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(54) Title: NOVEL COMPOSITIONS AND METHODS FOR THE TREATMENT OF IMMUNE RELATED DISEASES

(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.

COMPOSITIONS AND METHODS FOR THE TREATMENT OF IMMUNE RELATED DISEASES

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Field of the Invention

The present invention relates to compositions and methods useful for the diagnosis and treatment of immune related diseases.

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Background of the Invention

All references, including any patents or patent application, cited in this specification are hereby incorporated by reference. No admission is made that any reference constitutes prior art. The discussion of the references states what their authors assert, and the applicants reserve the right to challenge the accuracy and pertinency of the cited documents. It will be clearly understood that, although a number of prior art publications are referred to herein, this reference does not constitute an admission that any of these documents form part of the common general knowledge in the art, in Australia or in any other country.

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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.*

T lymphocytes (T cells) are an important component of a mammalian immune response. T cells recognize antigens which are associated with a self-molecule encoded by genes within the major histocompatibility complex (MHC). The antigen may be displayed together with MHC molecules on the surface of antigen presenting cells, virus infected cells, cancer cells, grafts, *etc.* The T cell system eliminates these altered cells which pose a health threat to the host mammal. T cells include helper T cells and cytotoxic T cells. Helper T cells proliferate extensively following recognition of an antigen-MHC complex on an antigen presenting cell. Helper T cells also secrete a variety of cytokines, *i.e.*, lymphokines, which play a central role in the activation of B cells, cytotoxic T cells and a variety of other cells which participate in the immune response.

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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

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(proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

5 CD4+ T cells are known to be important regulators of inflammation. Herein, CD4+ T cells were activated and the profile of genes differentially expressed upon activation was analyzed. As such, the activation specific genes may be potential therapeutic targets. *In vivo* co-stimulation is necessary for a productive immune proliferative response. The list of costimulatory molecules is quite extensive and it is

still unclear just which co-stimulatory molecules play critical roles in different types and stages of inflammation. In this application the focus is on genes which are specifically upregulated or downregulated by stimulation with anti-CD3/ICAM, or anti-CD3/anti-CD28 and may be useful in targeting inflammatory processes which are associated with these different molecules.

Despite the above identified advances in T cell research, there is a great need for additional diagnostic and therapeutic agents capable of detecting the presence of a T cell mediated disorders in a mammal and for effectively reducing these disorders. Accordingly, it is an objective of the present invention to identify polypeptides that are overexpressed in activated T cells as compared to resting T cells, and to use those polypeptides, and their encoding nucleic acids, to produce compositions of matter useful in the therapeutic treatment and diagnostic detection of T cell mediated disorders in mammals.

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Summary of the Invention

A. Embodiments

The present invention concerns compositions and methods useful for the diagnosis and treatment of immune related disease 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. 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 immune-related and inflammatory diseases. 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.

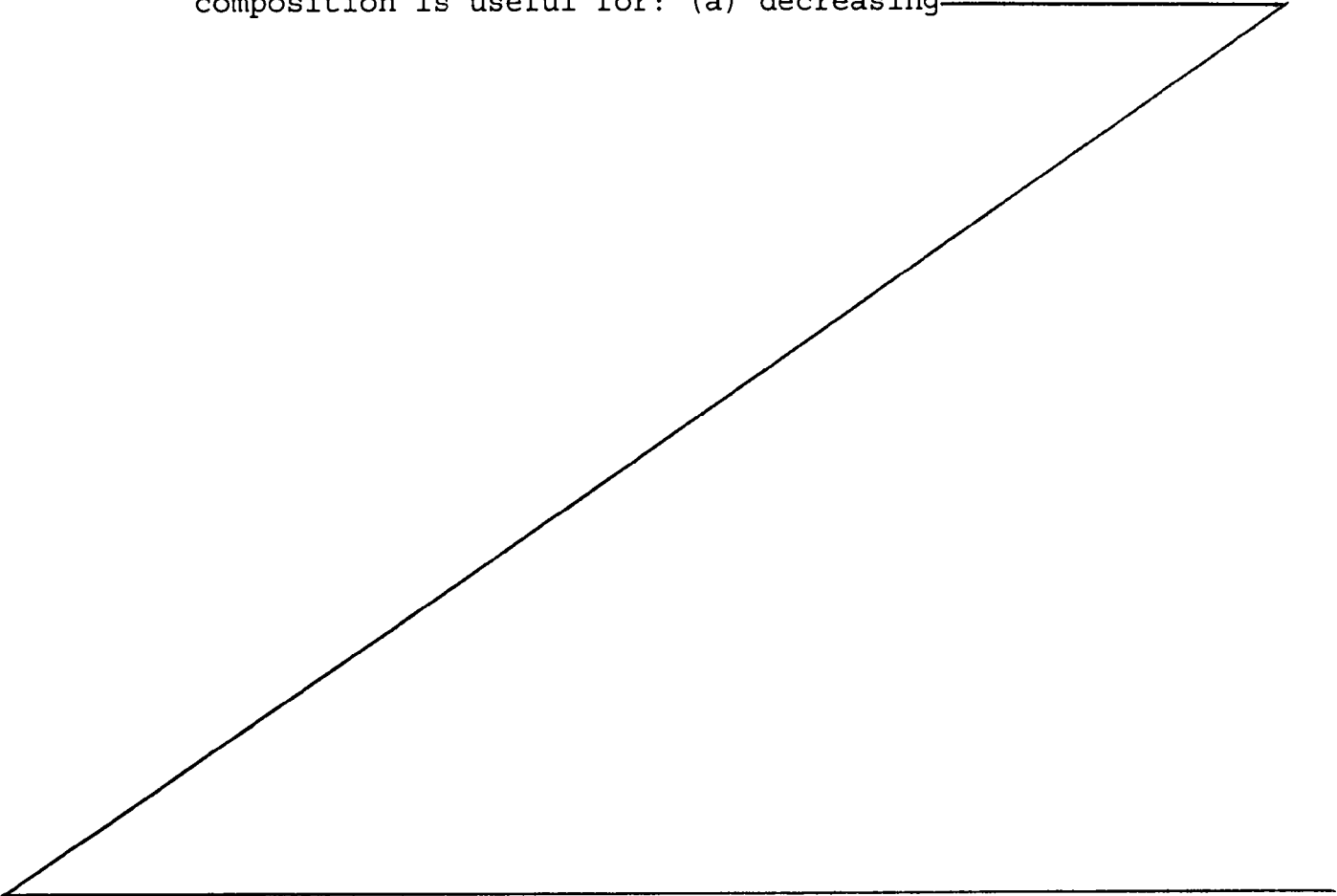
10 In a first aspect the present invention relates to a composition of matter comprising (a) an isolated polypeptide having at least 80% amino acid sequence identity to an amino acid sequence of the polypeptide shown in Figure 7 (SEQ ID NO:7), or (b) an antibody that specifically binds to said polypeptide, in combination with a carrier, wherein said carrier is a pharmaceutically acceptable carrier.

In a second aspect the present invention relates to an article of manufacture, comprising:

20 a container;
a label on said container; and
a composition of matter comprising (a) an isolated polypeptide having at least 80% amino acid sequence identity to an amino acid sequence of the polypeptide shown in Figure 7 (SEQ ID NO:7), or (b) an antibody that specifically 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.

30 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
5 in admixture with a carrier or excipient. In one aspect, the composition comprises a therapeutically effective amount of the polypeptide or antibody. In another aspect, when the composition comprises an immune stimulating molecule, the composition is useful for: (a) increasing
10 infiltration of inflammatory cells into a tissue of a mammal in need thereof, (b) stimulating or enhancing an immune response in a mammal in need thereof, (c) increasing the proliferation of T-lymphocytes in a mammal in need thereof in response to an antigen, (d) stimulating
15 the activity of T-lymphocytes or (e) increasing the vascular permeability. In a further aspect, when the composition comprises an immune inhibiting molecule, the composition is useful for: (a) decreasing



infiltration of inflammatory cells into a tissue of a mammal in need thereof, (b) inhibiting or reducing an immune response in a mammal in need thereof, (c) decreasing the activity of T-lymphocytes or (d) decreasing the proliferation of T-lymphocytes 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: 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 thrombocytopenia, thyroiditis, diabetes mellitus, immune-mediated renal disease, demyelinating diseases of the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy, hepatobiliary diseases such as infectious, autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis, inflammatory bowel disease, gluten-sensitive enteropathy, and Whipple's disease, autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis, allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria, immunologic diseases of the lung such as eosinophilic pneumonias, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis, transplantation associated diseases including graft rejection and graft -versus-host-disease.

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 an immune related disease 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 a third aspect the present invention relates to 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) an isolated polypeptide having at least 80% amino acid sequence identity to an amino acid sequence of the polypeptide shown in Figure 7 (SEQ ID NO:7), or (b) an antibody that specifically binds to said polypeptide.

In a fourth aspect the present invention relates to a method of diagnosing an immune related disease in a mammal, said method comprising detecting the level of expression of a gene encoding the polypeptide shown in Figure 7 (SEQ ID NO:7) (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.

In a fifth aspect the present invention relates to a method of diagnosing an immune related disease in a mammal, said method comprising (a) contacting an antibody that specifically binds to the polypeptide shown in Figure 7 (SEQ ID NO:7) 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.

In another embodiment, the present invention concerns a method of diagnosing an immune disease 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 a deficiency or abnormality of the immune system.

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.

5 In a sixth aspect the present invention relates to a method for determining the presence of a polypeptide in a sample suspected of containing said polypeptide, said method comprising exposing said sample to an antibody that specifically binds to the polypeptide shown in Figure 7 (SEQ ID NO:7) and determining binding of said antibody to
10 a component of said sample.

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
15 antibody to detect the presence of the PRO polypeptide. Preferably the carrier is pharmaceutically acceptable.

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

In another embodiment, the invention provides a method of diagnosing an immune-related disease in a mammal which comprises detecting the presence or absence of a PRO
25 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 an immune-related disease in said mammal.

In another embodiment, the present invention concerns
30 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;
35 and

(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
5 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
10 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:

- 15 (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
20 response to determine if the test compound is an effective
antagonist.

In another embodiment, the invention provides a
method for identifying a compound that inhibits the
expression of a PRO polypeptide in cells that normally
25 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:

- 30 (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.

35 In a seventh aspect the present invention relates to
a method of identifying a compound that inhibits the
activity of the polypeptide shown in Figure 7 (SEQ ID

NO:7), 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).

5 In an eighth aspect the present invention relates to a method of identifying a compound that inhibits the expression of a gene encoding the polypeptide shown in Figure 7 (SEQ ID NO:7), said method comprising contacting
10 cells which normally express said polypeptide with a candidate compound, and determining the lack of expression said gene.

In a ninth aspect the present invention relates to a method of identifying a compound that mimics the activity of the polypeptide shown in Figure 7 (SEQ ID NO:7), said
15 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.

In a tenth aspect the present invention relates to a
20 method of stimulating the immune response in a mammal, said method comprising administering to said mammal an effective amount of the polypeptide shown in Figure 7 (SEQ ID NO:7), wherein said immune response is stimulated.

In an eleventh aspect the present invention relates
25 to a method of diagnosing an inflammatory immune response in a mammal, said method comprising detecting the level of expression of a gene encoding the polypeptide shown in Figure 7 (SEQ ID NO:7) (a) in a test sample of tissue cells obtained from the mammal, and (b) in a control
30 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
35 were obtained.

In yet another embodiment, the present invention

concerns a method for treating an immune-related disorder 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
5 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
10 further preferred embodiment, the nucleic acid is comprised within a vector, more preferably an adenoviral, adeno-associated viral, lentiviral or retroviral vector.

In yet another aspect, the invention provides a recombinant viral particle comprising a viral vector
15 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
20 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
25 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
30 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.

In a still further embodiment, the invention provides
35 a method of increasing the activity of T-lymphocytes 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 the activity of T-lymphocytes in the mammal is increased.

5 In a still further embodiment, the invention provides a method of decreasing the activity of T-lymphocytes 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 the activity of T-lymphocytes in the mammal is decreased.

10 In a still further embodiment, the invention provides a method of increasing the proliferation of T-lymphocytes 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 the proliferation of T-lymphocytes in the mammal is increased.

15 In a still further embodiment, the invention provides a method of decreasing the proliferation of T-lymphocytes 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 the proliferation of T-lymphocytes in the mammal is decreased.

B. Additional Embodiments

25 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

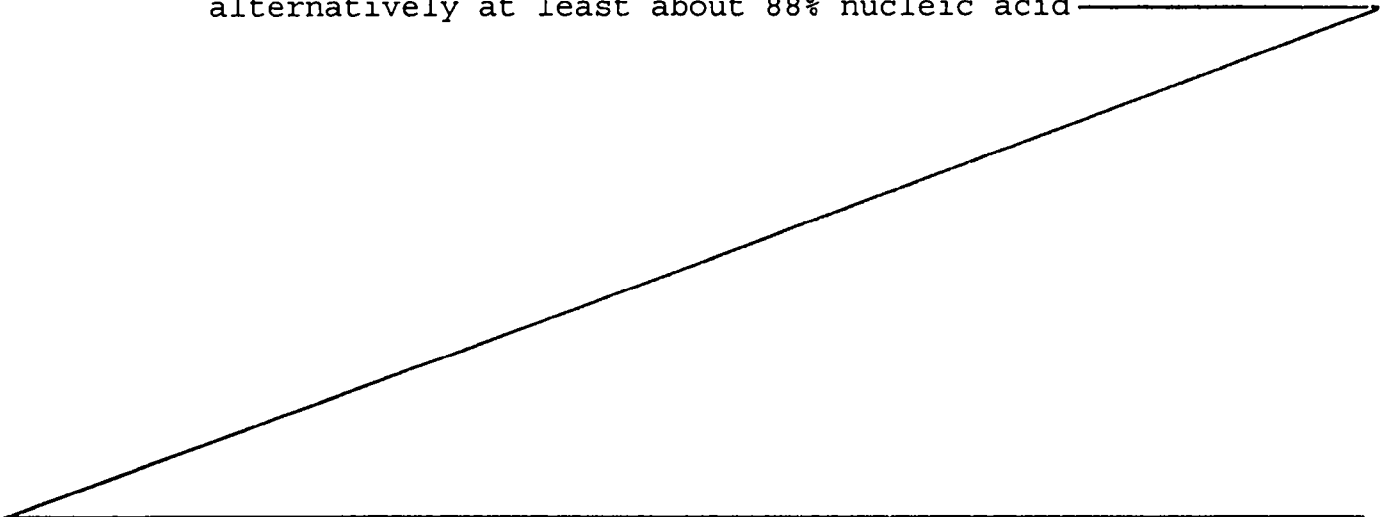
an epitope tag sequence or a Fc region of an immunoglobulin.

In another embodiment, the invention provides an antibody which specifically binds to any of the above or
5 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
10 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
15 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
20 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
25 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).

5 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.

10 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
15 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
20 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
25 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.
30 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
35 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
40 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

Figure 1 shows a nucleotide sequence (SEQ ID NO:1) of a native sequence PRO71202 cDNA, wherein SEQ ID NO:1 is a clone designated herein as "DNA304790".

Figure 2 shows the amino acid sequence (SEQ ID NO:2) derived from the coding sequence of SEQ ID NO:1 shown in Figure 1.

Figure 3 shows a nucleotide sequence (SEQ ID NO:3) of a native sequence cDNA, wherein SEQ ID NO:3 is a clone designated herein as "DNA258961".

Figure 4 shows a nucleotide sequence (SEQ ID NO:4) of a native sequence PRO53256 cDNA, wherein SEQ ID NO:4 is a clone designated herein as "DNA259323".

Figure 5 shows the amino acid sequence (SEQ ID NO:5) derived from the coding sequence of SEQ ID NO:4 shown in Figure 4.

Figure 6 shows a nucleotide sequence (SEQ ID NO:6) of a native sequence PRO52254 cDNA, wherein SEQ ID NO:6 is a clone designated herein as "DNA257697".

Figure 7 shows the amino acid sequence (SEQ ID NO:7) derived from the coding sequence of SEQ ID NO:6 shown in Figure 6.

Figure 8 shows a nucleotide sequence (SEQ ID NO:8) of a native sequence PRO71203 cDNA, wherein SEQ ID NO:8 is a clone designated herein as "DNA304791".

Figure 9 shows the amino acid sequence (SEQ ID NO:9) derived from the coding sequence of SEQ ID NO:8 shown in Figure 8.

Figure 10 shows a nucleotide sequence (SEQ ID NO:10) of a native sequence PRO52892 cDNA, wherein SEQ ID NO:10 is a clone designated herein as "DNA258959".

Figure 11 shows the amino acid sequence (SEQ ID NO:11) derived from the coding sequence of SEQ ID NO:10 shown in Figure 10.

Figure 12 shows a nucleotide sequence (SEQ ID NO:12) of a native sequence PRO71204 cDNA, wherein SEQ ID NO:12 is a clone designated herein as "DNA304792".

Figure 13 shows the amino acid sequence (SEQ ID NO:13) derived from the coding sequence of SEQ ID NO:12 shown in Figure 12.

Figure 14 shows a nucleotide sequence (SEQ ID NO:14) of a native sequence cDNA, wherein SEQ ID NO:14 is a clone designated herein as "DNA260010".

5 Figure 15 shows a nucleotide sequence (SEQ ID NO:15) of a native sequence cDNA, wherein SEQ ID NO:15 is a clone designated herein as "DNA268707".

Figure 16 shows a nucleotide sequence (SEQ ID NO:16) of a native sequence PRO71205 cDNA, wherein SEQ ID NO:16 is a clone designated herein as "DNA304793".

10 Figure 17 shows the amino acid sequence (SEQ ID NO:17) derived from the coding sequence of SEQ ID NO:16 shown in Figure 16.

Figure 18 shows a nucleotide sequence (SEQ ID NO:18) of a native sequence cDNA, wherein SEQ ID NO:18 is a clone designated herein as "DNA257797".

Figure 19 shows a nucleotide sequence (SEQ ID NO:19) of a native sequence PRO71206 cDNA, wherein SEQ ID NO:19 is a clone designated herein as "DNA304794".

15 Figure 20 shows the amino acid sequence (SEQ ID NO:20) derived from the coding sequence of SEQ ID NO:19 shown in Figure 19.

Figure 21 shows a nucleotide sequence (SEQ ID NO:21) of a native sequence PRO52174 cDNA, wherein SEQ ID NO:21 is a clone designated herein as "DNA287258".

20 Figure 22 shows the amino acid sequence (SEQ ID NO:22) derived from the coding sequence of SEQ ID NO:21 shown in Figure 21.

Figure 23 shows a nucleotide sequence (SEQ ID NO:23) of a native sequence PRO71207 cDNA, wherein SEQ ID NO:23 is a clone designated herein as "DNA304795".

Figure 24 shows the amino acid sequence (SEQ ID NO:24) derived from the coding sequence of SEQ ID NO:23 shown in Figure 23.

25 Figure 25 shows a nucleotide sequence (SEQ ID NO:25) of a native sequence cDNA, wherein SEQ ID NO:25 is a clone designated herein as "DNA260158".

Figure 26 shows a nucleotide sequence (SEQ ID NO:26) of a native sequence PRO71208 cDNA, wherein SEQ ID NO:26 is a clone designated herein as "DNA304796".

30 Figure 27 shows the amino acid sequence (SEQ ID NO:27) derived from the coding sequence of SEQ ID NO:26 shown in Figure 26.

Figure 28 shows a nucleotide sequence (SEQ ID NO:28) of a native sequence PRO71209 cDNA, wherein SEQ ID NO:28 is a clone designated herein as "DNA304797".

Figure 29 shows the amino acid sequence (SEQ ID NO:29) derived from the coding sequence of SEQ ID NO:28 shown in Figure 28.

35 Figure 30 shows a nucleotide sequence (SEQ ID NO:30) of a native sequence PRO71210 cDNA, wherein SEQ ID NO:30 is a clone designated herein as "DNA304798".

Figure 31 shows the amino acid sequence (SEQ ID NO:31) derived from the coding sequence of SEQ ID NO:30 shown in Figure 30.

40 Figure 32A-B shows a nucleotide sequence (SEQ ID NO:32) of a native sequence PRO69553 cDNA, wherein SEQ ID NO:32 is a clone designated herein as "DNA287281".

Figure 33 shows the amino acid sequence (SEQ ID NO:33) derived from the coding sequence of SEQ ID NO:32 shown in Figure 32A-B.

Figure 34 shows a nucleotide sequence (SEQ ID NO:34) of a native sequence PRO52268 cDNA, wherein SEQ ID NO:34 is a clone designated herein as "DNA257714".

5 Figure 35 shows the amino acid sequence (SEQ ID NO:35) derived from the coding sequence of SEQ ID NO:34 shown in Figure 34.

Figure 36 shows a nucleotide sequence (SEQ ID NO:36) of a native sequence PRO52633 cDNA, wherein SEQ ID NO:36 is a clone designated herein as "DNA304799".

10 Figure 37 shows the amino acid sequence (SEQ ID NO:37) derived from the coding sequence of SEQ ID NO:36 shown in Figure 36.

Figure 38A-B shows a nucleotide sequence (SEQ ID NO:38) of a native sequence PRO69458 cDNA, wherein SEQ ID NO:38 is a clone designated herein as "DNA304800".

Figure 39 shows the amino acid sequence (SEQ ID NO:39) derived from the coding sequence of SEQ ID NO:38 shown in Figure 38A-B.

15 Figure 40 shows a nucleotide sequence (SEQ ID NO:40) of a native sequence PRO71211 cDNA, wherein SEQ ID NO:40 is a clone designated herein as "DNA304801".

Figure 41 shows the amino acid sequence (SEQ ID NO:41) derived from the coding sequence of SEQ ID NO:40 shown in Figure 40.

20 Figure 42 shows a nucleotide sequence (SEQ ID NO:42) of a native sequence PRO51927 cDNA, wherein SEQ ID NO:42 is a clone designated herein as "DNA257338".

Figure 43 shows the amino acid sequence (SEQ ID NO:43) derived from the coding sequence of SEQ ID NO:42 shown in Figure 42.

Figure 44 shows a nucleotide sequence (SEQ ID NO:44) of a native sequence PRO69903 cDNA, wherein SEQ ID NO:44 is a clone designated herein as "DNA287659".

25 Figure 45 shows the amino acid sequence (SEQ ID NO:45) derived from the coding sequence of SEQ ID NO:44 shown in Figure 44.

Figure 46 shows a nucleotide sequence (SEQ ID NO:46) of a native sequence cDNA, wherein SEQ ID NO:46 is a clone designated herein as "DNA269148".

30 Figure 47 shows a nucleotide sequence (SEQ ID NO:47) of a native sequence PRO71212 cDNA, wherein SEQ ID NO:47 is a clone designated herein as "DNA304802".

Figure 48 shows the amino acid sequence (SEQ ID NO:48) derived from the coding sequence of SEQ ID NO:47 shown in Figure 47.

Figure 49 shows a nucleotide sequence (SEQ ID NO:49) of a native sequence PRO71213 cDNA, wherein SEQ ID NO:49 is a clone designated herein as "DNA304803".

35 Figure 50 shows the amino acid sequence (SEQ ID NO:50) derived from the coding sequence of SEQ ID NO:49 shown in Figure 49.

Figure 51 shows a nucleotide sequence (SEQ ID NO:51) of a native sequence cDNA, wherein SEQ ID NO:51 is a clone designated herein as "DNA257606".

40 Figure 52 shows a nucleotide sequence (SEQ ID NO:52) of a native sequence PRO71214 cDNA, wherein SEQ ID NO:52 is a clone designated herein as "DNA304804".

Figure 53 shows the amino acid sequence (SEQ ID NO:53) derived from the coding sequence of SEQ ID NO:52 shown in Figure 52.

Figure 54 shows a nucleotide sequence (SEQ ID NO:54) of a native sequence PRO69531 cDNA, wherein SEQ ID NO:54 is a clone designated herein as "DNA304805".

5 Figure 55 shows the amino acid sequence (SEQ ID NO:55) derived from the coding sequence of SEQ ID NO:54 shown in Figure 54.

Figure 56 shows a nucleotide sequence (SEQ ID NO:56) of a native sequence PRO71215 cDNA, wherein SEQ ID NO:56 is a clone designated herein as "DNA304806".

10 Figure 57 shows the amino acid sequence (SEQ ID NO:57) derived from the coding sequence of SEQ ID NO:56 shown in Figure 56.

Figure 58 shows a nucleotide sequence (SEQ ID NO:58) of a native sequence PRO71216 cDNA, wherein SEQ ID NO:58 is a clone designated herein as "DNA304807".

Figure 59 shows the amino acid sequence (SEQ ID NO:59) derived from the coding sequence of SEQ ID NO:58 shown in Figure 58.

15 Figure 60 shows a nucleotide sequence (SEQ ID NO:60) of a native sequence PRO71217 cDNA, wherein SEQ ID NO:60 is a clone designated herein as "DNA304808".

Figure 61 shows the amino acid sequence (SEQ ID NO:61) derived from the coding sequence of SEQ ID NO:60 shown in Figure 60.

20 Figure 62 shows a nucleotide sequence (SEQ ID NO:62) of a native sequence PRO35770 cDNA, wherein SEQ ID NO:62 is a clone designated herein as "DNA174145".

Figure 63 shows the amino acid sequence (SEQ ID NO:63) derived from the coding sequence of SEQ ID NO:62 shown in Figure 62.

Figure 64 shows a nucleotide sequence (SEQ ID NO:64) of a native sequence PRO71218 cDNA, wherein SEQ ID NO:64 is a clone designated herein as "DNA304809".

25 Figure 65 shows the amino acid sequence (SEQ ID NO:65) derived from the coding sequence of SEQ ID NO:64 shown in Figure 64.

Figure 66 shows a nucleotide sequence (SEQ ID NO:66) of a native sequence PRO66272 cDNA, wherein SEQ ID NO:66 is a clone designated herein as "DNA281432".

30 Figure 67 shows the amino acid sequence (SEQ ID NO:67) derived from the coding sequence of SEQ ID NO:66 shown in Figure 66.

Figure 68 shows a nucleotide sequence (SEQ ID NO:68) of a native sequence cDNA, wherein SEQ ID NO:68 is a clone designated herein as "DNA262708".

Figure 69 shows a nucleotide sequence (SEQ ID NO:69) of a native sequence PRO52338 cDNA, wherein SEQ ID NO:69 is a clone designated herein as "DNA257789".

35 Figure 70 shows the amino acid sequence (SEQ ID NO:70) derived from the coding sequence of SEQ ID NO:69 shown in Figure 69.

Figure 71 shows a nucleotide sequence (SEQ ID NO:71) of a native sequence PRO51950 cDNA, wherein SEQ ID NO:71 is a clone designated herein as "DNA257363".

40 Figure 72 shows the amino acid sequence (SEQ ID NO:72) derived from the coding sequence of SEQ ID NO:71 shown in Figure 71.

Figure 73 shows a nucleotide sequence (SEQ ID NO:73) of a native sequence PRO71219 cDNA, wherein SEQ ID NO:73 is a clone designated herein as "DNA304810".

Figure 74 shows the amino acid sequence (SEQ ID NO:74) derived from the coding sequence of SEQ ID NO:73 shown in Figure 73.

5 Figure 75 shows a nucleotide sequence (SEQ ID NO:75) of a native sequence cDNA, wherein SEQ ID NO:75 is a clone designated herein as "DNA259680".

Figure 76 shows a nucleotide sequence (SEQ ID NO:76) of a native sequence cDNA, wherein SEQ ID NO:76 is a clone designated herein as "DNA263464".

10 Figure 77 shows a nucleotide sequence (SEQ ID NO:77) of a native sequence PRO71220 cDNA, wherein SEQ ID NO:77 is a clone designated herein as "DNA304811".

Figure 78 shows the amino acid sequence (SEQ ID NO:78) derived from the coding sequence of SEQ ID NO:77 shown in Figure 77.

Figure 79 shows a nucleotide sequence (SEQ ID NO:79) of a native sequence cDNA, wherein SEQ ID NO:79 is a clone designated herein as "DNA304992".

15 Figure 80 shows a nucleotide sequence (SEQ ID NO:80) of a native sequence PRO71222 cDNA, wherein SEQ ID NO:80 is a clone designated herein as "DNA304813".

Figure 81 shows the amino acid sequence (SEQ ID NO:81) derived from the coding sequence of SEQ ID NO:80 shown in Figure 80.

20 Figure 82 shows a nucleotide sequence (SEQ ID NO:82) of a native sequence PRO52035 cDNA, wherein SEQ ID NO:82 is a clone designated herein as "DNA257455".

Figure 83 shows the amino acid sequence (SEQ ID NO:83) derived from the coding sequence of SEQ ID NO:82 shown in Figure 82.

Figure 84 shows a nucleotide sequence (SEQ ID NO:84) of a native sequence PRO52650 cDNA, wherein SEQ ID NO:84 is a clone designated herein as "DNA304814".

25 Figure 85 shows the amino acid sequence (SEQ ID NO:85) derived from the coding sequence of SEQ ID NO:84 shown in Figure 84.

Figure 86 shows a nucleotide sequence (SEQ ID NO:86) of a native sequence cDNA, wherein SEQ ID NO:86 is a clone designated herein as "DNA304815".

30 Figure 87 shows a nucleotide sequence (SEQ ID NO:87) of a native sequence PRO23781 cDNA, wherein SEQ ID NO:87 is a clone designated herein as "DNA304816".

Figure 88 shows the amino acid sequence (SEQ ID NO:88) derived from the coding sequence of SEQ ID NO:87 shown in Figure 87.

Figure 89 shows a nucleotide sequence (SEQ ID NO:89) of a native sequence PRO71224 cDNA, wherein SEQ ID NO:89 is a clone designated herein as "DNA304817".

35 Figure 90 shows the amino acid sequence (SEQ ID NO:90) derived from the coding sequence of SEQ ID NO:89 shown in Figure 89.

Figure 91 shows a nucleotide sequence (SEQ ID NO:91) of a native sequence PRO70559 cDNA, wherein SEQ ID NO:91 is a clone designated herein as "DNA290812".

40 Figure 92 shows the amino acid sequence (SEQ ID NO:92) derived from the coding sequence of SEQ ID NO:91 shown in Figure 91.

Figure 93 shows a nucleotide sequence (SEQ ID NO:93) of a native sequence PRO71225 cDNA, wherein SEQ ID NO:93 is a clone designated herein as "DNA304818".

Figure 94 shows the amino acid sequence (SEQ ID NO:94) derived from the coding sequence of SEQ ID NO:93 shown in Figure 93.

5 Figure 95 shows a nucleotide sequence (SEQ ID NO:95) of a native sequence cDNA, wherein SEQ ID NO:95 is a clone designated herein as "DNA154627".

Figure 96 shows a nucleotide sequence (SEQ ID NO:96) of a native sequence cDNA, wherein SEQ ID NO:96 is a clone designated herein as "DNA260031".

10 Figure 97 shows a nucleotide sequence (SEQ ID NO:97) of a native sequence cDNA, wherein SEQ ID NO:97 is a clone designated herein as "DNA304819".

Figure 98 shows a nucleotide sequence (SEQ ID NO:98) of a native sequence cDNA, wherein SEQ ID NO:98 is a clone designated herein as "DNA260167".

Figure 99 shows a nucleotide sequence (SEQ ID NO:99) of a native sequence PRO47351 cDNA, wherein SEQ ID NO:99 is a clone designated herein as "DNA304820".

15 Figure 100 shows the amino acid sequence (SEQ ID NO:100) derived from the coding sequence of SEQ ID NO:99 shown in Figure 99.

Figure 101 shows a nucleotide sequence (SEQ ID NO:101) of a native sequence cDNA, wherein SEQ ID NO:101 is a clone designated herein as "DNA304821".

20 Figure 102 shows a nucleotide sequence (SEQ ID NO:102) of a native sequence cDNA, wherein SEQ ID NO:102 is a clone designated herein as "DNA106195".

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

I. Definitions

25 In the claims of this application and in the description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprise" or variations such as "comprises" or "comprising" is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

30 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
35 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 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 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 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. 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 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 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:

5

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

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.

40

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.

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

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 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 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 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 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 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

5 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
10 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
15 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
20 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.

25 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
30 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
35 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,
40 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.

5 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.

10 "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
15 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
20 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.

25 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,
30 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 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
35 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 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, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the antibody
5 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 antibody includes the antibody in situ within recombinant cells since at least one component of the
10 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 without substantially binding to any other polypeptide or polypeptide epitope.

15 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
20 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 includes a discontinuous solid phase of discrete particles, such as those described in U.S. Patent No.
25 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.

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

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.*
35

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.

Examples of immune-related and inflammatory diseases, some of which are immune or T cell mediated, which can be treated according to the invention include systemic lupus erythematosus, rheumatoid arthritis, juvenile chronic arthritis, spondyloarthropathies, systemic sclerosis (scleroderma), idiopathic inflammatory myopathies (dermatomyositis, polymyositis), Sjögren's syndrome, systemic vasculitis, sarcoidosis, autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria), autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated thrombocytopenia), thyroiditis (Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, atrophic thyroiditis), diabetes mellitus, immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis), demyelinating diseases of the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy, hepatobiliary diseases such as infectious hepatitis (hepatitis A, B, C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis, inflammatory bowel disease (ulcerative colitis: Crohn's disease), gluten-sensitive enteropathy, and Whipple's disease, autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis, allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria, immunologic diseases of the lung such as eosinophilic pneumonias, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis, transplantation associated diseases including graft rejection and graft -versus-host-disease. Infectious diseases including viral diseases such as AIDS (HIV infection), hepatitis A, B, C, D, and E, herpes, *etc.*, bacterial infections, fungal infections, protozoal infections and parasitic infections.

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.

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.

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, thiotepe, 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 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 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, 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, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M},
30 /* 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},
/* 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},
35 /* 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, 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, 0},
/* 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},
40 /* 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}
};

```

Table 1 (cont')

```

/*
*/
#include <stdio.h>
#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 DINSO 8 /* penalty for a gap */
15 #define DINS1 1 /* penalty per base */
#define PINSO 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 *name[2]; /* seq names: getseqs() */
char *prog; /* prog name for err msgs */
40 char *seq[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();

```

60

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[ ];
{
35 prog = av[0];
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");
40 fprintf(stderr, "Any lines beginning with ';' or '<' are ignored\n");
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 jmps */
readjmps(); /* get the actual jmps */
print(); /* print stats, alignment */
55 cleanup(0); /* unlink any tmp files */
}
60

```

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  {
    char      *px, *py;          /* seqs and ptrs */
    int        *ndely, *dely;     /* keep track of dely */
    int        ndelx, delx;       /* keep track of delx */
    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 */
    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;
    ins1 = (dna)? DINS1 : PINS1;

30  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 */
    }
    else
40        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**

```

5      for (py = seqx[1], yy = 1; yy <= len1; py++, yy++) {
        mis = col0[yy-1];
        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;
                ndely[yy]++;
20            }
        } 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) {
35            if (col1[yy-1] - ins0 >= delx) {
                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 (cont²)

...nw

```

id = xx - yy + len1 - 1;
if (mis >= delx && mis >= dely[yy])
    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;
15            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 {
    col1[yy] = dely[yy];
    ij = dx[id].ijmp;
25    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) {
            writejumps(id);
            ij = dx[id].ijmp = 0;
30            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);
45        if (col1[yy] > smax) {
            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];
        dmax = id;
55    }
    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
{
30     int     lx, ly, firstgap, lastgap;    /* overlap */

    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 */
55         lastgap = dmax0 - (len0 - 1);
        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
       * 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",
60         nm, (nm == 1)? "" : "es", lx, pct);

```

Table 1 (cont')

```

5      fprintf(fx, "<gaps in first sequence: %d", gapx);
      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);
      else
20      fprintf(fx,
              "\n<score: %d (Dayhoff PAM 250 matrix, gap penalty = %d + %d per residue)\n",
              smax, PINS0, PINS1);
      if (endgaps)
          fprintf(fx,
25      "<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
          fprintf(fx, "<endgaps not penalized\n");
30  }
      static nm;          /* matches in core -- for checking */
      static lmax;        /* lengths of stripped file names */
      static ij[2];        /* jmp index for a path */
      static nc[2];        /* number at start of current line */
35      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 */
      static char out[2][P_LINE]; /* output line */
40      static char star[P_LINE]; /* set by stars() */

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

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

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

```

...getmat

pr_align

Table 1 (cont')

```

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

            more++;

            if (pp[i].spc) { /* leading space */
                *po[i]++ = ' ';
                pp[i].spc--;
15            }
            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]))
                    *ps[i] = toupper(*ps[i]);
25                po[i]++;
                ps[i]++;

                /*
                * 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
                    */
                    siz[i] = pp[i].n[ij[i]]++;
                    while (ni[i] == pp[i].x[ij[i]])
                        siz[i] += pp[i].n[ij[i]]++;
35                }
                ni[i]++;
            }
        }
        if (++nn == olen || !more && nn) {
45            dumpblock();
            for (i = 0; i < 2; i++)
                po[i] = out[i];
            nn = 0;
        }
50    }

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

```

...pr_align

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 /= 10, px--)
40                     *px = j%10 + '0';
                  if (i < 0)
                      *px = '-';
              }
              else
45                 *pn = ' ';
              i++;
          }
      }
      *pn = '\0';
      nc[ix] = i;
      for (pn = nline; *pn; pn++)
50         (void) putc(*pn, fx);
      (void) putc('\n', fx);
  }

55  /*
   * put out a line (name, [num], seq, [num]): dumpblock()
   */
   static
   putline(ix)
60  {
      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);
10     for (; i < lmax+P_SPC; i++)
          (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();

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

/*
 * read, return ptr to seq, set dna, len, maxlen
 * skip lines starting with ';', '<', or '>'
 * seq in upper or lower case
 */
30 char    *
getseq(file, len)
35     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';

```

Table 1 (cont')

...getseq

```

5      py = pseq + 4;
      *len = tlen;
      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';
    *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()
{
    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--)
                ;

```

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;
40            i0++;
        }
    }
    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);
15         }
        if ((fj = fopen(jname, "w")) == 0) {
            fprintf(stderr, "%s: can't write %s\n", prog, jname);
            exit(1);
20         }
    }
    (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

PRO	XXXXXXXXXXXXXXXXXX	(Length = 15 amino acids)
Comparison Protein	XXXXXXXXYYYYYY	(Length = 12 amino acids)

% amino acid sequence identity =

(the number of identically matching amino acid residues between the two polypeptide sequences as 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

35 PRO	XXXXXXXXXXX	(Length = 10 amino acids)
Comparison Protein	XXXXXXXXYYYYYYZZYZ	(Length = 15 amino acids)

% amino acid sequence identity =

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

40 5 divided by 10 = 50%

Table 4

PRO-DNA	NNNNNNNNNNNNNNNN	(Length = 14 nucleotides)
Comparison DNA	NNNNNNLLLLLLLLLLLL	(Length = 16 nucleotides)

45 % 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) =

6 divided by 14 = 42.9%

Table 5

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

5

% 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) =

4 divided by 12 = 33.3%

10

II. Compositions and Methods of the Invention

A. Full-Length PRO Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding 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 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.

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 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 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 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.

5 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
10 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
15 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
20 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

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

5 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
10 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
15 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.

20

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
25 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
30 ordinarily skilled artisan, for example, CaCl₂, CaPO₄, 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
35 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,
40 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^r*; *E. coli* W3110 strain 37D6, which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT rbs7 ilvG kan^r*; *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. drosophilum* (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 reesia* (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]). Methylophilic 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 Methylophs, 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 2 μ 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*.

5 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)].
10 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
15 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
20 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,
25 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,
30 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
35 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
40 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.

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 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

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 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 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 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 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.

10 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.

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 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 lines from transgenic animals are well known in the art (see, e.g., Small *et al.*, *Mol. Cell. Biol.* 5: 642-648 [1985]).

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 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 standard lymphokine (IL-2) detection assay. *Current Protocols in Immunology*, above, 3.15, 6.3.

A proliferative T cell response in an MLR assay may be due to direct mitogenic properties of an assayed molecule or to external antigen induced activation. Additional verification of the T cell stimulatory activity of the PRO polypeptides can be obtained by a costimulation assay. T cell activation requires an antigen specific signal mediated through the T-cell receptor (TCR) and a costimulatory signal mediated through a second ligand binding interaction, for example, the B7 (CD80, CD86)/CD28 binding interaction. CD28 crosslinking increases lymphokine secretion by activated T cells. T cell activation has both negative

and positive controls through the binding of ligands which have a negative or positive effect. CD28 and CTLA-4 are related glycoproteins in the Ig superfamily which bind to B7. CD28 binding to B7 has a positive costimulation effect of T cell activation; conversely, CTLA-4 binding to B7 has a T cell deactivating effect. Chambers, C. A. and Allison, J. P., *Curr. Opin. Immunol.* (1997) 9:396. Schwartz, R. H., *Cell* (1992) 71:1065; Linsey, P. S. and Ledbetter, J. A., *Annu. Rev. Immunol.* (1993) 11:191; June, C. H. *et al, Immunol. Today* (1994) 15:321; Jenkins, M. K., *Immunity* (1994) 1:405. In a costimulation assay, the PRO polypeptides are assayed for T cell costimulatory or inhibitory activity.

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.

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.

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 T 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. 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 T cell mediated immune response by inhibiting T 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 IL2 and blocks binding of IL2 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 T-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 T 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.

Animal models for delayed type hypersensitivity provides an assay of cell mediated immune function as well. Delayed type hypersensitivity reactions are a T cell mediated *in vivo* immune response characterized by inflammation which does not reach a peak until after a period of time has elapsed after challenge with an antigen. These reactions also occur in tissue specific autoimmune diseases such as multiple sclerosis (MS) and experimental autoimmune encephalomyelitis (EAE, a model for MS). A suitable procedure is described in detail in *Current Protocols in Immunology*, above, unit 4.5.

EAE is a T cell mediated autoimmune disease characterized by T cell and mononuclear cell inflammation and subsequent demyelination of axons in the central nervous system. EAE is generally considered to be a relevant animal model for MS in humans. Bolton, C., *Multiple Sclerosis* (1995) 1:143. Both acute and relapsing-remitting models have been developed. The compounds of the invention can be tested for T cell stimulatory or inhibitory activity against immune mediated demyelinating disease using the protocol described in *Current Protocols in Immunology*, above, units 15.1 and 15.2. See also the models for myelin disease in which oligodendrocytes or Schwann cells are grafted into the central nervous system as described in Duncan, I. D. *et al*, *Molec. Med. Today* (1997) 554-561.

Contact hypersensitivity is a simple delayed type hypersensitivity *in vivo* assay of cell mediated immune function. In this procedure, cutaneous exposure to exogenous haptens which gives rise to a delayed type hypersensitivity reaction which is measured and quantitated. Contact sensitivity involves an initial sensitizing phase followed by an elicitation phase. The elicitation phase occurs when the T lymphocytes encounter an antigen to which they have had previous contact. Swelling and inflammation occur, making

this an excellent model of human allergic contact dermatitis. A suitable procedure is described in detail in *Current Protocols in Immunology*, Eds. J. E. Cologan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach and W. Strober, John Wiley & Sons, Inc., 1994, unit 4.2. See also Grabbe, S. and Schwarz, T, *Immun. Today* 19 (1): 37-44 (1998) .

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, units 15.5. See also the model
10 using a monoclonal antibody to CD18 and VLA-4 integrins described in Issekutz, A.C. *et al.*, *Immunology* (1996) 88:569.

 A model of asthma has been described in which antigen-induced airway hyper-reactivity, pulmonary eosinophilia and inflammation are induced by sensitizing an animal with ovalbumin and then challenging the animal with the same protein delivered by aerosol. Several animal models (guinea pig, rat,
15 non-human primate) show symptoms similar to atopic asthma in humans upon challenge with aerosol antigens. Murine models have many of the features of human asthma. Suitable procedures to test the compounds of the invention for activity and effectiveness in the treatment of asthma are described by Wolyniec, W. W. *et al.*, *Am. J. Respir. Cell Mol. Biol.* (1998) 18:777 and the references cited therein.

 Additionally, the compounds of the invention can be tested on animal models for psoriasis like
20 diseases. Evidence suggests a T cell pathogenesis for psoriasis. The compounds of the invention can be tested in the scid/scid mouse model described by Schon, M. P. *et al.*, *Nat. Med.* (1997) 3:183, in which the mice demonstrate histopathologic skin lesions resembling psoriasis. Another suitable model is the human skin/scid mouse chimera prepared as described by Nickoloff, B. J. *et al.*, *Am. J. Path.* (1995) 146:580.

 Recombinant (transgenic) animal models can be engineered by introducing the coding portion of
25 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 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
30 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]); 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
35 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 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.
40 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* 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 T cell proliferation stimulation or inhibition of the 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 T 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 T 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.

5 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
10 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
15 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.

20 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
25 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
30 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
35 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
40 (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, T 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
5 polyclonal, monoclonal, humanized, bispecific, and heteroconjugate antibodies.

1. Polyclonal Antibodies

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
10 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 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
15 employed include Freund's complete adjuvant and MPL-TDM adjuvant (monophosphoryl Lipid A, synthetic trehalose dicorynomycolate). The immunization protocol 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
20 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 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.
25 Generally, either peripheral blood lymphocytes ("PBLs") are used if cells of human origin are desired, or 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
30 rodent, bovine and human origin. Usually, rat or mouse myeloma cell lines are employed. The 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
35 substances prevent the growth of HGPRT-deficient cells.

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,
40 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].

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, 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 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.

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 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 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.

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
5 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
10 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
15 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
20 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
25 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
30 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
35 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
 5 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
 10 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
 15 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)
 20 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
 25 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
 30 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
 35 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. 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-pyridylthiol) 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)-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 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).

5 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 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 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
20 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.

