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(54) **SECRETED HUMAN PROTEINS**

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(57) **ABSTRACT**

Fifteen secreted human proteins and full-length cDNA sequences encoding the proteins have been identified. The proteins have various potential uses as therapeutics, such as for stimulating blood cell generation in patients receiving cancer chemotherapy, for treatment of bone marrow transplantation patients, and for healing fractured bones. The proteins and cDNA sequences can also be used, inter alia, for targeting other proteins to the membrane or extracellular milieu.

SECRETED HUMAN PROTEINS

TECHNICAL AREA OF THE INVENTION

[0001] This invention relates to proteins secreted from bone marrow and from fetal liver, and to polynucleotides encoding the secreted proteins. The invention also relates to therapeutic and diagnostic utilities for the polynucleotides and proteins.

BACKGROUND OF THE INVENTION

[0002] Human tissues, such as fetal liver and bone marrow stromal cells, secrete a variety of protein factors. Some of these factors are required for the formation of blood and bone cells and for other physiological processes. Regulatory factors which are known to be involved in hematopoiesis and/or bone development include SCF, IL-3, IL-6, GM-CSF, M-CSF, EPO, TPO, bone morphogenic proteins, erythroid potentiating factor, and TGF-β. However, it is believed that additional secreted protein factors which control hematopoiesis and bone morphogenesis remain to be identified. Other secreted proteins may play a role in cell-cell interaction and regulation of cell growth, both of which are related to cancer. There is a need to identify such proteins.

SUMMARY OF THE INVENTION

[0003] It is an object of the invention to provide novel secreted proteins and polynucleotide sequences which encode the proteins. These and other objects of the invention are provided by one or more of the embodiments described below.

[0004] One embodiment of the invention is an isolated and purified protein having an amino acid sequence which is at least 85% identical to an amino acid sequence selected from the group consisting of the amino acid sequences shown in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30. Percent identity can be determined using a Smith-Waterman homology search algorithm using an affine gap search with a gap open penalty of 12 and a gap extension penalty of 1.

[0005] Another embodiment of the invention is an isolated and purified polypeptide comprising at least 8 contiguous amino acids of an amino acid sequence selected from the group consisting of the amino acid sequences shown in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30.

[0006] Still another embodiment of the invention is a fusion protein comprising a first protein segment and a second protein segment fused together by means of a peptide bond. The first protein segment consists of at least 8 contiguous amino acids of an amino acid sequence selected from the group consisting of the amino acid sequences shown in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30.

[0007] Yet another embodiment of the invention is a preparation of antibodies which specifically bind to a protein having an amino acid sequence selected from the group consisting of the amino acid sequences shown in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30.

[0008] Even another embodiment of the invention is a cDNA molecule which encodes a protein having an amino acid sequence which is at least 85% identical to an amino acid sequence selected from the group consisting of the amino acid sequences shown in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30. Percent identity is determined using a Smith-Waterman homology search algorithm using an affine gap search with a gap open penalty of 12 and a gap extension penalty of 1.

[0009] A further embodiment of the invention is a cDNA molecule which encodes at least 8 contiguous amino acids of an amino acid sequence selected from the group consisting of the amino acid sequences shown in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30.

[0010] Another embodiment of the invention is a cDNA molecule comprising a nucleotide sequence selected from the group consisting of at least 69 contiguous nucleotides of SEQ ID NO:1, at least 550 contiguous nucleotides of SEQ ID NO:3, at least 180 contiguous nucleotides of SEQ ID NO:5; at least 27 contiguous nucleotides of SEQ ID NO:7, and at least 11 contiguous nucleotides of SEQ ID NO:9.

[0011] Still another embodiment of the invention is a cDNA molecule which is at least 85% identical to a nucleotide sequence selected from the group consisting of the nucleotide sequences shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27 and 29. Percent identity is determined using a Smith-Waterman homology search algorithm using an affine gap search with a gap open penalty of 12 and a gap extension penalty of 1.

[0012] Even another embodiment of the invention is an isolated and purified polynucleotide molecule comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of the nucleotide sequences shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27 and 29 after washing with 0.2× SSC at 65° C. The nucleotide sequence encodes a protein having an amino acid sequence selected from the group consisting of the amino acid sequences shown in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30.

[0013] Yet another embodiment of the invention is a polynucleotide construct comprising a promoter and a polynucleotide segment encoding at least 8 contiguous amino acids of a protein as shown in SEQ ID NOS:2, 4, 6, 8, or 10. The polynucleotide segment is located downstream from the promoter. Transcription of the polynucleotide segment initiates at the promoter.

[0014] A further embodiment of the invention is a host cell comprising a polynucleotide construct. The polynucleotide construct comprises a promoter and a polynucleotide segment encoding at least 8 contiguous amino acids of a protein as shown in SEQ ID NOS:2, 4, 6, 8, or 10. The polynucleotide segment is located downstream from the promoter. Transcription of the polynucleotide segment initiates at the promoter.

[0015] Even another embodiment of the invention is a method of producing a human protein. A host cell comprising a polynucleotide construct is cultured in a culture medium. The polynucleotide construct comprises a promoter and a polynucleotide segment encoding at least 8 contiguous amino acids of a protein as shown in SEQ ID NOS:2, 4, 6, 8, or 10. The polynucleotide segment is located downstream from the promoter. Transcription of the poly-

nucleotide segment initiates at the promoter. The human protein is purified from the cell or the culture medium.

[0016] The present invention thus provides the art with the amino acid sequences of fifteen full-length novel human secreted proteins and with polynucleotide molecules which encode these proteins. The invention can be used to, inter alia, to produce secreted proteins for therapeutic and diagnostic purposes.

DETAILED DESCRIPTION OF THE INVENTION

[0017] Fifteen cDNA clones have been identified which encode novel human secreted proteins. One cDNA clone (ch1268) contains a 1313 basepair insert (SEQ ID NO:1) that encodes a polypeptide of 325 amino acids (SEQ ID NO:2). The open reading frame encoding this polypeptide is located from nucleotides 163 to 1137 of SEQ ID NO:1. Amino acids 1 to 19 of SEQ ID NO:2 form a cleavable signal peptide.

[0018] Another cDNA clone (ch1256) contains a 1941 basepair insert (SEQ ID NO:3) that encodes a polypeptide of 435 amino acids (SEQ ID NO:4). The open reading frame encoding this polypeptide is located from nucleotides 262 to nucleotide 1566 of SEQ ID NO:3. Amino acids 1 to 24 of SEQ ID NO:4 form a cleavable signal peptide.

[0019] Yet another cDNA clone (ch1284) contains a 1839 basepair insert (SEQ ID NO:5) that encodes a polypeptide of 339 amino acids (SEQ ID NO:6). The open reading frame encoding this polypeptide is located from nucleotides 40 to 1056 of SEQ ID NO:5. Amino acids 1 to 25 of SEQ ID NO:6 form a cleavable signal peptide.

[0020] Even another cDNA clone (ch1297) contains a 1831 basepair insert (SEQ ID NO:7) that encodes a polypeptide of 399 amino acids (SEQ ID NO:8). The open reading frame encoding this polypeptide is located from nucleotides 90 to 1286 of SEQ ID NO:7. Amino acids 1-19 of SEQ ID NO:8 form a cleavable signal peptide.

[0021] Still another cDNA clone (ch1233) contains a 4222 basepair insert (SEQ ID NO:9) that encodes a polypeptide of 709 amino acids (SEQ ID NO:10). The open reading frame encoding this polypeptide is located from nucleotides 238 to 2367 of SEQ ID NO:9. The open reading frame does not encode a cleavable signal peptide.

[0022] Another cDNA clone (ch 050) contains a 960 base pair inserts (SEQ ID NO:11) that encodes a polypeptide of 240 amino acids (SEQ ID NO:12). The open reading frame encoding this polypeptide is located from nucleotide 78 to 798. Amino acids 20 to 40 of the polypeptide contain a potential non-cleavable signal peptide and/or a transmembrane domain.

[0023] A further cDNA clone (ch1001) contains a 2832 bp insert (SEQ ID NO:13) that encodes a polypeptide of 613 amino acids (SEQ ID NO:14). The open reading frame encoding this polypeptide is located from nucleotide 317 to 2155. Amino acids 1 to 23 of the polypeptide contain a cleavable signal peptide.

[0024] Yet another cDNA clone (ch1007) contains a 3030 bp insert (SEQ ID NO:15) that encodes a polypeptide of 285 amino acids (SEQ ID NO:16). The open reading frame encoding this polypeptide is located from nucleotide 31 to 885. Amino acids 1 to 24 of the polypeptide contain a cleavable signal peptide.

[0025] Another cDNA clone (ch1035) contains a 2133 bp insert (SEQ ID NO:17) that encodes a polypeptide of 483 amino acids (SEQ ID NO:18). The open reading frame encoding this polypeptide is located from nucleotide 185 to 1633. Amino acids 1 to 20 of the polypeptide contain a cleavable signal peptide.

[0026] Still another cDNA clone (ch1063) contains a 1590 bp insert (SEQ ID NO:19) that encodes a polypeptide of 289 amino acids (SEQ ID NO:20). The open reading frame encoding this polypeptide is located from nucleotide 100 to 966. Amino acids 1 to 22 of the polypeptide contain a cleavable signal peptide.

[0027] Another cDNA clone (ch1572) contains a 1994 bp insert (SEQ ID NO:21) that encodes a polypeptide of 585 amino acids (SEQ ID NO:22). The open reading frame is located from nucleotides 132 to 1886. A hydrophobic stretch is found at positions 14 to 33, which can act as a signal sequence, and is followed by a potential signal peptidase cleavage site between amino acids 33 and 34.

[0028] Yet another cDNA clone (ch1569) contains a 1340 bp insert (SEQ ID NO:23) that encodes a polypeptide of 280 amino acids (SEQ ID NO:24). The open reading frame is located from nucleotide 79 to 919. Hydrophobic stretches are located at positions 1 to 20 and 180 to 206.

[0029] A further cDNA clone (ch1570) contains a 1011 bp insert (SEQ ID NO:25) that encodes a polypeptide of 286 amino acids (SEQ ID NO:26). The open reading frame is located from nucleotide 128 to 986. Hydrophobic stretches are found at amino acids 27 to 53, 61 to 86, 96 to 118, 206 to 246, and 257 to 279.

[0030] A still further cDNA clone (ch1529) contains a 2027 bp insert (SEQ ID NO:27) that encodes a polypeptide of 340 amino acids (SEQ ID NO:28). The open reading frame is located from nucleotide 270 to 1284. Hydrophobic stretches are found at amino acids 19 to 44, 144 to 164, 180 to 223, 231 to 255, and 260 to 280.

[0031] A further cDNA clone (ch1515) contains a 2390 bp insert (SEQ ID NO:29) that encodes a polypeptide of 347 amino acids (SEQ ID NO:30). A hydrophobic stretch of 30 amino acids is found at amino acid positions 55 to 85

[0032] The present invention provides both full-length and mature forms of the disclosed proteins. Full-length forms of the proteins have the amino acid sequences shown in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30. In the case of proteins which are membrane-bound, such as cell surface receptor proteins, soluble forms of the proteins can be obtained by deleting the nucleotide sequences which encode part or all of the intracellular and transmembrane domains of the protein and expressing a fully secreted form of the protein in a host cell. For example, the full-length forms of the proteins can be processed enzymatically to remove the signal sequence, resulting in mature forms of the proteins.

[0033] Other domains with predicted functions can also be identified. For example, transmembrane domains can be identified by examination of the amino acid sequences disclosed herein. A transmembrane domain typically con-

tains a long stretch of 15-30 hydrophobic amino acids. Techniques for identifying intracellular and transmembrane domains, such as homology searches, can be used to identify such domains in proteins of the invention using amino acid and polynucleotide sequences disclosed herein.

[0034] Secreted proteins of the invention have a variety of uses. For example, the proteins can be used in assays to determine biological activities, such as cytokine, cell proliferation, or cellular differentiation activities, tissue growth or regeneration, activin or inhibin activity, chemotactic or chemokinetic activity, hemostatic or thrombolytic activity, receptor/ligand activity, tumor inhibition, or anti-inflammatory activity. Assays for these activities are known in the art, as disclosed below.

[0035] Proteins of the invention can also be used as biomarkers, to identify tissues or cell types which express the proteins, or to identify a stage- or disease-specific alteration in protein expression. Proteins of the invention can be used in protein interaction assays, to identify ligands or binding proteins. Compounds which affect the biological activities of the secreted proteins or their ability to interact with specific ligands can be identified using proteins of the invention in screening assays, such as the yeast two-hybrid assay. Proteins and antibodies of the invention can also be used to design diagnostic tests and therapeutic compositions for diseases which may be associated with altered expression of these proteins.

[0036] Polynucleotide molecules which encode the proteins disclosed herein can be used to propagate additional copies of the polynucleotides or to express proteins, polypeptides, or fusion proteins of the invention. The polynucleotide molecules disclosed herein can also be used, for example, as biomarkers for tissues or chromosomes, as molecular weight markers for DNA gels, to elicit immune responses, such as the formation of antibodies against single- or double-stranded DNA, and in DNA-ligand interaction assays, to detect proteins or other molecules which interact with the polynucleotide sequences.

[0037] Disease states may be associated with alterations in the expression of genes which encode proteins of the invention. Polynucleotide sequences disclosed herein can thus be used to determine the involvement of any of these sequences in disease states. For example, a gene in a diseased cell can be sequenced and compared with a wild-type coding sequence of the invention. Alternatively, nucleotide probes can be constructed and used to detect normal or mutant forms of mRNA in a diseased cell. Polynucleotide molecules of the invention can also be used to design diagnostic tests and therapeutic compositions for diseases which may be associated with altered expression of these genes.

Polypeptide Fragments

[0038] The invention provides polypeptide fragments of each of the disclosed proteins. Polypeptide fragments of the invention can comprise at least 8, 10, 12, 15, 18, 19, 20, 25, 50, 75, 100, 125, 130, 135, 140, 145, 150, 200, 250, 300, or 320 contiguous amino acids selected from SEQ ID NO:2. One preferred polypeptide fragment comprises amino acids 1-19 of SEQ ID NO:2.

[0039] Other polypeptide fragments can comprise at least 8, 10, 12, 15, 20, 24, 25, 50, 75, 100, 150, 200, 250, 300, 350, 400, or 430 contiguous amino acids of SEQ ID NO:4. A preferred polypeptide fragment comprises amino acids 1-24 of SEQ ID NO:4.

[0040] Still other polypeptide fragments can comprise at least 8, 10, 12, 15, 20, 25, 30, 50, 75, 100, 150, 200, 250, 300, or 330 contiguous amino acids of SEQ ID NO:6. A preferred polypeptide fragment comprises amino acids 1-25 of SEQ ID NO:6.

[0041] Even other polypeptide fragments can comprise at least 8, 10, 12, 15, 19, 20, 25, 30, 50, 75, 100, 150, 200, 250, 300, 350, or 375 contiguous amino acids of SEQ ID NO:8. A preferred polypeptide fragment comprises amino acids 1-19 of SEQ ID NO:8.

[0042] Yet other polypeptide fragments can comprise at least 8, 10, 12, 15, 20, 25, 30, 50, 52, 73, 75, 100, 150, 175, 180, 190, 200, 230, or 231 contiguous amino acids selected from amino acids 1-53, 137-210, 291-521, or 516-709 of SEQ ID NO:10, or at least 15, 16, 17, 18, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, or 90 contiguous amino acids selected from amino acids 45-145 of SEQ ID NO:10, or at least 8, 10, 12, 15, 20, 25, 30, 50, 75, 100, 150, 250, 300, 350, 400, 450, 500, 550, 600, 650, or 700 contiguous amino acids of SEQ ID NO:10.

[0043] Other polypeptide fragments can comprise at least 8, 10, 12, 15, 18, 19, 20, 25, 50, 75, 100, 125, 130, 140, 145, 150, 200, 250, 300, 350, 400, 450, 500, 550, or 580 contiguous amino acids of SEQ ID NO:22. Preferred fragments comprise amino acids 14-33 and amino acids 34-585.

[0044] Yet other polypeptide fragments can comprise at least 8, 10, 12, 15, 18, 19, 20, 25, 50, 75, 100, 125, 130, 140, 145, 150, 200, 250, and 275 contiguous amino acids of SEQ ID NO:24. Preferred fragments comprise amino acids 1-20; amino acids 21-280; and amino acids 180-206.

[0045] Other polypeptide fragments can comprise at least 8, 10, 12, 15, 18, 19, 20, 25, 50, 75, 100, 125, 130, 140, 145, 150, 200, 250, 275, and 280 contiguous amino acids of SEQ ID NO:26. Preferred fragments comprise amino acids 27-53; 62-86; 96-118; 206-246; and 257-279.

[0046] Further polypeptide fragments can comprise at least 8, 10, 12, 15, 18, 19, 20, 25, 50, 75, 100, 125, 130, 140, 145, 150, 200, 250, 300, 325, or 330 contiguous amino acids of SEQ ID NO:28. Preferred fragments comprise amino acids 19-44; 144-164; 180-223; 231-255; and 260-280.

[0047] Other preferred fragments can comprise at least 8, 10, 12, 15, 18, 19, 20, 25, 50, 75, 100, 125, 130, 140, 145, 150, 200, 250, 300, 325, 340 or 345 contiguous amino acids of SEQ ID NO:30. A preferred fragment comprises amino acids 55-85.

Biologically Active Variants

[0048] Variants of the secreted proteins and polypeptides disclosed herein can also occur. Variants can be naturally or non-naturally occurring. Naturally occurring variants are found in humans or other species and comprise amino acid sequences which are substantially identical to the amino acid sequences shown in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30. Species homologs of the secreted proteins can be obtained using subgenomic polynucleotides of the invention, as described below, to make suitable probes or primers to screening cDNA expression

libraries from other species, such as mice, monkeys, yeast, or bacteria, identifying cDNAs which encode homologs of the secreted proteins, and expressing the cDNAs as is known in the art.

[0049] Non-naturally occurring variants which retain substantially the same biological activities as naturally occurring protein variants, such as cytokine, cell proliferation, or cellular differentiation activities, tissue growth or regeneration, activin or inhibin activity, chemotactic or chemokinetic activity, hemostatic or thrombolytic activity, receptor/ligand activity, tumor inhibition, or anti-inflammatory activity, are also included here. Preferably, naturally or non-naturally occurring variants have amino acid sequences which are at least 85%, 90%, or 95% identical to the amino acid sequences shown in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30. More preferably, the molecules are at least 98% or 99% identical. Percent identity is determined using the Smith-Waterman homology search algorithm using an affine gap search with a gap open penalty of 12 and a gap extension penalty of 1. The Smith-Waterman homology search algorithm is taught in Smith and Waterman, *Adv. Appl. Math.* (1981) 2:482-489.

[0050] Guidance in determining which amino acid residues can be substituted, inserted, or deleted without abolishing biological or immunological activity can be found using computer programs well known in the art, such as DNASTAR software. Preferably, amino acid changes in secreted-protein variants are conservative amino acid changes, i.e., substitutions of similarly charged or uncharged amino acids. A conservative amino acid change involves substitution of one of a family of amino acids which are related in their side chains. Naturally occurring amino acids are generally divided into four families: acidic (aspartate, glutamate), basic (lysine, arginine, histidine), non-polar (alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), and uncharged polar (glycine, asparagine, glutamine, cystine, serine, threonine, tyrosine) amino acids. Phenylalanine, tryptophan, and tyrosine are sometimes classified jointly as aromatic amino acids.

[0051] It is reasonable to expect that an isolated replacement of a leucine with an isoleucine or valine, an aspartate with a glutamate, a threonine with a serine, or a similar replacement of an amino acid with a structurally related amino acid will not have a major effect on the biological properties of the resulting variant. Whether an amino acid change results in a functional secreted protein or polypeptide can readily be determined by testing the altered protein or polypeptide in a functional assay, for example, as disclosed in U.S. Pat. No. 5,654,173 and described in detail below.

[0052] Variants of the secreted proteins disclosed herein include glycosylated forms, aggregative conjugates with other molecules, and covalent conjugates with unrelated chemical moieties. Covalent variants can be prepared by linking functionalities to groups which are found in the amino acid chain or at the N- or C-terminal residue, as is known in the art. Variants also include allelic variants, species variants, and muteins. Truncations or deletions of regions which do not affect functional activity of the proteins are also variants.

[0053] A subset of mutants, called muteins, is a group of polypeptides in which neutral amino acids, such as serines, are substituted for cysteine residues which do not participate in disulfide bonds. These mutants may be stable over a broader temperature range than native secreted proteins. See Mark et al., U.S. Pat. No. 4,959,314.

[0054] Preferably, amino acid changes in the secreted protein or polypeptide variants are conservative amino acid changes, i.e., substitutions of similarly charged or uncharged amino acids. A conservative amino acid change involves substitution of one of a family of amino acids which are related in their side chains. Naturally occurring amino acids are generally divided into four families: acidic (aspartate, glutamate), basic (lysine, arginine, histidine), non-polar (alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), and uncharged polar (glycine, asparagine, glutamine, cystine, serine, threonine, tyrosine) amino acids. Phenylalanine, tryptophan, and tyrosine are sometimes classified jointly as aromatic amino acids.

[0055] It is reasonable to expect that an isolated replacement of a leucine with an isoleucine or valine, an aspartate with a glutamate, a threonine with a serine, or a similar replacement of an amino acid with a structurally related amino acid will not have a major effect on the biological properties of the resulting secreted protein or polypeptide variant. Properties and functions of secreted protein or polypeptide variants are of the same type as a secreted protein or polypeptide comprising amino acid sequences encoded by the nucleotide sequence shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29, although the properties and functions of variants can differ in degree. Whether an amino acid change results in a secreted protein or polypeptide variant with the appropriate differential expression pattern can readily be determined. For example, nucleotide probes can be selected from the marker gene sequences disclosed herein and used to detect corresponding mRNA in Northern blots or in tissue sections, as is known in the art. Alternatively, antibodies which specifically bind to protein products of genes can be used to detect expression of secreted proteins or variants thereof.

[0056] Secreted protein variants include glycosylated forms, aggregative conjugates with other molecules, and covalent conjugates with unrelated chemical moieties. Secreted protein variants also include allelic variants, species variants, and muteins. Truncations or deletions of regions which do not affect the differential expression of the secreted protein genes are also variants. Covalent variants can be prepared by linking functionalities to groups which are found in the amino acid chain or at the N- or C-terminal residue, as is known in the art.

[0057] It will be recognized in the art that some amino acid sequence of the polypeptide of the invention can be varied without significant effect on the structure or function of the protein. If such differences in sequence are contemplated, it should be remembered that there are critical areas on the protein which determine activity. In general, it is possible to replace residues that form the tertiary structure, provided that residues performing a similar function are used. In other instances, the type of residue may be completely unimportant if the alteration occurs at a non-critical region of the protein. The replacement of amino acids can also change the selectivity of binding to cell surface receptors. Ostade et al., *Nature* 361:266-268 (1993) describes certain mutations resulting in selective binding of TNF-alpha to only one of the two known types of TNF receptors. Thus, the polypep-

tides of the present invention may include one or more amino acid substitutions, deletions or additions, either from natural mutations or human manipulation.

[0058] The invention further includes variations of the disclosed polypeptide which show comparable expression patterns or which include antigenic regions. Such mutants include deletions, insertions, inversions, repeats, and type substitutions. Guidance concerning which amino acid changes are likely to be phenotypically silent can be found in Bowie, J. U., et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions,"*Science* 247:1306-1310 (1990).

[0059] Of particular interest are substitutions of charged amino acids with another charged amino acid and with neutral or negatively charged amino acids. The latter results in proteins with reduced positive charge to improve the characteristics of the disclosed protein. The prevention of aggregation is highly desirable. Aggregation of proteins not only results in a loss of activity but can also be problematic when preparing pharmaceutical formulations, because they can be immunogenic. (Pinckard et al., *Clin. Exp. Immunol.* 2:331-340 (1967); Robbins et al., *Diabetes* 36:838-845 (1987); Cleland et al., *Crit. Rev. Therapeutic Drug Carrier Systems* 10:307-377 (1993)).

[0060] Amino acids in the polypeptides of the present invention that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham and Wells, *Science* 244:1081-1085 (1989)). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for biological activity such as receptor binding, or in vitro proliferative activity. Sites that are critical for ligand-receptor binding can also be determined by structural analysis such as crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith et al., *J. Mol. Biol.* 224:899-904 (1992) and de Vos et al. *Science* 255:306-312 (1992)).

[0061] As indicated, changes are preferably of a minor nature, such as conservative amino acid substitutions that do not significantly affect the folding or activity of the protein. Of course, the number of amino acid substitutions a skilled artisan would make depends on many factors, including those described above. Generally speaking, the number of substitutions for any given polypeptide will not be more than 50, 40, 30, 25, 20, 15, 10, 5 or 3.

[0062] Non-limiting examples of amino acid substitutions include substituting the amino acids at one or both of positions 33 and 34 of SEQ ID NO:22, thereby eliminating the potential signal peptidase cleavage site; and substituting one or more of the amino acids at positions 8, 130, 134, 145 and 151 of SEQ ID NO:26; positions 39, 56, 62, 102 and 107 of SEQ ID NO;28; and positions 147, 155 and 237 of SEQ ID NO:30, thereby preventing N-glycosylation at the substituted site(s).

Fusion Proteins

[0063] Fusion proteins comprising proteins or polypeptide fragments of the invention also be constructed. Fusion proteins are useful for generating antibodies against amino acid sequences and for use in various assay systems. For example, fusion proteins can be used to identify proteins which interact with a protein of the invention or which interfere with its biological function. Physical methods, such as protein affinity chromatography, or library-based assays for protein-protein interactions, such as the yeast two-hybrid or phage display systems, can also be used for this purpose. Such methods are well known in the art and can also be used as drug screens. Fusion proteins comprising a signal sequence and/or a transmembrane domain of one or more of the disclosed proteins can be used to target other protein domains to cellular locations in which the domains are not normally found, such as bound to a cellular membrane or secreted extracellularly.

[0064] A fusion protein comprises two protein segments fused together by means of a peptide bond. Amino acid sequences for use in fusion proteins of the invention can be selected from the amino acid sequences shown in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30 or from biologically active variants of those sequences, such as those described above. The first protein segment can consist of a full-length secreted protein.

[0065] Other first protein segments can consist of at least 8, 10, 12, 15, 18, 19, 20, 25, 50, 75, 100, 125, 130, 135, 140, 145, 150, 200, 250, 300, or 320 contiguous amino acids selected from SEQ ID NO:2 or at least amino acids 1-19 of SEQ ID NO:2.

[0066] Still other first protein segments can consist of at least 8, 10, 12, 15, 20, 24, 25, 50, 75, 100, 150, 200, 250, 300, 350, 400, or 430 contiguous amino acids of SEQ ID NO:4 or at least amino acids 1-24 of SEQ ID NO:4.

[0067] Yet other first protein segments can consist of at least 8, 10, 12, 15, 20, 25, 30, 50, 75, 100, 150, 200, 250, 300, or 330 contiguous amino acids of SEQ ID NO:6 or at least amino acids 1-25 of SEQ ID NO:6.

[0068] Even other first protein segments can consist of at least 8, 10, 12, 15, 19, 20, 25, 30, 50, 75, 100, 150, 200, 250, 300, 350, or 375 contiguous amino acids of SEQ ID NO:8 or at least amino acids 1-19 of SEQ ID NO:8.

[0069] Other first protein segments can consist of at least 8, 10, 12, 15, 20, 25, 30, 50, 52, 73, 75, 100, 150, 175, 180, 190, 200, 230, or 231 contiguous amino acids selected from amino acids 1-53, 137-210, 291-521, or 516-709 of SEQ ID NO:10, at least 15, 16, 17, 18, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, or 90 contiguous amino acids selected from amino acids 45-145 of SEQ ID NO 10, or at least 8, 10, 12, 15, 20, 25, 30, 50, 75, 100, 150, 250, 300, 350, 400, 450, 500, 550, 600, 650, or 700 contiguous amino acids of SEQ ID NO:10.

[0070] Other first protein segments can consist of at least 8, 10, 12, 15, 20, 24, 25, 50, 75, 100, 125, 130, 150, 175, 200, 225, 230, 235 or 239 contiguous amino acids of SEQ ID NO:12, at least 8, 10, 12, 15, 20, 24, 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, 400, 450, 500, 550, 600, 605 or 610 contiguous amino acids of SEQ ID NO:14, or at least 8, 10, 12, 15, 20, 24, 25, 50, 75, 100, 125, 150, 175, 200, 225, 250, 275 or 280 contiguous amino acids of SEQ ID NO:16.

[0071] Other first protein segments can consist of at least 8, 10, 12, 15, 20, 24, 25, 50, 75, 100, 125, 130, 150, 175, 200, 250, 275, 300, 350, 400, 425, 450, 475 or 480 contiguous amino acids of SEQ ID NO:18, or at least 8, 10, 12,

15, 20, 24, 25, 50, 75, 100, 125, 150, 200, 225, 250, 275, 280 or 285 contiguous amino acids of SEQ ID NO:20.

[0072] The second protein segment can be a full-length protein or a polypeptide fragment. Proteins commonly used in fusion protein construction include β-galactosidase, β-glucuronidase, green fluorescent protein (GFP), autofluorescent proteins, including blue fluorescent protein (BFP), glutathione-S-transferase (GST), luciferase, horseradish peroxidase (HRP), and chloramphenicol acetyltransferase (CAT). Additionally, epitope tags can be used in fusion protein constructions, including histidine (His) tags, FLAG tags, influenza hemagglutinin (HA) tags, Myc tags, VSV-G tags, and thioredoxin (Trx) tags. Other fusion constructions can include maltose binding protein (MBP), S-tag, Lex a DNA binding domain (DBD) fusions, GAL4 DNA binding domain fusions, and herpes simplex virus (HSV) BP16 protein fusions.

[0073] These fusions can be made, for example, by covalently linking two protein segments or by standard procedures in the art of molecular biology. Recombinant DNA methods can be used to prepare fusion proteins, for example, by making a DNA construct which comprises coding sequences selected from SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27 and 29 in proper reading frame with nucleotides encoding the second protein segment and expressing the DNA construct in a host cell, as is known in the art. Many kits for constructing fusion proteins are available from companies that supply research labs with tools for experiments, including, for example, Promega Corporation (Madison, Wis.), Stratagene (La Jolla, Calif.), Clontech (Mountain View, Calif.), Santa Cruz Biotechnology (Santa Cruz, Calif.), MBL International Corporation (MIC; Watertown, Mass.), and Quantum Biotechnologies (Montreal, Canada; 1-888-DNA-KITS).

Isolation and Production of Secreted Proteins

[0074] Secreted proteins can be extracted from human cells, such as bone marrow, spleen, thymus, or peripheral blood lymphocytes, using standard biochemical methods. These methods include, but are not limited to, size exclusion chromatography, ammonium sulfate fractionation, ion exchange chromatography, affinity chromatography, crystallization, electrofocusing, and preparative gel electrophoresis. An isolated and purified secreted protein or polypeptide is separated from other compounds which normally associate with the protein or polypeptide in a cell, such as other proteins, carbohydrates, lipids, or subcellular organelles. A preparation of isolated and purified secreted proteins or polypeptides is at least 80% pure; preferably, the preparations are 90%, 95%, or 99% pure. Purity of the preparations can be assessed by any means known in the art. For example, the purity of a preparation can be assessed by examining electrophoretograms of protein or polypeptide preparations at several pH values and at several polyacrylamide concentrations, as is known in the art.

[0075] Proteins, fusion proteins, or polypeptides of the invention can be produced by recombinant DNA methods. For production of recombinant proteins, fusion proteins, or polypeptides, coding sequences selected from the nucleotide sequences shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27 and 29 can be expressed in prokaryotic or eukaryotic host cells using expression systems known in the art. These expression systems include bacterial, yeast, insect, and mammalian cells (see below).

[0076] The resulting expressed protein can then be purified from the culture medium or from extracts of the cultured cells using purification procedures known in the art. For example, for proteins fully secreted into the culture medium, cell-free medium can be diluted with sodium acetate and contacted with a cation exchange resin, followed by hydrophobic interaction chromatography. Using this method, the desired protein or polypeptide is typically greater than 95% pure. Further purification can be undertaken, using, for example, any of the techniques listed above.

[0077] It may be necessary to modify a protein produced in yeast or bacteria, for example by phosphorylation or glycosylation of the appropriate sites, in order to obtain a functional protein. Such covalent attachments can be made using known chemical or enzymatic methods.

[0078] Proteins or polypeptides of the invention can also be expressed in cultured host cells in a form which will facilitate purification. For example, a secreted protein or polypeptide can be expressed as a fusion protein comprising, for example, maltose binding protein, glutathione-S-transferase, or thioredoxin, and purified using a commercially available kit. Kits for expression and purification of such fusion proteins are available from companies such as New England BioLabs, Pharmacia, and Invitrogen. Proteins, fusion proteins, or polypeptides can also be tagged with an epitope, such as a "Flag" epitope (Kodak), and purified using an antibody which specifically binds to that epitope.

