

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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
18 January 2001 (18.01.2001)

PCT

(10) International Publication Number
WO 01/04297 A2

(51) International Patent Classification⁷: **C12N 15/12**,
C07K 14/705, 14/47, 16/18, 16/28

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(21) International Application Number: PCT/JP00/03942

(22) International Filing Date: 16 June 2000 (16.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(30) Priority Data:
11/194359 8 July 1999 (08.07.1999) JP

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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Published:

— Without international search report and to be republished
upon receipt of that report.

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

(54) Title: HUMAN PROTEINS HAVING HYDROPHOBIC DOMAINS AND DNAs ENCODING THESE PROTEINS

(57) Abstract: The present invention provides human proteins having hydrophobic domains, DNAs encoding these proteins, expression vectors for these DNAs, transformed eukaryotic cells expressing these DNAs and antibodies directed to these proteins.

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DESCRIPTION

Human Proteins Having Hydrophobic
Domains and DNAs Encoding These Proteins

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TECHNICAL FIELD

The present invention relates to human proteins having hydrophobic domains, DNAs encoding these proteins, expression vectors for these DNAs, eukaryotic cells expressing these DNAs and antibodies directed to these proteins. The proteins of the present invention can be employed as pharmaceuticals or as antigens for preparing antibodies directed to these proteins. The human cDNAs of the present invention can be utilized as probes for genetic diagnosis and gene sources for gene therapy. Furthermore, the cDNAs can be utilized as gene sources for producing the proteins encoded by these cDNAs in large quantities. Cells into which these genes are introduced to express secretory proteins or membrane proteins in large quantities can be utilized for detection of the corresponding receptors or ligands, screening of novel small molecule pharmaceuticals and the like. The antibodies of the present invention can be utilized for the detection, quantification, purification and the like of the proteins of the present invention.

25

BACKGROUND ART

Cells secrete many proteins extracellularly. These secretory proteins play important roles in the proliferation control, the differentiation induction, the material transport, the biophylaxis, and the like of the cells. Unlike intracellular proteins, the secretory proteins exert their actions outside the cells. Therefore, they can be administered in the intracorporeal manner such as the injection or the drip, so that they possess hidden potentialities as pharmaceuticals. In fact, a number of human secretory proteins such as interferons, interleukins, erythropoietin, thrombolytic agents and the like are currently employed as pharmaceuticals. In addition, secretory proteins other than those described above are undergoing clinical trials for developing their use as pharmaceuticals. It is believed that the human cells produce many unknown secretory proteins. Availability of these secretory proteins as well as genes encoding them is expected to lead to development of novel pharmaceuticals utilizing them.

On the other hand, membrane proteins play important roles, as signal receptors, ion channels, transporters and the like in the material transport and the signal transduction through the cell membrane. Examples thereof include receptors for various cytokines, ion

channels for the sodium ion, the potassium ion, the chloride ion and the like, transporters for saccharides and amino acids and the like. The genes for many of them have already been cloned. It has been clarified that abnormalities in these membrane proteins are involved in a number of previously cryptogenic diseases. Therefore, discovery of a new membrane protein is expected to lead to elucidation of the causes of many diseases, so that isolation of new genes encoding the membrane proteins has been desired.

Heretofore, due to difficulty in the purification from human cells, many of these secretory proteins and membrane proteins have been isolated by genetic approaches. A general method is the so-called expression cloning method, in which a cDNA library is introduced into eukaryotic cells to express cDNAs, and the cells secreting, or expressing on the surface of membrane, the protein having the activity of interest are then screened. However, only genes for proteins with known functions can be cloned by using this method.

In general, a secretory protein or a membrane protein possesses at least one hydrophobic domain within the protein. After synthesis on ribosomes, such domain works as a secretory signal or remains in the phospholipid membrane to be entrapped in the membrane. Accordingly, if the existence of a highly hydrophobic domain is observed in the amino acid sequence of a protein encoded by a cDNA when the

whole base sequence of the full-length cDNA is determined, it is considered that the cDNA encodes a secretory protein or a membrane protein.

5 OBJECTS OF INVENTION

The main object of the present invention is to provide novel human proteins having hydrophobic domains, DNAs encoding these proteins, expression vectors for these DNAs, transformed eukaryotic cells that are capable of
10 expressing these DNAs and antibodies directed to these proteins. This object as well as other objects and advantages of the present invention will become apparent to those skilled in the art from the following description with reference to the accompanying drawings.

15

BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03394.

20 Fig. 2 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03395.

Fig. 3 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded
25 by clone HP10685.

Fig. 4 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10686.

Fig. 5 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10689.

Fig. 6 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10690.

Fig. 7 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10694.

Fig. 8 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10696.

Fig. 9 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10697.

Fig. 10 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10699.

SUMMARY OF INVENTION

As the result of intensive studies, the present inventors have successfully cloned cDNAs encoding proteins

having hydrophobic domains from the human full-length cDNA bank, thereby completing the present invention. Thus, the present invention provides a human protein having hydrophobic domain(s), namely a protein comprising any one of an amino acid sequence selected from the group consisting of SEQ ID NOS: 1 to 10. Moreover, the present invention provides a DNA encoding said protein, exemplified by a cDNA comprising any one of a base sequence selected from the group consisting of SEQ ID NOS: 11 to 30, an expression vector that is capable of expressing said DNA by in vitro translation or in eukaryotic cells, a transformed eukaryotic cell that is capable of expressing said DNA and of producing said protein and an antibody directed to said protein.

DETAILED DESCRIPTION OF THE INVENTION

The proteins of the present invention can be obtained, for example, by a method for isolating proteins from human organs, cell lines or the like, a method for preparing peptides by the chemical synthesis based on the amino acid sequence of the present invention, or a method for producing proteins by the recombinant DNA technology using the DNAs encoding the hydrophobic domains of the present invention. Among these, the method for producing proteins by the recombinant DNA technology is preferably employed. For example, the proteins can be expressed in

vitro by preparing an RNA by in vitro transcription from a vector having the cDNA of the present invention, and then carrying out in vitro translation using this RNA as a template. Alternatively, incorporation of the translated
5 region into a suitable expression vector by the method known in the art may lead to expression of a large amount of the encoded protein in prokaryotic cells such as *Escherichia coli*, *Bacillus subtilis*, etc., and eukaryotic cells such as yeasts, insect cells, mammalian cells, etc.

10 In the case where the protein of the present invention is produced by expressing the DNA by in vitro translation, the protein of the present invention can be produced in vitro by incorporating the translated region of this cDNA into a vector having an RNA polymerase promoter,
15 and then adding the vector to an in vitro translation system such as a rabbit reticulocyte lysate or a wheat germ extract, which contains an RNA polymerase corresponding to the promoter. The RNA polymerase promoters are exemplified by T7, T3, SP6 and the like. The vectors containing promoters for
20 these RNA polymerases are exemplified by pKA1, pCDM8, pT3/T7 18, pT7/3 19, pBluescript II and the like. Furthermore, the protein of the present invention can be expressed in the secreted form or the form incorporated in the microsome membrane when a canine pancreas microsome or the like is
25 added to the reaction system.

In the case where the protein of the present invention is produced by expressing the DNA in a microorganism such as *Escherichia coli* etc., a recombinant expression vector in which the translated region of the cDNA of the present invention is incorporated into an expression vector having an origin which is capable of replicating in the microorganism, a promoter, a ribosome-binding site, a cDNA-cloning site, a terminator and the like is constructed. After transformation of the host cells with this expression vector, the resulting transformant is grown, whereby the protein encoded by the cDNA can be produced in large quantities in the microorganism. In this case, a protein fragment containing any translated region can be obtained by adding an initiation codon and a termination codon in front of and behind the selected translated region to express the protein. Alternatively, the protein can be expressed as a fusion protein with another protein. Only the portion of the protein encoded by the cDNA can be obtained by cleaving this fusion protein with a suitable protease. The expression vectors for *Escherichia coli* are exemplified by the pUC series, pBluescript II, the pET expression system, the pGEX expression system and the like.