40 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-(methacrylate) 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 T cell mediated diseases, including those characterized by infiltration of inflammatory cells into a tissue, stimulation of T-cell proliferation, inhibition of T-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, juvenile chronic arthritis, osteoarthritis, spondyloarthropathies, systemic sclerosis (scleroderma), idiopathic inflammatory myopathies (dermatomyositis, polymyositis), Sjögren's syndrome, systemic vasculitis, sarcoidosis, autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria), autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated thrombocytopenia), thyroiditis (Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, atrophic thyroiditis), diabetes mellitus, immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis), demyelinating diseases of the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy, hepatobiliary diseases such as infectious hepatitis (hepatitis A, B, C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis, inflammatory bowel disease (ulcerative colitis: Crohn's disease), gluten-sensitive enteropathy, and Whipple's disease, autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis, allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria, immunologic diseases of the lung such as eosinophilic pneumonias, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis, transplantation associated diseases including graft rejection and graft -versus-host-disease.

In systemic lupus erythematosus, the central mediator of disease is the production of auto-reactive antibodies to self proteins/tissues and the subsequent generation of immune-mediated inflammation. Antibodies either directly or indirectly mediate tissue injury. Though T lymphocytes have not been shown to be directly involved in tissue damage, T lymphocytes are required for the development of auto-reactive antibodies. The genesis of the disease is thus T lymphocyte dependent. Multiple organs and systems are affected clinically including kidney, lung, musculoskeletal system, mucocutaneous, eye, central nervous system, cardiovascular system, gastrointestinal tract, bone marrow and blood.

Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disease that mainly involves the synovial membrane of multiple joints with resultant injury to the articular cartilage. The pathogenesis is T lymphocyte dependent and is associated with the production of rheumatoid factors, auto-antibodies directed against self IgG, with the resultant formation of immune complexes that attain high levels in joint fluid and blood. These complexes in the joint may induce the marked infiltrate of lymphocytes and monocytes into the synovium and subsequent marked synovial changes; the joint space/fluid is infiltrated by similar cells with the addition of numerous neutrophils. Tissues affected are primarily the joints, often in symmetrical pattern. However, extra-articular disease also occurs in two major forms. One form is the development of extra-articular lesions with ongoing progressive joint disease and typical lesions of pulmonary fibrosis, vasculitis, and cutaneous ulcers. The second form of extra-articular disease is the so called Felty's syndrome which occurs late in the RA disease course, sometimes after joint disease has become quiescent, and involves the presence of neutropenia, thrombocytopenia and splenomegaly. This can be accompanied by vasculitis in multiple organs with formations of infarcts, skin ulcers and gangrene. Patients often also develop rheumatoid nodules in the subcutis tissue overlying affected joints; the nodules late stage have necrotic centers surrounded by a mixed inflammatory cell

infiltrate. Other manifestations which can occur in RA include: pericarditis, pleuritis, coronary arteritis, interstitial pneumonitis with pulmonary fibrosis, keratoconjunctivitis sicca, and rheumatoid nodules.

Juvenile chronic arthritis is a chronic idiopathic inflammatory disease which begins often at less than 16 years of age. Its phenotype has some similarities to RA; some patients which are rheumatoid factor positive are classified as juvenile rheumatoid arthritis. The disease is sub-classified into three major categories: pauciarticular, polyarticular, and systemic. The arthritis can be severe and is typically destructive and leads to joint ankylosis and retarded growth. Other manifestations can include chronic anterior uveitis and systemic amyloidosis.

Spondyloarthropathies are a group of disorders with some common clinical features and the common association with the expression of HLA-B27 gene product. The disorders include: ankylosing spondylitis, Reiter's syndrome (reactive arthritis), arthritis associated with inflammatory bowel disease, spondylitis associated with psoriasis, juvenile onset spondyloarthropathy and undifferentiated spondyloarthropathy. Distinguishing features include sacroileitis with or without spondylitis; inflammatory asymmetric arthritis; association with HLA-B27 (a serologically defined allele of the HLA-B locus of class I MHC); ocular inflammation, and absence of autoantibodies associated with other rheumatoid disease. The cell most implicated as key to induction of the disease is the CD8+ T lymphocyte, a cell which targets antigen presented by class I MHC molecules. CD8+ T cells may react against the class I MHC allele HLA-B27 as if it were a foreign peptide expressed by MHC class I molecules. It has been hypothesized that an epitope of HLA-B27 may mimic a bacterial or other microbial antigenic epitope and thus induce a CD8+ T cells response.

Systemic sclerosis (scleroderma) has an unknown etiology. A hallmark of the disease is induration of the skin; likely this is induced by an active inflammatory process. Scleroderma can be localized or systemic; vascular lesions are common and endothelial cell injury in the microvasculature is an early and important event in the development of systemic sclerosis; the vascular injury may be immune mediated. An immunologic basis is implied by the presence of mononuclear cell infiltrates in the cutaneous lesions and the presence of anti-nuclear antibodies in many patients. ICAM-1 is often upregulated on the cell surface of fibroblasts in skin lesions suggesting that T cell interaction with these cells may have a role in the pathogenesis of the disease. Other organs involved include: the gastrointestinal tract: smooth muscle atrophy and fibrosis resulting in abnormal peristalsis/motility; kidney: concentric subendothelial intimal proliferation affecting small arcuate and interlobular arteries with resultant reduced renal cortical blood flow, results in proteinuria, azotemia and hypertension; skeletal muscle: atrophy, interstitial fibrosis; inflammation; lung: interstitial pneumonitis and interstitial fibrosis; and heart: contraction band necrosis, scarring/fibrosis.

Idiopathic inflammatory myopathies including dermatomyositis, polymyositis and others are disorders of chronic muscle inflammation of unknown etiology resulting in muscle weakness. Muscle injury/inflammation is often symmetric and progressive. Autoantibodies are associated with most forms. These myositis-specific autoantibodies are directed against and inhibit the function of components, proteins and RNA's, involved in protein synthesis.

Sjögren's syndrome is due to immune-mediated inflammation and subsequent functional destruction of the tear glands and salivary glands. The disease can be associated with or accompanied by inflammatory

connective tissue diseases. The disease is associated with autoantibody production against Ro and La antigens, both of which are small RNA-protein complexes. Lesions result in keratoconjunctivitis sicca, xerostomia, with other manifestations or associations including biliary cirrhosis, peripheral or sensory neuropathy, and palpable purpura.

5 Systemic vasculitis are diseases in which the primary lesion is inflammation and subsequent damage to blood vessels which results in ischemia/necrosis/degeneration to tissues supplied by the affected vessels and eventual end-organ dysfunction in some cases. Vasculitides can also occur as a secondary lesion or sequelae to other immune-inflammatory mediated diseases such as rheumatoid arthritis, systemic sclerosis, *etc.*, particularly in diseases also associated with the formation of immune complexes. Diseases in
10 the primary systemic vasculitis group include: systemic necrotizing vasculitis: polyarteritis nodosa, allergic angiitis and granulomatosis, polyangiitis; Wegener's granulomatosis; lymphomatoid granulomatosis; and giant cell arteritis. Miscellaneous vasculitides include: mucocutaneous lymph node syndrome (MLNS or Kawasaki's disease), isolated CNS vasculitis, Behet's disease, thromboangiitis obliterans (Buerger's disease) and cutaneous necrotizing venulitis. The pathogenic mechanism of most of the types of vasculitis listed is
15 believed to be primarily due to the deposition of immunoglobulin complexes in the vessel wall and subsequent induction of an inflammatory response either via ADCC, complement activation, or both.

Sarcoidosis is a condition of unknown etiology which is characterized by the presence of epithelioid granulomas in nearly any tissue in the body; involvement of the lung is most common. The pathogenesis involves the persistence of activated macrophages and lymphoid cells at sites of the disease with subsequent
20 chronic sequelae resultant from the release of locally and systemically active products released by these cell types.

Autoimmune hemolytic anemia including autoimmune hemolytic anemia, immune pancytopenia, and paroxysmal nocturnal hemoglobinuria is a result of production of antibodies that react with antigens expressed on the surface of red blood cells (and in some cases other blood cells including platelets as well)
25 and is a reflection of the removal of those antibody coated cells via complement mediated lysis and/or ADCC/Fc-receptor-mediated mechanisms.

In autoimmune thrombocytopenia including thrombocytopenic purpura, and immune-mediated thrombocytopenia in other clinical settings, platelet destruction/removal occurs as a result of either antibody or complement attaching to platelets and subsequent removal by complement lysis, ADCC or FC-receptor
30 mediated mechanisms.

Thyroiditis including Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, and atrophic thyroiditis, are the result of an autoimmune response against thyroid antigens with production of antibodies that react with proteins present in and often specific for the thyroid gland. Experimental models exist including spontaneous models: rats (BUF and BB rats) and chickens (obese chicken strain); inducible
35 models: immunization of animals with either thyroglobulin, thyroid microsomal antigen (thyroid peroxidase).

Type I diabetes mellitus or insulin-dependent diabetes is the autoimmune destruction of pancreatic islet β cells; this destruction is mediated by auto-antibodies and auto-reactive T cells. Antibodies to insulin or the insulin receptor can also produce the phenotype of insulin-non-responsiveness.

Immune mediated renal diseases, including glomerulonephritis and tubulointerstitial nephritis, are the result of antibody or T lymphocyte mediated injury to renal tissue either directly as a result of the production of autoreactive antibodies or T cells against renal antigens or indirectly as a result of the deposition of antibodies and/or immune complexes in the kidney that are reactive against other, non-renal antigens. Thus other immune-mediated diseases that result in the formation of immune-complexes can also induce immune mediated renal disease as an indirect sequelae. Both direct and indirect immune mechanisms result in inflammatory response that produces/induces lesion development in renal tissues with resultant organ function impairment and in some cases progression to renal failure. Both humoral and cellular immune mechanisms can be involved in the pathogenesis of lesions.

Demyelinating diseases of the central and peripheral nervous systems, including Multiple Sclerosis; idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome; and Chronic Inflammatory Demyelinating Polyneuropathy, are believed to have an autoimmune basis and result in nerve demyelination as a result of damage caused to oligodendrocytes or to myelin directly. In MS there is evidence to suggest that disease induction and progression is dependent on T lymphocytes. Multiple Sclerosis is a demyelinating disease that is T lymphocyte-dependent and has either a relapsing-remitting course or a chronic progressive course. The etiology is unknown; however, viral infections, genetic predisposition, environment, and autoimmunity all contribute. Lesions contain infiltrates of predominantly T lymphocyte mediated, microglial cells and infiltrating macrophages; CD4+ T lymphocytes are the predominant cell type at lesions. The mechanism of oligodendrocyte cell death and subsequent demyelination is not known but is likely T lymphocyte driven.

Inflammatory and Fibrotic Lung Disease, including Eosinophilic Pneumonias; Idiopathic Pulmonary Fibrosis, and Hypersensitivity Pneumonitis may involve a dysregulated immune-inflammatory response. Inhibition of that response would be of therapeutic benefit.

Autoimmune or Immune-mediated Skin Disease including Bullous Skin Diseases, Erythema Multiforme, and Contact Dermatitis are mediated by auto-antibodies, the genesis of which is T lymphocyte-dependent.

Psoriasis is a T lymphocyte-mediated inflammatory disease. Lesions contain infiltrates of T lymphocytes, macrophages and antigen processing cells, and some neutrophils.

Allergic diseases, including asthma; allergic rhinitis; atopic dermatitis; food hypersensitivity; and urticaria are T lymphocyte dependent. These diseases are predominantly mediated by T lymphocyte induced inflammation, IgE mediated-inflammation or a combination of both.

Transplantation associated diseases, including Graft rejection and Graft-Versus-Host-Disease (GVHD) are T lymphocyte-dependent; inhibition of T lymphocyte 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 MLR can be utilized therapeutically to enhance the immune response to infectious agents), diseases of immunodeficiency (molecules/derivatives/agonists) which stimulate the MLR 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 T lymphocyte 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 T lymphocyte response in the MLR have utility *in vivo* in enhancing the immune response against neoplasia. Molecules which enhance the T lymphocyte proliferative response in the MLR (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 lymphocyte response in the MLR 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 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 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, 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, 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 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.*, 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 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 multiple sclerosis, 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 stimulated T-cells

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 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, activated CD4+ T cells) sample is greater than hybridization signal of a probe from a control (in this instance, non-stimulated CD4 + T cells) 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 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.

In this experiment, CD4+ T cells were purified from a single donor using the RossetteSep™ protocol from (Stem Cell Technologies, Vancouver BC) which contains anti-CD8, anti-CD16, anti-CD19, anti-CD36 and anti-CD56 antibodies used to produce a population of isolated CD4 + T cells. Isolated CD4+ T cells were activated with an anti-CD3 antibody (used at a concentration that does not stimulate proliferation) together with either ICAM-1 or anti-CD28 antibody. At 24 or 72 hours cells were harvested,

RNA extracted and analysis run on Affimax (Affymetrix Inc. Santa Clara, CA) microarray chips. Non-stimulated (resting) cells were harvested immediately after purification, and subjected to the same analysis. Genes were compared whose expression was upregulated at either of the two timepoints in activated vs. resting cells.

5 Below are the results of these experiments, demonstrating that various PRO polypeptides of the present invention are significantly overexpressed in isolated CD4 + T cells activated by anti-CD3/ICAM-1 or anti-CD3/anti-CD28 as compared to isolated resting CD4+ T cells. As described above, these data demonstrate that the PRO polypeptides of the present invention are useful not only as diagnostic markers for the presence of one or more immune disorders, but also serve as therapeutic targets for the treatment of those
10 immune disorders.

The results of this experiment are Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:3), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 15 (SEQ ID NO:15), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23),
15 Figure 25 (SEQ ID NO:25), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32A-B (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38A-B (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 47 (SEQ ID NO:47), Figure 49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56),
20 Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 69 (SEQ ID NO:69), Figure 71 (SEQ ID NO:71), Figure 73 (SEQ ID NO:73), Figure 75 (SEQ ID NO:75), Figure 76 (SEQ ID NO:76), Figure 77 (SEQ ID NO:77), Figure 79 (SEQ ID NO:79), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 87 (SEQ ID NO:87), Figure 89 (SEQ ID NO:89), Figure 91 (SEQ ID NO:91), Figure 93 (SEQ ID NO:93), Figure 95 (SEQ ID NO:95),
25 Figure 96 (SEQ ID NO:96), Figure 97 (SEQ ID NO:97), Figure 98 (SEQ ID NO:98), Figure 99 (SEQ ID NO:99), Figure 101 (SEQ ID NO:101) and Figure 102 (SEQ ID NO:102), show increase in expression upon stimulation with anti-CD3/ICAM1 and also show increase in expression upon stimulation with anti-CD3/anti-CD28

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EXAMPLE 2: Use of PRO as a hybridization probe

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

DNA comprising the coding sequence of full-length or mature PRO as disclosed herein is employed
35 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 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.

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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 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 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 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.

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 µg pRK5-PRO DNA is mixed with about 1 µg DNA encoding the VA RNA gene [Thimmappaya et al., *Cell*, 31:543 (1982)] and dissolved in
5 500 µl of 1 mM Tris-HCl, 0.1 mM EDTA, 0.227 M CaCl₂. To this mixture is added, dropwise, 500 µl of 50 mM HEPES (pH 7.35), 280 mM NaCl, 1.5 mM NaPO₄, 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
10 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 µCi/ml ³⁵S-cysteine and 200 µCi/ml ³⁵S-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
15 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 Sompanyrac et al., *Proc. Natl. Acad. Sci.*, 12:7575 (1981). 293 cells are grown to maximal density in a spinner flask and 700 µg pRK5-PRO DNA is added. The cells are first concentrated
20 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 µg/ml bovine insulin and 0.1 µg/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
25 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 into CHO cells using known reagents such as CaPO₄ 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 ³⁵S-methionine. After determining the presence of PRO polypeptide, the culture medium
30 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 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
35 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 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
40 by any selected method, such as by Ni²⁺-chelate affinity chromatography.

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

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 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 Fugene® (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 µm filtered PS20 with 5% 0.2 µm 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 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. 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 µm filter. The filtrate was either stored at 4°C or immediately loaded onto 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 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. 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 µl of 1 M Tris buffer, pH 9. The highly purified protein is subsequently desalted into storage buffer as described above for the poly-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

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.

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

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 (Pharmlngen) 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 A₂₈₀ 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 A₂₈₀ 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 Ni²⁺-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.

5 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
10 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
15 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
20 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.

25 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
30 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
35 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
40 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.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A composition of matter comprising (a) an
5 isolated polypeptide having at least 80% amino acid
sequence identity to an amino acid sequence of the
polypeptide shown in Figure 7 (SEQ ID NO:7), or (b) an
antibody that specifically binds to said polypeptide, in
combination with a carrier, wherein said carrier is a
10 pharmaceutically acceptable carrier.

2. A composition of matter according to claim 1,
comprising a therapeutically effective amount of (a), or
(b).
15

3. An article of manufacture, comprising:
a container;
a label on said container; and
a composition of matter comprising (a) an isolated
20 polypeptide having at least 80% amino acid sequence
identity to an amino acid sequence of the polypeptide
shown in Figure 7 (SEQ ID NO:7), or (b) an antibody that
specifically binds to said polypeptide, contained within
said container, wherein label on said container indicates
25 that said composition of matter can be used for treating
an immune related disease.

4. A method of treating an immune related disorder
in a mammal in need thereof comprising administering to
30 said mammal a therapeutically effective amount of (a) an
isolated polypeptide having at least 80% amino acid
sequence identity to an amino acid sequence of the
polypeptide shown in Figure 7 (SEQ ID NO:7), or (b) an
antibody that specifically binds to said polypeptide.

35

5. A method according to claim 4, wherein the immune
related disorder is systemic lupus erythematosus,

rheumatoid arthritis, osteoarthritis, juvenile chronic arthritis, a spondyloarthropathy, systemic sclerosis, an idiopathic inflammatory myopathy, Sjögren's syndrome, systemic vasculitis, sarcoidosis, autoimmune hemolytic anemia, autoimmune thrombocytopenia, thyroiditis, diabetes mellitus, immune mediated renal disease, a demyelinating disease of the central or peripheral nervous system, idiopathic demyelinating polyneuropathy, Guillain Barré syndrome, a chronic inflammatory demyelinating polyneuropathy, a hepatobiliary disease, infectious or autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, sclerosing cholangitis, inflammatory bowel disease, gluten sensitive enteropathy, Whipple's disease, an autoimmune or immune mediated skin disease, a bullous skin disease, erythema multiforme, contact dermatitis, psoriasis, an allergic disease, asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity, urticaria, an immunologic disease of the lung, eosinophilic pneumonias, idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, a transplantation associated disease, graft rejection or graft versus host disease.

6. A method for determining the presence of a polypeptide in a sample suspected of containing said polypeptide, said method comprising exposing said sample to an antibody that specifically binds to the polypeptide shown in Figure 7 (SEQ ID NO:7) and determining binding of said antibody to a component of said sample.

7. A method of diagnosing an immune related disease in a mammal, said method comprising detecting the level of expression of a gene encoding the polypeptide shown in Figure 7 (SEQ ID NO:7) (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.

5 8. A method of diagnosing an immune related disease in a mammal, said method comprising (a) contacting an antibody that specifically binds to the polypeptide shown in Figure 7 (SEQ ID NO:7) with a test sample of tissue cells obtained from said mammal and (b) detecting the
10 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.

15

 9. A method of identifying a compound that inhibits the activity of the polypeptide shown in Figure 7 (SEQ ID NO:7), said method comprising contacting cells which normally respond to said polypeptide with (a) said
20 polypeptide and (b) a candidate compound, and determining the lack responsiveness by said cell to (a).

 10. A method of identifying a compound that inhibits the expression of a gene encoding the polypeptide shown in
25 Figure 7 (SEQ ID NO:7), said method comprising contacting cells which normally express said polypeptide with a candidate compound, and determining the lack of expression said gene.

30 11. A method according to claim 10, wherein said candidate compound is an antisense nucleic acid.

 12. A method of identifying a compound that mimics the activity of the polypeptide shown in Figure 7 (SEQ ID
35 NO:7), 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.

13. A method of stimulating the immune response in a mammal, said method comprising administering to said
5 mammal an effective amount of the polypeptide shown in Figure 7 (SEQ ID NO:7), wherein said immune response is stimulated.

14. A method of diagnosing an inflammatory immune
10 response in a mammal, said method comprising detecting the level of expression of a gene encoding the polypeptide shown in Figure 7 (SEQ ID NO:7) (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
15 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.

20

15. A composition according to claim 1, an article of manufacture according to claim 3, or a method according to any one of claims 4, 6 to 10 or 12 to 14, substantially as herein described with reference to any one of the
25 examples.

[illegible]

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FIGURE 2

HEGVTGARPVKTLLAGATSLPAARNGNGVGDPSTWPRGSAMELKQSLSTHLEAEKPLRRYGAVEETAWKTERLG
RNQLDIISMAETTMPEEIELEMAKIQRLREVLVRRESELRFMMDDIQLCKDIMDLKQELQNLVAIPEKEKTKLQ
KQREDELIQKIHKLQKRDFLVDDAEVERLREQEEDKEMADFLRIKLKPLDKVTKSPASSRAEKKAEPSPSKPTV
AKTGLALIKCCGATQCNIM

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FIGURE 3

CATTTTAAACTTTTTTTTAAATTTATTTTGGTAGCTAGGTTTTATATTGTTCTTAAATTTATTTACTCTATT
TTATTTTCCATCACTTCTTTGTCCCAGATTCATGAAATTTGCTGATGTCCATTTTATGCTACTTTTGAACCTCT
TCTCTTTGTGTTTGTTCCTTATTACAACTCCAAGACATTTCTTAGAATTGTCTACAGATTTCTGTGTAGCT
ACTTATTGGTAGCTTCTTAATTCATACTTGTCCAGACCATTAGACATTATTACATGCTCTGTCTTGGGCCTATC
ATTAACATTAGCTTAGGGATTCTGATTTCAAAGACATAAAGAATTGGCAAACTCTTCTTACAGAACTTAAACA
AGTTTTAAAGTTACATTTCTATACATCTAATACATAATACCTTCTTAGCCATTAATGTAATTCCTCTGGATAAAG
ATAATATATTCAAAAAAATTGGGACCAAAAAATGCACTTGTTTCTTGCTCATATATATATAGATGTAAAATTNT
TTAATTTCTTGTTTGTTCCTTGGTTACATTGAATACAGATTTGCTGAACAGTTTTGATGTTATTTTTTAAT
AAAATTTGTATTGTTAAAGTGCCTTGAAATTTCTAATAAATAACTTCA

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FIGURE 4

AAATATGTGGGTTGGAAGAAAGAACGTGTAGTAGCAGAGTTTGGGATGGGAAAATCGTGTGGTTCTGCCACAT
GATCCAAGCTTTGCTATCAAAAAGGTAGAAGATGTCCAAGAACTTGTTGATAATGAATTGGGCTTCCAGCAAGTT
GTTCTAAATGTCCAAACAAAATAAAAACTTTTCTTGTAATATCTGGATGAAAAGAGAGTAGTTGGGTGTTTAAT
TGCAGAACCCATCAAACAGGCATTTTCGTGTCCTGTCTGAACCAATTGGTCCAGAATCCCCAAGCTCTACGGAATG
TCCTAGGGCTTGGCAATGTTTCAGATGTACCAGAACCTGCAGTCTGTGGGATAAGTAGAATCTGGGTTTTTCAGACT
GAAGAGAAGAAAGCGCATTTGCAAGACGACTGGTTGATACCCTCAGGAATTGCTTCATGTTGGCTGTTTTCTCAG
CACTGATGAAATAGCATTTTCTGACCCAACACCAGATGGCAAGTTATTTGCAACCAAGTACTGCAACACCCCTAA
TTTCCTCGTATATAATTTTAATAGTTAAAGCTGATTTTCAGTTATAAAGGAGTTACTATCTGGATAAGTTCAAAGA
GCTCCTTATTATAAAAATACAACTATTTAATATCAAAATAAAAAATACCGAGACT

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FIGURE 5

KYVGWKKERVVAEFWDGKIVLVLPDPSFAIKKVEDVQELVDNELGFQQVVPKCPNKIKTFLVISG

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FIGURE 6

GGCACGAGAAAAAACATTAAGACAGAACTTAAAAACAATAGATTGACTATAATCCAAAGACGAGTGACCTCTAA
CCACAATTTTCATTTATTTTTAAATGTTTCCTTCATGGCCTTTCTTGTGGCTCACCCCTATGCAGTTTGTGTATTT
GTTGACAACTTTATGTGTTTTTAATATGGTTTTTGCCAACTTGGTTTTTCCGAGACCGTCTTTTCTCAGAGGCT
CAGTTTTACCGTCCTATCTGCAGTCGGCTACTTTTCAGTGGGCAGAAGAGGCCACATCTGCTTCCTGTAGGCCCTC
TGGGCAGAAGCATGCGCTGGTGTCTCCTCCTGATCTGGGCCCAGGGGCTGAGGCAGGCTCCCTCGCCTCAGGAA
TGATGACAGGCACAATAGAAACAACGGGGAACATTTCTGCAGAGAAAGGTGGCTCTATCATCTTACAATGTCACC
TCTCCTCCACCACGGCACAAGTGACCCAGGTCAACTGGGAGCAGCAGGACCAGCTTCTGGCCATTTGTAATGCTG
ACTTGGGGTGGCACATCTCCCCATCCTTCAAGGATCGAGTGGCCCCAGGTCTGGCCTGGGCCCTCACCTCCAGT
CGCTGACCGTGAACGATACAGGGGAGTACTTCTGCATCTATCACACCTACCCTGATGGGACGTACACTGGGAGAA
TCTTCTGGAGGTCTTAGAAAGCTCAGTGGCTGAGCACGGTGCCAGGTTCCAGATTCCATTGCTTGGAGCCATGG
CCGCGACGCTGGTGGTCATCTGCACAGCAGTCATCTGTTGGTTCGCGTTGACTAGAAAGAAGAAAGCCCTCAGAA
TCCATTCTGTGGAAGGTGACCTCAGGAGAAAATCAGCTGGACAGGAGGAATGGAGCCCCAGTGCTCCCTCACCCC
CAGGAAGCTGTGTCCAGGCAGAAGCTGCACCTGCTGGGCTCTGTGGAGAGCAGCGGGGAGAGGACTGTGCCGAGC
TGCACTGACTACTTCAATGTCTTGAGTTACAGAAGCCTGGGTAAGTGCAGCTTCTTACAGAGACTGGTTAGCAAC
CAGAGGCATCTTCTGGAAGATACACTTTTGTCTTTGCTATTATAGATGAATATATAAGCAGCTGTACTCTCCATC
AGTGCTGCGTGTGTGTGTGTGTGTATGTGTGTGTGTGTTTCAGTTGAGTGAATAAATGTCATCCTCTTCTCCAT
CTTCATTTCTTGGCCTTTTCGTTCTATTCCATTTTGCAATTATGGCAGGCCTAGGGTGAGTAACGTGGATCTTGA
TCATAAATGCAAAATTAAAAAATATCTTGACCTGGTTTTAAAAAAAAAAAAAAAAAAAAA

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FIGURE 7

MRWCLLLIWAQGLRQAPLASGMMTGTTGNISAEKGGSIILQCHLSSTTAQVTQVNWEQQDQLLAICNADLGW
HISPSFKDRVAPGPGGLGLTLQSLTVNDTGEYFCIYHTYPDGTYTGRIFLEVLESSVAEHGARFQIPLLGAMAATL
VVICTAVIVVVALTRKKKALRIHSVEGDLRRKSAGQEEWSPSAPSPPGSCVQAEAAPAGLCGEQRGEDCAELHDY
FNVLSYRSLGNCSTFTETG

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FIGURE 8

GTCAGTCGCGAGCGAACGACCAAGAGGGTGTTCGACTGCTAGAGCCGAGCGAAGCG**ATGC**CCTAAATCAAAGGAAC
TTGTTTCTTCAGGCTCTTCTGGCAGTGATTCTGACAGTGAGGTTGACAAAAAGTTAAAGAGGAAAAAGCAAGTTG
CTCCAGAAAAACCTGTAAAGAAACAAAAGACAGGTGAGACTTCGAGAGCCCTGTATCTTCTAAACAGAGCAGCA
GCAGCAGAGATGATAACATGTTTCAGATTGGGAAAATGAGGTACGTTAGTGTTTCGCGATTTTAAAGGCAAAGTGC
TAATTGATATTAGAGAATATTGGATGGATCCTGAAGGTGAAATGAAACCAGGAAGAAAAGGTATTTCTTTAAATC
CAGAACAATGGAGCCAGCTGAAGGAACAGATTTCTGACATTGATGATGCAGTAAGAAAAC**TGTA**AAATTTCGAGCC
ATATAAATAAAACCTGTACTGTTCTAGTTGTTTTAATCTGTCTTTTACATTAGCTTTTGTTTTCTAAATGTTCT
CCAAGCTATTGTATGTTTGATTGCAGAAGAATTTGTAAGATGAATACTTTTTTTTAAATGTGCATTATTAAAAAT
ATTGAGTGAAGCTAATTGTCAACTTTATTAAGGATTACTTTGTCTGCCCACCACCTAGTGTAATAATAAATCAAG
TAATACAATCTTAACTGTTGTGGCCTTTTTTGATCATAAGAGTTGGTACTGTTTAAGGCCAAAAGTAACAGTTTT
TATAGATCTTTTAGTTTCAACTCAGCTTTTACAATAAAAAGGATTTGTATTGCATTGAGTTTATAAACTTTTGGT
TTGTGAACTTCATATTTGATCTTTCTCTTCCAATCAAATGTCTAGGCTTGTTTGACTTCCACCCCCAATGGTTT
TTCCTCTTTTTATTTACTTCATTTTCCTTTAATAACTTAATCTCTTCATGTTTCAGTTTTTACTTCACTCTTTAT
TCTTTTCTTTGATTATGGTATGCTTATTTGGAAAGTCAGTGAAACTGTCAAAATGTTATCTCAATAAGATACTTA
TATGAGAACTACAATCACCGAATCTACTGTATTCAATATTAGCAGATCTAATTTGATAAACAACATGGCTTGTTG
GAAAACTGAGCAGGTGTTTGTTTACCCATAGTGTTCTGTGTAGTTATTGCTTAGTCTGCAGAAAATAATGACTTA
GATGAGATGTCTGACTTGCTTCACTTATTAAACATGTTCAACCATGGGATGATGTCTGTAACATCAGATATTGTT
CAACTAGACTAGGATTTAATAAAAAATTGTGAAAGCTTAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

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FIGURE 9

MPKSKELVSSGSSGSDSDSEVDKKLKRKKQVAPEKPVKKQKTGETSRALSSSKQSSSRDDNMFQIGKMRYVSVR
DFKGKVLIDIREYWMDPEGEMKPGRKGISLNPEQWSQLKEQISDIDDAVRKL

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FIGURE 10

GCGCGGGGGCCCGAGCCGCTCAGTCTCCCTGCTCTCCGTGGTCCCGGCTCGCGTGTAGCGGCGGGCGGGCGGTCT
CCGGTGAGGAGGCGCGCGGGGCCATGACGTACAGCTCCACAAAGGTCGGAGAGATCTTCTCGGCGGGCCGGCGCCG
CCTTCACGAAGCTCGGGGAGCTGACGATGCAGCTGCATCCCGTGGCCGACTCTTCTCCTGCGGGCGCGAAGTGGA
CGGAGACGGAAATAGAGATGCTGAGGGCTGCTGTGAAGCGATTTGGGGACGATCTTAATCACATCAGCTGTGTCA
TCAAGGAACGGACAGTGGCCCAGATAAAGGCCACTGTGAAACGCAAGGTATATGAAGATTCTGGCATCCCCCTTC
CAGCTGAGTCACCCAAGAAAGGGCCCAAGAAGGTGGCATCTGGTGTCTTGTCACCTCCTCCAGCTGCCCCCTCCTC
CCAGCAGCTCCAGTGTCCCTGAGGCCGGGGGTCCCCCATAAAGAAACAGAAGGCTGATGTGACACTCAGTGCTC
TGAACGACTCCGATGCCAACAGTGACGTGGTGGATATTGAAGGGCTAGGAGAACTCCTCCAGCTAAGAAACTCA
ACTTCGACCAGGACAGCCTGACCCTGGATTCTGGCCTTCTCATGACCTCTGCTGATCCTCCTCTCCTCTCCTGCT
GAGCCTTCCACCTCTGACCTCTCACTGTTTCATGCCGGACCTGTGGATCTCCTGGGACTCCGAGCAAGGCCTGCAC
GAGAGAGGGCTGAAAGGCTGCTGGGGCTGCCACCTCGCTATTCCCGCATAAGCATCTGCCCCCAACCCCTTTGAC
CTTCATCTGATGGACATTTTATACAGAAAACAATAAAGATTTCCCTCTCAGCTT

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FIGURE 11

AGARAAQSPCSPWSRLACSGGGGVS GEEARGAMTSASTKVGEIFSAAGAAFTKLGELTMQLHPVADSSPAGAKWT
ETEIEMLRAAVKRFGDDLNHISCVIKERTVAQIKATVKKRVYEDSGIPLPAESPKKGPKKVASGVLSEPPAAPP
SSSSVPEAGGPPIKKQADVTL SALNDSANDVVDIEGLGETPPAKKLNFDQDSLTLDSGLLMTSADPPLLSC

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FIGURE 12

CGGATGATTCAGGCATGGCTCTGCTAACACTTTATTAAAAGCATGGATTAATTTTACTTCCAAGTTTATTTTAC
TGCACCATCCCATTGTGGAAACAACCTAGCTTACTCAGCTTTTTTTTCCCTTTTATAAAGGAAAGAACAGAAAAGT
AAAAGGAGGAAAGAAAACAAGAGGTGAGTGAGGCAACTGAAAAGTGTCTTGACCTGCGGTGCTATAGAGCAGG
CTCTTCTAGGTTGGCAGTTGCC**ATG**GAACTCTGGACCCAAAATGTTGGCCCCCGTTTGCCTGGTGGAATAACAA
TGAGCAGCTATTGGTGAACCAGCAAGCTATACAGATTCTTGAAAAGATTTCTCAGCCAGTGGTGGTGGTGGCCAT
TGTAGGACTGTACCGTACAGGGAAATCCTACTTGATGAACCATCTGGCAGGACAGAATCATGGCTTCCCTCTGGG
CTCCACGGTGCAGTCTGAAACCAAGGGCATCTGGATGTGGTGCGTGCCCCACCCATCCAAGCCAAACCACACCCT
GGTCCTTCTGGACACCGAAGGTCTGGGCGATGTGGAAAAGGGTGACCCCTAAGAATGACTCCTGGATCTTTGCCCT
GGCTGTGCTCCTGTGCAGCACCTTTGTCTACAACAGCATGAGCACCATCAACCACCAGGCCCTGGAGCAGCTGCA
TTATGTGACGGAGCTCAGAACTAATTAAGGCAAAGTCCTCCCCAAGGCCTGATGGAGCAGAAGATTCCACAGA
GTTTGTGAGTTTCTTCCAGACTTTCTTTGGACAGTACGGGATTTCACTCTGGAGCTGAAGTTGAACGGTCACCC
TATCAGAGAAGATGAATACCTGGAGAATGCCTTGAAGCTGATTCAAGGCAATAATCCAGAGTTCAAACATCCAA
TTTTCCCAGGGAGTGATCAGGCGTTTCTTTCCAAAACGGAAGTGTTCGTCTTTGACCGGCCAACAAATGACAA
AGACCTTCTAGCCAATATTGAGAAGGTGTCAGAAAAGCAACTGGATCCCAAATTCCAGGAACAAACAAACATTTT
CTGTTCTTACATCTTCACTCATGCAAGAACCAAGACCTCAGGGAGGGAATCACAGTCACTGGGAATCGTCTGGG
AACTCTGGCAGTGACTTATGTAGAGGCCATCAACAGTGGAGCAGTGCCTTGTCTGGAGAATGCAGTGATAACTCT
GGCCCAGCGTGAGAACTCAGCGGCCGTGCAGAGGGCATCTGACTACTACAGCCAGCAGATGGCCCAGCGAGTGAA
GCTCCCCACAGACACGCTCCAGGAGCTGCTGGACATGCATGCGGCCTGTGAGAGGGAAGCCATTGCAATCTTCAT
GGAGCACTCCTTCAAGGATGAAAATCAGGAATTCCAGAAGAAGTTCATGGAAACCACAATGAATAAGAAGGGGGA
TTTCTTGCTGCAGAAATGAAGAGTCATCTGTTCAATACTGCCAGGCTAACTCAATGAGCTCTCAAAGGGACTAAT
GGAAAGTATCTCAGCAGGAAGTTTCTCTGTTCCCTGGAGGGCACAAGCTCTACATGGAAACAAAGGAAAGGATTGA
ACAGGACTATTGGCAAGTTCCCAGGAAAGGAGTAAAGGCAAAAGAGGTCTTCCAGAGGTTCTGGAGTCACAGAT
GGTGATAGAGGAATCCATCTTGCACTCAGATAAAGCCCTCACTGATAGAGAGAAGGCAGTAGCAGTGGATCGGGC
CAAGAAGGAGGCAGCTGAGAAGGAACAGGAACCTTTAAAACAGAAATTACAGGAGCAGCAGCAACAGATGGAGGC
TCAAGTTAAGAGTCGCAAGGAAAAACATAGCCCAACTGAAGGAGAAGCTGCAGATGGAGAGAGAACACCTACTGAG
AGAGCAGATTATGATGTTGGAGCACACGCAGAAGGTCCAAAATGATTGGCTTCATGAAGGATTTAAGAAGAAGTA
TGAGGAGATGAATGCAGAGATAAGTCAATTTAAACGTATGATTGATACTACAAAAAATGATGATACTCCCTGGAT
TGCACGAACCTTGACAAACCTTGCCGATGAGCTAACTGCAATATTGTCTGCTCCTGCTAAATTAATTGGTCATGG
TGTCAAAGGTGTGAGCTCACTCTTTAAAAGCATAAGCTCCCTTTT**TA**AGGATATTATAGATTGTACATATATGC
TTTGACTATTTTTGATCTGTATGTTTTTCATTTTCATTCAGCAAGTTTTTTTTTTTT

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FIGURE 13

MESGPKMLAPVCLIVENNNEQLLVNQQAIIQILEKISQPVVVVAIVGLYRTGKSYLMNHLAQNHGFPLGSTVQSET
KGIWMWCVPHPSPKNHTLVLLDTEGLGDVEKGDPKNDWIFALAVLLCSTFVYNSMSTINHQALEQLHYVTELTE
LIKAKSSPREDDGAEDSTEFVSFFPDFLWTVRDTLELKLNGHPITEDEYLENALKLIQGNPRVQTSNFPRECIR
RFFPKRRCFVDRPTNDKDLLANIEKVSEKQLDPKFQEQTNIFCSYIFTHARTKTLREGITVTGNRLGTLAVTYV
EAINSGAVPCLENAVITLAQRENSAAVQRASDYYSQMAQRVKLPTDTLQELDMHAACEREAIAIFMEHSFKDE
NQEFQKKFMETTMNKKGDFLLQNEESSVQYCQAKLNELSKGLMESISAGSFVPGGHKLYMETKERIEQDYWQVP
RKGVKAKEVFQRFLESQMVIEESILQSDKALTDREKAVAVDRAKKEAAEKEQELLKQKLQEQQQQMEAQVKSKE
NIAQLKEKLQMERHLLREQIMMLEHTQKVQNDWLHEGFKKKYEEMNAEISQFKRMIDTTKNDDTPWIARTLDNL
ADELTAILSAPAKLIGHGVKGVSSLFKKHKLFF

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FIGURE 14

CTTCTCATTAGCATTAACTAGTTATGCCCAGCTTGGGAGAGCCTTCTTTGGGCTTATCATTTATTATAAGCCAG
AAATAGGTGACTAATCAGAGATAAATGTATGGGTTGTCTGTATCTAGTTTTATGCCTTTTTTTTTGCCTAAGACG
TAGTCAAATTAATATTTTAACTAATACATCTTAGCAGAGTTTAGTTAAGCACAAAGTTAACAGTGGGTAGGATTG
AATCTTGAAAGTAATCATGTCTGTAATGTTTTTCATGCATGCAAAAAGCACAGACAAAACCACTCATGCCCTATT
AATAAACAAAATACAGATCAAAGTTTTCAAAGTAATCACTCTATTTATTCTAAATGTCTGTGGCTTTAGGAAAA
TACCACCAGCTAGTACTTACCTATTTAAAGATGTAGAATTTATTATCCTCTAATATTCTTATCAGTTGTTTCCAC
AACTTTAGTTTACTATTGGACTTTCAAAAATTTAAAGAATTACAAGTAAAATTCATTAAACACTTGTGTGTGAAT
AGTAATACACAGTAATTAGTACAGCATGTTGCTTCTTCAACAAATTGAGTTTTTCAGGGAAATCAGCAAGTAAATG
AAATATAAATTTTTGGTAAAAGTATCAAACATTCACTTGCCCATTTTTCTCTTAAACTTTATTATCTAATCAA
ACATAGTTTTCCATAAGATGTAATAAAATATAGATAAGGTTGGAATATTTGAGGATCCATTTGTGGAAGTGAATT
TAATGAGACTTCATTGGTGATACACTCAATTTTTACTGGGTAATTAGCTAATAATGTTGGTCACTGTCTCACAGT
TCAAGTAGCTTTAAGATGATGTGGCAAGGAAAACACAAAGCTTTTGGGTAACCAGCGTTCTTAAATGTATGGTTT
TTGACCAGGTGAACCCTTTAGAAGTGATTTCTGTTTTTAAAAGTATGTACTTAAAATACCTTTGGCTGTGATGAAT
GTAGATCCCAGCAGAATACCAAAATCCTATTTTTTTTTGACTGAGTATTTGTAGATGCTTAATGACTGAAATGAAT
TTGGAGGCACTGATGAAAGTGATTTTTTTTAAAGTTCTCAGGTACTGTTCAATTATTTAATGTTAAGTTTAGTATC
AAGATACAGTTGTTTTTAAAATGCCAAAATGCTGTTTATTATACAGAATATTTTATTACATTTGCAATATCTTTG
TATATAGTGATTTTTTTCTTGATAATAAATGGAAAAATTCTAAAACAAA

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FIGURE 15

AATTCGGCACGAGAAAAGCCAGAGTGAGGATTTGGGAAGAAAACCCATGGAAAGTAGCAGTGTTGTGAGTTGCAG
AGACAGGAAAGATAGAAGACGTTCCATGTGTTATTCTGATGGTCGAAGTTTACATTTGGAAAAAATGGAAATCA
CACACCATCCTCCAGTGTGGGCAGCTCTGTAGAAATTAGTTTAGAAAATTCTGAACTGTTTAAAGATTTGTCTGA
TGCCATTGAGCAAACCTTTCAGAGGAGAAATAGTGAAACCAAAGTGCACGTAGCACGAGGCTACAGAAGGATTT
AGAAAACGAAGGTCTTGTATGGATTTCACTTCCACTTCCTTCCACTTCCAAAAAGCCAAAAGAAGAACAATATG
TACATTTGACAGCAGTGGATTTGAAAGTATGTCTCCATAAAAGAAACTGTGTCTCCAGACAAAACCGCAGAT
GGCACCTCCCGTCTCAGATCCAGAAAACAGCCAGGGCCCTGCTGCTGGTTCTTCCGATGAACCTGGTAAGAGGAG
GAAGAGCTTTTGTATATCTACACTTGCAAATACTAAAGCCACTTCCCAGTTCAAAGGCTACCGGAGAAGATCCTC
TCTTAATGGGAAGGGAGAGAGCTCTCTGACTGCCTTGGAAAGGATTGACATTAATGGAGAAAAGAAAGCAGTATTG
ACATTTCTGTCANAGTCTGTGGCAAGAGGGAAAGTACCATCTATGCTGAAATGATCTGNCTAGTTCCATTCTTTG
TTCAACCTCAGNGTTCAAAAGTTCCTATTAATAACTCNTTTGGGTGACCTACTTTTGTGA

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FIGURE 16

ATGGGTGAGAGAACTCTTCACGCTGCAGTGCCACACCAGGTTATCCAGAATCTGAATCCATCATGATGGCCCC
ATTTGTCTAGTGGAAAACCAGGAAGAGCAGCTGACAGTGAATTCAAAGGCATTAGAGATTCTTGACAAGATTTCT
CAGCCCGTGGTGGTGGTGCCATTGTAGGGCTATACCGCACAGGAAAATCCTATCTCATGAATCGTCTTGCCAGGA
AAGCGCAATGGCTTCCCTCTGGGCTCCACGGTGCACTCTGAAACTAAGGGCATCTGGATGTGGTGTGTGCCCCAC
CTCTCTAAGCCAAACCACACCCTGGTCCCTTCTGGACACCGAGGGCCTGGGCGATGTAGAAAAGAGTAACCCTAAG
AATGACTCGTGGATCTTTGCCCTGGCTGTGCTTCTAAGCAGCAGCTTTGTCTATAACAGCGTGAGCACCATCAAC
CACCAGGCCCTGGAGCAGCTGCACTATGTGACTGAGCTAGCAGAGCTAATCAGGGCAAAATCCTGCCCCAGACCT
GATGAAGCTGAGGACTCCAGCGAGTTTGCGAGTTTCTTTCCAGACTTTATTTGGACTGTTCCGGGATTTTACCCTG
GAGCTAAAGTTAGATGGAAACCCCATCACAGAAGTAGTACCTGGAGAATGCCTTGAAGCTGATTCCAGGCAAG
AATCCCAAATTCAAAATCAAACATGCCTAGAGAGTGTATCAGGCATTTCTTCCGAAAACGGAAGTGCTTTGTCT
TTTGACCGGCCTACAAATGACAAGCAATATTTAAATCATATGGACGAAGTGCCAGAAGAAAATCTGGAAAGGCAT
TTCCTTATGCAATCAGACAACTTCTGTTCTTATATCTTCACCCATGCAAAGACCAAGACCCTGAGAGAGGGAATC
ATTGTCACTGGAAAGCGGCTGGGGACTCTGGTGGTGACTTATGTAGATGCCATCAACAGTGGAGCAGTACCTTGT
CTGGAGAATGCAGTGACAGCACTGGCCCAGCTTGAGAACCCAGCGGCTGTGCAGAGGGCAGCCGACCACTATAGC
CAGCAGATGGCCCAGCAACTGAGGCTCCCCACAGACACGCTCCAGGAGCTGCTGGACGTGCATGCAGCCTGTGAG
AGGGAAGCCATTGCAGTCTTCATGGAGCACTCCTTCAAGGATGAAAACCATGAATTCAGAAGAAGCTTGTGGAC
ACCATAGAGAAAAAGAAGGGAGACTTTGTGCTGCAGAATGAAGAGGCATCTGCCAAATATTGCCAGGCTGAGCTT
AAGCGGCTTTTCAAGCAGCTGACAGAAAGCATTGAGAGGAATTTTCTCTGTTTCTGGAGGACACAATCTCTAC
TTAGAAGAAAAGAAACAGGTTGAGTGGGACTATAAGCTAGTGCCAGAAAAGGAGTTAAGGCAAACGAGGTCCTC
CAGAACTTCTGCAGTCACAGGTGGTTGTAGAGGAATCCATCCTGCAGTCAGACAAAGCCCTCACTGCTGGAGAG
AAGGCCATAGCAGCGGAGCGGGCCATGAAGGAAGCAGCTGAGAAGGAACAGGAGCTGCTAAGAGAAAAACAGAAG
GAGCAGCAGCAATGATGGAGGCTCAAGAGAGAAGCTTCCAGGAAAACATAGCTCAACTCAAGAAGAAGATGGAG
AGGGAAAGGGAAAACCTTCTCAGAGAGCATGAAAGGCTGCTAAAAACACAAGCTGAAGGTACAAGAAGAAATGCTT
AAGGAAGAATTTCAAAGAAATCTGAGCAGTTAAATAAAGAGATTAATCAACTGAAAGAAAAAATTGAAAGCACT
AAAAATGAACAGTTAAGGCTCTTAAAGATCCTTGACATGGCTAGCAACATAATGATTGTCACTCTACCTGGGGCT
TCCAAGCTACTTGAGTAGGGACAAAATATCTTGGCTCACGTATTTAA