[0079] The coding sequences disclosed herein can also be used to construct transgenic animals, such as cows, goats, pigs, or sheep. Female transgenic animals can then produce proteins, polypeptides, or fusion proteins of the invention in their milk. Methods for constructing such animals are known and widely used in the art.

[0080] Alternatively, synthetic chemical methods, such as solid phase peptide synthesis, can be used to synthesize a secreted protein or polypeptide. General means for the production of peptides, analogs or derivatives are outlined in Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins—A Survey of Recent Developments, B. Weinstein, ed. (1983). Substitution of D-amino acids for the normal L-stereoisomer can be carried out to increase the half-life of the molecule. Variants can be similarly produced.

Antibodies

[0081] Isolated and purified proteins, polypeptides, variants, or fusion proteins can be used as immunogens, to obtain preparations of antibodies which specifically bind to epitopes of the disclosed proteins. The antibodies can be used, inter alia, to detect wild-type secreted protein or secreted protein complexes in human tissue and fractions thereof. The antibodies can also be used to detect the presence of mutations in a gene which result in under- or over-expression of a secreted protein of the invention or in expression of a secreted protein with altered size or electrophoretic mobility.

[0082] Any type of antibody known in the art can be generated to bind specifically to epitopes of secreted proteins of the invention. For example, preparations of polyclonal and monoclonal antibodies can be made using stan-

dard methods which are well known in the art. Single-chain antibodies can also be prepared. Single-chain antibodies which specifically bind to epitopes of the disclosed proteins can be isolated, for example, from single-chain immunoglobulin display libraries, as is known in the art. The library is "panned" against a disclosed amino acid sequence, and a number of single chain antibodies which bind with high-affinity to different epitopes of a protein of the invention can be isolated. Hayashi et al., 1995, *Gene* 160:129-30. Single-chain antibodies can also be constructed using a DNA amplification method, such as the polymerase chain reaction (PCR), using hybridoma cDNA as a template. Thirion et al., 1996, *Eur. J. Cancer Prev.* 5:507-11.

[**0083**] Single-chain antibodies can be mono- or bispecific, and can be bivalent or tetravalent. Construction of tetravalent, bispecific single-chain antibodies is taught, for example, in Coloma and Morrison, 1997, *Nat. Biotechnol.* 15:159-63. Construction of bivalent, bispecific; single-chain antibodies is taught inter alia in Mallender and Voss. 1994, *J. Biol. Chem.* 269:199-206.

[**0084**] A nucleotide sequence encoding a single-chain antibody can be constructed using manual or automated nucleotide synthesis, cloned into an expression construct using standard recombinant DNA methods, and introduced into a cell to express the coding sequence, as described below. Alternatively, single-chain antibodies can be produced directly using, for example, filamentous phage technology. Verhaar et al., 1995, *Int. J. Cancer* 61:497-501; Nicholls et al., 1993, *J. Immunol. Meth.* 165:81-91.

[**0085**] Monoclonal and other antibodies can also be "humanized" in order to prevent a patient from mounting an immune response against the antibody when it is used therapeutically. Such antibodies may be sufficiently similar in sequence to human antibodies to be used directly in therapy or may require alteration of a few key residues. Sequence differences between, for example, rodent antibodies and human sequences can be minimized by replacing residues which differ from those in the human sequences, for example, by site directed mutagenesis of individual residues, or by grafting of entire complementarily determining regions. Alternatively, one can produce humanized antibodies using recombinant methods, as described in GB2188638B. Antibodies which specifically bind to secreted protein epitopes can contain antigen binding sites which are either partially or fully humanized, as disclosed in U.S. Pat. No. 5,565,332.

[**0086**] Rodents, such as mice and rats, can be genetically engineered to produce a large repertoire of human antibodies. Segments of human immunoglobulin loci can be introduced into the germlines of these rodents. Either miniloci, containing 1-2 VH segments, or large continuous fragments of human heavy and light immunoglobulin loci can be used. If desired, gene targeting can be used to create rodents which do not make rodent antibodies. The engineered rodents produce fully human antibodies. In particular, human monoclonal antibodies with high affinity and specificity against a wide variety of antigens, including human antigens, can be produced. Methods of producing fully human antibodies from transgenic rodents are taught, for example, in Wagner et al. *Eur. J. Immunol.* 24: 2672-81 (1994); Lonberg et al., *Nature* 368: 856 59 (1994); Green et al., *Nature Genet.* 7: 13-21 (1994); Jakobovits, *Curr. Opin. Biotechnol.* 6: 561-66 (1995); Jakobovits et al, *Ann. N.Y Acad. Sci.* 764: 525-35 (1995); Bruggemann & Neuberger, *Immunol. Today* 17: 391-97 (1996); and Mendez et al., *Nature Genet.* 15: 146-56(1997).

[**0087**] Other types of antibodies can be constructed and used therapeutically. For example, chimeric antibodies can be constructed as disclosed in WO 93/03151. Binding proteins which are derived from immunoglobulins and which are multivalent and multispecific, such as the "diabodies" described in WO 94/13804, can also be prepared.

[**0088**] Secreted protein-specific antibodies specifically bind to epitopes present in a full-length secreted protein having an amino acid sequence as shown in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18 or 20, to polypeptide fragments, or to variants, either alone or as part of a fusion protein. Preferably, the epitopes are not present in other human proteins. Typically, at least 6, 8, 10, or 12 contiguous amino acids are required to form an epitope. However, epitopes which involve non-contiguous amino acids may require more, e.g., at least 15, 25, or 50 amino acids.

[**0089**] Antibodies which specifically bind to epitopes of the disclosed proteins, polypeptides, fusion proteins, or biologically active variants can be used in immunochemical assays, including but not limited to Western blots, ELISAs, radioimmunoassays, immunohistochemical assays, immunoprecipitations, or other immunochemical assays known in the art. Typically, antibodies of the invention provide a detection signal at least 5-, 10-, or 20-fold higher than a detection signal provided with other proteins when used in such immunochemical assays. Preferably, antibodies which specifically bind to epitopes of the disclosed proteins do not detect other proteins in immunochemical assays and can immunoprecipitate a secreted protein or polypeptide of the invention from solution.

[**0090**] Antibodies can be purified by methods well known in the art. Preferably, the antibodies are affinity purified, by passing the antibodies over a column to which a protein, polypeptide, variant, or fusion protein of the invention is bound. The bound antibodies can then be eluted from the column, for example, using a buffer with a high salt concentration.

Polynucleotide Sequences

[**0091**] Genes which encode the secreted proteins of the invention have the coding sequences shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27 and 29. Polynucleotide molecules of the invention contain less than a whole chromosome and can be single- or double-stranded. Preferably, the polynucleotide molecules are intron-free. Polynucleotide molecules of the invention can comprise at least 11, 15, 18, 21, 30, 33, 42, 54, 60, 66, 72, 84, 90, 10, 120, 140, 160, 180, 200, 240, 300, 330, 400, 420, 500, 540, 600, 660, 700, 720, 800, 840, 900, 960, 1000, 1100, or 1200 or more contiguous nucleotides selected from nucleotides 109-1313 of SEQ ID NO:1, at least 37, 42, 54, 60, 66, 72, 84, 90, 10, 120, 140; 160, 180, 200, 240, 300, 330, 400, 420, 500, 540, 600, 660, 700, 720, 800, 840, 900, 960, 1000, 1100, 1200, or 1230 contiguous nucleotides selected from nucleotides 84 to 1313 of SEQ ID NO:1, at least 69, 72, 84, 90, 10, 120, 140, 160, 180, 200, 240, 300, 330, 400, 420, 500, 540, 600, 660, 700, 720, 800, 840, 900, 960, 1000, 1100, 1200, 1250, or 1300 contiguous nucleotides selected

from SEQ ID NO:1, the 1313 contiguous nucleotides of SEQ ID NO:1, or the complements thereof.

[0092] Other polynucleotide molecules of the invention can comprise at least 11, 15, 18, 21, 30, 33, 42, 54, 60, 66, 72, 84, 90, 10, 120, 140, 160, 180, 200, 240, 300, 330, 400, 420, 500, 540, 600, 660, 700, 720, or 800 contiguous nucleotides selected from nucleotides 1-818 of SEQ ID NO:3, at least 11, 15, 18, 21, 30, 33, 42, 54, 60, 66, 72, 84, 90, 100, 120, 140, 160, or 180 contiguous nucleotides selected from nucleotides 1762-1941 of SEQ ID NO:3 at least 550, 600, 660, 700, 720, 800, 840, 900, 960, 1000, 1100, 1200, 1250, 1295, 1300, 1350, 1400, or 1411 contiguous nucleotides selected from SEQ ID NO:3, at least 30, 33, 42, 54, 60, 66, 72, 84, 90, 10, 120, 140, 160, 180, 200, 240, 300, 330, 400, 420, 500, 550, 600, 660, 700, 720, 800, 840, 900, 960, 1000, 1100, 1200, 1250, 1295, 1300, 1350 , 1400, or 1420 contiguous nucleotides selected from nucleotides 1-1425 of SEQ ID NO:3, at least 68, 72, 84, 90, 10, 120, 140, 160, 180, 200, 240, or 300 contiguous nucleotides selected from nucleotides 1637-1941 of SEQ ID NO:3, at least 97, 100, 120, 140, 160, 180, 200, 250, 300, 350, 400, 450, 500, 550, 600, 660, 700, 720, 800, 840, 900, 960, 1000, 1100, 1200, 1250, 1295, 1300, 1350, 1400, 1450, 1500, 1550, 1600, or 1650 contiguous nucleotides selected from nucleotides 1-1652 of SEQ ID NO:3, at least 97, 100, 120, 140, 160, 180, 200, 250, 300, 350, 400, 450, 500, 550, 600, 660, 700, 720, 800, 840, 900, 960, 1000, 1100, or 1200 contiguous nucleotides selected from nucleotides 262-1556 of SEQ ID NO:3, the 1941 contiguous nucleotides of SEQ ID NO:3, or the complements thereof.

[0093] Still other polynucleotide molecules of the invention can comprise at least 11 contiguous nucleotides selected from nucleotides molecules 1-32 of SEQ ID NO:5, at least 11, 15, 18, 21, 30, 33, 42, 54, 60, 66; 72, 84, 90, 10, 120, 140, 160, 180, 200, 240, 300, 330, 400, 420, 500, 540, 600, or 640 contiguous nucleotides selected from nucleotides 191-1839 of SEQ ID NO:5, at least 180, 200, 250, 300, 350, 400, 450, 500, 550, 600, 660, 700, 720, 800, 840, 900, 960, 1000, 1017, 1100, 1200, 1250, 1295, 1300, 1350, 1400, 1450, 1500, 1550, 1600, 1650, 1700, 1750, or 1800 contiguous nucleotides selected from SEQ ID NO:5, the 1839 contiguous nucleotides of SEQ ID NO:5, or the complements thereof.

[0094] Even other polynucleotide molecules of the invention can comprise at least 27, 30, 33, 42, 54, 57, 60, 66, 72, 84, 90, 10, 120, 140, 160, 180, 200, 240, 300, 330, 400, 420, 500, 540, 600, 700, 720, 800, 840, 900, 960, 1000, 1017, 1100, 1200, 1250, 1295, 1300, 1350, 1400, 1450, 1500, 1550, 1600, 1650, 1700, 1750, or 1800 contiguous nucleotides selected from SEQ ID NO:7, at least 11, 15, 18, 21, 30, 33, 42, 54, 57, 60, 66, 72, 84, 90, 10, 120, 140, 160, 180, 200, 240, 300, 330, 400, 420, 500, 540, 600, 700, 720, 800, 840, 900, 960, 1000, 1017, 1100, 1197, 1200, 1250, 1295, 1300, 1350, 1400, 1450, 1500, 1550, 1600, 1650, 1700, 1750, or 1800 contiguous nucleotides selected from nucleotides 16-1831 of SEQ ID NO:7, the 1831 contiguous nucleotides of SEQ ID NO:7, or the complements thereof.

[0095] Other polynucleotide molecules of the invention can comprise at least 11, 15, 18, 21, 30, 33, 42, 54, 57, 60, 66, 72, 84, 90, 10, 120, 140, 160, 180, 200, 240, 300, 330, 400, 420, 500, 540, 600, 700, 720, 800, 840, 900, 960, 1000, 1017, 1100, 1197, 1200, 1250, 1295, 1300, 1350, 1400, 1450, 1500, 1550, 1600, 1650, 1700, 1750, 1800, 1850, 1900, 1950, 2000, 2100, 2200, 2300, 2400, 2500, 2600, 2700, 2800, 2900, 3000, 3100, 3200, 3300, 3400, 3500, 3600, 3700, 3800, 3900, 4000, or 4220 contiguous nucleotides selected from SEQ ID NO:9, the 4222 contiguous nucleotides of SEQ ID NO:9, or the complements thereof.

[0096] The complements of the nucleotide sequences shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27 and 29 are contiguous nucleotide sequences which form Watson-Crick base pairs with a contiguous nucleotide sequence as shown in SEQ ID NOS: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27 and 29. The complements of the nucleotide sequences shown in SEQ ID NOS: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27 and 29 (the antisense strand) can be used provide antisense oligonucleotides. Polynucleotide molecules of the invention also include molecules which encode single-chain antibodies which specifically bind to the disclosed proteins, ribozymes which specifically bind to mRNA encoding the disclosed proteins, and fusion proteins comprising amino acid sequences of the disclosed proteins.

[0097] Degenerate polynucleotide sequences which encode amino acid sequences of the secreted proteins and variants, as well as homologous nucleotide sequences which are at least 65%, 75%, 85%, 90%, 95%, 98%, or 99% identical to the nucleotide sequences shown in SEQ ID NOS: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27 and 29 are also polynucleotide molecules of the invention. Percent sequence identity is determined by any method known in the art, for example, using computer programs which employ the Smith-Waterman algorithm, such as the MPSRCH program (Oxford Molecular), using an affine gap search with the following parameters: a gap open penalty of 12 and a gap extension penalty of 1.

[0098] Typically, homologous polynucleotide sequences can be confirmed by hybridization under stringent conditions, as is known in the art. For example, using the following wash conditions: 2× SSC (0.3 M NaCl, 0.03 M sodium citrate, pH 7.0), 0.1% SDS, room temperature twice, 30 minutes each; then 2× SSC, 0.1% SDS, 50° C. once, 30 minutes; then 2× SSC, room temperature twice, 10 minutes each, homologous sequences can be identified which contain at most about 25-30% basepair mismatches. More preferably, homologous nucleic acid strands contain 15-25% basepair mismatches, even more preferably 5-15% basepair mismatches.

[0099] Species homologs of polynucleotide molecules which encode proteins of the invention can be identified by making suitable probes or primers and screening cDNA expression libraries from other species, such as mice, monkeys, yeast, or bacteria, as well as human cDNA expression libraries. It is well known that the Tm of a double-stranded DNA decreases by 1-1.5° C. with every 1% decrease in homology (Bonner et al., *J. Mol. Biol.* 81, 123 (1973). Homologous human polynucleotides or polynucleotides of other species can therefore be identified, for example, by hybridizing a putative homologous polynucleotide with a polynucleotide having the nucleotide sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27 and 29 to form a test hybrid, comparing the melting temperature of the test hybrid with the melting temperature of a hybrid of a polynucleotide consisting of a nucleotide sequence of SEQ

ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27 and 29 and a perfectly complementary polynucleotide, and calculating the number or percent of basepair mismatches within the test hybrid.

[0100] Nucleotide sequences which hybridize to the coding sequences shown in SEQ ID NOS: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27 and 29 or their complements following stringent hybridization and/or wash conditions are also polynucleotide molecules of the invention. Stringent wash conditions are well known and understood in the art and are disclosed, for example, in Sambrook et al., Molecular Cloning A Laboratory Manual, 2d ed., 1989, at pages 9.50-9.51.

[0101] Typically, for stringent hybridization conditions a combination of temperature and salt concentration should be chosen that is approximately 12-20° C. below the calculated Tm of the hybrid under study. The Tm of a hybrid between a nucleotide sequence as shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27 and 29 and a polynucleotide sequence which is 65%, 75%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical can be calculated, for example, using the equation of Bolton and McCarthy, *Proc. Natl. Acad. Sci. U.S.A.* 48, 1390 (1962):

$$T_m = 81.5° \text{ C.} - 16.6(\log_{10}[Na^+]) + 0.41(\%G+C) - 0.63(\%\text{formamide}) - 600/l),$$

[0102] where l=the length of the hybrid in basepairs.

[0103] Stringent wash conditions include, for example, 4× SSC at 65° C., or 50% formamide, 4× SSC at 42° C., or 0.5× SSC, 0.1% SDS at 65° C. Highly stringent wash conditions include, for example, 0.2× SSC at 65° C.

[0104] Polynucleotide molecules of the invention can be isolated and purified free from other nucleotide sequences using standard nucleic acid purification techniques. For example, restriction enzymes and probes can be used to isolate polynucleotide fragments which comprise nucleotide sequences encoding one or more of the secreted proteins disclosed herein. Isolated and purified polynucleotide molecules are in preparations which are free or at least 90% free of other molecules.

[0105] Complementary DNA (cDNA) molecules which encode secreted proteins of the invention are also polynucleotide molecules of the invention. cDNA molecules can be made with standard molecular biology techniques, using mRNA as a template. cDNA molecules can thereafter be replicated using molecular biology techniques known in the art and disclosed in manuals such as Sambrook et al., 1989. An amplification technique, such as the polymerase chain reaction (PCR), can be used to obtain additional copies of polynucleotide molecules of the invention, using either human genomic DNA or cDNA as a template.

[0106] Alternatively, synthetic chemistry techniques can be used to synthesize polynucleotide molecules of the invention. The degeneracy of the genetic code allows polynucleotide molecules with alternate nucleotide sequences to be synthesized which will encode a protein having an amino acid sequence as shown in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 or 30 or a biologically active variant of one of those proteins. All such polynucleotide molecules are within the scope of the present invention.

[0107] The invention also provides polynucleotide probes which can be used to detect complementary nucleotide sequences, for example, in hybridization protocols such as Northern or Southern blotting or in situ hybridizations. Polynucleotide probes of the invention comprise at least 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, or 40 or more contiguous nucleotides selected from SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27 and 29. Polynucleotide probes of the invention can comprise a detectable label, such as a radioisotopic, fluorescent, enzymatic, or chemiluminescent label.

[0108] Isolated genes corresponding to the cDNA sequences disclosed herein are also provided. Standard molecular biology methods can be used to isolate the corresponding genes using the cDNA sequences provided herein. These methods include preparation of probes or primers from the nucleotide sequences shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27 and 29 for use in identifying or amplifying the genes from human genomic libraries or other sources of human genomic DNA.

[0109] Polynucleotide molecules of the invention can also be used as primers to obtain additional copies of the polynucleotides, using polynucleotide amplification methods. Polynucleotide molecules can be propagated in vectors and cell lines using techniques well known in the art. Polynucleotide molecules can be on linear or circular molecules. They can be on autonomously replicating molecules or on molecules without replication sequences. They can be regulated by their own or by other regulatory sequences, as is known in the art.

Polynucleotide Constructs

[0110] Polynucleotide molecules comprising the coding sequences disclosed herein can be used in a polynucleotide construct, such as a DNA or RNA construct. Polynucleotide molecules of the invention can be used, for example, in an expression construct to express all or a portion of a secreted protein, variant, fusion protein, or single-chain antibody in a host cell. An expression construct comprises a promoter which is functional in a chosen host cell. The skilled artisan can readily select an appropriate promoter from the large number of cell type-specific promoters known and used in the art. The expression construct can also contain a transcription terminator which is functional in the host cell. The expression construct comprises a polynucleotide segment which encodes all or a portion of the desired protein. The polynucleotide segment is located downstream from the promoter. Transcription of the polynucleotide segment initiates at the promoter. The expression construct can be linear or circular and can contain sequences, if desired, for autonomous replication.

Host Cells

[0111] An expression construct can be introduced into a host cell. The host cell comprising the expression construct can be any suitable prokaryotic or eukaryotic cell. Expression systems in bacteria include those described in Chang et al., *Nature* (1978) 275: 615; Goeddel et al., *Nature* (1979) 281: 544; Goeddel et al., *Nucleic Acids Res.* (1980) 8: 4057; EP 36,776; U.S. Pat. No. 4,551,433; deBoer et al., *Proc. Natl. Acad. Sci. USA* (1983) 80: 21-25; and Siebenlist et al., *Cell* (1980) 20: 269.

[0112] Expression systems in yeast include those described in Hinnen et al., *Proc. Natl. Acad. Sci. USA* (1978)

75: 1929; Ito et al., *J. Bacteriol.* (1983) 153: 163; Kurtz et al., *Mol. Cell. Biol.* (1986) 6: 142; Kunze et al., *J. Basic Microbiol.* (1985) 25: 141; Gleeson et al., *J. Gen. Microbiol.* (1986) 132: 3459, Roggenkamp et al., *Mol. Gen. Genet.* (1986) 202: 302); Das et al., *J Bacteriol.* (1984) 158: 1165; De Louvencourt et al., *J. Bacteriol.* (1983) 154: 737, Van den Berg et al., *Bio/Technology* (1990) 8: 135; Kunze et al., *J. Basic Microbiol.* (1985) 25: 141;Cregg et al., *Mol. Cell. Biol.* (1985) 5: 3376; U.S. Pat. No. 4,837,148; U.S. Pat. No. 4,929,555; Beach and Nurse, Nature (1981) 300: 706; Davidow et al., Curr. Genet. (1985) 1p: 380; Gaillardin et al., Curr. *Genet.* (1985) 10: 49; Ballance et al., *Biochem. Biophys. Res. Commun.* (1983) 112: 284-289; Tilburn et al., *Gene* (1983) 26: 205-22;, Yelton et al., *Proc. Natl. Acad. Sci. USA* (1984) 81: 1470-1474; Kelly and Hynes, *EMBO J.* (1985) 4: 475479; EP 244,234; and WO 91/00357.

[0113] Expression of heterologous genes in insects can be accomplished as described in U.S. Pat. No. 4,745,051; Friesen et al. (1986) "The Regulation of Baculovirus Gene Expression" in: THE MOLECULAR BIOLOGY OF BACULOVIRUSES (W. Doerfler, ed.); EP 127,839; EP 155,476; Vlak et al., *J. Gen. Virol.* (1988) 69: 765-776; Miller et al., *Ann. Rev. Microbiol.* (1988) 42: 177; Carbonell et al., *Gene* (1988) 73: 409; Maeda et al., *Nature* (1985) 315:. 592-594; Lebacq-Verheyden et al., *Mol. Cell Biol.* (1988) 8: 3129; Smith et al., *Proc. Natl. Acad. Sci. USA* (1985) 82: 8404; Miyajima et al., *Gene* (1987) 58: 273; and Martin et al., *DNA* (1988) 7:99. Numerous baculoviral strains and variants and corresponding permissive insect host cells from hosts are described in Luckow et al., *Bio/Technology* (1988) 6:47-55, Miller et al., in GENERIC ENGINEERING (Setlow, J. K. et al. eds.), Vol. 8 (Plenum Publishing, 1986), pp. 277-279; and Maeda et al., *Nature,* (1985) 315: 592-594.

[0114] Mammalian expression can be accomplished as described in Dijkema et al., *EMBO J.* (1985) 4: 761; *Gormanetal., Proc. Natl. Acad. Sci. USA* (1982b) 79: 6777; Boshart et al., *Cell* (1985) 41: 521; and U.S. Pat. No. 4,399,216. Other features of mammalian expression can be facilitated as described in Ham and Wallace, *Meth Enz.* (1979) 58: 44; Barnes and Sato, *Anal. Biochem.* (1980) 102: 255; U.S. Pat. No. 4,767,704; U.S. Pat. No. 4,657,866; U.S. Pat. No. 4,927,762; U.S. Pat. No. 4,560,655; WO 90/103430, WO 87/00195, and U.S. RE 30,985.

[0115] Expression constructs can be introduced into host cells using any technique known in the art. These techniques include transferrin-polycation-mediated DNA transfer, transfection with naked or encapsulated nucleic acids, liposome-mediated cellular fusion, intracellular transportation of DNA-coated latex beads, protoplast fusion, viral infection, electroporation, "gene gun," and calcium phosphate-mediated transfection.

[0116] Expression of an endogenous gene encoding a protein of the invention can also be manipulated by introducing by homologous recombination a DNA construct comprising a transcription unit in frame with the endogenous gene, to form a homologously recombinant cell comprising the transcription unit. The transcription unit comprises a targeting sequence, a regulatory sequence, an exon, and an unpaired splice donor site. The new transcription unit can be used to turn the endogenous gene on or off as desired. This method of affecting endogenous gene expression is taught in U.S. Pat. No. 5,641,670.

[0117] The targeting sequence is a segment of at least 10, 12, 15, 20, or 50 contiguous nucleotides selected from the nucleotide sequences shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27 and 29. The transcription unit is located upstream to a coding sequence of the endogenous gene. The exogenous regulatory sequence directs transcription of the coding sequence of the endogenous gene.

Functional Assays

[0118] A protein of the invention can exhibit cytokine, cell proliferation (either inducing or inhibiting), or cell differentiation (either inducing or inhibiting) activity, or can induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor-dependent cell proliferation assays; hence, the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the invention can be evidenced by any one of a number of routine factor-dependent cell proliferation assays for cell lines including, 32D (a mouse IL-3-dependent lymphoblast cell line, ATCC No. CRL-11346), DA2, DA1G, T10 (a human myeloma cell line, ATCC No. CRL-9068), B9, B9/11, BaF3, MC9/G, M+(preB M+), 2E8 (a mouse IL-7-dependent Lymphoblast cell line, ATCC No. TIB-239), RB5, DA1, 123, T1165, HT2 (a mouse lymphoma cell line, ATCC No. CRL-8629), CTLL2, TF-I (a human IL-5-unresponsive Lymphoblast cell line, ATCC No. CRL-2003), Mo7e, and CMK.

[0119] Assays for T-cell or thymocyte proliferation include those described in Current Protocols in Immunology, Coligan et al., eds., Greene Publishing Associates and Wiley-Interscience (particularly chapter 3, In Vitro Assays for Mouse Lymphocyte Function 3.1-3.19; and chapter 7, Immunologic Studies in Humans); Takai et al., *J. Immunol.* 137:3494-3500, 1986; Bertagnolli et al., *J. Immunol.* 145:1706-1712, 1990; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Bertagnolli, et al., *J Immunol.* 149:3778-3783, 1992; and Bowman et al., *J. Immunol.* 152:1756-1761, 1994.

[0120] Assays for cytokine production and/or proliferation of spleen cells, lymph node cells, or thymocytes include those described in Kruisbeek and Shevach, Polyclonal T Cell Stimulation, in Current Protocols in Immunology, vol. I, pp. 3.12.1-3.12.14, and Schreiber, Measurement of Mouse and Human Interleukin Gamma, in Current Protocols in Immunology vol. 1, pp. 6.8.1-6.8.8.

[0121] Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include those described in Bottomly, Measurement of Human and Murine Interleukin 2 and Interleukin 4, in Current Protocols in Immunology vol. 1, pp. 6.3.1-6.3.12; deVries et al., *J Exp. Med.* 173: 1205-1211, 1991; Moreau et al., *Nature* 336:690-692, 1988; Greenberger et al., *Proc. Natl. Acad. Sci. U.S.A.* 80:2931-2938, 1983; Nordan, R., Measurement of mouse and human interleukin 6, in Current Protocols in Immunology vol. 1, pp. 6.6.1-6.6.5; Smith et al., *Proc. Natl. Acad. Sci. U.S.A.* 83:1857-1861, 1986; Bennett et al., Measurement of Human Interleukin 11, in Current Protocols in Immunology vol. 1, pp. 6.15.1; Ciarletta et al., Measurement of mouse and human Interleukin 9, in Current Protocols in Immunology vol. 1, p. 6.13.1.

[0122] Assays for T cell clone responses to antigens (which will identify, among others, proteins that affect

APC-T cell interactions as well as direct T cell effects by measuring proliferation and cytokine production) include those described in Current Protocols in Immunology especially chapters 3 (In Vitro Assays for Mouse Lymphocyte Function), chapter 6 (Cytokines and Their Cellular Receptors), and chapter 7 (Immunologic Studies in Humans); Weinberger et al., *Proc. Natl. Acad. Sci. USA* 77:6091-6095, 1980; Weinberger et al., *Eur. J Immun.* 11:405-411, 1981; Takai et al., *J Immunol.* 137:3494-3500, 1986; and Takai et al., *J: Immunol.* 140:508-512, 1988.

[0123] Assays for tissue generation activity include those described for bone, cartilage, and tendon in WO 95/16035, for neuronal tissue in WO 95/05846, and for skin and endothelial tissue in WO 91/07491. Assays for wound healing activity include, for example, those described in Winter, Epidermal Wound Healing, polypeptides 71-112 (Maibach and Rovee, eds.), Year Book Medical Publishers, Inc., Chicago, and Eaglstein and Mertz, J. *Invest. Dermatol* 71:382-84 (1978).

[0124] A protein of the present invention can also demonstrate activity as a receptor, receptor ligand, or inhibitor or agonist of a receptor/ligand interaction. Examples of such receptors and ligands include cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands, including cellular adhesion molecules such as selecting, integrins, and their ligands, and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses. Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the invention, including fragments of receptors and ligands, can itself be useful as an inhibitor of receptor/ligand interactions.

[0125] Suitable assays for receptor-ligand activity include those described in Current Protocols in Immunology, chapter 7.28, Measurement of Cellular Adhesion Under Static Conditions, pages 7.28.1-7.28.22, Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stittetal., Cell 80:661-670, 1995.

[0126] Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above. Assays for embryonic stem cell differentiation which can identify proteins which influence embryonic hematopoiesis include those described in Johansson et al. *Cellular Biology* 15:141-151, 1995; Keller et al., *Molecular and Cellular Biology* 13:473-486, 1993; and McClanahan et al., *Blood* 81:2903-2915, 1993.

[0127] Assays for stem cell survival and differentiation include those described in Freshney, Methylcellulose colony forming assays, in Culture of Hematopoietic Cells, Freshney et al. eds., pp. 265-268, Wiley-Liss, Inc., New York, N.Y. 1994; Hirayamaet all, *Proc. Natl. Acad. Sci. USA* 89:5907-5911, 1992; McNiece and Briddell, Primitive hematopoietic colony forming cells with high proliferative potential, in Culture of Hematopoietic Cells, pp. 23-39; Neben et al., *Experimental Hematology* 22:353-359, 1994; Ploemacher, Cobblestone area forming cell assay, in Culture of Hematopoietic Cells, pp. 1-21; Spooncer et al., Long term bone marrow cultures in the presence of stromal cells, in Culture of Hematopoietic Cells, pp. 163-179; Sutherland, Long term culture initiating cell assay, in Culture of Hematopoietic Cells, pp. 139-162. Such assays can be used to identify proteins which regulate lympho-hematopoiesis.

Therapeutic Uses of Secreted Proteins and Polynucleotides Molecules

[0128] A protein of the present invention can be used to support colony forming cells or factor-dependent cell lines, to regulate hematopoiesis, and to treat myeloid or lymphoid cell deficiencies. The protein can be used, either alone or in combination with other cytokines, to support the growth and proliferation of erythroid progenitor cells. Proteins of the invention can also be used to treat various anemias, in conjunction with irradiation or chemotherapy to stimulate the production of erythroid precursors or erythroid cells.

[0129] A protein of the invention which has CSF activity can be used to support the growth and proliferation of myeloid cells, such as granulocytes, monocytes, or macrophages. Proteins with such activity can be used, for example, in conjunction with chemotherapy to prevent or treat myelo-suppression. Proteins of the invention can also be used to support the growth and proliferation of megakaryocytes and platelets, thereby allowing prevention or treatment of platelet disorders such as thrombocytopenia. Proteins with such activity can be used to support the growth and proliferation of hematopoietic stem cells, either in place of or in conjunction with platelet transfusions. Proteins of the invention can be used to treat stem cell disorders, such as aplastic anemia and paroxysmal nocturnal hemoglobinuria, or to repopulate the stem cell compartment after irradiation or chemotherapy, either in vivo or ex vivo. For example, a protein of the invention can be used in conjunction with homologous or heterologous bone marrow transplantation or peripheral progenitor cell transplantation.

[0130] Proteins of the invention, or fragments thereof, can be useful for treatment and diagnosis of a variety of conditions in which the rate of cell growth, and cell-cell interactions, are disrupted. Such conditions include cancer.

[0131] A protein of the invention also can have utility in compositions used for growth or differentiation of bone, cartilage, tendon, ligament, or nerve tissue, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions, and ulcers.