In the case where the protein of the present invention is produced by expressing the DNA in eukaryotic cells, the protein of the present invention can be produced

as a secretory protein, or as a membrane protein on the surface of cell membrane, by incorporating the translated region of the cDNA into an expression vector for eukaryotic cells that has a promoter, a splicing region, a poly(A) addition site and the like, and then introducing the vector into the eukaryotic cells. The expression vectors are exemplified by pKA1, pED6dpc2, pCDM8, pSVK3, pMSG, pSVL, pBK-CMV, pBK-RSV, EBV vectors, pRS, pYES2 and the like. Examples of eukaryotic cells to be used in general include mammalian cultured cells such as monkey kidney COS7 cells, Chinese hamster ovary CHO cells and the like, budding yeasts, fission yeasts, silkworm cells, Xenopus oocytes and the like. Any eukaryotic cells may be used as long as they are capable of expressing the proteins of the present invention. The expression vector can be introduced into the eukaryotic cells by using a method known in the art such as the electroporation method, the calcium phosphate method, the liposome method, the DEAE-dextran method and the like.

After the protein of the present invention is expressed in prokaryotic cells or eukaryotic cells, the protein of interest can be isolated and purified from the culture by a combination of separation procedures known in the art. Examples of the separation procedures include treatment with a denaturing agent such as urea or a detergent, sonication, enzymatic digestion, salting-out or

solvent precipitation, dialysis, centrifugation, ultrafiltration, gel filtration, SDS-PAGE, isoelectric focusing, ion-exchange chromatography, hydrophobic chromatography, affinity chromatography, reverse phase chromatography and the like.

The proteins of the present invention also include peptide fragments (of 5 amino acid residues or more) containing any partial amino acid sequences in the amino acid sequences represented by SEQ ID NOS: 1 to 10. These peptide fragments can be utilized as antigens for preparation of antibodies. Among the proteins of the present invention, those having the signal sequences are secreted in the form of mature proteins after the signal sequences are removed. Therefore, these mature proteins shall come within the scope of the protein of the present invention. The N-terminal amino acid sequences of the mature proteins can be easily determined by using the method for the determination of cleavage site of a signal sequence [JP-A 8-187100]. Furthermore, some membrane proteins undergo the processing on the cell surface to be converted to the secreted forms. Such proteins or peptides in the secreted forms shall also come within the scope of the protein of the present invention. In the case where sugar chain-binding sites are present in the amino acid sequences of the proteins, expression of the proteins in appropriate eukaryotic cells

affords the proteins to which sugar chains are added. Accordingly, such proteins or peptides to which sugar chains are added shall also come within the scope of the protein of the present invention.

5 The DNAs of the present invention include all the DNAs encoding the above-mentioned proteins. These DNAs can be obtained by using a method for chemical synthesis, a method for cDNA cloning and the like.

 The cDNAs of the present invention can be cloned,
10 for example, from cDNA libraries derived from the human cells. The cDNAs are synthesized by using poly(A)⁺ RNAs extracted from human cells as templates. The human cells may be cells delivered from the human body, for example, by the operation or may be the cultured cells. The cDNAs can be
15 synthesized by using any method such as the Okayama-Berg method [Okayama, H. and Berg, P., Mol. Cell. Biol. 2: 161-170 (1982)], the Gubler-Hoffman method [Gubler, U. and Hoffman, J., Gene 25: 263-269 (1983)] and the like. However, it is desirable to use the capping method [Kato, S. et al.,
20 Gene 150: 243-250 (1994)], as exemplified in Examples, in order to obtain a full-length clone in an effective manner. In addition, commercially available human cDNA libraries can be utilized. The cDNAs of the present invention can be cloned from the cDNA libraries by synthesizing an
25 oligonucleotide on the basis of base sequences of any

portion in the cDNA of the present invention and screening the cDNA libraries using this oligonucleotide as a probe for colony or plaque hybridization according to a method known in the art. In addition, the cDNA fragments of the present invention can be prepared from an mRNA isolated from human cells by the RT-PCR method in which oligonucleotides which hybridize with both termini of the cDNA fragment of interest are synthesized, which are then used as the primers.

The cDNAs of the present invention are characterized in that they comprise any one of the base sequences represented by SEQ ID NOS: 11 to 20 or the base sequences represented by SEQ ID NOS: 21 to 30. Table 1 summarizes the clone number (HP number), the cells from which the cDNA clone was obtained, the total number of bases of the cDNA, and the number of the amino acid residues of the encoded protein, for each of the cDNAs.

Table 1

SEQ ID NO	HP number	Cell	Number of bases	Number of amino acid residues
1, 11, 21	HP03394	Umbilical cord blood	2007	339
2, 12, 22	HP03395	Thymus	2264	487
3, 13, 23	HP10685	Umbilical cord blood	1907	262
4, 14, 24	HP10686	PMA-U937	1727	166
5, 15, 25	HP10689	Umbilical cord blood	2150	416
6, 16, 26	HP10690	Umbilical cord blood	1986	117
7, 17, 27	HP10694	Umbilical cord blood	2170	324
8, 18, 28	HP10696	Umbilical cord blood	1738	137
9, 19, 29	HP10697	Thymus	1930	311
10, 20, 30	HP10699	Umbilical cord blood	1892	543

The same clones as the cDNAs of the present invention can be easily obtained by screening the cDNA libraries constructed from the human cell lines or human tissues utilized in the present invention using an oligonucleotide probe synthesized on the basis of the base sequence of the cDNA provided in any one of SEQ ID NOS: 11 to 30.

In general, the polymorphism due to the individual differences is frequently observed in human genes. Accordingly, any cDNA in which one or plural nucleotides are added, deleted and/or substituted with other nucleotides in SEQ ID NOS: 11 to 30 shall come within the scope of the present invention.

Similarly, any protein in which one or plural

amino acids are added, deleted and/or substituted with other amino acids resulting from the above-mentioned changes shall come within the scope of the present invention, as long as the protein possesses the activity of the protein having any one of the amino acid sequences represented by SEQ ID NOS: 1 to 10.

The cDNAs of the present invention also include cDNA fragments (of 10 bp or more) containing any partial base sequence in the base sequences represented by SEQ ID NOS: 11 to 20 or in the base sequences represented by SEQ ID NOS: 21 to 30. Also, DNA fragments consisting of a sense strand and an anti-sense strand shall come within this scope. These DNA fragments can be utilized as the probes for the genetic diagnosis.

The antibody of the present invention can be obtained from a serum after immunizing an animal using the protein of the present invention as an antigen. A peptide that is chemically synthesized based on the amino acid sequence of the present invention and a protein expressed in eukaryotic or prokaryotic cells can be used as an antigen. Alternatively, an antibody can be prepared by introducing the above-mentioned expression vector for eukaryotic cells into the muscle or the skin of an animal by injection or by using a gene gun and then collecting a serum therefrom (JP-A 7-313187). Animals that can be used include a mouse, a rat,

a rabbit, a goat, a chicken and the like. A monoclonal antibody directed to the protein of the present invention can be produced by fusing B cells collected from the spleen of the immunized animal with myelomas to generate hybridomas.