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FIGURE 17

MGERTLHAAVPTPGYPESESIMMAPICLVENQEEQLTVNSKALEILDKISQPVVVVAIVGLYRTGKSYLMNRLAG
KRNGFPLGSTVQSETKGIWMWCVPHLSKPNHTLVLLDTEGLGDVEKSNPKNDWIFALAVLLSSSFVYNSVSTIN
HQALEQLHYVTELAELIRAKSCPRPDEAEDSSEFASFFPDFIWTVRDFTLELKLDGNPITEDEYLENALKLIPGK
NPKIQNSNMPRECIRHFFRKRKCFVDRPTNDKQYLNHMDEVPEENLERHFLMQSDNFCSYIFTHAKTKTLREGI
IVTGKRLGTLVVITYVDAINSGAVPCLENVATALAQLENPAAVQRAADHYSQQMAQQLRLPTDTLQELLDVHAACE
REAIAVFMEHSFKDENHEFQKKLVDTIKKKGDFVLQNEEASAKYCQAEKRLSEHLTESILRGIFSVPGGHNL
LEEKKQVEWDYKLVPRKGVKANEVLQNFLOSQVVVEESILQSDKALTAGEKATAAERAMKEAAEKEQELLREKQK
EQQMMEAQERSFQENIAQLKKKMERERENLLREHERLLKHKLKVQEEMLKKEEFQKKSEQLNKEINQLKEKIEST
KNEQLRLLKILDMASNIMIVTLPGASKLLGVGTKYLGSR

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FIGURE 18

GGTTTTXTGGXXGGGGGTTTTCAACXCXGGCTCTTGTTCTTTTTGCAGGACCCATCGATTCTGAATTCGGCACGAG
CATCAGTATGCTTATGGATTTGATGACAGGCATAGCCTGGGCATATCACCTCATTGGTAAAGGGCTAGAGCCTTT
CTTTTTTATGGCACTTCTTTTTTTGAGATAGGGTCTTACTCTGTCCACCTGGCTAGAGTACACTGGTACAATCAC
GGCTCAATGTAGGCTTAACCTCCTGGGCTCAGGTGTATGTCACTATGCCCGGCTACTTTTTGTATTTTTTGGTAG
AGACGGCTTCGCCACGTTGCCCAGGCTGCAAGCGATATGCCTAGGCTCAAGCGATCTGCCACCTCAACTTCCGG
AAGTGCTGAGATTACAGGTGTGAGCCACTGCACCCAGCCTTTGCTTTATTTTTTATTTTTTGAGAGGTATGATT
TTCTAGAGATTTTTTCTCATGGCTACTATTAGATCAGGAATGGGTGATTGGAGATTATTAGATTCTAGGTAAAC
TTCTACCACTTTACCCTAATACATAAAACTTTTTCTAAATXAATGATGGAAGGAATXAAXXXAXCXXCCXCXT
XXCCXCTAXTACAAAAXCXTAGCCCTTAXAACXTTXXGXXAGCTXXXTTXXCCTXXXXTCCCTXXTCXXXCC
CCXXCCTXXTTXXCXXXCTXXCTCXAXCCCCACXAXTTXCXXTXXXXCTXCXXAATAXATTXCXCXCXTXXC
TCCTCAXXXXCTXXTCXXXCTCXX

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FIGURE 19

TTCCAGCTCACTTGCGGTGGCAGCACAACTTAGGGAAATAATACCATCCAGTGCTTTGCCTAATGGCACAGTTCA
GCATATCCTC**ATG**CCAGATGATGAAGGTGAAGGTGAATTGTGTTGGAAAAAAGTAGACTTAGGGGACATGAAGAA
TGTGGATGTCTTATCTTTTCAGTCATGCTCCTTCATTCAATTTTCTTTCTAATTCATGTTGGTCTAAACCAAAGGA
AGATAAAGCAGTAGATACATCAGATTTGGAAGTTGCAGAAGATCCTATGGGCCTCCAAGGAATAGATCTGATCAC
AGCAGCATTGCTTTTTTGTCTAGGAGATTCTCCAGGAGGGAGGGGTATATCTGATAGCCGCATGGCTGATATTTA
TCACATTGACGTTGGGACTCAGACTTTTTCACTTCCATCTGCAATATTAGCTACAAGTACAATGGTTGGGAGAT
AGCTTCAGCTTCAGCTTGTGATCATGCCAATCCACAGCTTTCAAATCCAAGTCCGTTTCAGACACTTGGGCTGGA
TTTAGTATTGGAATGTGTGCTAGGTACCAACCCAAGCAGCGTTCAATGTTTACCTTTGTGTGTGGACAGTTATT
TAGAAGGAAAGAATTTTCTTCCCCTTTAAGAATGTGCATGGTGACATTCATGCTGGACTCAATGGCTGGATGGA
ACAGAGGTGCCCTTTAGCTTACTATGTTGTACCTATTCTCAGCGTAGATTTTGTCCATCAATACAAGGAGCAAA
GATTATACATGACCGCCATTTGAGGTCATTTGGAGTTTCAGCCATGTGTATCTACAGTATTAGTGGAGCCTGCTAG
AAACTGTGTGTTGGGATTACATAATGACCATCTAAGTAGTCTTCCTTTTGGGTCTGCAGCATATTGCAGGCTT
TCTCGATGGCTTCAGCTTATGTCAGCTCTCATGTGTATCCAAGTTAATGAGGGATGTGTGTGGCAGCCTGCTTCA
GTCTCGTGGCATGGTCATACTGCAGTGGGGGAAAAGGAAGTATCCAGAAGGAAATTCATCATGGCAGATAAAAGA
AAAGGTATGGCGATTTAGTACTGCATTTTGTCTGTTAATGAATGGAATTTGCTGACATCCTAAGCATGGCAGA
CCACTGAAGAAATGCAGTTACAATGTTGTGCGAGAAACGGGAGGAAGCAATCCCTTTGCCATGTATGTGTGTGAC
ACGAGAACTCACTAAAGAAGGACGTTCACTACGCTCAGTTTTAAACCTGTACTTT**TAAA**AGTTGTAATATTACTA
GCACATATATGCAAGCACCTAGTATAATTTCTTTGTAATATGTGAACTTTATTAATGTATTAAATATTACAAC
AGCTAAATTTATTGTCACTGTGTATATAATGTTTTGAAGTGACATCTATTTTTATAAAGTACTGTTTAGTTGGAA
AAAGTGCCTTAATGTTTGAATGTGTGAAATTTTGGAACTTGCTGGACAGGGTGATTTAATTTTTAGCTACAT
AATTTTAAGAATTAGTATTTTCAGTGGTGTGCATATTTTGGTTCTTAAATTTTTGCTTCTTAAACTAAAAAAATC
CTGACCAATTTATTTGTTGTTTTCTGTGGGTGCGACCCATGCAATCAAAAAGCAAAATTTTGATTGAGATTTTT
TACAGCATAGGTTTTTTCATATAAAAAATATTCTGAATTTGTTAAGCACTGCCATAATATCATTATAATGTTTTGT
CTTTTAGTGCTTCCCTATACAATTGTTAATGCACAAATGATCTCTAATATATACTTACATACGTAAATCATAAA
GTTTGGTAATGCAGTTTATCGTTTTAAAAATAATCCACAAAGATGTTTTTATCTCACATACTTACAACCTCAACAC
ACAGAGTGACCATGTGCAGCTTTCTTTTTTGTAGATGCCACATCCGAAGACTCATCGCAGTGTGTTATATGACA
GGACAAAAGCAAAAACAAACAAAAAGCAAGCCTGTGAATATAATTTAATTTGAAACTGCTCCTGGTATTATATATT
TGCTAGTTATCTAATGTTTTTAAAAAGAAAATATACCTCATTTAGGTTTGAATTTGGGCGTATTGTGTAATTTCAAA
TATTCAGAATGCAAGGGCTTGACTATTAAATGTTTGCCTTTGATGTTTATAAACATTACAACCTATGTTGTTTTA
AGACATTTAAAAACGTGAAATTTGTTATCTTTGTAAATGACAAATCATGTAGAAACCTGTCTTGGTTGACAATCT
CTTTGAAACATTTCCGAGTTAATTTCCCATAGGCTTCACCACCAAGAAAGTAAGAATTGCATCTTTACATAATGA
TCAAGGTATAATGGAAAAATATACCTATTCTTGAAGTAGTTTTATTATAGTTTTCAAATTGATTTATACCATTATT
AACCTGATGTGGTCTGCTTAAAAAATGAATATATCAGTATTTAGAAATAAATTGCAAAGGTGGGAATATATACTT
AAATAATTTGTCTTAAGTAAATTAGCATTGTTGGTAGTCTGAAATGGTGACAGATTACTTGTAAAAATTGTGAAAAC
TCTGTTGTGTCCTCTCTTCTTACATTTGTCCCTGAGAGTACTCCACGATTACTAGGTTCTTGATTCCCTTATATG
GCAATCAGGCAGAGGCGTTCCTTAAGCATTAGAGAGTTCTGAAGCTTAAGATTTGTTTTGGTTGGATGAAGTCCT
TAGTACAGTTGAAAAACAGAGCATTAAAGACTAATCAATTGTTTTGCCTCACCAGTCATTTTAAATAGTAGAATA
CTTATTTCTCAGTGCTTAAATTTCTTTTTCAACTGTGAGATTGAATAAACAGTCTCTATTTCTGTGGAAAAAAC
AACAGAAAAGAGATATTAAATACCATAAAATGTAACCTGTCCTTTTAAAGTTTTGCTGAAGAATGTGTCTGTGGT
TAGGATAGCACAAAGCATTAACTTTTGTTTTATAGTTATGCTTTTTAAATTCATTGTTTTTAAATTTAGACTTCT
TATTTCCACACTGGATTATGAGATACTTAACAATTTTCCACCTTATATTTCTTTTACACATTTTGCTGTTCTCT
TTTTTGTTATTGTTATGCCACCATAACATTTTGTAAATGTTTTCTTTGTGAAACATTTGTTCAAGTTCTAATA
AAATTAATGTTTTCCCTTAACATGGCTCAATAACTTAAAAACGTTCAATTAATAAATTTTAACTTGTGTTGA
CAAAAAAAAAAAAAAA

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FIGURE 20

MPDDEGE GELCWKKVDLGDMKNVDVLSFSHAPSFNFLSNSCWSKPKEDKAVDTS DLEVAEDPMGLQGIDLITAAL
LFCLGDSPGGRGISDSRMADIYHIDVGTQTFSLPSAILATSTMVGEIASASACDHANPQLSNPSPFQTLGLDLVL
ECVARYQPKQRSMTFVCGQLFRRKEFSSHFKNVHGDIHAGLNGWMEQRCPLAYYGCTYSQRRFCPSIQGAKIIH
DRHLRSFGVQPCVSTVLVEPARNCVLGLHNDHLSSLFFEVLQHIAGFLDGFSLCQLSCVSKLMRDVCGSLLQSRG
MVILQWGRKRYPEGNSSWQIKEKVWRFSTAFCSVNEWKFADILSMADHLKKCSYNVVEKREEAIPLCMCVTREL
TKEGRSLRSVLKPVL

FIGURE 21

[illegible]

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FIGURE 22

MPVAVGPYQSQPSCFDRVKMGFVMGCAVGMAAGALFGTFSCLRIGMRGRELMGGIGKTMMQSGGTFGTFMAIGM
GIRC

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FIGURE 23

AGACTCCCTGTCCTTTGCGGTTTGGGAGATGATGAGAAACCACAGAATTGCTAGTAGTTTATGTGGAGATCAGGTC
TTCTCCAAGAAAAAAGAAAAAACAACATGGCTGCAAAGGAGAACTGGAGGCAGTGTTAAATGTG
GCCCTGAGGGTGCCAAGCATCATGCTGTTGGATGTCCTGTACAGATGGGATGTCAGCTCCTTTTTCCAGCAGATC
CAAAGAAGTAGCCTTAGTAATAACCCTCTTTCCAGTATAAGTATTTGGCTCTTAATATGCATTATGTAGGTTAT
ATCTTAAGTGTGGTGCTGCTAACATTGCCAGGCAGCATCTGGTTCAGCTTTATCTATATTTTTTACTGCTCTG
CTCCTCTATGCTGGACATCAAATTTCCAGGGACTATGTTCCGGAGTGAAGTGGAGTTTGCTATGAGGGACCAATG
TATTTAGAACCTCTCTCTATGAATCGGTTTACCACAGCCTTAATAGGTGAGTTGGTGGTGTGTACTTTATGCTCC
TGTGTCATGAAAAAAGCAGATTTGGCTGTTTTCAGCTCACATGCTTCCTCTGCTAGCAGACTCTGCCTTGTT
CCTTTGGAGACAATTGTTATCATCAATAAATTTGCTATGATTTTTACTGGATTGGAAGTTCTCTATTTTTCTTGGG
TCTAATCTTTTGGTACCTTATAACCTTGCTAAATCTGCATACAGAGAATTGGTTCAGGTAGTGGAGGTATATGGC
CTTCTCGCCTTGGGAATGTCCCTGTGGAATCAACTGGTAGTCCCTGTTCTTTTCATGGTTTCTGGCTCGTCTTA
TTTGCTCTTCAGATTTACTCCTATTTTCAGTACTCGAGATCAGCCTGCATCACGTGAGAGGCTTCTTTTCTTTTT
CTGACAAGTATTGCGGAATGCTGCAGCACTCCTTACTCTCTTTTGGGTTTGGTCTTCACGGTTTCTTTTGTGGC
TTGGGTGTTCTCACACTCTGCAAGTTTTACTTGCAGGGTTATCGAGCTTTCATGAATGATCTGCCATGAATCGG
GGCATGACAGAAGGAGTAACGCTGTTAATCCTGGCAGTGCAGACTGGGCTGATAGAACTGCAGGTGTTTCATCGG
GCATTCTTGCTCAGTATTATCCTTTTTCATTGTCGTAGCTTCTATCCTACAGTCTATGTTAGAAATTGCAGATCCT
ATTGTTTTGGCACTGGGAGCATCTAGAGACAAGAGCTTGTGGAACACTTCCGTGCTGAAGCCTTTGTTTATTT
TTATTGGTATTCCTGCTTATATGGCTTATATGATTTGCCAGTTTTTCCACATGGATTTTTGGCTTCTTATCATT
ATTTCCAGCAGCATTCTTACCTCTCTTCAGGTTCTGGGAACACTTTTTATTTATGTCTTATTTATGGTTGAGGAA
TTCAGAAAAGAGCCAGTGGAAAACATGGATGATGTCTACTATGTGAATGGCACTTACCGCTGCTGGAGTTT
CTTGTTGGCCCTCTGTGTTGGTGGCCTATGGCGTCTCAGAGACCATCTTTGGAGAATGGACAGTGATGGGCTCAATG
ATCATCTTCATTTCCTACTATAACGTGTGGCTTCGGGCCCAGCTGGGGTGAAGAGCTTTCTTCTCCGCAGG
GATGCTGTGAATAAGATTAAATCGTTACCCATTGCTACGAAAGAGCAGCTTGAGAAACACAATGATATTTGTGCC
ATCTGTTATCAGGACATGAAATCTGCTGTGATCACGCCTTGCAAGTCAATTTTTTCCATGCAGGCTGTCTTAAGAAA
TGGCTGTATGTCCAGGAGACCTGCCCTCTGTGCCACTGCCATCTGAAAAACTCCTCCAGCTTCCAGGATTAGGA
ACTGAGCCAGTTCTACAGCCTCATGCTGGAGCTGAGCAAAACGTCATGTTTCCAGGAAGGTACTGAACCCCCAGGC
CAGGAGCATACTCCAGGGACCAGGATACAGGAAGTTCCAGGGACAATAATGAGTACATTGCCAGACGACCAGAT
AACCAGGAAGGGGCTTTTGACCCCAAAGAATATCCTCACAGTGCAGAAAGATGAAGCACATCCTGTTGAATCAGCC
TAGAGGAGAAGCAGCAGGAATGATGCTTTGATACTCTGGAGGAGAAGTTAACTCAAGATGGAATTCATGTTCTGA
TTTGAGGAATGAAAATGAGATGATCAGGCAGGAACTGACATTCCAAGGATCTAATCCAGGAAGTACTCTCAGTG
GGGACCACCTGCTTTTCATCCCTGACATTGTGGGAGAAATTTGCAATGTATGCTAATCAAATGTATTTATATG
TTCTCTGCTGATGTTTTATAGAGGTTTGTGAAGAAATTCACCTCAGCAACTTCAGAACTGCCCTGATACGT
GTGAGAGAGAAATAAAATCAGATTTTGAGTGTTGAAGGGACTGAGGAAGTGAGGATAAAGAGCATGAGGACAGCA
TGGAAGAAGGAGGCAGAAGTGAAGTGAACCTTCACTCTCCATGGGACAGATCAATCTCATTATCAAGTCTGAA
TAGCAACCAGCCCTCTCCTCCACCCCGTTTTCTCCTCAGTTAATTGGAGCTCAGTCAGGTGATTATTGAGTCTTGT
ACAGCACTGAAATGAAATCAAAGATGAAGAAGCATTGATTGTATTGGAAGATTGAAGCACGCTCATACTTTGTAT
GTGCTTTAGGGAAGGGGTGGGTGGGCACTTGGGCCCTGCGGGTGCATTTCATGTAATCTGAGACTCTTGAACTTTA
TGACGGAGTCTTCAATATTTGATGTATATGAACTTTTGTAAATATGTTGTATACTTCGCTGGCTGTGTGAAG
TAAACTAAAATCTGATGAACACTTTGGAGTCTGCTTTAGTGAAGGAGACCAAAGTGGGAAGGGCTTTAGGGCAC
TGATAGAGGCCCTGGGTGTAATTTTCAATCCTGTGTAATGTTTAAATCTTGCAACTGAATCAAAACAGTGTTAA
TTATGGCAATATTTGCACTTTGGGAATGAGTACATAACTGTATGATCACACTCTGCAATGCCACTTTTAAAGCT
GTTAATAGACTTTGCACCTTTTCTTTGACAAGGATGTGTATATTTAAATTTTTTACATTCATCATGGCTACAGGT
AGAAGTGGGGAGGGGGGAATGTAATTTTTTATGGGAATTTTGATATGAAAAGAACTAGTCATTTATTTATACAA
TAGGCTTGGCTCAAAAAGTGTTTTTTTCAGACCTCGGTATTCCTAATGTGGGATGTGACTTTATTTTATTTTAGTA
GCAAATTTGGATGTAGACTGACAGACATAGCTGAATGTCTTAATAAATTTAAATTTGAAGAT

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FIGURE 24

MMRNHRIASSLCGDQVFSKKKKKKKKNNMAAKEKLEAVLNVALRVPSIMLLDVLYRWDVSSFFQQIQRSSLSNNP
LFQYKYLALNMHYVGYILSVVLLTLPRQHLVQLYLYFLTALLLYAGHQISRDYVRSELEFAYEGPMYLEPLSMNR
FTTALIGQLVVCTLCSCVMKTKQIWLFSAHMLPLLARLCLVPLETIVIINKFAMIFTGLEVLVYFLGSNLLVPYNL
AKSAYRELVQVVEVYGLLALGMSLWNQLVVPVLFMVFWLVLFALQIYSYFSTRDQPASRERLLFLFLTSIAECCS
TPYSLGLVFTVSFVALGVTLCKFYLG YRAFMNDPAMNRGMTEGVTLILAVQTGLIELQVVHRAFLLSIILF
IVVASILQSMLEIADPIVLALGASRDKSLWKHFRAVSLCLFLLVFPAYMAYMICQFFHMDFWLLIIISSILTSL
QVLGTLFIYVLFMVVEEFRKEPVENMDDVIYYVNGTYRLLEFLVALCVVAYGVSETIFGEWTVMGSMIIFIHSYYN
VWLRAQLGWKSFLLRDAVNKIKSLPIATKEQLEKHNDICAICYQDMKSAVITPCSHFFHAGCLKKWLYVQETCP
LCHCHLKNSSQLPGLGTEPVLQPHAGAEQNVMFQEGTEPPGQEHTPGTRIQEGSRDNNEYIARRPDNQEGAFDPK
EYPHSAKDEAHPVESA

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FIGURE 25

TTGCTTCTCCACCAACGTAACAATTTATAAAGCAAGAGATGAGAAAAAGAGATTATTGGGAAATGTACTGAATAA
TGAGGAGTCTGGGGAATAGAACAAAAGTTGTAAGTCGTAACCTGACCCATCTTACTTCACTGGTAATCAAGTACA
GTCGAAAGGATGAAATAAAGAAGTGAGTAGTTTAAAAACTCTGTTGGACCAGCACCTTGAATCAAATGGATGTTT
TAGGGTTCTGTTTCCCACTGAACCAAGAATTGTATCCCTCCATCTCTCCTTGAGGAGAGGCCCTATGTTAGACCT
TGGCTACTCATCATTAAAGATAAAATCTTAATAGATAAACTGGAATTCCTTGAATCCATGAAAAGACAGTGTTCA
TTAAGGGTTTGTGCAGTGGATGCTCCTTATGTCCCATGGTAGAATAAGATCTCCTTAGCTCCGCCAAGTTAAAGG
CTCTTGCAAGGGCACTTAGAGATGTT

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FIGURE 26

GGAGAAGCAGCTTGAGGCATCATTAGATGCACTGCTGAGTCAAGTGGCTGATCTGAAGAACTCTCTGGGGAGTTT
CATTGCAAGTTGGAGAACGAGTATGGCCGGCTGACCTGGCCATCTGTCTGGACAGCTTTGCCTTGCTTTCTGG
ACAGCTGAACACTCTGAACAAGGTCTTGAAGCATGAAAAACACCGCTGTTCCGTAACCAGGTCATCATTCTCT
GGTGTGTCTCCAGACCGAGATGAAGATCTCATGCGGCAGACTGAAGGACGGGTGCCTGTTTTACGCCATGAGGT
AGTCCCTGACCATCTGAGAACCAAGCCTGACCCTGAAGTGGAAGAACAGGAGAAGCAACTGACGACAGATGCTGC
CCGCATTGGTGCAGATGCAGCCCAGAAGCAGATCCAGAGCTTGAATAAAATGTGTTCAAACCTTCTGGAGAAAAT
CAGCAAAGAGGAGCGAGAATCAGAGAGTGGAGGTCTCCGGCCGAACAAGCAGACCTTTAACCCTACAGACACTAA
TGCCTTGGTGGCAGCTGTTGCCTTTGGGAAAGGACTATCTAATTGGAGACCTTCAGGCAGCAGTGGTCCTGGCCA
GGCAGGCCAGCCAGGAGCTGGGACGATCCTTGCAAGAACCTCAGGATTACAGCAGGTGCAGATGGCAGGAGCTCC
AAGCCAGCAGCAGCCAATGCTCAGTGGGGTACAAATGGCTCAGGCAGGTCAACCAGGGAAAATGCCAAGTGAAT
AAAAACCAACATCAAGTCGGCTTCCATGCATCCCTACCAGCGGCCCTCCTGCCTGGGTTTCATTCTGGCTATCCC
TCTAAGGCGCAAGGTGAAGAAGCTTCTGGGCCAGGAAGGAAAAAAAAATGCCACCTGCAGCTCTGGTGAAGCTT
GGGCCTGCTCTCCTTTCCATCCTCTAAGGAGCCAACTTGGCTTTTACCTGTCAAATAGTCATAAAGTCCCCTATC
CTTTACCCACCTTATACACACGAGGCTTTCTCAGGAAGTGGCTCTGCCAGGCAGGACTATGTGGGAAAGGGTTT
TTCCTTAGCACACGAAAAAGCCCCTTCCCCTGGATTTCATGTTTCTTATTTTGGAGGGAGAAGGGAATTGCACTTC
ACACTGCCATCAGGGTTTAGTTGACCTCATAATGGTGCCCACTTTCTCGACTTTGGCCAGGATTTCTTCAAAGA
AAACGACTTTCCTTCATTTCCCTAAGCCTGTGGCCCAAATGGTGGACCAGAATGATGGTGGAGGGGGCAACCCC
CAGTAGCTTTGCCTGCTTTTATAAAGTTGAACAAATTGAATTTAGACATTCAGGCTAACCTGCCTTTCTTAGTAC
TCCTTTGTTGGCATGGGCAGGGGTTGAGTCAGCAGAAGTGGACCAAAGGATTCCTCTGAATAAAGTTATTTAAAT
TGAAAAAAAAAAAAAAAA

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FIGURE 27

MRQTEGRVPVFSHEVVPDHLRTKPDPEVEEQEKQLTTDAARIGADAAQKQIQSLNKMCSNLLEKISKEERESESG
GLRPNKQTFNPTDTNALVAAVAFGKGLSNWRPSGSSGPGQAGQPGAGTILACTSGLQOVQMAGAPSQQQPMLSGV
QMAQAGQPGKMPSGIKTNIKSASMHPYQRPSCLGFI LAIPLRRKVKKLLGQEGKKNAHLQLW

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FIGURE 28

GGAGCTCCAGGCGCACATCCGCAGTCAGCCACCTCGCGCGCGCTCCAGGAGCAAGG**ATG**GAGAGGGCTGGTGATC
AGGATGCCCTTCTGTCTATCTGTCTACCTACAGCCTGGTTTGGGTCATGGCAGCAGTGGTGCTGTGCACAGCACAA
GTGCAAGTGGTGACCCAGGATGAAAGAGAGCAGCTGTACACACCTGCTTCCTTAAATGCTCTCTGCAAAATGCC
CAGGAAGCCCTCATTGTGACATGGCAGAAAAAGAAAGCTGTAAGCCCAGAAAAATGGTCACCTTCAGCGAGAAC
CATGGGGTGGTGATCCAGCCTGCCTATAAGGACAAGATAAACATTACCCAGCTGGGACTCCAAAACCTCAACCATC
ACCTTCTGGAATATCACCTGGAGGATGAAGGGTGTTACATGTGTCTCTTCAATACCTTTGGTTTTGGGAAGATC
TCAGGAACGGCCTGCCTCACCGTCTATGTACAGCCCATAGTATCCCTTCACTACAAATTCCTCTGAAGACCACCTA
AATATCACTTGCTCTGCCACTGCCCGCCAGCCCCCATGGTCTTCTGGAAGGTCCCTCGGTCAAGGATTGAAAAT
AGTACAGTGACTCTGTCTCACCCAAATGGGACCACGTCTGTTACCAGCATCCTCCATATCAAAGACCTAAGAAT
CAGGTGGGGAAGGAGGTGATCTGCCAGGTGCTGCACCTGGGGACTGTGACCGACTTTAAGCAAACCGTCAACAAA
GGCTATTGGTTTTAGTTCCGCTATTGCTAAGCATTGTTTTCCCTGGTAATTCTTCTCGTCTAATCTCAATCTTA
CTGTACTGGAAACGTACCGGAATCAGGACCGAGAGCCCT**TAA**CTAAGTCACACAGCACCCCTGAAAGTGATTCCCT
GGTCTACTTGAATTTGACACAAGAGAAAAGCAGGAGGAAAAGGGGCCATTCTCAAAGGACCTGAAAGAGCAAAA
GAGGTGGGAGCGAAAGCCTTAAGGATCCCACGACTTTTTACTGCCATCTGAGCTACTCAGTGTTTGAATCCCAAG
AGGAAGTCAGTTTACCTCTCAGGTCTGTTGTAGGACTTGATTTTGTAAAGCAATGCCATGTTATGTGGTTGAAAG
GGCACTGGACTTAGTATCAGGAGCACTGAGCTCACAGACTGACTTGGGCTCCTACTGGTGGGGACCTCTGTTAGT
CACTTTACCTCATCCAAAGTATAAAGGAATTGGACCAAATAAFTTACCACATAGCTCTAAAACCTTAATTTAAAT
GTAATTCAGAAAAAAAAGGGAATAAGCAAAGGGGGAAGAATTGAAAGAGAGAGAGAAGAAAGAATACAGAGAG
CTTACCTTTTGCCTTTCTGTTGATGTTACATCTCTTCTTCCTATGTTCTTAGGTCTATGAGTCTGTTTCCCCATC
ATTTGGTATCTAGTCCAGTTCCTGCTTACTGCTTTGCTAATAGCTGGCCTTGCTAGAATCCTTGGTTCACTGCTG
TTCTTCATGTGCTTCTATGAGATTTACTCCAACACAAATAGGACTGAATTTATTGTGAAGTAACATTGGCAATCT
TAACTTATTCAATTAACCTATTTTTATAGCTAGATAAATATTGTTAGTCTTAGACAATAGCTCACATTTTTTGAG
AAGCATGCCCTCCCTGTCCATTTGTCTTATAACATGACCCAGCCCTATTTTACGTCATTCTAAATTACGCCTCAT
ATAATGAAAATACATTATGAAAACAGATGTTTAGGAGATTTCTGTATAGCAGTCAGCCAATTCATATGCTTTGT
CTCTGCTGGCTTCTTTTTCCATGCGTTAACTTTTCCAATAGCAGAGGAGGCAAAATATGAGCATACAATCCCTTT
GTTCTAAAGATATTGTTCCAGCTAGTGGAATGATGTTGAATCTTTAATAACCATAATTAGTTGCTTTTTCAGTAT
CTTCTGCTTTGTCTGTCTATCCAGTGGCCTAGGAATTAAGTGTAGTTGTTTTTGCTGTTAAATTGGATATT
TATATATATATATATAGCAAGATTTTCATGTGTTATTTAATTCTGTATTGTTTCTTATATTTGTAGTAAATATT
GAACAATTAAAAGTGTTGACTCCAAAAAAAAAAAAAAAAAAAA

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FIGURE 29

MERLVIRMPFCHLSTYSLVWVMAAVVLC TAQVQVVTQDEREQLYTPASLKCSLQNAQEALIVTWQKKKAVSPENM
VTFSENHGVVIQPAYKDKINITQLGLQNSTITFWNITLEDGECYMCLFNTFGFGKISGTACLT VYVQPIVSLHYK
FSEDHLNITCSATARPAPMVFWKVPRSGIENSTVTL SHPNGTTSVTSILHIKDPKNQVGKEVICQVLHLGTVTDF
KQTVNKGWFSVPLLLSIVSLVILLVLISILLYWKRHRNQDREP

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FIGURE 30

AGCGAAGTGTGGTGGCTTCCAAGGAATACAAACATAAAGGCCTTCGACCGTTGCAAATAGACTAAAGTGAAAACA
AATCTGAATGAAGATGAAGTTATTTTCAGACCATTTCAGGCAGCTCAGGAGTTCAAAGTTTTCTGTGGAATCAGC
TGCCCTTGTGGCTTTCTCTACTTCCTCTTACTCATGTGGCCGGAAGAAAAAGTGAACCCATATGAAGAAGTGGA
CCAAGAAAAATACTCTAATTTAGTTTCAGTCTGTCTTGTTCATCCAGAGGCGTCGCCCAGACCCGGGATCGGTGGA
GGAAGATGCTTTGCTCTGTGGACCCGTGAGCAAGCATAAGCTGCCAAACCAAGGTGAGGACAGACGAGTGCCACA
AAACTGGTTTCCTATCTTCAATCCAGAGAGAAGTGATAAAACCAATGCAAGTGATCCTTCAGTTCCTTTGAAAAT
CCCCTTGCAAAGGAATGTGATACCAAGTGTGACCCGAGTCCTTCAGCAGACCATGACAAAACAACAGGTTTTCTT
GTTGGAGAGGTGGAACAGCGGATGATTCTGGAAC TGGGAGAAGATGGCTTTAAAGAATACACTTCAAACGCTCTT
TTTACAAGGGAAACGTTTCCACGAAGCCTTGGAAGCATACTTTACCCCAGGAAACCTTAAAGAGAGAGATGA
AAATCTCCTCAAGTCTGGTTACATTGAAAGTGTCCAGCATATTCTGAAAGATGTCAGTGGAGTGCGAGCTCTTGA
AAGTGCTGTTCAACATGAAACCTTAAACTATATAGGTCTGCTGGACTGTGTGGCTGAGTATCAGGGCAAGCTCTG
TGTGATTGATTGGAAGACATCAGAGAAACCAAGCCTTTTATTCAAAGTACATTGACAACCCACTGCAAGTTGT
GGCATAACATGGGTGCCATGAACCATGATACCAACTACAGCTTTCAGGTTCAATGTGGCTTAATTGTGGTGGCCTA
CAAAGATGGATCACCTGCCCACCCACATTTTCATGGATGCAGAGCTCTGTTCCAGTACTGGACCAAGTGGCTTCT
TCGACTAGAAGAATATACGGAAGAAAAAGAACCAAGATATTTCAGAAACCAGAAATATTTCAGAAATAGGGAGCAAG
TTGCTATTTGGGAACATTCAGCACCTTCTCACAGTTTGGGAACATATATTGCTGTTTACTCCAGTGTAATAATGA
GGTGCCACTGGATCTGAGTGCTACACGAACACAAGTAGAAGTATTAATTTGTTGAAATGTGTTGTTACCAAAAAG
ACTGAAAAGCCCCAAAGTCTAGATATAAAGACCTAGACTTCGGCACGCGAAATCCCAGCTATGCTACCTCTTATT
TACCTGAAAGGAGGACACGCAGGATGGGCAGTCATGCTGGTGACTCTTGTA TCCCTTGAGGGACATTGGGGGGG
GGGGGGCGTGGTCCCAGGCAGGATGCCCAGTCTTTGAGCTGAGATTGGAAGGCAGTGAGGCTGAGGGTGCCAAGA
TTTCCCCAGGGTTCACCCAGAGGGGAAGGGGCTACATGCCCCCAGCTGTGTGCAGGGAGGACACATCAGCCCACT
ACCGCTGCCAACACCAATGCCTAAAACCTGTTTCATACATTGGGGTTTTCTATATATTTTCAGCTGGGAAAAGCTT
ACATTTAACCTTTTGAAAAAATAAATACGTGATTAGCCTCAACTAAACATTGCTGACTATAAAGACAGTATATTC
ACCATGTCGCTGGCAATATGTCATTGCGTAACACCAATAACCCCCCAGAAGTAGCCAGAGGCCAGTTTGAACAT
CACAATTCTAAGTGTTTTAGTAACTATTTCTGGCGTGAGTCAACAGATCATGTAGATAGAGTCAATTATTGTTTG
TGGAGTTTTTTCAGCTATAGGGGAGGGGAAC TATTAATCCATTTGTTTCTATTCAATAGGTAATAAAAATTAGT
TGTCCCTGGGTTTGGGAACTTAAATGCCCATACAGCCCTGGGGAAGGGTTTTCTGTCTTATGGAGTGAGTCTT
AGCATTTAAGTTATACAGTTGCTGCCTTAAATAGTAGCCTGCTACAATGACTTCTTTGGGTAGCCATTTTCATA
AGAAATAAAATACAAGATATGAGTAAAAAAAAAAAAAAAAAAAA

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FIGURE 31

MKMKLFQTICRQLRSSKFSVESAAALVAFSTSSYS CGRKKKVN PYEEVDQEKYSNLVQSVLSSRGVAQTPGSVEED
ALLCGFVSKHKLPNQGEDRRVPQNWFP IFNPERSDKPNASDPSVPLKIPLQRNVIPSVTRVLQQTMTKQQVFILLE
RWKQRMILELGEDGFKEYTSNVFLQGKRFHEALES ILSPQETLKERDENLLKSGYIESVQHILKDVSGVRALESA
VQHETLNYIGLLDCVAEYQGKLCVIDWKTSEKPKPFIQSTFDNPLQVVAYMGAMNHD TNYSFQVQCGLIVVAYKD
GSPAHPHFMDAELCSQYWKWLLRLEEYTEKKKNQNIQKPEYSE

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FIGURE 32A

ATGGCCTCAGGAGCCGGAGGAGTCTGGAGGGGGCGGTGGCGGCAAGATCCGGACGCGGCGTTGCCACCAGGGGCCA
ATTAAGCCTTACCAGCAGGGGCGACAACAGCATCAGGGCATTCTTAGCAGGGTTACAGAATCTGTTAAGAATATT
GTGCCAGGGTGGTTACAAAGATACTTCAACAAGAATGAAGATGTATGCAGCTGTTCAACAGACACAAGCGAGGTT
CCACGCTGGCCAGAAAATAAAGAGGACCATCTGGTATATGCCGATGAGGAGAGCTCTAATATTACTGATGGGAGA
ATCACACCTGAGCCAGCAGTCAGTAATACAGAAGAACCTTCAACAACACTAGTACTGCTTCAAATTATCCAGATGTG
TTAACAAAGGCCTTCTCTTCATCGGAGCCATCTGAATTTTTCCATGTTGGAATCCCCTGCATTACACTGTCAGCCA
TCTACATCCTCGGCATTCCCAATTGGCAGTTCGGGATTTTCCCTTGTAAGGAAATTAAAGATTCTACCTCTCAG
CATGATGATGATAACATCTCAACTACCAGTGGTTTTTCTTCAAGAGCTTCTGATAAAGATATAACTGTTTCAAAG
AACACTTCATTGCCACCTCTGTGGTCCCCAGAAGCTGAACGTTCTCACTCACTCTCACAGCACACTGCCACCAGC
TCAAAAAACCAGCATTCAACTTGCTGCCTTTGGAACACTTTCCCTTCACTTGGGAATTCTTCAATCCTTAAA
ACCGTCAGCTTGGAGATTCTCCTTTTATCCTGGAAAAACAACATACGGTGGGGCAGCAGCTGCTGTAAGACAG
TCTAAACTACGAAATACACCTTATCAGGCACCAGT TAGAAGACAAAATGAAAGCTAAGCAACTCAGTCACAATCT
TACGGTGTGACCAGTTCAACAGCTCGGCGAATATTGCAGTCTTTAGAGAAGATGTCAAGCCCTTTAGCGGATGCA
AAAAGAATTCCATCCATTGTTTCTTCTCCTCTGAATTCTCCTCTTGATAGGAGTGGGATAGATATCACAGATTTT
CAGGCCAAAAGAGAAAAGGTGGATTCTCAATATCCTCCTGTTTCAAGAGACTTATGACCCCAAAGCCAGTTTCCATA
GCAACAAATCGAAGTGTTTATTTTAAACCATCTCTGACTCCTTCTGGTGAATTCAGGAAGACTAATCAAAGAATA
GATAACAAGTGCAGTACTGGATATGAAAAAATATGACACCCGGACAAAATAGAGAACAACGAGAAAAGTGGCTTT
TCATATCCAAATTTAGTTTGCCTGCAGCCAATGGTTTATCTTCTGGAGTAGGTGGTGGAGGTGGCAAGATGAGA
CGAGAAAGACACGCCTTTGTTGCTTCTAAACCTCTGGAGGAGGAGGAAATGGAAGTTCCAGTATTACCGAAAATC
TCTCTACCGATCACCAGTTCTTCACTGCCTACCTTTAATTTTAGTTCCCTGAGATCACAACCTTCTCTCCATCA
CCCATCAATTCGTCTCAAGCATTAAACAAACAAGGTACAAATGACCTCTCCGAGCAGCACTGGCAGTCCCATGTTT
AAATTTTCATCTCCAATCGTAAATCTACTGAGGCAAAATGTACTACCTCCATCATCTATTGGATTTACATTTAGT
GTGCCTGTTGCAAAAACAGCAGAACCTTCTGGTTCTAGTAGTACTTTAGAACCAATTATAAGTAGTTACGTCAT
CATGTCACTACAGTGAACAGTACAAATTGTAAGAAGACACCACCTGAAGATTGTGAGGGTCTTTTAGACCTGCA
GAAATCCTGAAAGAAGGAAGTGTTCTAGATATTCTGAAAAGCCCTGGTTTCGCATCGCCGAAGATAGATTCTGTT
GCTGCTCAGCCCACCGCAACAAGCCCAGTAGTTTATACAAGACCAGCAATAAGTAGCTTTTCTTCTAGTGGAAAT
GGGTTTGGGGAGAGTTTAAAAGCTGGGTCTCATGTCAGTGTGATACATGTCTACTCCAGAACAAAGTTACAGAC
AACAAATGCATAGCCTGTCAAGCAGCAAAATGTCAACCCAGAGATACTGCTAAACAGACTGGAATTGAAACACCA
AATAAAAGTGGCAAAACAACCTCTTCTGCATCAGGGACAGGCCTTGGAGACAAATTTAAACAGTGATAGGCACT
TGGGATTGTGATACCTGTTTAGTGCAAAATAAACCTGAAGCAATAAAATGTGTAGCCTGTGAAACACCGAAACCT
GGAACCTGTGTGAAGCGAGCCCTTACATTGACAGTGGTTTCGGAAGTGCTGAGACTATGACTGCTTATCTTCC
AGCTGCACTGTAACCACTGGTACCTTAGGATTTGGAGATAAATTCAAAGGCCCATTTGGATCTTGGGAGTGTTCA
GTATGCTGTGTTTCTAATAATGCAGAAGACAATAAGTGTGTGTCTGTATGTCTGAGAAACCAGGAAGTTCAAGTA
CCTGCTTCAAGTAGCAGCACTGTACCTGTCTCTCTGCCTTCTGGAGGCTCTCTAGGATTGGAAAAGTTCAAGAAA
CCCAGGGAAGCTGGGACTGTGAATTGTGCCTAGTGCAGAATAAGGCAGACTCTACCAAATGTTTGGCATGTGAA
AGTGCAAAGCCAGGCACAAAATCTGGGTTTAAAGGCTTTGACACATCTTCTCATCTTGAAGTCTCAGCAGCCTCC
TCATCCTTCAAATTTGGTGTCTCATCATCTCTTCTGGGCCTTCTCAGACTTTAACAAGCACTGGAAATTTTAAA
TTTGGAGATCAGGGAGGATTCAAATAGGTGTGTCTGATTTCTGGGTCTATAAACCCCATGAGTGAAGGCTTT
AAATTTTCTAAACCAATAGGAGATTTTAAATTTGGAGTTTCATCTGAATCTAAGCCCGAAGAAGTTAAAAAGAT
AGTAAGAATGATAATTTTAAAGTTTGGACTTTCTTCTGGTTTAAAGCAACCCAGTTTCTTTAACTCCATTTCAATTT
GGGGTATCTAATCTTGGACAGGAAGAAAAGAAAGAGGAAGTCCCAATCTTCTCTGCAGGTTTTAGCTTTGGT
ACAGGTGTTATTAACCTCCACCCCTGCTCCTGCTAACACCATAGTGACCTCTGAGAACAAGAGCAGCTTCAACCTT
GGAACCATAGAAACCAAGAGTGCTTCAGTGGCTCCTTTACATGTAAGACATCAGAAGCTAAAAAGAAAGAAATG
CCTGCCACCAAAGGAGGATTCTTTTTGGCAACGTGGAGCCTGCCTCTCTGCCATCTGCCTCAGTGTGTTTTG
GGAAGGACAGAAGAGAAACAGCAAGAGCCTGTCTACTTCCCTAGTTTTTGGGAAGAAAGCTGACAATGAA
GAGCCAAAGTGTCAACCAAGTGTCTTCTTTGGGAATTCAGAGCAAACCAAAGATGAGAATTTCTTCAAAGTCCACA
TTTAGTTTTAGTATGACAAAACCATCTGAGAAGGAATCTGAACAGCCAGCAAAGCCACTTTTGCCCTTTGGAGCT
CAAACCTAGTACTACAGCTGATCAAGGTGCAGCAAAGCCAGTTTTTAGTTTCTTGAACAACAGTTCCTCTAGTTCA