[0132] Proteins of the present invention can induce cartilage and/or bone growth in circumstances where bone is not normally formed and thus have an application in healing bone fractures and cartilage damage or defects in humans and other animals. A preparation employing a protein of the invention can have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma- or surgery-induced craniofacial defects and also is useful in cosmetic plastic surgery.

[0133] A protein of this invention can also be used in the treatment of periodontal disease and in other tooth repair processes. Such agents can provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells, or induce differentiation of progenitors of bone-forming

cells. A protein of the invention can be used to treat osteoporosis or osteoarthritis, for example, through stimulation of bone and/or cartilage repair or by blocking inflammation. Mechanisms of destroying tissue mediated by inflammatory processes, such as collagenase or osteoclast activity, can also be inhibited.

[0134] Tendon or ligament formation can also be influenced by a protein of the invention. A protein of the invention which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed can be used to heal tendon or ligament tears, deformities, and other tendon or ligament defects in humans and other animals. A preparation employing a tendon/ligament-like tissue inducing protein can be used to prevent damage to tendon or ligament tissue, as well as in the improved fixation of tendon or ligament to bone or other tissues, and to repair defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the invention contributes to the repair of congenital, trauma-induced, or other tendon or ligament defects of other origin and can also be used in cosmetic plastic surgery, for attachment or repair of tendons or ligaments.

[0135] A protein of the invention can also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, i.e. for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders. More specifically, a protein can be used in the treatment of diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Other conditions which can be treated in accordance with the invention include mechanical and traumatic disorders, such as spinal cord disorders and head trauma, and cerebrovascular diseases, such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies can be treated using a protein of the invention.

[0136] Proteins of the invention can also be used to promote better or faster closure of non-healing wounds, including pressure ulcers, ulcers associated with vascular insufficiency, or surgical and traumatic wounds.

[0137] A protein of the invention can also affect generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal, or cardiac), and vascular (including vascular endothelium) tissue, or for promoting the growth of cells of which such tissues are comprised. Part of the desired effects can be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention can also exhibit angiogenic activity.

[0138] A protein of the present invention can be useful for gut protection or regeneration, and for treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage. A protein of the invention can also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells or for inhibiting the growth of tissues described above.

[0139] Secreted proteins and polynucleotides of the invention can be used in a composition. Compositions of the invention relate to isolated (purified) polypeptides and polynucleotides. These compositions are substantially free of other human proteins or human polynucleotides. A composition containing A is "substantially free of" B when at least 85% by weight of the total A+B in the composition is A. Preferably, A comprises at least about 90% by weight of the total of A+B in the composition, more preferably at least about 96% or even 99% by weight.

[0140] A protein of the invention can be used in a pharmaceutical composition. Compositions comprising proteins or polynucleotides of the invention have therapeutic applications, both for human patients and veterinary patients, such as domestic animals and thoroughbred horses. Such compositions can optionally include a pharmaceutically acceptable carrier. In addition to protein and carrier, such a composition can also contain diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. Characteristics of a carrier will depend on the route of administration. Compositions of the invention can also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IFN, TNFO, TNF1, TNF2, G-CSF, Meg-CSF, thrombopoietin, stem cell factor, erythropoietin, or growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β), or insulin-like growth factor (IGF).

[0141] A pharmaceutical composition can also contain other agents which either enhance the activity of the protein or complement its activity or use in treatment. Such additional factors and/or agents can be included in the pharmaceutical composition to produce a synergistic effect with a protein of the invention or to minimize side effects. Conversely, a protein of the invention can be included in formulations of a particular factor, such as a cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent to minimize side effects of the factor.

[0142] A protein of the present invention can be active in multimers (e.g., heterodimers or homodimers) or complexes with itself or other proteins, and compositions of the invention can comprise a protein of the invention in such a multimeric or complexed form. For example, a composition of the invention can be in the form of a complex of a protein or proteins of the invention together with protein or peptide antigens. The protein or peptide antigen will deliver a stimulatory signal to both B and T Lymphocytes. B Lymphocytes will respond to antigen through their surface immunoglobulin receptor. T Lymphocytes will respond to antigen through the T cell receptor (TCR) following presentation of the antigen by MHC proteins. MHC proteins and structurally related proteins, including those encoded by class I and class II MHC genes on host cells, can present the peptide antigen(s) to T Lymphocytes. Antigen components could also be supplied as purified MUC-peptide complexes alone or, with co-stimulatory molecules which can directly signal T cells. Alternatively, antibodies able to bind surface immunoglobulin and other molecules on B cells, as well as antibodies able to bind the TCR and other molecules on T cells, can be combined with a composition of the invention.

[0143] A composition of the invention can be in the form of a liposome in which a protein of the invention is com-

bined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids, which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. Preparation of liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Pat. No. 4,235,871, U.S. Pat. No. 4,501,728, U.S. Pat. No. 4,837,028, and U.S. Pat. No. 4,737,323.

[0144] A therapeutically effective amount of a protein of the invention is administered to a mammal having a condition to be treated. The amount of protein which is therapeutically effective is that amount of protein which is sufficient to treat, heal, prevent, or ameliorate the condition, or to increase the rate of such treatment. Proteins of the invention can be administered either alone or in combination with other therapeutic agents, such as cytokines, lymphokines, or other hematopoietic factors. Other therapeutic agents can be administered simultaneously or sequentially with proteins of the invention, as determined by the attending physician.

[0145] Compositions of the invention can be inhaled, ingested, applied topically, or administered by cutaneous, subcutaneous, intraperitoneal, parenteral or intravenous injection. When a therapeutically effective amount of protein of the present invention is administered orally, protein of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the invention can additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5-95%, 25-90%, 30-80%, 40-75%, or 50% protein of the invention by weight. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils can be added.

[0146] The liquid form of the composition can further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol, or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5-90%, 1-80%, 5-75%, 10-65%, 20-50%, 10-50%, or 25-40% by weight of protein of the invention.

[0147] When a therapeutically effective amount of protein of the present invention is administered by intravenous, cutaneous, or subcutaneous injection, a pyrogen-free, parenterally acceptable aqueous solution of the protein is preferred. The skilled artisan can readily prepare an acceptable protein solution with suitable pH, isotonicity, and stability. A solution of the composition for intravenous, cutaneous, or subcutaneous injection should also contain an isotonic vehicle, such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicles as are known in the art. Stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art can also be added to the composition.

[0148] The amount of protein of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated and on the nature of prior treatments which the patient has undergone. Ultimately, the attending physician will decide the amount of protein of the present invention with which to treat each individual patient. Initially, the attending physician will administer low doses of protein of the present invention and observe the patient's response. Larger doses of protein of the present invention can be administered until the optimal therapeutic-effect is obtained for the patient, and at that point the dosage is not increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.01 μg to about 100 mg (preferably about 0.1 μg to about 10 mg, more preferably about 0.1 μg to about 1 mg) of protein of the present invention per kg body weight.

[0149] Duration of intravenous therapy using a composition of the invention will vary, depending on the severity of the disease being treated and the condition and potential idiosyncratic response of each individual patient. It is contemplated that the duration of each application of a composition of the invention will be in the range of 12 to 24 hours of continuous intravenous administration. Ultimately, the attending physician will decide on the appropriate duration of intravenous therapy.

[0150] A composition of the invention which is useful for bone, cartilage, tendon or ligament regeneration can be administered topically, systematically, or locally in an implant or device. Encapsulation or injection in a viscous form for delivery to the site of bone, cartilage or tissue damage is also possible. Topical administration can be suitable for wound healing and tissue repair. Optionally, therapeutic agents other than a protein of the invention can be included in the composition, as described above.

[0151] For affecting bone or cartilage formation, a composition of the invention would include a matrix capable of delivering the composition to the site of bone or cartilage damage and for providing a structure for the developing bone and cartilage. Optimally, the matrix would be capable of resorption into the body. Matrices can be formed of materials presently in use for other implanted medical applications, the choice of material being based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance, and interface properties. Suitable biodegradable matrix materials include chemically defined calcium sulfate, tricalciumphosphate, hydroxyapatite, polylactic acid, polyglycolic acid, polyanhydride, bone or dermal collagen, pure proteins, and extracellular matrix components. Suitable non-biodegradable and chemically defined matrix materials include sintered hydroxyapatite, bioglass, aluminates, or other ceramics. Individual matrix components can be modified, for example, to affect pore size, particle size, particle shape, and biodegradability. Combinations of materials can be used, as is known in the art.

[0152] Sequestering agents, such as carboxymethyl cellulose or an autologous blood clot, can be employed to prevent protein compositions from dissociating from the matrix. Sequestering agents include cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium

alginate, polyethylene glycol, polyoxyethylene oxide, carboxyvinyl polymer and polyvinyl alcohol. The amount of sequestering agent is based on total formulation weight, such as 0.5-20% or 1-10%, and should be an amount of sequestering agent which prevents desorbtion of the protein from the polymer matrix but which permits progenitor cells to infiltrate the matrix, so that the protein can assist the osteogenic activity of the progenitor cells.

[0153] Compositions comprising proteins of the invention can provide an environment which will attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon-or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors ex vivo. Such cells can then be returned to the body to effect tissue repair. Compositions of the invention can also be used to treat tendonitis, carpal tunnel syndrome, and other tendon or ligament defects. Such compositions can optionally include an appropriate matrix and/or sequestering agent as a pharmaceutically acceptable carrier, as is well known in the art.

[0154] The dosage regimen of a protein-containing pharmaceutical composition to be used in tissue regeneration will be determined by the attending physician considering various factors which modify the action of the proteins, e.g. amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of a wound, type of damaged tissue (e.g., bone), the patient's age, sex, and diet, the severity of any infection, time of administration, and other clinical factors. The dosage can vary with the type of matrix used in the reconstitution and whether other therapeutic agents, such as growth factors, are included. Progress of the treatment can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, using X-rays, histomorphometric determinations, or tetracycline labeling.

[0155] Polynucleotides of the invention can also be used for gene therapy. Polynucleotides can be introduced either in vivo or ex vivo into cells for expression in a mammalian subject. Cells can be cultured ex vivo in the presence of proteins of the invention in order to produce a desired effect on or activity in such cells. Treated cells can then be introduced in vivo for therapeutic purposes, as is known in the art. Polynucleotides of the invention can be administered by known methods of introducing polynucleotides into a cell or organism (including in the form of viral vectors or naked DNA).

[0156] Polynucleotides of the invention can also be delivered to subjects for the purpose of screening test compounds for those which are useful for enhancing transfer of polynucleotides of the invention to a cell or for enhancing subsequent biological effects of the polynucleotides within the cell. Such biological effects include hybridization to complementary mRNA and inhibition of its translation, expression of the polynucleotide to form mRNA and/or protein, and replication and integration of the polynucleotide.

[0157] Test compounds which can be screened include any substances, whether natural products or synthetic, which can be administered to the subject. Libraries or mixtures of compounds can be tested. The compounds or substances can be those for which a pharmaceutical effect is previously known or unknown. The compounds or substances can be delivered before, after, or concomitantly with the polynucleotides. They can be administered separately or in admixture with the polynucleotides.

[0158] Integration of delivered polynucleotides can be monitored by any means known in the art. For example, Southern blotting of the delivered polynucleotides can be performed. A change in the size of the fragments of the delivered polynucleotides indicates integration. Replication of the delivered polynucleotides can be monitored inter alia by detecting incorporation of labeled nucleotides combined with hybridization to a specific nucleotide probe. Expression of a polynucleotide of the invention can be monitored by detecting production of mRNA which hybridizes to the delivered polynucleotide or by detecting protein. Proteins of the invention can be detected immunologically. Thus, delivery of polynucleotides of the invention according to the present invention provides an excellent system for screening test compounds for their ability to enhance delivery, integration, hybridization, expression, replication or integration in an animal, preferably a mammal, more preferably a human.

Research Uses of the Polynucleotides and Secreted Proteins

[0159] Polynucleotides of the invention can be used for a variety of research purposes. Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products. For example, polynucleotides can be used to express recombinant protein for analysis, characterization, or therapeutic use. Polynucleotides can be used as markers for tissues in which the corresponding protein is preferentially expressed, either constitutively or at a particular stage of tissue differentiation or development or in disease states. Polynucleotides can also be used as molecular weight markers on Southern gels or, when labeled, for example, with a fluorescent tag or a radiolabel, polynucleotides can be used as chromosome markers, to identify chromosomes for gene mapping.

[0160] Potential genetic disorders can be identified by comparing the sequences of wild-type polynucleotides of the invention with endogenous nucleotide sequences in patients. Polynucleotides of the invention can also be used as probes for the discovery of novel, related DNA sequences, to derive PCR primers for genetic fingerprinting, as probes to "subtract-out" known sequences in the process of discovering other novel polynucleotides, for selecting and making oligomers for attachment to a gene chip or other support, to raise anti-protein antibodies using DNA immunization techniques, and as immunogens, to raise anti-DNA antibodies or to elicit another immune response.

[0161] Where the polynucleotide encodes a protein which binds or potentially binds to another protein, such as in a receptor-ligand interaction, the polynucleotide can also be used in interaction trap assays, such as the yeast two-hybrid assay, to identify polynucleotides encoding the protein with which binding occurs or to identify inhibitors of the binding interaction, for example in drug screening assays.

[0162] Proteins of the invention can similarly be used in assays to determine biological activity, including use in a panel of multiple proteins for high-throughput screening, to raise antibodies or to elicit another immune response, as a

reagent in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids, as markers for tissues in which the protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state), and to identify related receptors or ligands. Where the protein binds or potentially binds to another protein such as, for example, in a receptor-ligand interaction, the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

EXAMPLES

Example 1

Identification of Trans-Membrane Human Proteins

[0163] A cDNA clone designated ch1572 was isolated from a fetal liver library. The cDNA contained a 1994 base pair insert (SEQ ID NO:21) encoding a 585 amino acid protein (SEQ ID NO:22). The amino acid sequence contained a hydrophobic region of amino acids at positions 14 to 33, followed by a potential signal peptidase cleavage site between amino acids 33 and 34.

[0164] Five potential N-linked glycoprotein sites were identified, at amino acids 89, 106, 189, 220 and 315 of SEQ ID NO:22. When the protein was translated in the presence of endoplasmic reticulum membranes, the molecular weight increased in a manner consistent with glycosylation.

[0165] A cDNA clone designated ch1569 was isolated from a fetal liver library. The cDNA contained a 1340 base pair insert (SEQ ID NO:23) encoding a 280 amino acid protein (SEQ ID NO:24). Hydrophobic regions were found at amino acids 1 to 20 and 180 to 206, and a potential signal peptidase cleavage site was located between amino acids 20 and 21. No potential glycosylation sites were found. Where the protein was translated in the presence of rough endoplasmic reticulum, decreased molecular weights was observed, consistent with removal of the signal peptide.

[0166] A cDNA clone designated ch1570 was isolated from a fetal liver library. The cDNA contained a 1011 base pair insert (SEQ ID NO:25) encoding a 286 amino acid protein (SEQ ID NO:26). Five hydrophobic stretches were found, at positions 27 to 53, 62 to 86, 96 to 118, 206 to 246, and 257 to 279. Potential glycosylation sites were found at positions 8, 130, 134, 145, and 151. When the protein was translated in the presence of endoplasmic reticulum, the molecular weight increased, consistent with glycosylation.

[0167] A cDNA clone designated ch1529 was isolated from a fetal liver library. The cDNA contained a 2027 base pair insert (SEQ ID NO:27) encoding a 340 amino acid protein. Five hydrophobic stretches were found, at amino acid positions 19 to 44, 144 to 164, 180 to 223, 231 to 255, and260 to 280.

[0168] Potential N-linked glycosylation sites were found at positions 39, 56, 62, 102 and 107. When the protein was translated in the presence of rough endoplasmic reticulum, the molecular weight increased, consistent with glycosylation of the protein.

[0169] A cDNA clone designated ch1515 was isolated from a fetal liver library. The cDNA contained a 2390 base pair insert (SEQ ID NO:29) encoding a 347 amino acid protein (SEQ ID NO:30). The protein contained a 30 amino acid hydrophobic region between amino acids 55 to 85, which could act as a signal peptide and/or a transmembrane domain.

[0170] Potential N-linked glycosylation sites were found at positions 147, 155 and 237. When the protein was translated in the presence of rough endoplasmic reticulum, an increase in molecular weight was observed, consistent with glycosylation.

[0171] Further objects, features, and advantages of the present invention will readily occur to the skilled artisan provided with the disclosure above. The complete contents of all references cited in this disclosure are expressly incorporated herein by reference.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 30

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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
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<221> NAME/KEY: CDS
<222> LOCATION: (163)...(1137)

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cctctggacc ccgaggttgg accctactgt gacacaccta cc atg cgg aca ctc 174
Met Arg Thr Leu
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ttc aac ctc ctc tgg ctt gcc ctg gcc tgc agc cct gtt cac act acc      222
Phe Asn Leu Leu Trp Leu Ala Leu Ala Cys Ser Pro Val His Thr Thr
 5                  10                  15                  20

ctg tca aag tca gat gcc aaa aaa gcc gcc tca aag acg ctg ctg gag      270
Leu Ser Lys Ser Asp Ala Lys Lys Ala Ala Ser Lys Thr Leu Leu Glu
                25                  30                  35

aag agt cag ttt tca gat aag ccg gtg caa gac cgg ggt ttg gtg gtg      318
Lys Ser Gln Phe Ser Asp Lys Pro Val Gln Asp Arg Gly Leu Val Val
            40                  45                  50

acg gac ctc aaa gct gag agt gtg gtt ctt gag cat cgc agc tac tgc      366
Thr Asp Leu Lys Ala Glu Ser Val Val Leu Glu His Arg Ser Tyr Cys
        55                  60                  65

tcg gca aag gcc cgg gac aga cac ttt gct ggg gat gta ctg ggc tat      414
Ser Ala Lys Ala Arg Asp Arg His Phe Ala Gly Asp Val Leu Gly Tyr
    70                  75                  80

gtc act cca tgg aac agc cat ggc tac gat gtc acc aag gtc ttt ggg      462
Val Thr Pro Trp Asn Ser His Gly Tyr Asp Val Thr Lys Val Phe Gly
 85                  90                  95                  100

agc aag ttc aca cag atc tca ccc gtc tgg ctg cag ctg aag aga cgt      510
Ser Lys Phe Thr Gln Ile Ser Pro Val Trp Leu Gln Leu Lys Arg Arg
                105                 110                 115

ggc cgt gag atg ttt gag gtc acg ggc ctc cac gac gtg gac caa ggg      558
Gly Arg Glu Met Phe Glu Val Thr Gly Leu His Asp Val Asp Gln Gly
            120                 125                 130

tgg atg cga gct gtc agg aag cat gcc aag ggc ctg cac ata gtg cct      606
Trp Met Arg Ala Val Arg Lys His Ala Lys Gly Leu His Ile Val Pro
        135                 140                 145

cgg ctc ctg ttt gag gac tgg act tac gat gat ttc cgg aac gtc tta      654
Arg Leu Leu Phe Glu Asp Trp Thr Tyr Asp Asp Phe Arg Asn Val Leu
    150                 155                 160

gac agt gag gat gag ata gag gag ctg agc aag acc gtg gtc cag gtg      702
Asp Ser Glu Asp Glu Ile Glu Glu Leu Ser Lys Thr Val Val Gln Val
165                 170                 175                 180

gca aag aac cag cat ttc gat ggc ttc gtg gtg gag gtc tgg aac cag      750
Ala Lys Asn Gln His Phe Asp Gly Phe Val Val Glu Val Trp Asn Gln
                185                 190                 195

ctg cta agc cag aag cgc gtg ggc ctc atc cac atg ctc acc cac ttg      798
Leu Leu Ser Gln Lys Arg Val Gly Leu Ile His Met Leu Thr His Leu
            200                 205                 210

gcc gag gct ctg cac cag gcc cgg ctg ctg gcc ctc ctg gtc atc ccg      846
Ala Glu Ala Leu His Gln Ala Arg Leu Leu Ala Leu Leu Val Ile Pro
        215                 220                 225

cct gcc atc acc ccc ggg acc gac cag ctg ggc atg ttc acg cac aag      894
Pro Ala Ile Thr Pro Gly Thr Asp Gln Leu Gly Met Phe Thr His Lys
    230                 235                 240

gag ttt gag cag ctg gcc ccc gtg ctg gat ggt ttc agc ctc atg acc      942
Glu Phe Glu Gln Leu Ala Pro Val Leu Asp Gly Phe Ser Leu Met Thr
245                 250                 255                 260

tac gac tac tct aca gcg cat cag cct ggc cct aat gca ccc ctg tcc      990
Tyr Asp Tyr Ser Thr Ala His Gln Pro Gly Pro Asn Ala Pro Leu Ser
                265                 270                 275

tgg gtt cga gcc tgc gtc cag gtc ctg gac ccg aag tcc aag tgg cga     1038
Trp Val Arg Ala Cys Val Gln Val Leu Asp Pro Lys Ser Lys Trp Arg
            280                 285                 290

agc aaa atc ctc ctg ggg ctc aac ttc tat ggt atg gac tac gcg acc     1086
Ser Lys Ile Leu Leu Gly Leu Asn Phe Tyr Gly Met Asp Tyr Ala Thr
        295                 300                 305
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tcc aag gat gcc cgt gag cct gtt gtc ggg gcc agt gtt cat gga gcc     1134
Ser Lys Asp Ala Arg Glu Pro Val Val Gly Ala Ser Val His Gly Ala
    310                 315                 320

tct tgagtctgca ttcgtactct tagcaaactt ggaaaatttg aggccaaatt          1187
Ser
325

cttcaaatat tttttctgtt tcttctcttc tgtcttctcg tttggagacc acaaacacta   1247

gatccattga atttgtccca cagctcacga atacaccttt tacctttaa aaaaaaaaaa    1307

aaaaaa                                                              1313


<210> SEQ ID NO 2
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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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Val His Thr Thr Leu Ser Lys Ser Asp Ala Lys Lys Ala Ala Ser Lys
            20                  25                  30

Thr Leu Leu Glu Lys Ser Gln Phe Ser Asp Lys Pro Val Gln Asp Arg
        35                  40                  45

Gly Leu Val Val Thr Asp Leu Lys Ala Glu Ser Val Val Leu Glu His
    50                  55                  60

Arg Ser Tyr Cys Ser Ala Lys Ala Arg Asp Arg His Phe Ala Gly Asp
65                  70                  75                  80

Val Leu Gly Tyr Val Thr Pro Trp Asn Ser His Gly Tyr Asp Val Thr
                85                  90                  95

Lys Val Phe Gly Ser Lys Phe Thr Gln Ile Ser Pro Val Trp Leu Gln
            100                 105                 110

Leu Lys Arg Arg Gly Arg Glu Met Phe Glu Val Thr Gly Leu His Asp
        115                 120                 125

Val Asp Gln Gly Trp Met Arg Ala Val Arg Lys His Ala Lys Gly Leu
    130                 135                 140

His Ile Val Pro Arg Leu Leu Phe Glu Asp Trp Thr Tyr Asp Asp Phe
145                 150                 155                 160

Arg Asn Val Leu Asp Ser Glu Asp Glu Ile Glu Glu Leu Ser Lys Thr
                165                 170                 175

Val Val Gln Val Ala Lys Asn Gln His Phe Asp Gly Phe Val Val Glu
            180                 185                 190

Val Trp Asn Gln Leu Leu Ser Gln Lys Arg Val Gly Leu Ile His Met
        195                 200                 205

Leu Thr His Leu Ala Glu Ala Leu His Gln Ala Arg Leu Leu Ala Leu
    210                 215                 220

Leu Val Ile Pro Pro Ala Ile Thr Pro Gly Thr Asp Gln Leu Gly Met
225                 230                 235                 240

Phe Thr His Lys Glu Phe Glu Gln Leu Ala Pro Val Leu Asp Gly Phe
                245                 250                 255

Ser Leu Met Thr Tyr Asp Tyr Ser Thr Ala His Gln Pro Gly Pro Asn
            260                 265                 270

Ala Pro Leu Ser Trp Val Arg Ala Cys Val Gln Val Leu Asp Pro Lys
        275                 280                 285
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Ser Lys Trp Arg Ser Lys Ile Leu Leu Gly Leu Asn Phe Tyr Gly Met
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Asp Tyr Ala Thr Ser Lys Asp Ala Arg Glu Pro Val Val Gly Ala Ser
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Val His Gly Ala Ser
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<210> SEQ ID NO 3
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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (262)...(1566)

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ctgcgagccc ccgccgcagg accacggccc gctccccgcc gccgcgaggg ccccgagcga    180

aggaaggaag ggaggcgcgc tgtgcgcccc gcggagcccg cgaaccccgc tcgctgccgg    240

ctgcccagcc tggctggcac c atg ctg ccc gcg cgc tgc gcc cgc ctg ctc      291
                       Met Leu Pro Ala Arg Cys Ala Arg Leu Leu
                        1               5                  10

acg ccc cac ttg ctg ctg gtg ttg gtg cag ctg tcc cct gct cgc ggc      339
Thr Pro His Leu Leu Leu Val Leu Val Gln Leu Ser Pro Ala Arg Gly
                15                  20                  25

cac cgc acc aca ggc ccc agg ttt cta ata agt gac cgt gac cca cag      387
His Arg Thr Thr Gly Pro Arg Phe Leu Ile Ser Asp Arg Asp Pro Gln
            30                  35                  40

tgc aac ctc cac tgc tcc agg act caa ccc aaa ccc atc tgt gcc tct      435
Cys Asn Leu His Cys Ser Arg Thr Gln Pro Lys Pro Ile Cys Ala Ser
        45                  50                  55

gat ggc agg tcc tac gag tcc atg tgt gag tac cag cga gcc aag tgc      483
Asp Gly Arg Ser Tyr Glu Ser Met Cys Glu Tyr Gln Arg Ala Lys Cys
    60                  65                  70

cga gac ccg acc ctg ggc gtg gtg cat cga ggt aga tgc aaa gat gct      531
Arg Asp Pro Thr Leu Gly Val Val His Arg Gly Arg Cys Lys Asp Ala
75                  80                  85                  90

ggc cag agc aag tgt cgc ctg gag cgg gct caa gcc ctg gag caa gcc      579
Gly Gln Ser Lys Cys Arg Leu Glu Arg Ala Gln Ala Leu Glu Gln Ala
                95                  100                 105

aag aag cct cag gaa gct gtg ttt gtc cca gag tgt ggc gag gat ggc      627
Lys Lys Pro Gln Glu Ala Val Phe Val Pro Glu Cys Gly Glu Asp Gly
            110                 115                 120

tcc ttt acc cag gtg cag tgc cat act tac act ggg tac tgc tgg tgt      675
Ser Phe Thr Gln Val Gln Cys His Thr Tyr Thr Gly Tyr Cys Trp Cys
        125                 130                 135

gtc acc ccg gat ggg aag ccc atc agt ggc tct tct gtg cag aat aaa      723
Val Thr Pro Asp Gly Lys Pro Ile Ser Gly Ser Ser Val Gln Asn Lys
    140                 145                 150

act cct gta tgt tca ggt tca gtc acc gac aag ccc ttg agc cag ggt      771
Thr Pro Val Cys Ser Gly Ser Val Thr Asp Lys Pro Leu Ser Gln Gly
155                 160                 165                 170

aac tca gga agg aaa gat gac ggg tct aag ccg aca ccc acg atg gag      819
Asn Ser Gly Arg Lys Asp Asp Gly Ser Lys Pro Thr Pro Thr Met Glu
                175                 180                 185
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acc cag ccg gtg ttc gat gga gat gaa atc aca gcc cca act cta tgg      867
Thr Gln Pro Val Phe Asp Gly Asp Glu Ile Thr Ala Pro Thr Leu Trp
            190                 195                 200

att aaa cac ttg gtg atc aag gac tcc aaa ctg aac aac acc aac ata      915
Ile Lys His Leu Val Ile Lys Asp Ser Lys Leu Asn Asn Thr Asn Ile
        205                 210                 215

aga aat tca gag aaa gtc tat tcg tgt gac cag gag agg cag agt gcc      963
Arg Asn Ser Glu Lys Val Tyr Ser Cys Asp Gln Glu Arg Gln Ser Ala
    220                 225                 230

ctg gaa gag gcc cag cag aat ccc cgt gag ggt att gtc atc cct gaa     1011
Leu Glu Glu Ala Gln Gln Asn Pro Arg Glu Gly Ile Val Ile Pro Glu
235                 240                 245                 250

tgt gcc cct ggg gga ctc tat aag cca gtg caa tgc cac cag tcc act     1059
Cys Ala Pro Gly Gly Leu Tyr Lys Pro Val Gln Cys His Gln Ser Thr
                255                 260                 265

ggc tac tgc tgg tgt gtg ctg gtg gac aca ggg cgc ccg ctg cct ggg     1107
Gly Tyr Cys Trp Cys Val Leu Val Asp Thr Gly Arg Pro Leu Pro Gly
            270                 275                 280

acc tcc aca cgc tac gtg atg ccc agt tgt gag agc gac gcc agg gcc     1155
Thr Ser Thr Arg Tyr Val Met Pro Ser Cys Glu Ser Asp Ala Arg Ala
        285                 290                 295

aag act aca gag gcg gat gac ccc ttc aag gac agg gag cta cca ggc     1203
Lys Thr Thr Glu Ala Asp Asp Pro Phe Lys Asp Arg Glu Leu Pro Gly
    300                 305                 310

tgt cca gaa ggg aag aaa atg gag ttt atc acc agc cta ctg gat gct     1251
Cys Pro Glu Gly Lys Lys Met Glu Phe Ile Thr Ser Leu Leu Asp Ala
315                 320                 325                 330

ctc acc act gac atg gtt cag gcc att aac tca gca gcg ccc act gga     1299
Leu Thr Thr Asp Met Val Gln Ala Ile Asn Ser Ala Ala Pro Thr Gly
                335                 340                 345

ggt ggg agg ttc tca gag cca gac ccc agc cac acc ctg gag gag cgg     1347
Gly Gly Arg Phe Ser Glu Pro Asp Pro Ser His Thr Leu Glu Glu Arg
            350                 355                 360

gta gtg cac tgg tat ttc agc cag ctg gac agc aat agc agc aac gac     1395
Val Val His Trp Tyr Phe Ser Gln Leu Asp Ser Asn Ser Ser Asn Asp
        365                 370                 375

att aac aag cgg gag atg aag ccc ttc aag cgc tac gtg aag aag aaa     1443
Ile Asn Lys Arg Glu Met Lys Pro Phe Lys Arg Tyr Val Lys Lys Lys
    380                 385                 390

gcc aag ccc aag gaa tgt gcc cgg cgt ttc acc gac tac tgt gac ctg     1491
Ala Lys Pro Lys Glu Cys Ala Arg Arg Phe Thr Asp Tyr Cys Asp Leu
395                 400                 405                 410

aac aaa gac aag gtc att tca ctg cct gag ctg aag ggc tgc ctg ggt     1539
Asn Lys Asp Lys Val Ile Ser Leu Pro Glu Leu Lys Gly Cys Leu Gly
                415                 420                 425

gtt agc aaa gaa gta gga cgc ctc gtc taaggagcag aaaacccaag           1586
Val Ser Lys Glu Val Gly Arg Leu Val
            430                 435

ggcaggtgga gagtccaggg aggcaggatg gatcaccaga cacctaacct tcagcgttgc   1646

ccatggccct gccacatccc gtgtaacata agtggtgccc accatgtttg cacttttaat   1706

aactcttact tgcgtgtttt gtttttggtt tcattttaaa acaccaatat ctaataccac   1766

agtgggaaaa ggaaagggaa gaaagacttt attctctctc ttattgtaag tttttggatc   1826

tgctactgac aacttttaga gggttttggg ggggtggggg agggtgttgt tggggctgag   1886

aagaaagaga tttatatgct gtatataaat atatatgtaa aaaaaaaaaa aaaaa        1941
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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 4

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Val Leu Val Gln Leu Ser Pro Ala Arg Gly His Arg Thr Thr Gly Pro
            20   25   30

Arg Phe Leu Ile Ser Asp Arg Asp Pro Gln Cys Asn Leu His Cys Ser
        35   40   45

Arg Thr Gln Pro Lys Pro Ile Cys Ala Ser Asp Gly Arg Ser Tyr Glu
    50   55   60

Ser Met Cys Glu Tyr Gln Arg Ala Lys Cys Arg Asp Pro Thr Leu Gly
65   70   75   80

Val Val His Arg Gly Arg Cys Lys Asp Ala Gly Gln Ser Lys Cys Arg
                85   90   95

Leu Glu Arg Ala Gln Ala Leu Glu Gln Ala Lys Lys Pro Gln Glu Ala
            100   105   110

Val Phe Val Pro Glu Cys Gly Glu Asp Gly Ser Phe Thr Gln Val Gln
        115   120   125

Cys His Thr Tyr Thr Gly Tyr Cys Trp Cys Val Thr Pro Asp Gly Lys
    130   135   140