5 In addition to the activities and uses described above, the polynucleotides and proteins of the present invention may exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for
10 proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

15 Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or
20 therapeutic use; 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); as molecular weight markers on Southern gels; as chromosome
25 markers or tags (when labeled) to identify chromosomes or to

map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive
5 PCR primers for genetic fingerprinting; as a probe 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, including for examination of expression patterns; to raise
10 anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction),
15 the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

20 The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled
25 reagent) in assays designed to quantitatively determine

levels of the protein (or its receptor) in biological fluids; 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 a disease state); and, of course, to isolate correlative 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.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may 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, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines

including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may,
5 among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene
10 Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; 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
15 133:327-341, 1991; Bertagnolli, et al., J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or
20 thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ ,
25 Schreiber, R.D. In Current Protocols in Immunology. J.E.e.a.

Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without
5 limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-
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15 Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement
20 of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens
25 (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, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; 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; Takai et al., J. Immunol. 140:508-512, 1988.

Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically,

infectious diseases caused by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitus, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down

regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign

by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (e.g., B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this manner prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used

include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function in vivo on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief

from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/lpr/lpr mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the

present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the in vitro activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to
5 isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would
10 now be capable of delivering a costimulatory signal to, and thereby activate, T cells in vivo.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor
15 immunity. Tumor cells (e.g., sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the
20 tumor cell can be transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected ex vivo with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-
25 1-like activity and/or B7-3-like activity. The transfected

tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection in vivo.

5 The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In
10 addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (e.g., a cytoplasmic-domain truncated portion) of an MHC class I α
15 chain protein and β_2 microglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of
20 a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be
25 cotransfected with a DNA encoding a peptide having the

activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome
5 tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described
10 in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al.,
15 Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-
20 2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowman et al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341,
25 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without
5 limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: In vitro antibody production, Mond, J.J. and Brunswick, M. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

10 Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W
15 Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et
20 al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without
limitation, those described in: Guery et al., J. Immunol.
25 134:536-544, 1995; Inaba et al., Journal of Experimental

Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al.,
5 Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

10 Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808,
15 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology
20 1:639-648, 1992.

 Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122,
25 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al.,

Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even
5 marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells
10 alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation
15 of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and
20 consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complementary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells
25 which are capable of maturing to any and all of the above-

mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either in-vivo or ex-vivo (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those

described in: Methylcellulose colony forming assays, Freshney, M.G. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 1-21, Wiley-Liss, Inc., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland, H.J. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may 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 induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may 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 may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the

present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to 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 for return in vivo to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or

sequestering agent as a carrier as is well known in the art.

The protein of the present invention may 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, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and

traumatic wounds and the like.

It is expected that a protein of the present invention may also exhibit activity for 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 comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may 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.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent

Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

5 Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

10 Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are
15 characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female
20 mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin- β group, may be
25 useful as a fertility inducing therapeutic, based upon the

ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

10 Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other

trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or
5 infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the
10 ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

15 The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce
20 the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E.
25 Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach,

W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; 5 Muller et al Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit 10 hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, 15 surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke)).

20 The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., 25 Thrombosis Res. 45:413-419, 1987; Humphrey et al.,

Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Receptor/Ligand Activity

A protein of the present invention may also
5 demonstrate activity as receptors, receptor ligands or
inhibitors or agonists of receptor/ligand interactions.
Examples of such receptors and ligands include, without
limitation, cytokine receptors and their ligands, receptor
kinases and their ligands, receptor phosphatases and their
10 ligands, receptors involved in cell-cell interactions and
their ligands (including without limitation, cellular
adhesion molecules (such as selectins, integrins and their
ligands) and receptor/ligand pairs involved in antigen
presentation, antigen recognition and development of
15 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 present invention (including,
without limitation, fragments of receptors and ligands) may
20 themselves be useful as inhibitors of receptor/ligand
interactions.

The activity of a protein of the invention may,
among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity
25 include without limitation those described in: Current

Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 5 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; Stitt et al., Cell 80:661-670, 1995.

10 Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell- 15 cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an 20 inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)),

ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over
5 production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Tumor Inhibition Activity

In addition to the activities described above for
10 immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor
15 precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or
20 cell types which promote tumor growth.

Other Activities

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing,

infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or cardiac cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an

antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

5 Examples

The present invention is specifically illustrated in more detail by the following Examples, but Examples are not intended to restrict the present invention. The basic procedures with regard to the recombinant DNA and the enzymatic reactions were carried out according to the literature ["Molecular Cloning. A Laboratory Manual", Cold Spring Harbor Laboratory, 1989]. Unless otherwise stated, restriction enzymes and various modifying enzymes to be used were those available from Takara Shuzo. The buffer compositions and the reaction conditions for each of the enzyme reactions were as described in the attached instructions. The cDNA synthesis was carried out according to the literature [Kato, S. et al., Gene 150: 243-250 (1994)].

20 (1) Selection of cDNAs Encoding Proteins Having Hydrophobic Domains

The cDNA libraries constructed from phorbol ester-stimulated histiocytic lymphoma cell line U937 (ATCC CRL 1593) mRNA, human thymus mRNA (Clontech) and human umbilical

cord blood mRNA were used as cDNA libraries.

Full-length cDNA clones were selected from the respective libraries and the whole base sequences thereof were determined to construct a homo-protein cDNA bank consisting of the full-length cDNA clones. The hydrophobicity/hydrophilicity profiles were determined for the proteins encoded by the full-length cDNA clones registered in the homo-protein cDNA bank by the Kyte-Doolittle method [Kyte, J. & Doolittle, R. F., J. Mol. Biol. 157: 105-132 (1982)] to examine the presence or absence of a hydrophobic domain. A clone that has a hydrophobic region being assumed as a secretory signal or a transmembrane domain in the amino acid sequence of the encoded protein was selected as a clone candidate.

(2) Protein Synthesis by In Vitro Translation

The plasmid vector bearing the cDNA of the present invention was used for in vitro transcription/translation with a T_NT rabbit reticulocyte lysate kit (Promega). In this case, [³⁵S]methionine was added to label the expression product with a radioisotope. Each of the reactions was carried out according to the protocols attached to the kit. Two micrograms of the plasmid was subjected to the reaction at 30°C for 90 minutes in the reaction solution of a total volume of 25 µl containing 12.5 µl µ of T_NT rabbit reticulocyte lysate, 0.5 µl of a buffer solution (attached

to the kit), 2 μ l of an amino acid mixture (without methionine), 2 μ l of [35 S]methionine (Amersham) (0.37 MBq/ μ l), 0.5 μ l of T7 RNA polymerase, and 20 U of RNasin. The experiment in the presence of a membrane system was carried out by adding 2.5 μ l of a canine pancreas microsome fraction (Promega) to the reaction system. To 3 μ l of the reaction solution was added 2 μ l of the SDS sampling buffer (125 mM Tris-hydrochloride buffer, pH 6.8, 120 mM 2-mercaptoethanol, 2% SDS solution, 0.025% bromophenol blue and 20% glycerol) and the resulting mixture was heated at 95°C for 3 minutes and then subjected to SDS-polyacrylamide gel electrophoresis. The molecular weight of the translation product was determined by carrying out the autoradiography.

(3) Expression in COS7

Escherichia coli cells harboring the expression vector for the protein of the present invention were cultured at 37°C for 2 hours in 2 ml of the 2 x YT culture medium containing 100 μ g/ml of ampicillin, the helper phage M13K07 (50 μ l) was added thereto, and the cells were then cultured at 37°C overnight. Single-stranded phage particles were obtained by polyethylene glycol precipitation from a supernatant separated by centrifugation. The particles were suspended in 100 μ l of 1 mM Tris-0.1 mM EDTA, pH 8 (TE).

