gly	Gly	Val	Gln	Pro	Gly	440	445	450
Gly	Thr	Leu	Cys	Ser	Ser	Asn	Ser	Ser	Ser	Leu	Gly	Gly	Gly	Pro	455	460	465
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 <213> Homo sapien

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 <212> PRT
 <213> Homo sapien

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Ala	Leu	Asp	His	Ala	Gly	Tyr	Ser	Gly	Leu	Tyr	Glu	Ala	Ile	Glu
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Thr	Asp	Ile	Ile	Ser	Asp	Leu	Ser	Glu	Cys	Leu	Ile	Asn	Gln	Glu
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Cys	Glu	Glu	Ile	Leu	Gln	Ile	Cys	Ser	Thr	Lys	Gly	Met	Met	Ala
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Gly	Ala	Glu	Lys	Leu	Val	Glu	Cys	Leu	Leu	Arg	Ser	Asp	Lys	Glu
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Lys	Phe	Ser	Glu	Leu	Trp	Ile	Val	Glu	Lys	Gly	Ile	Lys	Asp	Val
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Glu	Thr	Glu	Asp	Leu	Glu	Asp	Lys	Met	Glu	Thr	Ser	Asp	Ile	Gln
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Ile	Gly	Leu	Thr	Ala	Ser	Val	Gly	Val	Gly	Asp	Ala	Lys	Asn	Thr	
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Asp	Glu	Ala	Leu	Asp	Tyr	Ile	Cys	Lys	Leu	Cys	Ala	Ser	Leu	Asp	
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Ala	Ser	Val	Ile	Ala	Thr	Val	Lys	His	Asn	Leu	Glu	Glu	Leu	Glu	
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Arg Lys Cys Lys	Ala Leu Ala Cys Tyr	Thr Ala Asp Val Arg Val			
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Cys Phe Val Ser	Arg Pro His Pro Lys	Pro Lys Gln Phe Ser Ser			
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Phe Glu Lys Arg	Ala Lys Ile Phe Cys	Ala Arg Gln Asn Cys Ser			
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His Asp Trp Gly	Ile His Val Lys Tyr	Lys Thr Phe Glu Ile Pro			
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Val Ile Lys Ile	Glu Ser Phe Val Val	Glu Asp Ile Ala Thr Gly			
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Val Gln Thr Leu	Tyr Ser Lys Trp Lys	Asp Phe His Phe Glu Lys			
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WO 2005/051988

PCT/US2004/006460

<211> 318
 <212> PRT
 <213> Homo sapien

<400> 69

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<210> 70

<211> 1414

<212> DNA

<213> Homo sapien

<400> 70

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<211> 3132
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<213> Homo sapien

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<210> 72
<211> 543
<212> PRT

<213> Homo sapien

<400> 72

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

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				335					340					345	
Asp	Arg	Arg	Phe	Ser	Arg	Ser	Asp	Glu	Leu	Thr	Arg	His	Ile	Arg	
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Ile	His	Thr	Gly	Gln	Lys	Pro	Phe	Gln	Cys	Arg	Ile	Cys	Met	Arg	
				365					370					375	
Asn	Phe	Ser	Arg	Ser	Asp	His	Leu	Thr	Thr	His	Ile	Arg	Thr	His	
				380					385					390	
Thr	Gly	Glu	Lys	Pro	Phe	Ala	Cys	Asp	Ile	Cys	Gly	Arg	Lys	Phe	
				395					400					405	
Ala	Arg	Ser	Asp	Glu	Arg	Lys	Arg	His	Thr	Lys	Ile	His	Leu	Arg	
				410					415					420	
Gln	Lys	Asp	Lys	Lys	Ala	Asp	Lys	Ser	Val	Val	Ala	Ser	Ser	Ala	
				425					430					435	
Thr	Ser	Ser	Leu	Ser	Ser	Tyr	Pro	Ser	Pro	Val	Ala	Thr	Ser	Tyr	
				440					445					450	
Pro	Ser	Pro	Val	Thr	Thr	Ser	Tyr	Pro	Ser	Pro	Ala	Thr	Thr	Ser	
				455					460					465	
Tyr	Pro	Ser	Pro	Val	Pro	Thr	Ser	Phe	Ser	Ser	Pro	Gly	Ser	Ser	
				470					475					480	
Thr	Tyr	Pro	Ser	Pro	Val	His	Ser	Gly	Phe	Pro	Ser	Pro	Ser	Val	
				485					490					495	
Ala	Thr	Thr	Tyr	Ser	Ser	Val	Pro	Pro	Ala	Phe	Pro	Ala	Gln	Val	
				500					505					510	
Ser	Ser	Phe	Pro	Ser	Ser	Ala	Val	Thr	Asn	Ser	Phe	Ser	Ala	Ser	
				515					520					525	
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Glu Ile Cys

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 <211> 1906
 <212> DNA
 <213> Homo sapien

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<210> 74
 <211> 391
 <212> PRT

<213> Homo sapien

<400> 74

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

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Ile Gly Leu Val	Gln Asp Asn Arg Met	Asn Glu Gly Asp Ala Tyr			
	335	340			345
Tyr Leu Leu Lys	Asp Phe Ala Leu Thr	Ile Lys Ser Ile Ser Val			
	350	355			360
Ser Leu Arg Glu	Leu Cys Glu Asn Glu	Asp Asp Asn Val Val Leu			
	365	370			375
Ala Phe Glu Gln	Leu Ser Thr Thr Phe	Trp Glu Lys Leu Asn Lys			
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Val					

<210> 75
 <211> 3906
 <212> DNA
 <213> Homo sapien

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<210> 76
 <211> 482
 <212> PRT
 <213> Homo sapien

<400> 76
 Met Ser Glu Ile Arg Lys Asp Thr Leu Lys Ala Ile Leu Leu Glu
 1 5 10 15
 Leu Glu Cys His Phe Thr Trp Asn Leu Leu Lys Glu Asp Ile Asp
 20 25 30
 Leu Phe Glu Val Glu Asp Thr Ile Gly Gln Gln Leu Glu Phe Leu
 35 40 45
 Thr Thr Lys Ser Arg Leu Ala Leu Tyr Asn Leu Leu Ala Tyr Val
 50 55 60
 Lys His Leu Lys Gly Gln Asn Lys Asp Ala Leu Glu Cys Leu Glu
 65 70 75

Gln	Ala	Glu	Glu	Ile	Ile	Gln	Gln	Glu	His	Ser	Asp	Lys	Glu	Glu	
				80					85					90	
Val	Arg	Ser	Leu	Val	Thr	Trp	Gly	Asn	Tyr	Ala	Trp	Val	Tyr	Tyr	
				95					100					105	
His	Met	Asp	Gln	Leu	Glu	Glu	Ala	Gln	Lys	Tyr	Thr	Gly	Lys	Ile	
				110					115					120	
Gly	Asn	Val	Cys	Lys	Lys	Leu	Ser	Ser	Pro	Ser	Asn	Tyr	Lys	Leu	
				125					130					135	
Glu	Cys	Pro	Glu	Thr	Asp	Cys	Glu	Lys	Gly	Trp	Ala	Leu	Leu	Lys	
				140					145					150	
Phe	Gly	Gly	Lys	Tyr	Tyr	Gln	Lys	Ala	Lys	Ala	Ala	Phe	Glu	Lys	
				155					160					165	
Ala	Leu	Glu	Val	Glu	Pro	Asp	Asn	Pro	Glu	Phe	Asn	Ile	Gly	Tyr	
				170					175					180	
Ala	Ile	Thr	Val	Tyr	Arg	Leu	Asp	Asp	Ser	Asp	Arg	Glu	Gly	Ser	
				185					190					195	
Val	Lys	Ser	Phe	Ser	Leu	Gly	Pro	Leu	Arg	Lys	Ala	Val	Thr	Leu	
				200					205					210	
Asn	Pro	Asp	Asn	Ser	Tyr	Ile	Lys	Val	Phe	Leu	Ala	Leu	Lys	Leu	
				215					220					225	
Gln	Asp	Val	His	Ala	Glu	Ala	Glu	Gly	Glu	Lys	Tyr	Ile	Glu	Glu	
				230					235					240	
Ile	Leu	Asp	Gln	Ile	Ser	Ser	Gln	Pro	Tyr	Val	Leu	Arg	Tyr	Ala	
				245					250					255	
Ala	Lys	Phe	Tyr	Arg	Arg	Lys	Asn	Ser	Trp	Asn	Lys	Ala	Leu	Glu	
				260					265					270	
Leu	Leu	Lys	Lys	Ala	Leu	Glu	Val	Thr	Pro	Thr	Ser	Ser	Phe	Leu	
				275					280					285	
His	His	Gln	Met	Gly	Leu	Cys	Tyr	Arg	Ala	Gln	Met	Ile	Gln	Ile	
				290					295					300	
Lys	Lys	Ala	Thr	His	Asn	Arg	Pro	Lys	Gly	Lys	Asp	Lys	Leu	Lys	
				305					310					315	
Val	Asp	Glu	Leu	Ile	Ser	Ser	Ala	Ile	Phe	His	Phe	Lys	Ala	Ala	
				320					325					330	
Met	Glu	Arg	Asp	Ser	Met	Phe	Ala	Phe	Ala	Tyr	Thr	Asp	Leu	Ala	
				335					340					345	
Asn	Met	Tyr	Ala	Glu	Gly	Gly	Gln	Tyr	Ser	Asn	Ala	Glu	Asp	Ile	
				350					355					360	
Phe	Arg	Lys	Ala	Leu	Arg	Leu	Glu	Asn	Ile	Thr	Asp	Asp	His	Lys	
				365					370					375	
His	Gln	Ile	His	Tyr	His	Tyr	Gly	Arg	Phe	Gln	Glu	Phe	His	Arg	
				380					385					390	
Lys	Ser	Glu	Asn	Thr	Ala	Ile	His	His	Tyr	Leu	Glu	Ala	Leu	Lys	
				395					400					405	
Val	Lys	Asp	Arg	Ser	Pro	Leu	Arg	Thr	Lys	Leu	Thr	Ser	Ala	Leu	

				410						415					420
Lys	Lys	Leu	Ser	Thr	Lys	Arg	Leu	Cys	His	Asn	Ala	Leu	Asp	Val	
				425					430					435	
Gln	Ser	Leu	Ser	Ala	Leu	Gly	Phe	Val	Tyr	Lys	Leu	Glu	Gly	Glu	
				440					445					450	
Lys	Arg	Gln	Ala	Ala	Glu	Tyr	Tyr	Glu	Lys	Ala	Gln	Lys	Ile	Asp	
				455					460					465	
Pro	Glu	Asn	Ala	Glu	Phe	Leu	Thr	Ala	Leu	Cys	Glu	Leu	Arg	Leu	
				470					475					480	
Ser	Ile														

<210> 77
 <211> 2224
 <212> DNA
 <213> Homo sapien

<400> 77
 gctgacacct gccagtgga agctggcatc cctccccttg tgggttcaga 50
 gctgcaagaa gcaccaggct cggccacttc agaagcccca gcctcgacct 100
 agcccaccct ctcagggcca cagtgcagaa gcctgcacac ctgccaagtc 150
 tctccgactc cttgcagctg ctgtcagcat ggcccaggct cctgctgacc 200
 cgggcagaga aggccacctt gaacaaagaa tcctgcaggt gctgacagag 250
 gctggctccc cggtgaaact tgcccagctg gtgaaggaat gccaagcacc 300
 caagagggag ctcaaccaag tcctctaccg aatgaaaaag gagttgaaag 350
 tctccctcac atcccctgcc acctggtgct tgggcgggac tgatcctgaa 400
 ggcgagggtc ctgcagagct ggccttgctc agccctgccg agaggcccca 450
 gcaacatgca gctacaattc cagagacccc tggccctcag ttcagccaac 500
 aacgggagga agacatctac aggtttctca aagacaatgg tccccagagg 550
 gccctggtca tcgcccgaagc actgggaatg aggacagcaa aagatgtgaa 600
 ccgagacttg tacaggatga agagcaggca ccttctggac atggatgagc 650
 agtccaaagc atggacgatt taccgcccag aagattctgg aagaagagca 700
 aagtcagcct caattattta ccagcacaaat ccaatcaaca tgatctgcca 750
 gaatggaccc aacagctgga tttccattgc aaactccgaa gccatccaga 800
 ttggacacgg gaacatcatt acaagacaga cagtctccag ggaggacggt 850
 tccgccggtc cacgccacct cccttcaatg gcaccagggt attcctcaac 900
 ttggggggacc ctagttgatc cctggggggcc ccaggacatc cacatggagc 950
 ggtccatact gagacgggtg cagctgggac acagcaatga gatgaggctc 1000
 cacggcgtcc cgtccgaggg ccctgccac atccccctg gcagccccc 1050
 agtctctgcc actgctgccg gccagaagc ttcgtttgaa gcaagaattc 1100

ccagtccagg aactcaccct gagggggaag ccgcccagag aatccacatg 1150
 aaatcgtgct ttctcgagga cgccaccatc ggcaacagca acaaaatgtc 1200
 tatcagccca ggggtggctg gcccaggagg agtcgcaggg tctggagagg 1250
 gggagccagg ggaggacgca ggtcgtcgtc ccgcagacac acaatccaga 1300
 agtcactttc ctcgagacat tggtcagccc atcactccca gccactcgaa 1350
 gctcaccccc aagctggaaa ctatgactct tggaaacagg agtcacaaag 1400
 ctgcagaagg cagccactat gtggatgaag cctcacacga ggggagctgg 1450
 tggggaggtg ggatttagtg cacagcctca cgtggggctt ggacacaggc 1500
 tgggggtggg cgcattgtag ggagactagc ctgctgctct ctgcattcct 1550
 tagcgtcttg tttgacctgc ttgcttccag acataacctg catgaatcag 1600
 ttttggggga atggacctgg catggggatg ggttcaggcc aggtcttttg 1650
 atggccagga gtagatgaca gggagttgcc ttggggaacc tttggtgtgc 1700
 caagaggagg tgggtagatg ggagtggggc tcgggtcccc aggcccaggg 1750
 gactctctcc actctttcct gggctcgggg catctgcctg gagttacctt 1800
 ccatcatggc tacctgctgt ggtttgaatg tttgagtccc aacaaaattc 1850
 atatcaaac ataatcccaa ctgggtgcag tggctcacgc ctgtaatccc 1900
 agcactttgg gaggccgagg cgggcggatc aataggtcag gaaatccaga 1950
 ccgtcctggc taacatggtg aaaccccgtc tctactaaaa aaaaaaatac 2000
 aaaaaattag ccgggcggtg tggcgggcac ctggagtccc agctactccg 2050
 gaggctgagg gaggagaatg gtgtgaaccc gggaggtgga gcttccagtg 2100
 agccgagatc gcgccactgc actccaggct gggcgacaga gcgagactcc 2150
 gtctcaaaaa aataaatata taaataaaaa ataaaccacc cataaaaaaa 2200
 aaaaaaaaaa aaaaaaaaaa aaaa 2224

<210> 78
 <211> 429
 <212> PRT
 <213> Homo sapien

<400> 78
 Met Ala Gln Ala Pro Ala Asp Pro Gly Arg Glu Gly His Leu Glu
 1 5 10 15
 Gln Arg Ile Leu Gln Val Leu Thr Glu Ala Gly Ser Pro Val Lys
 20 25 30
 Leu Ala Gln Leu Val Lys Glu Cys Gln Ala Pro Lys Arg Glu Leu
 35 40 45
 Asn Gln Val Leu Tyr Arg Met Lys Lys Glu Leu Lys Val Ser Leu
 50 55 60
 Thr Ser Pro Ala Thr Trp Cys Leu Gly Gly Thr Asp Pro Glu Gly
 65 70 75