Pro Ile Ser Gly Ser Ser Val Gln Asn Lys Thr Pro Val Cys Ser Gly
145   150   155   160

Ser Val Thr Asp Lys Pro Leu Ser Gln Gly Asn Ser Gly Arg Lys Asp
                165   170   175

Asp Gly Ser Lys Pro Thr Pro Thr Met Glu Thr Gln Pro Val Phe Asp
            180   185   190

Gly Asp Glu Ile Thr Ala Pro Thr Leu Trp Ile Lys His Leu Val Ile
        195   200   205

Lys Asp Ser Lys Leu Asn Asn Thr Asn Ile Arg Asn Ser Glu Lys Val
    210   215   220

Tyr Ser Cys Asp Gln Glu Arg Gln Ser Ala Leu Glu Glu Ala Gln Gln
225   230   235   240

Asn Pro Arg Glu Gly Ile Val Ile Pro Glu Cys Ala Pro Gly Gly Leu
                245   250   255

Tyr Lys Pro Val Gln Cys His Gln Ser Thr Gly Tyr Cys Trp Cys Val
            260   265   270

Leu Val Asp Thr Gly Arg Pro Leu Pro Gly Thr Ser Thr Arg Tyr Val
        275   280   285

Met Pro Ser Cys Glu Ser Asp Ala Arg Ala Lys Thr Thr Glu Ala Asp
    290   295   300

Asp Pro Phe Lys Asp Arg Glu Leu Pro Gly Cys Pro Glu Gly Lys Lys
305   310   315   320

Met Glu Phe Ile Thr Ser Leu Leu Asp Ala Leu Thr Thr Asp Met Val
                325   330   335

Gln Ala Ile Asn Ser Ala Ala Pro Thr Gly Gly Gly Arg Phe Ser Glu
            340   345   350

Pro Asp Pro Ser His Thr Leu Glu Glu Arg Val Val His Trp Tyr Phe

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        355                 360                 365

Ser Gln Leu Asp Ser Asn Ser Ser Asn Asp Ile Asn Lys Arg Glu Met
    370                 375                 380

Lys Pro Phe Lys Arg Tyr Val Lys Lys Lys Ala Lys Pro Lys Glu Cys
385                 390                 395                 400

Ala Arg Arg Phe Thr Asp Tyr Cys Asp Leu Asn Lys Asp Lys Val Ile
                405                 410                 415

Ser Leu Pro Glu Leu Lys Gly Cys Leu Gly Val Ser Lys Glu Val Gly
            420                 425                 430

Arg Leu Val
        435


<210> SEQ ID NO 5
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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (40)...(1056)

<400> SEQUENCE: 5

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                                          Met Ala Ala Ala Cys
                                           1               5

ggg ccg gga gcg gcc ggg tac tgc ttg ctc ctc ggc ttg cat ttg ttt      102
Gly Pro Gly Ala Ala Gly Tyr Cys Leu Leu Leu Gly Leu His Leu Phe
                10                  15                  20

ctg ctg acc gcg ggc cct gcc ctg ggc tgg aac gac cct gac aga atg      150
Leu Leu Thr Ala Gly Pro Ala Leu Gly Trp Asn Asp Pro Asp Arg Met
            25                  30                  35

ttg ctg cgg gat gta aaa gct ctt acc ctc cac tat gac cgc tat acc      198
Leu Leu Arg Asp Val Lys Ala Leu Thr Leu His Tyr Asp Arg Tyr Thr
        40                  45                  50

acc tcc cgc agg ctg gat ccc atc cca cag ttg aaa tgt gtt gga ggc      246
Thr Ser Arg Arg Leu Asp Pro Ile Pro Gln Leu Lys Cys Val Gly Gly
    55                  60                  65

aca gct ggt tgt gat tct tat acc cca aaa gtc ata cag tgt cag aac      294
Thr Ala Gly Cys Asp Ser Tyr Thr Pro Lys Val Ile Gln Cys Gln Asn
70                  75                  80                  85

aaa ggc tgg gat ggg tat gat gta cag tgg gaa tgt aag acg gac tta      342
Lys Gly Trp Asp Gly Tyr Asp Val Gln Trp Glu Cys Lys Thr Asp Leu
                90                  95                  100

gat att gca tac aaa ttt gga aaa act gtg gtg agc tgt gaa ggc tat      390
Asp Ile Ala Tyr Lys Phe Gly Lys Thr Val Val Ser Cys Glu Gly Tyr
            105                 110                 115

gag tcc tct gaa gac cag tat gta cta aga ggt tct tgt ggc ttg gag      438
Glu Ser Ser Glu Asp Gln Tyr Val Leu Arg Gly Ser Cys Gly Leu Glu
        120                 125                 130

tat aat tta gat tat aca gaa ctt ggc ctg cag aaa ctg aag gag tct      486
Tyr Asn Leu Asp Tyr Thr Glu Leu Gly Leu Gln Lys Leu Lys Glu Ser
    135                 140                 145

gga aag cag cac ggc ttt gcc tct ttc tct gat tat tat tat aag tgg      534
Gly Lys Gln His Gly Phe Ala Ser Phe Ser Asp Tyr Tyr Tyr Lys Trp
150                 155                 160                 165

tcc tcg gcg gat tcc tgt aac atg agt gga ttg att acc atc gtg gta      582
Ser Ser Ala Asp Ser Cys Asn Met Ser Gly Leu Ile Thr Ile Val Val
                170                 175                 180
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ctc ctt ggg atc gcc ttt gta gtc tat aag ctg ttc ctg agt gac ggg      630
Leu Leu Gly Ile Ala Phe Val Val Tyr Lys Leu Phe Leu Ser Asp Gly
            185                 190                 195

cag tat tct cct cca ccg tac tct gag tat cct cca ttt tcc cac cgt      678
Gln Tyr Ser Pro Pro Pro Tyr Ser Glu Tyr Pro Pro Phe Ser His Arg
        200                 205                 210

tac cag aga ttc acc aac tca gca gga cct cct ccc cca ggc ttt aag      726
Tyr Gln Arg Phe Thr Asn Ser Ala Gly Pro Pro Pro Pro Gly Phe Lys
    215                 220                 225

tct gag ttc aca gga cca cag aat act ggc cat ggt gca act tct ggt      774
Ser Glu Phe Thr Gly Pro Gln Asn Thr Gly His Gly Ala Thr Ser Gly
230                 235                 240                 245

ttt ggc agt gct ttt aca gga caa caa gga tat gaa aat tca gga cca      822
Phe Gly Ser Ala Phe Thr Gly Gln Gln Gly Tyr Glu Asn Ser Gly Pro
                250                 255                 260

ggg ttc tgg aca ggc ttg gga act ggt gga ata cta gga tat ttg ttt      870
Gly Phe Trp Thr Gly Leu Gly Thr Gly Gly Ile Leu Gly Tyr Leu Phe
            265                 270                 275

ggc agc aat aga gcg gca aca ccc ttc tca gac tcg tgg tac tac ccg      918
Gly Ser Asn Arg Ala Ala Thr Pro Phe Ser Asp Ser Trp Tyr Tyr Pro
        280                 285                 290

tcc tat cct ccc tcc tac cct ggc acg tgg aat agg gct tac tca ccc      966
Ser Tyr Pro Pro Ser Tyr Pro Gly Thr Trp Asn Arg Ala Tyr Ser Pro
    295                 300                 305

ctt cat gga ggc tcg ggc agc tat tcg gta tgt tca aac tca gac acg     1014
Leu His Gly Gly Ser Gly Ser Tyr Ser Val Cys Ser Asn Ser Asp Thr
310                 315                 320                 325

aaa acc aga act gca tca gga tat ggt ggt acc agg aga cga             1056
Lys Thr Arg Thr Ala Ser Gly Tyr Gly Gly Thr Arg Arg Arg
                330                 335

taaagtagaa agttggagtc aaacactgga tgcagaaatt ttggattttt catcactttc   1116

tctttagaaa aaaagtacta cctgttaaca attgggaaaa ggggatattc aaaagttctg   1176

tggtgttatg tccagtgtag ctttttgtat tctattattt gaggctaaaa gttgatgtgt   1236

gacaaaatac ttatgtgttg tatgtcagtg taacatgcag atgtatattg cagtttttga   1296

aagtgatcat tactgtggaa tgctaaaaat acattaattt ctaaaacctg tgatgcccta   1356

agaagcatta agaatgaagg tgttgtacta atagaaacta agtacagaaa atttcagttt   1416

taggtggttg tagctgatga gttattacct catagagact ataatattct atttggtatt   1476

atattatttg atgtttgctg ttcttcaaac atttaaatca agctttggac taattatgct   1536

aatttgtgag ttctgatcac ttttgagctc tgaagctttg aatcattcag tggtggagat   1596

ggccttctgg taactgaata ttaccttctg taggaaaagg tggaaaataa gcatctagaa   1656

ggttgttgtg aatgactctg tgctggcaaa aatgcttgaa acctctatat ttctttcgtt   1716

cataagaggt aaaggtcaaa tttttcaaca aaagtctttt aataacaaaa gcatgcagtt   1776

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<210> SEQ ID NO 6
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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6
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Met Ala Ala Ala Cys Gly Pro Gly Ala Ala Gly Tyr Cys Leu Leu Leu
 1               5                  10                  15

Gly Leu His Leu Phe Leu Leu Thr Ala Gly Pro Ala Leu Gly Trp Asn
            20                  25                  30

Asp Pro Asp Arg Met Leu Leu Arg Asp Val Lys Ala Leu Thr Leu His
        35                  40                  45

Tyr Asp Arg Tyr Thr Thr Ser Arg Arg Leu Asp Pro Ile Pro Gln Leu
    50                  55                  60

Lys Cys Val Gly Gly Thr Ala Gly Cys Asp Ser Tyr Thr Pro Lys Val
65                  70                  75                  80

Ile Gln Cys Gln Asn Lys Gly Trp Asp Gly Tyr Asp Val Gln Trp Glu
                85                  90                  95

Cys Lys Thr Asp Leu Asp Ile Ala Tyr Lys Phe Gly Lys Thr Val Val
            100                 105                 110

Ser Cys Glu Gly Tyr Glu Ser Ser Glu Asp Gln Tyr Val Leu Arg Gly
        115                 120                 125

Ser Cys Gly Leu Glu Tyr Asn Leu Asp Tyr Thr Glu Leu Gly Leu Gln
    130                 135                 140

Lys Leu Lys Glu Ser Gly Lys Gln His Gly Phe Ala Ser Phe Ser Asp
145                 150                 155                 160

Tyr Tyr Tyr Lys Trp Ser Ser Ala Asp Ser Cys Asn Met Ser Gly Leu
                165                 170                 175

Ile Thr Ile Val Val Leu Leu Gly Ile Ala Phe Val Val Tyr Lys Leu
            180                 185                 190

Phe Leu Ser Asp Gly Gln Tyr Ser Pro Pro Pro Tyr Ser Glu Tyr Pro
        195                 200                 205

Pro Phe Ser His Arg Tyr Gln Arg Phe Thr Asn Ser Ala Gly Pro Pro
    210                 215                 220

Pro Pro Gly Phe Lys Ser Glu Phe Thr Gly Pro Gln Asn Thr Gly His
225                 230                 235                 240

Gly Ala Thr Ser Gly Phe Gly Ser Ala Phe Thr Gly Gln Gln Gly Tyr
                245                 250                 255

Glu Asn Ser Gly Pro Gly Phe Trp Thr Gly Leu Gly Thr Gly Gly Ile
            260                 265                 270

Leu Gly Tyr Leu Phe Gly Ser Asn Arg Ala Ala Thr Pro Phe Ser Asp
        275                 280                 285

Ser Trp Tyr Tyr Pro Ser Tyr Pro Pro Ser Tyr Pro Gly Thr Trp Asn
    290                 295                 300

Arg Ala Tyr Ser Pro Leu His Gly Gly Ser Gly Ser Tyr Ser Val Cys
305                 310                 315                 320

Ser Asn Ser Asp Thr Lys Thr Arg Thr Ala Ser Gly Tyr Gly Gly Thr
                325                 330                 335

Arg Arg Arg
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<210> SEQ ID NO 7
<211> LENGTH: 1831
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (90)...(1286)

<400> SEQUENCE: 7

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gaattcggca cgagctggcg gccaccagaa gtttgagcct ctttggtagc aggaggctgg     60

aagaaaggac agaagtagct ctggctgtg atg ggg atc tta ctg ggc ctg cta      113
                              Met Gly Ile Leu Leu Gly Leu Leu
                               1               5

ctc ctg ggg cac cta aca gtg gac act tat ggc cgt ccc atc ctg gaa      161
Leu Leu Gly His Leu Thr Val Asp Thr Tyr Gly Arg Pro Ile Leu Glu
     10                  15                  20

gtg cca gag agt gta aca gga cct tgg aaa ggg gat gtg aat ctt ccc      209
Val Pro Glu Ser Val Thr Gly Pro Trp Lys Gly Asp Val Asn Leu Pro
 25                  30                  35                  40

tgc acc tat gac ccc ctg caa ggc tac acc caa gtc ttg gtg aag tgg      257
Cys Thr Tyr Asp Pro Leu Gln Gly Tyr Thr Gln Val Leu Val Lys Trp
                 45                  50                  55

ctg gta caa cgt ggc tca gac cct gtc acc atc ttt cta cgt gac tct      305
Leu Val Gln Arg Gly Ser Asp Pro Val Thr Ile Phe Leu Arg Asp Ser
             60                  65                  70

tct gga gac cat atc cag cag gca aag tac cag ggc cgc ctg cat gtg      353
Ser Gly Asp His Ile Gln Gln Ala Lys Tyr Gln Gly Arg Leu His Val
         75                  80                  85

agc cac aag gtt cca gga gat gta tcc ctc caa ttg agc acc ctg gag      401
Ser His Lys Val Pro Gly Asp Val Ser Leu Gln Leu Ser Thr Leu Glu
     90                  95                 100

atg gat gac cgg agc cac tac acg tgt gaa gtc acc tgg cag act cct      449
Met Asp Asp Arg Ser His Tyr Thr Cys Glu Val Thr Trp Gln Thr Pro
105                 110                 115                 120

gat ggc aac caa gtc gtg aga gat aag att act gag ctc cgt gtc cag      497
Asp Gly Asn Gln Val Val Arg Asp Lys Ile Thr Glu Leu Arg Val Gln
                125                 130                 135

aaa ctc tct gtc tcc aag ccc aca gtg aca act ggc agc ggt tat ggc      545
Lys Leu Ser Val Ser Lys Pro Thr Val Thr Thr Gly Ser Gly Tyr Gly
            140                 145                 150

ttc acg gtg ccc cag gga atg agg att agc ctt caa tgc cag gct cgg      593
Phe Thr Val Pro Gln Gly Met Arg Ile Ser Leu Gln Cys Gln Ala Arg
        155                 160                 165

ggt tct cct ccc atc agt tat att tgg tat aag caa cag act aat aac      641
Gly Ser Pro Pro Ile Ser Tyr Ile Trp Tyr Lys Gln Gln Thr Asn Asn
    170                 175                 180

cag gaa ccc atc aaa gta gca acc cta agt acc tta ctc ttc aag cct      689
Gln Glu Pro Ile Lys Val Ala Thr Leu Ser Thr Leu Leu Phe Lys Pro
185                 190                 195                 200

gcg gtg ata gcc gac tca ggc tcc tat ttc tgc act gcc aag ggc cag      737
Ala Val Ile Ala Asp Ser Gly Ser Tyr Phe Cys Thr Ala Lys Gly Gln
                205                 210                 215

gtt ggc tct gag cag cac agc gac att gtg aag ttt gtg gtc aaa gac      785
Val Gly Ser Glu Gln His Ser Asp Ile Val Lys Phe Val Val Lys Asp
            220                 225                 230

tcc tca aag cta ctc aag acc aag act gag gca cct aca acc atg aca      833
Ser Ser Lys Leu Leu Lys Thr Lys Thr Glu Ala Pro Thr Thr Met Thr
        235                 240                 245

tac ccc ttg aaa gca aca tct aca gtg aag cag tcc tgg gac tgg acc      881
Tyr Pro Leu Lys Ala Thr Ser Thr Val Lys Gln Ser Trp Asp Trp Thr
    250                 255                 260

act gac atg gat ggc tac ctt gga gag acc agt gct ggg cca gga aag      929
Thr Asp Met Asp Gly Tyr Leu Gly Glu Thr Ser Ala Gly Pro Gly Lys
265                 270                 275                 280

agc ctg cct gtc ttt gcc atc atc ctc atc atc tcc ttg tgc tgt atg      977
Ser Leu Pro Val Phe Ala Ile Ile Leu Ile Ile Ser Leu Cys Cys Met
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               285                 290                 295

gtg gtt ttt acc atg gcc tat atc atg ctc tgt cgg aag aca tcc caa     1025
Val Val Phe Thr Met Ala Tyr Ile Met Leu Cys Arg Lys Thr Ser Gln
            300                 305                 310

caa gag cat gtc tac gaa gca gcc agg gca cat gcc aga gag gcc aac     1073
Gln Glu His Val Tyr Glu Ala Ala Arg Ala His Ala Arg Glu Ala Asn
        315                 320                 325

gac tct gga gaa acc atg agg gtg gcc atc ttc gca agt ggc tgc tcc     1121
Asp Ser Gly Glu Thr Met Arg Val Ala Ile Phe Ala Ser Gly Cys Ser
    330                 335                 340

agt gat gag cca act tcc cag aat ctg ggc aac aac tac tct gat gag     1169
Ser Asp Glu Pro Thr Ser Gln Asn Leu Gly Asn Asn Tyr Ser Asp Glu
345                 350                 355                 360

ccc tgc ata gga cag gag tac cag atc atc gcc cag atc aat ggc aac     1217
Pro Cys Ile Gly Gln Glu Tyr Gln Ile Ile Ala Gln Ile Asn Gly Asn
                365                 370                 375

tac gcc cgc ctg ctg gac aca gtt cct ctg gat tat gag ttt ctg gcc     1265
Tyr Ala Arg Leu Leu Asp Thr Val Pro Leu Asp Tyr Glu Phe Leu Ala
            380                 385                 390

act gag ggc aaa agt gtc tgt taaaaatgcc ccattaggcc aggatctgct       1316
Thr Glu Gly Lys Ser Val Cys
        395

gacataattg cctagtcagt ccttgccttc tgcatggcct tcttccctgc tacctctctt   1376

cctggatagc ccaaagtgtc cgcctaccaa cactggagcc gctgggagtc actggctttg   1436

ccctggaatt tgccagatgc atctcaagta agccagctgc tggatttggc tctgggccct   1496

tctagtatct ctgccggggg cttctggtac tcctctctaa ataccagagg gaagatgccc   1556

atagcactag gacttggtca tcatgcctac agacactatt caactttggc atcttgccac   1616

cagaagaccc gagggaggct cagctctgcc agctcagagg accagctata ttcaggatca   1676

tttctctttc ttcagggcca gacagctttt aattgaaatt gttatttcac aggccagggt   1736

tcagttctgc tcctccacta taagtctaat gttctgactc tctcctggtg ctcaataaat   1796

atctaatcat aacagcaaaa aaaaaaaaaa aaaaa                              1831


<210> SEQ ID NO 8
<211> LENGTH: 399
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

Met Gly Ile Leu Leu Gly Leu Leu Leu Leu Gly His Leu Thr Val Asp
 1               5                  10                  15

Thr Tyr Gly Arg Pro Ile Leu Glu Val Pro Glu Ser Val Thr Gly Pro
            20                  25                  30

Trp Lys Gly Asp Val Asn Leu Pro Cys Thr Tyr Asp Pro Leu Gln Gly
        35                  40                  45

Tyr Thr Gln Val Leu Val Lys Trp Leu Val Gln Arg Gly Ser Asp Pro
    50                  55                  60

Val Thr Ile Phe Leu Arg Asp Ser Ser Gly Asp His Ile Gln Gln Ala
65                  70                  75                  80

Lys Tyr Gln Gly Arg Leu His Val Ser His Lys Val Pro Gly Asp Val
                85                  90                  95

Ser Leu Gln Leu Ser Thr Leu Glu Met Asp Asp Arg Ser His Tyr Thr
            100                 105                 110
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Cys Glu Val Thr Trp Gln Thr Pro Asp Gly Asn Gln Val Val Arg Asp
        115                 120                 125

Lys Ile Thr Glu Leu Arg Val Gln Lys Leu Ser Val Ser Lys Pro Thr
    130                 135                 140

Val Thr Thr Gly Ser Gly Tyr Gly Phe Thr Val Pro Gln Gly Met Arg
145                 150                 155                 160

Ile Ser Leu Gln Cys Gln Ala Arg Gly Ser Pro Pro Ile Ser Tyr Ile
                165                 170                 175

Trp Tyr Lys Gln Gln Thr Asn Asn Gln Glu Pro Ile Lys Val Ala Thr
            180                 185                 190

Leu Ser Thr Leu Leu Phe Lys Pro Ala Val Ile Ala Asp Ser Gly Ser
        195                 200                 205

Tyr Phe Cys Thr Ala Lys Gly Gln Val Gly Ser Glu Gln His Ser Asp
    210                 215                 220

Ile Val Lys Phe Val Val Lys Asp Ser Ser Lys Leu Leu Lys Thr Lys
225                 230                 235                 240

Thr Glu Ala Pro Thr Thr Met Thr Tyr Pro Leu Lys Ala Thr Ser Thr
                245                 250                 255

Val Lys Gln Ser Trp Asp Trp Thr Thr Asp Met Asp Gly Tyr Leu Gly
            260                 265                 270

Glu Thr Ser Ala Gly Pro Gly Lys Ser Leu Pro Val Phe Ala Ile Ile
        275                 280                 285

Leu Ile Ile Ser Leu Cys Cys Met Val Val Phe Thr Met Ala Tyr Ile
    290                 295                 300

Met Leu Cys Arg Lys Thr Ser Gln Gln Glu His Val Tyr Glu Ala Ala
305                 310                 315                 320

Arg Ala His Ala Arg Glu Ala Asn Asp Ser Gly Glu Thr Met Arg Val
                325                 330                 335

Ala Ile Phe Ala Ser Gly Cys Ser Ser Asp Glu Pro Thr Ser Gln Asn
            340                 345                 350

Leu Gly Asn Asn Tyr Ser Asp Glu Pro Cys Ile Gly Gln Glu Tyr Gln
        355                 360                 365

Ile Ile Ala Gln Ile Asn Gly Asn Tyr Ala Arg Leu Leu Asp Thr Val
    370                 375                 380

Pro Leu Asp Tyr Glu Phe Leu Ala Thr Glu Gly Lys Ser Val Cys
385                 390                 395


<210> SEQ ID NO 9
<211> LENGTH: 4222
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (238)...(2364)

<400> SEQUENCE: 9

ggatccaaag aattcggcac gagagactcc ctaacctgtg tctggacaag tctgatgtcc     60

tgtgtggccc aagaagaact gaccccgtgt ctggagctcc caccgttatt gcatccctgc    120

tgtggctcac ctgctgctgt ctccaggagc ccctgagaag atttgcctcc tctcccctgc    180

taagctccag gtcctgagat tgaattaggg gctggagctc actgcactcc agcagtc atg   240
                                                                 Met
                                                                  1
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gga ccc agg ata ggg cca gcg ggt gag gta ccc cag gta cca gac aag      288
Gly Pro Arg Ile Gly Pro Ala Gly Glu Val Pro Gln Val Pro Asp Lys
            5                  10                  15

gaa acc aaa gcc aca atg ggc aca gaa aac aca cct gga ggc aaa gcc      336
Glu Thr Lys Ala Thr Met Gly Thr Glu Asn Thr Pro Gly Gly Lys Ala
         20                  25                  30

agc cca gac cct cag gac gtg cgg cca agt gtg ttc cat aac atc aag      384
Ser Pro Asp Pro Gln Asp Val Arg Pro Ser Val Phe His Asn Ile Lys
     35                  40                  45

ctg ttc gtt ctg tgc cac agc ctg ctg cag ctg gcg cag ctc atg atc      432
Leu Phe Val Leu Cys His Ser Leu Leu Gln Leu Ala Gln Leu Met Ile
 50                  55                  60                  65

tcc ggc tac cta aag agc tcc atc tcc aca gtg gag aag cgc ttc ggc      480
Ser Gly Tyr Leu Lys Ser Ser Ile Ser Thr Val Glu Lys Arg Phe Gly
                 70                  75                  80

ctc tcc agc cag acg tcg ggg ctg ctg gcc tcc ttc aac gag gtg ggg      528
Leu Ser Ser Gln Thr Ser Gly Leu Leu Ala Ser Phe Asn Glu Val Gly
            85                  90                  95

aac aca gcc ttg att gtg ttt gtg agc tat ttt ggc agc cgg gtg cac      576
Asn Thr Ala Leu Ile Val Phe Val Ser Tyr Phe Gly Ser Arg Val His
        100                 105                 110

cga ccc cga atg att ggc tat ggg gct atc ctt gtg gcc ctg gcg ggc      624
Arg Pro Arg Met Ile Gly Tyr Gly Ala Ile Leu Val Ala Leu Ala Gly
    115                 120                 125

ctg ctc atg act ctc ccg cac ttc atc tcg gag cca tac cgc tac gac      672
Leu Leu Met Thr Leu Pro His Phe Ile Ser Glu Pro Tyr Arg Tyr Asp
130                 135                 140                 145

aac acc agc cct gag gat atg cca cag gac ttc aag gct tcc ctg tgc      720
Asn Thr Ser Pro Glu Asp Met Pro Gln Asp Phe Lys Ala Ser Leu Cys
                150                 155                 160

ctg ccc aca acc tcg gcc cca gcc tcg gcc ccc tcc aat ggc aac tgc      768
Leu Pro Thr Thr Ser Ala Pro Ala Ser Ala Pro Ser Asn Gly Asn Cys
            165                 170                 175

tca agc tac aca gaa acc cag cat ctg agt gtg gtg ggg atc atg ttc      816
Ser Ser Tyr Thr Glu Thr Gln His Leu Ser Val Val Gly Ile Met Phe
        180                 185                 190

gtg gca cag acc ctg ctg ggc gtg ggc ggg gtg ccc att cag ccc ttt      864
Val Ala Gln Thr Leu Leu Gly Val Gly Gly Val Pro Ile Gln Pro Phe
    195                 200                 205

ggc atc tcc tac atc gat gac ttt gcc cac aac agc aac tcg ccc ctc      912
Gly Ile Ser Tyr Ile Asp Asp Phe Ala His Asn Ser Asn Ser Pro Leu
210                 215                 220                 225

tac ctc ggg atc ctg ttt gca gtg acc atg atg ggg cca ggc ctg gcc      960
Tyr Leu Gly Ile Leu Phe Ala Val Thr Met Met Gly Pro Gly Leu Ala
                230                 235                 240

ttt ggg ctg ggc agc ctc atg ctg cgc ctt tat gtg gac att aac cag     1008
Phe Gly Leu Gly Ser Leu Met Leu Arg Leu Tyr Val Asp Ile Asn Gln
            245                 250                 255

atg cca gaa ggt ggt atc agc ctg acc ata aag gac ccc cga tgg gtg     1056
Met Pro Glu Gly Gly Ile Ser Leu Thr Ile Lys Asp Pro Arg Trp Val
        260                 265                 270

ggt gcc tgg tgg ctg ggt ttc ctc atc gct gcc ggt gca gtg gcc ctg     1104
Gly Ala Trp Trp Leu Gly Phe Leu Ile Ala Ala Gly Ala Val Ala Leu
    275                 280                 285

gct gcc atc ccc tac ttc ttc ttc ccc aag gaa atg ccc aag gaa aaa     1152
Ala Ala Ile Pro Tyr Phe Phe Phe Pro Lys Glu Met Pro Lys Glu Lys
290                 295                 300                 305
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cgt gag ctt cag ttt cgg cga aag gtc tta gca gtc aca gac tca cct     1200
Arg Glu Leu Gln Phe Arg Arg Lys Val Leu Ala Val Thr Asp Ser Pro
                310                 315                 320

gcc agg aag ggc aag gac tct ccc tct aag cag agc cct ggg gag tcc     1248
Ala Arg Lys Gly Lys Asp Ser Pro Ser Lys Gln Ser Pro Gly Glu Ser
            325                 330                 335

acg aag aag cag gat ggc cta gtc cag att gca cca aac ctg act gtg     1296
Thr Lys Lys Gln Asp Gly Leu Val Gln Ile Ala Pro Asn Leu Thr Val
        340                 345                 350

atc cag ttc att aaa gtc ttc ccc agg gtg ctg ctg cag acc cta cgc     1344
Ile Gln Phe Ile Lys Val Phe Pro Arg Val Leu Leu Gln Thr Leu Arg
    355                 360                 365

cac ccc atc ttc ctg ctg gtg gtc ctg tcc cag gta tgc ttg tca tcc     1392
His Pro Ile Phe Leu Leu Val Val Leu Ser Gln Val Cys Leu Ser Ser
370                 375                 380                 385

atg gct gcg ggc atg gcc acc ttc ctg ccc aag ttc ctg gag cgc cag     1440
Met Ala Ala Gly Met Ala Thr Phe Leu Pro Lys Phe Leu Glu Arg Gln
                390                 395                 400

ttt tcc atc aca gcc tcc tac gcc aac ctg ctc atc ggc tgc ctc tcc     1488
Phe Ser Ile Thr Ala Ser Tyr Ala Asn Leu Leu Ile Gly Cys Leu Ser
            405                 410                 415

ttc cct tcg gtc atc gtg ggc atc gtg gtg ggt ggc gtc ctg gtc aag     1536
Phe Pro Ser Val Ile Val Gly Ile Val Val Gly Gly Val Leu Val Lys
        420                 425                 430

cgg ctc cac ctg ggc cct gtg gga tgc ggt gcc ctt tgc ctg ctg ggg     1584
Arg Leu His Leu Gly Pro Val Gly Cys Gly Ala Leu Cys Leu Leu Gly
    435                 440                 445

atg ctg ctg tgc ctc ttc ttc agc ctg ccg ctc ttc ttt atc ggc tgc     1632
Met Leu Leu Cys Leu Phe Phe Ser Leu Pro Leu Phe Phe Ile Gly Cys
450                 455                 460                 465

tcc agc cac cag att gcg ggc atc aca cac cag acc agt gcc cac cct     1680
Ser Ser His Gln Ile Ala Gly Ile Thr His Gln Thr Ser Ala His Pro
                470                 475                 480

ggg ctg gag ctg tct cca agc tgc atg gag gcc tgc tcc tgc cca ttg     1728
Gly Leu Glu Leu Ser Pro Ser Cys Met Glu Ala Cys Ser Cys Pro Leu
            485                 490                 495

gac ggc ttt aac cct gtc tgc gac ccc agc act cgt gtg gaa tac atc     1776
Asp Gly Phe Asn Pro Val Cys Asp Pro Ser Thr Arg Val Glu Tyr Ile
        500                 505                 510

aca ccc tgc cac gca ggc tgc tca agc tgg gtg gtc cag gat gct ctg     1824
Thr Pro Cys His Ala Gly Cys Ser Ser Trp Val Val Gln Asp Ala Leu
    515                 520                 525

gac aac agc cag gtt ttc tac acc aac tgc agc tgc gtg gtg gag ggc     1872
Asp Asn Ser Gln Val Phe Tyr Thr Asn Cys Ser Cys Val Val Glu Gly
530                 535                 540                 545

aac ccc gtg ctg gca gga tcc tgc gac tca acg tgc agc cat ctg gtg     1920
Asn Pro Val Leu Ala Gly Ser Cys Asp Ser Thr Cys Ser His Leu Val
                550                 555                 560

gtg ccc ttc ctg ctc ctg gtc agc ctg ggc tcg gcc ctg gcc tgt ctc     1968
Val Pro Phe Leu Leu Leu Val Ser Leu Gly Ser Ala Leu Ala Cys Leu
            565                 570                 575

acc cac aca ccc tcc ttc atg ctc atc cta aga gga gtg aag aaa gaa     2016
Thr His Thr Pro Ser Phe Met Leu Ile Leu Arg Gly Val Lys Lys Glu
        580                 585                 590

gac aag act ttg gct gtg ggc atc cag ttc atg ttc ctg agg att ttg     2064
Asp Lys Thr Leu Ala Val Gly Ile Gln Phe Met Phe Leu Arg Ile Leu
    595                 600                 605
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gcc tgg atg ccc agc ccc gtg atc cac ggc agc gcc atc gac acc acc     2112
Ala Trp Met Pro Ser Pro Val Ile His Gly Ser Ala Ile Asp Thr Thr
610                 615                 620                 625

tgt gtg cac tgg gcc ctg agc tgt ggg cgt cga gct gtc tgt cgc tac     2160
Cys Val His Trp Ala Leu Ser Cys Gly Arg Arg Ala Val Cys Arg Tyr
                630                 635                 640

tac aat aat gac ctg ctc cga aac cgg ttc atc ggc ctc cag ttc ttc     2208
Tyr Asn Asn Asp Leu Leu Arg Asn Arg Phe Ile Gly Leu Gln Phe Phe
            645                 650                 655

ttc aaa aca ggt tct gtg atc tgc ttc gcc tta gtt ttg gct gtc ctg     2256
Phe Lys Thr Gly Ser Val Ile Cys Phe Ala Leu Val Leu Ala Val Leu
        660                 665                 670

agg cag cag gac aaa gag gca agg acc aaa gag agc aga tcc agc cct     2304
Arg Gln Gln Asp Lys Glu Ala Arg Thr Lys Glu Ser Arg Ser Ser Pro
    675                 680                 685

gcc gta gag cag caa ttg cta gtg tcg ggg cca ggg aag aag cca gag     2352
Ala Val Glu Gln Gln Leu Leu Val Ser Gly Pro Gly Lys Lys Pro Glu
690                 695                 700                 705

gat tcc cga gtg tgagctgtct tggggcccca cctggccaag agtagcagcc         2404
Asp Ser Arg Val

acagcagtac ctcctctgag tcctttgccc aagattgggt gtcaagagcc ctgtgttcca   2464

ttctggctcc tccactaaat tgctgtgtga cttcaggcaa gacattgatc ctctctcagc   2524

ctttgcttgc tagtctgaac caaagagttg tttgggcatt tgctgtgttg gccatttctg   2584

gagcaagagg gtcttcttcc tccttccccc agccagccag ctgtcctggg gccaggcttt   2644

cctgggtgga aagaagtata cctttccctg gggccctagg atagcaaagt gagccatagt   2704

gggccaggct gccctccatg ctgggcccca gcccaggtct gcactcgcct ggatcacctt   2764

ctttgagcct tagccatctc ctgtcaggta ggaatgaact tgccagcctt caggctcgtt   2824

cagctatgac catctgtgcg gtcagggtac actcagctct cctccccaac tccagcagcc   2884

tttaagaagt gtccctttgg cgccccctgg aggcagagca ctgagctgga ccctgggtag   2944

actcccacag ggaggacgga gctggcctca ggagtgggac acccagactt ggcagggcct   3004

tcaagaggcc tgtgtggggg ccccaggaat ccttagctga agcggggaga ctcactctcc   3064

atctcaggaa attctagccc ttgccctcag ggagccacgg ttgagggtga ggcccaacac   3124

ctgccttagg gccctgggtg ggcaagtctg ggccctgggg tagggaggga gactcaggcc   3184

cacacttggg tattttctaa tttcagacaa acacacactc agcgcgcact cactgattcc   3244

tacacattgc caagatttca cacatgtgac caggggccac caaagtccct gtgacctttg   3304

tgactaggat cctaatttct ctattttctc ctgggtgcct gggtctgtgt cacctggggc   3364

agtgtggata atgtttagtt ctgtgacact gttttttggg ggtggcacct ggttctccga   3424

tgcctgggct ggtgtcaggc ccaggactgt agtgctggga gcagtaaagc tcagctctgt   3484

gtaatgagtg atgctatggc ttgctcgtgt cttatgatcc aatccttttc tacatcagcc   3544

cttgttttgt tttatggcta gtcttatctg gcctggttat ttccttgcgg ggaggagagg   3604

gtttgctaat ctgctcccag cccaacctat taccacccca cctcgctggg acctactgct   3664

cgggaggcag cagacaggga gccaccagca gtggcttcct ggccctgtgc tgggggtggg   3724

gggaagctgg gggcacatgt ggcccttgcc ttctgagcag ctcccagtgc cagggctttg   3784

agactttccc acatgataaa agaaaaggga ggtacagaag ttccaattcc ctttttattt   3844

tgctggttgg tatctgtaaa tgtttaataa atatctgagc atgtatctat caacgccaag   3904
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aatttcaaag tctccttcaa caatatgagg cttttaggat gtttatattc cttcatccct   3964

cttgtttccc aggttttgca gggaaaaaaa gtctggaatt atagatacag cttattatta   4024

aatttgttct tgcataatgt ctcttctatt acaaaaattc tttcttcata aactgcatta   4084

gaggtttgca acaaccacat catttccatt aacttagatt taggttttac tggattcatt   4144

gctcaccatt attgcttgta tattacatct tttccaatct ttaaaaaaaa aaaaaaaaaa   4204

ctcgagagta cttctaga                                                4222


<210> SEQ ID NO 10
<211> LENGTH: 709
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