The cultured cells derived from monkey kidney, COS7, were cultured at 37°C in the presence of 5% CO₂ in the

Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal calf serum. 1×10^5 COS7 cells were inoculated into a 6-well plate (Nunc, well diameter: 3 cm) and cultured at 37°C for 22 hours in the presence of 5% CO₂. After the medium was removed, the cell surface was washed with a phosphate buffer solution followed by DMEM containing 50 mM Tris-hydrochloride (pH 7.5) (TDMEM). A suspension containing 1 µl of the single-stranded phage suspension, 0.6 ml of the DMEM medium and 3 µl of TRANSFECTAM™ (IBF) was added to the cells and the cells were cultured at 37°C for 3 hours in the presence of 5% CO₂. After the sample solution was removed, the cell surface was washed with TDMEM, 2 ml per well of DMEM containing 10% fetal calf serum was added, and the cells were cultured at 37°C for 2 days in the presence of 5% CO₂. After the medium was exchanged for a medium containing [³⁵S]cysteine or [³⁵S]methionine, the cells were cultured for one hour. After the medium and the cells were separated each other by centrifugation, proteins in the medium fraction and the cell membrane fraction were subjected to SDS-PAGE.

(4) Preparation of Antibodies

A plasmid vector containing the cDNA of the present invention was dissolved in a phosphate buffer solution (PBS: 145 mM NaCl, 2.68 mM KCl, 8.09 mM Na₂HPO₄, 2 mM KH₂PO₄, pH 7.2) to a concentration of 2 µg/µl. 25 µl each (a total of 50 µl) of the thus-prepared plasmid solution in

PBS was injected into the right and left musculi quadriceps femoris of three mice (ICR line) using a 26 guage needle. After similar injections were repeated for one month at intervals of one week, blood was collected. The collected blood was stored at 4°C overnight to coagulate the blood, and then centrifuged at 8,000 x g for five minutes to obtain a supernatant. NaN₃ was added to the supernatant to a concentration of 0.01% and the mixture was then stored at 4°C. The generation of an antibody was confirmed by immunostaining of COS7 cells into which the corresponding vector had been introduced or by Western blotting using a cell lysate or a secreted product.

(5) Clone Examples

<HP03394> (SEQ ID NOS: 1, 11, and 21)

Determination of the whole base sequence of the cDNA insert of clone HP03394 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 45-bp 5'-untranslated region, a 1020-bp ORF, and a 942-bp 3'-untranslated region. The ORF encodes a protein consisting of 339 amino acid residues and there existed a putative secretory signal at the N-terminus and one putative transmembrane domain at the C-terminus. Figure 1 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product

of 42 kDa that was somewhat larger than the molecular weight of 36,856 predicted from the ORF. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature
 5 protein starts from glutamine at position 21.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to human monocyte inhibitory receptor (Accession No. AAB68665). Table 2 shows the comparison
 10 between amino acid sequences of the human protein of the present invention (HP) and human monocyte inhibitory receptor (MI). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue
 15 similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 46.2% in the N-terminal region of 236 amino acid residues.

Table 2

20

HP MSPSPTALFCLGLCLG-RVPAQSGPLPKPSLQALPSSLVPLEKPVTLRCQGP PGVDLYRL

* *. ***, ***, ** *. . *. ***, ** *. . . . ***, ***. .. ***

MI MIPTFTALLCLGLSLGPRTHMQAGPLPKPTLWAEPGSVISWGN SVTIWCQGTLEAREYRL

HP EK-LSSSRYQDQAVL-----F-IPAMKRSLAGRYRCSYQNGSLWSPDQLELVATGV

25

. * *. . . . * . * * **, *. . ***, ***. ** ***, ***, ***, **.

MI DKEESPAPWDRQNPLEPKNKARFSIPSMTEDYAGRYRCYYRSPVGWSQPSDPLELVM TGA
 HP FAKPSLSAQPGPAVSSGGDVTLCQTRYGFDQFALYKEGDPAPYKN--PER---WYRAS F
 ..**.* ** *. * *. ** . *** **.* . * * * * ** .. * . . *. . . *. *
 MI YSKPTLSALPSPLVTSGKSVTLLCQSRSPMDTFLLIKERAAHPLLHLRSEHGAQQHQAE F
 5 HP PIITVTAHSGTYRCYSFSSRDPYLWSAPSDPLELVVTGTSVTPSRLPTEPPSSVAEFSE
 *. .**.* *. *****. * . . ** * *****. *. *. .*. . ** . *..*
 MI PMSPTSVHGGTYRCFSSHGFSHYLLSHPSDPLELIVSGSLEGPRPSPTRSVSTAAGPED
 HP ATAELTVSFTNEVFTTETSR SITASP KESDSPAGPARQYYTKGNLVRICLGAVILIILAG
 10 MI QPLMPTGSVPHSGLRRHWEVLIGVLVVSILLLSLLL FLLLQHW RQGKHRTLAQRQADFQR
 HP FLAEDWHSRRKRLRHRGRAVQRPLPPLPPLPLTRKSHGGQDGG RQDVHSRGLCS
 MI PPGAAEPEPKDGG LQRRSSPAADVQGENFCAAVKNTQPEDGVEMDTRQSPHDEDPQAVTY

15

Furthermore, the search of the GenBank using the
 base sequences of the present cDNA has revealed the
 registration of sequences that shared a homology of 90% or
 more (for example, Accession No. AA308708) among ESTs.
 20 However, since they are partial sequences, it can not be
 judged whether or not they encode the same protein as the
 protein of the present invention.

<HP03395> (SEQ ID NOS: 2, 12, and 22)

Determination of the whole base sequence of the
 25 cDNA insert of clone HP03395 obtained from cDNA library of

human thymus revealed the structure consisting of a 84-bp 5'-untranslated region, a 1464-bp ORF, and a 716-bp 3'-untranslated region. The ORF encodes a protein consisting of 487 amino acid residues and there existed at least six putative transmembrane domains. Figure 2 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

10 The search of the protein data base using the amino acid sequence of the present protein revealed that the present protein had additional 106 amino acid residues at the N-terminus as compared with human putative protein C3f (Accession No. AAC36007).

15 Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA182534) among ESTs. However, since they are partial sequences, it can not be
20 judged whether or not they encode the same protein as the protein of the present invention.

<HP10685> (SEQ ID NOS: 3, 13, and 23)

Determination of the whole base sequence of the cDNA insert of clone HP10685 obtained from cDNA library of
25 human umbilical cord blood revealed the structure consisting

of a 34-bp 5'-untranslated region, a 789-bp ORF, and a 1084-bp 3'-untranslated region. The ORF encodes a protein consisting of 262 amino acid residues and there existed a putative secretory signal at the N-terminus and one putative transmembrane domain at the C-terminus. Figure 3 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 27 kDa that was almost identical with the molecular weight of 27,330 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 29 kDa. In addition, there exists in the amino acid sequence of this protein one site at which N-glycosylation may occur (Asn-Thr-Ser at position 182). Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from serine at position 28.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA448745) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10686> (SEQ ID NOS: 4, 14, and 24)

Determination of the whole base sequence of the cDNA insert of clone HP10686 obtained from cDNA library of human lymphoma cell line U937 revealed the structure consisting of a 19-bp 5'-untranslated region, a 501-bp ORF, and a 1207-bp 3'-untranslated region. The ORF encodes a protein consisting of 166 amino acid residues and there existed three putative transmembrane domains. Figure 4 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

10 The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AI275139) among ESTs. However, since they are partial sequences, it can not be judged whether or not they
15 encode the same protein as the protein of the present invention.

<HP10689> (SEQ ID NOS: 5, 15, and 25)

Determination of the whole base sequence of the cDNA insert of clone HP10689 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 31-bp 5'-untranslated region, a 1251-bp ORF, and a 868-bp 3'-untranslated region. The ORF encodes a protein consisting of 416 amino acid residues and there existed one putative transmembrane domain. Figure 5 depicts the
20 hydrophobicity/hydrophilicity profile, obtained by the Kyte-
25

Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 44 kDa that was somewhat smaller than the molecular weight of 46,451 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 48 kDa. In addition, there exist in the amino acid sequence of this protein two sites at which N-glycosylation may occur (Asn-Gly-Thr at position 160 and Asn-Met-Ser at position 196).