Glu	Gly	Pro	Ala	Glu	Leu	Ala	Leu	Ser	Ser	Pro	Ala	Glu	Arg	Pro	
				80					85					90	
Gln	Gln	His	Ala	Ala	Thr	Ile	Pro	Glu	Thr	Pro	Gly	Pro	Gln	Phe	
				95					100					105	
Ser	Gln	Gln	Arg	Glu	Glu	Asp	Ile	Tyr	Arg	Phe	Leu	Lys	Asp	Asn	
				110					115					120	
Gly	Pro	Gln	Arg	Ala	Leu	Val	Ile	Ala	Gln	Ala	Leu	Gly	Met	Arg	
				125					130					135	
Thr	Ala	Lys	Asp	Val	Asn	Arg	Asp	Leu	Tyr	Arg	Met	Lys	Ser	Arg	
				140					145					150	
His	Leu	Leu	Asp	Met	Asp	Glu	Gln	Ser	Lys	Ala	Trp	Thr	Ile	Tyr	
				155					160					165	
Arg	Pro	Glu	Asp	Ser	Gly	Arg	Arg	Ala	Lys	Ser	Ala	Ser	Ile	Ile	
				170					175					180	
Tyr	Gln	His	Asn	Pro	Ile	Asn	Met	Ile	Cys	Gln	Asn	Gly	Pro	Asn	
				185					190					195	
Ser	Trp	Ile	Ser	Ile	Ala	Asn	Ser	Glu	Ala	Ile	Gln	Ile	Gly	His	
				200					205					210	
Gly	Asn	Ile	Ile	Thr	Arg	Gln	Thr	Val	Ser	Arg	Glu	Asp	Gly	Ser	
				215					220					225	
Ala	Gly	Pro	Arg	His	Leu	Pro	Ser	Met	Ala	Pro	Gly	Asp	Ser	Ser	
				230					235					240	
Thr	Trp	Gly	Thr	Leu	Val	Asp	Pro	Trp	Gly	Pro	Gln	Asp	Ile	His	
				245					250					255	
Met	Glu	Arg	Ser	Ile	Leu	Arg	Arg	Val	Gln	Leu	Gly	His	Ser	Asn	
				260					265					270	
Glu	Met	Arg	Leu	His	Gly	Val	Pro	Ser	Glu	Gly	Pro	Ala	His	Ile	
				275					280					285	
Pro	Pro	Gly	Ser	Pro	Pro	Val	Ser	Ala	Thr	Ala	Ala	Gly	Pro	Glu	
				290					295					300	
Ala	Ser	Phe	Glu	Ala	Arg	Ile	Pro	Ser	Pro	Gly	Thr	His	Pro	Glu	
				305					310					315	
Gly	Glu	Ala	Ala	Gln	Arg	Ile	His	Met	Lys	Ser	Cys	Phe	Leu	Glu	
				320					325					330	
Asp	Ala	Thr	Ile	Gly	Asn	Ser	Asn	Lys	Met	Ser	Ile	Ser	Pro	Gly	
				335					340					345	
Val	Ala	Gly	Pro	Gly	Gly	Val	Ala	Gly	Ser	Gly	Glu	Gly	Glu	Pro	
				350					355					360	
Gly	Glu	Asp	Ala	Gly	Arg	Arg	Pro	Ala	Asp	Thr	Gln	Ser	Arg	Ser	
				365					370					375	
His	Phe	Pro	Arg	Asp	Ile	Gly	Gln	Pro	Ile	Thr	Pro	Ser	His	Ser	
				380					385					390	
Lys	Leu	Thr	Pro	Lys	Leu	Glu	Thr	Met	Thr	Leu	Gly	Asn	Arg	Ser	
				395					400					405	
His	Lys	Ala	Ala	Glu	Gly	Ser	His	Tyr	Val	Asp	Glu	Ala	Ser	His	

410 415 420
 Glu Gly Ser Trp Trp Gly Gly Gly Ile
 425

<210> 79
 <211> 722
 <212> DNA
 <213> Homo sapien

<400> 79
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 gcatttaatg ttttgcacaa cttgcttggt ttgcaaataat gcgcacattt 100
 ctatgacaag atttattgct aaatattctt taaaactgca gcagttcaga 150
 taagatactg tcgaaaggac gtttggccca gcagcaggac ctccaccaat 200
 gaacggactc caattcttga tttgagcctt gggaaccaat caactttggt 250
 tccaagagtt tatgtgaact tccctccttt accagtaaaa tcttccccct 300
 attcttccct tctccagacc cgtggcttgc catagctgta catcttggt 350
 tataattctt tttgttcact cccaaagaaa ctgagtatct ttggagaatt 400
 ctttctttgt tgtcttttag cttcccagag ccaaacaaga aatatttttag 450
 gttttgtggg tcatgctggc ttggtcacag ctattcaact tgtatcttaa 500
 aattagccat agacagtatg aatgggtggg tctctgttcc aataaaacct 550
 taccctaaac actgaagttt gaattttatg taattttcaa ctgtcatgaa 600
 atactcatct tttgatcttt ttcagccact gaaaaatgta aaagccatcc 650
 ttaagttgca agctatacaa aaacagacag tggactggat ttgacccttg 700
 agccatttgt ccatgtgccc tc 722

<210> 80
 <211> 39
 <212> PRT
 <213> Homo sapien

<400> 80
 Thr Leu Lys Asn Lys Pro Lys Asn Pro Gln Phe Leu His Ile Phe
 1 5 10 15
 His Ala Phe Asn Val Leu His Asn Leu Leu Val Leu Gln Ile Cys
 20 25 30
 Ala His Phe Tyr Asp Lys Ile Tyr Cys
 35

<210> 81
 <211> 1826
 <212> DNA
 <213> Homo sapien

<400> 81
 agtctgcact ggagctgcct ggtgaccaga agtttggagt ccgctgacgt 50
 cgccgccag atggcctcca ggctgaccct gctgaccctc ctgctgctgc 100
 tgctggctgg ggatagagcc tcctcaaata caaatgctac cagctccagc 150

tcccaggatc cagagagttt gcaagacaga ggccaaggga aggtcgcaac 200
 aacagttatc tccaagatgc tattcggtga acccatcctg gaggtttcca 250
 gcttgccgac aaccaactca acaaccaatt cagccaccaa aataacagct 300
 aataccactg atgaaccac cacacaaccc accacagagc ccaccacca 350
 acccaccatc caaccacccc aaccaactac ccagctccca acagattctc 400
 ctaccagcc cactactggg tcttctgccc caggacctgt tactctctgc 450
 tctgacttgg agagtcattc aacagaggcc gtgttggggg atgctttggt 500
 agatttctcc ctgaagctct accacgcctt ctgagcaatg aagaagggtg 550
 agaccaacat ggctttttcc ccattcagca tcgccagcct ccttaccag 600
 gtctgctcg gggctgggca gaacaccaa acaaacctgg agagcatcct 650
 ctcttaccac aaggacttca cctgtgtcca ccaggccctg aagggttca 700
 cgaccaaagg tgtcacctca gtctctcaga tcttccacag ccagacctg 750
 gccataaggg acacctttgt gaatgcctct cggaccctgt acagcagcag 800
 cccagagtc ctaagcaaca acagtgcgc caacttgag ctcatcaaca 850
 cctgggtggc caagaacacc aacaacaaga tcagccggct gctagacagt 900
 ctgccctccg ataccgcct tgtcctctc aatgctatct acctgagtgc 950
 caagtggaag acaacatttg atcccaagaa aaccagaatg gaacccttc 1000
 acttcaaaaa ctgagttata aaagtgccca tgatgaatag caagaagtac 1050
 cctgtggccc atttcattga ccaaactttg aaagccaagg tggggcagct 1100
 gcagctctcc cacaatctga gtttggtgat cctggtacct cagaacctga 1150
 aacatcgtct tgaagacatg gaacaggctc tcagcccttc tgttttcaag 1200
 gccatcatgg agaaactgga gatgtccaag ttccagccca ctctcctaac 1250
 actacccgc atcaaagtga cgaccagcca ggatatgctc tcaatcatgg 1300
 agaaattgga attcttcgat ttttcttatg accttaacct gtgtgggctg 1350
 acagaggacc cagatcttca ggtttctgcg atgcagcacc agacagtgc 1400
 ggaactgaca gagactgggg tggaggcggc tgcagcctcc gccatctctg 1450
 tggcccgac cctgctggtc tttgaagtgc agcagccctt cctcttcgtg 1500
 ctctgggacc agcagcaciaa gttccctgtc ttcattggggc gagtatatga 1550
 cccagggcc tgagacctgc aggatcaggt tagggcgagc gctacctctc 1600
 cagcctcagc tctcagttgc agccctgctg ctgcctgcct ggacttgccc 1650
 ctgccacctc ctgcctcagg tgtccgctat ccacaaaag ggctcctgag 1700
 ggtctgggca agggacctgc ttctattagc ccttctccat ggccctgcca 1750
 tgctctccaa accacttttt gcagctttct ctagttcaag ttcaccagac 1800
 tctataaata aaacctgaca gacct 1826

<210> 82
 <211> 500
 <212> PRT
 <213> Homo sapien

<400> 82
 Met Ala Ser Arg Leu Thr Leu Leu Thr Leu Leu Leu Leu Leu Leu
 1 5 10 15
 Ala Gly Asp Arg Ala Ser Ser Asn Pro Asn Ala Thr Ser Ser Ser
 20 25 30
 Ser Gln Asp Pro Glu Ser Leu Gln Asp Arg Gly Glu Gly Lys Val
 35 40 45
 Ala Thr Thr Val Ile Ser Lys Met Leu Phe Val Glu Pro Ile Leu
 50 55 60
 Glu Val Ser Ser Leu Pro Thr Thr Asn Ser Thr Thr Asn Ser Ala
 65 70 75
 Thr Lys Ile Thr Ala Asn Thr Thr Asp Glu Pro Thr Thr Gln Pro
 80 85 90
 Thr Thr Glu Pro Thr Thr Gln Pro Thr Ile Gln Pro Thr Gln Pro
 95 100 105
 Thr Thr Gln Leu Pro Thr Asp Ser Pro Thr Gln Pro Thr Thr Gly
 110 115 120
 Ser Phe Cys Pro Gly Pro Val Thr Leu Cys Ser Asp Leu Glu Ser
 125 130 135
 His Ser Thr Glu Ala Val Leu Gly Asp Ala Leu Val Asp Phe Ser
 140 145 150
 Leu Lys Leu Tyr His Ala Phe Ser Ala Met Lys Lys Val Glu Thr
 155 160 165
 Asn Met Ala Phe Ser Pro Phe Ser Ile Ala Ser Leu Leu Thr Gln
 170 175 180
 Val Leu Leu Gly Ala Gly Gln Asn Thr Lys Thr Asn Leu Glu Ser
 185 190 195
 Ile Leu Ser Tyr Pro Lys Asp Phe Thr Cys Val His Gln Ala Leu
 200 205 210
 Lys Gly Phe Thr Thr Lys Gly Val Thr Ser Val Ser Gln Ile Phe
 215 220 225
 His Ser Pro Asp Leu Ala Ile Arg Asp Thr Phe Val Asn Ala Ser
 230 235 240
 Arg Thr Leu Tyr Ser Ser Ser Pro Arg Val Leu Ser Asn Asn Ser
 245 250 255
 Asp Ala Asn Leu Glu Leu Ile Asn Thr Trp Val Ala Lys Asn Thr
 260 265 270
 Asn Asn Lys Ile Ser Arg Leu Leu Asp Ser Leu Pro Ser Asp Thr
 275 280 285
 Arg Leu Val Leu Leu Asn Ala Ile Tyr Leu Ser Ala Lys Trp Lys
 290 295 300
 Thr Thr Phe Asp Pro Lys Lys Thr Arg Met Glu Pro Phe His Phe

	305		310		315
Lys Asn Ser Val	Ile Lys Val Pro Met	Met Asn Ser Lys Lys Tyr			
	320	325			330
Pro Val Ala His	Phe Ile Asp Gln Thr	Leu Lys Ala Lys Val Gly			
	335	340			345
Gln Leu Gln Leu	Ser His Asn Leu Ser	Leu Val Ile Leu Val Pro			
	350	355			360
Gln Asn Leu Lys	His Arg Leu Glu Asp	Met Glu Gln Ala Leu Ser			
	365	370			375
Pro Ser Val Phe	Lys Ala Ile Met Glu	Lys Leu Glu Met Ser Lys			
	380	385			390
Phe Gln Pro Thr	Leu Leu Thr Leu Pro	Arg Ile Lys Val Thr Thr			
	395	400			405
Ser Gln Asp Met	Leu Ser Ile Met Glu	Lys Leu Glu Phe Phe Asp			
	410	415			420
Phe Ser Tyr Asp	Leu Asn Leu Cys Gly	Leu Thr Glu Asp Pro Asp			
	425	430			435
Leu Gln Val Ser	Ala Met Gln His Gln	Thr Val Leu Glu Leu Thr			
	440	445			450
Glu Thr Gly Val	Glu Ala Ala Ala Ala	Ser Ala Ile Ser Val Ala			
	455	460			465
Arg Thr Leu Leu	Val Phe Glu Val Gln	Gln Pro Phe Leu Phe Val			
	470	475			480
Leu Trp Asp Gln	Gln His Lys Phe Pro	Val Phe Met Gly Arg Val			
	485	490			495
Tyr Asp Pro Arg	Ala				
	500				

<210> 83
 <211> 3243
 <212> DNA
 <213> Homo sapien

<400> 83
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 ttagagctct ggaagtagct ctccagcttc cttcgtactc gggggccgga 100
 cttgtacacc cgcacgagga gcggggacgg cgggcgcaga agtgggcccac 150
 catatctgga aactacagtc tatgctttga agcgcaaaag ggaataaaca 200
 tttaaagact cccccgggga cctggaggat ggacttttcc atggtggccg 250
 gagcagcagc ttacaatgaa aaatcaggta ggattacctc gctctcactc 300
 ttgtttcaga aagtctttgc tcagatcttt cctcagtgga gaaaggggaa 350
 tacagaagaa tgtctcccct acaagtgctc agagactggg gctcttggag 400
 aaaactatag ttggcaaatt cccattaacc acaatgactt caaaatttta 450
 aaaaataatg agcgtcagct gtgtgaagtc ctccagaata agtttggctg 500

tatctctacc ctggtctctc cagttcagga aggcaacagc aaatctctgc 550
 aagtgttcag aaaaatgctg actcctagga tagagttatc agtctggaaa 600
 gatgacctca ccacacatgc tgttgatgct gtggtgaatg cagccaatga 650
 agatcttctg catgggggag gcctggccct ggccctggta aaagctggtg 700
 gatttgaaat ccaagaagag agcaaacagt ttgttgccag atatggtaaa 750
 gtgtcagctg gtgagatagc tgtcacggga gcaggaggc ttccctgcaa 800
 acagatcatc catgctggtg ggctcgggtg gatggaatgg gataaacagg 850
 gatgtactgg aaagctgcag agggccattg taagtattct gaattatgtc 900
 atctataaaa atactcacat taagacagta gcaattccag ccttgagctc 950
 tgggattttt cagttccctc tgaatttggtg taaaagact attgtagaga 1000
 ctatccgggt tagtttgcaa gggaagccaa tgatgagtaa tttgaaagaa 1050
 attcacctgg tgagcaatga ggaccctact gttgctgcct ttaaagctgc 1100
 ttcagaattc atcctagggga agagtgagct gggacaagaa accaccctt 1150
 ctttcaatgc aatggtcgtg aacaacctga ccctccagat tgtccagggc 1200
 cacattgaat ggcagacggc agatgtaatt gttaattctg taaaccacaa 1250
 tgatattaca gttggacctg tggcaaagtc aattctacaa caagcaggag 1300
 ttgaaatgaa atcggaattt cttgccacaa aggctaaaca gtttcaacgg 1350
 tcccagttgg tactggtcac aaaaggattt aacttggtct gtaaataatat 1400
 ataccatgta ctgtggcatt cagaatttcc taaacctcag atattaaaac 1450
 atgcaatgaa ggagtgtttg gaaaaatgca ttgagcaaaa tataacttcc 1500
 atttcctttc ctgcccttgg gactggaaac atggaaataa agaaggaaac 1550
 agcagcagag attttgtttg atgaagtgtt aacatttgcc aaagaccatg 1600
 taaaacacca gttaactgta aaatttggtg tctttccaac agatttggag 1650
 atatataagg ctttcagttc tgaaatggca aagaggcca agatgctgag 1700
 tttgaacaat tacagtgtcc cccagtcaac cagagaggag aaaagagaaa 1750
 atgggcttga agctagatct cctgccatca atctgatggg attcaacgtg 1800
 gaagagatgt gtgaggcca cgcattggatc caaagaatcc tgagtctcca 1850
 gaaccaccac atcattgaga ataatacat tctgtacctt gggagaaagg 1900
 aacatgacat tttgtctcag cttcagaaaa cttcaagtgt ctccatcaca 1950
 gaaattatca gccaggaag gacagagtta gagattgaag gagcccgggc 2000
 tgacctcatt gaggtggtta tgaacattga agatatgctt tgtaaagtac 2050
 aggaggaaat ggcaaggaaa aaggagcgag gcctttggcg ctcgtagga 2100
 cagtggacta ttcagcaaca aaaaacccaa gacgaaatga aagaaaatat 2150
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agaaacagtt tgaaaaatgt ggtttgcagg ttctaaaggt ggagaagata 2250
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<210> 84
 <211> 854
 <212> PRT
 <213> Homo sapien