Met Gly Pro Arg Ile Gly Pro Ala Gly Glu Val Pro Gln Val Pro Asp
 1               5                  10                  15

Lys Glu Thr Lys Ala Thr Met Gly Thr Glu Asn Thr Pro Gly Gly Lys
            20                  25                  30

Ala Ser Pro Asp Pro Gln Asp Val Arg Pro Ser Val Phe His Asn Ile
        35                  40                  45

Lys Leu Phe Val Leu Cys His Ser Leu Leu Gln Leu Ala Gln Leu Met
    50                  55                  60

Ile Ser Gly Tyr Leu Lys Ser Ser Ile Ser Thr Val Glu Lys Arg Phe
65                  70                  75                  80

Gly Leu Ser Ser Gln Thr Ser Gly Leu Leu Ala Ser Phe Asn Glu Val
                85                  90                  95

Gly Asn Thr Ala Leu Ile Val Phe Val Ser Tyr Phe Gly Ser Arg Val
            100                 105                 110

His Arg Pro Arg Met Ile Gly Tyr Gly Ala Ile Leu Val Ala Leu Ala
        115                 120                 125

Gly Leu Leu Met Thr Leu Pro His Phe Ile Ser Glu Pro Tyr Arg Tyr
    130                 135                 140

Asp Asn Thr Ser Pro Glu Asp Met Pro Gln Asp Phe Lys Ala Ser Leu
145                 150                 155                 160

Cys Leu Pro Thr Thr Ser Ala Pro Ala Ser Ala Pro Ser Asn Gly Asn
                165                 170                 175

Cys Ser Ser Tyr Thr Glu Thr Gln His Leu Ser Val Val Gly Ile Met
            180                 185                 190

Phe Val Ala Gln Thr Leu Leu Gly Val Gly Gly Val Pro Ile Gln Pro
        195                 200                 205

Phe Gly Ile Ser Tyr Ile Asp Asp Phe Ala His Asn Ser Asn Ser Pro
    210                 215                 220

Leu Tyr Leu Gly Ile Leu Phe Ala Val Thr Met Met Gly Pro Gly Leu
225                 230                 235                 240

Ala Phe Gly Leu Gly Ser Leu Met Leu Arg Leu Tyr Val Asp Ile Asn
                245                 250                 255

Gln Met Pro Glu Gly Gly Ile Ser Leu Thr Ile Lys Asp Pro Arg Trp
            260                 265                 270

Val Gly Ala Trp Trp Leu Gly Phe Leu Ile Ala Ala Gly Ala Val Ala
        275                 280                 285

Leu Ala Ala Ile Pro Tyr Phe Phe Phe Pro Lys Glu Met Pro Lys Glu
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    290                 295                 300

Lys Arg Glu Leu Gln Phe Arg Arg Lys Val Leu Ala Val Thr Asp Ser
305                 310                 315                 320

Pro Ala Arg Lys Gly Lys Asp Ser Pro Ser Lys Gln Ser Pro Gly Glu
                325                 330                 335

Ser Thr Lys Lys Gln Asp Gly Leu Val Gln Ile Ala Pro Asn Leu Thr
            340                 345                 350

Val Ile Gln Phe Ile Lys Val Phe Pro Arg Val Leu Leu Gln Thr Leu
        355                 360                 365

Arg His Pro Ile Phe Leu Leu Val Val Leu Ser Gln Val Cys Leu Ser
    370                 375                 380

Ser Met Ala Ala Gly Met Ala Thr Phe Leu Pro Lys Phe Leu Glu Arg
385                 390                 395                 400

Gln Phe Ser Ile Thr Ala Ser Tyr Ala Asn Leu Leu Ile Gly Cys Leu
                405                 410                 415

Ser Phe Pro Ser Val Ile Val Gly Ile Val Val Gly Gly Val Leu Val
            420                 425                 430

Lys Arg Leu His Leu Gly Pro Val Gly Cys Gly Ala Leu Cys Leu Leu
        435                 440                 445

Gly Met Leu Leu Cys Leu Phe Phe Ser Leu Pro Leu Phe Phe Ile Gly
    450                 455                 460

Cys Ser Ser His Gln Ile Ala Gly Ile Thr His Gln Thr Ser Ala His
465                 470                 475                 480

Pro Gly Leu Glu Leu Ser Pro Ser Cys Met Glu Ala Cys Ser Cys Pro
                485                 490                 495

Leu Asp Gly Phe Asn Pro Val Cys Asp Pro Ser Thr Arg Val Glu Tyr
            500                 505                 510

Ile Thr Pro Cys His Ala Gly Cys Ser Ser Trp Val Val Gln Asp Ala
        515                 520                 525

Leu Asp Asn Ser Gln Val Phe Tyr Thr Asn Cys Ser Cys Val Val Glu
    530                 535                 540

Gly Asn Pro Val Leu Ala Gly Ser Cys Asp Ser Thr Cys Ser His Leu
545                 550                 555                 560

Val Val Pro Phe Leu Leu Leu Val Ser Leu Gly Ser Ala Leu Ala Cys
                565                 570                 575

Leu Thr His Thr Pro Ser Phe Met Leu Ile Leu Arg Gly Val Lys Lys
            580                 585                 590

Glu Asp Lys Thr Leu Ala Val Gly Ile Gln Phe Met Phe Leu Arg Ile
        595                 600                 605

Leu Ala Trp Met Pro Ser Pro Val Ile His Gly Ser Ala Ile Asp Thr
    610                 615                 620

Thr Cys Val His Trp Ala Leu Ser Cys Gly Arg Arg Ala Val Cys Arg
625                 630                 635                 640

Tyr Tyr Asn Asn Asp Leu Leu Arg Asn Arg Phe Ile Gly Leu Gln Phe
                645                 650                 655

Phe Phe Lys Thr Gly Ser Val Ile Cys Phe Ala Leu Val Leu Ala Val
            660                 665                 670

Leu Arg Gln Gln Asp Lys Glu Ala Arg Thr Lys Glu Ser Arg Ser Ser
        675                 680                 685

Pro Ala Val Glu Gln Gln Leu Leu Val Ser Gly Pro Gly Lys Lys Pro
    690                 695                 700
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Glu Asp Ser Arg Val
705


<210> SEQ ID NO 11
<211> LENGTH: 960
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (78)...(797)

<400> SEQUENCE: 11

gaattcggca cgagggccgg cctccgcccg gccccgaggg caggctctcc ccggaggctc     60

agccccctct gctcccc atg ggc aac tgc cag gca ggg cac aac ctg cac       110
                  Met Gly Asn Cys Gln Ala Gly His Asn Leu His
                   1               5                   10

ctg tgt ctg gcc cac cac cca cct ctg gtc tgt gcc act ttg atc ctg      158
Leu Cys Leu Ala His His Pro Pro Leu Val Cys Ala Thr Leu Ile Leu
             15                  20                  25

ctg ctc ctt ggc ctc tct ggc ctg ggc ctt ggc agc ttc ctc ctc acc      206
Leu Leu Leu Gly Leu Ser Gly Leu Gly Leu Gly Ser Phe Leu Leu Thr
         30                  35                  40

cac agg act ggc ctg cgc agc cct gac atc ccc cag gac tgg gtc tct      254
His Arg Thr Gly Leu Arg Ser Pro Asp Ile Pro Gln Asp Trp Val Ser
     45                  50                  55

ttt ttg aga tct ttt ggc cag ctg acc ctg tgt ccc agg aat ggg aca      302
Phe Leu Arg Ser Phe Gly Gln Leu Thr Leu Cys Pro Arg Asn Gly Thr
 60                  65                  70                  75

gtc aca ggg aag tgg cga ggg tct cac gtc gtg ggc ttg ctg acc acc      350
Val Thr Gly Lys Trp Arg Gly Ser His Val Val Gly Leu Leu Thr Thr
                 80                  85                  90

ttg aac ttc gga gac ggt cca gac agg aac aag acc cgg aca ttc cag      398
Leu Asn Phe Gly Asp Gly Pro Asp Arg Asn Lys Thr Arg Thr Phe Gln
             95                  100                 105

gcc aca gtc ctg gga agt cag atg gga ttg aaa gga tct tct gca gga      446
Ala Thr Val Leu Gly Ser Gln Met Gly Leu Lys Gly Ser Ser Ala Gly
        110                 115                 120

caa ctg gtc ctt atc aca gcc agg gtg acc aca gaa agg act gca gga      494
Gln Leu Val Leu Ile Thr Ala Arg Val Thr Thr Glu Arg Thr Ala Gly
    125                 130                 135

acc tgc cta tat ttt agt gct gtt cca gga atc cta ccc tcc agc cag      542
Thr Cys Leu Tyr Phe Ser Ala Val Pro Gly Ile Leu Pro Ser Ser Gln
140                 145                 150                 155

cca ccc ata tcc tgc tca gag gag ggg gct gga aat gcc acc ctg agc      590
Pro Pro Ile Ser Cys Ser Glu Glu Gly Ala Gly Asn Ala Thr Leu Ser
                160                 165                 170

cct aga atg ggt gag gaa tgt gtt agt gtc tgg agc cat gaa ggc ctt      638
Pro Arg Met Gly Glu Glu Cys Val Ser Val Trp Ser His Glu Gly Leu
            175                 180                 185

gtg ctg acc aag ctg ctc acc tcg gag gag ctg gct ctg tgt ggc tcc      686
Val Leu Thr Lys Leu Leu Thr Ser Glu Glu Leu Ala Leu Cys Gly Ser
        190                 195                 200

agg ctg ctg gtc ttg ggc tcc ttc ctg ctt ctc ttc tgt ggc ctt ctc      734
Arg Leu Leu Val Leu Gly Ser Phe Leu Leu Leu Phe Cys Gly Leu Leu
    205                 210                 215

tgc tgt gtc act gct atg tgc ttc cac ccg cgc cgg gag tcc cac tgg      782
Cys Cys Val Thr Ala Met Cys Phe His Pro Arg Arg Glu Ser His Trp
220                 225                 230                 235
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tct aga acc cgg ctc tgagggcact ggcctagttc ccgacttgtt tctcaggtgt      837
Ser Arg Thr Arg Leu
                240

gaatcaactt cttgggcctt ggctctgagt tggaaaaggt tttagaaaaa gtgaagagct    897

ggaatgtggg ggaaaataaa aagctttttt gcccaaaaaa aaaaaaaaaa aaaaaaaaaa    957

aaa                                                                  960


<210> SEQ ID NO 12
<211> LENGTH: 240
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12

Met Gly Asn Cys Gln Ala Gly His Asn Leu His Leu Cys Leu Ala His
 1               5                  10                  15

His Pro Pro Leu Val Cys Ala Thr Leu Ile Leu Leu Leu Leu Gly Leu
            20                  25                  30

Ser Gly Leu Gly Leu Gly Ser Phe Leu Leu Thr His Arg Thr Gly Leu
        35                  40                  45

Arg Ser Pro Asp Ile Pro Gln Asp Trp Val Ser Phe Leu Arg Ser Phe
    50                  55                  60

Gly Gln Leu Thr Leu Cys Pro Arg Asn Gly Thr Val Thr Gly Lys Trp
65                  70                  75                  80

Arg Gly Ser His Val Val Gly Leu Leu Thr Thr Leu Asn Phe Gly Asp
                85                  90                  95

Gly Pro Asp Arg Asn Lys Thr Arg Thr Phe Gln Ala Thr Val Leu Gly
            100                 105                 110

Ser Gln Met Gly Leu Lys Gly Ser Ser Ala Gly Gln Leu Val Leu Ile
        115                 120                 125

Thr Ala Arg Val Thr Thr Glu Arg Thr Ala Gly Thr Cys Leu Tyr Phe
    130                 135                 140

Ser Ala Val Pro Gly Ile Leu Pro Ser Ser Gln Pro Pro Ile Ser Cys
145                 150                 155                 160

Ser Glu Glu Gly Ala Gly Asn Ala Thr Leu Ser Pro Arg Met Gly Glu
                165                 170                 175

Glu Cys Val Ser Val Trp Ser His Glu Gly Leu Val Leu Thr Lys Leu
            180                 185                 190

Leu Thr Ser Glu Glu Leu Ala Leu Cys Gly Ser Arg Leu Leu Val Leu
        195                 200                 205

Gly Ser Phe Leu Leu Leu Phe Cys Gly Leu Leu Cys Cys Val Thr Ala
    210                 215                 220

Met Cys Phe His Pro Arg Arg Glu Ser His Trp Ser Arg Thr Arg Leu
225                 230                 235                 240


<210> SEQ ID NO 13
<211> LENGTH: 2832
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (317)...(2155)

<400> SEQUENCE: 13

ggatccaaag aattcggcac gaggctggct cagcccagag tccctgtctc ccgcccgccg     60
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gcccgagccg ccgcccctcc cccgcctccc gtgcgcccgg gacaatcctc gccttgtctg    120

tggcgccggc atctggagct ttctgtagcc tccggatacg ccttttttttc agggcgtagc    180

cccagccaag ctgctccccg cggcggccgc acagcagccc gagcgccccc tttccggagc    240

tcccctccgg agctgggatc caggcgcgta gcggagatcc caggatcctg ggtgctgtct    300

gggcccgctc cccacc atg acc ttc ttg ggg cct gga ccc cgg ttc ctg ctg    352
                  Met Thr Phe Leu Gly Pro Gly Pro Arg Phe Leu Leu
                   1               5                  10

ctg ctg ccg ctg ctg ctg ccc cct gcg gcc tca gcc tcc gac cgg ccc      400
Leu Leu Pro Leu Leu Leu Pro Pro Ala Ala Ser Ala Ser Asp Arg Pro
         15                  20                  25

cgg ggc cga gac ccg gtc aac cca gag aag ctg ctg gtg atc act gtg      448
Arg Gly Arg Asp Pro Val Asn Pro Glu Lys Leu Leu Val Ile Thr Val
     30                  35                  40

gcc aca gct gaa acc gag ggg tac ctg cgt ttc ctg cgc tct gcg gag      496
Ala Thr Ala Glu Thr Glu Gly Tyr Leu Arg Phe Leu Arg Ser Ala Glu
 45                  50                  55                  60

ttc ttc aac tac act gtg cgg acc ctg ggc ctg gga gag gag tgg cga      544
Phe Phe Asn Tyr Thr Val Arg Thr Leu Gly Leu Gly Glu Glu Trp Arg
                 65                  70                  75

ggg ggt gat gtg gct cga aca gtt ggt gga gga cag aag gtc cgg tgg      592
Gly Gly Asp Val Ala Arg Thr Val Gly Gly Gly Gln Lys Val Arg Trp
             80                  85                  90

tta aag aag gaa atg gag aaa tac gct gac cgg gag gat atg atc atc      640
Leu Lys Lys Glu Met Glu Lys Tyr Ala Asp Arg Glu Asp Met Ile Ile
         95                  100                 105

atg ttt gtg gat agc tac gac gtg att ctg gcc ggc agc ccc aca gag      688
Met Phe Val Asp Ser Tyr Asp Val Ile Leu Ala Gly Ser Pro Thr Glu
    110                 115                 120

ctg ctg aag aag ttc gtc cag agt ggc agc cgc ctg ctc ttc tct gca      736
Leu Leu Lys Lys Phe Val Gln Ser Gly Ser Arg Leu Leu Phe Ser Ala
125                 130                 135                 140

gag agc ttc tgc tgg ccc gag tgg ggg ctg gcg gag cag tac cct gag      784
Glu Ser Phe Cys Trp Pro Glu Trp Gly Leu Ala Glu Gln Tyr Pro Glu
                145                 150                 155

gtg ggc acg ggg aag cgc ttc ctc aat tct ggt gga ttc atc ggt ttt      832
Val Gly Thr Gly Lys Arg Phe Leu Asn Ser Gly Gly Phe Ile Gly Phe
            160                 165                 170

gcc acc acc atc cac caa atc gtg cgc cag tgg aag tac aag gat gat      880
Ala Thr Thr Ile His Gln Ile Val Arg Gln Trp Lys Tyr Lys Asp Asp
        175                 180                 185

gac gac gac cag ctg ttc tac aca cgg ctc tac ctg gac cca gga ctg      928
Asp Asp Asp Gln Leu Phe Tyr Thr Arg Leu Tyr Leu Asp Pro Gly Leu
    190                 195                 200

agg gag aaa ctc agc ctt aat ctg gat cat aag tct cgg atc ttt cag      976
Arg Glu Lys Leu Ser Leu Asn Leu Asp His Lys Ser Arg Ile Phe Gln
205                 210                 215                 220

aac ctc aac ggg gct tta gat gaa gtg gtt tta aag ttt gat cgg aac     1024
Asn Leu Asn Gly Ala Leu Asp Glu Val Val Leu Lys Phe Asp Arg Asn
                225                 230                 235

cgt gtg cgt atc cgg aac gtg gcc tac gac acg ctc ccc att gtg gtc     1072
Arg Val Arg Ile Arg Asn Val Ala Tyr Asp Thr Leu Pro Ile Val Val
            240                 245                 250

cat gga aac ggt ccc act aag ctg cag ctc aac tac ctg gga aac tac     1120
His Gly Asn Gly Pro Thr Lys Leu Gln Leu Asn Tyr Leu Gly Asn Tyr
        255                 260                 265
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gtc ccc aat ggc tgg act cct gag gga ggc tgt ggc ttc tgc aac cag     1168
Val Pro Asn Gly Trp Thr Pro Glu Gly Gly Cys Gly Phe Cys Asn Gln
    270                 275                 280

gac cgg agg aca ctc ccg ggg ggg cag cct ccc ccc cgg gtg ttt ctg     1216
Asp Arg Arg Thr Leu Pro Gly Gly Gln Pro Pro Pro Arg Val Phe Leu
285                 290                 295                 300

gcc gtg ttt gtg gaa cag cct act ccg ttt ctg ccc cgc ttc ctg cag     1264
Ala Val Phe Val Glu Gln Pro Thr Pro Phe Leu Pro Arg Phe Leu Gln
                305                 310                 315

cgg ctg cta ctc ctg gac tat ccc ccc gac agg gtc acc ctt ttc ctg     1312
Arg Leu Leu Leu Leu Asp Tyr Pro Pro Asp Arg Val Thr Leu Phe Leu
            320                 325                 330

cac aac aac gag gtc ttc cat gaa ccc cac atc gct gac tcc tgg ccg     1360
His Asn Asn Glu Val Phe His Glu Pro His Ile Ala Asp Ser Trp Pro
        335                 340                 345

cag ctc cag gac cac ttc tca gct gtg aag ctc gtg ggg ccg gag gag     1408
Gln Leu Gln Asp His Phe Ser Ala Val Lys Leu Val Gly Pro Glu Glu
    350                 355                 360

gct ctg agc cca ggc gag gcc agg gac atg gcc atg gac ctg tgt cgg     1456
Ala Leu Ser Pro Gly Glu Ala Arg Asp Met Ala Met Asp Leu Cys Arg
365                 370                 375                 380

cag gac ccc gag tgt gag ttc tac ttc agc ctg gac gcc gac gct gtc     1504
Gln Asp Pro Glu Cys Glu Phe Tyr Phe Ser Leu Asp Ala Asp Ala Val
                385                 390                 395

ctc acc aac ctg cag acc ctg cgt atc ctc att gag gag aac agg aag     1552
Leu Thr Asn Leu Gln Thr Leu Arg Ile Leu Ile Glu Glu Asn Arg Lys
            400                 405                 410

gtg atc gcc ccc atg ctg tcc cgc cac ggc aag ctg tgg tcc aac ttc     1600
Val Ile Ala Pro Met Leu Ser Arg His Gly Lys Leu Trp Ser Asn Phe
        415                 420                 425

tgg ggc gcc ctg agc ccc gat gag tac tac gcc cgc tcc gag gac tac     1648
Trp Gly Ala Leu Ser Pro Asp Glu Tyr Tyr Ala Arg Ser Glu Asp Tyr
    430                 435                 440

gtg gag ctg gtg cag cgg aag cga gtg ggt gtg tgg aat gta cca tac     1696
Val Glu Leu Val Gln Arg Lys Arg Val Gly Val Trp Asn Val Pro Tyr
445                 450                 455                 460

atc tcc cag gcc tat gtg atc cgg ggt gat acc ctg cgg atg gag ctg     1744
Ile Ser Gln Ala Tyr Val Ile Arg Gly Asp Thr Leu Arg Met Glu Leu
                465                 470                 475

ccc cag agg gat gtg ttc tcg ggc agt gac aca gac ccg gac atg gcc     1792
Pro Gln Arg Asp Val Phe Ser Gly Ser Asp Thr Asp Pro Asp Met Ala
            480                 485                 490

ttc tgt aag agc ttt cga gac aag ggc atc ttc ctc cat ctg agc aat     1840
Phe Cys Lys Ser Phe Arg Asp Lys Gly Ile Phe Leu His Leu Ser Asn
        495                 500                 505

cag cat gaa ttt ggc cgg ctc ctg gcc act tcc aga tac gac acg gag     1888
Gln His Glu Phe Gly Arg Leu Leu Ala Thr Ser Arg Tyr Asp Thr Glu
    510                 515                 520

cac ctg cac ccc gac ctc tgg cag atc ttc gac aac ccc gtc gac tgg     1936
His Leu His Pro Asp Leu Trp Gln Ile Phe Asp Asn Pro Val Asp Trp
525                 530                 535                 540

aag gag cag tac atc cac gag aac tac agc cgg gcc ctg gaa ggg aag     1984
Lys Glu Gln Tyr Ile His Glu Asn Tyr Ser Arg Ala Leu Glu Gly Lys
                545                 550                 555

gaa tcg tgg agc agc cat gcc cgg acg tgt act ggt tcc cac tgc tgt     2032
Glu Ser Trp Ser Ser His Ala Arg Thr Cys Thr Gly Ser His Cys Cys
            560                 565                 570
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cag aac aaa tgt gtg atg agc tgg tgg cag aga tgg agc act acg gcc     2080
Gln Asn Lys Cys Val Met Ser Trp Trp Gln Arg Trp Ser Thr Thr Ala
        575                 580                 585

agt ggt cag gcg gcc ggc atg agg att caa ggc tgg ctg gag gct acg     2128
Ser Gly Gln Ala Ala Gly Met Arg Ile Gln Gly Trp Leu Glu Ala Thr
    590                 595                 600

aga atg tgc cca ccg tgg aca tcc aca tgaagcaggt ggggtacgag           2175
Arg Met Cys Pro Pro Trp Thr Ser Thr
605                 610

gaccagtggc tgcagctgct gcggacgtat gtgggcccca tgaccgagag cctgtttccc   2235

ggttaccaca ccaaggcgcg ggcggtgatg aactttgtgg ttcgctaccg gccagacgag   2295

cagccgtctc tgcgggccac accacgactc atccaccttc accctcaacg ttgccctcaa   2355

ccacaagggc ctggactatg agggaggtgg ctgccgcttc ctgcgctacg actgtgtgat   2415

ctcctccccg aggaagggct gggcactcct gcaccccggc cgcctcaccc actaccacga   2475

ggggctgcca acgacctggg gcacacgcta catcatggtg tcctttgtcg acccctgaca   2535

ctcaaccact ctgccaaacc tgccctgcca ttgtgccttt ttaggggggcc tggcccccgt   2595

cctgggagtt gggggatggg tctctctgtc tccccacttc ctgagttcat gttccgcgtg   2655

cctgaactga atatgtcacc ttgctcccaa gacacggccc tctcaggaag ctcccggagt   2715

ccccgcctct ctcctccgcc cacaggggtt cgtgggcaca gggcttctgg ggactccccg   2775

cgtgataaat tattaatgtt ccgcagtctc actctgaata aaggacagtt tgtaagt      2832
```

<210> SEQ ID NO 14
<211> LENGTH: 613
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 14

```
Met Thr Phe Leu Gly Pro Gly Pro Arg Phe Leu Leu Leu Leu Pro Leu
 1               5                  10                  15

Leu Leu Pro Pro Ala Ala Ser Ala Ser Asp Arg Pro Arg Gly Arg Asp
            20                  25                  30

Pro Val Asn Pro Glu Lys Leu Leu Val Ile Thr Val Ala Thr Ala Glu
        35                  40                  45

Thr Glu Gly Tyr Leu Arg Phe Leu Arg Ser Ala Glu Phe Phe Asn Tyr
    50                  55                  60

Thr Val Arg Thr Leu Gly Leu Gly Glu Glu Trp Arg Gly Gly Asp Val
65                  70                  75                  80

Ala Arg Thr Val Gly Gly Gly Gln Lys Val Arg Trp Leu Lys Lys Glu
                85                  90                  95

Met Glu Lys Tyr Ala Asp Arg Glu Asp Met Ile Ile Met Phe Val Asp
            100                 105                 110

Ser Tyr Asp Val Ile Leu Ala Gly Ser Pro Thr Glu Leu Leu Lys Lys
        115                 120                 125

Phe Val Gln Ser Gly Ser Arg Leu Leu Phe Ser Ala Glu Ser Phe Cys
    130                 135                 140

Trp Pro Glu Trp Gly Leu Ala Glu Gln Tyr Pro Glu Val Gly Thr Gly
145                 150                 155                 160

Lys Arg Phe Leu Asn Ser Gly Gly Phe Ile Gly Phe Ala Thr Thr Ile
                165                 170                 175
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His Gln Ile Val Arg Gln Trp Lys Tyr Lys Asp Asp Asp Asp Asp Gln
            180                 185                 190

Leu Phe Tyr Thr Arg Leu Tyr Leu Asp Pro Gly Leu Arg Glu Lys Leu
        195                 200                 205

Ser Leu Asn Leu Asp His Lys Ser Arg Ile Phe Gln Asn Leu Asn Gly
    210                 215                 220

Ala Leu Asp Glu Val Val Leu Lys Phe Asp Arg Asn Arg Val Arg Ile
225                 230                 235                 240

Arg Asn Val Ala Tyr Asp Thr Leu Pro Ile Val Val His Gly Asn Gly
                245                 250                 255

Pro Thr Lys Leu Gln Leu Asn Tyr Leu Gly Asn Tyr Val Pro Asn Gly
            260                 265                 270

Trp Thr Pro Glu Gly Gly Cys Gly Phe Cys Asn Gln Asp Arg Arg Thr
        275                 280                 285

Leu Pro Gly Gly Gln Pro Pro Pro Arg Val Phe Leu Ala Val Phe Val
    290                 295                 300

Glu Gln Pro Thr Pro Phe Leu Pro Arg Phe Leu Gln Arg Leu Leu Leu
305                 310                 315                 320

Leu Asp Tyr Pro Pro Asp Arg Val Thr Leu Phe Leu His Asn Asn Glu
                325                 330                 335

Val Phe His Glu Pro His Ile Ala Asp Ser Trp Pro Gln Leu Gln Asp
            340                 345                 350

His Phe Ser Ala Val Lys Leu Val Gly Pro Glu Glu Ala Leu Ser Pro
        355                 360                 365

Gly Glu Ala Arg Asp Met Ala Met Asp Leu Cys Arg Gln Asp Pro Glu
    370                 375                 380

Cys Glu Phe Tyr Phe Ser Leu Asp Ala Asp Ala Val Leu Thr Asn Leu
385                 390                 395                 400

Gln Thr Leu Arg Ile Leu Ile Glu Glu Asn Arg Lys Val Ile Ala Pro
                405                 410                 415

Met Leu Ser Arg His Gly Lys Leu Trp Ser Asn Phe Trp Gly Ala Leu
            420                 425                 430

Ser Pro Asp Glu Tyr Tyr Ala Arg Ser Glu Asp Tyr Val Glu Leu Val
        435                 440                 445

Gln Arg Lys Arg Val Gly Val Trp Asn Val Pro Tyr Ile Ser Gln Ala
    450                 455                 460

Tyr Val Ile Arg Gly Asp Thr Leu Arg Met Glu Leu Pro Gln Arg Asp
465                 470                 475                 480

Val Phe Ser Gly Ser Asp Thr Asp Pro Asp Met Ala Phe Cys Lys Ser
                485                 490                 495

Phe Arg Asp Lys Gly Ile Phe Leu His Leu Ser Asn Gln His Glu Phe
            500                 505                 510

Gly Arg Leu Leu Ala Thr Ser Arg Tyr Asp Thr Glu His Leu His Pro
        515                 520                 525

Asp Leu Trp Gln Ile Phe Asp Asn Pro Val Asp Trp Lys Glu Gln Tyr
    530                 535                 540

Ile His Glu Asn Tyr Ser Arg Ala Leu Glu Gly Lys Glu Ser Trp Ser
545                 550                 555                 560