10 The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to *Arabidopsis thaliana* putative strictosidine synthase (Accession No. AAC27642). Table 3 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and *Arabidopsis thaliana* putative strictosidine synthase (AT). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 37.4% in the entire region other than the N-terminal region.

Table 3

HP MSEADGLRQRRPLRPQVVTTDDDGQAPEAKDGSSFSGRVFRVTFMLAVSLTVPLLGAAML

AT MMKLLLIVAT

HP LESPIDPQPLSFKEPPLLLGVLHPNTKLRQAERLFENQLVGPES--IAHIGDVMFTGTAD

5 .***** .. .** .** .*

AT SVALIFSVTDLSGEGPKHGGESMLTVQIPDFRLIPTTGALGPESFVDFDFGDPYTGLSD

HP GRVVK-LENGEI-----ETIARFG-SGPCKTRDDEPVCGRPLGIR-AGPNGTLFVADAY

.*. *.*.. . * ** **.*****. . .*.*.****

AT GRIVKWLANESRWIDFAVTTSAAREGCEGPHEHQRTHEHVCGRPLGLAFDKSTGDLYIADAY

10 HP KGLFEVNPWKREVKLLLSSETPIEGKNMSFVNDLTVTQDGRKIYFTDSSSKWQRRDYLLL

.**.*.* .. .*.* ..*.*.*.*. . .***** .***.*.

AT MGLLVGPTGGVANQVLPRE---LNEALRFTNSLDINPRTGVVYFTDSSSVYQRRNYIGA

HP VMEGTDDGRLLLEYDTVTREVKVLLDQLRFPNGVQLSPAEDFVLVAETTMARIRR-----V

.*. *...***.*. *.*.*.***.* * ***,**...*.**.*.* ** * .

15 AT MMSGDKTGRLMKYDN-TKQVTLLSNLAFVNGVALSQNGDYLLVVETAMCRILRYWLNET

HP YVSGLMKGGADLFVENMPGFPDNIRPSSSGGYWGMSTIRPNPGFSMLDFLSERPWIKRM

.. *..*****.*..**.***.* .. .* ...* .*

AT SVKSQSHDNYEIFAEGLPGFDPNKRSPRGGFVWGLNT---KHSKLTKFAMSNAWLGRA

HP IFKLFSQ-ETVMKFVPRY---SLVLELS-DSGAFRRSLHDPDGLVATYISEVHEHDGHLV

20 . * . . * . .** ** ***,. *****.*.*.*.

AT ALGLPVDWMKVHVSWAREYNGNGMAVRLSEDSGVILEVFEGKNENKWISEVEEKDGTW

HP LGSFRSPFLCRLSLQAV

.** ..**

AT VGSVNTPFAGMYKI

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AI750995) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10690> (SEQ ID NOS: 6, 16, and 26)

10 Determination of the whole base sequence of the cDNA insert of clone HP10690 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 27-bp 5'-untranslated region, a 354-bp ORF, and a 1605-bp 3'-untranslated region. The ORF encodes a protein
15 consisting of 117 amino acid residues and there existed one putative secretory signal at the N-terminus. Figure 6 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation
20 product of 15 kDa that was somewhat larger than the molecular weight of 12,647 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 14 kDa. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal
25 sequence, allows to expect that the mature protein starts

from aspartic acid at position 23.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA215334) among ESTs. However, since they are
5 partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10694> (SEQ ID NOS: 7, 17, and 27)

10 Determination of the whole base sequence of the cDNA insert of clone HP10694 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 240-bp 5'-untranslated region, a 975-bp ORF, and a 955-bp 3'-untranslated region. The ORF encodes a protein
15 consisting of 324 amino acid residues and there existed at least seven putative transmembrane domains. Figure 7 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product
20 of high molecular weight.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AI245647) among ESTs. However, since they are
25 partial sequences, it can not be judged whether or not they

encode the same protein as the protein of the present invention.

<HP10696> (SEQ ID NOS: 8, 18, and 28)

Determination of the whole base sequence of the
5 cDNA insert of clone HP10696 obtained from cDNA library of
human umbilical cord blood revealed the structure consisting
of a 94-bp 5'-untranslated region, a 414-bp ORF, and a 1230-
bp 3'-untranslated region. The ORF encodes a protein
consisting of 137 amino acid residues and there existed one
10 putative transmembrane domain at the N-terminus. Figure 8
depicts the hydrophobicity/hydrophilicity profile, obtained
by the Kyte-Doolittle method, of the present protein. In
vitro translation resulted in formation of a translation
product of 20 kDa that was somewhat larger than the
15 molecular weight of 14,492 predicted from the ORF.

The search of the GenBank using the base sequences
of the present cDNA has revealed the registration of
sequences that shared a homology of 90% or more (for example,
Accession No. D31289) among ESTs. However, since they are
20 partial sequences, it can not be judged whether or not they
encode the same protein as the protein of the present
invention.

<HP10697> (SEQ ID NOS: 9, 19, and 29)

Determination of the whole base sequence of the
25 cDNA insert of clone HP10697 obtained from cDNA library of

human thymus revealed the structure consisting of a 81-bp 5'-untranslated region, a 936-bp ORF, and a 913-bp 3'-untranslated region. The ORF encodes a protein consisting of 311 amino acid residues and there existed a putative secretory signal at the N-terminus and one putative transmembrane domain in the inner portion. Figure 9 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 37 kDa that was somewhat larger than the molecular weight of 33,901 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 51 kDa. In addition, there exist in the amino acid sequence of this protein six sites at which N-glycosylation may occur (Asn-Val-Thr at position 49, Asn-Leu-Thr at position 91, Asn-Thr-Ser at position 108, Asn-Phe-Ser at position 128, Asn-Leu-Thr at position 135 and Asn-Ile-Thr at position 190). Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from phenylalanine at position 33.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. W46202) among ESTs. However, since they are

partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10699> (SEQ ID NOS: 10, 20, and 30)

5 Determination of the whole base sequence of the cDNA insert of clone HP10699 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 4-bp 5'-untranslated region, a 1632-bp ORF, and a 256-bp 3'-untranslated region. The ORF encodes a protein
10 consisting of 543 amino acid residues and there existed at least six putative transmembrane domains. Figure 10 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product
15 of high molecular weight.

 The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to *Caenorhabditis elegans* hypothetical protein C15H9.5 (Accession No. AAB52667). Table 4 shows the
20 comparison between amino acid sequences of the human protein of the present invention (HP) and *Caenorhabditis elegans* hypothetical protein C15H9.5 (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an
25 amino acid residue similar to that of the protein of the

present invention, respectively. The both proteins shared a homology of 33.8% in the region of 461 amino acid residues other than the N-terminal and C-terminal regions.