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FIGURE 32B

AGTACACCAGCCACTTCTGCTGGTGGTGGCATATTGGTAGTTCACCTCTTCCTCCAATCCACCTGTGGCTACC
TTTGTGTTTGGACAGTCCAGCAATCCTGTGAGCAGCTCTGCCTTTGGTAACACTGCTGAATCCAGCACCTCTCAG
TCTTTGCTATTTTCTCAAGATAGCAAACCTAGCAACCACATCCAGCACAGGTACAGCTGTCAACCCATTTGTCTTT
GGTCCAGGAGCCAGCAGTAATAATACTACCACCTCTGGTTTCGGCTTTGGAGCCACAACCACATCTAGCTCTGCA
GGATCCTCCTTTGTATTTGGAACCTGACCCCTCAGCACCATCTGCCAGTCCAGCATTGGTGTACCAACAGACCCCA
ACATTTGGACAAAGTCAAGGTGCCAGCCAGCCCAATCCCCAGGCTTTGGATCTATATCATCTTCCACAGCATT
TTTCCCACTGGTTCTCAGCCTGCACCACCTACTTTGGGACAGTGTCAAGCAGTAGCCAGCCCCCTGTGTTTGG
CAGCAACCTAGTCAGTCTGCATTTGGCTCTGGAACAACCTCTAATTCTAGTTCGGCTTTCCAGTTTGGCAGCAGC
ACTACAAATTTCAACTTCACAAACAACAGTCCATCAGGAGTGTTCACATTTGGTGCAAATTCTAGCACACCTGCA
GCCTCAGCCCAGCCTTCAGGCTCGGGGGGCTTTCCATTTAACCAGTCTCCAGCAGCATTACAGTGGGGTCAAAT
GGGAAAAATGTGTTCTCTTCTTCTGGAACCTTCATTCTCTGGTCGCAAGATAAAGACTGCTGTTAGACGCAGGAAA
TAAAGGTCACATTGGTGTGTACTCAATTTTAAACAACAGCTGGTGCCTGCTTTTCAAGATACTGGATTGTACTTTG
TGCTGGGGTTATCTGAAGTCAGATCTGCCTAAGGACTTCTTTAATTTTGGAAATTTTCTCTTTCTCTTTCTGTTA
CAGAAGCCCCACCCTGCCTCACCCACCCTTTTTTAAATAAAATAAAATAGCTAGACTGGTGACTGATTCTTCAGCAA
AAATATTTTATGATCCAGCAGATTATTCACTGATTGACATAGTCTGGCTGTACCCAGGAATGGAGCCTGCACGG
TGAATGGCTTTGTATAGAACCTCTTTGTCTACACCATTATGTGCGCTGATAACGTTTCATGGAACGCGTTGAAATT
GTAATTATATCTGAGGAATTCTGTATAGATTAGAATTCTGTATAGATTAGAGAGTGTGAAACGGATGATTTCTA
TGCTGAGTTTGTGCTGGTGTATGTGTGAAGTGAGTGAGTTGGGTGTATTGTGCGCTAAACTTTTCTGATAGAGGA
AGCCTGATTAAAGAATGGTCCGTGCTAAGGACTTGTTAGATCTAGTTCACCTCTCCATTTAATAATTATATGCTAT
TTCTATATTTTCATTCTCCTATCACCTGTCTTGCCTTTTTCATTATTTTATTATGAACTTGTGTAAATACAATT
TTGTTTCTGTACTTTTTTGGCATAACATAAATCTGTGAACCTTGAATTTGAATTTTGTGTTAGAGATTTTTTTGTT
GTTTGTGTTAGTCTTGTCTCAGATTTTATTATGTAAATCCCATTTATCAAAGTTGCCTAAATCCATTTGGAAATCT
TTAAAAAAAATTTGGGGATTCTTAAAGTTGAATTTATTGGCTTTTCTGATCCAGTTTTGTTTGGACCAAAAACC
AGTATTGTACAAAGTATTAAGCATATATTTTATATTTACTAAAATGGTCTGTGGTGACTTTTGGATAATAAGGA
AAAGTTTAAATATTAAGCCATGTTTATTACAGTATAATTAACATGTAAACCATGGGATAAATGCCATCAATAAA
AAATTATGACAT

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FIGURE 33

MASGAGGVGGGGGKIRTRCHQGP IKPYQQGRQQHQGILSRVTESVKNIVPGWLQRYFNKNEDVCSCSTDTSEV
PRWPENKEDHLVYADEESSNITDGRITPEPAVSNTTEPSTTSTASNYPDVLT RPSLHRSHLNFMSLESPALHCQP
STSSAFPIGSSGFSLVKEIKDSTSQHDDDNISTTSGFSSRASDKDITVSKNTSLPPLWSPEAERSHLSQHTATS
SKKPAFNLSAFGTLSPSLGNSSILKTSQLGDSFPYPGKTTYGGAAA AVRQSKLRNTPYQAPVRRQMKAKQLSAQS
YGVTSSTARRILQSLEKMSSPLADAKRIPSIVSSPLNSPLDRSGIDITDFQAKREKVD SQYPPVQRLMTPKPVSI
ATNRSVYFKPSLTPSGEFRKTNQRIDNKCSTGYEKNMTPGQNRQRESGFSYPNFS LPAANGLSSGVGGGGGKMR
RERHAFVASKPLEEEEMEVPVLPKISLPITSSSLPTFNFSSPEITTSSPSPINSSQALTNKVQMTSPSSSTGSPMF
KFSSPIVKSTEANVLPSSIGFTFSVPVAKTAELSGSSSTLEPIISSSAHHVTTVNSTNCKKTPPEDCEGPFRPA
EILKEGSVLDILKSPGFASPKIDSVAQAQTATSPVVYTRPAISSFSSSGIGFGESLKAGSSWQCDTCLLQNKVTD
NKCIAQAAKLSPRDTAKQTGIETPNKSGKTTLSASGTGFGDKFKRPVIGTWDCDTCLVQNKPEAIKCVACETPKP
GTCVKRALTLTVVSESAETMTASSSSCTVTTGTLGFGDKFKRP IGWECSVCCVSNN AEDNKCVCSCMSEKPGSSV
PASSSSTVPVSLPSSGSLGLEKFKKPEGSDWCELCVQNKADSTKCLACESAKPGTKSGFKGFD TSSSSSNSAAS
SSFKFGVSSSSSGPSQTLTSTGNFKFGDQGGFKIGVSSDSGSINPMSEGFKFSKPIGDFKFGVSSSESKPEEVKDD
SKNDNFKFLSSGLSNPVSLTPFQFGVSNLGQEEKKEELPKSSSAGFSFGTGVINSTPAPANTIVTSENKSSFNL
GTIETKSASVAPFTCKTSEAKKEEMPATKGGF\$FGNVEPASLPSASVFLGRTEEKQQEPVTSTSLVFGKKADNE
EPKCQPVFSFGNSEQTKDENSSKSTFSFSMTKPSEKESEQPAKATFAFGAQTSTTADQGAAPVFSFLNNSSSSS
STPATSAGGGIFGSSTSSSNPPVATFVFGQSSNPVSSSAFGNTAESSTSQSLLFSQDSKLATTSSTGTAVTPFVF
GPGASSNNTTTSGFGFGATTSSSAGSSFVFGTGP SAPSASP AFGANQTPTFGQSQGASQPNPPGFGSISSTAL
FPTGSQPAPPTFGTVSSSSQPPVFGQQPSQSAFGSGTTPNSSSAFQFGSSTTNFNFTNNSPSGVFTFGANSSTPA
ASAQPSGSGGFPFNQSPA AFTVGSNGKNVFSSSGTSFSGRKIKTAVRRRK

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FIGURE 34

CGCTAAGCGTCCCAGCCGCATCCCTCCCGCAGCGACGGCGGCCCGGGACCCGCGGGCTGTGAACCATGAACACCC
GCAATAGAGTGGTGAACCTCCGGGCTCGGGCGCTCCCTGCCTCCCGCCCGACCCGGGATCCCCAGGACCCCTTCTG
GGCGGCAAGGGGAGCTGAGCCCCGTGGAAGACCAGAGAGAGGGTTTGGAGGCAGCCCCTAAGGGCCCTTCGCGGG
AGAGCGTCGTGCACGCGGGCCAGAGGCGCACAAAGTGCATACACCTTGATAGCACCAAATATAAACCGGAGAAATG
AGATACAAAGAATTGCGGAGCAGGAGCTGGCCAACCTGGAGAAGTGGAAAGGAGCAGAACAGAGCTAAACCGGTTC
ACCTGGTGCCAGACGGCTAGGTGGAAGCCAGTCAGAACTGAAGTCAGACAGAAACAACAACCTCCAGCTGATGC
AATCTAAATACAAGCAAAAGCTAAAAAGAGAAGAATCTGTAAGAATCAAGAAGGAAGCTGAAGAAGCTGAACTCC
AAAAAATGAAGGCAATTCAGAGAGAGAAGAGCAATAAACTGGAGGAGAAAAAAGACTTCAAGAAAACCTTAGAA
GAGAAGCATTTAGAGAGCATCAGCAATACAAAACCGCTGAGTTCTTGAGCAAACCTGAACACAGAATCGCCAGACA
GAAGTGCTGTCAAAGTGCTGTTTGTGGCCCAACAATCCTCAACATGGGCCAGAAGCTGGGCTTACAGAGATTCTC
TAAAGGCAGAAGAAAACAGAAAATTGCAAAAGATGAAGGATGAACAACATCAAAAGAGTGAATTACTGGAAGTGA
AACGGCAGCAGCAAGAGCAAGAAAGAGCCAAAATCCACCAGACTGAACACAGGAGGGTAAATAATGCTTTTCTGG
ACCGACTCCAAGGCAAAAGTCAACCAGGTGGCCTCGAGCAATCTGGAGGCTGTTGGAATATGAATAGCGGTAACA
GCTGGGGTATATGAGAAAAATATTGACTCCTATCTGGCCTTCATCAACTGACCTCGAAAAGCCTCATGAGATGCTT
TTTCTTAATGTGATTTTGTTTCAGCCTCACTGTTTTTACCTTAATTTCAACTGCCCACACACTTGACCGTGCAGTC
AGGAGTGACTGGCTTCTCCTTGTCCTCATTTATGCATGTTTGGAGGAGCTGATTCCTGAACCTCATATTTAACTC
TACTGCCAGGGAATGCTACATTATTTTTCTAATTGGAAGTATAATTAGAGTGATGTTGGTAGGGTAGAAAAAGA
GGGAGTCACTTGATGCTTTCAGGTTAATCAGAGCTATGGGTGCTACAGGCTTGTCTTTCTAAGTGACATATTCTT
ATCTAATTCTCAGATCAGGTTTTGAAAGCTTTGGGGTCTTTTATGATTTTAAATCCCTACTTTCTTTATGGTACA
AATATGTACAAAAGAAAAAGGTCTTATATTCTTTTACACAAATTTATAAATAAATTTTGAATCCTTCTGTAAAA
AAAAAAA

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FIGURE 35

MNTRNRVNSGLGASPASRPTRDPQDPSGRQGELSPVEDQREGLEAAPKGPSRESVVHAGQRRTSAYTLIAPNIN
RRNEIQRIAEQELANLEKWKEQNRAPVHLVPRRLGGSQSETEVRQKQQLQLMQSKYKQCLKREESVRIKKEAEE
AELQMKKAIQREKSNKLEEKRLQENLRREAFREHQYKTAEFLSKLNTESPDRSACQSAVCGPQSSTWARSWAY
RDSLKAEENRKLQKMKDEQHQKSELLELKRQQQEQERAKIHQTEHRRVNNAFLDRLQGKSQPGGLEQSGGCWNMN
SGNSWGI

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FIGURE 36

AGTGTCTCCTGATACCCGGATGTGAGGCGATCCGCTGGCGCTAGTCTGACCCCTCCGCCAGGCAAAAGGAAGAAGC
TGAAACCTATCAACACTCTTCAAAAATGCAATGGAATGTACCACGGACTGTATCTCGACTGGCACGCAGGACATGC
TTGGAACACATAATGCTGGTCTCTTTGGACACTGTCAAAATGTAAAGGGACCTTTACTTTTATACAATGCTGAA
TCCAAAGTGGTTTTTGGTACAAGGCCCTCAAAAACAATGGTTGCATTTATCTGCTGCCCAGTGTGTTGCAAAGGAA
AGGAGGCCATTGGATGCTCATCCACCCCAACCAGGAGTCCCTTCGCCATAAGCAAGGGAAGCAACATGTTTCATTC
AGGAGGGTTTTTTCATCCAGTGCCACAGCTCAGGGAACCTCCGGAAGGGAAGAGCCTGATCCTTTGCAAGAC
AAATCTATTAGTCTTTATCAACGATTCAAGAAGACATTTAGACAGTATGGAAAAGTTCTGATTCCAGTGCATCTA
ATAACTTCGGTGTGTTGGTTTGGAACATTTTATTA TGCAGCCTTGAAAGGAGTGAATGTCGTTTCTTTTCTAGAA
CTCATTGGGTTACCTGACAGTGTGGTAAGCATCCTGAAAACTCCCAGAGTGGAAATGCCCTCACAGCATATGCC
TTGTTTAAAGATTGCAACACCTGCTCGGTATACCGTGACTTTGGGAGGAACATCTGTCACTGTGAAGTATCTGCGC
AGTCATGGCTACATGTCCACGCCGCCACCCGTCAAGGAGTATCTGCAGGACAGGATGGAAGAGACAAAGGAGCTT
ATCACAGAGAAAATGGAAGAAACAAAAGATAGACTCACTGAAAAGTTACAAGAAACCAAAGAAAAAGTTTCCTTT
AAGAAAAAGTGGAATAAGGTGCCTTATATAGCAGTATAGAAAATTCCTGCACTTTAACCCCTTTGGAACTATGG
GCAAAGATACATGTGTCTGATTATTTTTTTGGTTAGTTGCCGAAATATACTAGTTCTCTGAGGGTTAAAGAAGTA
AAATACCTTTTTTAAAGTTAAATATCACTAGAAAAATCAGTGTTATTACAAGGGAAGAAATGAACCCAGTTTAAAG
ATTTGCCATCAGTAGCAGTATTAAGCAGTGGTTAATGTCTTAGAAGTCAGACTTCTTTTTCAAGGTCTTCAGAAC
CACACTTGATTTCTGTTTTGTTGCAGCTGTAATTGACACACACTAGGCAGCTGACTCCTTGAATATCCAGTGTGA
CCCATAAAATAGTCTGTTAATACCGGATCTTAATTTTATGTTATTCATTAAGATTTTAACTATATTAGTACGT
AATTTGGAGACAACTAGCATCATCAAACTGCCTGTAAATAAGGTGTTTAGTCTTTCTATAAAAACAGAATAGA
GCAGTTACCTACCAGTTAAAATATCTTATATGAAGAAAATAGAATAAAGATCCAGTCATATATGTAAATAAGATG
TACTGATTGTACGTAAATGAAAAATGGACCCTTTAAAAATTATTTTTACCTGAAGCTTGTGCATAATTTTTTTAA
GCAATATATATATGGTGATGGTACTTTTCAAAGTGTGTATTAGTGGTGATCACCTCAAACATAAACCTCTGTTG
TGAACCAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

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FIGURE 37

MQWNVPRTVSRLARRTCLEPHNAGLFGHCQNVKGP LLLYNAESKVVLVQGPQKQWLHLSAAQCVAKERRPLDAHP
PQPGVLRHKQGKQHVSFRRVFSSSATAQGTPEKKEEPLQDKSISLYQRFKKTFRQYGKVLIPVHLITSGVWFG
TFYYAALKGVNVVPFLELIGLPDSVVSILKNSQSGNALTAYALFKIATPARYTVTLGGTSVTVKYLRSHGYMSTP
PPVKEYLQDRMEETKELITEKMEETKDRLTEKLQETKEKVSFKKKVE

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FIGURE 38A

GGCACGAGGCTGCGCCTCGGGGGTCGGCGTCCAGGCTCGGAGCGCGGCACGGAGACGGCGGCAGCGCTGGACTAG
GTGGCAGGCCCTGCATCATGGAACTCTTTCTAATGCAAGTGGTACTTTTGCCATACGCCTTTTAAAGATACTGT
GTCAAGATAACCCTTCGCACAACGTGTTCTGTTCTCCTGTGAGCATCTCCTCTGCCCTGGCCATGGTTCTCCTAG
GGGCAAAGGGAAACACCGCAACCCAGATGGCCAGGCACTGTCTTTAAACACAGAGGAAGACATTTCATCGGGCTT
TCCAGTCGCTTCTCACTGAAGTGAACAAGGCTGGCACACAGTACCTGCTGAGAACGGCCAACAGGCTCTTTGGAG
AGAAAACTTGTCTAGTTCTCTCAACGTTTAAAGGAATCCTGTCTTCAATTCTACCATGCTGAGCTGAAGGAGCTTT
CCTTTATCAGAGCTGCAGAAGAGTCCAGGAAACACATCAACACCTGGGTCTCAAAAAAGACCGAAGGTAAATTG
AAGAGTTGTTGCCGGGTAGCTCAATTGATGCAGAAACCAGGCTGGTTCTTGTCAATGCCATCTACTTCAAAGGAA
AGTGAATGAACCGTTTGACGAAACATACACAAGGGAAATGCCCTTTAAATAAACAGGAGGAGCAAAGGCCAG
TGCAGATGATGATCAGGAGGCCACGTTTAAAGCTCGCCACGTGGGCGAGGTGCGCGCGCAGCTGCTGGAGCTGC
CCTACGCCAGGAAGGAGCTGAGCCTGCTGGTGCTGCTGCCTGACGACGGCGTGGAGCTCAGCACGGTGGAAAAAA
GTCTCACTTTTGGAGAACTCACAGCCTGGACCAAGCCAGACTGTATGAAGAGTACTGAGGTTGAAGTTCTCCTTC
CAAAATTTAACTACAAGAGGATTATGACATGGAATCTGTGCTTCGGCATTGGAATTGTTGATGCCTTCCAAC
AGGGCAAGGCTGACTTGTGCGCAATGTCAGCGGAGAGAGACCTGTGTCTGTCCAAGTTCGTGCACAAGAGTTTTG
TGGAGGTGAATGAAGAAGGCACCGAGGCAGCGGCAGCGTCGAGCTGCTTTGTAGTTGCAGAGTGTGCATGGAAT
CTGGCCCCAGGTTCTGTGCTGACCACTTTCTTTTCTTCATCAGGCACAACAGAGCCAACAGCATTCTGTTCT
GTGGCAGGTTCTCATCGCCAATAAGGGTGCCTTACCGTGCCTCGGCCATTTCCTCTTCTGTGTCCCCAGAT
CCCCACTACAGCTCCAAGAGGATGGGCCTAGAAAGCCAAGTGCAAAGATGAGGGCAGATTCTTACCTGTCTGCC
CTCATGATTTGCCAGCATGAATTCATGATGCTCCACACTCGCTTATGCTACTTAATCAGAATCTTGAGAAAATAG
ACCATAATGATTCCCTGTTGTATTTAAATTGCACTCCAAATCCCATAGGATGGCAAGCAAAGTTCTTCTAGAATT
CCACATGCAATTCCTCTGGCGACCTGTGCTTTCTGACACTGCGAATACATTCTTAACCCGCTGCCTCAGTG
GTAATAAATGGTGCTAGATATTGCTACTATTTTATAGATTTCTGGTGCTTAGCCTTATAAAAAAGGTTGTAAAA
TGTACATTTATATTTTATCTTTTTTTTTTTTTTTTTCTGAGACGCAGTCTGGCTCTCTGTGCGCCAGGCTGGAG
TGCAGTGGCTCGATCTCTGCTCACTGCAAGCTCCGCCTCCCGGGTTACAGCCATTCTCCTGCCTCAGCCTCCCGA
GTAGCTGGGACTACAGGCGCCCGCCACCACGCCCCGGCTAATTTTTTGTATTTTTTAGTAGAGACGGGGTTTTACCG
TGTTAGCCAGGATGGTGTGATCTCTCTGACCTCGTGATCCACCCGCTCGGCCTCCCAAAGTGCTGGGATTACAG
GCTTGAGCCACCGCGCCCGGCTATATTTTATCTTTTATCTTTTCTTTGACATTTACCAATCACCAAGCATGCAC
CAAACACTGCTTTAGGCACTGGGGACACAAAGGGGACAGAGCCATCCTCCTTTGACACCTGGTCTTCAGTTCTGT
GCCCCAAGTATATAGTTTTGACAATGACCAGGTTGGACTGTTTAAATGTCTTTCACTTACCACGTAATCCTCTTG
TAGGGATCACATCTTTCTTTATGATATTGTATTTCTCTACCTCTAACAGTAAAAATTCATTCACCCCTTAAAGC
TCACTTCAAATCTTCTTTGAGAAGTTTTCTTTCTCCGCAACCAGATGTACATATTTGAAGTCTCTTTGTACT
TGGAGGGCACTTCTTTCTGTTAGTCTTTTATTTTATTAATCTCTGTATCCTTAGATAGTCTCCAACAACCA
AAGGTTGGGACTCTGTCTTACATATCTGGGTGCCCTCATAGTGCAGTAATAAGTAAGTTGATTATATACGAGCT
ATGTAACCTATATTTTTTAATGTTGGATATCACTGAGTTTTTTTTTTTAAAGATTTTTTATTGAGGTAACTT
CACATAACATAAAATTAATATTTTAAAGTGAGAAGTTCAGTGCCACTTAGTATTGTTAACAATGTTGCATAACC
ACCACCTTTATTTAAAGTTCAAAAAAAATGTTCTCTCTAAAAGGAAACCCCATCCCATTAAGCAGATACTCTC
CATTCCTTCTTCTCCAGCCCCAGCAACCACCAATCTGCTTCTGTCTCTATGGTTTTATCTATTCTTGCTAT
TTTATATAAATCGAATTGTATGAGACCTTTTGTGTCTGGCTTCTTCACTTAGTACAAGTTTTTGAGATTTATTT
ACATAGTAGCATGTATCAACACTTCATTTTTATGGCCAAATAAAATGTATTATGTGTTTATAGCACAATTTATT
TATCCACTCATTGATGGACTTTGGGTTGTTTCTGACTTTGGCTATTGGGAATAGTGCTGCTATGAATGTT
TGTGTACCTGTATTTGTTGAATGCCTATTTTGCATTCTCTGGGTATATATCTAGGAGTGGAACTGCTGGGTCA
TATGTTAATTCTATGTTTAGCTTTTTGAGGAACAGACAACTGTTTTCCACAGCAGTTGAACCATTCACATTCC
CACCAGCAATGTATGAGAATTCCAATTTCTGTCCACTTCTCACCAACACTTATTATTTTCTTTTCTTTTTTT
AAAAAAAATAAGTTATGGCCATCTTAGTGGGTGTGAAGTGGTATCTCATTGTGTTTTTTATTGCAATTCCTATG
TAATGAGCTAGAACTAAAGTACAACTAGATGGGACATCCAGTCCCTTTGATAGATAATGCTGAGTAAAAAATG
AGATGAAAGACATTTGTTTGTTTTGAACATGAGTGACAGTTTGTAAAGGCTTTAGAGGAGGAATGAAAACA
AAGTGAAGTACACTTAGAAAAGGGCCAAGTGGACATCTGGATGTCAAGTGCTAGTTTCAATCTTTTTTTTTT
TTTTTTTTTTTTTTGAGACAGTGCCTCACTCTGTCAACCAGGCTGGAGTGTAGTGGCATGATCTGGGCTCACTGC

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FIGURE 38B

AACCTCCTCCTCCTGGATTCAAGCAATTCTCTTGCTTCAGCCTCCCAAGTAGCTGAGACTACAAGCACCCACCAC
CACACCCGGCTAATTTTGTATTTTTCAGTAGAGACGGGGTTTCGCCACATTGGCCGTGTTGGTCTTGAACCTCTG
GCCTCAAGCAATCCGCCTACCTCAGCCTCCCAAAGTGCTAGGATTACAGGCATAAGCCACTGAGCCCAGCCCTAG
TTCAGTATCTTTTATGTAAATTATAAACATCTGCAACATTATGTATCATATGCAGATACTTATTGCATTTCTTTT
ATTAGTGGTGAAAGTGTTCTATGCATTTATTGGCTCTTGAATTTCCCTCATCTATGAATTGTCATTACACACCTA
CTTTTCTGCTTCGTTTTTACATATGTCTTTGCCTATTAAAGATATTATCCCTCTGTTTTATATTTTCTCTCATT
TTGTATTGCCTTTTAAATTTTGTTATGATGTTTCAATAAACAGTGTTTTGTTTTCTCTATAAAAAAAAAA
AAAAA

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FIGURE 39

METLSNASGTFAIRLLKILCQDNPSHNVFCSPVSISSALAMVLLGAKGNTATQMAQALSINTEEDIHRAFQSLLT
EVNKAGTQYLLRTANRLFGEKTCQFLSTFKESCLQFYHAELKELSFIRAAEESRKHINTWVSKKTEGKIEELLPG
SSIDAETRLVLVNAIYFKGKWNPFDETYTREMPFKINQEEQRPVQMMYQEATFKLAHVGEVRAQLLELPYARKE
LSLLVLLPDDGVELSTVEKSLTFEKLTAWTKPDCMKSTEVEVLLPKFKLQEDYDMESVLRHLGIVDAFQQGKADL
SAMSAERDLCLSKFVHKSFVEVNEEGTEAAAASSCFVVAECCMESGPRFCADHPFLFFIRHNRRANSILFCGRFSS
P

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FIGURE 40

GGGCACAGCGGACACCAGGACTCCAAAATGGCGTCAGTTGGTGAGTGTCGGGCCCCAGTACCAGTGAAGGACAAG
AAACTTCTGGAGGTCAAAC TGGGGGAGCTGCCAAGCTGGATCTTGATGCGGGACTTCAGTCCTAGTGGCATTTC
GGAGCGTTTCAAAGAGGTTACTACCGGTACTACAACAAGTACATCAATGTGAAGAAGGGGAGCATCTCGGGGATT
ACCATGGTGCTGGCATGCTACGTGCTCTTTAGCTACTCCTTTTCTTCTACAAGCATCTCAAGCACGAGCGGCTCCGC
AAATACCACTGAAGAGGACACACTCTGCACCCCCCACCCACGACCTTGGCCCGAGCCCCCTCCGTGAGGAACAC
AATCTCAATCGTTGCTGAATCCTTTCATATCCTAATAGGAATTAACCTCCAAATAAAACATGACTGGTAAAAAAA
AA

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FIGURE 41

MASVGECPAPVPVKDKKLEVKLGELPSWILMRDFSPSGIFGAFQRGYYRYYNKYINVKKGSISGITMVLACYVL
FSYSFSYKHLKHERLRKYH

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FIGURE 42

AGCCGGCCTGCAACCTGCCGGGGCGGCTCCGCTACGCGCAGCCGCCTCAGTGGCTTCCTCCACAGCCACCTCCGG
AGGGATCTGGCTGAGGAGGAAGTGGAGGTGTCAGTGGCCCCGGCCTTTGCCCAATCTTGTGTGGGCACTGAAGG
GGGACTACAGGTTTCGAGAGTTATGGGTGCTACATGTGTGCTTTCAGAGCAGTAGTGTGAGGAAGCTTGGAGTGGG
ATGGCAGGACGGCCTCATCCCTATGATGGTAACCTCCAGTGATCCAGAGAATTGGGATCGGAAATTGCATAGTAGA
CCTCGTAAACTTTATAAACATTCAAGTACTTCCTCGCGTATTGCTAAAGGAGGAGTTGACCACACCAAAATGAGT
CTACATGGTGTAGTGGGGGACATGAGAGATCAAGAGATAGACGAAGGTCAAGTGACAGATCACGAGATTCTATCT
CATGAAAGAACGGAGTCTCAGCTCACTCCTTGTATTAGAAATGTGACTTCTCCAACACGACAGCACCATTGTTGA
CGAGAAAAAGATCACAGTTTCCTCTCGTCCAAGCAGTCCGCGTCTCAAAAAGCATCCCCAAATGGTTCCATTAGC
AGTGCTGGGAACAGCAGCAGAAACAGTAGTCAGTCAAGTTCAGATGGTAGCTGTAAGACAGCTGGGGAGATGGTG
TTTGTATATGAAAATGCAAAAAGAGGAGCTCGGAATATAAGAACGTCAGAACGAGTGACACTAATAGTGGATAAC
ACTAGATTTGTTGTAGACCCATCCATTTTTACTGCACAGCCAAATACAATGTTGGGCAGGATGTTTGGATCTGGC
CGAGAACATAACTTTACACGACCCAATGAGAAAGGAGAGTATGAGGTGGCAGAGGGAATTGGTTCCACTGTGTTT
CGAGCGATTCTGGATTACTATAAAACAGGAATAATCCGTTGTCTGATGGCATATCTATTCTGAACTGAGAGAA
GCATGTGACTATCTTTGTATCTCTTTTGAATATAGCACTATTAAATGTAGAGATCTCAGTGCCCTAATGCATGAG
TTATCAAATGATGGTGCTCGTAGACAATTTGAATTTTATCTGGAAGAAATGATCCTCCCTCTCATGGTAGCTAGT
GCCAGAGTGGGGAACGGGAATGTCATATAGTGGTGCTTACAGATGATGATGTGGTTGATTGGGATGAAGAATAT
CCACCACAGATGGGAGAAGAATATTCACAAATTATTTATAGCACAAAATTATATAGATTTTCAAGTATATTGAA
AACAGAGATGTGGCCAAGTCAGTTTGAAGGAGAGGGGTCTTAAGAAGATTAGATTGGGAATAGAAGGTTATCCT
ACCTACAAAGAAAAAGTAAAGAAAAGGCCTGGAGGCCGCCAGAAAGTGATCTACAACATATGTCCAAAGACCCTTT
ATTGCAATGTCCTGGGAGAAGGAAGAAGGAAAGAGTCGGCATGTAGACTTTCAGTGTGTAAAGAGTAAATCTATC
ACCAATCTTGCAGCAGCTGCAGCAGACATTCGCCAGGACCAGCTGGTAGTCATGCATCCAACCTCCACAAGTGGAT
GAGCTGGATATTCTCCCTATCCATCCCCCTTCTGGCAACAGTGACCTCGATCCTGATGCACAGAATCCAATGCTG
TGATGCTGATCTTCCTTGAAACCATAGCATGCTACTCTTCACAGTGACGTTGTACTCTCCTCATTCTGCACTGCA
AGGCCACTCTTCTTCATTGTGAGATGCACATAACAATGTTTAGGATATTGCAGTGTAGGCTTTTTTAAAGACCAA
AGGTAGCTGAATGGTTTTTTTTTAAATGAGTACAACCTTAGCATTTTGAAGTTCAGTTGTAAATGTATTTGTTT
ACCAGTAGGTTTGTGAAATTGGTTCTTTGTATGGGGGATGGTTCCTTTTTTACACAGCTAGGTCTTTTTCAGAAGTG
GTGGAAATTGGCAGCTGGGGTACTTTTCAGTTTGGACTGATATTCATCACACCTCAGATAAAATGCAGAGTAATAT
ATAGTTGCACTTTATAAATGGTGGTTAAATGGAAATGTTCAAGCCATTTTATAGTTGTGATGCACAATATAATTT
AAGTGCTTCTGTCAAAGTATTCCTCCAGTACAATTGTATAGTTTGTGCTGCCCTTGATGAGCAAAAAGTATTTATC
TTGGGCTTATCTGAATGATCAGGATGAGATTTAATGCCCATATCTTACCAGTTCAGTTATCTCCAGAGCCATTTT
ACCCTTTAGAGTGAGTCACATGCAGGGAGTGTGAATGTCAGAGGTGGTTTATTATCCAGTCTGCCTTACCCTTAA
TCTGTTTACAGATATTTATTTACTAATGCTTTTTTTTTCTTAAGAGTTATGGGATAGGAAAAATGAAGTGTGTTGCT
CTTCATTTACTAAATGATTGTAAACTTGAGTTTTTTCATCAAAATAAAATTCATTGTTTTAAAAA

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FIGURE 43

MILPLMVASAQSGERECHIVVLTDVVVDWDEEYPPQMGEYSQIIYSTKLYRFFKYIENRDVAKSVLKERGLKK
IRLGIEGYPTYKEKVKKRPGGRPEVIYNYVQRPFIRMSWEKEEGKSRHVDFQCVKSKSITNLAAAAADIPDQLV
VMHPTPQVDELDILPIHPPSGNSDLDPDAQNPML

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FIGURE 44

ATTTTGA CTGGCAAATGTGGCAGATTT CAGGGATGCAGGTGGATCCTTA ACTGAGGTCAAGGTGGAAGAGGAAG
AAAGGGATCCGCAGAGTCCTGAATTTGAAATTGAGGAGGAGGAAGAAATGTTGT CATCCGTCATACCAGATTCCA
GGAGAGAAAAATGAACTTCCCGATTTC CCCCACATTGATGAGTTTTTTACCCTTA ACTCAACACCATCTAGATCTG
CATATGATGAGCCTCATTGCTCGTAAATATTGAGAAACAGAACTAGAGTTGGAAAAACGACGACTGGATATCG
AGGCCGAAAGGCTGCAGGTAGAAAAGGAACGCCTACAAATCGAGAAAAGAGAGGCTGCGGCATTTAGACATGGAAC
ATGAGCGGCTTCAGCTAGAGAAGGAGCGGCTGCAGATTGAAAGAGAAAAGTTGAGGTTACAGATAGTCAATTCAG
AGAAAACCGTCCTTGGA AAAATGAACTTGGTCAAGGAGAAAAATCCATGCTTCAACCACAGGACATAGAAACAGAGA
AGTTAAAAC TTGAGCGAGAACGCTTGCAACTGGAAAAGGATAGGCTGCAGTTTTTTGAAGTTGAATCTGAGAAGC
TGCAGATTGAAAAGGAACGCTTACAGGTAGAGAAAGACAGACTTCGAATTCAGAAAGAAGGACACTTGCAGTGA
TTTTCCAGGCTTCCATTTAGCAAATGTTTGA AAAC TCTAGATTTTTCTCATATCAGGTGATATAATGATGTTGTC
TGGATTAGCTGTGTTTTCTTGTCTAATGT CAGTGTTCAGTAGGAAAAAGTTATATGTGGATAACTGTATGCCTAA
GTAGTATATAAAAGCTGTGCCCTAGCGTAAACAGTATAGCAGAAACTTACTGTGCTGGACTCTTTACCTTATAAT
ATTACATAGAGTCTTGTATTGTCTGTGTACCCAGAGTTTACAATTATGTCCATATAAAATTTAGCCCAGAAAGTT
CTCATCTGGGGTAGATTTTGGCCTTCAGAAGACCAATTTGGTGATGTCTGGAGACATGTTGGGTTGTCAAAACTG
GGGTGGGGAAAAGGTTGCTACTGTGCAATGCATACCTCCTCAACACCCCCCACACTCAGTAAAGAATTTTCCAA
CCCCAAATATCATTAGTCTTGAGGTTGAGAAACCTGTCTTAGCCTAACTGTATACCTCTATAGCTATGTTTTAT
AGTTTTAGAATATTA AAACCTCAGATATTTATGTGGGTAGGTACTTAAATGGCCAAAAACTTTAACTATGAAATG
TTACTGTGTAGTATATTGAATATAGGAAGTGATGAAGATTATAGGTATTTTATTCCCATGTTTCCATCTATAAAT
AGCCTTCTCAGATT CAGAAAACAATACAGAGAACATCAGAAATTTTCTAAAATGGGTCACTTTGAAAAGAATTCT
TTTTCTCACTATTAATGCTTTAGAAAGCAAGACGCAATTTTAAAGCTTTAGTTCCTTTTCTTCAGTCATTGTCTT
AGTTTGGGTACAAAAATGTCATTT CAGTAATGTACTGAAATCTTATAAGTGAATAGTTGAAGCTAGTAAAAATGA
TACCAGTATAAAAAATGGTACTTGTAGTCCATGAGCTTGAACCCAAATGACTGATTGTTTGACTTTTAAATAAGTA
ATAGCAGCCATTTGGGAGTAGGGGGTAGGTGGGGAAGATGTACTCCGTATCAAATAATAATGATGTTGAAATAAT
GATAGTAGGTATGTATTATGGATTGGAGAAGCACTTATTACACTATCTAACCTAATATGTAGAACAATTTCTTGAG
AGTTGTATCTGTCTGTTATTTCTGAATGTGAAGCTCAGAGAAGTGACACAGAGTAAATGGCTGATCTTCTATATTG
TAGTATATTTTGTCTTCCCTCTTCCCTGAGGAACAAAGCACGTATCTTTAGTCTCTTTGATATTTATTCTGAGA
CCAAGGGCTTGCTTGACCTGATGATTTTCCCTTCAGCTCTCTGAAGGTGCTTTTTCCACAATCCAAGTGATTCTGA
TACACACTAAAGTTGAGAATCACTGCACTAGATCACTTTGTGTTTTCTGATTTTCAAGGTTGATACGTAGCTTTA
ATACAGCTCCTCTGTTGACAGTTATTACTTTAATTTGCAATTTGTTCTTGTAGAATGGCTGGAAACTGTGTGT
TGACATTTGAGGATGGGTATGCAAGGAAAAAATATACTTCTGTTTACTTACTCTGACTTTGAAATAGTGTTATTT
TTCTATATCTGAAATAAATGCTTCTACCATAGAAAT

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FIGURE 45

MLSSVIPDSRRENELPDFPHIDEFFTLNSTPSRSAYDEPHLLVNIEKQKLELEKRRLDIEAERLQVEKERLQIEK
ERLRHLDMEHERLQLEKERLQIEREKLRLQIVNSEKPSLENELGQGEKSMLQPQDIETEKLKLERERLQLEKDRL
QFLKFESEKLQIEKERLQVEKDRLRIQKEGHLQ

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FIGURE 46

CTCGAAATTAACCCTCACTAAAGGGAACAAAAGCTGGAGCTCCACCGCGGTGGCGGCCGCTCTAGAACTAGTGGA
TCCCCCGGGCTGCAGGAATTCGGCACGAGGGCAAAATCCCAATATATAATTCTATACCTAGTAAAGATTGTAAAT
AACTAAAACAAAATGATAAGAGCTGTGAAGTGAATTTGATTGCTTACAGAAATCATGAAGTGAATTTTCTTCTC
TTTTTAAAGTGAGCATAAAGACTTAAGTGTATTGTTACCAGAGATATATTTAGATAGTATACATCATTTTGGCAG
GTAATCTTCTAGAACCTTTCATGTACTGTTTCCATCAAGGGAGGGGAAAGAAATAGAAAATATAATTTTATCTATA
TTTTCTTAAATATATCAATCTGTGCACACTCTTTCAGTTTTTTAATTACTCATGTAATATATGACTACATTTT
GCTTGTGTGCTTTTTGAAAACCATCTTCAGTCCCAATATCCTCTGTAGAAGTAATAGTTTTAACTCTCCTAGATC
TTCTTTTAGAGTGTTTTATGAGTGTTTAAATGTAGGAATGTGTATATATTATCTACAGCCACAGGAAATGTATAG
TTACGATTTTTACATACGTGTATGTATATTATTGTACAACCTTGCTATTTCTACTTGGGAGTTTTTTATTTTGGA
CATTACATTTACCTAATCTCTTGTGCACTGTCCAACAGTACTTTGCCTATAATAGACACTTAAGGAAGTTTTCC
TTCTTTTTATTCTTTATAATTACCAACNATGCTGAAAGGAACATCATCCTACATGAGCCCTTTTTGTACATATA
AGGCTCT

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FIGURE 47

GCGCGGACCTTTCAACAAGGGCTTTATTAATTCTCACGCTGCGGCCCTGGAAAGCGATGGAGGTGGCGGCTAATT
GCTCCCTACGGGTGAAGAGACCTCTGTTGGATCCCGCTTCGAGGGTTACAAGCTCTCTCTTGAGCCGCTGCCTT
GTTACCAGCTGGAGCTTGACGCAGCTGTGGCAGAGGTAAAACTTCGAGATGATCAATATACACTGGAACACATGC
ATGCTTTTGGAAATGTATAATTACCTGCCTGTGATTTCATGGTATCAAGACAGTGTCTACTATATTGATACCCTTG
GAAGAATTATGAATTTAACAGTAATGCTGGACACTGCCTTAGGAAAACACGAGAGGTGTTTCGACTTCCTACAG
ATTTGACAGCATGTGACAACCGTCTTTGTGCATCTATCCATTTCTCATCTTCTACCTGGGTACCTTGTGAGATG
GAACTGGAAGATTGTATGTCATTGGAACAGGTGAACGTGGAAATAGCGCTTCTGAAAAATGGGAGATTATGTTTA
ATGAAGAACTTGGGGATCCTTTTATTATAATTCACAGTATCTCACTGCTAAATGCTGAAGAACATTCTATAGCTA
CCCTACTTCTTCGAATAGAGAAAGAGGAATTGGATATGAAAGGAAGTGGTTTCTATGTTTCTCTGGAGTGGGTCA
CTATCAGTAAGAAAAATCAAGATAATAAAAAATATGAAATTATTAAGCGTGATATTCTCCGTGGAAAGTCAGTGC
CACATTATGCTGCTATGAGCCTGATGGAAATGGTCTAATGATTGTATCCTACAAGTCTTTCACATTTGTTTCAGG
CTGGTCAAGATCTTGAGAAAATATGGATGAAGACATATCAGAGAAAATCAAAGAACCTCTGTATTACTGGCAAC
AGACTGAAGATGATTTGACAGTAACCATACGGCTTCCAGAAGACAGTACTAAGGAGGACATTCAAATACAGTTTT
TGCCTGATCACATCAACATTGTACTGAAGGATCACCAGTTTTTTAGAAGGAAAACCTATTTCATCTATTGATCATG
AAAGCAGTACATGGATAATTAAAGAGAGTAATAGCTTGAGAGATTTCTTGATTAAGAAGAATGAAGGACTGACCT
GGCCAGAGCTAGTAATTGGAGATAAAACAAGGGGAACCTTATAAGAGATTTCAGCCCAGTGTGCTGCAATAGCTGAAC
GTTTGATGCATTTGACCTCTGAAGAACTGAATCCAAATCCAGATAAAGAAAAACCCTTGCAATGCTCAAGAGT
TAGAAGAATGTGATATTTTCTTTGAAGAGAGCTCCAGTTTATGCAGATTTGATGGCAATACATTAAAACTACTC
ATGTGGTGAATCTTGGAAGCAACCAGTACCTTTTCTCTGTCATAGTGGATCCTAAAGAAATGCCCTGCTTCTGTT
TGCGCCATGATGTTGATGCCCTACTCTGGCAACCACACTCCAGCAAACAAGATGATATGTGGGAGCACATCGCAA
CTTTCAATGCTTTAGGCTATGTCCAAGCATCAAAGAGAGACAAAAAATTTTTTGCCCTGTGCTCCAAATTACTCGT
ATGCAGCCCTTTGTGAGTGCCTTCGTCGAGTATTCATCTATCGTCAGCCTGCTCCCATGTCCACTGTACTTTACA
ACAGAAAGGAAGGCAGGCAAGTAGGACAGGTTGCTAAGCAGCAAGTAGCAAGCCTAGAAACCAATGATCCTATTT
TAGGATTTTCAGGCAACAAATGAGAGATTATTTGTTCTTACTACCAAAAACCTCTTTTTAATAAAAGTAAATACAG
AGAATTAAATTATTCTAACATATTGGCCTCTTTGTACTGGAAAAGTATTTCAGTGGTACCTGGAGGTCTGGACAGTT
ATACTGTAACCTCTTAAGTTTTAATGTGCTAAATATATCTTGATGATTTTTTATTTTTAATAACATTGGAAAT
ATATTCAAGAGATTATGATTCTGTAAAGCTGTGGAATGAAGCTGCAGATTTAGAGAACATTGGCTTCTGAAAAAA
AAAAAGAGTGAAGATAGTACTAGCAAGTATACTTATTTTTTAAACAGGCTAGAATCTCATGTTTTATATGAAAG
ATGTACAATTCAGTGTTTAAAAATAAAAAATATTTATTGTGTAAAAA

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FIGURE 48

ADLSTRALLILTLRPWKAMEVAANCSLRVKRPLLDPRFEGYKLSLEPLPCYQLELDAAVA EVKLRDDQYTLEHMH
AFGMYNLHCD SWYQDSVYYIDTLGRIMNLTVMLD TALGKPREVFRLP TDLTACDNRLCASIHFSSSTWVTLSDG
TGRLYVIGTGERGNSASEKWEIMFNEELGDPFIIHSISLLNAEEHSIATLLLRIEKEELDMKGS GFYVSLEWVT
ISKKNQDNKKYEIIKRDILRGKSVPHYAAIEPDGNGLMIVSYKSFTFVQAGQDLEENMDEDISEKIKEPLYYWQQ
TEDDLTVTIRLPEDSTKEDIQIQFLPDHINIVLKDHFLEGKLYSSIDHESSTWIIKESNSLEISLIKKNEGLTW
PELVIGDKQGELIRDSAQCAAI AERLMHLTSEELNPNPDKEKPPCNAQELEECDIFFEESSSLCRFDGNTLKTTH
VVNLGSNQYLF SVIVDPKEMPCFCLRHDVDALLWQPHSSKQDDMWEHIATFNALGYVQASKRDKKFFACAPNYSY
AALCECLRRVF IYRQPAPMSTVLYNRKEGRQVGQVAKQQVASLETNDPILGFQATNERL FVLTTKNLFLIKVNTE
N