Ser His Ala Arg Thr Cys Thr Gly Ser His Cys Cys Gln Asn Lys Cys
                565                 570                 575

Val Met Ser Trp Trp Gln Arg Trp Ser Thr Thr Ala Ser Gly Gln Ala
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           580                 585                 590

Ala Gly Met Arg Ile Gln Gly Trp Leu Glu Ala Thr Arg Met Cys Pro
        595                 600                 605

Pro Trp Thr Ser Thr
    610


<210> SEQ ID NO 15
<211> LENGTH: 3030
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (31)...(885)

<400> SEQUENCE: 15

ggatccaaag aattcggcac gagcgccgcg atg ccc gcg cgc cca gga cgc ctc      54
                                Met Pro Ala Arg Pro Gly Arg Leu
                                 1               5

ctc ccg ctg ctg gcc cgg ccg gcg gcc ctg act gcg ctg ctg ctg ctg      102
Leu Pro Leu Leu Ala Arg Pro Ala Ala Leu Thr Ala Leu Leu Leu Leu
     10                  15                  20

ctg ctg ggc cat ggc ggc ggc ggg cgc tgg ggc gcc cgg gcc cag gag      150
Leu Leu Gly His Gly Gly Gly Gly Arg Trp Gly Ala Arg Ala Gln Glu
 25                  30                  35                  40

gcg gcg gcg gcg gcg gcg gac ggg ccc ccc gcg gca gac ggc gag gac      198
Ala Ala Ala Ala Ala Ala Asp Gly Pro Pro Ala Ala Asp Gly Glu Asp
                 45                  50                  55

gga cag gac ccg cac agc aag cac ctg tac acg gcc gac atg ttc acg      246
Gly Gln Asp Pro His Ser Lys His Leu Tyr Thr Ala Asp Met Phe Thr
             60                  65                  70

cac ggg atc cag agc gcc gcg cac ttc gtc atg ttc ttc gcg ccc tgg      294
His Gly Ile Gln Ser Ala Ala His Phe Val Met Phe Phe Ala Pro Trp
         75                  80                  85

tgt gga cac tgc cag cgg ctg cag ccg act tgg aat gac ctg gga gac      342
Cys Gly His Cys Gln Arg Leu Gln Pro Thr Trp Asn Asp Leu Gly Asp
     90                  95                 100

aaa tac aac agc atg gaa gat gcc aaa gtc tat gtg gct aaa gtg gac      390
Lys Tyr Asn Ser Met Glu Asp Ala Lys Val Tyr Val Ala Lys Val Asp
105                 110                 115                 120

tgc acg gcc cac tcc gac gtg tgc tcc gcc cag ggg gtg cga gga tac      438
Cys Thr Ala His Ser Asp Val Cys Ser Ala Gln Gly Val Arg Gly Tyr
                125                 130                 135

ccc acc tta aag ctt ttc aag cca ggc caa gaa gct gtg aag tac cag      486
Pro Thr Leu Lys Leu Phe Lys Pro Gly Gln Glu Ala Val Lys Tyr Gln
            140                 145                 150

ggt cct cgg gac ttc cag aca ctg gaa aac tgg atg ctg cag aca ctg      534
Gly Pro Arg Asp Phe Gln Thr Leu Glu Asn Trp Met Leu Gln Thr Leu
        155                 160                 165

aac gag gag cca gtg aca cca gaa ccg gaa gtg gaa ccg cca gtg ccc      582
Asn Glu Glu Pro Val Thr Pro Glu Pro Glu Val Glu Pro Pro Val Pro
    170                 175                 180

ccg agc tca agc aag ggc tgt atg agc tct cag caa gca act ttg agc      630
Pro Ser Ser Ser Lys Gly Cys Met Ser Ser Gln Gln Ala Thr Leu Ser
185                 190                 195                 200

tgc acg ttg cac aag gcg acc act tta tca agt tct tcg ctc cgt ggt      678
Cys Thr Leu His Lys Ala Thr Thr Leu Ser Ser Ser Ser Leu Arg Gly
                205                 210                 215

gtg gtc act gca aag ccc tgg ctc caa cct ggg agc agc tgg ctc tgg      726
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Val Val Thr Ala Lys Pro Trp Leu Gln Pro Gly Ser Ser Trp Leu Trp
            220                 225                 230

gcc ttg aac att ccg aaa ctg tca aga ttg gca agg ttg att gta cac      774
Ala Leu Asn Ile Pro Lys Leu Ser Arg Leu Ala Arg Leu Ile Val His
        235                 240                 245

agc act atg aac tct gct ccg gaa acc agg ttc gtg gct atc cca ctc      822
Ser Thr Met Asn Ser Ala Pro Glu Thr Arg Phe Val Ala Ile Pro Leu
    250                 255                 260

ttc tct ggt tcc gag atg gga aaa agg tgg atc agt aca agg gaa agc      870
Phe Ser Gly Ser Glu Met Gly Lys Arg Trp Ile Ser Thr Arg Glu Ser
265                 270                 275                 280

ggg att tgg agt cac tgagggagta cgtggagtcg cagctgcagc gcacagagac      925
Gly Ile Trp Ser His
                285

tggagcgacg gagaccgtca cgccctcaga ggccccggtg ctggcagctg agcccgaggc    985

tgacaagggc actgtgttgg cactcactga aaataacttc gatgacacca ttgcagaagg   1045

aataaccttc atcaagtttt atgctccatg gtgtggtcat tgtaagactc tggctcctac   1105

ttgggaggaa ctctctaaaa aggaattccc tggtctggcg ggggtcaaga tcgccgaagt   1165

agactgcact gctgaacgga atatctgcag caagtattcg gtacgaggct accccacgtt   1225

attgcttttc cgaggaggga agaaagtcag tgagcacagt ggaggcagag accttgactc   1285

gttacaccgc tttgtcctga gccaagcgaa agacgaactt taggaacaca gttggaggtc   1345

acctctcctg cccagctccc gcaccctgcg tttaggagtt cagtcccaca gaggccactg   1405

ggttcccagt ggtggctgtt cagaaagcag aacatactaa gcgtgaggta tcttctttgt   1465

gtgtgtgttt tccaagccaa cacactctac agattcttta ttaagttaag tttctctaag   1525

taaatgtgta actcatggtc actgtgtaaa cattttcagt ggcgatatat ccccttttgac   1585

cttctcttga tgaaatttac atggtttcct ttgagactaa aatagcattg agggaaatga   1645

aattgctgga ctatttgtgg ctcctgagtt gagtgatttt ggtgaaagaa agcacatcca   1705

aagcatagtt tacctgccca cgagttctgg aaaggtggcc ttgtggcagt attgacgttc   1765

ctctgatctt aaggtcacag ttgactcaat actgtgttgg tccgtagcat ggagcagatt   1825

gaaatgcaaa aacccacacc tctggaagat accttcacgg ccgctgctgg agcttctgtt   1885

gctgtgaata cttctctcag tgtgagaggt tagccgtgat gaaagcagcg ttacttctga   1945

ccgtgcctga gtaagagaat gctgatgcca taactttatg tgtcgatact tgtcaaatca   2005

gttactgttc aggggatcct tctgtttctc acggggtgaa acatgtcttt agttcctcat   2065

gttaacacga agccagagcc cacatgaact gttggatgtc ttccttagaa agggtaggca   2125

tggaaaattc cacgaggctc attctcagta tctcattaac tcattgaaag attccagttg   2185

tatttgtcac ctggggtgac aagaccagac aggctttccc aggcctgggt atccagggag   2245

gctctgcagc cctgctgaag ggccctaact agagttctag agtttctgat tctgtttctc   2305

agtagtcctt ttagaggctt gctatacttg gtctgcttca aggaggtcga ccttctaatg   2365

tatgaagaat gggatgcatt tgatctcaag accaaagaca gatgtcagtg ggctgctctg   2425

gccctggtgt gcacggctgt ggcagctgtt gatgccagtg tcctctaact catgctgtcc   2485

ttgtgattaa acacttctat ctcccttggg aataagcaca tacaggctta agctctaaga   2545

taggtgtttg tccttttacc atcgagctac ttcccataat aaccactttg catccaacac   2605

tcttcaccca cctcccatac gcaaggggat gtggatactt ggcccaaagt aactggtggt   2665
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aggaatctta gaaacaagac cacttatact gtctgtctga ggcagaagat aacagcagca 2725

tctcgaccag cctctgcctt aaaggaaatc tttattaatc acgtgtggtt cacagataat 2785

tctttttta aaaaaaccca acctcctaga gaagcacaac tgtcaagagt ggcttcagct 2845

ttgcatcacg agtcttgtat tccaagaaaa tcaaagtggt acaatttgtt tgtttacact 2905

atgatacttt ctaaataaac tctttttttt aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2965

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 3025

aaaaa 3030

<210> SEQ ID NO 16
<211> LENGTH: 285
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 16

Met Pro Ala Arg Pro Gly Arg Leu Leu Pro Leu Leu Ala Arg Pro Ala
 1 5 10 15

Ala Leu Thr Ala Leu Leu Leu Leu Leu Leu Gly His Gly Gly Gly Gly
            20 25 30

Arg Trp Gly Ala Arg Ala Gln Glu Ala Ala Ala Ala Ala Ala Asp Gly
        35 40 45

Pro Pro Ala Ala Asp Gly Glu Asp Gly Gln Asp Pro His Ser Lys His
    50 55 60

Leu Tyr Thr Ala Asp Met Phe Thr His Gly Ile Gln Ser Ala Ala His
65 70 75 80

Phe Val Met Phe Phe Ala Pro Trp Cys Gly His Cys Gln Arg Leu Gln
                85 90 95

Pro Thr Trp Asn Asp Leu Gly Asp Lys Tyr Asn Ser Met Glu Asp Ala
            100 105 110

Lys Val Tyr Val Ala Lys Val Asp Cys Thr Ala His Ser Asp Val Cys
        115 120 125

Ser Ala Gln Gly Val Arg Gly Tyr Pro Thr Leu Lys Leu Phe Lys Pro
    130 135 140

Gly Gln Glu Ala Val Lys Tyr Gln Gly Pro Arg Asp Phe Gln Thr Leu
145 150 155 160

Glu Asn Trp Met Leu Gln Thr Leu Asn Glu Glu Pro Val Thr Pro Glu
                165 170 175

Pro Glu Val Glu Pro Pro Val Pro Pro Ser Ser Ser Lys Gly Cys Met
            180 185 190

Ser Ser Gln Gln Ala Thr Leu Ser Cys Thr Leu His Lys Ala Thr Thr
        195 200 205

Leu Ser Ser Ser Ser Leu Arg Gly Val Val Thr Ala Lys Pro Trp Leu
    210 215 220

Gln Pro Gly Ser Ser Trp Leu Trp Ala Leu Asn Ile Pro Lys Leu Ser
225 230 235 240

Arg Leu Ala Arg Leu Ile Val His Ser Thr Met Asn Ser Ala Pro Glu
                245 250 255

Thr Arg Phe Val Ala Ile Pro Leu Phe Ser Gly Ser Glu Met Gly Lys
            260 265 270

Arg Trp Ile Ser Thr Arg Glu Ser Gly Ile Trp Ser His
        275 280 285

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<210> SEQ ID NO 17
<211> LENGTH: 2133
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (185)...(1633)

<400> SEQUENCE: 17

ggatccaaag aattcggcac gaggagctac ggttctggct gcgtcctaga ggcatccggg 60

gcagtaaaac cgctgcgatc gcggaggcgg cggccaggcc gagaggcagg ccgggcaggg 120

gtgtcggacg cagggcgctg ggccgggttt cggcttcggc cacagctttt tttctcaagg 180

tgca atg aaa gcc ttc cac act ttc tgt gtt gtc ctt ctg gtg ttt ggg 229
Met Lys Ala Phe His Thr Phe Cys Val Val Leu Leu Val Phe Gly
1 5 10 15

agt gtc tct gaa gcc aag ttt gat gat ttt gag gat gag gag gac ata 277
Ser Val Ser Glu Ala Lys Phe Asp Asp Phe Glu Asp Glu Glu Asp Ile
20 25 30

gta gag tat gat gat aat gac ttc gct gaa ttt gag gat gtc atg gaa 325
Val Glu Tyr Asp Asp Asn Asp Phe Ala Glu Phe Glu Asp Val Met Glu
35 40 45

gac tct gtt act gaa tct cct caa cgg gtc ata atc act gaa gat gat 373
Asp Ser Val Thr Glu Ser Pro Gln Arg Val Ile Ile Thr Glu Asp Asp
50 55 60

gaa gat gag acc act gtg gag ttg gaa ggg cag gat gaa aac caa gaa 421
Glu Asp Glu Thr Thr Val Glu Leu Glu Gly Gln Asp Glu Asn Gln Glu
65 70 75

gga gat ttt gaa gat gca gat acc cag gag gga gat act gag agt gaa 469
Gly Asp Phe Glu Asp Ala Asp Thr Gln Glu Gly Asp Thr Glu Ser Glu
80 85 90 95

cca tat gat gat gaa gaa ttt gaa ggt tat gaa gac aaa cca gat act 517
Pro Tyr Asp Asp Glu Glu Phe Glu Gly Tyr Glu Asp Lys Pro Asp Thr
100 105 110

tct tct agc aaa aat aaa gac cca ata acg att gtt gat gtt cct gca 565
Ser Ser Ser Lys Asn Lys Asp Pro Ile Thr Ile Val Asp Val Pro Ala
115 120 125

cac ctc cag aac agc tgg gag agt tat tat cta gaa att ttg atg gtg 613
His Leu Gln Asn Ser Trp Glu Ser Tyr Tyr Leu Glu Ile Leu Met Val
130 135 140

act ggt ctg ctt gct tat atc atg aat tac atc att ggg aag aat aaa 661
Thr Gly Leu Leu Ala Tyr Ile Met Asn Tyr Ile Ile Gly Lys Asn Lys
145 150 155

aac agt cgc ctt gca cag gcc tgg ttt aac act cat agg gag ctt ttg 709
Asn Ser Arg Leu Ala Gln Ala Trp Phe Asn Thr His Arg Glu Leu Leu
160 165 170 175

gag agc aac ttt act tta gtg ggg gat gat gga act aac aaa gaa gcc 757
Glu Ser Asn Phe Thr Leu Val Gly Asp Asp Gly Thr Asn Lys Glu Ala
180 185 190

aca agc aca gga aag ttg aac cag gag aat gag cac atc tat aac ctg 805
Thr Ser Thr Gly Lys Leu Asn Gln Glu Asn Glu His Ile Tyr Asn Leu
195 200 205

tgg tgt tct ggt cga gtg tgc tgt gag ggc atg ctt atc cag ctg agg 853
Trp Cys Ser Gly Arg Val Cys Cys Glu Gly Met Leu Ile Gln Leu Arg
210 215 220

ttc ctc aag aga caa gac tta ctg aat gtc ctg gcc cgg atg atg agg 901
Phe Leu Lys Arg Gln Asp Leu Leu Asn Val Leu Ala Arg Met Met Arg

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    225                 230                 235

cca gtg agt gat caa gtg caa ata aaa gta acc atg aat gat gaa gac      949
Pro Val Ser Asp Gln Val Gln Ile Lys Val Thr Met Asn Asp Glu Asp
240                 245                 250                 255

atg gat acc tac gta ttt gct gtt ggc aca cgg aaa gcc ttg gtg cga      997
Met Asp Thr Tyr Val Phe Ala Val Gly Thr Arg Lys Ala Leu Val Arg
                260                 265                 270

cta cag aaa gag atg cag gat ttg agt gag ttt tgt agt gat aaa cct     1045
Leu Gln Lys Glu Met Gln Asp Leu Ser Glu Phe Cys Ser Asp Lys Pro
            275                 280                 285

aag tct gga gca aag tat gga ctg ccg gac tct ttg gcc atc ctg tca     1093
Lys Ser Gly Ala Lys Tyr Gly Leu Pro Asp Ser Leu Ala Ile Leu Ser
        290                 295                 300

gag atg gga gaa gtc aca gac gga atg atg gat aca aag atg gtt cac     1141
Glu Met Gly Glu Val Thr Asp Gly Met Met Asp Thr Lys Met Val His
    305                 310                 315

ttt ctt aca cac tat gct gac aag att gaa tct gtt cat ttt tca gac     1189
Phe Leu Thr His Tyr Ala Asp Lys Ile Glu Ser Val His Phe Ser Asp
320                 325                 330                 335

cag ttc tct ggt cca aaa att atg caa gag gaa ggt cag cct tta aag     1237
Gln Phe Ser Gly Pro Lys Ile Met Gln Glu Glu Gly Gln Pro Leu Lys
                340                 345                 350

cta cct gac act aag agg aca ctg ttg ttt aca ttt aat gtg cct ggc     1285
Leu Pro Asp Thr Lys Arg Thr Leu Leu Phe Thr Phe Asn Val Pro Gly
            355                 360                 365

tca ggt aac act tac cca aag gat atg gag gca ctg cta ccc ctg atg     1333
Ser Gly Asn Thr Tyr Pro Lys Asp Met Glu Ala Leu Leu Pro Leu Met
        370                 375                 380

aac atg gtg att tat tct att gat aaa gcc aaa aag ttc cga ctc aac     1381
Asn Met Val Ile Tyr Ser Ile Asp Lys Ala Lys Lys Phe Arg Leu Asn
    385                 390                 395

aga gaa ggc aaa caa aaa gca gat aag aac cgt gcc cga gta gaa gag     1429
Arg Glu Gly Lys Gln Lys Ala Asp Lys Asn Arg Ala Arg Val Glu Glu
400                 405                 410                 415

aac ttc ttg aaa ctg aca cat gtg caa aga cag gaa gca gca cag tct     1477
Asn Phe Leu Lys Leu Thr His Val Gln Arg Gln Glu Ala Ala Gln Ser
                420                 425                 430

cgg cgg gag gag aaa aaa aga gca gag aag gag cga atc atg aat gag     1525
Arg Arg Glu Glu Lys Lys Arg Ala Glu Lys Glu Arg Ile Met Asn Glu
            435                 440                 445

gaa gat cct gag aaa cag cgc agg ctg gag gag gct gca ttg agg cgt     1573
Glu Asp Pro Glu Lys Gln Arg Arg Leu Glu Glu Ala Ala Leu Arg Arg
        450                 455                 460

gag caa aag aag ttg gaa aag aag caa atg aaa atg aaa caa atc aaa     1621
Glu Gln Lys Lys Leu Glu Lys Lys Gln Met Lys Met Lys Gln Ile Lys
    465                 470                 475

gtg aaa gcc atg taaagccatc ccagagattt gagttctgat gccacctgta         1673
Val Lys Ala Met
480

agctctgaat tcacaggaaa catgaaaaac gccagtccat ttctcaacct taaatttcag   1733

acagtcttgg gcaactgaga aatccttatt tcatcatcta ctctgtttgg ggtttggggt   1793

tttacagaga ttgaagatac ctggaaaggg ctctgtttca agaatttttt tttccagata   1853

atcaaattat tttgattatt ttataaaagg aatgatctat gaaatctgtg taggttttaa   1913

atattttaaa aattataata caaatcatca gtgcttttag tacttcagtg tttaaagaaa   1973
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taccatgaaa tttataggta gataaccaga ttgttgcttt ttgtttaaac caagcagttg 2033

aaatggctat aaagactgac tctaaaccaa gattctgcaa ataatgattg gaattgcaca 2093

ataaacattg cttgatgttt aaaaaaaaaa aaaaaaaaaa 2133

<210> SEQ ID NO 18
<211> LENGTH: 483
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

Met Lys Ala Phe His Thr Phe Cys Val Val Leu Leu Val Phe Gly Ser
 1   5   10   15

Val Ser Glu Ala Lys Phe Asp Asp Phe Glu Asp Glu Glu Asp Ile Val
            20   25   30

Glu Tyr Asp Asp Asn Asp Phe Ala Glu Phe Glu Asp Val Met Glu Asp
        35   40   45

Ser Val Thr Glu Ser Pro Gln Arg Val Ile Ile Thr Glu Asp Asp Glu
    50   55   60

Asp Glu Thr Thr Val Glu Leu Glu Gly Gln Asp Glu Asn Gln Glu Gly
65   70   75   80

Asp Phe Glu Asp Ala Asp Thr Gln Glu Gly Asp Thr Glu Ser Glu Pro
                85   90   95

Tyr Asp Asp Glu Glu Phe Glu Gly Tyr Glu Asp Lys Pro Asp Thr Ser
            100   105   110

Ser Ser Lys Asn Lys Asp Pro Ile Thr Ile Val Asp Val Pro Ala His
        115   120   125

Leu Gln Asn Ser Trp Glu Ser Tyr Tyr Leu Glu Ile Leu Met Val Thr
    130   135   140

Gly Leu Leu Ala Tyr Ile Met Asn Tyr Ile Ile Gly Lys Asn Lys Asn
145   150   155   160

Ser Arg Leu Ala Gln Ala Trp Phe Asn Thr His Arg Glu Leu Leu Glu
                165   170   175

Ser Asn Phe Thr Leu Val Gly Asp Asp Gly Thr Asn Lys Glu Ala Thr
            180   185   190

Ser Thr Gly Lys Leu Asn Gln Glu Asn Glu His Ile Tyr Asn Leu Trp
        195   200   205

Cys Ser Gly Arg Val Cys Cys Glu Gly Met Leu Ile Gln Leu Arg Phe
    210   215   220

Leu Lys Arg Gln Asp Leu Leu Asn Val Leu Ala Arg Met Met Arg Pro
225   230   235   240

Val Ser Asp Gln Val Gln Ile Lys Val Thr Met Asn Asp Glu Asp Met
                245   250   255

Asp Thr Tyr Val Phe Ala Val Gly Thr Arg Lys Ala Leu Val Arg Leu
            260   265   270

Gln Lys Glu Met Gln Asp Leu Ser Glu Phe Cys Ser Asp Lys Pro Lys
        275   280   285

Ser Gly Ala Lys Tyr Gly Leu Pro Asp Ser Leu Ala Ile Leu Ser Glu
    290   295   300

Met Gly Glu Val Thr Asp Gly Met Met Asp Thr Lys Met Val His Phe
305   310   315   320

Leu Thr His Tyr Ala Asp Lys Ile Glu Ser Val His Phe Ser Asp Gln
                325   330   335

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Phe Ser Gly Pro Lys Ile Met Gln Glu Glu Gly Gln Pro Leu Lys Leu
            340                 345                 350

Pro Asp Thr Lys Arg Thr Leu Leu Phe Thr Phe Asn Val Pro Gly Ser
        355                 360                 365

Gly Asn Thr Tyr Pro Lys Asp Met Glu Ala Leu Leu Pro Leu Met Asn
    370                 375                 380

Met Val Ile Tyr Ser Ile Asp Lys Ala Lys Lys Phe Arg Leu Asn Arg
385                 390                 395                 400

Glu Gly Lys Gln Lys Ala Asp Lys Asn Arg Ala Arg Val Glu Glu Asn
                405                 410                 415

Phe Leu Lys Leu Thr His Val Gln Arg Gln Glu Ala Ala Gln Ser Arg
            420                 425                 430

Arg Glu Glu Lys Lys Arg Ala Glu Lys Glu Arg Ile Met Asn Glu Glu
        435                 440                 445

Asp Pro Glu Lys Gln Arg Arg Leu Glu Glu Ala Ala Leu Arg Arg Glu
    450                 455                 460

Gln Lys Lys Leu Glu Lys Lys Gln Met Lys Met Lys Gln Ile Lys Val
465                 470                 475                 480

Lys Ala Met
```

<210> SEQ ID NO 19
<211> LENGTH: 1590
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (100)...(966)

<400> SEQUENCE: 19

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ggatccaaag aattcggcac gagggtgggc tggcgagccg acgcggcggc ggaggaggct     60

gtgaggagtg tgtggaacag gacccgggac agaggaacc atg gct ccg cag aac       114
                                          Met Ala Pro Gln Asn
                                           1               5

ctg agc acc ttt tgc ctg ttg ctg cta tac ctc atc ggg gcg gtg att      162
Leu Ser Thr Phe Cys Leu Leu Leu Leu Tyr Leu Ile Gly Ala Val Ile
                10                  15                  20

gcc gga cga gat ttc tat aag atc ttg ggg gtg cct cga agt gcc tct      210
Ala Gly Arg Asp Phe Tyr Lys Ile Leu Gly Val Pro Arg Ser Ala Ser
            25                  30                  35

ata aag gat att aaa aag gcc tat agg aaa cta gcc ctg cag ctt cat      258
Ile Lys Asp Ile Lys Lys Ala Tyr Arg Lys Leu Ala Leu Gln Leu His
        40                  45                  50

ccc gac cgg aac cct gat gat cca caa gcc cag gag aaa ttc cag gat      306
Pro Asp Arg Asn Pro Asp Asp Pro Gln Ala Gln Glu Lys Phe Gln Asp
    55                  60                  65

ctg ggt gct gct tat gag gtt ctg tca gat agt gag aaa cgg aaa cag      354
Leu Gly Ala Ala Tyr Glu Val Leu Ser Asp Ser Glu Lys Arg Lys Gln
70                  75                  80                  85

tac gat act tat ggt gaa gaa gga tta aaa gat ggt cat cag agc tcc      402
Tyr Asp Thr Tyr Gly Glu Glu Gly Leu Lys Asp Gly His Gln Ser Ser
                90                  95                  100

cat gga gac att ttt tca cac ttc ttt ggg gat ttt ggt ttc atg ttt      450
His Gly Asp Ile Phe Ser His Phe Phe Gly Asp Phe Gly Phe Met Phe
            105                 110                 115

gga gga acc cct cgt cag caa gac aga aat att cca aga gga agt gat      498
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Gly Gly Thr Pro Arg Gln Gln Asp Arg Asn Ile Pro Arg Gly Ser Asp
        120                 125                 130

att att gta gat cta gaa gtc act ttg gaa gaa gta tat gca gga aat      546
Ile Ile Val Asp Leu Glu Val Thr Leu Glu Glu Val Tyr Ala Gly Asn
    135                 140                 145

ttt gtg gaa gta gtt aga aac aaa cct gtg gca agg cag gct cct ggc      594
Phe Val Glu Val Val Arg Asn Lys Pro Val Ala Arg Gln Ala Pro Gly
150                 155                 160                 165

aaa cgg aag tgc aat tgt cgg caa gag atg cgg acc acc cag ctg ggc      642
Lys Arg Lys Cys Asn Cys Arg Gln Glu Met Arg Thr Thr Gln Leu Gly
                170                 175                 180

cct ggg cgc ttc caa atg acc cag gag gtg gtc tgc gac gaa tgc cct      690
Pro Gly Arg Phe Gln Met Thr Gln Glu Val Val Cys Asp Glu Cys Pro
            185                 190                 195

aat gtc aaa cta gtg aat gaa gaa cga acg ctg gaa gta gaa ata gag      738
Asn Val Lys Leu Val Asn Glu Glu Arg Thr Leu Glu Val Glu Ile Glu
        200                 205                 210

cct ggg gtg aga gac ggc atg gag tac ccc ttt att gga gaa ggt gag      786
Pro Gly Val Arg Asp Gly Met Glu Tyr Pro Phe Ile Gly Glu Gly Glu
    215                 220                 225

cct cac gtg gat ggg gag cct gga gat tta cgg ttc cga atc aaa gtt      834
Pro His Val Asp Gly Glu Pro Gly Asp Leu Arg Phe Arg Ile Lys Val
230                 235                 240                 245

gtc aag cac cca ata ttt gaa agg aga gga gat gat ttg tac aca aat      882
Val Lys His Pro Ile Phe Glu Arg Arg Gly Asp Asp Leu Tyr Thr Asn
                250                 255                 260

gtg aca atc tca tta gtt gag tca ctg gtt ggc ttt gag atg gat att      930
Val Thr Ile Ser Leu Val Glu Ser Leu Val Gly Phe Glu Met Asp Ile
            265                 270                 275

act cac ttg gat ggt caa ggt aca tat ttc ccg gga taagatcacc          976
Thr His Leu Asp Gly Gln Gly Thr Tyr Phe Pro Gly
        280                 285

aggccaggag cgaagctatg gaagaaaggg gaagggctcc ccaactttga caacaacaat   1036

atcaagggct ctttgataat cacttttgat gtggattttc caaaagaaca gttaacagag   1096

gaagcgagag aaggtatcaa acagctactg aaacaagggt cagtgcagaa ggtatacaat   1156

ggactgcaag gatattgaga gtgaataaaa ttggactttg tttaaaataa gtgaataagc   1216

gatatttatt atctgcaagg ttttttttgtg tgtgtttttg tttttatttt caatatgcaa   1276

gttaggctta atttttttat ctaatgatca tcatgaaatg aataagaggg cttaagaatt   1336

tgtccatttg cattcggaaa agaatgacca gcaaaaggtt tactaatacc tctccctttg   1396

gggatttaat gtctggtgct gccgcctgag tttcaagaat taaagctgca agaggactcc   1456

aggagcaaaa gaaacccaat atagagggtt ggagttgtta gcaatttcat tcaaaatgcc   1516

aactggagaa gtctgttttt aaatacattt tgttgttatt tttaaaaaaa aaaaaaaaaa   1576

aaaaaaaaaa aaaa                                                     1590


<210> SEQ ID NO 20
<211> LENGTH: 289
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

Met Ala Pro Gln Asn Leu Ser Thr Phe Cys Leu Leu Leu Leu Tyr Leu
 1               5                  10                  15
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Ile Gly Ala Val Ile Ala Gly Arg Asp Phe Tyr Lys Ile Leu Gly Val
            20                  25                  30

Pro Arg Ser Ala Ser Ile Lys Asp Ile Lys Lys Ala Tyr Arg Lys Leu
        35                  40                  45

Ala Leu Gln Leu His Pro Asp Arg Asn Pro Asp Asp Pro Gln Ala Gln
    50                  55                  60

Glu Lys Phe Gln Asp Leu Gly Ala Ala Tyr Glu Val Leu Ser Asp Ser
65                  70                  75                  80

Glu Lys Arg Lys Gln Tyr Asp Thr Tyr Gly Glu Glu Gly Leu Lys Asp
                85                  90                  95

Gly His Gln Ser Ser His Gly Asp Ile Phe Ser His Phe Phe Gly Asp
            100                 105                 110

Phe Gly Phe Met Phe Gly Gly Thr Pro Arg Gln Gln Asp Arg Asn Ile
        115                 120                 125

Pro Arg Gly Ser Asp Ile Ile Val Asp Leu Glu Val Thr Leu Glu Glu
    130                 135                 140

Val Tyr Ala Gly Asn Phe Val Glu Val Val Arg Asn Lys Pro Val Ala
145                 150                 155                 160

Arg Gln Ala Pro Gly Lys Arg Lys Cys Asn Cys Arg Gln Glu Met Arg
                165                 170                 175

Thr Thr Gln Leu Gly Pro Gly Arg Phe Gln Met Thr Gln Glu Val Val
            180                 185                 190

Cys Asp Glu Cys Pro Asn Val Lys Leu Val Asn Glu Glu Arg Thr Leu
        195                 200                 205

Glu Val Glu Ile Glu Pro Gly Val Arg Asp Gly Met Glu Tyr Pro Phe
    210                 215                 220

Ile Gly Glu Gly Glu Pro His Val Asp Gly Glu Pro Gly Asp Leu Arg
225                 230                 235                 240

Phe Arg Ile Lys Val Val Lys His Pro Ile Phe Glu Arg Arg Gly Asp
                245                 250                 255

Asp Leu Tyr Thr Asn Val Thr Ile Ser Leu Val Glu Ser Leu Val Gly
            260                 265                 270

Phe Glu Met Asp Ile Thr His Leu Asp Gly Gln Gly Thr Tyr Phe Pro
        275                 280                 285

Gly
```

<210> SEQ ID NO 21
<211> LENGTH: 1994
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (132)...(1886)