<400> 84
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 35 40 45
 Leu Pro Tyr Lys Cys Ser Glu Thr Gly Ala Leu Gly Glu Asn Tyr
 50 55 60
 Ser Trp Gln Ile Pro Ile Asn His Asn Asp Phe Lys Ile Leu Lys
 65 70 75
 Asn Asn Glu Arg Gln Leu Cys Glu Val Leu Gln Asn Lys Phe Gly
 80 85 90
 Cys Ile Ser Thr Leu Val Ser Pro Val Gln Glu Gly Asn Ser Lys

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

Glu	Ile	Lys	Lys	Glu	Thr	Ala	Ala	Glu	Ile	Leu	Phe	Asp	Glu	Val
				440					445					450
Leu	Thr	Phe	Ala	Lys	Asp	His	Val	Lys	His	Gln	Leu	Thr	Val	Lys
				455					460					465
Phe	Val	Ile	Phe	Pro	Thr	Asp	Leu	Glu	Ile	Tyr	Lys	Ala	Phe	Ser
				470					475					480
Ser	Glu	Met	Ala	Lys	Arg	Ser	Lys	Met	Leu	Ser	Leu	Asn	Asn	Tyr
				485					490					495
Ser	Val	Pro	Gln	Ser	Thr	Arg	Glu	Glu	Lys	Arg	Glu	Asn	Gly	Leu
				500					505					510
Glu	Ala	Arg	Ser	Pro	Ala	Ile	Asn	Leu	Met	Gly	Phe	Asn	Val	Glu
				515					520					525
Glu	Met	Cys	Glu	Ala	His	Ala	Trp	Ile	Gln	Arg	Ile	Leu	Ser	Leu
				530					535					540
Gln	Asn	His	His	Ile	Ile	Glu	Asn	Asn	His	Ile	Leu	Tyr	Leu	Gly
				545					550					555
Arg	Lys	Glu	His	Asp	Ile	Leu	Ser	Gln	Leu	Gln	Lys	Thr	Ser	Ser
				560					565					570
Val	Ser	Ile	Thr	Glu	Ile	Ile	Ser	Pro	Gly	Arg	Thr	Glu	Leu	Glu
				575					580					585
Ile	Glu	Gly	Ala	Arg	Ala	Asp	Leu	Ile	Glu	Val	Val	Met	Asn	Ile
				590					595					600
Glu	Asp	Met	Leu	Cys	Lys	Val	Gln	Glu	Glu	Met	Ala	Arg	Lys	Lys
				605					610					615
Glu	Arg	Gly	Leu	Trp	Arg	Ser	Leu	Gly	Gln	Trp	Thr	Ile	Gln	Gln
				620					625					630
Gln	Lys	Thr	Gln	Asp	Glu	Met	Lys	Glu	Asn	Ile	Ile	Phe	Leu	Lys
				635					640					645
Cys	Pro	Val	Pro	Pro	Thr	Gln	Glu	Leu	Leu	Asp	Gln	Lys	Lys	Gln
				650					655					660
Phe	Glu	Lys	Cys	Gly	Leu	Gln	Val	Leu	Lys	Val	Glu	Lys	Ile	Asp
				665					670					675
Asn	Glu	Val	Leu	Met	Ala	Ala	Phe	Gln	Arg	Lys	Lys	Lys	Met	Met
				680					685					690
Glu	Glu	Lys	Leu	His	Arg	Gln	Pro	Val	Ser	His	Arg	Leu	Phe	Gln
				695					700					705
Gln	Val	Pro	Tyr	Gln	Phe	Cys	Asn	Val	Val	Cys	Arg	Val	Gly	Phe
				710					715					720
Gln	Arg	Met	Tyr	Ser	Thr	Pro	Cys	Asp	Pro	Lys	Tyr	Gly	Ala	Gly
				725					730					735
Ile	Tyr	Phe	Thr	Lys	Asn	Leu	Lys	Asn	Leu	Ala	Glu	Lys	Ala	Lys
				740					745					750
Lys	Ile	Ser	Ala	Ala	Asp	Lys	Leu	Ile	Tyr	Val	Phe	Glu	Ala	Glu
				755					760					765
Val	Leu	Thr	Gly	Phe	Phe	Cys	Gln	Gly	His	Pro	Leu	Asn	Ile	Val

				770						775					780
Pro	Pro	Pro	Leu	Ser	Pro	Gly	Ala	Ile	Asp	Gly	His	Asp	Ser	Val	
				785					790					795	
Val	Asp	Asn	Val	Ser	Ser	Pro	Glu	Thr	Phe	Val	Ile	Phe	Ser	Gly	
				800					805					810	
Met	Gln	Ala	Ile	Pro	Gln	Tyr	Leu	Trp	Thr	Cys	Thr	Gln	Glu	Tyr	
				815					820					825	
Val	Gln	Ser	Gln	Asp	Tyr	Ser	Ser	Gly	Pro	Met	Arg	Pro	Phe	Ala	
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Gln	His	Pro	Trp	Arg	Gly	Phe	Ala	Ser	Gly	Ser	Pro	Val	Asp		
				845					850						

<210> 85
 <211> 2621
 <212> DNA
 <213> Homo sapien

<220>
 <221> Unsure
 <222> 2086-2106
 <223> Unknown base

<400> 85
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 ccttgctcat gactcagaac tacatcgagt gaagtcagtg ttgaaaacgc 200
 ccattccctc caggtgagcc ttccccattg tggattagtg ttgtggcttc 250
 atggccctaa taggggtgtg tctgccagga actgcactgc atggggccca 300
 cagccctgcc ccagaagcag ctttggtctc gtttgctgag accgcttgct 350
 gtgcctcatc aatttcagga ggaaacagtg agatgcctct agattttaaa 400
 tctggtttcg gagagcacct aagccctctg atggaatgac tctcgtagga 450
 acttgatggg ggtaattcta agggggaaga gcttggggaac cgtgagggct 500
 gttaggctgc aagaaggga tggatatgtg agaccatgtg ggtttatattt 550
 ttgaagggtg aactggagta gctgaggatt ctgcagttga cgtcccagga 600
 tggctttgct cagccctccc ccgtagactg gaggaagcc taccgccaag 650
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 acggcaatgt gctatctttc acatgttgga cgtaaacc agaccaactc 950
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cctttcatct ctggttgagt ttcttccatt agaaggaagg attaaacctt 1050
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<210> 86

WO 2005/051988

PCT/US2004/006460

<211> 78
 <212> PRT
 <213> Homo sapien

<220>
 <221> unsure
 <222> 52-58
 <223> unknown amino acid

<220>
 <221> Unsure
 <222> 2086-2106
 <223> Unknown amino acid

<400> 86
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 Arg Val Leu Val Thr Gly Thr Ser Pro Trp Arg Gly Ala Val Leu
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 Cys Pro Cys Leu Leu Leu Leu Leu Gln Gln Ser Cys Gly Leu Ala
 35 40 45
 Gln Ala Leu Gln Gly Leu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Val Tyr
 50 55 60
 Met Cys Leu Pro Thr His Lys His Met Cys Thr His Ala His Thr
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 Cys Ser Ala

<210> 87
 <211> 2905
 <212> DNA
 <213> Homo sapien

<400> 87
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 ctgcaggaac cccgaacagt tccccctggg gcagggagtg gccataggtg 200
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<210> 88
 <211> 727
 <212> PRT
 <213> Homo sapien

<400> 88
 Met Gly Asn Gly Glu Ser Gln Leu Ser Ser Val Pro Ala Gln Lys
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 Gln Thr Leu Ile Asp Glu Met Val Asn Thr Ile Cys Asp Val Cys
 35 40 45
 Arg Asn Pro Glu Gln Phe Pro Leu Val Gln Gly Val Ala Ile Gly
 50 55 60
 Gly Ser Tyr Gly Arg Lys Thr Val Leu Arg Gly Asn Ser Asp Gly
 65 70 75
 Thr Leu Val Leu Phe Phe Ser Asp Leu Lys Gln Phe Gln Asp Gln
 80 85 90
 Lys Arg Ser Gln Arg Asp Ile Leu Asp Lys Thr Gly Asp Lys Leu
 95 100 105
 Lys Phe Cys Leu Phe Thr Lys Trp Leu Lys Asn Asn Phe Glu Ile
 110 115 120
 Gln Lys Ser Leu Asp Gly Ser Thr Ile Gln Val Phe Thr Lys Asn
 125 130 135
 Gln Arg Ile Ser Phe Glu Val Leu Ala Ala Phe Asn Ala Leu Ser
 140 145 150
 Leu Asn Asp Asn Pro Ser Pro Trp Ile Tyr Arg Glu Leu Lys Arg
 155 160 165
 Ser Leu Asp Lys Thr Asn Ala Ser Pro Gly Glu Phe Ala Val Cys
 170 175 180
 Phe Thr Glu Leu Gln Gln Lys Phe Phe Asp Asn Arg Pro Gly Lys
 185 190 195

Leu	Lys	Asp	Leu	Ile	Leu	Leu	Ile	Lys	His	Trp	His	Gln	Gln	Cys
				200					205					210
Gln	Lys	Lys	Ile	Lys	Asp	Leu	Pro	Ser	Leu	Ser	Pro	Tyr	Ala	Leu
				215					220					225
Glu	Leu	Leu	Thr	Val	Tyr	Ala	Trp	Glu	Gln	Gly	Cys	Arg	Lys	Asp
				230					235					240
Asn	Phe	Asp	Ile	Ala	Glu	Gly	Val	Arg	Thr	Val	Leu	Glu	Leu	Ile
				245					250					255
Lys	Cys	Gln	Glu	Lys	Leu	Cys	Ile	Tyr	Trp	Met	Val	Asn	Tyr	Asn
				260					265					270
Phe	Glu	Asp	Glu	Thr	Ile	Arg	Asn	Ile	Leu	Leu	His	Gln	Leu	Gln
				275					280					285
Ser	Ala	Arg	Pro	Val	Ile	Leu	Asp	Pro	Val	Asp	Pro	Thr	Asn	Asn
				290					295					300
Val	Ser	Gly	Asp	Lys	Ile	Cys	Trp	Gln	Trp	Leu	Lys	Lys	Glu	Ala
				305					310					315
Gln	Thr	Trp	Leu	Thr	Ser	Pro	Asn	Leu	Asp	Asn	Glu	Leu	Pro	Ala
				320					325					330
Pro	Ser	Trp	Asn	Val	Leu	Pro	Ala	Pro	Leu	Phe	Thr	Thr	Pro	Gly
				335					340					345
His	Leu	Leu	Asp	Lys	Phe	Ile	Lys	Glu	Phe	Leu	Gln	Pro	Asn	Lys
				350					355					360
Cys	Phe	Leu	Glu	Gln	Ile	Asp	Ser	Ala	Val	Asn	Ile	Ile	Arg	Thr
				365					370					375
Phe	Leu	Lys	Glu	Asn	Cys	Phe	Arg	Gln	Ser	Thr	Ala	Lys	Ile	Gln
				380					385					390
Ile	Val	Arg	Gly	Gly	Ser	Thr	Ala	Lys	Gly	Thr	Ala	Leu	Lys	Thr
				395					400					405
Gly	Ser	Asp	Ala	Asp	Leu	Val	Val	Phe	His	Asn	Ser	Leu	Lys	Ser
				410					415					420
Tyr	Thr	Ser	Gln	Lys	Asn	Glu	Arg	His	Lys	Ile	Val	Lys	Glu	Ile
				425					430					435
His	Glu	Gln	Leu	Lys	Ala	Phe	Trp	Arg	Glu	Lys	Glu	Glu	Glu	Leu
				440					445					450
Glu	Val	Ser	Phe	Glu	Pro	Pro	Lys	Trp	Lys	Ala	Pro	Arg	Val	Leu
				455					460					465
Ser	Phe	Ser	Leu	Lys	Ser	Lys	Val	Leu	Asn	Glu	Ser	Val	Ser	Phe
				470					475					480
Asp	Val	Leu	Pro	Ala	Phe	Asn	Ala	Leu	Gly	Gln	Leu	Ser	Ser	Gly
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Ser	Thr	Pro	Ser	Pro	Glu	Val	Tyr	Ala	Gly	Leu	Ile	Asp	Leu	Tyr
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Lys	Ser	Ser	Asp	Leu	Pro	Gly	Gly	Glu	Phe	Ser	Thr	Cys	Phe	Thr
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Val	Leu	Gln	Arg	Asn	Phe	Ile	Arg	Ser	Arg	Pro	Thr	Lys	Leu	Lys

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Asp Leu Ile Arg	Leu Val Lys His Trp	Tyr Lys Glu Cys Glu Arg			
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Lys Leu Lys Pro	Lys Gly Ser Leu Pro	Pro Lys Tyr Ala Leu Glu			
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Leu Leu Thr Ile	Tyr Ala Trp Glu Gln	Gly Ser Gly Val Pro Asp			
	575		580		585
Phe Asp Thr Ala	Glu Gly Phe Arg Thr	Val Leu Glu Leu Val Thr			
	590		595		600
Gln Tyr Gln Gln	Leu Gly Ile Phe Trp	Lys Val Asn Tyr Asn Phe			
	605		610		615
Glu Asp Glu Thr	Val Arg Lys Phe Leu	Leu Ser Gln Leu Gln Lys			
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Thr Arg Pro Val	Ile Leu Asp Pro Gly	Glu Pro Thr Gly Asp Val			
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Gly Gly Gly Asp	Arg Trp Cys Trp His	Leu Leu Asp Lys Glu Ala			
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Lys Val Arg Leu	Ser Ser Pro Cys Phe	Lys Asp Gly Thr Gly Asn			
	665		670		675
Pro Ile Pro Pro	Trp Lys Val Pro Thr	Met Gln Thr Pro Gly Ser			
	680		685		690
Cys Gly Ala Arg	Ile His Pro Ile Val	Asn Glu Met Phe Ser Ser			
	695		700		705
Arg Ser His Arg	Ile Leu Asn Asn Asn	Ser Lys Arg Asn Phe Trp			
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 <212> DNA
 <213> Homo sapien