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FIGURE 49

GGCCTTCAAGCGCGGGACGCGACAAAGTCATGGACCGCAACCCCTCGCCGCCGCCGCCGGGTGCGGACAAGG
AGGAGGAGGAGGAGGTGGCCGGTGGAGACTGCATAGGGAGCACGGTCTACAGCAAACACTGGCTCTTCGGCGTCC
TCAGCGGACTCATCCAGATTGTTAGCCCTGAAAACACCAAATCTAGCTCAGATGATGAGGAGCAGCTGACGGAGC
TTGATGAAGAAATGGAGAATGAAATTTGCAGAGTATGGGATATGTCAATGGATGAGGACGTGGCTTTATTCTCC
AAGAATTTAATGCTCCTGATATATTCATGGGAGTACTGGCCAAGTCCAAGTGTCTCGATTAAGAGAAATCTGTG
TGGGAATTTTAGGTAATATGGCCTGTTTCCAGGAGATATGTGTGTCCATCAGCAGTGATAAAAATCTTGGGCAGG
TGTTATTGCACTGTTTGTATGATTGAGACCCACCTACTCTGCTGGAAACAAGCAGGTTGTTGCTTACTTGCCCTT
CCCAGGCAGAAGTGGCCAGTGTGTTGGGTTGAAAGGATCCAGGAACATCCAGCTATTTATGATAGCATTGCTTCA
TTATGTCAAGTTCAACAAATGTTGACTTGCTGGTGAAGGTGGGGGAGGTTGTGGACAAGCTCTTTGATTGGATG
AGAACTAATGTTAGAATGGGTCAGAAATGGGGCTGCTCAGCCTCTGGACCAACCCAGGAAGAGTCTGAAGAGC
AGCCAGTGTTCGGCTTGTTGCCCTGTATACTTGAAGCTGCCAAACAAGTACGTTCTGAAATCCAGAATGGCTTG
ATGTTTACATGCACATTTTACAACCTGCTTACTACAGTGGATGATGGAATTCAGCAATTGTACATTGCTCTGACA
CTGAAAAAGACATTTGGAATTTACTTTTGGACCTGGTCTGCCATGAATTCTGCCAGTCTGATGATCCACCCATCA
TTCTTCAAGAACAGAAAACGGTGCTAGCCTCTGTTTTTTCAGTGTGTCTGCCATCTATGCCTCACAGACTGAGC
AAGAGTATCTAAAGATAGAAAAAGTAGATCTTCCTCTAATTGACAGCCTCATTTCGGGTCTTACAAAATATGGAAC
AGTGTGAGAAAAACCAGAGAACTCGGCAGAGTCTAACACAGAGGAACTAAAAGGACTGATTTAACCCAAGATG
ATTTCCACTTGAAATCTTAAAGGATATTTTATGTGAATTTCTTTCTAATATTTTTCAGGCATTAACAAAGGAGA
CGGTGGCTCAGGGAGTAAAGGAAGGCCAGTTGAGCAAACAGAAGTGTTCCTCTGCATTTCAAACCTTCTTCCTT
TCTATAGCCCTGTGGTGAAGATTTTATTAAAATCCTACGTGAAGTTGATAAGGCGCTTGCTGATGACTTGGAAA
AAAACCTCCCAAGTTTGAAGGTTGAGACTTAAAACCTGAATTGGAATTACTTCTGTACAAGAAATAAACTTTATT
TTTCTCACTGACAAAAAAAAAAAAAAAAA

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FIGURE 50

MDRNPSPPPPPGRDKEEEEEEVAGGDCIGSTVYSKHWLFGVLSGLIQIVSPENTKSSSDDEEQLTELDEEMENEIC
RVWDMSMDEDVALFLQEFNAPDIFMGVLAISKCPRLREICVGILGNMACFQEICVSISSDKNLGQVLLHCLYDS
PPTLLETSRLLLTCLSQAEEVASVWVERIQEHPAIYDSICFIMSSSTNVDLLVKVGEVVDKLFDLDEKLMLEWVRN
GAAQPLDQPQEESEEQPVFRLVPCILEAAKQVRSENPEWLDVYMHILQLLTTVDDGIQAIVHCPDTGKDIWNLLF
DLVCHEFCQSDDPPIILQEQKTVLASVFSVLSAIYASQTEQEYLKIEKVDLPLIDSLIRVLQNMEQCQKKPENSA
ESNTEETKRTDLTQDDFHLKILKDILCEFLSNIFQALTKETVAQGVKEGQLSKQKCSSAFQNLFPFYSPVVEDFI
KILREVDKALADDLEKNFSLKVQT

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FIGURE 51

TTTTTTTTTAGGCTGTAAAAATGGTAGCTGCTGTTTATTTTTCCAGTTGCCTGGAATTGCCTTTTCATTTGATGC
ATTCCAGCGGTTCTCTTGCTGCCCACATGGGACTCAGTAATGTTATTACATCAATATCTTGAAATGTTTCTTCAT
CTGTGTAATAAAGTAGTTGAAAATAATTTTAAATTATCACATGAGCATTAGTACTTTATAAAAATTGATCTAGAA
GACTCTTTAGAGAATGCTACCAGGTATTGTTTGTCAATAAGAAAACAAAATGAGGCCCTATGATTCTAGGTGAAT
TTTAAAAAATTTTTCCCAAGGAACAATTCTTAAACTTTTCAGTTACAGGGAAGAGAAGAAAATTGTACCTTCT
AACAGTTATTTGTTTTG

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FIGURE 52

AG**ATG**CGCGGTGCAGGTGGTGCAGGCGGTGCAGGCGGTTCATCTCGAGTCTGACGCTTTCCTCGTTTGTCTCAACC
ACGCTCTGAGCACAGAGAAGGAGGAAGTAATGGGGCTGTGCATAGGGGAGTTGAACGATGATACAAGGAGTGACT
CCAAATTTGCATATACTGGAAC TGAAATGCGCACAGTTGCTGAAAAGGTTGATGCCGTCAGAATTGTTACATTC
ATTCTGTATCATCTTACGACGTTCTGATAAGAGGAAGGACCGAGTAGAAATTTCTCCAGAGCAGCTGTCTGCAG
CTTCAACAGAGGCAGAGAGGTTGGCTGAACTGACAGGCCGCCCATGAGAGTTGTGGGCTGGTATCATTCCCATC
CTCATATAACTGTTTGGCCTTCACATGTTGATGTTGCGACACAAGCCATGTACCAGATGATGGATCAAGGCTTTG
TAGGACTTATTTTTCTCTGTTTCATAGAAGATAAGAACACAAAGACTGGCCGGGTACTCTACACTTGCTTCCAAT
CCATACAGGCCCAAAGAGTTCAGAGTCCCTTCATGGTCCACGAGACTTCTGGAGCTCCAGCCAGCACATCTCCA
TTGAGGGCCAGAAGGAAGAGGAAAGGTATGAGAGAATCGAAATCCCAATCCATATTGTACCTCATGTCACTATCG
GGAAAGTGTGCCTTGAATCAGCAGTAGAGCTGCCAAGATCCTGTGCCAGGAGGAGCAGGATGCGTATAGGAGGA
TCCACAGCCTTACACATCTGGACTCAGTAACCAAGATCCATAATGGCTCAGTGTTTACCAAGAATCTGTGCAGTC
AGATGTCGGCAGTCAGCGGGCCTCTCCTACAGTGGTTGGAGGACAGACTGGAGCAAAACCAACAGCATTTCAGG
AATTACAACAAGAAAAGGAAGAGCTTATGCAAGAACTTTCTTCTCTAGAA**TAA**ATCAGGAGACAAAATGGGGAAA
GATGAAAATATCCAGTGTAAGTTACTTAAGCTAAATCAATTTCAAAGAAGAAAACTTGGAGGACTCATTTTAC
CTGACTTCAAGACTTACTATAAAGCTATAGTAATCAAGATAGATGGTATTGGCAGAGGAACAGACACATACGTCA
ATGGAACAGATGAGAGAACCAGAAATAAACCCATATAAATATGCTCAGCTGATTTTGAAAAAGTGAAAAAGCAA
TTCAATGGAGGAAGAATAGCCTTTCTGACAAATTATGCTAGAGCAATTAGACACCCATGGCGAGGAGAAAAAGA
ACCTCTACTTAAACCTCACATCTTATATAAAATTTAACTCAAAATGTATAACGGACTTAAATGTGATACATAAAA
CTAGATAACTTTGAAAAAAGCCACAGGAGAAAAATCTTCAGGATCTTGGGCTAGGTGACAAGTTCTTGGACTTTG
CCCCGAAAGCACATCCATAAAAGACAAAATCTGATATATTGGACTTCTTCAAAATTTAAAACTTGTGATTTAAG
AAGAGGAAAAGATAAGCTACAGATTGAGATGAATTTGCAAACCATATATCTGATCAATTTGGAATATATAAAGTG
TACTAAAACTCAACTGAAGTCAGGCATGGTAGCTCATGCTTGTAATCTCACCCTTTGGGAGGCCAAGATGGGA
GGAGTGCTTGAGGTTAGGCGTTCCAGACCAGCCTGGGCAACATAGTGAGACTCTTGCTCTACAAAAAGTTTTTT
TAAAAAATTAAGTGGGCACCATGACACACACAGTAGTCCCAGCTACTAGGGAGGCAGGAGGATCACTTGAGCCC
AGGAGTTTGAGGCTGCGGTGAGCTGTGATCACACCACCACTCCAACCTGTGTAACAGAGTGAGGCTCATCTC
AAAAAAAAAAAAAGGCCACAAACTCAACAATAAAAAACAAACAGTCCAATTAGAAAATGGGCAAAAGACATGAAT
AGATGTTTCACTGAAGAGGATCTATAGATGGCAAGTAAGCATATGAAAAGCTGTAAACTCCATAAGTCATCAGG
GAATGCAATTGAAACCACAGCGAGGCTATGACTTACTTATCTCAATGGCTAAAGAAAAAATAGTGAAAATACCA
AATACTGATGAGGATACAACTGGATATTTTATACATTGCTGACAGGAATGTAAAATGGTACAGCCACTCTGGGA
AAGAGTTTATGAATTTCTTATCAAGTTAAACATAATTTTTTAATCAAGTTAAACATAAGACCCAGCAGTTGTGCT
CCTGGACATTCAATCCAGAGAAATGAAAACCTATATTGTACTTGTACTCAAATATTCATAGGAGCTTTATTTGTA
ATAGCCCCAACTGGAAACAACCCAGATGTCCTACAAACAGGTACATGGTTAAACAAACCATCCATAACTTGGAAT
ACTGCTCTGGAATGAAAAGGAATACTGTTGATCAAGAAGTTGGTTGTACCTCAGGGGTATTATGGTGAACAA
AAAAAAACCAGTCTCAAATGGTCACATACTGTATGATCGCATTTATATAACATTCTTGAGGTGACAAAATTATT
GAAATGAAGAACAGATTAATGGTTGCCAGGGATAGGGACTGGAGGGGGTGTGGGGTATGTATGACTATAAAGGGA
TGACGCAAGGAGTTTCTTTGTGCTGATGGAACAGTTCTATATGATTATGATGATTACGATGTTGATTATAACATT
TGATTATGAGGTTAAGCACATGAATCTTTACCTGTGCTGAAGTTGTATGGACCTACATACACACAAATGAATGCA
TGTAATACTGGTGATACTGAATAAAGTCTGTAGTCTAGATAGCAGTAAAAAAAAAAAAAAAAAAAAA

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FIGURE 53

MAVQVVQAVQAVHLESDAFLVCLNHALSTEKEEVMGLCIGELNDDTRSDSKFAYTGTEMRTVAEKVDAVRIVHIH
SVIILRRSDKRKDRVEISPEQLSAASTEAEERLAELTGRPMRVVGVYHSHPHITVWPSHVDVRTQAMYQMMDQGFV
GLIFSCFIEDKNTKTGRVLYTCFQSIQAQKSSESLHGPRDFWSSSQHISIEGQKEEERYERIEIPIHIVPHVTIG
KVCLESAVELPKILCQEEQDAYRRIHSLTHLDSVTKIHNCSVFTKNLCSQMSAVSGPLLQWLEDRLQNQQHLQE
LQQEKEELMQELSSLE

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FIGURE 54

CTGCCAGCCGCGCTGCTGCTGCTCCTCCTGCTGTGGGACCGCTGACCGCGCGGCTGCTCCGCTCTCCCCGCTCCA
AGCGCCGATCTGGGCACCCGCCACCAGC**ATGG**ACGCTCGCCGCGTGCCGCAGAAAGATCTCAGAGTAAAGAAAGAA
CTTAAAGAAATTCAGATATGTGAAGTTGATTTCCATGGAGACCTCGTCATCCTCTGATGACAGTTGTGACAGCTT
TGCTTCTGATAATTTTGCAAACACGAAACCTAAATTCAGGTCAGATATCAGTGAAGAAGTGGCAAGTGTTTTTTA
TGAGGACTCTGATAATGAATCTTTCTGCGGCTTTTTCAGAAAGTGAGGTGCAAGATGTATTAGACCATTGTGGATT
TTTACAGAAACCAAGGCCAGATGTCCTAACAAGTGGCCGGTATTTTTTCATGCCGACTCTGACGATGAATCATT
TTGCGGTTTTCTCAGAGAGTGAGATACAAGATGGAATGAGGCTGCAGTCAGTTCGGGAAGGCTGTAGGACCCGCAG
CCAGTGCAGGCACTCTGACCTCTCAGGGTGGCGATGAAGTTTCAGCGCGGAGTACCAGGGGAGCAACCAACAA
AAAAGCAGAGTCCCGCCAGCCCTCAGAGAATTCTGTGACTGATTCCAACCTCCGATTGAGAAGATGAAAGTGAAT
GAATTTTTTGGAGAAAAGGGCTTTAAATATAAAGCAAAACAAAGCAATGCTTGCAAACTCATGTCTGAATTAGA
AAGCTTCCCTGGCTCGTTCCGTGGAAGACATCCCCTCCCAGGCTCCGACTCACAATCAAGGAGACCCGGAAGGCG
TACATTTCCCGGTGTTGCTTCCAGGAGAAACCTGAACGGAGAGCTCGTCTCTTACCAGGTCAAGTCCCAGAT
CCTCGGGTCCCTTGACGCTCTACCCATGGAGGAGGAGGAGGAAGAGGATAAGTACATGTTGGTGAGAAAGAGGAA
GACCGTGGATGGCTACATGAATGAAGATGACCTGCCCAGAAGCCGTCGCTCCAGATCATCCGTGACCCCTCCGCA
TATAATTCGCCCAGTGAAGAAATTACAGAGGAGGAGTTGGAGAAGCTCTGCAGCAATTCTCGAGAGAAGATATA
TAACCGTTCACTGGGCTCTACTTGTCTCAATGCCGTCAGAAGACTATTGATACCAAAACAACTGCAGAAACCC
AGACTGCTGGGGCGTTTCGAGGCCAGTTCTGTGGCCCTGCCTTCGAAACCGTTATGGTGAAGAGGTCAGGGATGC
TCTGCTGGATCCGAACCTGGCATTGCCCGCCTTGTCGAGGAATCTGCAACTGCAGTTTCTGCCGGCAGCGAGATGG
ACGGTGTGCGACTGGGGTCTTGTGTATTTAGCCAAATATCATGGCTTTGGGAATGTGCATGCCTACTTTGAAAAG
CCTGAAACAGGAATTTGAAATGCAAGCA**TAA**TATCTGGAATTTTGTGCTGCCTTCTACTTCTCAAATCTTTT
TTGTAAGTTTCCAATTTTTTCACTGAAACCTGAGTTAAAAATCTTGATGATCAGCCTGTTTCATAAGAAACTC
CAATCAAGTTAATCTTAGCAGACATGTGTTTCTGGAGCATCACAGAAGGTATATTGCTAGTTACACTTTGCCCTC
CTGCAGTTTCTTCTCTGCTCCCAACCCCATCTCATAGCATCCCCCTCTATTTCCAATGCTCCTCTCAACCGCT
TAGTTTCTGAATTTCTTTTAAATTACAGTTTATGAAAGCATATTTTATTTACTTGGTGTGAAATAGCCCTCAT
AAAACCTAAGCACTTGGAACACAATAATAGTATTAACCTAAGTATCTATTGAATTTTCAAGAGAAGAGCCTTCTA
ACTTGTTTACACAAAAACGAGTATGATTTAGCATTCTACTAGTTGAAATTTTTAATAGAATCAAGGCACAAAAG
TCTTAAACCATGTGGAATAATTAGGTAATTATTGCAGATTGATGTCTCTCAATCCCATGTATTGCGCTTATGTT
ACAAGTTGTTGTCACAGTTGAGACTTAATTTCTCCTAATTTCTTCTGCCGAAGGGTAAGTGGTGGTCCAGCTT
ACACAATCATAATTCAAAGTTGGTGGGCAATGTAATACTTAATTAATAATGATGGAAGAGCTATCTGGAGAT
TATGAGTAAGCTGATTTGAATTTTCAGTATAAAACTTTAGTATAATTGTAGTTTGCAAAGTTTATTTCAAGTTTCA
ATGTAAGGTATTGCAATAAATCTTGGACAATTTGTATGGAACTTGATATTAAAACTAGTCTGTGGTTCTT
TGCAGTTTCTGTAAATTTATAAACCAGGCACAAGGTTCAAGTTTAGATTTTAAGCACTTTTATAACAATGATAA
GTGCCTTTTGGAGATGTAACTTTAGCAGTTTGTAACTTGACATCTCTGCCAGTCTAGTTTCTGGGCAGGTTT
CCTGTGTCAGTATTCCCCCTCCTTTGCATTAATCAAGGTATTTGGTAGAGGTGGAATCTAAGTGTGTTGATGT
CCAATTTACTTGATATGTAAACCATGCTGTGCTATTCAATGTTTGATGCATAATTGGACCTTGAATCGATAAG
TGTAATAACAGCTTTTGATCTGTAATGCTTTTATACAAAAGTTTATTTTAATAATAAATGTTTGTCT

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FIGURE 55

MDARRVPQKDLRVKKNLKKFRYVKLISMETSSSSDDSCDSFASDNFANTKPKFRSDISEELASVFYEDSDNESFC
GFSESEVQDVLHCGFLQKPRPDVTNELAGIFHADSDDESFCGFSESEIQDGMRLQSVREGCRTRSQCRHSGPLR
VAMKF PARSTRGATNKKAESRQPSSENSVTDSNSDSEDESGMNFLEKRALNIKQNKAMLAKLMSELESFPGSFRGR
HPLPGSDSQSRRPRRRTFPGVASRRNPERRARPLTRSRSRILGSLDALPMEEEEEDKYMLVRKRKTVDGYMNED
DLPRSRRSRSSVTLPHIIRPVEEITEEELENVCSNSREKIYNRSLGSTCHQCRQKTIDTKTNCRNPD CWGVRGQF
CGPCLRNRYGEEVRDALLDPNWHCPPCRGICNCSCFCRQRDGRCATGVLVYLAKYHGFGNVHAYLKSLKQEFEMQA

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FIGURE 56

GGCACGAGGTTTGTGTCTCTTGTGAACCCACTTGTGGAGCGAGAGGGAATTTGGGAGGGCCAGGGGTTAGTCTGG
CCTCTGTCTTAGCTGTCATTTTGGCGGTTTTTTTTTTTTTTTCTTCAGGGGATTTTCAGTCTCCACATAGTTTTGG
AGCCGGACTTTTGAAGAATGATTTCGTGAATCCGGAATGGGTGACAGCGTCATCACGGCATTTTATTGACAGACCA
TGGATTCTTACAGTGCACCAGAGTCAACTCCTAGTGCATCCTCAAGACCTGAAGATTACTTTATAGGTGCCACTC
CTCTGCAGAAACGATTAGAATCGGTCAGGAAGCAGAGTTCATTTATCCTGACTCCACCTCGAAGGAAAATTCCCC
AGTGTTCGCAGTTGCAGGAAGATGTTGACCCTCAAAAGGTTGCATTCTTCTGCATAAACAGTGGACTTTATATA
GTTTAACTCCCTTATATAAAATTCTCCTATAGTAATCTCAAAGAGTATTCTAGACTTCTCAATGCTTTTTATTGTTG
CTGAAAAGCAAAAAGGACTTGCTGTGGAAGTGGGAGAAGACTTCAACATCAAAGTGATTTTTTCTACTCTCCTAG
GAATGAAAGGAACACAAAAGGGACCCGGAAGCATTCTTGTCCAGATTGTGTCAAAATCTCAATTGCCATCTGAGA
ATAGAGAAGGTAAAGTGCTGTGGACTGGCTGGTTCTGCTGTGTATTTGGAGACAGTCTTCTGGAGACTGTTTCAG
AAGATTTTACCTGTCTGCCCTTATTCTTGCAAATGGAGCAGAGTCTAACACAGCAATAATTGGAACCTGGTTTC
AGAAAACCTTTGACTGTTATTTTCAGTCCTTTAGCAATCAATGCATTTAATCTTTCCTGGATGGCTGCCATGTGGA
CTGCATGCAAAATGGACCATTATGTGGCTACTACTGAATTTCTTTGGTCTGTACCCTGTAGCCCTCAAAGTCTGG
ACATTTCTTTTCGCAATACATCCAGAGGATGCAAAAGCTCTATGGGACAGTGTCCACAAAACACCTGGGGAGGTTA
CCCAGGAAGAAGTTGACCTATTCATGGATTGCCTTTATTCACATTTCCATAGACATTTCAAATTCATTTATCAG
CCACAAGATTAGTTCGTGTTTCAACATCTGTAGCTTCAGCACATACTGATGGAAAAATAAAGATTCTGTGTCATA
AATACCTTATTGGAGTGTTAGCATATTTGACAGAACTGGCAATTTTTCAAATTGAGTGAAGCCTTATGTGGACTA
TAAGTTATAGATTATATACTCTTATTGATAACTGCCTAATTGCTATGCTGAAAGAGACTGCAGGAGAAATAGGC
ATCTATCTCTGCATCTGTTTTCCCCACCATGCCTTTGGAGTTGCCAAGATGGAAGCCAAGAAGGATCTAGAAGAA
CAAAGAATATGGTAGTAGATGAGCCACAGCCAGGTGCCCATGTACTAATCATGATAACCTGACATGCCATTCTCA
AAATGCTGAGTTGTTAATTTCTTGTATCTTTAAATATATATATATAGGCTGGGCTGGTGGCTCACACCTGTAA
TTCCAGCACTTTGGGAGGCTGAGGTGGTGGATCAATTTGAGGCCAGGAATCAAGACCAGCCTGGCCAACATGGT
GAAACCCCTTCTCTACTGAAAATACAATAATTAGCTGGGCGTGGTGGCACATGCCTGTGATCCCAGCTACTGGGG
AGGCTGAGGCAGGAGAATCGTTTTAACCCAGAAGACAGGCTGCAGTGAGCCAAGACTGCACCACTGCACTCCAGC
CTGGGCAACAAAGTGAGACTCTGCCTCAAAAAATAAAAAAAAAAAAAAAAAAAAAAAAAA

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FIGURE 57

MDSYSAPESTPSASSRPEDYFIGATPLQKRLESVRKQSSFILTPPRRKIPQCSQLQEDVDPQKVAFL LHKQWTLY.
SLTPLYKFSYSNLKEYSRLLNAFIVA EKQKGLAVEVGEDFN IKVIFSTLLGMKGTQRDPEAFLVQIVSKSQLPSE
NREGKVLWTGWFC CVFGDSLLETVSEDFTC LPLFLANGAESNTAIIGTW FQKTFDCYFSPLAINAFNLSWMAAMW
TACKMDHYVATTEFLWSVPCSPQSLDISFAIHPEDAKALWDSVHKTPGEVTQEEVDLFMDCLYSHFHRHFKIHLS
ATRLVRVSTSVASAHTDGKIKILCHKYLIGVLAYLTELAIFQIE

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FIGURE 58

CGGAGCTGTAGCGGCACTGTAAC TGCAGGGCAGCGCCGCGTGTGTAA CGGCGGGGGCGTGTGCGCGGGAAGGAC
AATCGGGCCGGGACTCGCGGTGTCCGGGTGACCGCGGCTTCCCGGGAGCAGACCTCTGTGGGCAC TGTGAGGCGG
AACGGAGCGGCGGGG CAGGAGCTGTTCTGGGCAGCCTTCATCCCGCTGGAGTCTACCCCCAAGCCCTTCTCCTC
TTCCCAATTCTTGTACCTTCGAGGAGGCC **ATG**GAAACCCCAACACCTTTGCCGCTGTACCCGCTCCCCGACC
TGCAACCCAGCCCCACGGACAATCCAGATCGAGTTCCACAGCATAGCTCGTCGCTGCTGGAATCTCTGAACCGC
CACAGGCTAGAGGGAAAGTTCTGTGATGTGTCCCTCCTGGTGCAGGGCCGGGAACCTAGGGCTCATAAAGCAGTG
TTAGCTGCTGCCTCTCCTTACTTCCATGACAAGCTGCTTCTGGGGGATGCGCCTCGTCTCACTCTACCGAGTGTC
ATTGAAGCCGATGCCTTCGAGGGGCTGCTCCAGCTCATTTATTAGGGCGTCTCCGCTGCCACTGGATGCTCTT
CCTGCTCATCTCCTTGTGGCCAGTGGCCTTCAAATGTGGCAGGTAGTAGATCAGTGCTCAGAAATTCTTAGAGAA
TTAGAAACTTCAGGTGGTGGAAATTTAGCCCCGTGGAGGAACTCCTACCATGCCCTTCTTTCCACTACATCCTCT
ACAGGAGGCTGGTGCATTGCTCTTCGCCCTTTCCAGACCCAGTACAGTCTCTGCTTCTACTGAAAGCCCTGCT
TCCACTGAGAGCCCTGTGGGAGGGGAGGGAAGTGAAGTGGGAGAAGTGTGCAAATTCAGGTGGAAGAAAGAG
GAGGAGGAGGAAGATGATGATGATGAGGACCAGGGGTGAGCCACACTCTCTCAGACTCCTCAGCCCCAGAGAGTA
TCAGGGGTTTTTCCCCGTCCTCATGGACCCACCCACTGCCCATGACTGCTACTCCCCGAAAGCTTCCAGAGGGT
GAGAGTGCACCACTTGAGCTTCCTGCCCCCTGCACTGCCCCCAAATCTTCTACATTAAGCAGGAACCCCTTC
GAGCCTAAGGAGGAGATATCAGGAAGCGGAAC TCA GCCTGGAGGAGCAAAGGAGGAAACCAAAGTGT TTTCTGGA
GGGGACACTGAAGGGAATGGGGAGCTAGGGTTCTTGTGCTTCAGGGCCAGGGCCAACATCTGGGGGAGGGGGT
CCATCCTGAAACCAAGTGGATCTTCATGGGAATGAAATCCTGTGAGGGGTGGAGGACCTGGGGGAGCAGGCCAG
GCCGTGCATGGGCCTGTGAAGCTAGGGGGGACACCCCTGCAGATGGAAAACGCTTTGGTTGCCCTGTGTGGGAAG
CGGTTTGCACTGAAGCCAAAGCGTGACCGGCACATCATGCTGACCTTCAGCCTTCGGCCTTTTGGCTGTGGCATC
TGCAACAAGCGCTTCAAGCTGAAGCACCATCTGACAGAGCACATGAAGACCCATGCTGGAGCCCTGCATGCCTGT
CCCCACTGTGGCCGTGCGGTTCCGAGTCCATGCCTGTTTTCTCCGCCACCGGGACCTATGCAAGGGCCAGGGCTGG
GCCACTGCCCCACTGGACTTACAAG **TGA**CTGCTGAGGCTATACACTAGCTTCTAGAACAAGATAACCACTGCTGCT
GATGGATACTTTTCCCTCACTGCCATGGCACACCAGTCATGGATCTTGTAAATCATGCCAAGAGAAATAGATACATT
ATGGACCTCTTGTCTTAGATATGGGCCTCTCAGCCTGGCAGATGTGGAAACTCAAATTTCTCGTCCCCTCCAG
GTTTTGGCTAGCCAACCTGCAGGAAAGTGGTTTATAGGCCATTACACTTAAGTTGATCACTTGCCCATGGTGG
ACATTTTTGTGGTGGTGTATGTCCATTAAAGGAAACAGATTTTCAATTATTTAGTGAGAGAAGAGTTAGAGCAAAA
GACAGTGGTAAATGTTTTATTCCGTCTCCATGAGGAATTGAAGGAGTTGGTCTCCACCTAGAGATACATTTGATT
TACAGCTTAAGTAATTAGAGGCTAAGCTCTAAGCTTTTTTCTCTCATTGCTGGAATGATTTAAGCAGAAGTCCT
TTTGTGTACTTTTAAATTTGTATCTTTCCAGGAGCCCCCTCAGATTGTACCTTGCTTTCTCACCATAAGACACCTT
CCCACACTTTTTTAATGTTGTAGCTGAGCACTTTAACAAGTTGAGCATTCCATGTTTTATTCTTAGAACCTTCT
TTAATAGAGGGTCTTCCCTCAACAGCCTGTCCCTCTGGTCTACCTTTGACCACCACTGATAACTAATATATTGGT
CACAATGACTGGAATGTGACTAGTGATCTCAGGAGATGGCACTGTCTTAAAGTGTGCTGTGAGGGTGGCACCCTGC
TCTCTGAACAACTTACCTTGGTCAGAGGGACTCAGGTTTGGGACAGCACAAGCTGAAGGCTGGAGAGTAACTTGC
ATAGTAGGACCATACTCTTCCCTTTCCATCCCACCCACATATGATAGACAGCCCCCTCTGTTGAGATATGGAGGG
GACAGATACTGGAATCGGGGGTGGGACTTGCAGTTACTTAAATTTTTTAATAAACTGTGCCCTGAAACCTAAAA
AAAAAAAAAAAAAAAAAAAA

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FIGURE 59

METPTPLPPVPASPTCNPAVRTIQIEFPQHSSSLLLESINRHRLEGKFCDVSLVQGRELRAHKAVLAAASPYFHD
KLLLGDAVRTLTLSVIEADAFEGLLQLIYSGRLRLPLDALPAHLLVASGLQMWQVVDQCSEILRELETSGGGISA
RGGNSYHALLSTTSSTGGWCIRSSPFQTPVQSSASTESPASTESPVGGEGSELGEVLQIQVEEEEEEEEDDDDED
QGSATLSQTPQFQRVSGVFPRPHGPHPLPMTATPRKLPEGESAPLELPAPPALPPKIFYIKQEPFEPKEEISGSG
TQPGGAKEETKVFSGDTEGNGELGFLPSGPGFTSGGGGPSWKPVDLHGNEILSGGGPGGAGQAVHGPVKLGG
TPPADGKRFGCLCGKRFAVKPKRDRHIMLTFSLRPFGCGICNKRFKLKHHLTEHMKTHAGALHACPHCGRRFRVH
ACFLRHRDLCKGQGWATAHWYK

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FIGURE 60

TCGGCATGGTGTACCTGGTCCTCAGCCTCGGCATGGTGTACCTGGTCCTCAGCCTCGGCATGGTGTACCTGGTCC
TCAGCCTCGGCATGGTGTATCTGGTCCTCAGCCTCGGCATGGTGTATCTGGTCCTCAGCCTCGGCATGGTGTATC
TGGTCCTCAGCCTCGGCATGGTGTATCTGATCCTCAGCATAGTGTATGTAGTACTCAACCTCAGCATGGTGTATC
TGGTCCTCAGCCTCAGTATAGTGTATCTGGTCCTCAGCCTCAGCATAGTGTATCTGGTCCTCAGCCTCAGCATAG
TGTATCTGGTCCTCAGCCTCAGCATAGTGTATCTGGTCCTCAGCCTCAGCATAGTGTATCTGGTCCTCAGCCTCA
GCATAGTGTATCTGGTCCTCAGCCTCGGCATGGTGTATCTGATCCTCAACCTCAGCATAGTGTATCTGATGACAC
TTTGACCTATCTTTCCCAAATGATGTAAATGCTCCTGTGAGTTTCTGCTGCAGTAAATAGCTCTTCCTTTATTC
ACAGAAAGGAATAAGTTACATGGACTCCTTAGATTTATTATTTAAAGCATGATGGACCATTATGCTGATTCTGT
TTTTAATGTTATTTCACTTTGGAATTAGTCTTGTTCCCCGGGAAATCATTTCCTGGCTTCTAAGTTGACAGTTC
TCTGTTATTTGTTGTGCCTGAAAAGTTTGGTACAACCAGGCTAACAGAGGCAGTTAGTGCAGATGATGATGTCAA
AAATCTCTTTATAGGCTGAGCATGGTGGCTCACACCT

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FIGURE 61

MVYLVLSLGMVYLVLSLGMVYLVLSLGMVYLVLSLGMVYLVLSLGMVYLILSIVYVVLNLSMVYL
LSLSIVYLVLSLSIVYLVLSLSIVYLVLSLSIVYLVLSLSIVYLVLSLSIVYLVLSLGMVYLILNLSIVYLMTL

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FIGURE 62

GTCAGGGCCAAGGTCCTCTGCCTGAGTCCTGAGAGCAGCGCAGAGGCCTTGGAGGCTGCAGTGTCTCCGATGGAT
TACCCTGCGTCCTATAGCCTTGCAGGCACCCAGCACATGGAAGCCCTGCTGCAGTCCCTCGTGATTGTCTTACTC
GGCTTCAGGTCTCTCTTGAGTGACCAGCTCGGCTGTGAGGTTTTAAATCTGCTCACAGCCCAGCAGTATGAGATA
TTCTCCAGAAGCCTCCGCAAGAACAGAGAGTTGTTTTGTCCACGGCTTACCTGGCTCAGGGAAGACCATCATGGCC
ATGAAGATCATGGAGAAGATCAGGAATGTGTTTTACTGTGAGGCACACAGAATTCTCTACGTTTGTGAAAACCAG
CCTCTGAGGAACTTTATCAGTGATAGAAATATCTGCCGAGCAGAGACCCGAAAACCTTTCCTAAGAGAAAACTTT
GAACACATTCAACACATCGTCATTGACGAAGCTCAGAATTTCCGTACTGAAGATGGGGACTGCTATGGGAAGGCA
AAAAGCATCACTCGGAGAGCAAAGGTGGCCCAGGAATTCTCTGGATCTTTCTGGATTACTTTCAGACCAGCCAC
TTGGATTGCAGTGGCCTCCCTCCTCTCTCAGACCAATATCCAAGAGAAGAGCTCACCAGAATAGTTCGCAATGCA
GATCCAATAGCCAAGTACTTACAAAAAGAAATGCAAGTAATTAGAAGTAATCCTTCATTAAACATCCCCACTGGG
TGCTCGAGGTATTTCTGAAGCCGAATGGTCCCAGGGTGTTCAGGGAACCTTACGAATTAAGAAATACTTGACT
GTGGAGCAAATAATGACCTGTGTGGCAGACACGTGCAGGCGCTTCTTTGATAGGGGCTATTCTCAAAGGATGTT
GCTGTGCTTGTGTCAGCACCGCAAAAGAAGTGGAGCACTATAAGTATGAGCTCTTGAAAGCAATGAGGAAGAAAAGG
GTGGTGCAGCTCAGTGATGCATGTGATATGTTGGGTGATCACATTGTGTTGGACAGTGTTCGGCGATTCTCAGGC
CTGGAAGGAGCATAGTGTTGGGATCCATCCAAGGACAGCTGACCCAGCTATCTTACCCAATGTTCTGATCTGT
CTGGCTTCCAGGGCAAACAACACCTGTATATTTTTCCGTGGGGTGGCCATTAGGAAAGAACTCCAAATCAAAATG
CTATGTAAATGTCTATGGGTGACAGTCTGCTGATGGTAGAAACCTTTCTTTTTAGTTCACAAGTCAGAGATTG
ACGGAGCTGACACAAAGAGTTTGGAGCTCCCCATTTCTGGCTCTCCTTTTCAGGGGTTCCCTTCCCCAACCCCTTT
CAGCAGCGGTGGCTGCCCCCATTTCTGACCCCTGACTCTTCCAGCCAGAAAGATGGTGGTTTTCTAAAGGAACCT
TAGCTGTCTGCACAATGCCGATCTGTGTCTTGCAATTTGGGTAAAGCCATAAAAAATAAGAAACTCAGCCTGTG
GCCTTTCTTTCTTCCAAGGCTGGGCTTCTTTTTTTAAGTGACTTCATGCAGTTTGTGCTTTTAAAAATTTGTCC
AGAATCGTTTTCTGCAGAAGCATGGTCTGTTAGGAGCTTACTGGCCGTAGCAGAAGCAATTGTTTCCTGAATTCT
TGACATTTATCTTTGCTGTATTTCATTTAGGGCTTGGGAGAGTCCGAAGATAATTCAGTCACTGTGATTAATAA
TTTTGTGTCAGGACAAAGAATACCGTTATGATTATTTAATCCTTTAAATTTGTGGTCTCCAGAGCTTGTCTCAGAA
TGGCCAGACCAAGCCTTAATTGTGATAGTGAATTAATGGTCACTTTAAGGAGAAATTATAGGCCAAGATGAA
ATGAACATAAACCTGTTTGCCTGGCTTTTCACTGGAAGATGATATTAGAGACCAAAATCTGGTCTGAAGGTGTG
TATCAGCCCTAAGGTGAACCAGACTTGGGAAAGATGTCTTTAAAAATCAATGAGTTTATGTTTTAACTTCTCAG
CTTAGTTCTATGCATTGCTCTATAACACACCTAGTAAAGTTTATGTTATTTCTGAACTGTGATTTTTTTCTAT
TTACTTTTCATGGTTTGGTGGGCCATTGTTATGGACTGAATGTTTGTGTCCACCCTTCACCCCAAATTCCTCGTG
TTGAAGCCCCAACCTGCACTGTGGAGCTGGGGCTGCTAAGGAAGTAATTAAGGTTACATGAAGTCATGGTGGGGC
TCTGATCTGCTAAGGTTGGTGTCTTATAGGGAGAGACCCAGAGAGCTTGTTCCTCCCTCCCTGTGCATGCAA
ACAAGAGGGCATGGGAGCACACAGAGAGATGGCAGCCACCTACAAGCCAAGAGGAGAAGCCTCACAATCAAACCTC
TCGCTGCTGGCGAGAGTCTTGGACTCTGTCTTGGACTTCCAGCCTCCAGACTGTGAGAAACAAATTTCTGTTGTT
TCAGCTTCTCAGTCTCTGGTGTGTTTGTATTGCAGCCTGAGAACACAGCTGTACGATTATTTGTCAAACAGAAAA
CACTGATACTTAACAATGCTAATGCAATTATTTATTTGCTTTTCAGTCTCTACAAAACGTTCTAAAAACATAATC
TAAATATTAACAGTAAATATTTGCATAACTAATGAAACTAAGAAATCATATGACCAATATTTCACTTATTGGT
AATCTTACTCTACTGATTTCCCCCAGACTGTGATTTTTGAACTTCCTTGCCTTTCTCCTGTCTTTCTGTGTTA
TTCATGGAATTCAGTTATCTGGGCTTGAAATTGCAGGCTCTCCTAACTTAAGCAAAATCTGACAGATCAGCAAA
ATGAGATAAAATGTTTCTTTTTTCTTTCTGACTGCATTAAATCAGATACAACTCAGCATTAAAAAGCTATCTTTGT
AAATGTTGTACTAATAAATTAGTCTTATAAGATCCCTGGACTTTGGAGTTGTTGCAATGTCTTTGAGAGTAATT
CTTTAAAGTNTAATTTGCACTGGTTGTATCTCTTTATGATTTATTGCCCCACTAACAATATTTGAAACAATATA
ATATTTTAAATGTATAAATAATTATGAATTTTGTGTTAGAACAAAGAGGATTACTGATATTTGTTCCCTATGA
ATGGCAAAAGGTTTAGCTTACTACTGCATTTCTGTTTTAAATAAAAAGTTGAGAGTTTGTGTNTCATTAACCTGA
AAAAAAAAAAAAA

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FIGURE 63

MDYPASYSLAGTQHMEALLQSLVIVLLGFRSLLSDQLGCEVLNLLTAQQYEIFSRSLRKNRELFVHGLPGSGKTI
MAMKIMEKIRNVFHCEAHRILYVCENQPLRNFISDRNICRAETRKTFLRENFEHIQHIVIDEAQNFRTEDGDWYG
KAKSITRRAKGGPGILWIFLDYFQTSHLDCSGLPPLSDQYPREELTRIVRNADPIAKYLQKEMQVIRSNPSFNIP
TGCLEVFPEAEWSQGVQGTLRICKYLTVEQIMTCVADTCRRFFDRGYSPKDVAVLVSTAKEVEHYKYELLKAMRK
KRVVQLSDACDMLGDHIVLDSVRRFSGLERSIVFGIHPRTADPAILPNVLICLASRAKQHLYIFPWGGH

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FIGURE 64

TGGTAATAAGTGTCTACAACAAAATTCCCTTCCTTCATTGAAATAGACAGGTCTTTGCTCGACAGCTGGACAGAC
CATAACGACCATACCAAGGGACCTGGCATTTCCTGTAAGGTGCTGAGGAGGACTGAGTTGAGTTTACCAAATCAGC
CTTCTTGACCCTTCGGCTTAGCATTTCAGTCATTGACATTCTCTTATACCTGTGCCGCTGATCTCTAGACCTG
CCATGAGTGTGAAAGAGGCTTCGTTTTTTAGTGACACTTTACCCAACCAATTTCACTCAAGAATCTTCATATTC
TATTGTCTCACAATCAGAATAAATTGGCATTTCCTCACTCAGTCTACTAGGTGCTTTAATTGTGTTTAGAAATA
GCCTTTTGATTCTTTTGATTGTGTTTTTGCCCTAAGAGTCTTGATTTCGTACTAAATTACCTGACAAAACCTCA
CTCTCTCCAACATCAATTAAAGGGATTTAAAAATATAATTACACTTAAACACTAGAAAGAGTCAAGTTTTTAG
CATATGTTATGGCTTGCCAGTACGAGAAAAGTGA

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FIGURE 65

MSVKEASFFSDTLPNQFSLKNLHILLSHNQNKLAFFSSLSLLGALIVFRNSLLILLDLFFALRVLISVLNYLTKLT
LSNIN

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FIGURE 66

CACGAAGTTCTCGCGAGAGTCGTCTCCTCGATACCAAGCGCCTGTGTCTGGCAGAGCTGGTGTGAGACGAGACAA
TCCTGCCCCGCCGCCGGGATAATCAAGAGTTTTGGCCGGACCTTTGAGCATAACCGAGAGAGTGAGGAGCCAGA
CGACAAGCACACACTATGCGCTGAAACGGATTAATAAGGAACCTTAGTGATTTGGCCCGTGACCTCCAGCACAA
TGTTCTGCAGGTCCAGTTGGGGATGATATGTTTCATTGGCAAGCCACAATTATGGGACCTAATGACAGCCCATAT
CAAGGCGGTGTATTCTTTTTGACAATTCATTTTCCTACAGACTACCCCTTCAAACCACCTAAGGTTGCATTTACA
ACAAGAATTTATCATCCAAATATTAACAGTAATGGCAGCATTGTCTCGATATTCTAAGATCACAGTGGTGCCT
GCTTTACAATTTCTAAAGTTCTTTATCCATTTGTTTCACTGCTATGTGATCCAAACCCAGATGACCCCTAGTG
CCAGAGATTGCACGGATCTATAAAACAGACAGAGATAAGTACAACAGAATATCTCGGGAATGGACTCAGAAGTAT
GCCATGTGATGCTACCTTAAAGTCAGAATAACCTGCATTATAGCTGGAATAAACTTTAAATTACTGTTCTTTTT
TGATTTTCTTATCCGGCTGCTCCCCTATCAGACCTCATCTTTTTTAATTTTATTTTTTGTTTACCTCCCTCCATT
CATTCACATGCTCATCTGAGAAGACTTAAGTTCTTCCAGCTTTGGACAATAACTGCTTTTAGAACTGTAAAGTA
GTTACAAGAGAACAGTTGCCCAAGACTCAGAATTTTTAAAAAAAAAAAAATGGAGCATGTGTATTATGTGGCCAATG
TCTTCACTCTAAGTTGGTTATGAGACTAAAACCATTCCTCACTGCTCTAACATGCTGAAGAAATCATCTGAGGGG
GAGGGAGATGGATGCTCAGTTGTCACATCAAAGGATACAGCATTATTCTAGCAGCATCCATTCTTGTTTAAAGCCT
TCCACTGTTAGAGATTTGAGGTTACATGATATGCTTTATGCTCATAACTGATGTGGCTGGAGAATTGGTATTGAA
TTTATAGCATCAGCAGAACAGAAAATGTGATGTATTTTATGCATGTCAATAAAGGAATGACCTGTTCTTGTTCTA
CAGAGAATGGAAATTGGAAGTCAAACACCCCTTTGTATTCCAAAATAGGGTCTCAAACATTTTGTAATTTTCATTT
AAATTGTTAGGAGGCTTGGAGCTATTAGTTAATCTATCTTCCAATACACTGTTTAATATAGCACTGAATAAATGA
TGCAAGTTGTCAATGGATGAGTGATCAACTAATAGCTCTGCTAGTAATTGATTTATTTTTCTTCAATAAAGTTGC
ATAAACCAAAAAAAAAAAAAAAAAA

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FIGURE 67

MALKRINKELSDLARDPPAQCSAGPVGDDMFHWQATIMGPNDSPYQGGVFFLTIHFTDYPFKPPKVAFTTRIYH
PNINSNGSICLDILRSQWSPALTISKVLLSICSLLCDPNPDDPLVPEIARIYKTDRDKYNRISREWTQKYAM

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FIGURE 68

GGCACGAGGTGATTTTCCTACTCCACTGTTACTGGANCCACCAAGGCAGGAACTGTGTCTCTTTACCACTACAGT
TCCTGTATCTTTTAGGTGCGTAGTATTTCTTGGTGAGTCAGTCAGTCTCCAGACTCAGTCATTTTCTCTACATT
ACACATTCTTTCACATTCTTCTCCCACCAGTCTTCCTAGACTTGTTTCATTCTTCCCATCTTGTCTCTATGTAT
CTCTTCCCACCATTTCATTTTCCAGATAGCATCTAGACTGTTGTGTTAAAAAGCAAACTCCTTTCACACCACATT
CCATTAAATGCCTTCCCCTGGCCTTGAACACCAAACCAGGCCTTAAGGCTATGTCATCTCCTACCATTGATC
TCAGACCTAGCTGCAGTTGCACAATACAACCCCTGGCTCAAGTCTTCTGCACACATTGTTCCCTCACAGGCAGGA
ACCCTATGGTGAAGTATCAATAATTAAAACTTGCCCTGGGCCAGGCACAGTGGCTTATACCTATAATCCTAGCAC
TTTGGGAGGCCAAGGTGGATCAGTTGAGCCCAGGAGTTACAGACCAGTCTGGGCATCATAGAGAGACCTTGCCCTC
TACTAAAAAAAAAAAAAAAAAAAA