<400> SEQUENCE: 21

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gagagcagac caggcccggt ggagaattag gtgttgttgg gagctcctgc ctcccacagg     60

attccagctg cagggagcct cagggactct gggccgcacg gagttggggg cattccccag    120

agagcgtcgc c atg gtc tgc agg gag cag tta tca aag aat cag gtc aag     170
            Met Val Cys Arg Glu Gln Leu Ser Lys Asn Gln Val Lys
             1               5                  10

tgg gtg ttt gcc ggc att acc tgt gtg tct gtg gtg gtc att gcc gca      218
Trp Val Phe Ala Gly Ile Thr Cys Val Ser Val Val Val Ile Ala Ala
     15                  20                  25
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ata gtc ctt gcc atc acc ctg cgg cgg cca ggc tgt gag ctg gag gcc      266
Ile Val Leu Ala Ile Thr Leu Arg Arg Pro Gly Cys Glu Leu Glu Ala
 30                  35                  40                  45

tgc agc cct gat gcc gac atg ctg gac tac ctg ccg agc ctg ggc cag      314
Cys Ser Pro Asp Ala Asp Met Leu Asp Tyr Leu Pro Ser Leu Gly Gln
                 50                  55                  60

atc agc cag cga gat gcc ttg gag gtc acc tgg tac cac gca gcc aac      362
Ile Ser Gln Arg Asp Ala Leu Glu Val Thr Trp Tyr His Ala Ala Asn
             65                  70                  75

agc aac aaa gcc atg aca gct gcc ctg aac agc aac atc aca gtc ctg      410
Ser Asn Lys Ala Met Thr Ala Ala Leu Asn Ser Asn Ile Thr Val Leu
         80                  85                  90

gag gct gac gtc aat gta gaa ggg ctc ggc aca gcc aat gag aca gga      458
Glu Ala Asp Val Asn Val Glu Gly Leu Gly Thr Ala Asn Glu Thr Gly
     95                  100                 105

gtt ccc atc atg gca cac ccc ccc act atc tac agt gac aac aca ctg      506
Val Pro Ile Met Ala His Pro Pro Thr Ile Tyr Ser Asp Asn Thr Leu
110                 115                 120                 125

gag cag tgg ctg gac gct gtg ctg ggc tct tcc caa aag ggc atc aaa      554
Glu Gln Trp Leu Asp Ala Val Leu Gly Ser Ser Gln Lys Gly Ile Lys
                130                 135                 140

ctg gac ttc aag aac atc aag gca gtg ggc ccc tcc ctg gac ctc ctg      602
Leu Asp Phe Lys Asn Ile Lys Ala Val Gly Pro Ser Leu Asp Leu Leu
            145                 150                 155

cgg cag ctg aca gag gaa ggc aaa gtc cgg cgg ccc ata tgg atc aac      650
Arg Gln Leu Thr Glu Glu Gly Lys Val Arg Arg Pro Ile Trp Ile Asn
        160                 165                 170

gct gac atc tta aag ggc ccc aac atg ctc atc tca act gag gtc aat      698
Ala Asp Ile Leu Lys Gly Pro Asn Met Leu Ile Ser Thr Glu Val Asn
    175                 180                 185

gcc aca cag ttc ctg gcc ctg gtc cag gag aag tat ccc aag gct acc      746
Ala Thr Gln Phe Leu Ala Leu Val Gln Glu Lys Tyr Pro Lys Ala Thr
190                 195                 200                 205

cta tct cca ggc tgg acc acc ttc tac atg tcc acg tcc cca aac agg      794
Leu Ser Pro Gly Trp Thr Thr Phe Tyr Met Ser Thr Ser Pro Asn Arg
                210                 215                 220

acg tac acc caa gcc atg gtg gag aag atg cac gag ctg gtg gga gga      842
Thr Tyr Thr Gln Ala Met Val Glu Lys Met His Glu Leu Val Gly Gly
            225                 230                 235

gtg ccc cag agg gtc acc ttc cct gta cgg tct tcc atg gtg cgg gct      890
Val Pro Gln Arg Val Thr Phe Pro Val Arg Ser Ser Met Val Arg Ala
        240                 245                 250

gcc tgg ccc cac ttc agc tgg ctg ctg agc caa tct gag agg tac agc      938
Ala Trp Pro His Phe Ser Trp Leu Leu Ser Gln Ser Glu Arg Tyr Ser
    255                 260                 265

ctg acg ctg tgg cag gct gcc tcg gac ccc atg tcg gtg gaa gat ctg      986
Leu Thr Leu Trp Gln Ala Ala Ser Asp Pro Met Ser Val Glu Asp Leu
270                 275                 280                 285

ctc tac gtc cgg gat aac act gct gtc cac caa gtc tac tat gac atc     1034
Leu Tyr Val Arg Asp Asn Thr Ala Val His Gln Val Tyr Tyr Asp Ile
                290                 295                 300

ttt gag cct ctc ctg tca cag ttc aag cag ctg gcc ttg aat gcc aca     1082
Phe Glu Pro Leu Leu Ser Gln Phe Lys Gln Leu Ala Leu Asn Ala Thr
            305                 310                 315

cgg aaa cca atg tac tac acg gga ggc agc ctg atc cct ctt ctc cag     1130
Arg Lys Pro Met Tyr Tyr Thr Gly Gly Ser Leu Ile Pro Leu Leu Gln
        320                 325                 330
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ctg cct ggg gat gac ggt ctg aat gtg gag tgg ctg gtt cct gac gtc     1178
Leu Pro Gly Asp Asp Gly Leu Asn Val Glu Trp Leu Val Pro Asp Val
    335                 340                 345

cag ggc agc ggt aaa aca gca aca atg acc ctc cca gac aca gaa ggc     1226
Gln Gly Ser Gly Lys Thr Ala Thr Met Thr Leu Pro Asp Thr Glu Gly
350                 355                 360                 365

atg atc ctg ctg aac act ggc ctc gag gga aca gtg gct gaa aac ccc     1274
Met Ile Leu Leu Asn Thr Gly Leu Glu Gly Thr Val Ala Glu Asn Pro
                370                 375                 380

gtg ccc att gtt cat act cca agt ggc aac atc ctg acg ctg gag tcc     1322
Val Pro Ile Val His Thr Pro Ser Gly Asn Ile Leu Thr Leu Glu Ser
            385                 390                 395

tgc ctg cag cag ctg gcc aca cat ccc ggg cac tgg ggc atc cat ttg     1370
Cys Leu Gln Gln Leu Ala Thr His Pro Gly His Trp Gly Ile His Leu
        400                 405                 410

caa ata gcg gag ccc gca gcc ctc cgg cca tcc ctg gcc ttg ctg gca     1418
Gln Ile Ala Glu Pro Ala Ala Leu Arg Pro Ser Leu Ala Leu Leu Ala
    415                 420                 425

cgc ctc tcc agc ctt ggc ctc ttg cat tgg cct gtg tgg gtt ggg gcc     1466
Arg Leu Ser Ser Leu Gly Leu Leu His Trp Pro Val Trp Val Gly Ala
430                 435                 440                 445

aaa atc tcc cac ggg agt ttt ttg gtc ccc ggc cat gtg gct ggc aga     1514
Lys Ile Ser His Gly Ser Phe Leu Val Pro Gly His Val Ala Gly Arg
                450                 455                 460

gag ctg ctt aca gct gtg gct gag gtc ttc ccc cac gtg act gtg gca     1562
Glu Leu Leu Thr Ala Val Ala Glu Val Phe Pro His Val Thr Val Ala
            465                 470                 475

cca ggc tgg cct gag gag gtg ctg ggc agt ggc tac agg gaa cag ctg     1610
Pro Gly Trp Pro Glu Glu Val Leu Gly Ser Gly Tyr Arg Glu Gln Leu
        480                 485                 490

ctc aca gat atg cta gag ttg tgc cag ggg ctc tgg caa cct gtg tcc     1658
Leu Thr Asp Met Leu Glu Leu Cys Gln Gly Leu Trp Gln Pro Val Ser
    495                 500                 505

ttc cag atg cag gcc atg ctg ctg ggc cac agc aca gct gga gcc ata     1706
Phe Gln Met Gln Ala Met Leu Leu Gly His Ser Thr Ala Gly Ala Ile
510                 515                 520                 525

gcc agg ctg ctg gca tcc tcc ccc cgg gcc acc gtc aca gtg gag cac     1754
Ala Arg Leu Leu Ala Ser Ser Pro Arg Ala Thr Val Thr Val Glu His
                530                 535                 540

aac cca gct ggg ggc gac tat gcc tct gtg agg aca gca ttg ctg gca     1802
Asn Pro Ala Gly Gly Asp Tyr Ala Ser Val Arg Thr Ala Leu Leu Ala
            545                 550                 555

gct agg gct gtg gac agg acc cga gtc tac tac agg cta ccc cag ggc     1850
Ala Arg Ala Val Asp Arg Thr Arg Val Tyr Tyr Arg Leu Pro Gln Gly
        560                 565                 570

tac cac aag gac ttg ctg gct cat gtt ggt aga aac tgagcaccca          1896
Tyr His Lys Asp Leu Leu Ala His Val Gly Arg Asn
    575                 580                 585

ggggtggtgg gccagcggac ctcagggcgg aggcttccca cggggaggca ggaagaaata   1956

aaggtctttg gcttacaaaa aaaaaaaaca aaaaaaaa                           1994


<210> SEQ ID NO 22
<211> LENGTH: 585
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22
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Met Val Cys Arg Glu Gln Leu Ser Lys Asn Gln Val Lys Trp Val Phe
 1               5                  10                  15

Ala Gly Ile Thr Cys Val Ser Val Val Val Ile Ala Ala Ile Val Leu
            20                  25                  30

Ala Ile Thr Leu Arg Arg Pro Gly Cys Glu Leu Glu Ala Cys Ser Pro
        35                  40                  45

Asp Ala Asp Met Leu Asp Tyr Leu Pro Ser Leu Gly Gln Ile Ser Gln
    50                  55                  60

Arg Asp Ala Leu Glu Val Thr Trp Tyr His Ala Ala Asn Ser Asn Lys
65                  70                  75                  80

Ala Met Thr Ala Ala Leu Asn Ser Asn Ile Thr Val Leu Glu Ala Asp
                85                  90                  95

Val Asn Val Glu Gly Leu Gly Thr Ala Asn Glu Thr Gly Val Pro Ile
            100                 105                 110

Met Ala His Pro Pro Thr Ile Tyr Ser Asp Asn Thr Leu Glu Gln Trp
        115                 120                 125

Leu Asp Ala Val Leu Gly Ser Ser Gln Lys Gly Ile Lys Leu Asp Phe
    130                 135                 140

Lys Asn Ile Lys Ala Val Gly Pro Ser Leu Asp Leu Leu Arg Gln Leu
145                 150                 155                 160

Thr Glu Glu Gly Lys Val Arg Arg Pro Ile Trp Ile Asn Ala Asp Ile
                165                 170                 175

Leu Lys Gly Pro Asn Met Leu Ile Ser Thr Glu Val Asn Ala Thr Gln
            180                 185                 190

Phe Leu Ala Leu Val Gln Glu Lys Tyr Pro Lys Ala Thr Leu Ser Pro
        195                 200                 205

Gly Trp Thr Thr Phe Tyr Met Ser Thr Ser Pro Asn Arg Thr Tyr Thr
    210                 215                 220

Gln Ala Met Val Glu Lys Met His Glu Leu Val Gly Gly Val Pro Gln
225                 230                 235                 240

Arg Val Thr Phe Pro Val Arg Ser Ser Met Val Arg Ala Ala Trp Pro
                245                 250                 255

His Phe Ser Trp Leu Leu Ser Gln Ser Glu Arg Tyr Ser Leu Thr Leu
            260                 265                 270

Trp Gln Ala Ala Ser Asp Pro Met Ser Val Glu Asp Leu Leu Tyr Val
        275                 280                 285

Arg Asp Asn Thr Ala Val His Gln Val Tyr Tyr Asp Ile Phe Glu Pro
    290                 295                 300

Leu Leu Ser Gln Phe Lys Gln Leu Ala Leu Asn Ala Thr Arg Lys Pro
305                 310                 315                 320

Met Tyr Tyr Thr Gly Gly Ser Leu Ile Pro Leu Leu Gln Leu Pro Gly
                325                 330                 335

Asp Asp Gly Leu Asn Val Glu Trp Leu Val Pro Asp Val Gln Gly Ser
            340                 345                 350

Gly Lys Thr Ala Thr Met Thr Leu Pro Asp Thr Glu Gly Met Ile Leu
        355                 360                 365

Leu Asn Thr Gly Leu Glu Gly Thr Val Ala Glu Asn Pro Val Pro Ile
    370                 375                 380

Val His Thr Pro Ser Gly Asn Ile Leu Thr Leu Glu Ser Cys Leu Gln
385                 390                 395                 400

Gln Leu Ala Thr His Pro Gly His Trp Gly Ile His Leu Gln Ile Ala
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               405                 410                 415

Glu Pro Ala Ala Leu Arg Pro Ser Leu Ala Leu Leu Ala Arg Leu Ser
            420                 425                 430

Ser Leu Gly Leu Leu His Trp Pro Val Trp Val Gly Ala Lys Ile Ser
        435                 440                 445

His Gly Ser Phe Leu Val Pro Gly His Val Ala Gly Arg Glu Leu Leu
    450                 455                 460

Thr Ala Val Ala Glu Val Phe Pro His Val Thr Val Ala Pro Gly Trp
465                 470                 475                 480

Pro Glu Glu Val Leu Gly Ser Gly Tyr Arg Glu Gln Leu Leu Thr Asp
                485                 490                 495

Met Leu Glu Leu Cys Gln Gly Leu Trp Gln Pro Val Ser Phe Gln Met
            500                 505                 510

Gln Ala Met Leu Leu Gly His Ser Thr Ala Gly Ala Ile Ala Arg Leu
        515                 520                 525

Leu Ala Ser Ser Pro Arg Ala Thr Val Thr Val Glu His Asn Pro Ala
    530                 535                 540

Gly Gly Asp Tyr Ala Ser Val Arg Thr Ala Leu Leu Ala Ala Arg Ala
545                 550                 555                 560

Val Asp Arg Thr Arg Val Tyr Tyr Arg Leu Pro Gln Gly Tyr His Lys
                565                 570                 575

Asp Leu Leu Ala His Val Gly Arg Asn
            580                 585


<210> SEQ ID NO 23
<211> LENGTH: 1340
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (79)...(918)

<400> SEQUENCE: 23

ggcgcttgcg ctgagcagcc cgcgagggcg gaagtgggag ctgcgaccgc gctccctgtg     60

aggtgggcaa gcggcgaa atg gcg ccc tcc ggg agt ctt gca gtt ccc ctg      111
                    Met Ala Pro Ser Gly Ser Leu Ala Val Pro Leu
                     1               5                  10

gca gtc ctg gtg ctg ttg ctt tgg ggt gct ccc tgg acg cac ggg cgg      159
Ala Val Leu Val Leu Leu Leu Trp Gly Ala Pro Trp Thr His Gly Arg
             15                  20                  25

cgg agc aac gtt cgc gtc atc acg gac gag aac tgg aga gaa ctg ctg      207
Arg Ser Asn Val Arg Val Ile Thr Asp Glu Asn Trp Arg Glu Leu Leu
         30                  35                  40

gaa gga gac tgg atg ata gaa ttt tat gcc ccg tgg tgc cct gct tgt      255
Glu Gly Asp Trp Met Ile Glu Phe Tyr Ala Pro Trp Cys Pro Ala Cys
     45                  50                  55

caa aat ctt caa ccg gaa tgg gaa agt ttt gct gaa tgg gga gaa gat      303
Gln Asn Leu Gln Pro Glu Trp Glu Ser Phe Ala Glu Trp Gly Glu Asp
 60                  65                  70                  75

ctt gag gtt aat att gcg aaa gta gat gtc aca gag cag cca gga ctg      351
Leu Glu Val Asn Ile Ala Lys Val Asp Val Thr Glu Gln Pro Gly Leu
                 80                  85                  90

agt gga cgg ttt atc ata act gct ctt cct act att tat cat tgt aaa      399
Ser Gly Arg Phe Ile Ile Thr Ala Leu Pro Thr Ile Tyr His Cys Lys
             95                  100                 105
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gat ggt gaa ttt agg cgc tat ctg ggt cca agg act aag aag gac ttc      447
Asp Gly Glu Phe Arg Arg Tyr Leu Gly Pro Arg Thr Lys Lys Asp Phe
        110                 115                 120

ata aac ttt ata agt gat aaa gag tgg aag agt att gag ccc gtt tca      495
Ile Asn Phe Ile Ser Asp Lys Glu Trp Lys Ser Ile Glu Pro Val Ser
    125                 130                 135

tca tgg ttt ggt cca ggt tct gtt ctg atg agt agt atg tca gca ctc      543
Ser Trp Phe Gly Pro Gly Ser Val Leu Met Ser Ser Met Ser Ala Leu
140                 145                 150                 155

ttt cag cta tct atg tgg atc agg acg tgc cat aac tac ttt att gaa      591
Phe Gln Leu Ser Met Trp Ile Arg Thr Cys His Asn Tyr Phe Ile Glu
                160                 165                 170

gac ctt gga ttg cca gtg tgg gga tca tat act gtt ttt gct tta gca      639
Asp Leu Gly Leu Pro Val Trp Gly Ser Tyr Thr Val Phe Ala Leu Ala
            175                 180                 185

act ctg ttt tcc gga ctg tta tta gga ctc tgt atg ata ttt gtg gca      687
Thr Leu Phe Ser Gly Leu Leu Leu Gly Leu Cys Met Ile Phe Val Ala
        190                 195                 200

gat tgc ctt tgt cct tca aaa agg cgc aga cca cag cca tac cca tac      735
Asp Cys Leu Cys Pro Ser Lys Arg Arg Arg Pro Gln Pro Tyr Pro Tyr
    205                 210                 215

cct tca aaa aaa tta tta tca gaa tct gca caa cct ttg aaa aaa gtg      783
Pro Ser Lys Lys Leu Leu Ser Glu Ser Ala Gln Pro Leu Lys Lys Val
220                 225                 230                 235

gag gag gaa caa gag gcg gat gaa gaa gat gtt tca gaa gaa gaa gct      831
Glu Glu Glu Gln Glu Ala Asp Glu Glu Asp Val Ser Glu Glu Glu Ala
                240                 245                 250

gaa agt aaa gaa gga aca aac aaa gac ttt cca cag aat gcc ata aga      879
Glu Ser Lys Glu Gly Thr Asn Lys Asp Phe Pro Gln Asn Ala Ile Arg
            255                 260                 265

caa cgc tct ctg ggt cca tca ttg gcc aca gat aaa tcc tagttaaatt       928
Gln Arg Ser Leu Gly Pro Ser Leu Ala Thr Asp Lys Ser
        270                 275                 280

ttatagttat cttaatatta tgattttgat aaaaacagaa gattgatcat tttgtttggt    988

ttgaagtgaa ctgtgacttt tttgaatatt gcagggttca gtctagattg tcattaaatt   1048

gaagagtcta cattcagaac ataaaagcac taggtataca agtttgaaat atgatttaag   1108

cacagtatga tggtttaaat agttctctaa tttttgaaaa atcgtgccaa gcaataagat   1168

ttatgtgtat ttgtttaata ataacctatt tcaagtctga gttttgaaaa tttacatttc   1228

ccaagtattg cattattgag gtatttaaga agattatttt agagaaaaat atttctcatt   1288

tgatataatt tttctctgtt tcactgtgaa aaaaaaaaaa aaaaaaaaaa aa           1340


<210> SEQ ID NO 24
<211> LENGTH: 280
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24

Met Ala Pro Ser Gly Ser Leu Ala Val Pro Leu Ala Val Leu Val Leu
 1               5                  10                  15

Leu Leu Trp Gly Ala Pro Trp Thr His Gly Arg Arg Ser Asn Val Arg
            20                  25                  30

Val Ile Thr Asp Glu Asn Trp Arg Glu Leu Leu Glu Gly Asp Trp Met
        35                  40                  45

Ile Glu Phe Tyr Ala Pro Trp Cys Pro Ala Cys Gln Asn Leu Gln Pro
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    50                  55                  60

Glu Trp Glu Ser Phe Ala Glu Trp Gly Glu Asp Leu Glu Val Asn Ile
65                  70                  75                  80

Ala Lys Val Asp Val Thr Glu Gln Pro Gly Leu Ser Gly Arg Phe Ile
                85                  90                  95

Ile Thr Ala Leu Pro Thr Ile Tyr His Cys Lys Asp Gly Glu Phe Arg
            100                 105                 110

Arg Tyr Leu Gly Pro Arg Thr Lys Lys Asp Phe Ile Asn Phe Ile Ser
        115                 120                 125

Asp Lys Glu Trp Lys Ser Ile Glu Pro Val Ser Ser Trp Phe Gly Pro
    130                 135                 140

Gly Ser Val Leu Met Ser Ser Met Ser Ala Leu Phe Gln Leu Ser Met
145                 150                 155                 160

Trp Ile Arg Thr Cys His Asn Tyr Phe Ile Glu Asp Leu Gly Leu Pro
                165                 170                 175

Val Trp Gly Ser Tyr Thr Val Phe Ala Leu Ala Thr Leu Phe Ser Gly
            180                 185                 190

Leu Leu Leu Gly Leu Cys Met Ile Phe Val Ala Asp Cys Leu Cys Pro
        195                 200                 205

Ser Lys Arg Arg Arg Pro Gln Pro Tyr Pro Tyr Pro Ser Lys Lys Leu
    210                 215                 220

Leu Ser Glu Ser Ala Gln Pro Leu Lys Lys Val Glu Glu Glu Gln Glu
225                 230                 235                 240

Ala Asp Glu Glu Asp Val Ser Glu Glu Glu Ala Glu Ser Lys Glu Gly
                245                 250                 255

Thr Asn Lys Asp Phe Pro Gln Asn Ala Ile Arg Gln Arg Ser Leu Gly
            260                 265                 270

Pro Ser Leu Ala Thr Asp Lys Ser
        275                 280


<210> SEQ ID NO 25
<211> LENGTH: 1011
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (128)...(985)

<400> SEQUENCE: 25

ggagacttta acatcagaaa aaggatggac ttgttgcagt tgctgtagca ttcaaagtca     60

aggtgatcat ttcaaaccaa gcatcagcaa caattaaaaa tattcacttg gtatctgtag    120

tttaata atg gac caa cat caa cat ttg aat aaa aca gca gag tca gca      169
        Met Asp Gln His Gln His Leu Asn Lys Thr Ala Glu Ser Ala
         1               5                  10

tct tca gag aaa aag aaa aca aga cgc tgc aat gga ttc aag atg ttc      217
Ser Ser Glu Lys Lys Lys Thr Arg Arg Cys Asn Gly Phe Lys Met Phe
 15                  20                  25                  30

ttg gca gcc ctg tca ttc agc tat att gct aaa gca cta ggt gga atc      265
Leu Ala Ala Leu Ser Phe Ser Tyr Ile Ala Lys Ala Leu Gly Gly Ile
                35                  40                  45

att atg aaa att tcc atc act caa ata gaa agg aga ttt gac ata tcc      313
Ile Met Lys Ile Ser Ile Thr Gln Ile Glu Arg Arg Phe Asp Ile Ser
             50                  55                  60

tct tct ctt gct ggt tta att gat gta agc ttt gaa att gga aat ttg      361
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Ser Ser Leu Ala Gly Leu Ile Asp Val Ser Phe Glu Ile Gly Asn Leu
         65                  70                  75

ctt gtg att gta ttt gta agt tac ttt gga tct aaa cta cac aga ccg      409
Leu Val Ile Val Phe Val Ser Tyr Phe Gly Ser Lys Leu His Arg Pro
     80                  85                  90

aag tta att gga att ggt tgt ctc ctt atg gga act gga agt att ttg      457
Lys Leu Ile Gly Ile Gly Cys Leu Leu Met Gly Thr Gly Ser Ile Leu
 95                 100                 105                 110

aca gct tta cca cat ttc ttc atg gga tat tat agg tat tct aaa gaa      505
Thr Ala Leu Pro His Phe Phe Met Gly Tyr Tyr Arg Tyr Ser Lys Glu
                115                 120                 125

acc cat att aat cca tca gaa aat tca aca tca agt tta tca acc tgt      553
Thr His Ile Asn Pro Ser Glu Asn Ser Thr Ser Ser Leu Ser Thr Cys
            130                 135                 140

tta att aat caa acc tta cca ttc aat gga aca tca cct gag ata gta      601
Leu Ile Asn Gln Thr Leu Pro Phe Asn Gly Thr Ser Pro Glu Ile Val
        145                 150                 155

gaa aaa gat tgt gta aag gaa tct ggg tca cac atg tgg atc tat gtc      649
Glu Lys Asp Cys Val Lys Glu Ser Gly Ser His Met Trp Ile Tyr Val
    160                 165                 170

ttc atg ggg aat atg ctt cgt ggc ata ggg gaa acc ccc ata gta cca      697
Phe Met Gly Asn Met Leu Arg Gly Ile Gly Glu Thr Pro Ile Val Pro
175                 180                 185                 190

ttg ggg att tca tac att gat gat ttt gca aaa gaa gga cat tct tcc      745
Leu Gly Ile Ser Tyr Ile Asp Asp Phe Ala Lys Glu Gly His Ser Ser
                195                 200                 205

ttg tat tta ggt agt ttg aat gca ata gga atg att ggt cca gtc att      793
Leu Tyr Leu Gly Ser Leu Asn Ala Ile Gly Met Ile Gly Pro Val Ile
            210                 215                 220

ggc ttt gca ctg gga tct ctg ttt gct aaa ata tac gtg gat att gga      841
Gly Phe Ala Leu Gly Ser Leu Phe Ala Lys Ile Tyr Val Asp Ile Gly
        225                 230                 235

tat gta gat ctg agc act atc aga ata act cct aag gac tct cgt tgg      889
Tyr Val Asp Leu Ser Thr Ile Arg Ile Thr Pro Lys Asp Ser Arg Trp
    240                 245                 250

gtt gga gct tgg tgg ctt ggt ttc ctt gtg tct gga cta ttt tcc att      937
Val Gly Ala Trp Trp Leu Gly Phe Leu Val Ser Gly Leu Phe Ser Ile
255                 260                 265                 270

att tct tcc ata cca ttt ttt ttc ttg ccg aaa aat cca aat aaa cca      985
Ile Ser Ser Ile Pro Phe Phe Phe Leu Pro Lys Asn Pro Asn Lys Pro
                275                 280                 285

taaaaaaaaa aaaaaaaaaa aaaaaa                                       1011


<210> SEQ ID NO 26
<211> LENGTH: 286
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

Met Asp Gln His Gln His Leu Asn Lys Thr Ala Glu Ser Ala Ser Ser
 1               5                  10                  15

Glu Lys Lys Lys Thr Arg Arg Cys Asn Gly Phe Lys Met Phe Leu Ala
            20                  25                  30

Ala Leu Ser Phe Ser Tyr Ile Ala Lys Ala Leu Gly Gly Ile Ile Met
        35                  40                  45

Lys Ile Ser Ile Thr Gln Ile Glu Arg Arg Phe Asp Ile Ser Ser Ser
    50                  55                  60
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Leu Ala Gly Leu Ile Asp Val Ser Phe Glu Ile Gly Asn Leu Leu Val
65                  70                  75                  80

Ile Val Phe Val Ser Tyr Phe Gly Ser Lys Leu His Arg Pro Lys Leu
                85                  90                  95

Ile Gly Ile Gly Cys Leu Leu Met Gly Thr Gly Ser Ile Leu Thr Ala
            100                 105                 110

Leu Pro His Phe Phe Met Gly Tyr Tyr Arg Tyr Ser Lys Glu Thr His
        115                 120                 125

Ile Asn Pro Ser Glu Asn Ser Thr Ser Ser Leu Ser Thr Cys Leu Ile
    130                 135                 140

Asn Gln Thr Leu Pro Phe Asn Gly Thr Ser Pro Glu Ile Val Glu Lys
145                 150                 155                 160

Asp Cys Val Lys Glu Ser Gly Ser His Met Trp Ile Tyr Val Phe Met
                165                 170                 175

Gly Asn Met Leu Arg Gly Ile Gly Glu Thr Pro Ile Val Pro Leu Gly
            180                 185                 190

Ile Ser Tyr Ile Asp Asp Phe Ala Lys Glu Gly His Ser Ser Leu Tyr
        195                 200                 205

Leu Gly Ser Leu Asn Ala Ile Gly Met Ile Gly Pro Val Ile Gly Phe
    210                 215                 220

Ala Leu Gly Ser Leu Phe Ala Lys Ile Tyr Val Asp Ile Gly Tyr Val
225                 230                 235                 240

Asp Leu Ser Thr Ile Arg Ile Thr Pro Lys Asp Ser Arg Trp Val Gly
                245                 250                 255

Ala Trp Trp Leu Gly Phe Leu Val Ser Gly Leu Phe Ser Ile Ile Ser
            260                 265                 270

Ser Ile Pro Phe Phe Phe Leu Pro Lys Asn Pro Asn Lys Pro
        275                 280                 285


<210> SEQ ID NO 27
<211> LENGTH: 2027
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (270)...(1286)

<400> SEQUENCE: 27

gacatttcat tgtaaacgac tgggagtatc tgagcaaatt atttcttagc tgactttaga     60

gaaaacggct acctatctga ccccaaaacg acttgaggaa actgtttcca cggtcctgct    120

gcagagggga agcacagtcg tcaagaagag agtggggtca ggatcaaaac acatttagtg    180

tgacttaggg aaagaaaaca ttttccctct ttgaacctct ctggatacag tcattttgcc    240

tctacttgag gatcaactgt tcaacctca atg gcc ttt cag gac ctc ctg ggt      293
                                Met Ala Phe Gln Asp Leu Leu Gly
                                 1               5

cac gct ggt gac ctg tgg aga ttc cag atc ctt cag act gtt ttt ctc      341
His Ala Gly Asp Leu Trp Arg Phe Gln Ile Leu Gln Thr Val Phe Leu
     10                  15                  20

tca atc ttt gct gtt gct aca tac ctt cat ttt atg ctg gag aac ttc      389
Ser Ile Phe Ala Val Ala Thr Tyr Leu His Phe Met Leu Glu Asn Phe
 25                  30                  35                  40

act gca ttc ata cct ggc cat cgc tgc tgg gtc cac atc ctg gac aat      437
Thr Ala Phe Ile Pro Gly His Arg Cys Trp Val His Ile Leu Asp Asn
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                45                  50                  55

gac act gtc tct gac aat gac act ggg gcc ctc agc caa gat gca ctc      485
Asp Thr Val Ser Asp Asn Asp Thr Gly Ala Leu Ser Gln Asp Ala Leu
            60                  65                  70

ttg aga atc tcc acc cca ctg gac tca aac atg agg cca gag aag tgt      533
Leu Arg Ile Ser Thr Pro Leu Asp Ser Asn Met Arg Pro Glu Lys Cys
         75                  80                  85

cgt cgc ttt gtt cat cct cag tgg cag ctc ctt cac ctg aat ggg acc      581
Arg Arg Phe Val His Pro Gln Trp Gln Leu Leu His Leu Asn Gly Thr
     90                  95                 100

ttc ccc aac aca agt gac gca gac atg gag ccc tgt gtg gat ggc tgg      629
Phe Pro Asn Thr Ser Asp Ala Asp Met Glu Pro Cys Val Asp Gly Trp
105                 110                 115                 120

gtg tat gac aga atc tcc ttc tca tcc gcc atc gtg act gag tgg gat      677
Val Tyr Asp Arg Ile Ser Phe Ser Ser Ala Ile Val Thr Glu Trp Asp
                125                 130                 135

ctg gta tgt gac tct caa tca ctg act tca gtg gct aaa ttt gta ttc      725
Leu Val Cys Asp Ser Gln Ser Leu Thr Ser Val Ala Lys Phe Val Phe
            140                 145                 150

atg gct gga atg atg gtg gga ggc atc cta ggc ggt cat tta tca gac      773
Met Ala Gly Met Met Val Gly Gly Ile Leu Gly Gly His Leu Ser Asp
        155                 160                 165

agg ttt ggg aga agg ttc gtg ctc aga tgg tgt tac ctc cag gtt gcc      821
Arg Phe Gly Arg Arg Phe Val Leu Arg Trp Cys Tyr Leu Gln Val Ala
    170                 175                 180

att gtt ggc acc tgt gca gcc ttg gct ccc acc ttc ctc att tac tgc      869
Ile Val Gly Thr Cys Ala Ala Leu Ala Pro Thr Phe Leu Ile Tyr Cys
185                 190                 195                 200

tta cta cgc ttc ttg tct ggg att gct gca atg agc ctc ata aca aat      917
Leu Leu Arg Phe Leu Ser Gly Ile Ala Ala Met Ser Leu Ile Thr Asn
                205                 210                 215

act att atg tta ata gcc gag tgg gca aca cac aga ttc cag gcc atg      965
Thr Ile Met Leu Ile Ala Glu Trp Ala Thr His Arg Phe Gln Ala Met
            220                 225                 230

gga att aca ttg gga atg tgc cct tct ggt att gca ttt atg acc ctg     1013
Gly Ile Thr Leu Gly Met Cys Pro Ser Gly Ile Ala Phe Met Thr Leu
        235                 240                 245

gca ggc ctg gct ttt gcc att cga gac tgg cat atc ctc cag ctg gtg     1061
Ala Gly Leu Ala Phe Ala Ile Arg Asp Trp His Ile Leu Gln Leu Val
    250                 255                 260

gtg tct gta cca tac ttt gtg atc ttt ctg acc tca agt tgg ctg cta     1109
Val Ser Val Pro Tyr Phe Val Ile Phe Leu Thr Ser Ser Trp Leu Leu
265                 270                 275                 280

gag tct gct cgg tgg ctc att atc aac aat aaa cca gag gaa ggc tta     1157
Glu Ser Ala Arg Trp Leu Ile Ile Asn Asn Lys Pro Glu Glu Gly Leu
                285                 290                 295

aag gaa ctt aga aaa gct gca cac agg agt gga atg aag aat gcc aga     1205
Lys Glu Leu Arg Lys Ala Ala His Arg Ser Gly Met Lys Asn Ala Arg
            300                 305                 310

gac acc cta acc ctg gag att ttg aaa tcc acc atg aaa aaa gaa ctg     1253
Asp Thr Leu Thr Leu Glu Ile Leu Lys Ser Thr Met Lys Lys Glu Leu
        315                 320                 325

gag gca gca caa aaa aaa aaa acc ttc tct gtg tgaaatgctc cacatgccca   1306
Glu Ala Ala Gln Lys Lys Lys Thr Phe Ser Val
    330                 335

acatatgtaa aaggatctcc ctcctgtcct ttacgagatt tgcaaacttt atggcctatt   1366
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ttggccttaa tctccatgtc cagcatctgg ggaacaatgt tttcctgttg cagactctct   1426

ttggtgcagt catcctcctg gccaactgtg ttgcaccttg ggcactgaaa tacatgaacc   1486

gtcgagcaag ccagatgctt ctcatgttcc tactggcaat ctgccttctg gccatcatat   1546

ttgtgccaca agaaatgcag acgctgcgtg aggttttggc aacactgggc ttaggagcgt   1606

ctgctcttgc caataccctt gcttttgccc atggaaatga agtaattccc accataatca   1666

gggcaagagc tatggggatc aatgcaacct ttgctaatat agcaggagcc ctggctcccc   1726

tcatgatgat cctaagtgtg tattctccac ccctgccctg gatcatctat ggagtcttcc   1786

ccttcatctc tggctttgct ttcctcctcc ttcctgaaac caggaacaag cctctgtttg   1846

acaccatcca ggatgagaaa aatgagagaa aagaccccag agaaccaaag caagaggatc   1906

cgagagtgga agtgacgcag ttttaaggaa ttccaggagc tgactgccga tcaatgagcc   1966

agatgaaggg aacaatcagg actattccta gacactagca aaaaaaaaaa aaaaaaaaaa   2026

a                                                                   2027
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<210> SEQ ID NO 28
<211> LENGTH: 339
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