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<211> 582

<212> PRT

<213> Homo sapien

<400> 90

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His	Cys	Gln	Arg	Asn	Ile	Gly	Met	Cys	Pro	Thr	Cys	Lys	Glu	Pro
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Phe	Pro	Lys	Ser	Asp	Met	Glu	Thr	His	Met	Ala	Ala	Glu	His	Cys
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Gln	Val	Thr	Cys	Lys	Cys	Asn	Lys	Lys	Leu	Glu	Lys	Arg	Leu	Leu
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Lys	Lys	His	Glu	Glu	Thr	Glu	Cys	Pro	Leu	Arg	Leu	Ala	Val	Cys
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Gln	His	Cys	Asp	Leu	Glu	Leu	Ser	Ile	Leu	Lys	Leu	Lys	Glu	His
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Glu	Asp	Tyr	Cys	Gly	Ala	Arg	Thr	Glu	Leu	Cys	Gly	Asn	Cys	Gly
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Arg	Asn	Val	Leu	Val	Lys	Asp	Leu	Lys	Thr	His	Pro	Glu	Val	Cys
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Ser	Gln	Leu	Leu	Arg	Gln	Ile	Glu	Ala	Leu	Asp	Pro	Pro	Met	Arg
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Leu	Pro	Arg	Arg	Pro	Leu	Arg	Ala	Phe	Glu	Ser	Asp	Val	Phe	His
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Ser	Val	Ala	Glu	Gln	Asp	Phe	Trp	Arg	Ala	Val	Cys	Glu	Ala	Asp	
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Val	Glu	Glu	Pro	Asp	Val	Ile	Phe	Gln	Asn	Phe	Leu	Gln	Gln	Ala	
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Gln	Leu	Glu	Glu	Glu	Val	Leu	Phe	His	His	Gln	Asp	Gln	Cys	Asp	
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Gln	Arg	Pro	Ala	Thr	Ala	Thr	Asn	His	Val	Thr	Glu	Gly	Ile	Pro	
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Val	Ser	Val	Ile	Arg	Pro	Pro	Gln	Asn	Leu	Tyr	Pro	Glu	Asn	Ile	
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Val	Pro	Ser	Phe	Ser	Pro	Gly	Pro	Ser	Gly	Arg	Tyr	Gly	Ala	Ser	
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 <212> PRT
 <213> Homo sapien

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 35 40 45
 Tyr Pro Pro Pro Pro Ala Gly His Ser Gly Pro Gly Pro Ala Gly
 50 55 60
 Phe Pro Val Pro Asn Gln Pro Val Tyr Asn Gln Pro Val Tyr Asn
 65 70 75
 Gln Pro Val Gly Ala Ala Gly Val Pro Trp Met Pro Ala Pro Gln
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 Pro Pro Leu Asn Cys Pro Pro Gly Leu Glu Tyr Leu Ser Gln Ile
 95 100 105
 Asp Gln Ile Leu Ile His Gln Gln Ile Glu Leu Leu Glu Val Leu
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 Gly Gln Arg Val Tyr Phe Ala Ala Glu Asp Thr Asp Cys Cys Thr
 140 145 150
 Arg Asn Cys Cys Gly Pro Ser Arg Pro Phe Thr Leu Arg Ile Ile
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Phe	Thr	Asp	Ala	Asp	Asn	Phe	Gly	Ile	Gln	Phe	Pro	Leu	Asp	Leu	
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Gly Ser Gln His Phe Ser Ser Gly Lys His Tyr Trp Glu Val Asp	350		355		360
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Ala Tyr Ser Arg Tyr Gln Pro Gln Ser Gly Tyr Trp Val Ile Gly	395		400		405
Leu Gln His Asn His Glu Tyr Arg Ala Tyr Glu Asp Ser Ser Pro	410		415		420
Ser Leu Leu Leu Ser Met Thr Val Pro Pro Arg Arg Val Gly Val	425		430		435
Phe Leu Asp Tyr Glu Ala Gly Thr Val Ser Phe Tyr Asn Val Thr	440		445		450
Asn His Gly Phe Pro Ile Tyr Thr Phe Ser Lys Tyr Tyr Phe Pro	455		460		465
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<213> Homo sapien

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Thr	Asn	Phe	Arg	Cys	Ala	Leu	Arg	Ser	Thr	Arg	Arg	Phe	Val	Met
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<212> DNA

<213> Homo sapien

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<211> 578

<212> PRT

<213> Homo sapien

<400> 101

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Pro	Gly	Arg	Arg	Gly	Arg	Arg	Arg	Gly	Cys	Ala	Pro	Ser	Pro	Arg	185	190	195	
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Pro	Leu	Leu	Tyr	Ser	Leu	Val	Arg	Ala	Ile	Ser	Glu	Ala	Gly	Ala	365	370	375
Pro	Pro	Gly	Ser	Ala	Gly	Pro	Leu	Leu	Leu	Gln	Pro	Gln	Arg	His	380	385	390
Arg	Ala	Ala	Gly	Cys	Phe	Leu	Gly	Thr	Cys	Leu	Asp	Leu	Leu	Asp	395	400	405
Ser	Phe	Thr	Leu	Val	Glu	Leu	Met	Leu	Glu	Gly	Arg	Val	Pro	Leu	410	415	420
Pro	Ala	His	Leu	Arg	Tyr	Leu	Leu	Ile	Ala	Val	Tyr	Phe	Leu	Thr	425	430	435
Leu	Ala	Ser	Pro	Val	Leu	Trp	Leu	Tyr	Glu	Leu	Asn	Ala	Ala	Ala	440	445	450
Ala	Ala	Ala	Ala	Ser	Trp	Gly	Gln	Ala	Ser	Gly	Pro	Gly	Ser	Cys	455	460	465
Ser	Arg	Leu	Leu	Arg	Leu	Leu	Gly	Gly	Cys	Leu	Val	Asp	Val	Pro	470	475	480
Leu	Leu	Ala	Leu	Arg	Cys	Leu	Leu	Val	Val	Ser	Tyr	Gln	Gln	Pro	485	490	495
Leu	Ser	Ile	Phe	Met	Leu	Lys	Asn	Leu	Phe	Phe	Leu	Gly	Cys	Arg	500	505	510
Gly	Leu	Glu	Ala	Leu	Glu	Gly	Cys	Trp	Asp	Arg	Gly	Asn	Arg	Ala	515	520	525
Ser	Pro	Ser	Arg	Ala	Arg	Gly	Gly	Tyr	Gly	Ala	Pro	Pro	Ser	Ala	530	535	540
Pro	Pro	Pro	Pro	Pro	Pro	Pro	Pro	Gln	Gly	Gly	Ser	Gln	Leu	Gly	545	550	555
His	Cys	Ile	Ser	Glu	Asn	Glu	Gly	Gly	Ala	His	Gly	Tyr	Val	Asn	560	565	570
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575

<210> 102

<211> 1820

<212> DNA

<213> Homo sapien

<400> 102

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 <212> PRT
 <213> Homo sapien

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Leu	Asp	Glu	Gly	Phe	Thr	Thr	Val	Met	Asp	Leu	Leu	Leu	Glu	Tyr
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Glu	Val	Ile	Cys	Ile	Tyr	Trp	Thr	Lys	Tyr	Tyr	Thr	Leu	His	Asn
				275					280					285
Ala	Ile	Ile	Glu	Asp	Cys	Val	Arg	Lys	Gln	Leu	Lys	Lys	Glu	Arg
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Pro	Ile	Ile	Leu	Asp	Pro	Ala	Asp	Pro	Thr	Leu	Asn	Val	Ala	Glu
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Gly	Tyr	Arg	Trp	Asp	Ile	Val	Ala	Gln	Arg	Ala	Ser	Gln	Cys	Leu
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Lys	Gln	Asp	Cys	Cys	Tyr	Asp	Asn	Arg	Glu	Asn	Pro	Ile	Ser	Ser
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Trp	Asn	Val	Lys	Arg	Ala	Arg	Asp	Ile	His	Leu	Thr	Val	Glu	Gln
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Arg	Gly	Tyr	Pro	Asp	Phe	Asn	Leu	Ile	Val	Asn	Pro	Tyr	Glu	Pro
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Ile	Arg	Lys	Val	Lys	Glu	Lys	Ile	Arg	Arg	Thr	Arg	Gly	Tyr	Ser
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Gly	Leu	Gln	Arg	Leu	Ser	Phe	Gln	Val	Pro	Gly	Ser	Glu	Arg	Gln
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Leu	Leu	Ser	Ser	Arg	Cys	Ser	Leu	Ala	Lys	Tyr	Gly	Ile	Phe	Ser
				410					415					420
His	Thr	His	Ile	Tyr	Leu	Leu	Glu	Thr	Ile	Pro	Ser	Glu	Ile	Gln
				425					430					435
Val	Phe	Val	Lys	Asn	Pro	Asp	Gly	Gly	Ser	Tyr	Ala	Tyr	Ala	Ile
				440					445					450
Asn	Pro	Asn	Ser	Phe	Ile	Leu	Gly	Leu	Lys	Gln	Gln	Ile	Glu	Asp
				455					460					465
Gln	Gln	Gly	Leu	Pro	Lys	Lys	Gln	Gln	Gln	Leu	Glu	Phe	Gln	Gly
				470					475					480
Gln	Val	Leu	Gln	Asp	Trp	Leu	Gly	Leu	Gly	Ile	Tyr	Gly	Ile	Gln
				485					490					495
Asp	Ser	Asp	Thr	Leu	Ile	Leu	Ser	Lys	Lys	Lys	Gly	Glu	Ala	Leu
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 <212> DNA
 <213> Homo sapien

<400> 104
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 <213> Homo sapien

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 Ser Thr Ile Ser Val Ser Gln Cys Glu Ile Phe Leu Gly Ile Ile
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 Tyr Thr Ser Thr Pro Trp Glu Pro Glu Ser Leu Glu Asp Lys Met
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 Gly Thr Tyr Ser Thr Leu Leu Ile Lys Thr Glu Val Ala Glu Tyr
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 Gly Arg Tyr Thr Gly Val Arg Ile Ile His Pro Leu Ile Ala Leu
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 Tyr Cys Leu Lys Glu Leu Glu Arg Ser Tyr His Leu Asp Lys Cys
 110 115 120
 Gln Ile Ala Leu Asn Ile Leu Glu Glu Asn Leu Phe Tyr Asp Ser
 125 130 135
 Gly Ile Gly Arg Asp Lys Phe Gln His Asp Val Gln Thr Leu Leu
 140 145 150
 Leu Thr Arg Gln Arg Lys Val Tyr Gly Asp Glu Thr Asp Thr Leu
 155 160 165

Phe	Ser	Pro	Leu	Met	Glu	Ala	Leu	Gln	Asn	Lys	Asp	Ile	Glu	Lys	170	175	180
Val	Leu	Ser	Ala	Gly	Ser	Arg	Arg	Phe	Pro	Gln	Asn	Ala	Phe	Ile	185	190	195
Cys	Gln	Ala	Leu	Ala	Arg	His	Phe	Tyr	Ile	Lys	Glu	Lys	Asp	Phe	200	205	210
Asn	Thr	Ala	Leu	Asp	Trp	Ala	Arg	Gln	Ala	Lys	Met	Lys	Ala	Pro	215	220	225
Lys	Asn	Ser	Tyr	Ile	Ser	Asp	Thr	Leu	Gly	Gln	Val	Tyr	Lys	Ser	230	235	240
Glu	Ile	Lys	Trp	Trp	Leu	Asp	Gly	Asn	Lys	Asn	Cys	Arg	Ser	Ile	245	250	255
Thr	Val	Asn	Asp	Leu	Thr	His	Leu	Leu	Glu	Ala	Ala	Glu	Lys	Ala	260	265	270
Ser	Arg	Ala	Phe	Lys	Glu	Ser	Gln	Arg	Gln	Thr	Asp	Ser	Lys	Asn	275	280	285
Tyr	Glu	Thr	Glu	Asn	Trp	Ser	Pro	Gln	Lys	Ser	Gln	Arg	Arg	Tyr	290	295	300
Asp	Met	Tyr	Asn	Thr	Ala	Cys	Phe	Leu	Gly	Glu	Ile	Glu	Val	Gly	305	310	315
Leu	Tyr	Thr	Ile	Gln	Ile	Leu	Gln	Leu	Thr	Pro	Phe	Phe	His	Lys	320	325	330
Glu	Asn	Glu	Leu	Ser	Lys	Lys	His	Met	Val	Gln	Phe	Leu	Ser	Gly	335	340	345
Lys	Trp	Thr	Ile	Pro	Pro	Asp	Pro	Arg	Asn	Glu	Cys	Tyr	Leu	Ala	350	355	360
Leu	Ser	Lys	Phe	Thr	Ser	His	Leu	Lys	Asn	Leu	Gln	Ser	Asp	Leu	365	370	375
Lys	Arg	Cys	Phe	Asp	Phe	Phe	Ile	Asp	Tyr	Met	Val	Leu	Leu	Lys	380	385	390
Met	Arg	Tyr	Thr	Gln	Lys	Glu	Ile	Ala	Glu	Ile	Met	Leu	Ser	Lys	395	400	405
Lys	Val	Ser	Arg	Cys	Phe	Arg	Lys	Tyr	Thr	Glu	Leu	Phe	Cys	His	410	415	420
Leu	Asp	Pro	Cys	Leu	Leu	Gln	Ser	Lys	Glu	Ser	Gln	Leu	Leu	Gln	425	430	435
Glu	Glu	Asn	Cys	Arg	Lys	Lys	Leu	Glu	Ala	Leu	Arg	Ala	Asp	Arg	440	445	450
Phe	Ala	Gly	Leu	Leu	Glu	Tyr	Leu	Asn	Pro	Asn	Tyr	Lys	Asp	Ala	455	460	465
Thr	Thr	Met	Glu	Ser	Ile	Val	Asn	Glu	Tyr	Ala	Phe	Leu	Leu	Gln	470	475	480
Gln	Asn	Ser	Lys	Lys	Pro	Met	Thr	Asn	Glu	Lys	Gln	Asn	Ser	Ile	485	490	495
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Gln Phe Val Gly Leu Ser His Gln Tyr Pro Gly Pro Tyr Phe Leu	530		535		540
Ala Cys Leu Leu Phe Trp Pro Glu Asn Gln Glu Leu Asp Gln Asp	545		550		555
Ser Lys Leu Ile Glu Lys Tyr Val Ser Ser Leu Asn Arg Ser Phe	560		565		570
Arg Gly Gln Tyr Lys Arg Met Cys Arg Ser Lys Gln Ala Ser Thr	575		580		585
Leu Phe Tyr Leu Gly Lys Arg Lys Gly Leu Asn Ser Ile Val His	590		595		600
Lys Ala Lys Ile Glu Gln Tyr Phe Asp Lys Ala Gln Asn Thr Asn	605		610		615
Ser Leu Trp His Ser Gly Asp Val Trp Lys Lys Asn Glu Val Lys	620		625		630
Asp Leu Leu Arg Arg Leu Thr Gly Gln Ala Glu Gly Lys Leu Ile	635		640		645
Ser Val Glu Tyr Gly Thr Glu Glu Lys Ile Lys Ile Pro Val Ile	650		655		660
Ser Val Tyr Ser Gly Pro Leu Arg Ser Gly Arg Asn Ile Glu Arg	665		670		675
Val Ser Phe Tyr Leu Gly Phe Ser Ile Glu Gly Pro Leu Ala Tyr	680		685		690
Asp Ile Glu Val Ile	695				

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<211> 16

<212> PRT

<213> Homo sapien

<400> 107

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Ile

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<211> 1948

<212> DNA

<213> Homo sapien

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 <212> PRT
 <213> Homo sapien

<400> 109
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 Gly Cys Arg Glu Gln Leu Glu Leu Phe Gln Thr Pro Gly Ser Cys
 35 40 45
 Tyr Pro Ala Gln Pro Leu Ser Pro Gly Pro Gln Pro His Asp Ser
 50 55 60
 Pro Ser Leu Leu Gln Cys Pro Leu Pro Ser Leu Ser Leu Gly Pro
 65 70 75
 Ala Val Val Ala Glu Pro Pro Val Gln Leu Ser Pro Ser Pro Leu
 80 85 90
 Leu Phe Ala Ser His Thr Gly Ser Ser Leu Gln Gly Ser Ser Ser
 95 100 105

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Lys Leu Ser Ala Leu Gln Pro Ser Leu Thr Ala Gln Thr Ala Pro
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 Pro Gln Pro Leu Glu Leu Glu His Pro Thr Arg Gly Lys Leu Gly
 125 130 135
 Ser Ser Pro Asp Asn Pro Ser Ser Ala Leu Gly Leu Ala Arg Leu
 140 145 150
 Gln Ser Arg Glu His Lys Pro Ala Leu Ser Ala Ala Thr Trp Gln
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 Gly Leu Val Val Asp Pro Ser Pro His Pro Leu Leu Ala Phe Pro
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 Leu Leu Ser Ser Ala Gln Val His Phe
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 <211> 841
 <212> DNA
 <213> Homo sapien

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<210> 111
 <211> 138
 <212> PRT
 <213> Homo sapien