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FIGURE 69

GGGGCGGAGAGAGGCGAGCACCGGGAAGGGGAGCGTGGGGCCGCTGGAAATCGGGTGAATTTAAGGTCCATCGAGTA
CGTTTCTTTAATTATGTTCCATCAGGAATCCGCTGTGTGGCTTACAATAACCAGTCAAACAGATTGGCTGTTTCA
CGAACAGATGGCACTGTGGAAATTTATAACTTGTGAGCAAACTACTTTTCAGGAGAAATTTTCCAGGTGATGAG
TCTCGGGCTACAGAAGCTTTGTGCTGGGCAGAAAGGACAGCGACTCTTTAGTGCTGGGCTCAATGGCGAGATTATG
GAGTATGATTTACAGGCGTTAAACATCAAGTATGCTATGGATGCCTTTGGAGGACCTATTTGGAGCATGGCTGCC
AGCCCCAGTGGCTCTCAACTTTTGGTTGGTTGTGAAGATGGATCTGTGAACTATTTCAAATTACCCAGACAAA
ATCCAGTTTGAAGAAATTTTGATCGGCAGAAAAGTCGCATCCTGAGTCTCAGCTGGCATCCCTCTGGTACCCAC
ATTGCAGCTGGTTCCATAGACTACATTAGTGTGTTTGATGTCAAATCAGGCAGCGCTGTTTATAAGATGATTGTG
GACAGGCAGTATATGGGCGTGTCTAAGCGGAAGTGCATCGTGTGGGGTGTGCGCTTCTTGTCCGATGGCACTATC
ATAAGTGTGGACTCTGCTGGGAAGGTGCAGTTCTGGGACTCAGCCACTGGGACGCTTGTGAAGAGCCATCTCATC
GCTAATGCTGACGTGCAGTCCATTGCTGTAGCTGACCAAGAAGACAGTTTCGTGGTGGGCACAGCCGAGGGAAAC
GTCTTCCATTTTCAGCTGGTCCCTGTGACATCTAACAGCAGTGAGAAGCAGTGGGTGCGGACAAAACCGTTCCAG
CATCACACTCATGACATGCGCACTGTGGCCACAGCCCAACAGCGCTGATATCTGGAGGCACTGACACCCACTTA
GTCTTTTCGTCTCTCATGGAGAAGGTGGAAGTAAAGAATTACGATGCCGCTCTCCGAAAAATCACCTTTCCCCAC
CGATGTCTCATCTCCTGTTCTAAAAAGAGGCAGCTTCTCCTCTTCCAGTTTGCTCATCACTTAGAACCTTTGGCGA
CTGGGATCCACAGTTGCAACAGGCAAGAATGGGGATACTCTTCCACTCTCTAAAAATGCAGATCATTACTGCAC
CTAAAGACAAAGGGTCTGAGAACATTATCTGTAGCTGTATCTCCCATGTGGAAGTTGGATAGCCTATTCTACA
GTTTCTCGGTTTTTCTCTATCGGCTGAATTATGAACATGACAACATAAGCCTCAAAGGGTTTTCAAAATGCCA
GCATTCCTTCGCTCTGCCCTTCAGATTTTGTTCGAAAGATTCAACAAAGCTCTTTGTAGCATCAAATCAAGGA
GCTCTGCATATTGTTTCAGCTGTCAGGAGGAAGCTTCAAGCACCTGCATGCTTCCAGCCTCAGTCAGGAACAGTG
GAGGCCATGTGTCTTTTGGCAGTCAGTCCAGATGGGAATTGGCTAGCTGCATCAGGTACCAGTGCTGGAGTCCAT
GTCTACAACGTAAAAACAGCTAAAGCTTCACTGCACGGTGCCTGCTTACAATTTCCCAGTGACTGCTATGGCTATT
GCCCCAATACCAACAACCTTGTATCGCTCATTCCGACCAGCAGGTATTTGAGTACAGCATCCAGACAAACAG
TATACAGATTGGAGCCGGACTGTCCAGAAGCAGGGCTTTACCACCTTTGGCTCCAAAGGGATACTCCTATCACA
CACATCAGTTTTTCATCCCAAGAGACCGATGCACATCCTTCTCCATGATGCCATACATGTTCTGCATCATTGACAAG
TCATTGCCCCTTCCAAATGACAAAACCTTACTCTACAATCCATTTCTCCACGAATGAATCAGATGTCATCCGG
AGGCGCACAGCTCATGCTTTTAAATTTCTAAGATATATAAGCCTCTACTCTTCATGGATCTTTTGGATGAAAGA
ACACTCGTGGCAGTAGAACGGCCTCTGGATGACATCATTGCTCAGCTCCACCCACCCATTAAAAAGAAGAAATTT
GGAACCTTAAACAGGGCACTGTCTGTGTCCTTTCCTTGAAGTGTCTACCCCTGTTGCTTTTACAAATCATGGTAAT
AAAACAAGTTATTCTTG

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FIGURE 70

MGEFKVHRVRFFNYVPSGIRCVAYNNQSNRLAVSRDGTVEIYNLSANYFQEKFFPGHESRATEALCWAEGQRLF
SAGLNGEIMEYDLQALNIKYAMDAFGGPIWSMAASPSGSQLLVGCEDGSVKLFQITPDKIQFERNFDRQKSRILS
LSWHPSGTHIAAGSIDYISVFDVKSGSAVHKMIVDRQYMGVSKRKCIWGVAFLLSDGTIISVDSAGKVQFWDSAT
GTLVKSHLIANADVQSIADQEDSFVVGTAEGTVFHFQLVPVTSNSSEKQWVRTKPFQHHTHDMRTVAHSPTAL
ISGGTDTHLVFRPLMEKVEVKNYDAALRKITFFHRCLISCSKKRQLLLFQFAHHELEWRLGSTVATGKNQDITLPL
SKNADHLLHLKTKGPENIICSCISPCGSWIAYSTVSRFFLYRLNYEHDNISLKRVS KMPPAFRLSALQILFSEDST
KLFVASNQGALHIVQLSGGSFKHLHAFQPQSGTVEAMCLLAVSPDGNWLAASGTSAGVHVYNVKQLKLHCTVPAY
NFPVTAMAIAPNTNNLVIAHSDQQVFEYSIPDKQYTDWSRTVQKQGFHHLWLQRDTPITHISFHPKRP MHILLHD
AYMFCIIDKSLPLPNDKTLLYNPFPPTNESDVIRRTAHAFKISKIYKPLLFMDLLDERTLVAVERPLDDIIAQL
PPPIKKKKFGT

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FIGURE 71

GAGGCGCCGGCGGCCACGCCGCGGAAGGCGCGGGCCGAGCAGAGCCGGGCGTTGGAGCCC GCGCGCATGGAGG
CGTTGCCGGCAGCCCCCTGAGGGCAGCGGGGAGACAAGACCCGGCGACCTCGCGCATCCCTCGAGCCGCCACGCG
CTCTCGCCACCGGGCGGGCAGCGGGCCGCGGAGCCGCGCGGGCCATGCGACGGGCGGCCAGCAGAAGGAGAACAC
GCTGCTTCACCTCTTCGCCGGCGGGTGTGGAGGCACAGTTGGTGCTATTTCACTTGTCCACTAGAAGTCATTAA
GACACGGTTGCAGTCTTCAAGATTAGCTCTCCGGACAGTCTACTATCCTCAGGTTTCATCTGGGGACCATTAGTGG
AGCTGGAATGGTGAGACCAACATCCGTGACACCTGGACTCTTTCAGGTTCTGAAGTCGATCTTGGAGAAAGAGGG
ACCAAAGTCACCTTTTTAGAGGCTTGGGTCCAAATTTGGTTGGAGTTGCACCATCAAGGGCTGTATACTTTGCATG
TTACTCCAAAGCCAAAGAGCAATTTAATGGCATTTCGTGCCTAACAGCAATATTGTGCATATTTTCTCAGCTGG
CTCTGCAGCTTTTATCACAAATTCCTTAATGAATCCTATATGGATGGTTAAAAACCGAATGCAGCTAGAACAGAA
AGTGAGGGGCTCTAAGCAGATGAATACACTCCAGTGTGCTCGTTACGTTTACCAGACCGAAGGCATTCTGTGGCTT
CTATAGAGGATTAAGTGCCTCGTATGCTGGAATTTCCGAACTATAATCTGCTTTGCTATTTATGAAAAGTTTAAA
GAAGTATCTGAAAGAAGCTCCATTAGCCTCTTCTGCAAATGGGACTGAGAAAAATTCACAAGTTTTTTTGGACT
TATGGCAGCTGCTGCTCTTTCTAAGGGCTGTGCCTCCTGCATTGCTTATCCACACGAAGTCATAAGGACGAGGCT
CCGGGAAGAGGGCACCAAGTACAAGTCTTTTGTCCAGACGGCGCGCCTGGTGTTCCGGGAAGAAGGCTACCTTGC
CTTTTATAGAGGACTGTTTGGCCAGCTTATCCGGCAGATCCCAAATACTGCCATTGTGTTGTCTACTTATGAGTT
AATTGTGTACCTGTTAGAAGACCGTACTCAGTAACAGGCCGGAAAAATTGTGCTCTAGAAGAATAAACTGAAAAA
CTCTAGAGAATTTTTTTTCCCCATTGATGTTTAGAAAGTTTGAGACTGAAACAGGAAAGGCCATAAAATATCTGG
TTCATATCACCTGTTGGACATTTCCTTTGGATTTCATGCTTCTGGAAGGTTTAAATTCATTAACGTTAATAGTT
AATTATAACTTTTTTTTAACTTAAGAGGATTCAGGGTTAAGCACCAACTAAATTAAATCATGCTATTTAATTTAA
GTATAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAACC

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FIGURE 72

MATGGQQKENTLLHLFAGGCGGTVGAIFTCPLEVIKTRLQSSRLALRTVYYPQVHLGTISGAGMVRPTSVTPGLF
QVLKSILEKEGPKSLFRGLGPNLVGVAPSRVYFACYSKAKEQFNGIFVPNSNIVHIFSAGSAAFITNSLMNPIW
MVKTRMQLEQKVRGSKQMNTLQCARYVYQTEGIRGFYRGLTASYAGISETIICFAIYESLKKYLKEAPLASSANG
TEKNSTSFFGLMAAAALSKGCASCIAYPHEVIRTRLREEGTKYKSFVQTARLVFREEGYLAFYRGLFAQLIRQIP
NTAIVLSTYELIVYLLEDRTQ

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FIGURE 73

ATGGCATCTAGTCCTGAGCTTCCCACCGAAGATGAACAGGGTTCTGGGGCATCGACGATCTCCATATTTCAATTG
CAAGCTGAACAGGAAGACACCCAGAAGAAAGCCTTCACGTGCTGGATAAACTCACAGTTGGCCAGGCACACTTCT
CCCTCAGTTATATCCGACCTATTCACAGACATTAAAAAGGGGCATGTCCTCCTGGATCTGCTAGAAAGTACTTTCT
GGGCAACAGTTGCCTCGGGATAAAGGATCTAATACCTTCCAGTGTTAGAAATCAATATAGAACATGCCTTGACATTC
CTAAGAAACCGATCAATTAAGCTAATAAATATTCAATGTTACTGATATCATTGATGGAAACCCATCCATTATCCTT
GGCCTAATTTGGACAATTATCCTGCACTTTTCATATTGAGAAGCTTGCCCAGACTCTTCTTGCAATTACAATCAG
CCTTCCCTGGATGATGTGAGTGTGGTTGACTCATCTCCTGCCTCAAGTCCTCCAGCTAAGAAATGCTCTAAAGTG
CAAGCAAGATGGCAAATGTCTGCAAGAAAGGCCCTTCTTTTGTGGGCTCAGGAACAATGCGCCACCTATGAGTCT
GTCAATGTGACCGATTTTAAGTCAAGTTGGAGAAATGGGATGGCTTTTTTGGCCATCATTATGCCTTGCGACCA
GACCTAATTGACATGAAGAGTGTGAAGCATAGATCCAACAAAGACAATCTGAGAGAGGCCTTCAGAATTGCAGAA
CAAGAATTAAAAATCCCCAGATTGCTGGAACCAGAAGCTTACAAAACTTCTTGAACATTTAGCAGTCAACTCTCT
TCAGCTGATGTGAGTCAGCTAGTTCCAGCACACTCTCTGACCAGATGTG

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FIGURE 74

MASSPELPTEDQGSWGIDDLHISLQAEQEDTQKKAFTCWINSQLARHTSPSVISDLFTDIKKGHVLLDLLEVLS
GQQLPRDKGSNTFQCRINIEHALTFLNRSIKLINIHVTDIIDGNPSIILGLIWTIILHFHIEKLAQTLSCNYNQ
PSLDDVSVVDSSPASSPPAKKCSKVQARWQMSARKALLWAEQCATYESVNVDFKSSWRNGMAFLAIHALRP
DLIDMKSVKHRSNKDNLREAFRIAEQELKIPRLLEPEAYKNF

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FIGURE 75

TTTAGATGACTGAAACTATTTTATAATAAAATATGGTTAACACTGTTGCCAAAAGCACAATTTCTTTACAATTAA
TATTCCTCATTAAATATTGCCCAAATACTTATATATCCTACTCCTGCTGATCACCAAATTTGTACAGTCTTATCT
TGCAAATATAGTACATATACAATTAAACAGTTGGAAAACATATAGAGATTGACCACAAATAAGGCCCAAGGTA
CTGCTGTGTAATGTATCTACCATCAGGTTGATCAGGCCAGTTGTTATATTTGACAGCAAGAAAAATATTAAGTGT
TTTCTGTTTAGAGC

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FIGURE 76

ACCCCTCACTAAAGGGAACAAAAGCTGGAGCTCAAGGATCCTTAATTAAATTAATCCCCCCCCCCCCCGGNATG
CGCGTTGCGCGCCGGACGCGGAACGTCTGCCGGTGTCCCCGCGCTGCTGGTCCCGGGGTCCCTGAACCGCGGGCG
GCCCCGCTCCCTCTGCTGGCCATGGCCCCCCCCGCGCGTGCCGGTCCCCGATGTCACCGCCGCGCCGCTGCTG
CTGCTGCTGCTGCTGAGTCTGGCGCTGCTGGGCGCCCCGGGCCCGCGCCGAGCCCGCGGGAGTGCCGTCCCCGCG
CAGAGCCGCCCATGCGTGGACTGCCACGCCCTTCGAGTTCATGCAGCGCGCCCTGCAGGACCTGCGGAAGACAGCC
TGCAGCCTGGACGCGCGGACGGAGACCCTACTGCTGCAGGCAGAGCGCCGTGCCCTGTGTGCCTGCTGGCCAGCG
GGGCACTGAGGACCACGCTGCTCCGTGTGAATAAA TGCCAGTGGCAAAAAAAAAAAAAAAAAAAAAA

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FIGURE 77

ATTTCTTGTTCTTTTCATTGCCCTAGATTGTGTTCAATTAGACCTTCAGGACCTCTCCAAGAAGCCTCCGGACTGG
AAGAACTCATCATTTCTTCAGACTGGAATTTTATCGGCTCTTACAGGTTGAAATCTCCTTTTCATCTTAAAGGCATT
GACCTACAGACAATTTCATTCCCGTGAGTTACCAGACTGTTATGTCTTTTCAGAATACGATTATCTTTGACAATAAA
GCTCACAGTGGCAAAATCAAAATCTATTTTGACAGTGATGCCAAAATTGAAGAATGTAAAGACTTGAACATATTT
GGATCTACTCAGAAAAATGCTCAGTATGTCCTGGTGTTTGATGCATTTGTCATTGTGATTGTGCTTGGCATCTCTT
ATTCTGTGTACAAGATCCATTGTTCTTGCTCTAAGGTTACGGAAGAGATTCTAAATTTCTTCTGGAGAAGTAC
AAGCGGCCTGTGTGTGACACCGACCAGTGGGAGTTCATCAACGGCTGGTATGTCCTGGTGATTATCAGCGACCTA
ATGACAATCATTGGCTCCATATTAAAAATGGAAATCAAAGCAAAGAATCTCACAACTATGATCTCTGCAGCATT
TTTCTTGGAACTCTACGCTCTTGGTTTGGGTTGGAGTCATCAGATACCTGGGTTATTTCCAGGCATATAATGTG
CTGATTTTAAACAATGCAGGCCTCACTGCCAAAAGTTCTTCGGTTTTGTGCTTGTGCTGGTATGATTTATCTGGGT
TACACATTCTGTGGCTGGATTGTCTTAGGACCATAACATGACAAGTTTGAAAATCTGAACACAGTTGCTGAGTGT
CTGTTTTCTCTGGTCAACGGTGATGACATGTTTGCAACCTTTGCCCAAATCCAGCAGAAGAGCATCTTGGTGTGG
CTGTTTCAGTCGTCTGTATTTATATTCTTCATCAGCCTTTTTATATATATGATTCTCAGTCTTTTTATTGCACCTT
ATTACAGATTCTTATGACACCATTAAAGAAATCCAACAGAATGGGTTTTCTGAAACGGATTTGCAGGAATTCCTG
AAGGAATGCAGTAGCAAAGAAGAGTATCAGAAAGAGTCCTCAGCCTTCCTGTCTGCATCTGCTGTGCGAGGAGG
AAAAGAAGTGATGATCACTTGATACCTATTAGCTAAAGTTCTGCTAAAGATGATTAAAGTTTCAGGCATCCTTATC
CAGCGGCTGAGCAGAGGAACCCCAATGACTTGGACAAGCAGTTCCAAAATGACTCTCTTATTTAATTGTGGAGT
GGGAAAGAGGACTCACAGTTAGCCAGCTGACCATGACTGAAGTTCCAGCTTACTTTTTATAAACTTGAATGATA
AAGAATAGACCATGGGCTACTACTGGGCATTAGTGCAATATAACAGCGATAATAAAATCTCTATTAGTCTGTTA
ATTTATGACATGATCTCGGAATGGAAAAAGATCATTTTCAGAGTGTGCGAAATAATAGTCTTTAACCATGTAATTA
AATATGTGTGTTTATTGTCAAATAAGGATTTGTTTAAAGGTGATTCTTGGGTTTGAAGACATTTGTTAATTCAT
GGTCTGTACAGAAATGAAGCTGGTTGCAATACCAATCTAGAGAGTCCAAGCTGGCGAACTATTAAGCTGTTTAAA
GATCACCCCTT

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FIGURE 78

ISCSFIALDCVQLDLQDLSSKPPDWKNSSFFRLEFYRLLQVEISFHLKGIDLQTIHSRELPDCYVFQNTIIFDNK
AHSGKIKIYFDSDAKIEECKDLNIFGSTQKNAQYVLVFDADFVIVICLASLILCTRSIVLALRLRKRFLNFFLEKY
KRPVCDTDQWEFINGWYVLVLIISDLMTIIGSILKMEIKAKNLTNYDLCSIFLGTSTLLVWVG VIRYLGYFQAYNV
LILTMQASLPKVLRFACAGMIYLG YTF CGWIVLGPYHDKFENLNTVAECLFSLVNGDDMFATFAQIQQKSILVW
LFSRLYLYSFISLFIYMILSLFIALITDSYDTIKKFQONGFPETDLQEFLEKCSSKEEYQKESSAFLSCICRRR
KRSDDHLPIS

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FIGURE 79

AAGGGGTTCCAGTACTTCTCTACCCTGGAAGAAGCAGAGAAGCACCTGAGGCAGGAGCCAGGGACCCAGCCCTAC
AACATCAGAGAAGACTCCATTCTGGACCAAAGGTTGCCCTGCTCAAGGCATAATGGGGCCACCCGTGGGCATCC
ACAGTTTGCAGGGTGTTCGGAAGGTTCTTGTCACCTGTGATTGGATGCTGGATGCCGCCTGATAGACATGCTGGC
CTGGCTGAGAAACCCCTGAGCAGGTAACCCAGGGAAGAGAAGGAAGCCAGGCCTGGAGGTCCACGGCAGTGGGAG
TGGGGCTCACTGGCTTCCTGTGGGATGACTGGAAAATGACCTCGCTGCTGTTCCCTGGCATGACCCTCTTTGGAA
GAGTGGTTTGGAGAGAGCCTTCTAGAATGACAGACTGTGAGAGGAAGCAGGGGCAGGGGTTTCCAGCCCGGGCTG
TGCGAGGCATCCTGGGGCTGGCAGCACCTTCCCGGCTCACCAGTGCCACCTGCGGGGGAGGGACGGGGCAGGCAG
GAGTCTGGGAGGCGGGTCCGCTCCTCTTGCTCTGCGGCATCTGTGCTCTCCGAGAGAAAACCAAGGTGTGTCAAAT
GACGTCAAGTCTCTATTTAAAAATAATTTTGTGTTTCTAAATGGAAAAAGTGATAGCTTTGGTGATTTTGTAAA
AGTCATAAATGCTTATTGTAAAAAATACAGGAAACCACCCCTCACCCTGTCCACTTGGGTGATCATTCCAGACCC
CTCCCCAAACATGCATATGTACCTGTCCGTCAGTGTGTGGATGTATGTTTACAGTTCTACATAAATGGGATCATT
TTATACATGGTGCTCTGGAACCCACATTTTTTCATGCAGTCATTTGCAGTGAATTATTTATTGTGATAATAAATAG
CATTAGAATACAAAAAAAAAAAAAAAAA

FIGURE 80

[illegible]

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FIGURE 81

MELQDPKMNGALPSDAVGYRQEREGFLPSRGPAPGSKPVQFMDFEGKTSFGMSVFNLNSNAIMGSGILGLAYAMAH
TGVIFFLALLLCIALSSYSIHLLLTGAGIAGIRAYEQLGQRAFGPAGKV VVATVICLHNVGAMSSYLFIKSEL
PLVIGTFLYMDPEGDWFLKGNLLIIIVSVLIIILPLALMKHLGYLGYSGLSLTCMLFFLVSVIYKKFQLGCAIGH
NETAMESEALVGLPSQGLNSSCEAQMFTVDSQMSYTVPIMAFVCHPEVLPITYELCRPSKRRMQAVANVSIGA
MFCMYGLTATFGYLTIFYSSVKAEMLMYSQKDPLILCVRLAVLLAVTLTPVVLFPIRRALQQLLFPKGAFSWPR
HVAIALILLVLNVLVICVPTIRDIFGVIGSTSAPSLIFILPSIFYLRIVPSEVEPFILSWPKIQALCFGVLGVLF
TAVSLSFMFANWATSQSRMSGH

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FIGURE 82

GTGATGGAACATAGGTTAAGATGCCATACTGTTGAAAGCAGTAAACCAAACACTCTTACGTTAAAAGACAATGCT
TTCAATATGTCAGATAAAACCAGTGAAGATATATGCTACAACTCAGTCGTTTACTAGAAAGCAATAGGAAGCTT
GAAGACCAAGTTCAGCGTTGTATCTGGTTCCAGCAGCTGCTGCTTTCCTTAACAATGCTCTTGCTTGCTTTTGTC
ACCTCTTCTTCTATTTATTGTACAGTTAAAGAAGTGGTGCCGGGTAGGAACCACGGTTCCTTCGTCCATTAGTT
GGAAAAGTACCAGACCTAAAACCTCTACCAAGCTACTAAAACCATTGCACATCTGTGCTTCCTAAAAGGAAATATG
CAGCACGTGGAGGGGAACACATACATGCTTGAATAAACTGCTAGAATAAGAAATGCTGGAGAAATTGATTA
TAAGAGACTATAGCTATTTAGTAAAGTAAGTAAAGGCATATCCATTGTGTAAATTAATAGTTTAAATATAATTTA
TTTTTTCCTTTTGATCTGAATACTTTTAAAGCTTAAGTTTTATCGTGTAATACATTAGCTAAACTGAAAAGTAT
AAGTAACATGCTTTGTTGCAGCCAAAAATGTAATCTGCTTTTTTATGACAGAATTATTATAGCTGAGCTGACTT
ACTAGCTTTTCTATACTATGTATATAGAAGAACATGTATATTGAGAAAGAAAACATACTTATATAGAGGAATTTA
TGTAACCATGACTTTGTAATTTTGAGAATTCCTCCAGTGATGGTCAGTATTCTTTTGGAATGTAAACCGATTTA
ATGCCAAACCACCTTAACCTTTGTTTCTCAGTGTTCCTTAACAGCCTGCCTTTTATTAATCTCAGGCTTTTTTAT
GAACACTCTCATTTAGTAGAATTTGGAAAACTAAGCGTGGTTGGAATTTCTTTGAATTCTGTTAGTAATGCCCCA
AAAGAAAAGTCTCAAGCAGTCCCCCTATCCAGTCATTTTATGGAGTTTCATGTTGTCCACTATAGCTGGACACT
GAACCTTTTGCCTAATTTATTATAAAGGCCTGACCCTCTATTGTCCCATCTTCACCCCCATTCCAGAGCAGAGGA
GTCTCTGTGGACCATGAATTGCACTGTCTCCCTCCCTCAATTTCTAAATGAAAGGTATTAGATATAAATTTTTTTGA
AAGGTTAGTTGTTTGAGATGCTAAGCAGGATAATAAATTTAGATTTTAAAATGTTCCCTGTAAAAGTCAGCCCAT
GACAAGGAAATTTACAAAATACTAGAGTATCTAGAAGGGTGAAAACAAAAAAAAAAAAAAAAAAAAA

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FIGURE 83

VMEHRLRCHTVESSKPNTILTKDNAFNMSDKTSEDICLQLSRLLESNRKLEDQVQRCIWFQQLLSLTMLLLAFV
TSFFYLLYS

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FIGURE 84

GGAAGTGCTTTTGAATGAGGTACTGAGGGCCAAGGTGTTGGAAGTTCCTAATTCTTTCTCGGTAACTGTGAAA
CTCTGCGTATTGGGAAGGCCTGGCCTCAGTCATCAGGCCAGGAGAGGTACTGGACGCCGCGCACGCACTCGTCTG
CCAGCGAGGCCCCAAAGGGGAAGCCTAGCGGAGCTCAGTGTGGCAGCTGCTGGCCTCTGGGCCGCTACTTGTCAAT
ACCATGCCTTTCTGTAAATATTTGTGGTGAAACAGTAACCTCAGAACAGACATGAAAGCTCACCTAATTGTTTAC
ATGGAAAGTGAAATTATATGTCCATTTTGCAAGTTGTCAGGTGTGAATTATGATGAAATGTGTTTTATATCGAA
ACAGCTCATTTTGAGCAGAATACACTTGAAAGAACTTTGAGAGGATAAATACAGTACAATATGGAACCTTCAGAT
AACAAGAAAGACAACACCCTACAGTGTGGAATGGAAGTTAATTCAAGTATTCTTTAGGTTGTGCATCTAATCAT
CCAAAAAATTCAGCTCAAAACCTGACTAAAGATAGTACTTTAAAAACATGAAGGCTTCTATTTCAGAGAACTTAACT
GAATCTAGAAAATTCTGAAAAGTAGGGAAAAACAGTCCAGCCTGACCGAAATAAAAGGATCTGTTTATGAAACA
ACATACAGTCTCTCTGAATGTCCATTCTGTGGAATAATAGAGGAGCACAGTGAAGATATGGAAGCTCATGTGAAA
ACAAAGCATGCCAATCTTTTAGACATTCCATTGGAAGACTGTGATCAACCACTCTATGATTGTCTATGTGTGGG
CTCATATGTACAAATTACCATATTCTTCAGGAACATGTTGACTTGCATTTGGAAGAAAACAGCTTTTCAGCAAGGC
ATGGATAGAGTCCAGTGTCTGGTGATCTACAATTGGCTCACCAGCTTCAGCAAGAAGAAGACAGAAAGAGGAGA
TCTGAAGAATCAAGACAAGAAATAGAAGAATTTTCAAGCTGCAGAGACAATATGGTTTAGATAATTCTGGAGGA
TACAAACAACAACAACCTACGAAATATGGAGATAGAAGTAAATAGGGGAAGAATGCCTCCATCTGAATTTTCATAGG
AGAAAAGCTGATATGATGGAATCATTAGCTCTTGGTTTTGACGATGGAAAAACAAAACTTCCGGAATTATTGAA
GCACTTCATAGGTATTATCAGAATGCTGCCACAGATGTGAGACGGGTGTGGCTTTCTTCAGTGGTGGATCACTTT
CATTCATCTTTAGGCGACAAAGGTTGGGGTTGTGGTTACAGAAATTTCCAAATGCTACTTTCATCATTATTACAA
AATGATGCTTACAACGATTGCTTAAAAGGTATGTTGATTCTTGCATTCCAAAAATTCATCTATGATTGAAGAT
GCATGGAAGGAAGTTTTGATCCTCAGGGGGCCTCTCAACTTAATAACAGGTTACAGGGAACAAAGGCCTGGATT
GGAGCATGTGAAGTATATATACTCCTGACCTCCCTAAGGGTAAAGTGTGCATATTGTTGATTTTCACAAATCACT
GGTCTTTTGGGTACACACCCTCGCTTATTTGAATGGATATTGAAGTATTATTCTTCAGAGGGAGAAGGGAGTCCA
AAGGTAGTGTGTACATCTAAACCTCCTATCTATCTTCAGCATCAAGGTCACAGTCGAAGTGTATTGGAATTGAA
GAGAAAAAAACCGAACATTATGCTTACTAATACTTGATCCTGGATGTCCTTCTCGAGAAATGCAGAAATTATTA
AAGCAAGACATAGAGGCTAGCAGTCTCAAGCAACTTCGGAATCTATGGGAAATTTAAAAACATAAGCAATACCAG
ATATTGGCAGTAGAGGTGCTCTTTCTCTAGAGGAGAACTTGCCAGGAGACAAGCTTCTCAAGTCTTTACAGCC
GAGAAGATTCTTGAAGAATCAAGCATTTAAGCATTTTCAGTGATTGAGAACAATACTTTGTTTTCTAAATGTAGA
TATTGAACTCCTTAATACAATTATGAATCTGTGAATTTCTTAAAGTCTTAACATATAATTTAATTTCTAAATGC
CTGTGTAAATTGAATTATACCTATCATACTTCATTGTTTGGTAAATTATTTCAATAAAATGTCTTGTGTTTTGCAT
TGTGAAAAAAAAAAAAAAAA

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FIGURE 85

MLSCNICGETVTSEPDMDKAHLIVHMESEIICPFCKLSGVNYDEMCFHIETAHFEQNTLERNFERINTVQYGTSDN
KKDNTLQCGMEVNSSILSGCASNHPKNSAQNLTKDSTLKHEGFYSENLTESRKFLKSREKQSSLTEIKGSVYETT
YSPPECPCFCGKIEEHSEDMETHVKTKHANLLDIPLEDQDQPLYDCPMCGLICITNYHILQEHVDLHLEENSFQQGM
DRVQCSGDLQLAHQLQQEEDRKRRSEESRQEIEEFQKLQRQYGLDNSGGYKQQQLRNMEIEVNRGRMPFSEFHR
KADMMESLALGFDDGKTKTSGIIEALHRYYQNAATDVRRVWLSSVVDHFHSSLGDKGWGCGYRNFQMLSSLLQN
DAYNDCLKGMLIPCIPKIQSMIEDAWKEGFDPOGASQLNNRLQGTKAWIGACEVYILLTSLRVKCHIVDFHKSTG
PLGTHPRLFEWILNYYSSSEGEKSPKVVCTSKPPIYLQHQHSRTVIGIEEKKNRTLCLLLIDPGCPSREMQLLK
QDIEASSLKQLRKSMGNLKHKQYQILAVEGALSLEEKLARRQASQVFTAEEKIP

FIGURE 86

GTCAAAGTCTCCCGGAGCCCAATTTCGGGAAGCGGTGAGTTCTGAAAGAAGTTCTCGTACCGTAGTTTCCCAAGT
CTGCGAATCCCCAACCATGAGCGCCTCGGGCGTACTGTCTTTACCCAGCAAGGATGGGAGCAGGTGCTGGCCAA
AGTGAAACGGGCTGTGGTTTACCTGGACGCCGCTGCGCCGAGAGCCTGCACTGGGGCTGCGGATCCACCCGTCT
CCTGGAGGCGGTGGGGGGTCTGACTGTCACTGCGAGAGTTCGAGCCCGACGCAATTGGTGGTGGAGCCAAGCA
GCCCAAGGCAGTGTTTGTGCTGAGCTGCCTGCTGAAAGGCCGGACCGTGGAGATCCTACGGGACATCATCTGCCG
CAGTCACTTCCAGTATTGTGTGGTGGTCACAACCGTGAGCCACGCTGTCCACCTCACAGCTAATCATGTCCAGC
GGCGGCAGCGGCCGAGATGGAGGGGCAGCAGCCGGTGTTTCGAGCAGCTGGAGGAGAAGCTGTGTGAATGGATGGG
CAACATGAACTACACGCCGAGGTGTTCCATGTCCCGTTATTGCTTGCCCTGTTGCTCCCCACTTTGCCCTTGAC
TCCAGCTTTTGCATCCCTTTTCCACTGCTACCCCAGGATGTGCACCTCCTTAATAGCGCCCGACCGGACAAGAG
GAAGCTGGGAAGCCTGGGTGATGTGGACTCCACTACGCTAACCCAGAGCTGCTGCTGCAGATCAGATGCCTAGT
GTCAGGCCTCAGTTCTCTGTGTGAACATTTAGGAGTACGGGAGGAGTGTTTTGCTGTAGGTTTCTTAAGTCAGGT
CATCGCTGCGGATCTGGCCAATTATGCCCCTGCAAAGAACAGGAAGAAGACTGCTGCAGGCAGGGCATCAGTGGT
TTTTGTGGACAGAACCTGGATCTCACAGGAGCAGTTGGACATCATGGAGACAACCTAGTAGAGAAGATCATTTC
AGCACTTCCCCAGCTCCCAGGCCACACAAATGATGTGATGGTTAACATGATAGCGCTCACTGCACTCCATACTGA
GGAGGAAAATTATAATGTGGTTGCACCAGGCTGTCTTTCACAATCCAGTGACACCACAGCCAAAGCCCTATGGGA
AGCTTTACTGAACACTAAGCACAAAGAGGCAGTGATGGAAGTTCGGAGACATCTAGTGGAAGCGGCAAGCAGAGA
AAACCTGCCAATCAAGATGAGTATGGGGAGAGTCAACCCGGGACAGCTCATGTCTTATATTAGCTCTTCAAGAA
CAACCTCAAAGCTTAATGAATCATTGTGGCCTCCTCCAGCTTGGACTGGCCACAGCTCAAACGTTGAAACACCC
ACAGACTGCCAAGTGGGACAACCTTTCTGGCTTTTGAAAGGCTCCTTCTTCAGAGCATTGGGGAGTCAGCAATGTC
CGTTGTGTTAAATCAGCTGCTGCCCATGATTAAGCCTGTAACCCAGAGAACCAACGAGGACTACAGCCCTGAGGA
ACTGCTGATCCTTCTCATATATATTTATTCTGTCACTGGAGAGCTCACGGTAGACAAAGACCTGTGTGAAGCAGA
AGAAAAAGTCAAGAAAGCATTGGCTCAGGTCTTCTGTGAGGAATCTGGATTGTACCTTTGCTGCAAAAAATTAC
GGACTGGGACTCTTCAATTAATCTGACATTTACAAAATCCAAAATTGCCGTGGATGAACCTTTTACTTCACTTCG
GGATATTGCTGGAGCTCGGAGTCTCCTGAAACAGTTTAAGTCTGTATATGTTTCTGGAATCATACCCACCAGGC
ATCTTATAAGCCATTGTTGAAGCAAGTTGTGGAGGAAATATTTCAATCCCGAGAGGCCAGATTCCGTTGATATTGA
ACACATGTCTTCAGGCCTCACTGATCTCCTTAAAACTGGATTTAGCATGTTTATGAAGGTGAGCCGGCCTCATCC
TAGTGACTACCCCCCTCTGATCCTCTTTGTGGTAGGTGGGGTCACAGTCTCTGAAGTGAAAATGGTCAAAGATCT
TGTGGCATCGTTGAAGCCAAGGAACCCAGGTAATCGTGCTGTCCACACGACTCCTGAAGCCACTTAACATTCCTGA
GCTGTTATTTGCAACTGACCGACTGCATCCAGACCTTGGCTTCTGAGCATCCGCTAAGAAGATAAGACCTACTCA
AGCTGGAAATGCCGATGCAATTTTCTGCCACCCTCCAAATACTCCTCCACAACCAGCGTCCCTGCTACTAATTG
CGAGAATGATGGAATCTGCCTGAAGGGTCTTGATACCTACTCAGTGAGGTACTTTGCTTGGATTGCTGTGATTG
TTAAAAAAAAAAAAAAAAAAGTTTTTTTATTTTCTGAAGGCGACAGTCTGTCTTTTGGCGAGTCCAATTAGTGAT
CGTTTCCATTATCCTTAACCTCTGTTTGTGATCTTCCTGATTCCACCTACAAGTTCATTAGTTCTAAATAAAA
GCCTGTTGGCAAGTGTTGGTAGATTACAACCTCTTTTTATTTGAAGTTGCTCGAGAAGTTAGACATGCTTTAGAAT
TATGAGTGTGGGGAAAATTTGATGTTCTTAGGATTATATAACTGAGGAGGGAACATTGCAAAATAGGGTCTGAGG
CTTTGTTTCTCTCTTGCTCTGAAACATTTCTGAAAAGGCAAGGAAGGGAGGGTTAGTGTCTGGGGCAGTGCTGGT
AGCCTGCATGTGTTGTAAATCATCCTGCCATAACAAAGGACTGCATTGTTCTAGCTGGCCCACTGGGCAGGTCTG
CCAGGCTACTTGAACCTGTAGTGGGAAGGTGGTTGATTGGAGGGTTATCTGTATATAAAAGGTTTTCTCCCCCTCC
AAAGAAAGACTCCAGTACAAGATACCTGGTCCCAGGGAGTCTAAATTGTAACAGCAACCCCTGTGGACTTTGTGG
GTATGAGTTTTGATTGAAATATAAAGCTTTCTTTTCTGTAAGTTTAAAGTTTTTCATCTGACCATAGCAGAAAAAC
CTAGACCCACCTAGTGAAACTTTGTAAGAACTCCAGGGCAAAAACGAACCACCTGCAACCCACATGTTTGTAGGT
GTATGGTCGATGGAAGTTTCTGGCATCCATGTTGGTAATAAAGAGATAAAACTGAAAAAAAAAAAAAAAAAAAAA
AAAAAAAAAAAAAAAAAAAA

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FIGURE 87

CTTCCGAGCAAGATGGCGCCGCGGGCATTCTTCCACTGCCCCTCTGAGGGAACGCTAAGTAGTGTGTCCGGCGC
CGTGTTCAGCTCCGCGTTGTTCCGCGAGAAAGCGAGAGGCCGAGCCCGGGCTGGTGCG**ATG**GCCGCGGTGGTGG
CCAAGCGGGAAGGGCCGCGTTCATCAGCGAGGCGGCCGTGCGGGGCAACGCCGCCGTCTGGATTATTGCCGGA
CCTCGGTGTCAGCGCTGTCTGGGGGCCACGGCCGGCATCTCGGCCCTACCGGCCTCTACGGCTTCATCTTCTACC
TGCTCGCCTCCGTCTCTCTCCCTGCTCCTCATTCTCAAGGCGGGAAGGAGGTGGAACAAATATTTCAAATCAC
GGAGACCTCTCTTTACAGGAGGCCTCATCGGGGGCCTCTTCACCTACGTCCTGTTCTGGACGTTCTCTACGGCA
TGGTGACGTCTACT**TGA**AATGGGGGCCCGGGGGACTTTTTTAAAAAACAGATCGGGAGGACTGTGGCCAGCAAT
TAACACCATGTAGACTTCCTTAGTTCTTAAGTGGTTGAATTCGCTGCTTGTCTGTAACGTTATAAATAATTTAT
ATCTGAAGACGGAGAGCCTGTAATATTCTTCAGATTAAATGAAGCGTGAGACAAAAAAAAAAAAAAAAAAAAA

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FIGURE 88

MAAVVAKREGPPFISEAAVRGNAAVLDYCRISVSALS GATAGILGLTGLYGFIFYLLASVLLSLLLILKAGRWN
KYFKSRREPLFTGGLIGGLFTYVLFWTFLYGMVHVY

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FIGURE 89

CGGACGCGTGGGTTGTTCTGGAAGCTGTGCGTCACCGTAATGAGGCTTGTAATTCCTTGATAACTATGACTTGGCT
AGTGAATGGGCAGCCAAATACATCTGTAATCGCATCATTGAGTTCAAACCTGGACAGGACAGATATTTTACACTG
GGTTTACCAACAGGGAGTACACCTTTAGGATGCTATAAAAACTAATAGAATATCATAAGAATGGACACCTTTCT
TTTAAATATGTGAAGACCTTTAATATGGATGAATATGTAGGACTTCCAAGAAATCATCCTGAAAGCTACCATTCT
TATATGTGGAATAATTTTTTTAAGCATATCGATATAGATCCTAATAATGCACATATCCTTGACGGGAATGCTGCA
GATTTACAAGCAGAATGTGATGCTTTTGAAAAACAAAATAAAGAAGCTGGAGGAATAGATCTTTTGTGGAGGA
ATTGGTCCAGATGGTCATATCGCTTTCAATGAGCCTGGATCCAGTTTAGTGTCAAGGACAAGATTAAAGACTCTA
GCAATGGATACCATCTTGGCAAATGCCAAATATTTTGATGGAGATTTATCAAAAGTGTCAACTATGGCTCTAACT
GTTGGTGTGGGGACAGTGATGGATGCTAGAGAAGTAATGATCCTTATAACAGGGGCACACAAGGCATTTGCCCTG
TACAAAGCAATAGAAGGAGTCAATCACATGTGGACTGTTTCCGCTTTCCAGCAGCATCCCCGGACTATTTTTGTA
TGCGATGAAGATGCTACTTTAGAATTAAGAGTTAAACTGTGAAATACTTTAAAGGTCTAATGCATGTGCACAAT
AACTTGTGGATCCACTATTCAGTATGAAAGATGGAACTGAAGGAGACTGGAGCAAAATTCAGCTTGAATGAAC
AGAGCACTTTTACTAAGTAGTAGATGAATTTTCAGCTATGCAATATGACAAAACATGGGGAATTTGAAGATTG
TCATTTTTTCATTGAGTCTCTATGTTAAACATTCATATTTTGAATATTTATATCTTGTACTTGGGTTTAAGAG
AAGTAGCTGGCTCTCAAGATTGACTGGCTATTTATTATAAAGTACTGAAGTCACATAGCCACCTATAAACAGCA
TAGAAATGCTGCTGCTGTTTAAAAAGTCATTTAAAGGTAGAGTGTCCACATCAGGCACCATTTGTGATATGACTC
CAGTGGCATATATTTCAATTTTTTAATGACAAGACACTCCAAACCTTTCAGATAACAACTATCATTGCAGACCTT
CACTTTTGGAAATGCAATCTTTATATTTTCTGTGCATCACACACATGCTTTTCTGCACGTGGTTGCCTTAGTCATC
TTCCTACAGCACCATCTAGACATCAAAAATGTGCTATATATCATTGGTAAAGGAAATTTGAAGAGATGACAGTG
CCTAAAAGTACAGTTTACATCCTTTTGAAAAGTATGTGTAAGTGCATGTTTTTGTGCACCTTCTTCTATAGCAC
TTTTTTACAAATATCTTATTTTTATTTAACGACTTGGGTTTCATGTCCTAATATAAGTATCTTGACAATTATGAG
CTTTATACCTAGCAAGCCACTTCAGGAAATCTTTTGGAGAATATTTTCTGATTATTGTTAACTTAATATACAA
TTAGCTTTATTCTTTATAAAATGTCTAAAAGAATAATACGAAGTATATATAAAAGGAATTACTGTAAACTACATT
GCCATAGCAATTTACATAAAAGTATATTGTTTTCTATCTTTAACTCAAATAAAGCGTGAATAAATAAGTTATCT
AAATTTCCAAAAAAAAAAAAAAAAA

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FIGURE 90

MRLVILDNYDLASEWAAKYICNRIIQFKPGQDRYFTLGLPTGSTPLGCKLIEYHKNHLSFKYVKTFNMDEYV
GLPRNHPE SYHSYMWNFFKHIDIDPNNAHILDGNAADLQAECDAFENKIKEAGGIDLFVGGIGPDGHIAFNEPG
SSLVSRTLKTLAMDTILANAKYFDGDLSKVSTMALTVGVGTVM DAREVMILITGAHKAFALYKAIEGVNHMWTV
SAFQQHPRTIFVCDE DATLELRVKTVKYFKGLMHVHNKLVDPLFSMKDGN