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Met Ala Phe Gln Asp Leu Leu Gly His Ala Gly Asp Leu Trp Arg Phe
 1               5                  10                  15

Gln Ile Leu Gln Thr Val Phe Leu Ser Ile Phe Ala Val Ala Thr Tyr
            20                  25                  30

Leu His Phe Met Leu Glu Asn Phe Thr Ala Phe Ile Pro Gly His Arg
        35                  40                  45

Cys Trp Val His Ile Leu Asp Asn Asp Thr Val Ser Asp Asn Asp Thr
    50                  55                  60

Gly Ala Leu Ser Gln Asp Ala Leu Leu Arg Ile Ser Thr Pro Leu Asp
65                  70                  75                  80

Ser Asn Met Arg Pro Glu Lys Cys Arg Arg Phe Val His Pro Gln Trp
                85                  90                  95

Gln Leu Leu His Leu Asn Gly Thr Phe Pro Asn Thr Ser Asp Ala Asp
            100                 105                 110

Met Glu Pro Cys Val Asp Gly Trp Val Tyr Asp Arg Ile Ser Phe Ser
        115                 120                 125

Ser Ala Ile Val Thr Glu Trp Asp Leu Val Cys Asp Ser Gln Ser Leu
    130                 135                 140

Thr Ser Val Ala Lys Phe Val Phe Met Ala Gly Met Met Val Gly Gly
145                 150                 155                 160

Ile Leu Gly Gly His Leu Ser Asp Arg Phe Gly Arg Arg Phe Val Leu
                165                 170                 175

Arg Trp Cys Tyr Leu Gln Val Ala Ile Val Gly Thr Cys Ala Ala Leu
            180                 185                 190

Ala Pro Thr Phe Leu Ile Tyr Cys Leu Leu Arg Phe Leu Ser Gly Ile
        195                 200                 205

Ala Ala Met Ser Leu Ile Thr Asn Thr Ile Met Leu Ile Ala Glu Trp
    210                 215                 220

Ala Thr His Arg Phe Gln Ala Met Gly Ile Thr Leu Gly Met Cys Pro
225                 230                 235                 240
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Ser Gly Ile Ala Phe Met Thr Leu Ala Gly Leu Ala Phe Ala Ile Arg
               245                 250                 255

Asp Trp His Ile Leu Gln Leu Val Val Ser Val Pro Tyr Phe Val Ile
           260                 265                 270

Phe Leu Thr Ser Ser Trp Leu Leu Glu Ser Ala Arg Trp Leu Ile Ile
       275                 280                 285

Asn Asn Lys Pro Glu Glu Gly Leu Lys Glu Leu Arg Lys Ala Ala His
   290                 295                 300

Arg Ser Gly Met Lys Asn Ala Arg Asp Thr Leu Thr Leu Glu Ile Leu
305                 310                 315                 320

Lys Ser Thr Met Lys Lys Glu Leu Glu Ala Ala Gln Lys Lys Lys Thr
               325                 330                 335

Phe Ser Val
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<210> SEQ ID NO 29
<211> LENGTH: 2389
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (204)...(1244)

<400> SEQUENCE: 29

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gggaaacagg aagtcgccca tcctcctcgc ccggcggcag ctgtccccga gcgggaggag     60

cccgaggggg cgcgagcccc gcatgaatca ttgtagtcaa tcattttcca gttctcagcc    120

gctcagttgt gatcaaggga cacgtggttt ccgaactgcc agctcagaat aggaaaataa    180

cttgggattt tatattggaa gac atg gat ctt gct gcc aac gag atc agc att    233
                         Met Asp Leu Ala Ala Asn Glu Ile Ser Ile
                          1               5                  10

tat gac aaa ctt tca gag act gtt gat ttg gtg aga cag acc ggc cat      281
Tyr Asp Lys Leu Ser Glu Thr Val Asp Leu Val Arg Gln Thr Gly His
                 15                  20                  25

cag tgt ggc atg tca gag aag gca att gaa aaa ttt atc aga cag ctg      329
Gln Cys Gly Met Ser Glu Lys Ala Ile Glu Lys Phe Ile Arg Gln Leu
             30                  35                  40

ctg gaa aag aat gaa cct cag aga ccc ccc ccg cag tat cct ctc ctt      377
Leu Glu Lys Asn Glu Pro Gln Arg Pro Pro Pro Gln Tyr Pro Leu Leu
         45                  50                  55

ata gtt gtg tat aag gtt ctc gca acc ttg gga tta atc ttg ctc act      425
Ile Val Val Tyr Lys Val Leu Ala Thr Leu Gly Leu Ile Leu Leu Thr
     60                  65                  70

gcc tac ttt gtg att caa cct ttc agc cca tta gca cct gag cca gtg      473
Ala Tyr Phe Val Ile Gln Pro Phe Ser Pro Leu Ala Pro Glu Pro Val
 75                  80                  85                  90

ctt tct gga gct cac acc tgg cgc tca ctc atc cat cac att agg ctg      521
Leu Ser Gly Ala His Thr Trp Arg Ser Leu Ile His His Ile Arg Leu
                 95                 100                 105

atg tcc ttg ccc att gcc aag aag tac atg tca gaa aat aag gga gtt      569
Met Ser Leu Pro Ile Ala Lys Lys Tyr Met Ser Glu Asn Lys Gly Val
            110                 115                 120

cct ctg cat ggg ggt gat gaa gac aga ccc ttt cca gac ttt gac ccc      617
Pro Leu His Gly Gly Asp Glu Asp Arg Pro Phe Pro Asp Phe Asp Pro
        125                 130                 135

tgg tgg aca gac gac tgt gag cag aat gag tca gag ccc att cct gcc      665
Trp Trp Thr Asp Asp Cys Glu Gln Asn Glu Ser Glu Pro Ile Pro Ala
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    140                 145                 150

aac tgc act ggc tgt gcc cag aaa cac ctg aag gtg atg ctc ctg gaa      713
Asn Cys Thr Gly Cys Ala Gln Lys His Leu Lys Val Met Leu Leu Glu
155                 160                 165                 170

gac gcc cca agg aaa ttt gag agg ctc cat cca ctg gtg atc aag acg      761
Asp Ala Pro Arg Lys Phe Glu Arg Leu His Pro Leu Val Ile Lys Thr
                175                 180                 185

gga aag ccc ctg ttg gag gag gag att cag cat ttt ttg tgc cag tac      809
Gly Lys Pro Leu Leu Glu Glu Glu Ile Gln His Phe Leu Cys Gln Tyr
            190                 195                 200

cct gag gcg aca gaa ggc ttc tct gaa ggg ttt ttc gcc aag tgg tgg      857
Pro Glu Ala Thr Glu Gly Phe Ser Glu Gly Phe Phe Ala Lys Trp Trp
        205                 210                 215

cgc tgc ttt cct gag cgg tgg ttc cca ttt cct tat cca tgg agg aga      905
Arg Cys Phe Pro Glu Arg Trp Phe Pro Phe Pro Tyr Pro Trp Arg Arg
    220                 225                 230

cct ctg aac aga tca caa atg tta cgt gag ctt ttt cct gtt ttc act      953
Pro Leu Asn Arg Ser Gln Met Leu Arg Glu Leu Phe Pro Val Phe Thr
235                 240                 245                 250

cac ctg cca ttt cca aaa gat gcc tct tta aac aag tgc tcc ttt ctt     1001
His Leu Pro Phe Pro Lys Asp Ala Ser Leu Asn Lys Cys Ser Phe Leu
                255                 260                 265

cac cca gaa cct gtt gtg ggg agt aag atg cat aag atg cct gac cta     1049
His Pro Glu Pro Val Val Gly Ser Lys Met His Lys Met Pro Asp Leu
            270                 275                 280

ttt atc att ggc agc ggt gag gcc atg ttg cag ctc atc cct ccc ttc     1097
Phe Ile Ile Gly Ser Gly Glu Ala Met Leu Gln Leu Ile Pro Pro Phe
        285                 290                 295

cag tgc cga aga cat tgt cag tct gtg gcc atg cca ata gag cca ggg     1145
Gln Cys Arg Arg His Cys Gln Ser Val Ala Met Pro Ile Glu Pro Gly
    300                 305                 310

gat atc ggc tat gtc gac act acc cac tgg aag gtc tac gtt ata gcc     1193
Asp Ile Gly Tyr Val Asp Thr Thr His Trp Lys Val Tyr Val Ile Ala
315                 320                 325                 330

aga ggg gtc cag cct ttg gtc atc tgc gat gga acc gct ttc tca gaa     1241
Arg Gly Val Gln Pro Leu Val Ile Cys Asp Gly Thr Ala Phe Ser Glu
                335                 340                 345

ctg taggaaatag aactgtgcac aggaacagct tccagagccg aaaaccaggt          1294
Leu

tgaaagggga aaaataaaaa caaaaacgat gaaactgctt tctgggggtt ggttacttag   1354

ttacctgccc tttgcatgca tgtgtgaacc agctgtgagc tgcagggcag tggccagagc   1414

ctcgccctcc tgactcttcc tgcaggtggc tcaggaagga ttcagcctgg ccacttggct   1474

aggactctgc cagcacccat ctgagactga cctcttccgg gcctttggac actatgacct   1534

tgatgctgcc cttcaggcag gaaacagggc tggtgccttt cttcacctgc atggccagct   1594

tccttccctg gcagtggaga gggcagccaa caggttctaa tgtcagagcc atcctttacc   1654

aggtgggcct gcttgtcccc gtcttgcctg ccacatcact ctacttttttg gaaggccatg   1714

gctgattaaa gaagttcttg tagtttccca agcaaagtgg aatctagaaa cagtgaaaaa   1774

agttcagata actttgaatt gcattcaaga agtacacttc tttcccattg tccgtggctc   1834

ttggagtctc cgtgatgcca ggctagagtc tgattatata ataattcaaa atggtaactc   1894

ccaaggtaat gctttcttcc atttcatcag gttcttttat ccccactgca ccccctcccc   1954

ttctcccttg cctatctgga tggcttctca gaagctcggc cctagtcctc cctgccttgg   2014
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cggggccaga gcccactact gctgaggcag cactgctctc gtcagctgtg ttgcctttac 2074

caagtgtctt cagagggtta tgagttagag tagctggcct ggggagaggg tgcctccctg 2134

ggtttgatct ttagggtctg actttctgca gagaagatgt tttacagatg tgtcaaagct 2194

gatgtaatgt ggttgggggga ggaaatccag acccaaagtg tttgtcagct gggtgtgcaa 2254

ctgcctatgt gatcctctgt cttaaaatga tttctgtctg tgctgcgaaa caaagacaag 2314

gtgaggtgtt tttctttttt gtaataatat aaagctgtgt gtttcaaaaa aaaaaaaaaa 2374

aaaaaaaaaa aaaaa 2389

<210> SEQ ID NO 30
<211> LENGTH: 347
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 30

Met Asp Leu Ala Ala Asn Glu Ile Ser Ile Tyr Asp Lys Leu Ser Glu
1 5 10 15

Thr Val Asp Leu Val Arg Gln Thr Gly His Gln Cys Gly Met Ser Glu
20 25 30

Lys Ala Ile Glu Lys Phe Ile Arg Gln Leu Leu Glu Lys Asn Glu Pro
35 40 45

Gln Arg Pro Pro Pro Gln Tyr Pro Leu Leu Ile Val Val Tyr Lys Val
50 55 60

Leu Ala Thr Leu Gly Leu Ile Leu Leu Thr Ala Tyr Phe Val Ile Gln
65 70 75 80

Pro Phe Ser Pro Leu Ala Pro Glu Pro Val Leu Ser Gly Ala His Thr
85 90 95

Trp Arg Ser Leu Ile His His Ile Arg Leu Met Ser Leu Pro Ile Ala
100 105 110

Lys Lys Tyr Met Ser Glu Asn Lys Gly Val Pro Leu His Gly Gly Asp
115 120 125

Glu Asp Arg Pro Phe Pro Asp Phe Asp Pro Trp Trp Thr Asp Asp Cys
130 135 140

Glu Gln Asn Glu Ser Glu Pro Ile Pro Ala Asn Cys Thr Gly Cys Ala
145 150 155 160

Gln Lys His Leu Lys Val Met Leu Leu Glu Asp Ala Pro Arg Lys Phe
165 170 175

Glu Arg Leu His Pro Leu Val Ile Lys Thr Gly Lys Pro Leu Leu Glu
180 185 190

Glu Glu Ile Gln His Phe Leu Cys Gln Tyr Pro Glu Ala Thr Glu Gly
195 200 205

Phe Ser Glu Gly Phe Phe Ala Lys Trp Trp Arg Cys Phe Pro Glu Arg
210 215 220

Trp Phe Pro Phe Pro Tyr Pro Trp Arg Arg Pro Leu Asn Arg Ser Gln
225 230 235 240

Met Leu Arg Glu Leu Phe Pro Val Phe Thr His Leu Pro Phe Pro Lys
245 250 255

Asp Ala Ser Leu Asn Lys Cys Ser Phe Leu His Pro Glu Pro Val Val
260 265 270

Gly Ser Lys Met His Lys Met Pro Asp Leu Phe Ile Ile Gly Ser Gly
275 280 285

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Glu Ala Met Leu Gln Leu Ile Pro Pro Phe Gln Cys Arg Arg His Cys
    290                 295                 300

Gln Ser Val Ala Met Pro Ile Glu Pro Gly Asp Ile Gly Tyr Val Asp
305                 310                 315                 320

Thr Thr His Trp Lys Val Tyr Val Ile Ala Arg Gly Val Gln Pro Leu
                325                 330                 335

Val Ile Cys Asp Gly Thr Ala Phe Ser Glu Leu
            340                 345
```

1. An isolated nucleic acid molecule comprising a polynucleotide selected from the group consisting of:

(a) a polynucleotide encoding amino acids from about 1 to about 325 of SEQ ID NO:2; about 1 to about 435 of SEQ ID NO:4; about 1 to about 339 of SEQ ID NO:6; about 1 to about 399 of SEQ ID NO:8; about 1 to about 709 of SEQ ID NO:10; about 1 to about 240 of SEQ ID NO:12; about 1 to about 613 of SEQ ID NO:14; about 1 to about 285 of SEQ ID NO:16; about 1 to about 483 of SEQ ID NO:18; about 1 to about 289 of SEQ ID NO:20; about 1 to about 585 of SEQ ID NO:22; about 1 to about 280 of SEQ ID NO:24; about 1 to about 286 of SEQ ID NO:26; about 1 to about 340 of SEQ ID NO:28; and about 1 to about 347 of SEQ ID NO:30;

(b) a polynucleotide encoding amino acids from about 2 to about 325 of SEQ ID NO:2; about 2 to about 435 of SEQ ID NO:4; about 2 to about 339 of SEQ ID NO:6; about 2 to about 399 of SEQ ID NO:8; about 2 to about 709 of SEQ ID NO:10; about 2 to about 240 of SEQ ID NO:12; about 2 to about 613 of SEQ ID NO:14; about 2 to about 285 of SEQ ID NO:16; about 2 to about 483 of SEQ ID NO:18; about 2 to about 289 of SEQ ID NO:20; about 2 to about 585 of SEQ ID NO:22; about 2 to about 280 of SEQ ID NO:24; about 2 to about 286 of SEQ ID NO:26; about 2 to about 340 of SEQ ID NO:28; and about 2 to about 347 of SEQ ID NO:30;

(c) a polynucleotide encoding amino acids from about 26 to about 273 of SEQ ID NO:2; about 25 to about 435 of SEQ ID NO:4; about 26 to about 339 of SEQ ID NO:6; about 20 to about 399 of SEQ ID NO:8; about 20 to about 240 of SEQ ID NO:12; about 24 to about 613 of SEQ ID NO:14; about 25 to about 285 of SEQ ID NO:16; about 21 to about 483 of SEQ ID NO:18; about 23 to about 289 of SEQ ID NO:20; about 14 to about 585 of SEQ ID NO:22; about 21 to about 280 of SEQ ID NO:24; about 27 to about 286 of SEQ ID NO:26; about 19 to about 340 of SEQ ID NO:28; and about 55 to about 347 of SEQ ID NO:30;

(d) the polynucleotide complement of the polynucleotide of (a), (b), or (c); and

(e) a polynucleotide at least 90% identical to the polynucleotide of (a), (b), (c), or (d).

2. An isolated nucleic acid molecule comprising at least 690 contiguous nucleotides from the coding region of any one of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27 and 29.

3. The isolated nucleic acid molecule of claim 2, which comprises at least 900 contiguous nucleotides from the coding region of any one of SEQ ID NO:1, 3, 5, 7, 9, 13, 17, 21, 27, and 29.

4. The isolated nucleic acid molecule of claim 3, which comprises at least 1200 contiguous nucleotides from the coding region of any one of SEQ ID NO:3, 9, 13, 17, and 21.

5. An isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide wherein, except for at least one conservative amino acid substitution, said polypeptide has an amino acid sequence selected from the group consisting of:

(a) amino acids from about 1 to about 325 of SEQ ID NO:2; about 1 to about 435 of SEQ ID NO:4; about 1 to about 339 of SEQ ID NO:6; about 1 to about 399 of SEQ ID NO:8; about 1 to about 709 of SEQ ID NO:10; about 1 to about 240 of SEQ ID NO:12; about 1 to about 613 of SEQ ID NO:14; about 1 to about 285 of SEQ ID NO:16; about 1 to about 483 of SEQ ID NO:18; about 1 to about 289 of SEQ ID NO:20; about 1 to about 585 of SEQ ID NO:22; about 1 to about 280 of SEQ ID NO:24; about 1 to about 286 of SEQ ID NO:26; about 1 to about 340 of SEQ ID NO:28; and about 1 to about 347 of SEQ ID NO:30;

(b) amino acids from about 2 to about 325 of SEQ ID NO:2; about 2 to about 435 of SEQ ID NO:4; about 2 to about 339 of SEQ ID NO:6; about 2 to about 399 of SEQ ID NO:8; about 2 to about 709 of SEQ ID NO:10; about 2 to about 240 of SEQ ID NO:12; about 2 to about 613 of SEQ ID NO:14; about 2 to about 285 of SEQ ID NO:16; about 2 to about 483 of SEQ ID NO:18; about 2 to about 289 of SEQ ID NO:20; about 2 to about 585 of SEQ ID NO:22; about 2 to about 280 of SEQ ID NO:24; about 2 to about 286 of SEQ ID NO:26; about 2 to about 340 of SEQ ID NO:28; and about 2 to about 347 of SEQ ID NO:30; and

(c) amino acids from about 26 to about 273 of SEQ ID NO:2; about 25 to about 435 of SEQ ID NO:4; about 26 to about 339 of SEQ ID NO:6; about 20 to about 399 of SEQ ID NO:8; about 20 to about 240 of SEQ ID NO:12; about 24 to about 613 of SEQ ID NO:14; about 25 to about 285 of SEQ ID NO:16; about 21 to about 483 of SEQ ID NO:18; about 23 to about 289 of SEQ ID NO:20; about 14 to about 585 of SEQ ID NO:22; about 21 to about 280 of SEQ ID NO:24; about 27 to about 286 of SEQ ID NO:26; about 19 to about 340 of SEQ ID NO:28; and about 55 to about 347 of SEQ ID NO:30.

6. The isolated nucleic acid molecule of claim 1, which is DNA.

7. A method of making a recombinant vector comprising inserting a nucleic acid molecule of claim 1 into a vector in operable linkage to a promoter.

8. A recombinant vector produced by the method of claim 7.

9. A method of making a recombinant host cell comprising introducing the recombinant vector of claim 8 into a host cell.

10. A recombinant host cell produced by the method of claim 9.

11. A recombinant method of producing a polypeptide, comprising culturing the recombinant host cell of claim 10 under conditions such that said polypeptide is expressed and recovering said polypeptide.

12. An isolated polypeptide comprising amino acids at least 95% identical to amino acids selected from the group consisting of:

(a) amino acids from about 1 to about 325 of SEQ ID NO:2; about 1 to about 435 of SEQ ID NO:4; about 1 to about 339 of SEQ ID NO:6; about 1 to about 399 of SEQ ID NO:8; about 1 to about 709 of SEQ ID NO:10; about 1 to about 240 of SEQ ID NO:12; about 1 to about 613 of SEQ ID NO:14; about 1 to about 285 of SEQ ID NO:16; about 1 to about 483 of SEQ ID NO:18; about 1 to about 289 of SEQ ID NO:20; about 1 to about 585 of SEQ ID NO:22; about 1 to about 280 of SEQ ID NO:24; about 1 to about 286 of SEQ ID NO:26; about 1 to about 340 of SEQ ID NO:28; and about 1 to about 347 of SEQ ID NO:30;

(b) amino acids from about 2 to about 325 of SEQ ID NO:2; about 2 to about 435 of SEQ ID NO:4; about 2 to about 339 of SEQ ID NO:6; about 2 to about 399 of SEQ ID NO:8; about 2 to about 709 of SEQ ID NO:10; about 2 to about 240 of SEQ ID NO:12; about 2 to about 613 of SEQ ID NO:14; about 2 to about 285 of SEQ ID NO:16; about 2 to about 483 of SEQ ID NO:18; about 2 to about 289 of SEQ ID NO:20; about 2 to about 585 of SEQ ID NO:22; about 2 to about 280 of SEQ ID NO:24; about 2 to about 286 of SEQ ID NO:26; about 2 to about 340 of SEQ ID NO:28; and about 2 to about 347 of SEQ ID NO:30; and

(c) amino acids from about 26 to about 273 of SEQ ID NO:2; about 25 to about 435 of SEQ ID NO:4; about 26 to about 339 of SEQ ID NO:6; about 20 to about 399 of SEQ ID NO:8; about 20 to about 240 of SEQ ID NO:12; about 24 to about 613 of SEQ ID NO:14; about 25 to about 285 of SEQ ID NO:16; about 21 to about 483 of SEQ ID NO:18; about 23 to about 289 of SEQ ID NO:20; about 14 to about 585 of SEQ ID NO:22; about 21 to about 280 of SEQ ID NO:24; about 27 to about 286 of SEQ ID NO:26; about 19 to about 340 of SEQ ID NO:28; and about 55 to about 347 of SEQ ID NO:30.

13. An isolated polypeptide wherein, except for at least one conservative amino acid substitution, said polypeptide has an amino acid sequence selected from the group consisting of:

(a) amino acids from about 1 to about 325 of SEQ ID NO:2; about 1 to about 435 of SEQ ID NO:4; about 1 to about 339 of SEQ ID NO:6; about 1 to about 399 of SEQ ID NO:8; about 1 to about 709 of SEQ ID NO:10; about 1 to about 240 of SEQ ID NO:12; about 1 to about 613 of SEQ ID NO:14; about 1 to about 285 of SEQ ID NO:16; about 1 to about 483 of SEQ ID NO:18; about 1 to about 289 of SEQ ID NO:20; about 1 to about 585 of SEQ ID NO:22; about 1 to about 280 of SEQ ID NO:24; about 1 to about 286 of SEQ ID NO:26; about 1 to about 340 of SEQ ID NO:28; and about 1 to about 347 of SEQ ID NO:30;

(b) amino acids from about 2 to about 325 of SEQ ID NO:2; about 2 to about 435 of SEQ ID NO:4; about 2 to about 339 of SEQ ID NO:6; about 2 to about 399 of SEQ ID NO:8; about 2 to about 709 of SEQ ID NO:10; about 2 to about 240 of SEQ ID NO:12; about 2 to about 613 of SEQ ID NO:14; about 2 to about 285 of SEQ ID NO:16; about 2 to about 483 of SEQ ID NO:18; about 2 to about 289 of SEQ ID NO:20; about 2 to about 585 of SEQ ID NO:22; about 2 to about 280 of SEQ ID NO:24; about 2 to about 286 of SEQ ID NO:26; about 2 to about 340 of SEQ ID NO:28; and about 2 to about 347 of SEQ ID NO:30; and

(c) amino acids from about 26 to about 273 of SEQ ID NO:2; about 25 to about 435 of SEQ ID NO:4; about 26 to about 339 of SEQ ID NO:6; about 20 to about 399 of SEQ ID NO:8; about 20 to about 240 of SEQ ID NO:12; about 24 to about 613 of SEQ ID NO:14; about 25 to about 285 of SEQ ID NO:16; about 21 to about 483 of SEQ ID NO:18; about 23 to about 289 of SEQ ID NO:20; about 14 to about 585 of SEQ ID NO:22; about 21 to about 280 of SEQ ID NO:24; about 27 to about 286 of SEQ ID NO:26; about 19 to about 340 of SEQ ID NO:28; and about 55 to about 347 of SEQ ID NO:30.

14. An isolated polypeptide comprising amino acids selected from the group consisting of:

(a) amino acids from about 1 to about 325 of SEQ ID NO:2; about 1 to about 435 of SEQ ID NO:4; about 1 to about 339 of SEQ ID NO:6; about 1 to about 399 of SEQ ID NO:8; about 1 to about 709 of SEQ ID NO:10; about 1 to about 240 of SEQ ID NO:12; about 1 to about 613 of SEQ ID NO:14; about 1 to about 285 of SEQ ID NO:16; about 1 to about 483 of SEQ ID NO:18; about 1 to about 289 of SEQ ID NO:20; about 1 to about 585 of SEQ ID NO:22; about 1 to about 280 of SEQ ID NO:24; about 1 to about 286 of SEQ ID NO:26; about 1 to about 340 of SEQ ID NO:28; and about 1 to about 347 of SEQ ID NO:30;

(b) amino acids from about 2 to about 325 of SEQ ID NO:2; about 2 to about 435 of SEQ ID NO:4; about 2 to about 339 of SEQ ID NO:6; about 2 to about 399 of SEQ ID NO:8; about 2 to about 709 of SEQ ID NO:10; about 2 to about 240 of SEQ ID NO:12; about 2 to about 613 of SEQ ID NO:14; about 2 to about 285 of SEQ ID NO:16; about 2 to about 483 of SEQ ID NO:18; about 2 to about 289 of SEQ ID NO:20; about 2 to about 585 of SEQ ID NO:22; about 2 to about 280 of SEQ ID NO:24; about 2 to about 286 of SEQ ID NO:26; about 2 to about 340 of SEQ ID NO:28; and about 2 to about 347 of SEQ ID NO:30; and

(c) amino acids from about 26 to about 273 of SEQ ID NO:2; about 25 to about 435 of SEQ ID NO:4; about 26 to about 339 of SEQ ID NO:6; about 20 to about 399

of SEQ ID NO:8; about 20 to about 240 of SEQ ID NO:12; about 24 to about 613 of SEQ ID NO:14; about 25 to about 285 of SEQ ID NO:16; about 21 to about 483 of SEQ ID NO:18; about 23 to about 289 of SEQ ID NO:20; about 14 to about 585 of SEQ ID NO:22; about 21 to about 280 of SEQ ID NO:24; about 27 to about 286 of SEQ ID NO:26; about 19 to about 340 of SEQ ID NO:28; and about 55 to about 347 of SEQ ID NO:30.

15. An epitope-bearing portion of the polypeptide of any one of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30.

16. The epitope-bearing portion of claim 15, which comprises about 8 to 25 contiguous amino acids of any one of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30.

17. The epitope-bearing portion of claim 15, which comprises about 10 to 15 contiguous amino acids of any one of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, and 30.

18. An isolated antibody that binds specifically to the polypeptide of claim 12.

19. An isolated antibody that binds specifically to a polypeptide of claim 13.

20. An isolated antibody that binds specifically to the polypeptide of claim 14.

21. An isolated nucleic acid molecule comprising a polynucleotide selected from the group consisting of:

(a) a polynucleotide encoding amino acids from about 1 to about 13 and about 34 to about 585 of SEQ ID NO:22, wherein said amino acids about 13 and about 34 are joined by a peptide bond;

(b) a polynucleotide encoding amino acids from about 1 to about 20 and about 180 to about 280 of SEQ ID NO:24, wherein said amino acids about 20 and about 180 are joined by a peptide bond;

(c) a polynucleotide encoding amino acids from about 1 to about 179 of SEQ ID NO:24;

(d) a polynucleotide encoding amino acids from about 21 to about 206 of SEQ ID NO:24;

(e) a polynucleotide encoding amino acids from about 1 to about 26 and about 61 to about 286 of SEQ ID NO:26, wherein said amino acids about 26 and about 61 are joined by a peptide bond;

(f) a polynucleotide encoding amino acids from about 27 to about 53 and about 257 to about 286 of SEQ ID NO:26, wherein said amino acids about 27 and about 257 are joined by a peptide bond;

(g) a polynucleotide encoding amino acids from about 1 to about 18 and about 144 to about 340 of SEQ ID NO:28, wherein said amino acids about 18 and about 144 are joined by a peptide bond;

22. A fusion protein comprising a first protein segment and a second protein segment fused together by means of a peptide bond, wherein the first protein segment consists of at least 8 contiguous amino acids of an amino acid sequence selected from the group consisting of the amino acid sequences shown in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30.

23. The fusion protein of claim 22 wherein the first protein segment consists of an amino acid sequence selected from the group consisting of amino acid sequence shown in SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30.

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专利名称(译)	分泌人类蛋白质		
公开(公告)号	US20040009950A1	公开(公告)日	2004-01-15
申请号	US10/458143	申请日	2003-06-09
[标]申请(专利权)人(译)	希龙公司		
申请(专利权)人(译)	Chiron公司		
当前申请(专利权)人(译)	Chiron公司		
[标]发明人	GARCIA PABLO D		
发明人	GARCIA, PABLO D.		
IPC分类号	G01N33/53 A61K31/7088 A61K38/00 A61P1/02 A61P7/04 A61P7/06 A61P17/02 A61P19/00 A61P19/02 A61P19/10 A61P21/00 A61P25/00 A61P25/14 A61P25/18 A61P25/28 A61P29/00 A61P41/00 A61P43/00 C07K14/47 C07K16/18 C07K19/00 C12N1/15 C12N1/19 C12N1/21 C12N5/10 C12N15/09 C12N15/12 C12N15/19 A61K48/00 A61K38/17 C12P21/02 C12N5/06 C07H21/04		
CPC分类号	C07K14/47 C07K2319/02 C07K2319/00 A61P1/02 A61P17/02 A61P19/00 A61P19/02 A61P19/10 A61P21/00 A61P25/00 A61P25/14 A61P25/18 A61P25/28 A61P29/00		
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摘要(译)

已经鉴定了15种分泌的人蛋白质和编码蛋白质的全长cDNA序列。这些蛋白质具有作为治疗剂的各种潜在用途，例如用于刺激接受癌症化疗的患者中的血细胞生成，用于治疗骨髓移植患者，以及用于治愈骨折的骨骼。蛋白质和cDNA序列尤其也可用于将其他蛋白质靶向膜或细胞外环境。