<400> 111
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 Phe Trp Lys Ala Leu Thr Phe Met Ala Val Gly Gly Gly Leu Ala
 50 55 60
 Val Ala Gly Leu Pro Ala Leu Gly Phe Thr Gly Ala Gly Ile Ala
 65 70 75
 Ala Asn Ser Val Ala Ala Ser Leu Met Ser Trp Ser Ala Ile Leu
 80 85 90
 Asn Gly Gly Gly Val Pro Ala Gly Gly Leu Val Ala Thr Leu Gln
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 Ser Leu Gly Ala Gly Gly Ser Ser Val Val Ile Gly Asn Ile Gly
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 125 130 135

Asp Glu Glu

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 <211> 1326
 <212> DNA
 <213> Homo sapien

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 aagcttgagc accagcaggt tgggtgtacg atgtgtcagc agagcatgca 200
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 gttcatcatg caccgcatgc tcgcccagca cagagatgtc tgtcggagtg 400
 aacaggccca gctcgggaaa ggggaaagaa tttcagctcc tgaaagggaa 450
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<210> 113

<211> 317

<212> PRT

<213> Homo sapien

<400> 113

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

Arg	Pro	Lys	Thr	Arg	Ser	Ile	Asn	Arg	Phe	Pro	Leu	His	Ser	Glu
				215					220					225
Ser	Ser	Ser	Lys	Lys	Ala	Pro	Arg	Ser	Lys	Asn	Lys	Thr	Leu	Asp
				230					235					240
Pro	Leu	Leu	Met	Ser	Glu	Pro	Lys	Pro	Arg	Thr	Ser	Ser	Pro	Arg
				245					250					255
Gly	Asp	Lys	Ala	Ala	Tyr	Asp	Ile	Leu	Arg	Arg	Cys	Ser	Gln	Cys
				260					265					270
Gly	Ile	Leu	Leu	Pro	Leu	Pro	Ile	Leu	Asn	Gln	His	Gln	Glu	Lys
				275					280					285
Cys	Arg	Trp	Leu	Ala	Ser	Ser	Lys	Arg	Lys	Thr	Ser	Glu	Lys	Phe
				290					295					300
Gln	Leu	Asp	Leu	Glu	Lys	Glu	Arg	Tyr	Tyr	Lys	Phe	Lys	Arg	Phe
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His Phe

<210> 114
 <211> 5801
 <212> DNA
 <213> Homo sapien

<400> 114
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<210> 115

<211> 1514

<212> PRT

<213> Homo sapien

<400> 115

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

Ser	Thr	Ala	Arg	His	Gly	Thr	Ala	Arg	Gly	Leu	Pro	Leu	Lys	Glu
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Val	Leu	Glu	Tyr	Val	Ile	Pro	Glu	Leu	Ser	Ile	Gln	Cys	Leu	Arg
				365					370					375
Gln	Ala	Ser	Asn	Ser	Pro	Lys	Val	Ser	Glu	Gln	Leu	Leu	Lys	Leu
				380					385					390
Asp	Glu	Gln	Gly	Leu	Ser	Phe	Gln	His	Lys	Ile	Gly	Ile	Leu	Tyr
				395					400					405
Cys	Lys	Ala	Gly	Gln	Ser	Thr	Glu	Glu	Glu	Met	Tyr	Asn	Asn	Glu
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Thr	Ala	Gly	Pro	Ala	Phe	Glu	Glu	Phe	Leu	Asp	Leu	Leu	Gly	Gln
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Arg	Val	Arg	Leu	Lys	Gly	Phe	Ser	Lys	Tyr	Arg	Ala	Gln	Leu	Asp
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Asn	Lys	Thr	Asp	Ser	Thr	Gly	Thr	His	Ser	Leu	Tyr	Thr	Thr	Tyr
				455					460					465
Lys	Asp	Tyr	Glu	Leu	Met	Phe	His	Val	Ser	Thr	Leu	Leu	Pro	Tyr
				470					475					480
Met	Pro	Asn	Asn	Arg	Gln	Gln	Leu	Leu	Arg	Lys	Arg	His	Ile	Gly
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Phe	Thr	Pro	Lys	Ser	Ile	Arg	Ser	His	Phe	Gln	His	Val	Phe	Val
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Ile	Val	Lys	Val	His	Asn	Pro	Cys	Thr	Glu	Asn	Val	Cys	Tyr	Ser
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Ile	Pro	Lys	Gly	Val	Thr	Phe	Pro	Lys	Ser	Ala	Val	Phe	Arg	Asp
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Phe	Leu	Leu	Ala	Lys	Val	Ile	Asn	Ala	Glu	Asn	Ala	Ala	His	Lys
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Ser	Glu	Lys	Phe	Arg	Ala	Met	Ala	Thr	Arg	Thr	Arg	Gln	Glu	Tyr
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Leu	Lys	Asp	Leu	Ala	Glu	Asn	Phe	Val	Thr	Thr	Ala	Thr	Val	Asp
				605					610					615
Thr	Ser	Val	Lys	Phe	Ser	Phe	Ile	Thr	Leu	Gly	Ala	Lys	Lys	Lys
				620					625					630
Glu	Lys	Val	Lys	Pro	Arg	Lys	Asp	Ala	His	Leu	Phe	Ser	Ile	Gly
				635					640					645
Ala	Ile	Met	Trp	His	Val	Ile	Ala	Arg	Asp	Phe	Gly	Gln	Ser	Ala
				650					655					660
Asp	Ile	Glu	Cys	Leu	Leu	Gly	Ile	Ser	Asn	Glu	Phe	Ile	Met	Leu
				665					670					675
Ile	Glu	Lys	Asp	Ser	Lys	Asn	Val	Val	Phe	Asn	Cys	Ser	Cys	Arg

680										685					690				
Asp	Val	Ile	Gly	Trp	Thr	Ser	Gly	Leu	Val	Ser	Ile	Lys	Val	Phe					
				695					700					705					
Tyr	Glu	Arg	Gly	Glu	Cys	Val	Leu	Leu	Ser	Ser	Val	Asp	Asn	Cys					
				710					715					720					
Ala	Glu	Asp	Ile	Arg	Glu	Ile	Val	Gln	Arg	Leu	Val	Ile	Val	Thr					
				725					730					735					
Arg	Gly	Cys	Glu	Thr	Val	Glu	Met	Thr	Leu	Arg	Arg	Asn	Gly	Leu					
				740					745					750					
Gly	Gln	Leu	Gly	Phe	His	Val	Asn	Phe	Glu	Gly	Ile	Val	Ala	Asp					
				755					760					765					
Val	Glu	Pro	Phe	Gly	Phe	Ala	Trp	Lys	Ala	Gly	Leu	Arg	Gln	Gly					
				770					775					780					
Ser	Arg	Leu	Val	Glu	Ile	Cys	Lys	Val	Ala	Val	Ala	Thr	Leu	Thr					
				785					790					795					
His	Glu	Gln	Met	Ile	Asp	Leu	Leu	Arg	Thr	Ser	Val	Thr	Val	Lys					
				800					805					810					
Val	Val	Ile	Ile	Gln	Pro	His	Asp	Asp	Gly	Ser	Pro	Arg	Arg	Gly					
				815					820					825					
Cys	Ser	Glu	Leu	Cys	Arg	Ile	Pro	Met	Val	Glu	Tyr	Lys	Leu	Asp					
				830					835					840					
Ser	Glu	Gly	Thr	Pro	Cys	Glu	Tyr	Lys	Thr	Pro	Phe	Arg	Arg	Asn					
				845					850					855					
Thr	Thr	Trp	His	Arg	Val	Pro	Thr	Pro	Ala	Leu	Gln	Pro	Leu	Ser					
				860					865					870					
Arg	Ala	Ser	Pro	Ile	Pro	Gly	Thr	Pro	Asp	Arg	Leu	Pro	Cys	Gln					
				875					880					885					
Gln	Leu	Leu	Gln	Gln	Ala	Gln	Ala	Ala	Ile	Pro	Arg	Ser	Thr	Ser					
				890					895					900					
Phe	Asp	Arg	Lys	Leu	Pro	Asp	Gly	Thr	Arg	Ser	Ser	Pro	Ser	Asn					
				905					910					915					
Gln	Ser	Ser	Ser	Ser	Asp	Pro	Gly	Pro	Gly	Gly	Ser	Gly	Pro	Trp					
				920					925					930					
Arg	Pro	Gln	Val	Gly	Tyr	Asp	Gly	Cys	Gln	Ser	Pro	Leu	Leu	Leu					
				935					940					945					
Glu	His	Gln	Gly	Ser	Gly	Pro	Leu	Glu	Cys	Asp	Gly	Ala	Arg	Glu					
				950					955					960					
Arg	Glu	Asp	Thr	Met	Glu	Ala	Ser	Arg	His	Pro	Glu	Thr	Lys	Trp					
				965					970					975					
His	Gly	Pro	Pro	Ser	Lys	Val	Leu	Gly	Ser	Tyr	Lys	Glu	Arg	Ala					
				980					985					990					
Leu	Gln	Lys	Asp	Gly	Ser	Cys	Lys	Asp	Ser	Pro	Asn	Lys	Leu	Ser					
				995					1000					1005					
His	Ile	Gly	Asp	Lys	Ser	Cys	Ser	Ser	His	Ser	Ser	Ser	Asn	Thr					
				1010					1015					1020					

Leu Ser Ser Asn Thr Ser Ser Asn Ser Asp Asp Lys His Phe Gly
 1025 1030 1035
 Ser Gly Asp Leu Met Asp Pro Glu Leu Leu Gly Leu Thr Tyr Ile
 1040 1045 1050
 Lys Gly Ala Ser Thr Asp Ser Gly Ile Asp Thr Ala Pro Cys Met
 1055 1060 1065
 Pro Ala Thr Ile Leu Gly Pro Val His Leu Ala Gly Ser Arg Ser
 1070 1075 1080
 Leu Ile His Ser Arg Ala Glu Gln Trp Ala Asp Ala Ala Asp Val
 1085 1090 1095
 Ser Gly Pro Asp Asp Glu Pro Ala Lys Leu Tyr Ser Val His Gly
 1100 1105 1110
 Tyr Ala Ser Ala Ile Ser Ala Gly Ser Ala Ala Glu Gly Ser Met
 1115 1120 1125
 Gly Asp Leu Ser Glu Ile Ser Ser His Ser Ser Gly Ser His His
 1130 1135 1140
 Ser Gly Ser Pro Ser Ala His Cys Ser Lys Ser Ser Gly Ser Leu
 1145 1150 1155
 Asp Ser Ser Lys Val Tyr Ile Val Ser His Ser Ser Gly Gln Gln
 1160 1165 1170
 Val Pro Gly Ser Met Ser Lys Pro Tyr His Arg Gln Gly Ala Val
 1175 1180 1185
 Asn Lys Tyr Val Ile Gly Trp Lys Lys Ser Glu Gly Ser Pro Pro
 1190 1195 1200
 Pro Glu Glu Pro Glu Val Thr Glu Cys Pro Gly Met Tyr Ser Glu
 1205 1210 1215
 Met Asp Val Met Ser Thr Ala Thr Gln His Gln Thr Val Val Gly
 1220 1225 1230
 Asp Ala Val Ala Glu Thr Gln His Val Leu Ser Lys Glu Asp Phe
 1235 1240 1245
 Leu Lys Leu Met Leu Pro Asp Ser Pro Leu Val Glu Glu Gly Arg
 1250 1255 1260
 Arg Lys Phe Ser Phe Tyr Gly Asn Leu Ser Pro Arg Arg Ser Leu
 1265 1270 1275
 Tyr Arg Thr Leu Ser Asp Glu Ser Ile Cys Ser Asn Arg Arg Gly
 1280 1285 1290
 Ser Ser Phe Gly Ser Ser Arg Ser Ser Val Leu Asp Gln Ala Leu
 1295 1300 1305
 Pro Asn Asp Ile Leu Phe Ser Thr Thr Pro Pro Tyr His Ser Thr
 1310 1315 1320
 Leu Pro Pro Arg Ala His Pro Ala Pro Ser Met Gly Ser Leu Arg
 1325 1330 1335
 Asn Glu Phe Trp Phe Ser Asp Gly Ser Leu Ser Asp Lys Ser Lys
 1340 1345 1350
 Cys Ala Asp Pro Gly Leu Met Pro Leu Pro Asp Thr Ala Thr Gly

1355	1360	1365
Leu Asp Trp Thr His Leu Val Asp Ala Ala Arg Ala Phe Glu Gly		
1370	1375	1380
Leu Asp Ser Asp Glu Glu Leu Gly Leu Leu Cys His His Thr Ser		
1385	1390	1395
Tyr Leu Asp Gln Arg Val Ala Ser Phe Cys Thr Leu Thr Asp Met		
1400	1405	1410
Gln His Gly Gln Asp Leu Glu Gly Ala Gln Glu Leu Pro Leu Cys		
1415	1420	1425
Val Asp Pro Gly Ser Gly Lys Glu Phe Met Asp Thr Thr Gly Glu		
1430	1435	1440
Arg Ser Pro Ser Pro Leu Thr Gly Lys Val Asn Gln Leu Glu Leu		
1445	1450	1455
Ile Leu Arg Gln Leu Gln Thr Asp Leu Arg Lys Glu Lys Gln Asp		
1460	1465	1470
Lys Ala Val Leu Gln Ala Glu Val Gln His Leu Arg Gln Asp Asn		
1475	1480	1485
Met Arg Leu Gln Glu Glu Ser Gln Thr Ala Thr Ala Gln Leu Arg		
1490	1495	1500
Lys Phe Thr Glu Trp Phe Phe Thr Thr Ile Asp Lys Lys Ser		
1505	1510	

<210> 116
 <211> 338
 <212> DNA
 <213> Homo sapien

<400> 116
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 tctttataact attggagggg tagaaggaac ttcctttcta gaccttgaag 100
 gttaagaat ttgaatctat aaaacaagct gacaatagac agattaacag 150
 gagaaaaagc atatacattt tttaatgtgg gccagatggc agaagcttaa 200
 ataacacccc aagctacagg aagtgaggcc tctgatgggg aggtagtgac 250
 acaggctgtg ggagggggta gggggaggaa gtctgtggtg agcaaagttt 300
 gccttattac actgataaag tgtaattaca ctaataaa 338

<210> 117
 <211> 23
 <212> PRT
 <213> Homo sapien

<400> 117
 Pro Lys Gly Arg Ala Leu Met Thr Leu Ser Pro Thr Lys Arg Leu
 1 5 10 15
 His Phe Phe Ile Leu Leu Glu Gly
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<210> 118
 <211> 542
 <212> DNA

<213> Homo sapien

<400> 118

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 ctggattata cagtaactct ttcctcataa ctttgcatac caaaattata 100
 tccatctttc agaaccctaaa ttcagtgtta tttccaaagt gttccaacat 150
 ctcccactca aaatgaatct tctccctagt actcccattg tttagtagct 200
 aattgttctt accagtttgt cttagagctc agtcattcct acacagcact 250
 tttcttcatt atactgctaa tttcattaca ctgtaagagt ggggacaagc 300
 tggttcttctt gtataccaga aagtagtgag tgcactgctg tgaagaaagc 350
 aggaactcaa aagttaagaa ttttgaatga gcctataaaa tgtgtctaata 400
 aaataataat gttcattttc aaatctcaac aattaaatgt ttaacaaata 450
 acacttgaaa taaatgttta ttagaaaaac caaaaaaatc tatgtcgggtg 500
 cggagaaaga gggtaatgaa atggcaggaa ttcgatatac gc 542

<210> 119

<211> 54

<212> PRT

<213> Homo sapien

<400> 119

Met	Trp	Thr	Cys	Phe	His	Phe	Ser	Trp	Met	Tyr	Ile	Pro	Arg	Arg
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Met	Ala	Gly	Leu	Tyr	Ser	Asn	Ser	Phe	Leu	Ile	Thr	Leu	His	Ile
				20					25					30
Lys	Ile	Ile	Ser	Ile	Phe	Gln	Asn	Pro	Asn	Ser	Val	Leu	Phe	Pro
				35					40					45
Lys	Cys	Ser	Asn	Ile	Ser	His	Ser	Lys						
				50										