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FIGURE 91

TCGGCTCGCGGCTTTCTGATTATGCAGAACTTAAATCTATGCCTCAGTGACCCATACAGCATTCCAGTTCCTATC
ACCTACTGTCTTGTCCCTATACTTGCAGCAGTTGTCCAGGGTTATTCTTTGTCTGTATTAGAATTTTTTTTCAGG
TTGCTTAAGGAATCTTGCAGATACTTGTGACAAAGAATCATAAATGCTGTTGTTAAACTGAATAATGAATTGAGT
CCCAAATGTTTCGTGCTAATTAATGCTTTTTTGAGTTGGAGATGAAATGAGAGTAATATCATCAAGCTGTGGATTAA
AGTTATCCTCAAAGCCCCATCATCTACAAAAGAATAGGACAGGAACTGCCTTTGTGCAGGTGCAAGACCATGTT
ACTTTTGAGCAGTGAGCTTGAGATGTCTGGGATACAAATTGGGTTCCTATTAATACTACTAATCATTCCTTTTTTT
TCTTTACCTTCAGCCACTCACAACCTGACCTTCACTACTATTACATCCTGGAGCTGTCGTTTTATTGGTCTTTGA
TGTTTTCTCAGTTCAGTGATATCAAAAGAAAGGACTTTGGCATTATGTTCTGCACCACCTTGATCTATTTTTCT
TGATTACCTTTTTCATATGTCAACAATATGGCCCGAGTAGGAACGCTGGTCCTTTGTCTTCATGATTCAGCTGATG
CTCTTCTGGAGGCTGCCAAATGGCAAATTATGCCAAGTTTCAGAAAATGTGTGATCTCCTGTTTGTATGTTTG
CCGTGGTTTTTTATCACACACGACTGGGTATATTTCTCTCTGGGTGTTAAATACCACATTATTTGAAAGCTGGG
AGATCGTTGGACCTTACCCTTCCTGGTGGGTTTTTAACCTACTGCTATTGCTAGTACAAGGGTTGAACTGCTTCT
GGTCTTACTTGATTGTGAAATAGCTTGCAAAGCTGTTTCAAGAGGCAAGGTGTCCAAGGATGATCGAAGTGATA
TTGAGTCTAGCTCAGATGAGGAGGACTCAGAACCTCCGGGAAAGAATCCCCACACTGCGACAACCAATGGGA
CCAGTGGTACCAACGGGTATCTCCTGACTGGCTCCTGCTCCATGGATGATTAATTACTCAAACTACAAGTCCCA
AGCAAAGTGAACATATTTGTTCTGGAAGTATTTAATAAGTTGCAAATGCAGTTCCTTTTCATAATATCTCAGCACC
AGAAACAAAATTAAGATTATCAAAGCATTTTGAATAGTGCACTGCCATGTGTCCTGTCTGTGAATGAAGAAGAA
TTACCATTCTCTCTTTGTAGGCATGCTGTATGTAATTGACACAAGGGAACAGTATTTGCATTGTACTGTCTTAG
AATATTATTTATTTTTTTGTATTTGTAAATCTGTGGACAAAAGAGGGTTTCCTCACTCCTTTTACTCACTGGGCT
CATGACAGTGAAGGAGATGCTCCATCTGCTTCTCCCCCTTTCTCTTGCTGTAGTCCAATGTGCTATGAGCATCAG
CTTACTTTGTCACTTAGAGCAAGCAAAACCCAGTGCAAGAGTCTCGTTCAGCTCTAAATAGGTTTGCTTTCTTTT
AGTTACAGTGCCCATTTTGAAATTGCCTATACAGTCTTAGTGACCATTTAAACCGGACGAACTAGGTGTTTAATT
TTCACTCTTCATGTTCAATTAGCAGTTCAAATTAAAGAAGATGGTTATTGGAGAAGCTTTTTTGAATGGTTTTGT
TTAAATTGCTTTGAAATAGATTTCAATTTCTTGTGCACACAGCCAAGATTTCTTCAATGGGTGTGAGCTAGTTGAG
GGTTAACCTTGTAGGTTGCAGANNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNGATGAGGTCAGTGCTCTGATT
TTGAAGGAGGATATTTCACTGAAGCTCATAGTTATAACAAGGAAATCACTGTTAAGAATGGGAATTTGTCCTGTG
TTCTGGGAATAACATAAAGAGAGCAACTGATTTTCAGCCAGGTTTTGCCACTACCCTATAATTAGTGAGTCTTAT
GTTATAAAGAAAGAAGTTAACTATATTTGGGGACAAAAAATATTTCAAGAGTTGATAAAGATTACCTGTGCAG
TGCAGAGCACTTTAATGCAACCAGCTTTCAAGAAAAAGCCCTATCTAGTACTTGATGTTGATGTTTTTATTTTGC
TGAGCAAAATAAAGCCAATGGGAGAAGGACAA

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FIGURE 92

MFSQFTDIKRKDFGIMFLHHLVSIFLITFSYVNNMARVGTIVLCLHDSADALLEAAKMANYAKFQKMCD
LLFVMFVAVFITTRLGIFPLWVLNTTLFESWEIVGPYPSSWWVFNLLLLLVQGLNCFWSYLIVKIACKAV
SRGKVSDDRSDIESSDEEDSEPPGKNPHTATTTNGTSGTNGYLLTGSCSMDD

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FIGURE 93

GGAGTCGTTGTTGTTGCTGTTTGTGAGCCTGTGCGGCGGCTTCTGTGGGCCGGAACCTTAAAGATAGCCGCA**AATG**

GCTGAAAATGGTGATAATGAAAAGATGGCTGCCCTGGAGGCCAAAATCTGTCATCAAATTGAGTATTATTTTGGC
GACTTCAATTTGCCACGGGACAAGTTTCTAAAGGAACAGATAAACTGGATGAAGGCTGGGTACCTTTGGAGATA
ATGATAAAATTC AACAGGTTGAACCGTCTAACACAGACTTTAATGTAATTGTGGAAGCATTGAGCAAATCCAAG
GCAGAACTCATGGAAATCAGTGAAGATAAACTAAAATCAGAAGGTCTCCAAGCAAACCCCTACCTGAAGTGACT
GATGAGTATAAAAAATGATGTAAAAAACAGATCTGTTATATTAAAGGCTTCCCAACTGATGCAACTCTTGATGAC
ATAAAAGAATGGTTAGAAGATAAAGGTCAAGTACTAAATATTGATGAGAAGAACATTGCATAAAGCATTTAAG
GGATCAATTTTTGTTGTTTGTATAGCATTGAATCTGCTAAGAAATTTGTAGAGACCCCTGGCCAGAAGTACAAA
GAAACAGACCTGCTAATACTTTTCAAGGACGATTACTTTGCCAAAAAAAATGAAGAAAGAAAACAAAATAAAGTG
GAAGCTAAATTAAGAGCTAAACAGGAGCAAGAAGCAAAAACAAAAGTTAGAAGAAGATGCTGAAATGAAATCTCTA
GAAGAAAAGATTGGATGCTTGCTGAAATTTTCGGGTGATTTAGATGATCAGACCTGTAGAGAAGATTTACACATA
CTTTTCTCAAATCATGGTGAAATAAAATGGATAGACTTCGTCAGAGGAGCAAAAGAGGGGATAATTCTATTTAAA
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ACTTGGAAGTACTAGAAGGAGAGGTGAAAAAGAAGCACTGAAGAAAATAATAGAAGACCAACAAGAATCCCTA
AACAAATGGAAGTCAAAAGGTCGTAGATTTAAAGGAAAAGGAAAGGTAATAAAGCTGCCCAGCCTGGGTCTGGT
AAAGGAAAAGTACAGTTTCAGGGCAAGAAAACGAAATTTGCTAGTGATGATGAACATGATGAACATGATGAAAT
GGTGCAACTGGACCTGTGAAAAGAGCAAGAGAAGAAACAGACAAAGAAGAACCTGCATCCAAACAACAGAAAACA
GAAATGGTGCTGGAGACCAG**TAG**TTTAGTAAACCAATTTTTTATTCATTTTAAATAGGTTTTAAACGACTTTTG
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GTTGTTTAACTTGCTTTTTGTTATGCAATGAGATTTCTTTGAATGTATTGTTCTGTTTGTGTTATTTTCAGATG
ATTCAAATATCAAAAGGAAGATTCTTCATTAAATGCGCTTTGTAATATGAGAATGTATTAGTACAACTAACTA
ATAAAATATATACTATATGAAAAGAGCAAAAAAAAAAAAAAAAAA

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FIGURE 94

MAENGDNEKMAALEAKICHQIEYYFGDFNLPRDKFLKEQIKLDEGWVPLEIMIKFNRLNRLTTDFNVIVEALSKS
KAELMEISEDKTKIRRSFSKPLPEVTDEYKNDVKNRSVYIKGFPTDATLDDIKEWLEDKGQVLNIQMRRTLHKAF
KGSIFVVFDSIESAKKFVETPGQKYKETDLLILFKDDYFAKKNEERKQNKVEAKLRAKQEQEAKQKLEEDAEMKS
LEEKIGCLLKFSGDLDDQTCREDLHILFSNHGEIKWIDFVRGAKEGIILFKEKAKEALGKAKDANNGNLQLRNKE
VTWEVLEGEVEKEALKKIIEDQQESLNKWKSKGRRFKGKGKGNKAAQPGSGKGKVQFQGKKTKFASDDEHDEHDE
NGATGPVKRAREETDKEEPASKQOKTENGAGDQ

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FIGURE 95

TTTTAACTTTGCAACAGGTTTTTATTTTTGCTTTATCTATTACAGTGTTTGAAACCTAAAGAAATACATTTTC
TCTTCAAATTTGGATGTGTATATAAATAACATTTGTCTGGACTCAGCACACTCAATGCCATGTTTTCTTCGCCTA
TGTCTGCTCTGAAATCAAGCTGTGTCTGTCTACCCAGGGGCCCTGAGAACATGGAAAATAGAGTTTATTGTTATT
AGAAAAATAAAAGCAAATGAATTTGCAAAGAAAAACAGTGAGAAGGATTAGATTCATCTTCCAAGGGTCCATAG
CTGGTAACCCAAGCCATTCTCGGGGGATATCCAGTCTCTTGAGTGGCTGGGACTCCATTACCCACTTTCCTTCTT
TAATAGGTCAAAGGCAATCCCACAAAAGCTGGCTAAAAAAGCCGACACCCAACCTCCAGAGTCTGAGGGTTCATG
AAGATGTGGACTTTTTTTTTTTGAGACAAGAG

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FIGURE 96

CTCTTACAGCAAATATCACTACCTGACATATTTTACTAGAATGTAAGCTCCATGAGGAGGGGATTTTGTTTTGTT
TACCATGGTGTTTTTAGTATTCAGAACATGCCTGCTTACATAGTAGTTGCTAAAAAATTTTTTGTTAAATGAAT
AAGTTGAATCATGTTGTTTCCAGTGTAGACAGAATAGGTATATGTGGTTGAAAAATGAACAGCACAAAGTTAGCT
CCCCAAAAATGGCAAAGTGAAATAAAGAAACATTTCTGAAGAACATTGTTGAACTGTAATCCCAGCACTTTGGGA
GGCTGGGGCAGTTGG

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FIGURE 97

GGCGGATTCTCGGGGCGAGGCGCTGGGAAGCCTGCAACCGGCCCCACAAATTCTAGCAGTGCCAAGAAGAAGGA
TAAAAGAGTTCAAGGTGGAAGAGTGATTGAGTCCCGTATCTGCAGTATGAAAAGAAGACAACCCAAAAGGCTCC
TGCAGGAGATGGGTACAGACCCGAGGGAAGATGTCTGAAGGTGGAAGGAAATCCAGCCTGCTCCAGAAAAGCAA
AGCAGATAGCAGTGGGGTCAGAAAGGGTGACCTGCAGTCCACGTTGCTGGAAGGGCATGGCACAGCTCCACCTGA
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TAGCACTGTAGCTATTTTTTATGTGATAATCTTGTGATAAAAAAGTAAACCTGTTTTGCAATTGAAGCCTCCA
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FIGURE 98

GAAGTCTAGAACAGGATGAGGTCTCAGTGGGACCTAGACCAAGGTTCTTGCTCTTCAGAATCATCACAGTAGCCA
TGGACTGGACTCTTCCATCTCAGGCACTGGCTTTGCCATCATTTTTTCAGATGTAGCCTTATCCTGCCCAGAAAGA
CTCAACACCTCACCAGGGGAAGGGATTTCTACAACCAAAACCTACTGCAGTTTTCACTTCTTTTTTTTTTCTT
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GAAAAAAAAATACTTGCACATTACAGAAATGCATAAAAGCAAAAGCAAATGTCACTCTGAATTTTCCCTTCACC
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GCTAATGTAAACATATATATTTAAATGTACACGCGCTGTTGTGCAACTTGCTTTATTCACTTAAATTTGGTAGG
TATAAAGATAGCTATCCTCTTTTAAAGGCTTTATCATTAAAGAATCCTATTAATGGATATTAAGTTGCTTTAGTT
TTGGTTGCTATTATGTCATTATTGTAAGAAACACTTTTGTG

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FIGURE 99

ATGCACACCGTGGCTACGTCCGGACCCAACGCGTCCTGGGGGGCACC GGCCAACGCCTCCGGCTGCCCGGGCTGT
GGCGCCAACGCCTCGGACGGCCCAGTCCCTTCGCCGCGGGCCGTGGACGCCTGGCTCGTGCCGCTCTTCTTCGCG
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CAGAAGCCAGGGAGCAGTGGGCTGGCCGCGCGGGCTGTGCGTCCTGGGGGAGGACAACGCCCTCTCTTGA

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FIGURE 100

MHTVATSGPNASWGAPANASGCPGCGANASDGPVP SPRAVDAWLVPLFFAALMLLGLVGNSLVIYVICRHKPMRT
VTNFYIANLAATDVTFLLCCVPFTALLYPLPGWVLGDFMCKFVNYIQQVSVQATCATLTAMSVDRWYVTVFPLRA
LHRRTPRLALAVSLSIWVGSAAVSAPVLALHRLSPGPRAYCSEAFPSRALERAFALYNLLALYLLPLLATCACYA
AMLRHLGRVAVRPAPADSALQGQVLAERAGAVRAKVSRLVAADVLLFAACWGP IQLFLVLQALGPAGSWHPRSYA
AYALKTWAHCMSYSNSALNPLLYAFLGSHFRQAFRRVCPCAPRRPRRPRRPGSPDPAAPHAELHRLGSHPPAPARA
QKPGSSGLAARGLCVLGEDNAPL

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FIGURE 101

GAGTAGCTCACCGTTACCCAAGTATGCTTCATCTCCAAACCAAACAACAGCTACATGTTCAAACGGGAGCCCC
AGAGGGATGTGAGCGAGTGAAGGTCTTTGAGGAAATGGCGTCTCGTCAGCCTATCTCGGCCCCCTCTCTTTTCATG
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FIGURE 102

AAGCTAAATAAATATAGCTTTATTTCATCTTTCAGAGATTGCCATTTAGCCTAGAAAATTACATCAAAAAGATGAAC
TGATTTTTGCTTGAAAAAGTCAACCAIGTTTAATTGCTCACACAATTTTAATTACAACAGATGTAATTTCTAATA
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CTCTAAAACTAGCTTTGGCAGTTAACAATGTGGAGAATTCAGCACAAAAAGCACCCCTAGCCCAGCCTTTTTATTT
TATTTTTTTAAATCTCTATTTAACCCCTTCAAAGTTTCCTTTGCAGCCATATGCATTTCTAGGTGGCTCTACCTGT
AGAAGGCTGCACTTTC AAGCGGCGAGGGACTTTAATTCTCACTTXCCACCACTCC

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 JANET K. JACKMAN
 BRISDELL HUNTE
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 WILLIAM I. WOOD
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<120> COMPOSITIONS AND METHODS FOR THE TREATMENT OF IMMUNE
 RELATED DISEASES

<130> P1977R1-PCT

<140> PCT/US03/028317
 <141> 2003-09-10

<150> US 60/410,340
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				20					25					30

Gly	Asp	Pro	Ser	Thr	Trp	Pro	Arg	Gly	Ser	Ala	Met	Glu	Leu	Lys
				35					40					45

Gln	Ser	Leu	Ser	Thr	His	Leu	Glu	Ala	Glu	Lys	Pro	Leu	Arg	Arg
				50					55					60

Tyr	Gly	Ala	Val	Glu	Glu	Thr	Ala	Trp	Lys	Thr	Glu	Arg	Leu	Gly
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	200	205	210
Arg Ala Glu Lys	Lys Ala Glu Pro Pro	Pro Ser Lys Pro Thr	Val
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 gtttccttca tggcctttct tgtggctcac cctatgcagt ttgtgtattt 150
 gttgacaact ttatgtgttt ttaatatggg ttttgccaaa cttgggtttt 200

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 ccgcgacgct ggtggctcat tgcacagcag tcatcgtggg ggtcgcgttg 800
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 cagcgggggag aggactgtgc cgagctgcat gactacttca atgtcctgag 1000
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 cttcatttcc ttggcctttt cgttctattc cattttgcat tatggcaggc 1250
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<210> 7

<211> 244

<212> PRT

<213> Homo sapiens

<400> 7

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Ala	Pro	Leu	Ala	Ser	Gly	Met	Met	Thr	Gly	Thr	Ile	Glu	Thr	Thr
				20					25					30
Gly	Asn	Ile	Ser	Ala	Glu	Lys	Gly	Gly	Ser	Ile	Ile	Leu	Gln	Cys
				35					40					45
His	Leu	Ser	Ser	Thr	Thr	Ala	Gln	Val	Thr	Gln	Val	Asn	Trp	Glu
				50					55					60
Gln	Gln	Asp	Gln	Leu	Leu	Ala	Ile	Cys	Asn	Ala	Asp	Leu	Gly	Trp
				65					70					75
His	Ile	Ser	Pro	Ser	Phe	Lys	Asp	Arg	Val	Ala	Pro	Gly	Pro	Gly
				80					85					90

Leu Gly Leu Thr Leu Gln Ser Leu Thr Val Asn Asp Thr Gly Glu
 95 100 105
 Tyr Phe Cys Ile Tyr His Thr Tyr Pro Asp Gly Thr Tyr Thr Gly
 110 115 120
 Arg Ile Phe Leu Glu Val Leu Glu Ser Ser Val Ala Glu His Gly
 125 130 135
 Ala Arg Phe Gln Ile Pro Leu Leu Gly Ala Met Ala Ala Thr Leu
 140 145 150
 Val Val Ile Cys Thr Ala Val Ile Val Val Val Ala Leu Thr Arg
 155 160 165
 Lys Lys Lys Ala Leu Arg Ile His Ser Val Glu Gly Asp Leu Arg
 170 175 180
 Arg Lys Ser Ala Gly Gln Glu Glu Trp Ser Pro Ser Ala Pro Ser
 185 190 195
 Pro Pro Gly Ser Cys Val Gln Ala Glu Ala Ala Pro Ala Gly Leu
 200 205 210
 Cys Gly Glu Gln Arg Gly Glu Asp Cys Ala Glu Leu His Asp Tyr
 215 220 225
 Phe Asn Val Leu Ser Tyr Arg Ser Leu Gly Asn Cys Ser Phe Phe
 230 235 240

Thr Glu Thr Gly

<210> 8
 <211> 1336
 <212> DNA
 <213> Homo sapiens

<400> 8
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 tgattctgac agtgagggtg acaaaaagtt aaagaggaaa aagcaagttg 150
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 taattgatat tagagaatat tggatggatc ctgaaggtga aatgaaacca 350
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 acagatttct gacattgatg atgcagtaag aaaactgtaa aattcgagcc 450
 atataaataa aacctgtact gttctagttg ttttaatctg tctttttaca 500
 ttagcttttg ttttctaaat gttctccaag ctattgtatg tttggattgc 550
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 attgagtga gctaattgtc aactttatta aggattactt tgtctgcca 650
 ccacctagtg taaaataaaa tcaagtaata caatcttaac tgttggtggc 700
 ttttttgatc ataagagttg gtactgttta aggccaaaag taacagtttt 750

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 atttgataaa caacatggct tgtgtgaaaa ctgagcaggt gtttgtttac 1150
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 ttgtgaaagc ttaaaaaaaaa aaaaaaaaaa aaaaaa 1336

<210> 9
 <211> 127
 <212> PRT
 <213> Homo sapiens

<400> 9
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 Asp Ser Asp Ser Glu Val Asp Lys Lys Leu Lys Arg Lys Lys Gln
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 Val Ala Pro Glu Lys Pro Val Lys Lys Gln Lys Thr Gly Glu Thr
 35 40 45
 Ser Arg Ala Leu Ser Ser Ser Lys Gln Ser Ser Ser Ser Arg Asp
 50 55 60
 Asp Asn Met Phe Gln Ile Gly Lys Met Arg Tyr Val Ser Val Arg
 65 70 75
 Asp Phe Lys Gly Lys Val Leu Ile Asp Ile Arg Glu Tyr Trp Met
 80 85 90
 Asp Pro Glu Gly Glu Met Lys Pro Gly Arg Lys Gly Ile Ser Leu
 95 100 105
 Asn Pro Glu Gln Trp Ser Gln Leu Lys Glu Gln Ile Ser Asp Ile
 110 115 120
 Asp Asp Ala Val Arg Lys Leu
 125

<210> 10
 <211> 880
 <212> DNA
 <213> Homo sapiens

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 gacgtcagcg tccacaaagg tcggagagat cttctcggcg gccggcgccg 150

ccttcacgaa gctcggggag ctgacgatgc agctgcatcc cgtggccgac 200
 tcttctcctg cgggcgcgaa gtggacggag acggaaatag agatgctgag 250
 ggctgctgtg aagcgatttg gggacgatct taatcacatc agctgtgtca 300
 tcaaggaacg gacagtggcc cagataaagg ccaactgtgaa acgcaaggta 350
 tatgaagatt ctggcatccc ccttcagct gagtcaccca agaaagggcc 400
 caagaaggtg gcatctggtg tcttgcacc tcttcagct gcccctctc 450
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 gctgacctc ctctctctc ctgctgagcc ttccacctct gacctctcac 700
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<210> 11
 <211> 224
 <212> PRT
 <213> Homo sapiens

<400> 11
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 Gly Ala Met Thr Ser Ala Ser Thr Lys Val Gly Glu Ile Phe Ser
 35 40 45
 Ala Ala Gly Ala Ala Phe Thr Lys Leu Gly Glu Leu Thr Met Gln
 50 55 60
 Leu His Pro Val Ala Asp Ser Ser Pro Ala Gly Ala Lys Trp Thr
 65 70 75
 Glu Thr Glu Ile Glu Met Leu Arg Ala Ala Val Lys Arg Phe Gly
 80 85 90
 Asp Asp Leu Asn His Ile Ser Cys Val Ile Lys Glu Arg Thr Val
 95 100 105
 Ala Gln Ile Lys Ala Thr Val Lys Arg Lys Val Tyr Glu Asp Ser
 110 115 120
 Gly Ile Pro Leu Pro Ala Glu Ser Pro Lys Lys Gly Pro Lys Lys
 125 130 135
 Val Ala Ser Gly Val Leu Ser Pro Pro Pro Ala Ala Pro Pro Pro
 140 145 150
 Ser Ser Ser Ser Val Pro Glu Ala Gly Gly Pro Pro Ile Lys Lys
 155 160 165

Gln	Lys	Ala	Asp	Val	Thr	Leu	Ser	Ala	Leu	Asn	Asp	Ser	Asp	Ala
				170					175					180
Asn	Ser	Asp	Val	Val	Asp	Ile	Glu	Gly	Leu	Gly	Glu	Thr	Pro	Pro
				185					190					195
Ala	Lys	Lys	Leu	Asn	Phe	Asp	Gln	Asp	Ser	Leu	Thr	Leu	Asp	Ser
				200					205					210
Gly	Leu	Leu	Met	Thr	Ser	Ala	Asp	Pro	Pro	Leu	Leu	Ser	Cys	
				215					220					

<210> 12
 <211> 2233
 <212> DNA
 <213> Homo sapiens

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 ctccagcagt ggtggtggtg gccattgtag gactgtaccg tacagggaaa 400
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 acccatccaa gccaaaccac accctgggtc ttctggacac cgaaggtctg 550
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 ggctgtgctc ctgtgcagca cctttgtcta caacagcatg agcaccatca 650
 accaccaggc cctggagcag ctgcattatg tgacggagct cacagaacta 700
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 gtttgtgagt ttcttccag actttctttg gacagtacgg gatttactc 800
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gccagcagat ggcccagcga gtgaagctcc ccacagacac gctccaggag 1300
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<210> 13
 <211> 633
 <212> PRT
 <213> Homo sapiens

<400> 13
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 20 25 30
 Leu Glu Lys Ile Ser Gln Pro Val Val Val Val Ala Ile Val Gly
 35 40 45
 Leu Tyr Arg Thr Gly Lys Ser Tyr Leu Met Asn His Leu Ala Gly
 50 55 60
 Gln Asn His Gly Phe Pro Leu Gly Ser Thr Val Gln Ser Glu Thr
 65 70 75
 Lys Gly Ile Trp Met Trp Cys Val Pro His Pro Ser Lys Pro Asn
 80 85 90
 His Thr Leu Val Leu Leu Asp Thr Glu Gly Leu Gly Asp Val Glu
 95 100 105
 Lys Gly Asp Pro Lys Asn Asp Ser Trp Ile Phe Ala Leu Ala Val
 110 115 120

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

Ser Gln Met Val Ile Glu Glu Ser Ile Leu Gln Ser Asp Lys Ala
 470 475 480
 Leu Thr Asp Arg Glu Lys Ala Val Ala Val Asp Arg Ala Lys Lys
 485 490 495
 Glu Ala Ala Glu Lys Glu Gln Glu Leu Leu Lys Gln Lys Leu Gln
 500 505 510
 Glu Gln Gln Gln Gln Met Glu Ala Gln Val Lys Ser Arg Lys Glu
 515 520 525
 Asn Ile Ala Gln Leu Lys Glu Lys Leu Gln Met Glu Arg Glu His
 530 535 540
 Leu Leu Arg Glu Gln Ile Met Met Leu Glu His Thr Gln Lys Val
 545 550 555
 Gln Asn Asp Trp Leu His Glu Gly Phe Lys Lys Lys Tyr Glu Glu
 560 565 570
 Met Asn Ala Glu Ile Ser Gln Phe Lys Arg Met Ile Asp Thr Thr
 575 580 585
 Lys Asn Asp Asp Thr Pro Trp Ile Ala Arg Thr Leu Asp Asn Leu
 590 595 600
 Ala Asp Glu Leu Thr Ala Ile Leu Ser Ala Pro Ala Lys Leu Ile
 605 610 615
 Gly His Gly Val Lys Gly Val Ser Ser Leu Phe Lys Lys His Lys
 620 625 630
 Leu Pro Phe

<210> 14
 <211> 1249
 <212> DNA
 <213> Homo sapiens

<400> 14
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 tagtcaaatt aatattttta ctaatacatc ttagcagagt ttagttaagc 200
 acaaagttaa cagtgggtag gattgaatct tgaaagtaat catgtctgta 250
 atgtttttca tgcattgcaa aagcacagac aaaaccactc atgccctatt 300
 aataaacaaa atacagatca aagttttcaa aagtaatcac tctattttatt 350
 ctaaagtgtc gtggcttttag gaaaatacca ccagctagta cttacctatt 400
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 aaatataaat ttttggtaaa agtatcaaac attcatcttg cccatttttc 650

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 aaatatagat aagggttgga tatttgagga tccatttgtg gaactgaatt 750
 taatgagact tcattggtga tacactcaat ttttactggg taattagcta 800
 ataatglttg tcaactgtctc acagttcaag tagctttaag atgatgtggc 850
 aaggaaaaca caaagctttt gggtaaccag cgttctttaa tgtatgggtt 900
 ttgaccaggt gaacccttta gaagtgattt ctgtttttaa agtatgtact 950
 taaaatacct ttggctgtga tgaatgtaga tcccagcaga ataccaaaat 1000
 cctatttttt ttgactgagt atttgtagat gcttaatgac tgaaatgaat 1050
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 attatttaat gttaagttta gtatcaagat acagttgttt ttaaaatgcc 1150
 aaaatgctgt ttattataca gaatatttta ttacatttgc aatatctttg 1200
 tatatagtga tttttttctt gataataaat ggaaaaattc taaaacaaa 1249

<210> 15
 <211> 810
 <212> DNA
 <213> Homo sapiens

<220>
 <221> unsure
 <222> 688, 734, 762, 788
 <223> unknown base

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 cacaccatcc tccagtgtgg gcagctctgt agaaattagt ttagaaaatt 200
 ctgaactgtt taaagatttg tctgatgcca ttgagcaaac ctttcagagg 250
 agaaatagtg aaaccaaagt ggcacgtagc acgaggctac agaaggattt 300
 agaaaacgaa ggtcttgtat ggatttcact tccacttcct tccacttccc 350
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 agtatgtctc ccataaaaga aactgtgtcc tccagacaaa aaccgcagat 450
 ggcacctccc gtctcagatc cagaaaacag ccagggccct gctgctggtt 500
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 gcaaatacta aagccacttc ccagttcaaa ggctaccgga gaagatcctc 600
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 ttaatggaga aagaaagcag tattgacatt tccctgcanag tctgtggcaa 700
 gagggaaagt accatctatg ctgaaatgat ctgnctagtt ccattctttg 750
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 acttttttga 810

<210> 16
 <211> 1923
 <212> DNA
 <213> Homo sapiens

<400> 16
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 cagcccgtgg tgggtggtggc cattgtaggg ctataccgca caggaaaatc 200
 ctatctcatg aatcgtcttg caggaaagcg caatggcttc cctctgggct 250
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<211> 640

<212> PRT

<213> Homo sapiens

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Leu	Leu	Ser	Ser	Ser	Phe	Val	Tyr	Asn	Ser	Val	Ser	Thr	Ile	Asn
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Leu	Ile	Arg	Ala	Lys	Ser	Cys	Pro	Arg	Pro	Asp	Glu	Ala	Glu	Asp
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Ser	Ser	Glu	Phe	Ala	Ser	Phe	Phe	Pro	Asp	Phe	Ile	Trp	Thr	Val
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Arg	Asp	Phe	Thr	Leu	Glu	Leu	Lys	Leu	Asp	Gly	Asn	Pro	Ile	Thr
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Asn	Ile	Ala	Gln	Leu	Lys	Lys	Lys	Met	Glu	Arg	Glu	Arg	Glu	Asn	545	550	555
Leu	Leu	Arg	Glu	His	Glu	Arg	Leu	Leu	Lys	His	Lys	Leu	Lys	Val	560	565	570
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      687, 689, 692-694, 697-698, 702, 704, 711, 713, 716, 718-719,
      721, 723-725, 728, 730-731, 736, 740, 742, 744, 746, 748-749,
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<212> PRT

<213> Homo sapiens

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Ala	Asp	His	Leu	Lys 350	Lys	Cys	Ser	Tyr	Asn 355	Val	Val	Glu	Lys	Arg 360
Glu	Glu	Ala	Ile	Pro 365	Leu	Pro	Cys	Met	Cys 370	Val	Thr	Arg	Glu	Leu 375

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 <212> PRT
 <213> Homo sapiens

<400> 24

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

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

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 <211> 476
 <212> DNA
 <213> Homo sapiens

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

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

Leu Trp

<210> 28
 <211> 2140
 <212> DNA
 <213> Homo sapiens

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<210> 29
 <211> 269
 <212> PRT
 <213> Homo sapiens

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

Pro	Ala	Pro	Met	Val	Phe	Trp	Lys	Val	Pro	Arg	Ser	Gly	Ile	Glu
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Asn	Ser	Thr	Val	Thr	Leu	Ser	His	Pro	Asn	Gly	Thr	Thr	Ser	Val
				185					190					195
Thr	Ser	Ile	Leu	His	Ile	Lys	Asp	Pro	Lys	Asn	Gln	Val	Gly	Lys
				200					205					210
Glu	Val	Ile	Cys	Gln	Val	Leu	His	Leu	Gly	Thr	Val	Thr	Asp	Phe
				215					220					225
Lys	Gln	Thr	Val	Asn	Lys	Gly	Tyr	Trp	Phe	Ser	Val	Pro	Leu	Leu
				230					235					240
Leu	Ser	Ile	Val	Ser	Leu	Val	Ile	Leu	Leu	Val	Leu	Ile	Ser	Ile
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Leu	Leu	Tyr	Trp	Lys	Arg	His	Arg	Asn	Gln	Asp	Arg	Glu	Pro	
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 <211> 2142
 <212> DNA
 <213> Homo sapiens

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<210> 31

<211> 344

<212> PRT

<213> Homo sapiens

<400> 31

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				20					25					30
Ser	Ser	Tyr	Ser	Cys	Gly	Arg	Lys	Lys	Lys	Val	Asn	Pro	Tyr	Glu
				35					40					45
Glu	Val	Asp	Gln	Glu	Lys	Tyr	Ser	Asn	Leu	Val	Gln	Ser	Val	Leu
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 taaaggcaga agaaaacaga aaattgcaaa agatgaagga tgaacaacat 800
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 tcatttatgc atgtttggag gagctgattc ctgaactcat atttaaactc 1200
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 aatcagagct atgggtgcta caggcttgtc tttctaagt acatattctt 1350
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 aaaaaaaaa 1508

<210> 35
 <211> 307
 <212> PRT
 <213> Homo sapiens

<400> 35
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 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		
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Ser Gly Asn Ser	Trp Gly Ile				
	305				

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 <211> 1686
 <212> DNA
 <213> Homo sapiens

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 gcaaggggaag caacatgttt cattcaggag gggttttttca tccagtgccca 400
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<210> 37
 <211> 272
 <212> PRT
 <213> Homo sapiens

<400> 37
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 35 40 45
 Val Leu Val Gln Gly Pro Gln Lys Gln Trp Leu His Leu Ser Ala
 50 55 60
 Ala Gln Cys Val Ala Lys Glu Arg Arg Pro Leu Asp Ala His Pro
 65 70 75
 Pro Gln Pro Gly Val Leu Arg His Lys Gln Gly Lys Gln His Val
 80 85 90
 Ser Phe Arg Arg Val Phe Ser Ser Ser Ala Thr Ala Gln Gly Thr
 95 100 105
 Pro Glu Lys Lys Glu Glu Pro Asp Pro Leu Gln Asp Lys Ser Ile
 110 115 120
 Ser Leu Tyr Gln Arg Phe Lys Lys Thr Phe Arg Gln Tyr Gly Lys
 125 130 135
 Val Leu Ile Pro Val His Leu Ile Thr Ser Gly Val Trp Phe Gly
 140 145 150
 Thr Phe Tyr Tyr Ala Ala Leu Lys Gly Val Asn Val Val Pro Phe
 155 160 165

Leu Glu Leu Ile Gly Leu Pro Asp Ser Val Val Ser Ile Leu Lys
 170 175 180
 Asn Ser Gln Ser Gly Asn Ala Leu Thr Ala Tyr Ala Leu Phe Lys
 185 190 195
 Ile Ala Thr Pro Ala Arg Tyr Thr Val Thr Leu Gly Gly Thr Ser
 200 205 210
 Val Thr Val Lys Tyr Leu Arg Ser His Gly Tyr Met Ser Thr Pro
 215 220 225
 Pro Pro Val Lys Glu Tyr Leu Gln Asp Arg Met Glu Glu Thr Lys
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 Glu Lys Leu Gln Glu Thr Lys Glu Lys Val Ser Phe Lys Lys Lys
 260 265 270
 Val Glu

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 <211> 4130
 <212> DNA
 <213> Homo sapiens

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<210> 39

<211> 376

<212> PRT

<213> Homo sapiens

<400> 39

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

370

375

Pro

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 <211> 452
 <212> DNA
 <213> Homo sapiens

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 aa 452

<210> 41
 <211> 94
 <212> PRT
 <213> Homo sapiens

<400> 41
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 Lys Lys Leu Leu Glu Val Lys Leu Gly Glu Leu Pro Ser Trp Ile
 20 25 30
 Leu Met Arg Asp Phe Ser Pro Ser Gly Ile Phe Gly Ala Phe Gln
 35 40 45
 Arg Gly Tyr Tyr Arg Tyr Tyr Asn Lys Tyr Ile Asn Val Lys Lys
 50 55 60
 Gly Ser Ile Ser Gly Ile Thr Met Val Leu Ala Cys Tyr Val Leu
 65 70 75
 Phe Ser Tyr Ser Phe Ser Tyr Lys His Leu Lys His Glu Arg Leu
 80 85 90
 Arg Lys Tyr His

<210> 42
 <211> 2479
 <212> DNA
 <213> Homo sapiens

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 cctcagataa aatgcagagt aatatatagt tgcactttat aaatggtggt: 2050
 taaatggaaa tgttcaagcc attttatagt tgtgatgcac aatataattt: 2100
 aagtgtctct gtcaaagtat tcttcacagta caatttgtat agtttgctgc: 2150
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 attatccagt ctgccttacc cttaatctgt tcacagatat ttatttacta 2350
 atgctttttt tttcttaaga gttatgggat aggaaaatga agtgtttgct: 2400
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<210> 43
 <211> 184
 <212> PRT
 <213> Homo sapiens

<400> 43
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 Asp Glu Glu Tyr Pro Pro Gln Met Gly Glu Glu Tyr Ser Gln Ile
 35 40 45
 Ile Tyr Ser Thr Lys Leu Tyr Arg Phe Phe Lys Tyr Ile Glu Asn
 50 55 60
 Arg Asp Val Ala Lys Ser Val Leu Lys Glu Arg Gly Leu Lys Lys
 65 70 75
 Ile Arg Leu Gly Ile Glu Gly Tyr Pro Thr Tyr Lys Glu Lys Val
 80 85 90
 Lys Lys Arg Pro Gly Gly Arg Pro Glu Val Ile Tyr Asn Tyr Val
 95 100 105
 Gln Arg Pro Phe Ile Arg Met Ser Trp Glu Lys Glu Glu Gly Lys
 110 115 120
 Ser Arg His Val Asp Phe Gln Cys Val Lys Ser Lys Ser Ile Thr
 125 130 135
 Asn Leu Ala Ala Ala Ala Ala Asp Ile Pro Gln Asp Gln Leu Val
 140 145 150
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 Ile His Pro Pro Ser Gly Asn Ser Asp Leu Asp Pro Asp Ala Gln
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 Asn Pro Met Leu

<210> 44
 <211> 2286
 <212> DNA
 <213> Homo sapiens

<400> 44
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<210> 45
 <211> 183
 <212> PRT
 <213> Homo sapiens

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

Arg Leu Gln Val Glu Lys Asp Arg Leu Arg Ile Gln Lys Glu Gly
 170 175 180

His Leu Gln

<210> 46
 <211> 832
 <212> DNA
 <213> Homo sapiens

<220>
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 <222> 779
 <223> unknown base

<400> 46
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 aactaaaaca aaatgataag agctgtgaac tgaaattgta ttgcttacag 200
 aaatcatgaa ctgaattttc ttctcttttt aaagtgcagca taaagactta 250
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<210> 47
 <211> 2156
 <212> DNA
 <213> Homo sapiens

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<210> 48
 <211> 601
 <212> PRT
 <213> Homo sapiens

<400> 48
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 35 40 45
 Glu Pro Leu Pro Cys Tyr Gln Leu Glu Leu Asp Ala Ala Val Ala
 50 55 60
 Glu Val Lys Leu Arg Asp Asp Gln Tyr Thr Leu Glu His Met His
 65 70 75
 Ala Phe Gly Met Tyr Asn Tyr Leu His Cys Asp Ser Trp Tyr Gln
 80 85 90
 Asp Ser Val Tyr Tyr Ile Asp Thr Leu Gly Arg Ile Met Asn Leu
 95 100 105
 Thr Val Met Leu Asp Thr Ala Leu Gly Lys Pro Arg Glu Val Phe
 110 115 120
 Arg Leu Pro Thr Asp Leu Thr Ala Cys Asp Asn Arg Leu Cys Ala
 125 130 135
 Ser Ile His Phe Ser Ser Ser Thr Trp Val Thr Leu Ser Asp Gly
 140 145 150
 Thr Gly Arg Leu Tyr Val Ile Gly Thr Gly Glu Arg Gly Asn Ser
 155 160 165
 Ala Ser Glu Lys Trp Glu Ile Met Phe Asn Glu Glu Leu Gly Asp
 170 175 180
 Pro Phe Ile Ile Ile His Ser Ile Ser Leu Leu Asn Ala Glu Glu
 185 190 195
 His Ser Ile Ala Thr Leu Leu Leu Arg Ile Glu Lys Glu Glu Leu
 200 205 210
 Asp Met Lys Gly Ser Gly Phe Tyr Val Ser Leu Glu Trp Val Thr
 215 220 225
 Ile Ser Lys Lys Asn Gln Asp Asn Lys Lys Tyr Glu Ile Ile Lys
 230 235 240
 Arg Asp Ile Leu Arg Gly Lys Ser Val Pro His Tyr Ala Ala Ile
 245 250 255
 Glu Pro Asp Gly Asn Gly Leu Met Ile Val Ser Tyr Lys Ser Phe
 260 265 270
 Thr Phe Val Gln Ala Gly Gln Asp Leu Glu Glu Asn Met Asp Glu

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

<210> 49

<211> 1527

<212> DNA

<213> Homo sapiens

<400> 49

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<210> 50

<211> 475

<212> PRT

<213> Homo sapiens

<400> 50

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

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

<210> 51
 <211> 392
 <212> DNA
 <213> Homo sapiens

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 ctgtgtaata aagtagttga aaataatttt aaattatcac atgagcatta 200
 gtactttata aaaattgata tagaagactc tttagagaat gctaccagg 250
 attgtttgtc aataagaaaa caaatgagg cctatgatt ctaggtgaat 300
 tttaaaaaaa tttttcccca aggaacaatt cttaaaactt tcagttacag 350
 ggaagagaag aaaattgtac cttctaacag ttatttgttt tg 392

<210> 52
 <211> 2846
 <212> DNA
 <213> Homo sapiens

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 agtaatgggg ctgtgcatag gggagttgaa cgatgataca aggagtgact 150
 ccaaatttgc atatactgga actgaaatgc gcacagttgc tgaaaaggtt 200
 gatgccgtca gaattgttca cattcattct gtcacatct tacgacgttc 250

tgataagagg aaggaccgag tagaaatttc tccagagcag ctgtctgcag 300
 cttcaacaga ggcagagagg ttggctgaac tgacaggccg ccccatgaga 350
 gttgtgggct ggtatcattc ccatcctcat ataactgttt ggccttcaca 400
 tgttgatgtt cgcacacaag ccatgtacca gatgatggat caaggctttg 450
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<210> 53
 <211> 316
 <212> PRT
 <213> Homo sapiens

<400> 53
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 Lys Glu Glu Val Met Gly Leu Cys Ile Gly Glu Leu Asn Asp Asp
 35 40 45
 Thr Arg Ser Asp Ser Lys Phe Ala Tyr Thr Gly Thr Glu Met Arg
 50 55 60
 Thr Val Ala Glu Lys Val Asp Ala Val Arg Ile Val His Ile His
 65 70 75
 Ser Val Ile Ile Leu Arg Arg Ser Asp Lys Arg Lys Asp Arg Val
 80 85 90
 Glu Ile Ser Pro Glu Gln Leu Ser Ala Ala Ser Thr Glu Ala Glu
 95 100 105
 Arg Leu Ala Glu Leu Thr Gly Arg Pro Met Arg Val Val Gly Trp
 110 115 120
 Tyr His Ser His Pro His Ile Thr Val Trp Pro Ser His Val Asp
 125 130 135
 Val Arg Thr Gln Ala Met Tyr Gln Met Met Asp Gln Gly Phe Val

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

Glu

<210> 54
 <211> 2694
 <212> DNA
 <213> Homo sapiens

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 cttaaagaaa ttcagatatg tgaagttgat ttccatggag acctcgtcac 200
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 tattaataaac tagtctgtgg ttctttgcag tttcttgtaa attataaac 2350

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<210> 55

<211> 371

<212> PRT

<213> Homo sapiens

<400> 55

Met	Asp	Ala	Arg	Arg	Val	Pro	Gln	Lys	Asp	Leu	Arg	Val	Lys	Lys
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				20					25					30

Ser	Ser	Ser	Ser	Asp	Asp	Ser	Cys	Asp	Ser	Phe	Ala	Ser	Asp	Asn
				35					40					45

Phe	Ala	Asn	Thr	Arg	Leu	Gln	Ser	Val	Arg	Glu	Gly	Cys	Arg	Thr
				50					55					60

Arg	Ser	Gln	Cys	Arg	His	Ser	Gly	Pro	Leu	Arg	Val	Ala	Met	Lys
				65					70					75

Phe	Pro	Ala	Arg	Ser	Thr	Arg	Gly	Ala	Thr	Asn	Lys	Lys	Ala	Glu
				80					85					90

Ser	Arg	Gln	Pro	Ser	Glu	Asn	Ser	Val	Thr	Asp	Ser	Asn	Ser	Asp
				95					100					105

Ser	Glu	Asp	Glu	Ser	Gly	Met	Asn	Phe	Leu	Glu	Lys	Arg	Ala	Leu
				110					115					120

Asn	Ile	Lys	Gln	Asn	Lys	Ala	Met	Leu	Ala	Lys	Leu	Met	Ser	Glu
				125					130					135

Leu	Glu	Ser	Phe	Pro	Gly	Ser	Phe	Arg	Gly	Arg	His	Pro	Leu	Pro
				140					145					150

Gly	Ser	Asp	Ser	Gln	Ser	Arg	Arg	Pro	Arg	Arg	Arg	Thr	Phe	Pro
				155					160					165

Gly	Val	Ala	Ser	Arg	Arg	Asn	Pro	Glu	Arg	Arg	Ala	Arg	Pro	Leu
				170					175					180

Thr	Arg	Ser	Arg	Ser	Arg	Ile	Leu	Gly	Ser	Leu	Asp	Ala	Leu	Pro
				185					190					195

Met	Glu	Glu	Glu	Glu	Glu	Glu	Asp	Lys	Tyr	Met	Leu	Val	Arg	Lys
				200					205					210

Arg	Lys	Thr	Val	Asp	Gly	Tyr	Met	Asn	Glu	Asp	Asp	Leu	Pro	Arg
				215					220					225

Ser	Arg	Arg	Ser	Arg	Ser	Ser	Val	Thr	Leu	Pro	His	Ile	Ile	Arg
				230					235					240