<210> 120

<211> 1204

<212> DNA

<213> Homo sapien

<400> 120

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 ccaatcggag ggtaaagtgc agcaaacta ctgtacagta ggggtagaga 100
 tgcagaaagg cagaaaggag aaaattcagg ataactctcc tgaggggtga 150
 gccaaagcct gccatgtagt gcacgcagga catcaacaaa cacagataac 200
 aggaaatgat ccattccctg tggtcactta ttctaaaggc cccaaccttc 250
 aaagttcaag tagtgatatg gatgactcca cagaaaggga gcagtcacgc 300
 cttacttctt gccttaagaa aagagaagaa atgaaactga aggagtgtgt 350
 ttccatcctc ccacggaagg aaagcccctc tgtccgatcc tccaaagacg 400
 gaaagctgct ggctgcaacc ttgctgctgg cactgctgtc ttgctgcctc 450

acggtggtgt ctttctacca ggtggccgcc ctgcaagggg acctggccag 500
 cctccgggca gagctgcagg gccaccacgc ggagaagctg ccagcaggag 550
 caggagcccc caaggccggc ctggaggaag ctccagctgt caccgcggga 600
 ctgaaaatct ttgaaccacc agctccagga gaaggcaact ccagtcagaa 650
 cagcagaaat aagcgtgccg ttcagggtcc agaagaaaca gtcactcaag 700
 actgcttgca actgattgca gacagtgaaa caccaactat acaaaaagga 750
 tcttacacat ttgttccatg gcttctcagc tttaaaaggg gaagtgcctt 800
 agaagaaaaa gagaataaaa tattggtcaa agaaactggg tactttttta 850
 tatatgggtca ggttttatat actgataaga cctacgccat gggacatcta 900
 attcagagga agaagggtcca tgtctttggg gatgaattga gtctggtgac 950
 tttgtttcga tgtattcaaa atatgcctga aacactaccc aataattcct 1000
 gctattcagc tggcattgca aaactggaag aaggagatga actccaactt 1050
 gcaataccaa gagaaaatgc acaaatatca ctggatggag atgtcacatt 1100
 ttttgggtgca ttgaaactgc tgtgacctac ttacaccatg tctgtagcta 1150
 ttttcctccc tttctctgta cctctaagaa gaaagaatct aactgaaaat 1200
 acca 1204

<210> 121
 <211> 285
 <212> PRT
 <213> Homo sapien

<400> 121
 Met Asp Asp Ser Thr Glu Arg Glu Gln Ser Arg Leu Thr Ser Cys
 1 5 10 15
 Leu Lys Lys Arg Glu Glu Met Lys Leu Lys Glu Cys Val Ser Ile
 20 25 30
 Leu Pro Arg Lys Glu Ser Pro Ser Val Arg Ser Ser Lys Asp Gly
 35 40 45
 Lys Leu Leu Ala Ala Thr Leu Leu Leu Ala Leu Leu Ser Cys Cys
 50 55 60
 Leu Thr Val Val Ser Phe Tyr Gln Val Ala Ala Leu Gln Gly Asp
 65 70 75
 Leu Ala Ser Leu Arg Ala Glu Leu Gln Gly His His Ala Glu Lys
 80 85 90
 Leu Pro Ala Gly Ala Gly Ala Pro Lys Ala Gly Leu Glu Glu Ala
 95 100 105
 Pro Ala Val Thr Ala Gly Leu Lys Ile Phe Glu Pro Pro Ala Pro
 110 115 120
 Gly Glu Gly Asn Ser Ser Gln Asn Ser Arg Asn Lys Arg Ala Val
 125 130 135
 Gln Gly Pro Glu Glu Thr Val Thr Gln Asp Cys Leu Gln Leu Ile
 140 145 150

Ala	Asp	Ser	Glu	Thr	Pro	Thr	Ile	Gln	Lys	Gly	Ser	Tyr	Thr	Phe	
				155					160					165	
Val	Pro	Trp	Leu	Leu	Ser	Phe	Lys	Arg	Gly	Ser	Ala	Leu	Glu	Glu	
				170					175					180	
Lys	Glu	Asn	Lys	Ile	Leu	Val	Lys	Glu	Thr	Gly	Tyr	Phe	Phe	Ile	
				185					190					195	
Tyr	Gly	Gln	Val	Leu	Tyr	Thr	Asp	Lys	Thr	Tyr	Ala	Met	Gly	His	
				200					205					210	
Leu	Ile	Gln	Arg	Lys	Lys	Val	His	Val	Phe	Gly	Asp	Glu	Leu	Ser	
				215					220					225	
Leu	Val	Thr	Leu	Phe	Arg	Cys	Ile	Gln	Asn	Met	Pro	Glu	Thr	Leu	
				230					235					240	
Pro	Asn	Asn	Ser	Cys	Tyr	Ser	Ala	Gly	Ile	Ala	Lys	Leu	Glu	Glu	
				245					250					255	
Gly	Asp	Glu	Leu	Gln	Leu	Ala	Ile	Pro	Arg	Glu	Asn	Ala	Gln	Ile	
				260					265					270	
Ser	Leu	Asp	Gly	Asp	Val	Thr	Phe	Phe	Gly	Ala	Leu	Lys	Leu	Leu	
				275					280					285	

<210> 122
 <211> 376
 <212> DNA
 <213> Homo sapien

<400> 122
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 cttataagtt atggagttaa aatttttatgc agaagcaagg gaaaatcttc 100
 ctccagtgaa aaaatttctaa tgagatttttg aagacagaaa caaatcacat 150
 ttttttttggt tttgttttct aaatgtttta caagagaaaa tttcaaaagc 200
 ataatcagta agagggagaa aagtgtgctg aattccatgt atccagcttg 250
 cagccattgt taactcagga ctaatcttgt ttcggttcta cttccctttc 300
 accacccccca caccccaac acaaaattac tgattctaga tcatgtcatt 350
 tatttacaaa tacttttagta tgtatc 376

<210> 123
 <211> 1527
 <212> DNA
 <213> Homo sapien

<400> 123
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 caagtgcac ctgcacgcca acctgtgctc catgcgcgag ggcagcctgc 100
 agtgcgagtg cgagcacaac accaccggcc ccgactgcgg caagtgcag 150
 aagaatttcc gcaccgggtc ctggcggggc ggctcctacc tgccgctgcc 200
 ccatggctct cccaacgcct gtgccgctgc aggttccttt ggcaactgcg 250
 aatgctacgg tcaactccaac cgctgcagct acattgactt cctgaatgtg 300

gtgacctgcg tcagctgcaa gcacaacacg cgaggtcagc actgccagca 350
 ctgccggctg ggctactacc gcaacggctc ggcagagctg gatgatgaga 400
 acgtctgcat tgagtgtaac tgcaaccaga taggctccgt gcacgaccgg 450
 tgcaacgaga ccggcttctg cgagtgccgc gagggcgcgg cgggccccaa 500
 gtgcgacgac tgcctcccca cgcactactg gcgccagggc tgctacccca 550
 acgtgtgcga cgacgaccag ctgctgtgcc agaacggagg cacctgcctg 600
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 cccccgcagc aggggcgctt tgggactccg gtccccgcgc ctgcgatttg 1000
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 ggagaaacgc tgctcgcccc acaccccgtc ctgcctccca ccacacttac 1150
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 aaggaagggg tggggggcct ggaaacttcg ttctgtagag aactatTTTT 1400
 gtttgtattc actgtcccct gcaaggggga cggggcgggg gcactgggtca 1450
 ccgcgggggc cgatggtgga gaatccgagg agtaaagagt ttgctcactg 1500
 ctgccaaaaa aaaaaaaaaa aaaaaaa 1527

<210> 124
 <211> 2619
 <212> DNA
 <213> Homo sapien

<400> 124
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 gcggtgtgga gtccctgtcct gcctcagggc ttttcggagc ctggatcctc 150
 aaggaacaag tagacctggc cgcgggggagt ggggagggaa ggggtgtcta 200
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 aagtgcagag ctttcgtttg ccaagtgcgc tccagaccgc agacatgaaa 300

cttgtcttcc tcgtcctgct gttcctcggg gccctcggac tgtgtctggc 350
 tggccgtagg agaaggagtg ttcagtgggtg cgccgtatcc caacccgagg 400
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 cctgtcagct gcataaagag agactcccc atccagtgtg tccaggccat 500
 tgcggaaaac agggccgatg ctgtgaccct tgatgggtgg ttcataatcg 550
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 acacaggcct tcgcaggacc gctggatgga atgtccctac agggacactt 750
 cgtccattct tgaattggac gggccacct gagccattg aggcagctgt 800
 ggccaggctt ttctcagcca gctgtgttcc cgggtgcagat aaaggacagt 850
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 gaaggatatc ttgctgtggc ggtgggttagg agatcagaca ctagccttac 1700
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 aacaggctaa atttgggaga aatggatctg actgccccga caagttttgc 2250
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 ctggaagcct gtgaattcct caggaagtaa aaccgaagaa gatggcccag 2450
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<210> 125

<211> 711

<212> PRT

<213> Homo sapien

<400> 125

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

Ala	Asp	Lys	Gly	Gln	Phe	Pro	Asn	Leu	Cys	Arg	Leu	Cys	Ala	Gly	
				185					190					195	
Thr	Gly	Glu	Asn	Lys	Cys	Ala	Phe	Ser	Ser	Gln	Glu	Pro	Tyr	Phe	
				200					205					210	
Ser	Tyr	Ser	Gly	Ala	Phe	Lys	Cys	Leu	Arg	Asp	Gly	Ala	Gly	Asp	
				215					220					225	
Val	Ala	Phe	Ile	Arg	Glu	Ser	Thr	Val	Phe	Glu	Asp	Leu	Ser	Asp	
				230					235					240	
Glu	Ala	Glu	Arg	Asp	Glu	Tyr	Glu	Leu	Leu	Cys	Pro	Asp	Asn	Thr	
				245					250					255	
Arg	Lys	Pro	Val	Asp	Lys	Phe	Lys	Asp	Cys	His	Leu	Ala	Arg	Val	
				260					265					270	
Pro	Ser	His	Ala	Val	Val	Ala	Arg	Ser	Val	Asn	Gly	Lys	Glu	Asp	
				275					280					285	
Ala	Ile	Trp	Asn	Leu	Leu	Arg	Gln	Ala	Gln	Glu	Lys	Phe	Gly	Lys	
				290					295					300	
Asp	Lys	Ser	Pro	Lys	Phe	Gln	Leu	Phe	Gly	Ser	Pro	Ser	Gly	Gln	
				305					310					315	
Lys	Asp	Leu	Leu	Phe	Lys	Asp	Ser	Ala	Ile	Gly	Phe	Ser	Arg	Val	
				320					325					330	
Pro	Pro	Arg	Ile	Asp	Ser	Gly	Leu	Tyr	Leu	Gly	Ser	Gly	Tyr	Phe	
				335					340					345	
Thr	Ala	Ile	Gln	Asn	Leu	Arg	Lys	Ser	Glu	Glu	Glu	Val	Ala	Ala	
				350					355					360	
Arg	Arg	Ala	Arg	Val	Val	Trp	Cys	Ala	Val	Gly	Glu	Gln	Glu	Leu	
				365					370					375	
Arg	Lys	Cys	Asn	Gln	Trp	Ser	Gly	Leu	Ser	Glu	Gly	Ser	Val	Thr	
				380					385					390	
Cys	Ser	Ser	Ala	Ser	Thr	Thr	Glu	Asp	Cys	Ile	Ala	Leu	Val	Leu	
				395					400					405	
Lys	Gly	Glu	Ala	Asp	Ala	Met	Ser	Leu	Asp	Gly	Gly	Tyr	Val	Tyr	
				410					415					420	
Thr	Ala	Cys	Lys	Cys	Gly	Leu	Val	Pro	Val	Leu	Ala	Glu	Asn	Tyr	
				425					430					435	
Lys	Ser	Gln	Gln	Ser	Ser	Asp	Pro	Asp	Pro	Asn	Cys	Val	Asp	Arg	
				440					445					450	
Pro	Val	Glu	Gly	Tyr	Leu	Ala	Val	Ala	Val	Val	Arg	Arg	Ser	Asp	
				455					460					465	
Thr	Ser	Leu	Thr	Trp	Asn	Ser	Val	Lys	Gly	Lys	Lys	Ser	Cys	His	
				470					475					480	
Thr	Ala	Val	Asp	Arg	Thr	Ala	Gly	Trp	Asn	Ile	Pro	Met	Gly	Leu	
				485					490					495	
Leu	Phe	Asn	Gln	Thr	Gly	Ser	Cys	Lys	Phe	Asp	Glu	Tyr	Phe	Ser	
				500					505					510	
Gln	Ser	Cys	Ala	Pro	Gly	Ser	Asp	Pro	Arg	Ser	Asn	Leu	Cys	Ala	

	515		520		525
Leu Cys Ile Gly	Asp 530	Glu Gln Gly Glu	Asn 535	Lys Cys Val Pro	Asn 540
Ser Asn Glu Arg	Tyr 545	Tyr Gly Tyr Thr	Gly 550	Ala Phe Arg Cys	Leu 555
Ala Glu Asn Ala	Gly 560	Asp Val Ala Phe	Val 565	Lys Asp Val Thr	Val 570
Leu Gln Asn Thr	Asp 575	Gly Asn Asn Asn	Glu 580	Ala Trp Ala Lys	Asp 585
Leu Lys Leu Ala	Asp 590	Phe Ala Leu Leu	Cys 595	Leu Asp Gly Lys	Arg 600
Lys Pro Val Thr	Glu 605	Ala Arg Ser Cys	His 610	Leu Ala Met Ala	Pro 615
Asn His Ala Val	Val 620	Ser Arg Met Asp	Lys 625	Val Glu Arg Leu	Lys 630
Gln Val Leu Leu	His 635	Gln Gln Ala Lys	Phe 640	Gly Arg Asn Gly	Ser 645
Asp Cys Pro Asp	Lys 650	Phe Cys Leu Phe	Gln 655	Ser Glu Thr Lys	Asn 660
Leu Leu Phe Asn	Asp 665	Asn Thr Glu Cys	Leu 670	Ala Arg Leu His	Gly 675
Lys Thr Thr Tyr	Glu 680	Lys Tyr Leu Gly	Pro 685	Gln Tyr Val Ala	Gly 690
Ile Thr Asn Leu	Lys 695	Lys Cys Ser Thr	Ser 700	Pro Leu Leu Glu	Ala 705
Cys Glu Phe Leu	Arg 710	Lys			

<210> 126
 <211> 2224
 <212> DNA
 <213> Homo sapien

<400> 126
 gctgacacct gccagtgga agctggcatc cctccccttg tgggttcaga 50
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 agcccaccct ctcagggcca cagtgcagaa gcctgcacac ctgccaagtc 150
 tctccgactc cttgcagctg ctgtcagcat ggcccaggct cctgctgacc 200
 cgggcagaga aggccacctt gaacaaagaa tcctgcaggt gctgacagag 250
 gctggctccc cggtgaaact tgcccagctg gtgaaggaat gccaagcacc 300
 caagagggag ctcaaccaag tcctctaccg aatgaaaaag gagttgaaag 350
 tctccctcac atcccctgcc acctggtgct tgggcgggac tgatcctgaa 400
 ggcgagggtc ctgcagagct ggccttgtcc agccctgccg agaggcccca 450
 gcaacatgca gctacaattc cagagacccc tggccctcag ttcagccaac 500

aacgggagga agacatctac aggtttctca aagacaatgg tccccagagg 550
gccctgggtca tcgccaagc actgggaatg aggacagcaa aagatgtgaa 600
ccgagacttg tacaggatga agagcaggca ccttctggac atggatgagc 650
agtccaaagc atggacgatt taccgcccag aagattctgg aagaagagca 700
aagtcagcct caattattta ccagcacaat ccaatcaaca tgatctgcca 750
gaatggaccc aacagctgga tttccattgc aaactccgaa gccatccaga 800
ttggacacgg gaacatcatt acaagacaga cagtctccag ggaggacggc 850
tccgcccgtc cacgccacct cccttcaatg gcaccagggtg attcctcaac 900
ttggggggacc ctagttgatc cctggggggc ccaggacatc cacatggagc 950
ggtccatact gagacgggtg cagctgggac acagcaatga gatgaggctc 1000
cacggcgtcc cgtccgaggg ccctgcccac atccccctg gcagcccccc 1050
agtctctgcc actgctgccg gcccagaagc ttcgtttgaa gcaagaattc 1100
ccagtccagg aactcaccct gagggggaag ccgcccagag aatccacatg 1150
aaatcgtgct ttctcgagga cgccaccatc ggcaacagca acaaaatgtc 1200
tatcagccca ggggtggctg gcccaggagg agtcgcaggg tctggagagg 1250
gggagccagg ggaggacgca ggtcgtcgtc ccgcagacac acaatccaga 1300
agtcactttc ctcgagacat tggtcagccc atcactccca gccactcgaa 1350
gctcaccccc aagctggaaa ctatgactct tggaaacagg agtcacaaag 1400
ctgcagaagg cagccactat gtggatgaag cctcacacga ggggagctgg 1450
tggggaggtg ggatttagtg cacagcctca cgtggggctt ggacacaggc 1500
tgggggtggg cgcattgtag ggagactagc ctgctgctct ctgcattcct 1550
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caagaggagg tgggtagatg ggagtggggc tcgggtcccc aggccaggg 1750
gactctctcc actctttcct gggctcgggg catctgcctg gagttacctt 1800
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atatcaaaac ataatcccaa ctgggtgcag tggctcacgc ctgtaatccc 1900
agcacttttg gaggccgagg cgggcggatc aatagggtcag gaaatccaga 1950
ccgtcctggc taacatgggtg aaaccccgtc tctactaaaa aaaaaaatac 2000
aaaaaattag ccgggcgttg tggcgggcac ctggagtccc agctactccg 2050
gaggctgagg gaggagaatg gtgtgaaccc gggaggtgga gcttccagtg 2100
agccgagatc gcgccactgc actccaggct gggcgacaga gcgagactcc 2150
gtctcaaaaa aataaatata taaataaaaa ataaaccacc cataaaaaaa 2200

aaaaaaaaaa aaaaaaaaaa aaaa 2224

<210> 127
 <211> 429
 <212> PRT
 <213> Homo sapien

<400> 127
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 Gln Arg Ile Leu Gln Val Leu Thr Glu Ala Gly Ser Pro Val Lys
 20 25 30
 Leu Ala Gln Leu Val Lys Glu Cys Gln Ala Pro Lys Arg Glu Leu
 35 40 45
 Asn Gln Val Leu Tyr Arg Met Lys Lys Glu Leu Lys Val Ser Leu
 50 55 60
 Thr Ser Pro Ala Thr Trp Cys Leu Gly Gly Thr Asp Pro Glu Gly
 65 70 75
 Glu Gly Pro Ala Glu Leu Ala Leu Ser Ser Pro Ala Glu Arg Pro
 80 85 90
 Gln Gln His Ala Ala Thr Ile Pro Glu Thr Pro Gly Pro Gln Phe
 95 100 105
 Ser Gln Gln Arg Glu Glu Asp Ile Tyr Arg Phe Leu Lys Asp Asn
 110 115 120
 Gly Pro Gln Arg Ala Leu Val Ile Ala Gln Ala Leu Gly Met Arg
 125 130 135
 Thr Ala Lys Asp Val Asn Arg Asp Leu Tyr Arg Met Lys Ser Arg
 140 145 150
 His Leu Leu Asp Met Asp Glu Gln Ser Lys Ala Trp Thr Ile Tyr
 155 160 165
 Arg Pro Glu Asp Ser Gly Arg Arg Ala Lys Ser Ala Ser Ile Ile
 170 175 180
 Tyr Gln His Asn Pro Ile Asn Met Ile Cys Gln Asn Gly Pro Asn
 185 190 195
 Ser Trp Ile Ser Ile Ala Asn Ser Glu Ala Ile Gln Ile Gly His
 200 205 210
 Gly Asn Ile Ile Thr Arg Gln Thr Val Ser Arg Glu Asp Gly Ser
 215 220 225
 Ala Gly Pro Arg His Leu Pro Ser Met Ala Pro Gly Asp Ser Ser
 230 235 240
 Thr Trp Gly Thr Leu Val Asp Pro Trp Gly Pro Gln Asp Ile His
 245 250 255
 Met Glu Arg Ser Ile Leu Arg Arg Val Gln Leu Gly His Ser Asn
 260 265 270
 Glu Met Arg Leu His Gly Val Pro Ser Glu Gly Pro Ala His Ile
 275 280 285
 Pro Pro Gly Ser Pro Pro Val Ser Ala Thr Ala Ala Gly Pro Glu
 290 295 300

Ala Ser Phe Glu Ala Arg Ile Pro Ser Pro Gly Thr His Pro Glu
 305 310 315
 Gly Glu Ala Ala Gln Arg Ile His Met Lys Ser Cys Phe Leu Glu
 320 325 330
 Asp Ala Thr Ile Gly Asn Ser Asn Lys Met Ser Ile Ser Pro Gly
 335 340 345
 Val Ala Gly Pro Gly Gly Val Ala Gly Ser Gly Glu Gly Glu Pro
 350 355 360
 Gly Glu Asp Ala Gly Arg Arg Pro Ala Asp Thr Gln Ser Arg Ser
 365 370 375
 His Phe Pro Arg Asp Ile Gly Gln Pro Ile Thr Pro Ser His Ser
 380 385 390
 Lys Leu Thr Pro Lys Leu Glu Thr Met Thr Leu Gly Asn Arg Ser
 395 400 405
 His Lys Ala Ala Glu Gly Ser His Tyr Val Asp Glu Ala Ser His
 410 415 420
 Glu Gly Ser Trp Trp Gly Gly Gly Ile
 425

<210> 128
 <211> 1081
 <212> DNA
 <213> Homo sapien

<400> 128
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 gagaaaggac aagaagaccc aaagtcggca agcaaattta ttaacctgct 100
 gggctgctct acagaaatct gaggaggcag acaccgggct tacaggctaa 150
 ggggtataag taggtctgca ggggttttgt gtgtgtgtgc ggggggtgtcg 200
 ggggggcaag gccatttgtg gagacttttc ctcccagtat ggccacatcc 250
 tgcagtttgt cagtttttgc ccccgcttgg ctcagggtac caggatgtgg 300
 tttagcttag gggtaggttat agtggcacct aagttctggg aacttgcggt 350
 gggggcgacc ttttggacga aaaataagct gcagggcagc taggggaggg 400
 ggcttggttat attcctctgg gggcaggggtg tccctaactg ggctcagtcg 450
 gaaggaactt gaccaaagtc tgggctcagt tgggcatcac tcaggctaata 500
 ggtcgtgtgc tggatgccat cagaggggaag taccaatggg aaagtggaaa 550
 caatgtgcag ctttcaactg ggtggagggt gctattctgt ggacagtgag 600
 atgtttcctt ggcactgtca atagacaatc tgcgtagaga aattccaagc 650
 tgaaagccaa taatgttata ataaaataga gattcttcag aagatgaaag 700
 gaattaccag catggaaatt gtgtcatagg ctttaagggt aaagaagaag 750
 ccttttcttt tctgttcacc ctcaccaaga gcacaactta aatagggcat 800
 tttataacct gaacacaatt tatattggac ttaattatta tgtgtaatat 850

gtttataatc ctttagatct tataaatatg tgggtataagg aatgccatat 900
aatgtgccaa aaatctgagt gcattttaatt taatgcttgc ttatagtgc 950
aaagttaa at gatcttaatt ctttgcaatt atatatgaaa aatgactgat 1000
ttttcttaaa atatgtaact tatataaata tatctgtttg tacagatttt 1050
aaccataaaa acattttttgg aaaaccataa a 1081

<210> 129
<211> 12
<212> PRT
<213> Homo sapien

<400> 129
Thr Ala Asp Leu Glu Gly Val Met His Met Gly Leu
1 5 10

<210> 130
<211> 1121
<212> DNA
<213> Homo sapien

<400> 130
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gagccaagcc ctgccatgta gtgcacgcag gacatcaaca aacacagata 100
acaggaaatg atccattccc tgtgggtcact tattctaaag gcccacacct 150
tcaaagttca agtagtgata tggatgactc cacagaaagg gagcagtcac 200
gccttacttc ttgccttaag aaaagagaag aaatgaaact gaaggagtgt 250
gtttccatcc tcccacggaa ggaaagcccc tctgtccgat cctccaaaga 300
cggaaagctg ctggctgcaa ccttgctgct ggactgctg tcttgctgcc 350
tcacgggtgg gtctttctac caggtggccg ccctgcaagg ggacctggcc 400
agcctccggg cagagctgca gggccaccac gcggagaagc tgccagcagg 450
agcaggagcc cccaaggccg gcctggagga agctccagct gtcaccgcgg 500
gactgaaaat ctttgaacca ccagctccag gagaaggcaa ctccagtcag 550
aacagcagaa ataagcgtgc cgttcagggt ccagaagaaa cagtcactca 600
agactgcttg caactgattg cagacagtga aacaccaact atacaaaaag 650
gatcttacac atttgttcca tggcttctca gctttaaaag gggaagtgcc 700
ctagaagaaa aagagaataa aatattgggtc aaagaaactg gttacttttt 750
tatatatggg caggttttat atactgataa gacctacgcc atgggacatc 800
taattcagag gaagaaggct catgtctttg gggatgaatt gagtctgggtg 850
actttgtttc gatgtattca aaatatgcct gaaacactac ccaataattc 900
ctgctattca gctggcattg caaaactgga agaaggagat gaactccaac 950
ttgcaatacc aagagaaaat gcacaaatat cactggatgg agatgtcaca 1000
ttttttgggt cattgaaact gctgtgacct acttacacca tgtctgtagc 1050

tatttttcctc ccttttctctg tacctctaag aagaaagaat ctaactgaaa 1100

ataccaaaaaa aaaaaaaaaa a 1121

<210> 131

<211> 285

<212> PRT

<213> Homo sapien

<400> 131

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

<210> 132
 <211> 1318
 <212> DNA
 <213> Homo sapien

<400> 132
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 gaaatgttct cctttttatc atcaaactctg ctcaagaagg gctttttata 100
 gtagaataat atcagtggat gaaaacagct taacatttta ccatgcttaa 150
 gttttaagaa taaaataaaa attggaaata attggccaaa attgaaagga 200
 aaaatttttt taaaatttct ctaaagttag gcctggctgg gctttgacct 250
 tttccgtttt taaatcactc acagaggggtg ggacaggagg aagagtgaag 300
 gaaaagggtca aacctgtttt aagggcaacc tgcctttgtt ctgaattggt 350
 cttaagaaca ttaccagctc caggttttaa ttgttcagtt tcatgcagtt 400
 ccaatagctg atcattgttg agatgaggac aaaatccttt gtcctcacta 450
 gtttgcttta catttttgaa aagtattatt tttgtccaag tgcttatcaa 500
 ctaaaccttg tgtaggtaa gaatggaatt tattaagtga atcagtgtga 550
 cccttcttgt cataagatta tcttaaagct gaagccaaaa tatgcttcaa 600
 aagaagagga ctttattgtt cattgtagtt catacattca aagcatctga 650
 actgtagttt ctatagcaag ccaattacat ccataagtgg agaaggaaat 700
 agataaatgt caaagtatga ttgggtggagg gagcaagggt gaagataatc 750
 tgggggttgaa attttctagt tttcattctg tacattttta gttagacatc 800
 agatttgaaa tattaatgtt tacctttcaa tgtgtggtat cagctggact 850
 cagtaacacc cctttcttca gctgggggatg gggaatggat tattggaaaa 900
 tggaaagaag aaagtaacta aaagccttcc tttcacagtt tctggcatca 950
 ctaccactac tgattaaaca agaataagag aacattttat catcatctgc 1000
 tttattcaca taaatgaagt tgtgatgaat aaatctgctt ttatgcagac 1050
 acaaggaatt aagtggcttc gtcattgtcc ttctacctca aagataattt 1100
 attccaaaag ctaagataaa tggaagactc ttgaacttgt gaactgatgt 1150
 gaaatgcaga atctcttttg agtctttgct gtttggaaga ttgaaaaata 1200
 ttgttcagca tgggtgacca ccagaaagta atcttaagcc atctagatgt 1250
 cacaattgaa acaaactggg gagttggttg ctattgtaaa ataaaatata 1300
 ctgttttgaa aactttgt 1318

<210> 133
 <211> 35
 <212> PRT
 <213> Homo sapien

<400> 133
 Met Gly Asp His Gln Lys Val Ile Leu Ser His Leu Asp Val Thr

1	5	10	15
Ile Glu Thr Asn Trp Gly Val Gly Cys Tyr Cys Lys Ile Lys Tyr			
	20	25	30
Thr Val Leu Lys Thr			
	35		

<210> 134
 <211> 3211
 <212> DNA
 <213> Homo sapien

<400> 134
 atcggaaaag caccttgagt tactggcttc ccctttacct attccatcaa 50
 ccttccttcc acacagtagt actcccgtt tgcattctac agttcagagg 100
 ctaaagttgc caccaccaca gggatcttct gagagctgca cagttaacat 150
 cccacaacaa ccaccggaa gcctgagcat cgcattacca aacactgcct 200
 ttattcctat ccataacca ggtagtttcc caggctctcc tgttgctacc 250
 acggacccca tcacaaaatc tgcattccaa gtggtaggac tcaatcaaatt 300
 ggtgcctcaa attgagggaa acacaggga agtccctcag cctaccaatg 350
 tgaaggtagt tcttcagca gctggcctct cagctgctca gccaccagct 400
 tcctaccctt taccaggctc tccccttgct gccggcgtgt taccagcca 450
 gaactccagt gtgctcagca cagcagcaac ttctccccag ccagcgagcg 500
 caggtatcag ccaggcccag gcaactgttc ctctgcagt tcctaccac 550
 accccaggcc ctgccccgag cccaagccct gccttgacac acagtaccgc 600
 gcagagtgc agcacctctt acatcagtgc tgtggggaac acgaacgcta 650
 atgggacagt agtgccaccg cagcagatgg gctcagggtc ttgtggttct 700
 tgtgggcgaa ggtgcagctg tgggaccaat ggaaacctc agctaaatag 750
 ttactattat cctaatacaa tgcttgacc aatgtaccga gtcccttcat 800
 tctttactct gccatccatt tgcaatggca gctacctcaa ccaagcacat 850
 cagagcaatg gaaaccaact tccttttttt ctgcctcaga ctccatatgc 900
 aatggactg gtacatgacc cagtcattgg gagccaagcc aactatggca 950
 tgcagcagat ggcaggattt gggagattct atcctgtata tccagcacct 1000
 aacgtagttg ccaacaccag tgggtcgggg cccaagaaga atgggaatgt 1050
 ctcatgttac aattgtggtg taagcggaca ctacgcacag gactgtaagc 1100
 agtcgtccat ggaggccaat caacaaggca cttacagact gagatacgca 1150
 cctcccctcc ccccttctaa tgatacgttg gattctgcag actgaaacga 1200
 gtaaagcttg cctacttaat aactcaagt gtggggagtc atgggggtgtg 1250
 gaggggagga aaggaaaggt attttgtttc ttgtctata catttcctag 1300
 atttctatgc agttgggatt tttcatttct ctgtaccaaa tgtccaaaac 1350

aagaaagaat gcaatgcttt tgagcctctg gtctcctggg tcaacaacag 1400
gcttatatgt atgatacatg taattttaac cttcagacaa acttaaagt 1450
tggtgcgtgc tttttttttt ttttactctg aatacttgct gtgtgcaatg 1500
tttactgaat ctttaaaact gtgtatttga cttttttttt acaacactgg 1550
tgacagtcac atgggttttga aaaaaaaaaa aaatttttgc tcttcccagc 1600
ttttctcact ttcaccctaa acgacacttc ctccccagcc agcctcactc 1650
tgtctccggc ccgcagcagg agcagccagc agtgcattca cccactttt 1700
gtaaactgct ctgcatataa accaagggca gaatgtttca cctgatctt 1750
atgggaggaa tcgaactccc aaaatagtgt gtatatatgt aataaacagc 1800
gtcacgtaaa tacatatatg cagtgtttgt tgtccaaata gaaatgaaaa 1850
taagtgaag agagaggaag aagtcaacca tatgaaactg aaaaaatatg 1900
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 <213> Homo sapien