Pro	Val	Glu	Glu	Ile	Thr	Glu	Glu	Glu	Leu	Glu	Asn	Val	Cys	Ser

	245		250		255
Asn Ser Arg Glu	Lys Ile Tyr Asn Arg	Ser Leu Gly Ser Thr	Cys		
	260	265	270		
His Gln Cys Arg	Gln Lys Thr Ile Asp	Thr Lys Thr Asn Cys	Arg		
	275	280	285		
Asn Pro Asp Cys	Trp Gly Val Arg Gly	Gln Phe Cys Gly Pro	Cys		
	290	295	300		
Leu Arg Asn Arg	Tyr Gly Glu Glu Val	Arg Asp Ala Leu Leu	Asp		
	305	310	315		
Pro Asn Trp His	Cys Pro Pro Cys Arg	Gly Ile Cys Asn Cys	Ser		
	320	325	330		
Phe Cys Arg Gln	Arg Asp Gly Arg Cys	Ala Thr Gly Val Leu	Val		
	335	340	345		
Tyr Leu Ala Lys	Tyr His Gly Phe Gly	Asn Val His Ala Tyr	Leu		
	350	355	360		
Lys Ser Leu Lys	Gln Glu Phe Glu Met	Gln Ala			
	365	370			

<210> 56
 <211> 1859
 <212> DNA
 <213> Homo sapiens

<400> 56
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 ctgggcaaca aagtgagact ctgcctcaaa aaataaaaaa aaaaaaaaaa 1850
 aaaaaaaaaa 1859

<210> 57
 <211> 344
 <212> PRT
 <213> Homo sapiens

<400> 57
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 Arg Pro Glu Asp Tyr Phe Ile Gly Ala Thr Pro Leu Gln Lys Arg
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 Leu Glu Ser Val Arg Lys Gln Ser Ser Phe Ile Leu Thr Pro Pro
 35 40 45
 Arg Arg Lys Ile Pro Gln Cys Ser Gln Leu Gln Glu Asp Val Asp
 50 55 60
 Pro Gln Lys Val Ala Phe Leu Leu His Lys Gln Trp Thr Leu Tyr
 65 70 75
 Ser Leu Thr Pro Leu Tyr Lys Phe Ser Tyr Ser Asn Leu Lys Glu
 80 85 90
 Tyr Ser Arg Leu Leu Asn Ala Phe Ile Val Ala Glu Lys Gln Lys
 95 100 105
 Gly Leu Ala Val Glu Val Gly Glu Asp Phe Asn Ile Lys Val Ile
 110 115 120

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

<210> 58
 <211> 2717
 <212> DNA
 <213> Homo sapiens

<400> 58
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 aggccatgga aacccaaca cctttgccgc ctgtaccgc cccccgacc 300
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 <212> PRT
 <213> Homo sapiens

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 Val Gly Gly Glu Gly Ser Glu Leu Gly Glu Val Leu Gln Ile Gln

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Ser Gly Val Phe	Pro Arg Pro His Gly 245	Pro His Pro Leu 250	Met 255
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Thr Gln Pro Gly	Gly Ala Lys Glu Glu 305	Thr Lys Val Phe Ser 310	Gly 315
Gly Asp Thr Glu	Gly Asn Gly Glu Leu 320	Gly Phe Leu Leu Pro 325	Ser 330
Gly Pro Gly Pro	Thr Ser Gly Gly Gly 335	Gly Pro Ser Trp Lys 340	Pro 345
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Arg Phe Ala Val	Lys Pro Lys Arg Asp 395	Arg His Ile Met Leu 400	Thr 405
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<211> 787

<212> DNA

<213> Homo sapiens

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 <211> 149
 <212> PRT
 <213> Homo sapiens

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 80 85 90
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<211> 369

<212> PRT

<213> Homo sapiens

<400> 63

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Ser	Leu	Leu	Ser	Asp	Gln	Leu	Gly	Cys	Glu	Val	Leu	Asn	Leu	Leu
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Thr	Ala	Gln	Gln	Tyr	Glu	Ile	Phe	Ser	Arg	Ser	Leu	Arg	Lys	Asn
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Arg	Glu	Leu	Phe	Val	His	Gly	Leu	Pro	Gly	Ser	Gly	Lys	Thr	Ile
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Met	Ala	Met	Lys	Ile	Met	Glu	Lys	Ile	Arg	Asn	Val	Phe	His	Cys
				80					85					90
Glu	Ala	His	Arg	Ile	Leu	Tyr	Val	Cys	Glu	Asn	Gln	Pro	Leu	Arg
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Asn	Phe	Ile	Ser	Asp	Arg	Asn	Ile	Cys	Arg	Ala	Glu	Thr	Arg	Lys
				110					115					120
Thr	Phe	Leu	Arg	Glu	Asn	Phe	Glu	His	Ile	Gln	His	Ile	Val	Ile
				125					130					135
Asp	Glu	Ala	Gln	Asn	Phe	Arg	Thr	Glu	Asp	Gly	Asp	Trp	Tyr	Gly
				140					145					150
Lys	Ala	Lys	Ser	Ile	Thr	Arg	Arg	Ala	Lys	Gly	Gly	Pro	Gly	Ile
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Leu	Trp	Ile	Phe	Leu	Asp	Tyr	Phe	Gln	Thr	Ser	His	Leu	Asp	Cys
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Ser	Gly	Leu	Pro	Pro	Leu	Ser	Asp	Gln	Tyr	Pro	Arg	Glu	Glu	Leu
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Thr	Arg	Ile	Val	Arg	Asn	Ala	Asp	Pro	Ile	Ala	Lys	Tyr	Leu	Gln
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Lys	Glu	Met	Gln	Val	Ile	Arg	Ser	Asn	Pro	Ser	Phe	Asn	Ile	Pro
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Thr	Gly	Cys	Leu	Glu	Val	Phe	Pro	Glu	Ala	Glu	Trp	Ser	Gln	Gly
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Val	Gln	Gly	Thr	Leu	Arg	Ile	Lys	Lys	Tyr	Leu	Thr	Val	Glu	Gln
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Ile	Met	Thr	Cys	Val	Ala	Asp	Thr	Cys	Arg	Arg	Phe	Phe	Asp	Arg
				260					265					270
Gly	Tyr	Ser	Pro	Lys	Asp	Val	Ala	Val	Leu	Val	Ser	Thr	Ala	Lys
				275					280					285
Glu	Val	Glu	His	Tyr	Lys	Tyr	Glu	Leu	Leu	Lys	Ala	Met	Arg	Lys
				290					295					300
Lys	Arg	Val	Val	Gln	Leu	Ser	Asp	Ala	Cys	Asp	Met	Leu	Gly	Asp
				305					310					315
His	Ile	Val	Leu	Asp	Ser	Val	Arg	Arg	Phe	Ser	Gly	Leu	Glu	Arg
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Ser	Ile	Val	Phe	Gly	Ile	His	Pro	Arg	Thr	Ala	Asp	Pro	Ala	Ile
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 <211> 559
 <212> DNA
 <213> Homo sapiens

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 <211> 80
 <212> PRT
 <213> Homo sapiens

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 35 40 45
 Val Phe Arg Asn Ser Leu Leu Ile Leu Leu Asp Leu Phe Phe Ala
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 <211> 1450
 <212> DNA
 <213> Homo sapiens

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<210> 67

<211> 147

<212> PRT

<213> Homo sapiens

<400> 67

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Phe His Trp Gln Ala Thr Ile Met Gly Pro Asn Asp Ser Pro Tyr

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Pro Asn Ile Asn	Ser Asn Gly Ser Ile Cys Leu Asp Ile Leu Arg				
	80		85		90
Ser Gln Trp Ser	Pro Ala Leu Thr Ile Ser Lys Val Leu Leu Ser				
	95		100		105
Ile Cys Ser Leu	Leu Cys Asp Pro Asn Pro Asp Asp Pro Leu Val				
	110		115		120
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 <212> DNA
 <213> Homo sapiens

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 <222> 37
 <223> unknown base

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 <211> 2192
 <212> DNA
 <213> Homo sapiens

<400> 69
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gaatccgctg tgtggcttac aataaccagt caaacagatt ggctgtttca 150
 cgaacagatg gcactgtgga aatttataac ttgtcagcaa actactttca 200
 ggagaaatth ttcccaggte atgagtctcg ggctacagaa gctttgtgct 250
 gggcagaagg acagcgactc tttagtgtcg ggctcaatgg cgagattatg 300
 gagtatgatt tacaggcggt aaacatcaag tatgctatgg atgcctttgg 350
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 gacaggcagt atatggcggt gtctaagcgg aagtgcacg tgtggggtgt 650
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<210> 70
 <211> 686
 <212> PRT
 <213> Homo sapiens

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

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

Ile Ser Phe His	Pro Lys Arg Pro Met	His Ile Leu Leu His Asp
	590	595 600
Ala Tyr Met Phe	Cys Ile Ile Asp Lys	Ser Leu Pro Leu Pro Asn
	605	610 615
Asp Lys Thr Leu	Leu Tyr Asn Pro Phe	Pro Pro Thr Asn Glu Ser
	620	625 630
Asp Val Ile Arg	Arg Arg Thr Ala His	Ala Phe Lys Ile Ser Lys
	635	640 645
Ile Tyr Lys Pro	Leu Leu Phe Met Asp	Leu Leu Asp Glu Arg Thr
	650	655 660
Leu Val Ala Val	Glu Arg Pro Leu Asp	Asp Ile Ile Ala Gln Leu
	665	670 675
Pro Pro Pro Ile	Lys Lys Lys Lys Phe	Gly Thr
	680	685

<210> 71

<211> 1482

<212> DNA

<213> Homo sapiens

<400> 71

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gcggggagac aagaccggc gacctcgcg atccctcgag ccgccacgcg 150
ctctcgccac cgggcggcga cgggccgcgg agccggcgcg gccatggcga 200
cgggcggcca gcagaaggag aacacgctgc ttcacctctt cgccggcggg 250
tgtggaggca cagttggtgc tattttcact tgtccactag aagtcattaa 300
gacacgggtg cagtcttcaa gattagctct ccggacagtc tactatcctc 350
aggttcactt ggggaccatt agtggagctg gaatggtgag accaacaatc 400
gtgacacctg gactctttca ggttctgaag tcgatcttgg agaaagaggg 450
accaaagtca ctttttagag gcttgggtcc aaatttggtt ggagttgcac 500
catcaagggc tgtatacttt gcatgttact ccaaagccaa agagcaattt 550
aatggcattt tcgtgcctaa cagcaatatt gtgcatattt tctcagctgg 600
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tcttttgtcc agacggcgcg cctggtgttc cggaagaag gctaccttgc 1050

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cttttataga ggactgtttg cccagcttat ccggcagatc ccaaatactg 1100
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 ctctagagaa ttttttttcc ccattgatgt ttagaaagtt tgagactgaa 1250
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 aattataact tttttttaac ttaagaggat tcagggttaa gcaccaacta 1400
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 aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa cc 1482

<210> 72
 <211> 321
 <212> PRT
 <213> Homo sapiens

<400> 72
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 Pro Leu Glu Val Ile Lys Thr Arg Leu Gln Ser Ser Arg Leu Ala
 35 40 45
 Leu Arg Thr Val Tyr Tyr Pro Gln Val His Leu Gly Thr Ile Ser
 50 55 60
 Gly Ala Gly Met Val Arg Pro Thr Ser Val Thr Pro Gly Leu Phe
 65 70 75
 Gln Val Leu Lys Ser Ile Leu Glu Lys Glu Gly Pro Lys Ser Leu
 80 85 90
 Phe Arg Gly Leu Gly Pro Asn Leu Val Gly Val Ala Pro Ser Arg
 95 100 105
 Ala Val Tyr Phe Ala Cys Tyr Ser Lys Ala Lys Glu Gln Phe Asn
 110 115 120
 Gly Ile Phe Val Pro Asn Ser Asn Ile Val His Ile Phe Ser Ala
 125 130 135
 Gly Ser Ala Ala Phe Ile Thr Asn Ser Leu Met Asn Pro Ile Trp
 140 145 150
 Met Val Lys Thr Arg Met Gln Leu Glu Gln Lys Val Arg Gly Ser
 155 160 165
 Lys Gln Met Asn Thr Leu Gln Cys Ala Arg Tyr Val Tyr Gln Thr
 170 175 180
 Glu Gly Ile Arg Gly Phe Tyr Arg Gly Leu Thr Ala Ser Tyr Ala
 185 190 195
 Gly Ile Ser Glu Thr Ile Ile Cys Phe Ala Ile Tyr Glu Ser Leu
 200 205 210
 Lys Lys Tyr Leu Lys Glu Ala Pro Leu Ala Ser Ser Ala Asn Gly
 215 220 225

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Thr Glu Lys Asn Ser Thr Ser Phe Phe Gly Leu Met Ala Ala Ala
      230                      235                      240
Ala Leu Ser Lys Gly Cys Ala Ser Cys Ile Ala Tyr Pro His Glu
      245                      250                      255
Val Ile Arg Thr Arg Leu Arg Glu Glu Gly Thr Lys Tyr Lys Ser
      260                      265                      270
Phe Val Gln Thr Ala Arg Leu Val Phe Arg Glu Glu Gly Tyr Leu
      275                      280                      285
Ala Phe Tyr Arg Gly Leu Phe Ala Gln Leu Ile Arg Gln Ile Pro
      290                      295                      300
Asn Thr Ala Ile Val Leu Ser Thr Tyr Glu Leu Ile Val Tyr Leu
      305                      310                      315
Leu Glu Asp Arg Thr Gln
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<210> 73
<211> 874
<212> DNA
<213> Homo sapiens

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ccctcagtta tatccgacct attcacagac attaaaaagg ggcattgtct 200
cctggatctg ctagaagtac tttctgggca acagttgcct cgggataaag 250
gatctaatac cttccagtgt agaatcaata tagaacatgc cttgacattc 300
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actttcatat tgagaagctt gccagactc tttcttgcaa ttacaatcag 450
ccttccctgg atgatgtgag tgtgggtgac tcatctcttg cctcaagtc 500
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gaaaggccct tcttttgtgg gctcaggaac aatgcgccac ctatgagtct 600
gtcaatgtga ccgattttta gtcaagttgg agaaatggga tggctttttt 650
ggccatcatt catgccttgc gaccagacct aattgacatg aagagtgtga 700
agcatagatc caacaaagac aatctgagag aggccttcag aattgcagaa 750
caagaattaa aaatccccag attgctggaa ccagaagctt acaaaaactt 800
ctgaacattt agcagtcaac tctcttcagc tgatgtgagt cagctagttc 850
cagcacactc tctgaccaga tgtg 874

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<210> 74
<211> 267
<212> PRT
<213> Homo sapiens

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<400> 74
Met Ala Ser Ser Pro Glu Leu Pro Thr Glu Asp Glu Gln Gly Ser
 1          5          10          15

Trp Gly Ile Asp Asp Leu His Ile Ser Leu Gln Ala Glu Gln Glu
          20          25          30

Asp Thr Gln Lys Lys Ala Phe Thr Cys Trp Ile Asn Ser Gln Leu
          35          40          45

Ala Arg His Thr Ser Pro Ser Val Ile Ser Asp Leu Phe Thr Asp
          50          55          60

Ile Lys Lys Gly His Val Leu Leu Asp Leu Leu Glu Val Leu Ser
          65          70          75

Gly Gln Gln Leu Pro Arg Asp Lys Gly Ser Asn Thr Phe Gln Cys
          80          85          90

Arg Ile Asn Ile Glu His Ala Leu Thr Phe Leu Arg Asn Arg Ser
          95          100          105

Ile Lys Leu Ile Asn Ile His Val Thr Asp Ile Ile Asp Gly Asn
          110          115          120

Pro Ser Ile Ile Leu Gly Leu Ile Trp Thr Ile Ile Leu His Phe
          125          130          135

His Ile Glu Lys Leu Ala Gln Thr Leu Ser Cys Asn Tyr Asn Gln
          140          145          150

Pro Ser Leu Asp Asp Val Ser Val Val Asp Ser Ser Pro Ala Ser
          155          160          165

Ser Pro Pro Ala Lys Lys Cys Ser Lys Val Gln Ala Arg Trp Gln
          170          175          180

Met Ser Ala Arg Lys Ala Leu Leu Leu Trp Ala Gln Glu Gln Cys
          185          190          195

Ala Thr Tyr Glu Ser Val Asn Val Thr Asp Phe Lys Ser Ser Trp
          200          205          210

Arg Asn Gly Met Ala Phe Leu Ala Ile Ile His Ala Leu Arg Pro
          215          220          225

Asp Leu Ile Asp Met Lys Ser Val Lys His Arg Ser Asn Lys Asp
          230          235          240

Asn Leu Arg Glu Ala Phe Arg Ile Ala Glu Gln Glu Leu Lys Ile
          245          250          255

Pro Arg Leu Leu Glu Pro Glu Ala Tyr Lys Asn Phe
          260          265

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<210> 75
<211> 314
<212> DNA
<213> Homo sapiens

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tgcaaatata gtacatatac aattaaacag ttggaaaaca tatagagatt 200

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gaccacaaat aaggcccaca aggtactgct gtgtaatgta tctaccatca 250
 ggttgatcag gccagttggt atatttgaca gcaagaaaaa tattaactgt 300
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<210> 76
 <211> 517
 <212> DNA
 <213> Homo sapiens

<220>
 <221> unsure
 <222> 72
 <223> unknown base

<400> 76
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 gccccgctcc ctctgctggc catggccccc ccgcccgcgt gccgggtccc 200
 gatgtcaccg ccgcccgcgc tgcctgctgt gctgctgctg agtctggcgc 250
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 cctgcaggac ctgcggaaga cagcctgcag cctggacgcg cggacggaga 400
 ccctactgct gcaggcagag cgcctgccc tgtgtgcctg ctggccagcg 450
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 aaaaaaaaaa aaaaaaa 517

<210> 77
 <211> 1660
 <212> DNA
 <213> Homo sapiens

<400> 77
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 gaatacgatt atctttgaca ataaagctca cagtggcaaa atcaaaatct 250
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 aagaatagac catgggctac tactgggcat tagtgcaata taacagcgat 1400
 aataaaattc tctattagtc tgttaattta tgacatgac tcggaatgga 1450
 aaaagatcat ttcagagtgt gcgaaataat agtctttaac catgtaatta 1500
 aatatgtgtg tttattgtca aataaggatt tgttttaaag gtgattcttg 1550
 ggtttgaaga catttggtta ttcattggtc gtacagaaat gaagctgggt 1600
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<210> 78

<211> 386

<212> PRT

<213> Homo sapiens

<400> 78

Ile Ser Cys Ser Phe Ile Ala Leu Asp Cys Val Gln Leu Asp Leu
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Gln Asp Leu Ser Lys Lys Pro Pro Asp Trp Lys Asn Ser Ser Phe
 20 25 30

Phe Arg Leu Glu Phe Tyr Arg Leu Leu Gln Val Glu Ile Ser Phe
 35 40 45

His Leu Lys Gly Ile Asp Leu Gln Thr Ile His Ser Arg Glu Leu
 50 55 60

Pro Asp Cys Tyr Val Phe Gln Asn Thr Ile Ile Phe Asp Asn Lys
 65 70 75

Ala His Ser Gly Lys Ile Lys Ile Tyr Phe Asp Ser Asp Ala Lys
 80 85 90

Ile Glu Glu Cys Lys Asp Leu Asn Ile Phe Gly Ser Thr Gln Lys

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

<210> 79

<211> 926

<212> DNA

<213> Homo sapiens

<400> 79

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 acagtttgca ggggtgttccg gaagggtctt gtcactgtga ttggatgctg 200
 gatgccgcct gatagacatg ctggcctggc tgagaaaccc ctgagcaggt 250
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 aatgacagac tgtgagagga agcaggggca ggggtttcca gcccgggctg 450
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 tgcgggggag ggacggggca ggcaggagtc tgggaggcgg gtccgctcct 550
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 cattagaata caaaaaaaaa aaaaaa 926

<210> 80
 <211> 42
 <212> PRT
 <213> Homo sapiens

<400> 80
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 Leu Arg Gln Glu Pro Gly Thr Gln Pro Tyr Asn Ile Arg Glu Asp
 20 25 30
 Ser Ile Leu Asp Gln Lys Val Ala Leu Leu Lys Ala
 35 40

<210> 81
 <211> 2667
 <212> DNA
 <213> Homo sapiens

<400> 81
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 ccaggagtct ctctgcctca accactctct ctgccccctc atctctctga 150
 gctggtgtgt ctggtcctac cctctgtttg gggagctgtc tggctctgtc 200
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 cctgttgccct ttctgcaggt gtttccacga gcctatccct acccacctgt 300
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 gaaggaggga aacgaaatta aaattaacat ttcttctcag gaaaaaaaaa 750
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 gtgcattgag cttctgtcgt cctactccat ccacctctg ctgacctgtg 1150
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 gggcctgcgg ggaaggtagt ggtggccaca gtcctctgtc tgcacaatg 1250
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 cctcatgaaa cacttgggct acctggggta caccagtggc ctctctctga 1450
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<210> 82
 <211> 472
 <212> PRT
 <213> Homo sapiens

<400> 82
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 Ala Val Gly Tyr Arg Gln Glu Arg Glu Gly Phe Leu Pro Ser Arg
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 Gly Pro Ala Pro Gly Ser Lys Pro Val Gln Phe Met Asp Phe Glu
 35 40 45
 Gly Lys Thr Ser Phe Gly Met Ser Val Phe Asn Leu Ser Asn Ala
 50 55 60
 Ile Met Gly Ser Gly Ile Leu Gly Leu Ala Tyr Ala Met Ala His
 65 70 75
 Thr Gly Val Ile Phe Phe Leu Ala Leu Leu Leu Cys Ile Ala Leu
 80 85 90
 Leu Ser Ser Tyr Ser Ile His Leu Leu Leu Thr Cys Ala Gly Ile
 95 100 105
 Ala Gly Ile Arg Ala Tyr Glu Gln Leu Gly Gln Arg Ala Phe Gly
 110 115 120
 Pro Ala Gly Lys Val Val Val Ala Thr Val Ile Cys Leu His Asn
 125 130 135
 Val Gly Ala Met Ser Ser Tyr Leu Phe Ile Ile Lys Ser Glu Leu
 140 145 150
 Pro Leu Val Ile Gly Thr Phe Leu Tyr Met Asp Pro Glu Gly Asp
 155 160 165
 Trp Phe Leu Lys Gly Asn Leu Leu Ile Ile Ile Val Ser Val Leu
 170 175 180
 Ile Ile Leu Pro Leu Ala Leu Met Lys His Leu Gly Tyr Leu Gly
 185 190 195

Tyr Thr Ser Gly Leu Ser Leu Thr Cys Met Leu Phe Phe Leu Val
 200 205 210
 Ser Val Ile Tyr Lys Lys Phe Gln Leu Gly Cys Ala Ile Gly His
 215 220 225
 Asn Glu Thr Ala Met Glu Ser Glu Ala Leu Val Gly Leu Pro Ser
 230 235 240
 Gln Gly Leu Asn Ser Ser Cys Glu Ala Gln Met Phe Thr Val Asp
 245 250 255
 Ser Gln Met Ser Tyr Thr Val Pro Ile Met Ala Phe Ala Phe Val
 260 265 270
 Cys His Pro Glu Val Leu Pro Ile Tyr Thr Glu Leu Cys Arg Pro
 275 280 285
 Ser Lys Arg Arg Met Gln Ala Val Ala Asn Val Ser Ile Gly Ala
 290 295 300
 Met Phe Cys Met Tyr Gly Leu Thr Ala Thr Phe Gly Tyr Leu Thr
 305 310 315
 Phe Tyr Ser Ser Val Lys Ala Glu Met Leu His Met Tyr Ser Gln
 320 325 330
 Lys Asp Pro Leu Ile Leu Cys Val Arg Leu Ala Val Leu Leu Ala
 335 340 345
 Val Thr Leu Thr Val Pro Val Val Leu Phe Pro Ile Arg Arg Ala
 350 355 360
 Leu Gln Gln Leu Leu Phe Pro Gly Lys Ala Phe Ser Trp Pro Arg
 365 370 375
 His Val Ala Ile Ala Leu Ile Leu Leu Val Leu Val Asn Val Leu
 380 385 390
 Val Ile Cys Val Pro Thr Ile Arg Asp Ile Phe Gly Val Ile Gly
 395 400 405
 Ser Thr Ser Ala Pro Ser Leu Ile Phe Ile Leu Pro Ser Ile Phe
 410 415 420
 Tyr Leu Arg Ile Val Pro Ser Glu Val Glu Pro Phe Leu Ser Trp
 425 430 435
 Pro Lys Ile Gln Ala Leu Cys Phe Gly Val Leu Gly Val Leu Phe
 440 445 450
 Thr Ala Val Ser Leu Ser Phe Met Phe Ala Asn Trp Ala Thr Ser
 455 460 465
 Gln Ser Arg Met Ser Gly His
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<210> 83

<211> 1340

<212> DNA

<213> Homo sapiens

<400> 83

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aagatatatg tctacaactc agtcgtttac tagaaagcaa taggaagctt 150

gaagaccaag ttcagcgttg tatctgggtc cagcagctgc tgctttcctt 200
 aacaatgctc ttgcttgctt ttgtcacctc tttcttctat ttattgtaca 250
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 aaggtagtt gtttgagatg ctaagcagga taataaattt agattttaaa 1250
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<210> 84

<211> 84

<212> PRT

<213> Homo sapiens

<400> 84

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Pro	Asn	Thr	Leu	Thr	Leu	Lys	Asp	Asn	Ala	Phe	Asn	Met	Ser	Asp
				20					25					30

Lys	Thr	Ser	Glu	Asp	Ile	Cys	Leu	Gln	Leu	Ser	Arg	Leu	Leu	Glu
				35					40					45

Ser	Asn	Arg	Lys	Leu	Glu	Asp	Gln	Val	Gln	Arg	Cys	Ile	Trp	Phe
				50					55					60

Gln	Gln	Leu	Leu	Leu	Ser	Leu	Thr	Met	Leu	Leu	Leu	Ala	Phe	Val
				65					70					75

Thr Ser Phe Phe Tyr Leu Leu Tyr Ser
80

<210> 85
<211> 2194
<212> DNA
<213> Homo sapiens

<400> 85
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ccagcgaggc ccaaagggga agcctagcgg agctcagtgt ggcagctgct 200
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gtgaaacagt aacctcagaa ccagacatga aagctcacct aattgttcac 300
atggaaagtg aaattatatg tccattttgc aagttgtcag gtgtgaatta 350
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<210> 86
 <211> 578
 <212> PRT
 <213> Homo sapiens

<400> 86
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 Asp Met Lys Ala His Leu Ile Val His Met Glu Ser Glu Ile Ile
 20 25 30
 Cys Pro Phe Cys Lys Leu Ser Gly Val Asn Tyr Asp Glu Met Cys
 35 40 45
 Phe His Ile Glu Thr Ala His Phe Glu Gln Asn Thr Leu Glu Arg
 50 55 60
 Asn Phe Glu Arg Ile Asn Thr Val Gln Tyr Gly Thr Ser Asp Asn
 65 70 75
 Lys Lys Asp Asn Thr Leu Gln Cys Gly Met Glu Val Asn Ser Ser
 80 85 90
 Ile Leu Ser Gly Cys Ala Ser Asn His Pro Lys Asn Ser Ala Gln
 95 100 105
 Asn Leu Thr Lys Asp Ser Thr Leu Lys His Glu Gly Phe Tyr Ser
 110 115 120
 Glu Asn Leu Thr Glu Ser Arg Lys Phe Leu Lys Ser Arg Glu Lys
 125 130 135
 Gln Ser Ser Leu Thr Glu Ile Lys Gly Ser Val Tyr Glu Thr Thr
 140 145 150
 Tyr Ser Pro Pro Glu Cys Pro Phe Cys Gly Lys Ile Glu Glu His
 155 160 165
 Ser Glu Asp Met Glu Thr His Val Lys Thr Lys His Ala Asn Leu

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

	515		520		525
Gln Asp Ile Glu Ala Ser Ser Leu Lys	Gln Leu Arg Lys Ser Met				
530	535	540			
Gly Asn Leu Lys His Lys Gln Tyr Gln	Ile Leu Ala Val Glu Gly				
545	550	555			
Ala Leu Ser Leu Glu Glu Lys Leu Ala	Arg Arg Gln Ala Ser Gln				
560	565	570			
Val Phe Thr Ala Glu Lys Ile Pro					
575					

<210> 87
 <211> 3165
 <212> DNA
 <213> Homo sapiens

<400> 87
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 tggggcgtag tgctctttac ccagcaagga tgggagcagg tgctggccaa 150
 agtgaaacgg gctgtggttt acctggacgc cgctgcgcc gagagcctgc 200
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 ggcggcagcg gccgagatgg aggggcagca gccggtgttc gagcagctgg 500
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 gactccacta cgctaacccc agagctgctg ctgcagatca gatgcctagt 750
 gtcaggcctc agttctctgt gtgaacattt aggagtacgg gaggagtgtt 800
 ttgctgtagg ttctttaagt caggatcatg ctgcggatct ggccaattat 850
 gccctgcaa agaacaggaa gaagactgct gcaggcaggg catcagtggg 900
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 gaggcagtga tggaagtctg gagacatcta gtggaagcgg caagcagaga 1200
 aaacctgcca atcaagatga gtatggggag agtcacaccg ggacagctca 1250

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<210> 88

<211> 714

<212> PRT

<213> Homo sapiens

<400> 88

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Arg Ser Ser Cys Thr Val Val Ser Gln Val Cys Glu Ser Pro Thr
 20 25 30

Met Ser Ala Ser Gly Val Leu Ser Phe Thr Gln Gln Gly Trp Glu
 35 40 45

Gln Val Leu Ala Lys Val Lys Arg Ala Val Val Tyr Leu Asp Ala
 50 55 60

Ala Cys Ala Glu Ser Leu His Trp Gly Cys Gly Ser Thr Arg Leu
 65 70 75

Leu Glu Ala Val Gly Gly Pro Asp Cys His Leu Arg Glu Phe Glu
 80 85 90

Pro Asp Ala Ile Gly Gly Gly Ala Lys Gln Pro Lys Ala Val Phe
 95 100 105

Val Leu Ser Cys Leu Leu Lys Gly Arg Thr Val Glu Ile Leu Arg
 110 115 120

Asp Ile Ile Cys Arg Ser His Phe Gln Tyr Cys Val Val Val Thr
 125 130 135

Thr Val Ser His Ala Val His Leu Thr Ala Asn His Val Pro Ala
 140 145 150

Ala Ala Ala Ala Glu Met Glu Gly Gln Gln Pro Val Phe Glu Gln
 155 160 165

Leu Glu Glu Lys Leu Cys Glu Trp Met Gly Asn Met Asn Tyr Thr
 170 175 180

Ala Glu Val Phe His Val Pro Leu Leu Leu Ala Pro Val Ala Pro
 185 190 195

His Phe Ala Leu Thr Pro Ala Phe Ala Ser Leu Phe Pro Leu Leu
 200 205 210

Pro Gln Asp Val His Leu Leu Asn Ser Ala Arg Pro Asp Lys Arg
 215 220 225

Lys Leu Gly Ser Leu Gly Asp Val Asp Ser Thr Thr Leu Thr Pro
 230 235 240

Glu Leu Leu Leu Gln Ile Arg Cys Leu Val Ser Gly Leu Ser Ser
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Leu Cys Glu His Leu Gly Val Arg Glu Glu Cys Phe Ala Val Gly
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Ser	Leu	Ser	Gln	Val	Ile	Ala	Ala	Asp	Leu	Ala	Asn	Tyr	Ala	Pro	
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				290					295					300	
Phe	Val	Asp	Arg	Thr	Leu	Asp	Leu	Thr	Gly	Ala	Val	Gly	His	His	
				305					310					315	
Gly	Asp	Asn	Leu	Val	Glu	Lys	Ile	Ile	Ser	Ala	Leu	Pro	Gln	Leu	
				320					325					330	
Pro	Gly	His	Thr	Asn	Asp	Val	Met	Val	Asn	Met	Ile	Ala	Leu	Thr	
				335					340					345	
Ala	Leu	His	Thr	Glu	Glu	Glu	Asn	Tyr	Asn	Val	Val	Ala	Pro	Gly	
				350					355					360	
Cys	Leu	Ser	Gln	Ser	Ser	Asp	Thr	Thr	Ala	Lys	Ala	Leu	Trp	Glu	
				365					370					375	
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				380					385					390	
Arg	His	Leu	Val	Glu	Ala	Ala	Ser	Arg	Glu	Asn	Leu	Pro	Ile	Lys	
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Met	Ser	Met	Gly	Arg	Val	Thr	Pro	Gly	Gln	Leu	Met	Ser	Tyr	Ile	
				410					415					420	
Gln	Leu	Phe	Lys	Asn	Asn	Leu	Lys	Ala	Leu	Met	Asn	His	Cys	Gly	
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Leu	Leu	Gln	Leu	Gly	Leu	Ala	Thr	Ala	Gln	Thr	Leu	Lys	His	Pro	
				440					445					450	
Gln	Thr	Ala	Lys	Trp	Asp	Asn	Phe	Leu	Ala	Phe	Glu	Arg	Leu	Leu	
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Leu	Gln	Ser	Ile	Gly	Glu	Ser	Ala	Met	Ser	Val	Val	Leu	Asn	Gln	
				470					475					480	
Leu	Leu	Pro	Met	Ile	Lys	Pro	Val	Thr	Gln	Arg	Thr	Asn	Glu	Asp	
				485					490					495	
Tyr	Ser	Pro	Glu	Glu	Leu	Leu	Ile	Leu	Leu	Ile	Tyr	Ile	Tyr	Ser	
				500					505					510	
Val	Thr	Gly	Glu	Leu	Thr	Val	Asp	Lys	Asp	Leu	Cys	Glu	Ala	Glu	
				515					520					525	
Glu	Lys	Val	Lys	Lys	Ala	Leu	Ala	Gln	Val	Phe	Cys	Glu	Glu	Ser	
				530					535					540	
Gly	Leu	Ser	Pro	Leu	Leu	Gln	Lys	Ile	Thr	Asp	Trp	Asp	Ser	Ser	
				545					550					555	
Ile	Asn	Leu	Thr	Phe	His	Lys	Ser	Lys	Ile	Ala	Val	Asp	Glu	Leu	
				560					565					570	
Phe	Thr	Ser	Leu	Arg	Asp	Ile	Ala	Gly	Ala	Arg	Ser	Leu	Leu	Lys	
				575					580					585	
Gln	Phe	Lys	Ser	Val	Tyr	Val	Pro	Gly	Asn	His	Thr	His	Gln	Ala	
				590					595					600	
Ser	Tyr	Lys	Pro	Leu	Leu	Lys	Gln	Val	Val	Glu	Glu	Ile	Phe	His	
				605					610					615	

Pro Glu Arg Pro Asp Ser Val Asp Ile Glu His Met Ser Ser Gly
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Leu Thr Asp Leu Leu Lys Thr Gly Phe Ser Met Phe Met Lys Val
635 640 645
Ser Arg Pro His Pro Ser Asp Tyr Pro Leu Leu Ile Leu Phe Val
650 655 660
Val Gly Gly Val Thr Val Ser Glu Val Lys Met Val Lys Asp Leu
665 670 675
Val Ala Ser Leu Lys Pro Gly Thr Gln Val Ile Val Leu Ser Thr
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695 700 705
Asp Arg Leu His Pro Asp Leu Gly Phe
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<210> 89
<211> 673
<212> DNA
<213> Homo sapiens

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<210> 90
<211> 110
<212> PRT
<213> Homo sapiens

<400> 90
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Glu Ala Ala Val Arg Gly Asn Ala Ala Val Leu Asp Tyr Cys Arg
20 25 30
Thr Ser Val Ser Ala Leu Ser Gly Ala Thr Ala Gly Ile Leu Gly

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

<210> 91

<211> 1823

<212> DNA

<213> Homo sapiens

<400> 91

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<210> 92
 <211> 275
 <212> PRT
 <213> Homo sapiens

<400> 92
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 20 25 30
 Gln Asp Arg Tyr Phe Thr Leu Gly Leu Pro Thr Gly Ser Thr Pro
 35 40 45
 Leu Gly Cys Tyr Lys Lys Leu Ile Glu Tyr His Lys Asn Gly His
 50 55 60
 Leu Ser Phe Lys Tyr Val Lys Thr Phe Asn Met Asp Glu Tyr Val
 65 70 75
 Gly Leu Pro Arg Asn His Pro Glu Ser Tyr His Ser Tyr Met Trp
 80 85 90
 Asn Asn Phe Phe Lys His Ile Asp Ile Asp Pro Asn Asn Ala His
 95 100 105
 Ile Leu Asp Gly Asn Ala Ala Asp Leu Gln Ala Glu Cys Asp Ala
 110 115 120
 Phe Glu Asn Lys Ile Lys Glu Ala Gly Gly Ile Asp Leu Phe Val
 125 130 135
 Gly Gly Ile Gly Pro Asp Gly His Ile Ala Phe Asn Glu Pro Gly
 140 145 150
 Ser Ser Leu Val Ser Arg Thr Arg Leu Lys Thr Leu Ala Met Asp
 155 160 165
 Thr Ile Leu Ala Asn Ala Lys Tyr Phe Asp Gly Asp Leu Ser Lys
 170 175 180

Val	Ser	Thr	Met	Ala	Leu	Thr	Val	Gly	Val	Gly	Thr	Val	Met	Asp	
				185					190					195	
Ala	Arg	Glu	Val	Met	Ile	Leu	Ile	Thr	Gly	Ala	His	Lys	Ala	Phe	
				200					205					210	
Ala	Leu	Tyr	Lys	Ala	Ile	Glu	Gly	Val	Asn	His	Met	Trp	Thr	Val	
				215					220					225	
Ser	Ala	Phe	Gln	Gln	His	Pro	Arg	Thr	Ile	Phe	Val	Cys	Asp	Glu	
				230					235					240	
Asp	Ala	Thr	Leu	Glu	Leu	Arg	Val	Lys	Thr	Val	Lys	Tyr	Phe	Lys	
				245					250					255	
Gly	Leu	Met	His	Val	His	Asn	Lys	Leu	Val	Asp	Pro	Leu	Phe	Ser	
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Met	Lys	Asp	Gly	Asn											
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<210> 93
 <211> 2207
 <212> DNA
 <213> Homo sapiens

<220>
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 <222> 1823-1854
 <223> unknown base

<400> 93
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<210> 94
 <211> 192
 <212> PRT
 <213> Homo sapiens

<400> 94
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 Tyr Val Asn Asn Met Ala Arg Val Gly Thr Leu Val Leu Cys Leu
 35 40 45

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

<211> 1619

<212> DNA

<213> Homo sapiens

<400> 95

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<210> 96

<211> 408

<212> PRT

<213> Homo sapiens

<400> 96

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Lys	Ile	Cys	His	Gln	Ile	Glu	Tyr	Tyr	Phe	Gly	Asp	Phe	Asn	Leu
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Pro	Arg	Asp	Lys	Phe	Leu	Lys	Glu	Gln	Ile	Lys	Leu	Asp	Glu	Gly
				35					40					45

Trp	Val	Pro	Leu	Glu	Ile	Met	Ile	Lys	Phe	Asn	Arg	Leu	Asn	Arg
				50					55					60

Leu	Thr	Thr	Asp	Phe	Asn	Val	Ile	Val	Glu	Ala	Leu	Ser	Lys	Ser
				65					70					75

Lys	Ala	Glu	Leu	Met	Glu	Ile	Ser	Glu	Asp	Lys	Thr	Lys	Ile	Arg
				80					85					90

Arg	Ser	Pro	Ser	Lys	Pro	Leu	Pro	Glu	Val	Thr	Asp	Glu	Tyr	Lys
				95					100					105

Asn	Asp	Val	Lys	Asn	Arg	Ser	Val	Tyr	Ile	Lys	Gly	Phe	Pro	Thr
				110					115					120

Asp	Ala	Thr	Leu	Asp	Asp	Ile	Lys	Glu	Trp	Leu	Glu	Asp	Lys	Gly
				125					130					135

Gln	Val	Leu	Asn	Ile	Gln	Met	Arg	Arg	Thr	Leu	His	Lys	Ala	Phe
				140					145					150

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

Gly Asp Gln

<210> 97

<211> 481

<212> DNA

<213> Homo sapiens

<400> 97

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 <211> 315
 <212> DNA
 <213> Homo sapiens

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 aagttgaatc atgttggttc cagtgtagac agaataaggta tatgtgggtg 200
 aaaaatgaac agcacaaagt tagctcccca aaaatggcaa agtgaaataa 250
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 <212> DNA
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 aatccagcct gctccagaaa agcaaagcag atagcagtgg ggtcagaaa 250
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<210> 100
<211> 409
<212> PRT
<213> Homo sapiens

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

185										190				195			
Arg	Arg	Leu	Leu	Leu	Ser	Gln	Arg	Lys	Arg	Glu	Leu	Ala	Asp	Val			
200										205				210			
Leu	Asp	Ala	Gln	Ile	Glu	Met	Leu	Ser	Pro	Phe	Glu	Ala	Val	Ala			
215										220				225			
Thr	Arg	Phe	Lys	Glu	Gln	Tyr	Arg	Thr	Phe	Ala	Thr	Ala	Leu	Asp			
230										235				240			
Thr	Thr	Arg	His	Glu	Leu	Pro	Val	Arg	Ser	Ile	His	Leu	Glu	Gly			
245										250				255			
Asp	Gly	Gln	Gln	Leu	Leu	Asp	Ala	Leu	Gln	His	Glu	Leu	Val	Thr			
260										265				270			
Thr	Gln	Arg	Leu	Leu	Gly	Glu	Leu	Asp	Val	Gly	Asp	Ser	Glu	Glu			
275										280				285			
Asn	Val	Gln	Val	Leu	Asp	Leu	Leu	Ser	Glu	Leu	Lys	Asp	Val	Thr			
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Ala	Lys	Lys	Asp	Leu	Glu	Leu	Arg	Arg	Ser	Phe	Ala	Gln	Val	Leu			
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Glu	Leu	Ser	Ala	Glu	Ala	Ser	Lys	Glu	Ala	Ala	Leu	Ala	Asn	Gln			
320										325				330			
Glu	Val	Trp	Glu	Glu	Thr	Gln	Gly	Met	Ala	Pro	Pro	Ser	Arg	Trp			
335										340				345			
Tyr	Phe	Asn	Gln	Asp	Ser	Ala	Cys	Arg	Glu	Ser	Gly	Gly	Ala	Pro			
350										355				360			
Lys	Asn	Thr	Pro	Leu	Ser	Glu	Asp	Asp	Asn	Pro	Gly	Ala	Ser	Ser			
365										370				375			
Ala	Pro	Ala	Gln	Ala	Thr	Phe	Ile	Ser	Pro	Ser	Glu	Asp	Phe	Ser			
380										385				390			
Ser	Ser	Ser	Gln	Ala	Glu	Val	Pro	Pro	Ser	Leu	Ser	Arg	Ser	Gly			
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Arg Asp Leu Ser

<210> 101

<211> 716

<212> DNA

<213> Homo sapiens

<400> 101

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 <212> DNA
 <213> Homo sapiens

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<211> 398
 <212> PRT
 <213> Homo sapiens

<400> 103

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          35          40          45

Pro Leu Phe Phe Ala Ala Leu Met Leu Leu Gly Leu Val Gly Asn
          50          55          60

Ser Leu Val Ile Tyr Val Ile Cys Arg His Lys Pro Met Arg Thr
          65          70          75

Val Thr Asn Phe Tyr Ile Ala Asn Leu Ala Ala Thr Asp Val Thr
          80          85          90

Phe Leu Leu Cys Cys Val Pro Phe Thr Ala Leu Leu Tyr Pro Leu
          95          100          105

Pro Gly Trp Val Leu Gly Asp Phe Met Cys Lys Phe Val Asn Tyr
          110          115          120

Ile Gln Gln Val Ser Val Gln Ala Thr Cys Ala Thr Leu Thr Ala
          125          130          135

Met Ser Val Asp Arg Trp Tyr Val Thr Val Phe Pro Leu Arg Ala
          140          145          150

Leu His Arg Arg Thr Pro Arg Leu Ala Leu Ala Val Ser Leu Ser
          155          160          165

Ile Trp Val Gly Ser Ala Ala Val Ser Ala Pro Val Leu Ala Leu
          170          175          180

His Arg Leu Ser Pro Gly Pro Arg Ala Tyr Cys Ser Glu Ala Phe
          185          190          195

Pro Ser Arg Ala Leu Glu Arg Ala Phe Ala Leu Tyr Asn Leu Leu
          200          205          210

Ala Leu Tyr Leu Leu Pro Leu Leu Ala Thr Cys Ala Cys Tyr Ala
          215          220          225

Ala Met Leu Arg His Leu Gly Arg Val Ala Val Arg Pro Ala Pro
          230          235          240

Ala Asp Ser Ala Leu Gln Gly Gln Val Leu Ala Glu Arg Ala Gly
          245          250          255

Ala Val Arg Ala Lys Val Ser Arg Leu Val Ala Ala Val Val Leu
          260          265          270

Leu Phe Ala Ala Cys Trp Gly Pro Ile Gln Leu Phe Leu Val Leu
          275          280          285

Gln Ala Leu Gly Pro Ala Gly Ser Trp His Pro Arg Ser Tyr Ala
          290          295          300

Ala Tyr Ala Leu Lys Thr Trp Ala His Cys Met Ser Tyr Ser Asn
          305          310          315

Ser Ala Leu Asn Pro Leu Leu Tyr Ala Phe Leu Gly Ser His Phe

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	320		325		330
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Arg Arg Pro Arg	Arg Pro Gly Pro Ser	Asp Pro Ala Ala Pro	His		
	350		355		360
Ala Glu Leu His	Arg Leu Gly Ser His	Pro Ala Pro Ala Arg	Ala		
	365		370		375
Gln Lys Pro Gly	Ser Ser Gly Leu Ala	Ala Arg Gly Leu Cys	Val		
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Leu Gly Glu Asp	Asn Ala Pro Leu				
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 <211> 918
 <212> DNA
 <213> Homo sapiens

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

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

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 <211> 431
 <212> DNA
 <213> Homo sapiens

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<400> 106
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