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 <211> 319
 <212> PRT
 <213> Homo sapien

<400> 136

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Tyr	Ile	Phe	Ile	Thr	Gly	Cys	Asp	Ser	Gly	Phe	Gly	Asn	Leu	Ala	35	40	45	
Ala	Arg	Thr	Phe	Asp	Lys	Lys	Gly	Phe	His	Val	Ile	Ala	Ala	Cys	50	55	60	
Leu	Thr	Glu	Ser	Gly	Ser	Thr	Ala	Leu	Lys	Ala	Glu	Thr	Ser	Glu	65	70	75	
Arg	Leu	Arg	Thr	Val	Leu	Leu	Asp	Val	Thr	Asp	Pro	Glu	Asn	Val	80	85	90	
Lys	Arg	Thr	Ala	Gln	Trp	Val	Lys	Asn	Gln	Val	Gly	Glu	Lys	Gly	95	100	105	
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Pro	Thr	Asp	Trp	Leu	Thr	Leu	Glu	Asp	Tyr	Arg	Glu	Pro	Ile	Glu	125	130	135	
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Tyr	Ala	Val	Glu	Gly	Phe	Asn	Asp	Ser	Leu	Arg	Arg	Asp	Met	Lys	185	190	195	
Ala	Phe	Gly	Val	His	Val	Ser	Cys	Ile	Glu	Pro	Gly	Leu	Phe	Lys	200	205	210	
Thr	Asn	Leu	Ala	Asp	Pro	Val	Lys	Val	Ile	Glu	Lys	Lys	Leu	Ala	215	220	225	
Ile	Trp	Glu	Gln	Leu	Ser	Pro	Asp	Ile	Lys	Gln	Gln	Tyr	Gly	Glu	230	235	240	
Gly	Tyr	Ile	Glu	Lys	Ser	Leu	Asp	Lys	Leu	Lys	Gly	Asn	Lys	Ser	245	250	255	
Tyr	Val	Asn	Met	Asp	Leu	Ser	Pro	Val	Val	Glu	Cys	Met	Asp	His	260	265	270	
Ala	Leu	Thr	Ser	Leu	Phe	Pro	Lys	Thr	His	Tyr	Ala	Ala	Gly	Lys	275	280	285	
Asp	Ala	Lys	Ile	Phe	Trp	Ile	Pro	Leu	Ser	His	Met	Pro	Ala	Ala	290	295	300	
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Pro	Lys	Ala	Val															

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 <212> DNA
 <213> Homo sapien

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<210> 138
 <211> 277
 <212> PRT

<213> Homo sapien

<400> 138

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Leu	Glu	Arg	Ala	Ala	Gly	Val	Tyr	His	Arg	Glu	Ala	Arg	Ser	Gly	35	40	45	
Lys	Tyr	Lys	Leu	Thr	Tyr	Ala	Glu	Ala	Lys	Ala	Val	Cys	Glu	Phe	50	55	60	
Glu	Gly	Gly	His	Leu	Ala	Thr	Tyr	Lys	Gln	Leu	Glu	Ala	Ala	Arg	65	70	75	
Lys	Ile	Gly	Phe	His	Val	Cys	Ala	Ala	Gly	Trp	Met	Ala	Lys	Gly	80	85	90	
Arg	Val	Gly	Tyr	Pro	Ile	Val	Lys	Pro	Gly	Pro	Asn	Cys	Gly	Phe	95	100	105	
Gly	Lys	Thr	Gly	Ile	Ile	Asp	Tyr	Gly	Ile	Arg	Leu	Asn	Arg	Ser	110	115	120	
Glu	Arg	Trp	Asp	Ala	Tyr	Cys	Tyr	Asn	Pro	His	Ala	Lys	Glu	Cys	125	130	135	
Gly	Gly	Val	Phe	Thr	Asp	Pro	Lys	Gln	Ile	Phe	Lys	Ser	Pro	Gly	140	145	150	
Phe	Pro	Asn	Glu	Tyr	Glu	Asp	Asn	Gln	Ile	Cys	Tyr	Trp	His	Ile	155	160	165	
Arg	Leu	Lys	Tyr	Gly	Gln	Arg	Ile	His	Leu	Ser	Phe	Leu	Asp	Phe	170	175	180	
Asp	Leu	Glu	Asp	Asp	Pro	Gly	Cys	Leu	Ala	Asp	Tyr	Val	Glu	Ile	185	190	195	
Tyr	Asp	Ser	Tyr	Asp	Asp	Val	His	Gly	Phe	Val	Gly	Arg	Tyr	Cys	200	205	210	
Gly	Asp	Glu	Leu	Pro	Asp	Asp	Ile	Ile	Ser	Thr	Gly	Asn	Val	Met	215	220	225	
Thr	Leu	Lys	Phe	Leu	Ser	Asp	Ala	Ser	Val	Thr	Ala	Gly	Gly	Phe	230	235	240	
Gln	Ile	Lys	Tyr	Val	Ala	Met	Asp	Pro	Val	Ser	Lys	Ser	Ser	Gln	245	250	255	
Gly	Lys	Asn	Thr	Ser	Thr	Thr	Ser	Thr	Gly	Asn	Lys	Asn	Phe	Leu	260	265	270	
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<211> 7484

<212> DNA

<213> Homo sapien

<400> 139

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<210> 140
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 <212> DNA
 <213> Homo sapien

<400> 140
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<210> 141
 <211> 460
 <212> PRT
 <213> Homo sapien

<400> 141
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 35 40 45
 Ala Leu Glu Cys Leu Arg Lys Ala Glu Glu Leu Ile Gln Gln Glu
 50 55 60
 His Ala Asp Gln Ala Glu Ile Arg Ser Leu Val Thr Trp Gly Asn
 65 70 75
 Tyr Ala Trp Val Tyr Tyr His Met Gly Arg Leu Ser Asp Val Gln
 80 85 90
 Ile Tyr Val Asp Lys Val Arg His Val Cys Glu Lys Phe Ser Ser
 95 100 105
 Pro Tyr Arg Ile Glu Ser Pro Glu Leu Asp Cys Glu Glu Gly Trp
 110 115 120
 Thr Arg Leu Lys Cys Gly Gly Asn Gln Asn Glu Arg Ala Lys Val
 125 130 135
 Cys Phe Glu Lys Ala Leu Glu Lys Lys Pro Lys Asn Pro Glu Phe
 140 145 150
 Thr Ser Gly Leu Ala Ile Ala Ser Tyr Arg Leu Asp Asn Trp Pro
 155 160 165
 Pro Ser Gln Asn Ala Ile Asp Pro Leu Arg Gln Ala Ile Arg Leu
 170 175 180
 Asn Pro Asp Asn Gln Tyr Leu Lys Val Leu Leu Ala Leu Lys Leu
 185 190 195
 His Lys Met Arg Glu Glu Gly Glu Glu Glu Gly Glu Gly Glu Lys
 200 205 210

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

<210> 142
 <211> 2958
 <212> DNA
 <213> Homo sapien

<400> 142
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<210> 143
 <211> 808
 <212> PRT
 <213> Homo sapien

<400> 143
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 35 40 45
 Glu Ser Pro Arg Pro Gly Arg Asp Arg Asp Gly Val Arg Val Pro
 50 55 60
 Met Ala Ser Ser Arg Cys Pro Ala Pro Arg Gly Cys Arg Cys Leu
 65 70 75
 Pro Gly Ala Ser Leu Ala Trp Leu Gly Thr Val Leu Leu Leu Leu
 80 85 90
 Ala Asp Trp Val Leu Leu Arg Thr Ala Leu Pro Arg Ile Phe Ser

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

Thr	Val	Arg	Ser	Phe	Ala	Asn	Glu	Glu	Gly	Glu	Ala	Gln	Lys	Phe	440	445	450
Arg	Glu	Lys	Leu	Gln	Glu	Ile	Lys	Thr	Leu	Asn	Gln	Lys	Glu	Ala	455	460	465
Val	Ala	Tyr	Ala	Val	Asn	Ser	Trp	Thr	Thr	Ser	Ile	Ser	Gly	Met	470	475	480
Leu	Leu	Lys	Val	Gly	Ile	Leu	Tyr	Ile	Gly	Gly	Gln	Leu	Val	Thr	485	490	495
Ser	Gly	Ala	Val	Ser	Ser	Gly	Asn	Leu	Val	Thr	Phe	Val	Leu	Tyr	500	505	510
Gln	Met	Gln	Phe	Thr	Gln	Ala	Val	Glu	Val	Leu	Leu	Ser	Ile	Tyr	515	520	525
Pro	Arg	Val	Gln	Lys	Ala	Val	Gly	Ser	Ser	Glu	Lys	Ile	Phe	Glu	530	535	540
Tyr	Leu	Asp	Arg	Thr	Pro	Arg	Cys	Pro	Pro	Ser	Gly	Leu	Leu	Thr	545	550	555
Pro	Leu	His	Leu	Glu	Gly	Leu	Val	Gln	Phe	Gln	Asp	Val	Ser	Phe	560	565	570
Ala	Tyr	Pro	Asn	Arg	Pro	Asp	Val	Leu	Val	Leu	Gln	Gly	Leu	Thr	575	580	585
Phe	Thr	Leu	Arg	Pro	Gly	Glu	Val	Thr	Ala	Leu	Val	Gly	Pro	Asn	590	595	600
Gly	Ser	Gly	Lys	Ser	Thr	Val	Ala	Ala	Leu	Leu	Gln	Asn	Leu	Tyr	605	610	615
Gln	Pro	Thr	Gly	Gly	Gln	Leu	Leu	Leu	Asp	Gly	Lys	Pro	Leu	Pro	620	625	630
Gln	Tyr	Glu	His	Arg	Tyr	Leu	His	Arg	Gln	Val	Ala	Ala	Val	Gly	635	640	645
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Pro	Cys	Val	Leu	Ile	Leu	Asp	Asp	Ala	Thr	Ser	Ala	Leu	Asp	Ala	725	730	735
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DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 3
CONTENANT LES PAGES 1 À 304

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 3
CONTAINING PAGES 1 TO 304

NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

What is claimed:

1. Isolated nucleic acid having at least 80% nucleic acid sequence identity to a nucleotide
5 sequence encoding the polypeptide shown in Figures 1-596.

2. Isolated nucleic acid having at least 80% nucleic acid sequence identity to a nucleotide
sequence selected from the group consisting of the nucleotide sequence shown in Figures 1-596.

10 3. Isolated nucleic acid having at least 80% nucleic acid sequence identity to a nucleotide
sequence selected from the group consisting of the full-length coding sequence of the nucleotide sequence
shown in Figures 1-596.

4. A vector comprising the nucleic acid of Claim 1.

15 5. The vector of Claim 4 operably linked to control sequences recognized by a host cell
transformed with the vector.

6. A host cell comprising the vector of Claim 4.

20 7. The host cell of Claim 6, wherein said cell is a CHO cell, an *E.coli* cell or a yeast cell.

8. A process for producing a PRO polypeptide comprising culturing the host cell of Claim 6
under conditions suitable for expression of said PRO polypeptide and recovering said PRO polypeptide
25 from the cell culture.

9. An isolated polypeptide having at least 80% amino acid sequence identity to an amino
acid sequence of the polypeptide shown in Figures 1-596.

30 10. A chimeric molecule comprising a polypeptide according to Claim 9 fused to a
heterologous amino acid sequence.

11. The chimeric molecule of Claim 10, wherein said heterologous amino acid sequence is
an epitope tag sequence or an Fc region of an immunoglobulin.

35 12. An antibody which specifically binds to a polypeptide according to Claim 9.

13. The antibody of Claim 12, wherein said antibody is a monoclonal antibody, a humanized antibody or a single-chain antibody.

14. A composition of matter comprising (a) a polypeptide of Claim 9, (b) an agonist of said polypeptide, (c) an antagonist of said polypeptide, or (d) an antibody that binds to said polypeptide, in combination with a carrier.

15. The composition of matter of Claim 14, wherein said carrier is a pharmaceutically acceptable carrier.

16. The composition of matter of Claim 15 comprising a therapeutically effective amount of (a), (b), (c) or (d).

17. An article of manufacture, comprising:

a container;

a label on said container; and

a composition of matter comprising (a) a polypeptide of Claim 9, (b) an agonist of said polypeptide, (c) an antagonist of said polypeptide, or (d) an antibody that binds to said polypeptide, contained within said container, wherein label on said container indicates that said composition of matter can be used for treating an immune related disease.

18. A method of treating an immune related disorder in a mammal in need thereof comprising administering to said mammal a therapeutically effective amount of (a) a polypeptide of Claim 9, (b) an agonist of said polypeptide, (c) an antagonist of said polypeptide, or (d) an antibody that binds to said polypeptide.

19. The method of Claim 18, wherein a second immunosuppressive agent is administered.

20. The method of Claim 19, wherein said second immunosuppressive agent is cyclophosphamide.

21. The method of Claim 18, wherein the immune related disorder is: systemic lupus erythematosus, rheumatoid arthritis, osteoarthritis, juvenile chronic arthritis, spondyloarthropathies, systemic sclerosis, idiopathic inflammatory myopathies, Sjögren's syndrome, systemic vasculitis, sarcoidosis, autoimmune hemolytic anemia, autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis, lymphadenopathy, splenomegaly and leukopenia.

22. A method for determining the presence of a PRO polypeptide of the invention as described in Figures 1-596, in a sample suspected of containing said polypeptide, said method comprising exposing said sample to an anti-PRO antibody, where the and determining binding of said antibody to a component of said sample.

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23. A method of diagnosing an immune related disease in a mammal, said method comprising detecting the level of expression of a gene encoding a PRO polypeptide of the invention as described in Figures 1-596, (a) in a test sample of tissue cells obtained from the mammal, and (b) in a control sample of known normal tissue cells of the same cell type, wherein a higher or lower level of expression of said gene in the test sample as compared to the control sample is indicative of the presence of an immune related disease in the mammal from which the test tissue cells were obtained.

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24. A method of diagnosing an immune related disease in a mammal, said method comprising (a) contacting a PRO polypeptide of the invention as described in Figures 1-596, anti-PRO antibody with a test sample of tissue cells obtained from said mammal and (b) detecting the formation of a complex between the antibody and the polypeptide in the test sample, wherein formation of said complex is indicative of the presence of an immune related disease in the mammal from which the test tissue cells were obtained.

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25. A method of identifying a compound that inhibits the activity of a PRO polypeptide of the invention as described in Figures 1-596, said method comprising contacting cells which normally respond to said polypeptide with (a) said polypeptide and (b) a candidate compound, and determining the lack responsiveness by said cell to (a).

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26. A method of identifying a compound that inhibits the expression of a gene encoding a PRO polypeptide of the invention as described in Figures 1-596, said method comprising contacting cells which normally express said polypeptide with a candidate compound, and determining the lack of expression said gene.

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27. The method of Claim 26, wherein said candidate compound is an antisense nucleic acid.

28. A method of identifying a compound that mimics the activity of a PRO polypeptide of the invention as described in Figures 1-596, said method comprising contacting cells which normally respond to said polypeptide with a candidate compound, and determining the responsiveness by said cell to said candidate compound.

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29. A method of stimulating the immune response in a mammal, said method comprising

administering to said mammal an effective amount of a PRO polypeptide of the invention as described in Figures 1-596, antagonist, wherein said immune response is stimulated.

30. A method of diagnosing an inflammatory immune response in a mammal, said method comprising detecting the level of expression of a gene encoding a PRO polypeptide of the invention as described in Figures 1-596, (a) in a test sample of tissue cells obtained from the mammal, and (b) in a control sample of known normal tissue cells of the same cell type, wherein a higher or lower level of expression of said gene in the test sample as compared to the control sample is indicative of the presence of an inflammatory immune response in the mammal from which the test tissue cells were obtained.

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