5 Table 4

	HP	MAVSERRGLGRGSPAEWGQRLLLVLGGCSGRIHRLALTGEKRADIQLNSFGFYTNGLS
	CE	MIGNGNVIQADSRNIIISDFSYGNGTLSIAINNFTVPEKIKDSVDSTENADKL
10	HP	EVELSVLRLGLREAEKSLLVGFSLSRVRSGRVRSYSTRDFQDCPLQKNSSSFLVLFLIN
		..***** . *. *. *.**... ..*...
	CE	VSTTICPQVLCTYRFLQGVIGFSL-LGSSITRGVGNP-HVCQLQQTDDQGYDAIFFFA
	HP	TKDLQVQRKYGEQKTLFI-FPGLLPEAPSKPGL--PKPQATVPRKVDGGGSAAS-KPK
		. . *. * . . . * . * ***. . * . . * . . .
15	CE	DLP-NKQLRVYRSGIGRYIQICGTAHECQNTDAIRTPKPEELQPESSSGPVEQRGWFRNL
	HP	STPAVIQGPSGKDKDLVLGLSHLNNSYNFSFHVIGSQAE-EGQYSLNFHNC-NNSVPG-
		*.. . * . * ...*..** .. * ... *** . **** * ...*
	CE	FGRFLNPGAPQIAYDNYIPL-QVQENQFSTNMSIRFDGKIVGQYVFMFHNCYNRYAHGY
	HP	-KEHPFDITVMIREKNPDGFLSAAEMPLFKLYMVMSACFLAAGIFWVSILCR-NTYSVFK
20		. . *.** . *. * ...** ..*.. ..*..*** .*** *.
	CE	SDRAVDLTVDLVERNKHSYLSLQEIAPKPEIYLYMSILYFGLAVYWSHLLCRSSENIYR
	HP	IHWLMAALFTKSIISLLFHSINYYFINSQGHPIEGLAVMYIIAHLKGAALLFITIALIGS
		. * .**.*. * ..*..**..*****... * . * **.***.***.* **.*.***.
	CE	VHKFMAVLVFLKALSVFFHGLNYYFLSKYGMQKEIWAVLYYITHLLKGLLLFGTLILIGT
25	HP	GWAFIKYVLSDEKKVFGIVIPMQVLAVYIIIESREEGASDYVLWKEILFLVDLICCG

10

15

INDUSTRIAL APPLICABILITY

25

expressing these DNAs. Since all of the proteins of the present invention are secreted or exist in the cell membrane, they are considered to be proteins controlling the proliferation and/or the differentiation of the cells.

5 Accordingly, the proteins of the present invention can be employed as pharmaceuticals such as carcinostatic agents which act to control the proliferation and/or the differentiation of the cells, or as antigens for preparing antibodies against these proteins. The DNAs of the present
10 invention can be utilized as probes for the genetic diagnosis and gene sources for the gene therapy. Furthermore, the DNAs can be utilized for expressing these proteins in large quantities. Cells into which these genes are introduced to express these proteins can be utilized for
15 detection of the corresponding receptors or ligands, screening of novel small molecule pharmaceuticals and the like. The antibody of the present invention can be utilized for the detection, quantification, purification and the like of the protein of the present invention.

20 The present invention also provides genes corresponding to the polynucleotide sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs from which cDNA polynucleotide sequences are derived and may include
25 contiguous regions of the genome necessary for the regulated

expression of such genes. Corresponding genes may therefore include but are not limited to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements.

5 The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate
10 genomic libraries or other sources of genomic materials. An "isolated gene" is a gene that has been separated from the adjacent coding sequences, if any, present in the genome of the organism from which the gene was isolated.

Organisms that have enhanced, reduced, or modified
15 expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein are provided. The desired change in gene expression can be achieved through the use of antisense polynucleotides or ribozymes that bind and/or cleave the mRNA transcribed from the gene (Albert and
20 Morris, 1994, Trends Pharmacol. Sci. 15(7): 250-254; Lavarosky et al., 1997, Biochem. Mol. Med. 62(1): 11-22; and Hampel, 1998, Prog. Nucleic Acid Res. Mol. Biol. 58: 1-39; all of which are incorporated by reference herein). Transgenic animals that have multiple copies of the gene(s)
25 corresponding to the polynucleotide sequences disclosed

herein, preferably produced by transformation of cells with genetic constructs that are stably maintained within the transformed cells and their progeny, are provided. Transgenic animals that have modified genetic control regions that increase or reduce gene expression levels, or that change temporal or spatial patterns of gene expression, are also provided (see European Patent No. 0 649 464 B1, incorporated by reference herein). In addition, organisms are provided in which the gene(s) corresponding to the polynucleotide sequences disclosed herein have been partially or completely inactivated, through insertion of extraneous sequences into the corresponding gene(s) or through deletion of all or part of the corresponding gene(s). Partial or complete gene inactivation can be accomplished through insertion, preferably followed by imprecise excision, of transposable elements (Plasterk, 1992, Bioessays 14(9): 629-633; Zwaal et al., 1993, Proc. Natl. Acad. Sci. USA 90(16): 7431-7435; Clark et al., 1994, Proc. Natl. Acad. Sci. USA 91(2): 719-722; all of which are incorporated by reference herein), or through homologous recombination, preferably detected by positive/negative genetic selection strategies (Mansour et al., 1988, Nature 336: 348-352; U.S. Patent Nos. 5,464,764; 5,487,992; 5,627,059; 5,631,153; 5,614, 396; 5,616,491; and 5,679,523; all of which are incorporated by reference herein). These organisms with

altered gene expression are preferably eukaryotes and more preferably are mammals. Such organisms are useful for the development of non-human models for the study of disorders involving the corresponding gene(s), and for the development of assay systems for the identification of molecules that interact with the protein product(s) of the corresponding gene(s). Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize

overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any of the disclosed proteins.

Species homologs of the disclosed polynucleotides and proteins are also provided by the present invention. As used herein, a "species homologue" is a protein or polynucleotide with a different species of origin from that of a given protein or polynucleotide, but with significant sequence similarity to the given protein or polynucleotide, as determined by those of skill in the art. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous, or related to that encoded by the polynucleotides.

The invention also includes polynucleotides with

sequences complementary to those of the polynucleotides disclosed herein.

The present invention also includes polynucleotides capable of hybridizing under reduced stringency conditions, more preferably stringent conditions, and most preferably highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the table below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M-R.

Table 5

Stringency Condition	Poly-nucleotide Hybrid	Hybrid Length (bp) [†]	Hybridization Temperature and Buffer [†]	Wash Temperature and Buffer [†]
A	DNA : DNA	≥50	65°C; 1×SSC -or- 42°C; 1×SSC, 50% formamide	65°C; 0.3×SSC
B	DNA : DNA	<50	T _B *; 1×SSC	T _B *; 1×SSC
C	DNA : RNA	≥50	67°C; 1×SSC -or- 45°C; 1×SSC, 50% formamide	67°C; 0.3×SSC
D	DNA : RNA	<50	T _D *; 1×SSC	T _D *; 1×SSC
E	RNA : RNA	≥50	70°C; 1×SSC -or- 50°C; 1×SSC, 50% formamide	70°C; 0.3×SSC
F	RNA : RNA	<50	T _F *; 1×SSC	T _F *; 1×SSC
G	DNA : DNA	≥50	65°C; 4×SSC -or- 42°C; 4×SSC, 50% formamide	65°C; 1×SSC
H	DNA : DNA	<50	T _H *; 4×SSC	T _H *; 4×SSC
I	DNA : RNA	≥50	67°C; 4×SSC -or- 45°C; 4×SSC, 50% formamide	67°C; 1×SSC
J	DNA : RNA	<50	T _J *; 4×SSC	T _J *; 4×SSC
K	RNA : RNA	≥50	70°C; 4×SSC -or- 50°C; 4×SSC, 50% formamide	67°C; 1×SSC
L	RNA : RNA	<50	T _L *; 2×SSC	T _L *; 2×SSC
M	DNA : DNA	≥50	50°C; 4×SSC -or- 40°C; 6×SSC, 50% formamide	50°C; 2×SSC
N	DNA : DNA	<50	T _N *; 6×SSC	T _N *; 6×SSC
O	DNA : RNA	≥50	55°C; 4×SSC -or- 42°C; 6×SSC, 50% formamide	55°C; 2×SSC
P	DNA : RNA	<50	T _P *; 6×SSC	T _P *; 6×SSC
Q	RNA : RNA	≥50	60°C; 4×SSC -or- 45°C; 6×SSC, 50% formamide	60°C; 2×SSC
R	RNA : RNA	<50	T _R *; 4×SSC	T _R *; 4×SSC

‡ : The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

† : SSPE (1×SSPE is 0.15M NaCl, 10mM NaH₂PO₄, and 1.25mM EDTA, pH7.4) can be substituted for SSC (1×SSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

*T_B - T_R : The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, T_m(°C)=2(#of A + T bases) + 4(# of G + C bases). For hybrids between 18 and 49 base pairs in length, T_m(°C)=81.5 + 16.6(log₁₀[Na⁺]) + 0.41 (%G+C) - (600/N), where N is the number of bases in the hybrid, and [Na⁺] is the concentration of sodium ions in the hybridization buffer ([Na⁺] for 1×SSC=0.165M).

Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and Current Protocols in Molecular Biology, 1995, F.M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

10 Preferably, each such hybridizing polynucleotide has a length that is at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more
15 preferably, at least 75% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing polynucleotides when aligned so as to maximize overlap and
20 identity while minimizing sequence gaps.

CLAIMS

1. A protein comprising any one of an amino acid
sequence selected from the group consisting of SEQ ID NOS: 1
5 to 10.

2. An isolated DNA encoding the protein according to
Claim 1.

3. An isolated cDNA comprising any one of a base
sequence selected from the group consisting of SEQ ID NOS:
10 11 to 20.

4. The cDNA according to Claim 3 consisting of any
one of a base sequence selected from the group consisting of
SEQ ID NOS: 21 to 30.

5. An expression vector that is capable of expressing
15 the DNA according to any one of Claim 2 to Claim 4 by in
vitro translation or in eukaryotic cells.

6. A transformed eukaryotic cell that is capable of
expressing the DNA according to any one of Claim 2 to Claim
4 and of producing the protein according to Claim 1.

20 7. An antibody directed to the protein according to
Claim 1.

1/10

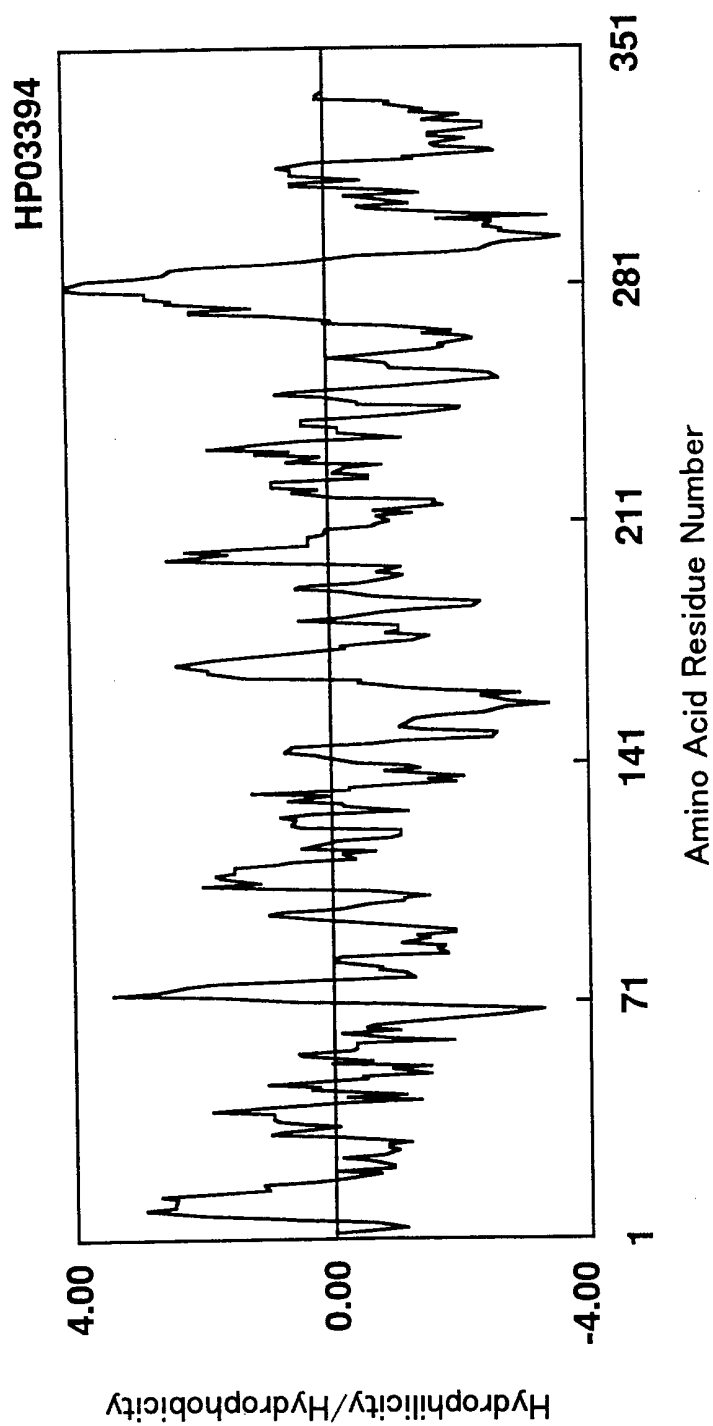


Fig.1

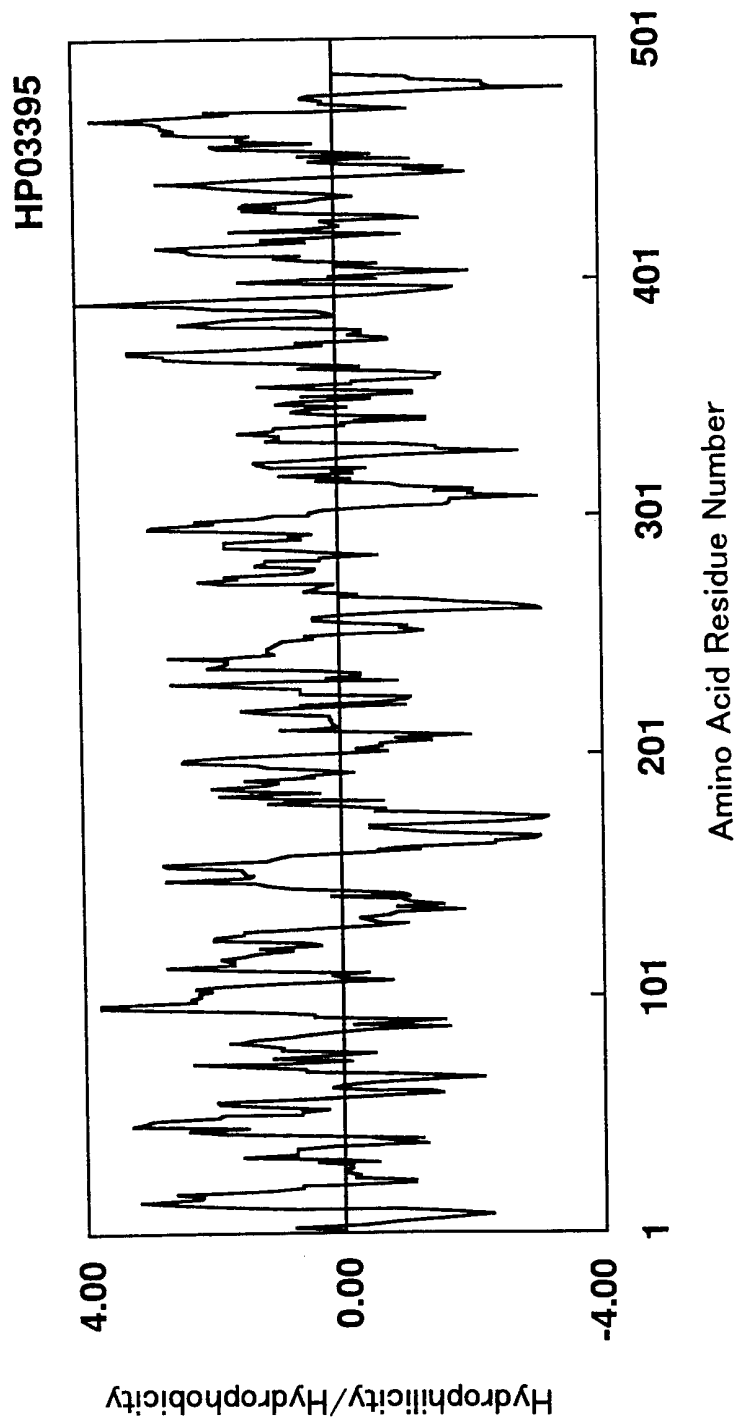


Fig.2

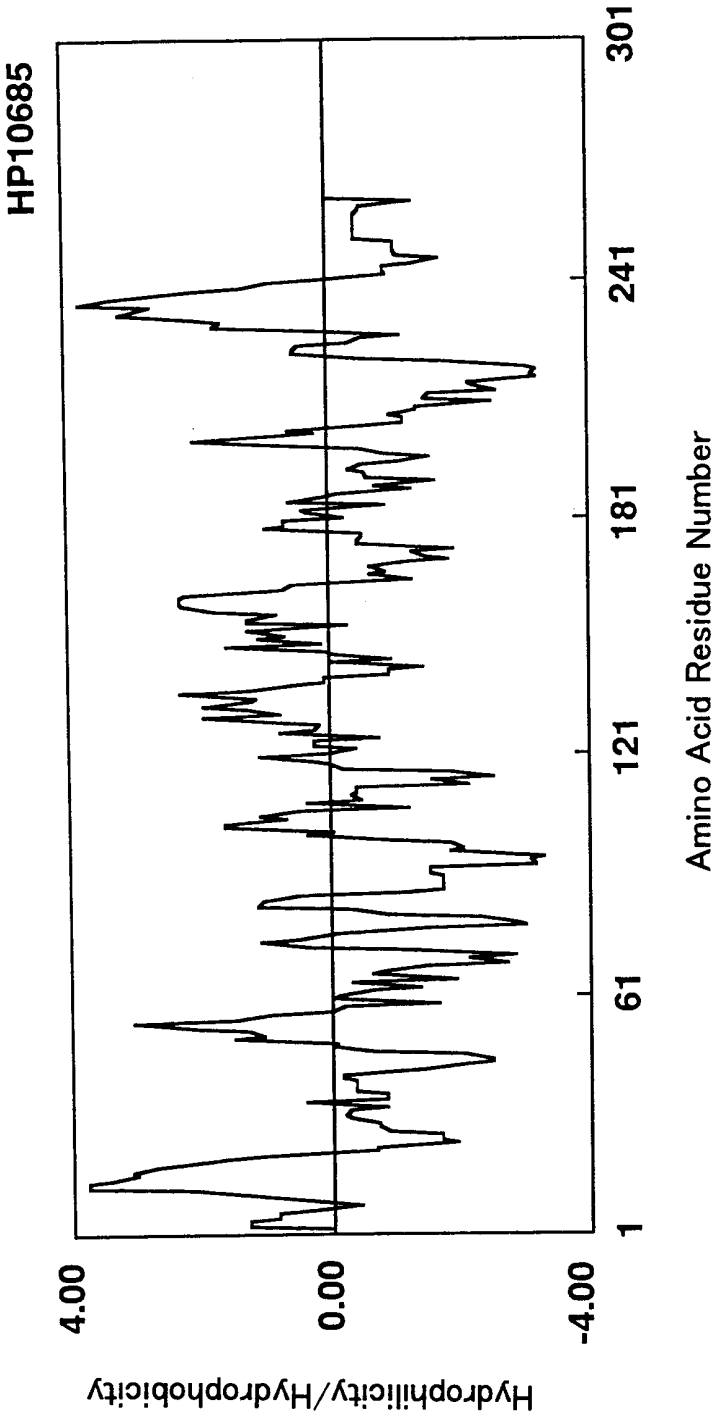


Fig.3

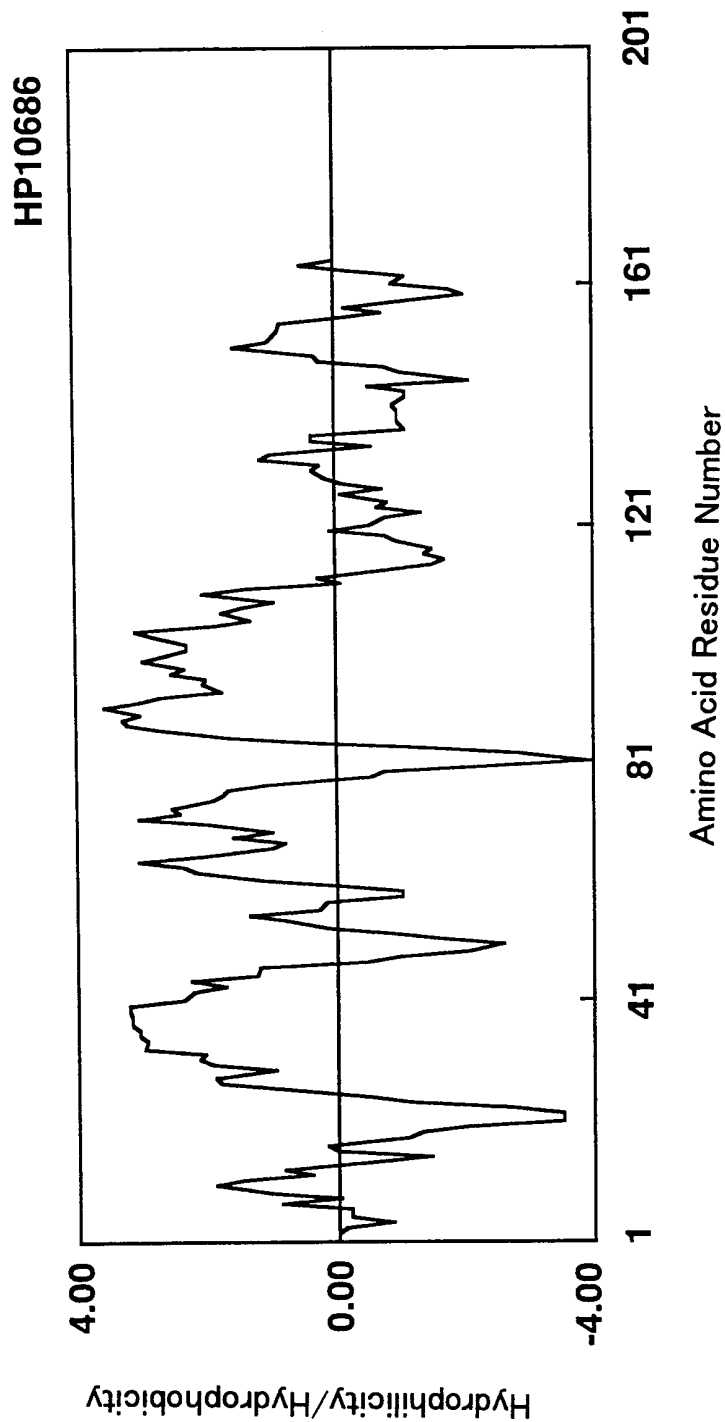


Fig.4

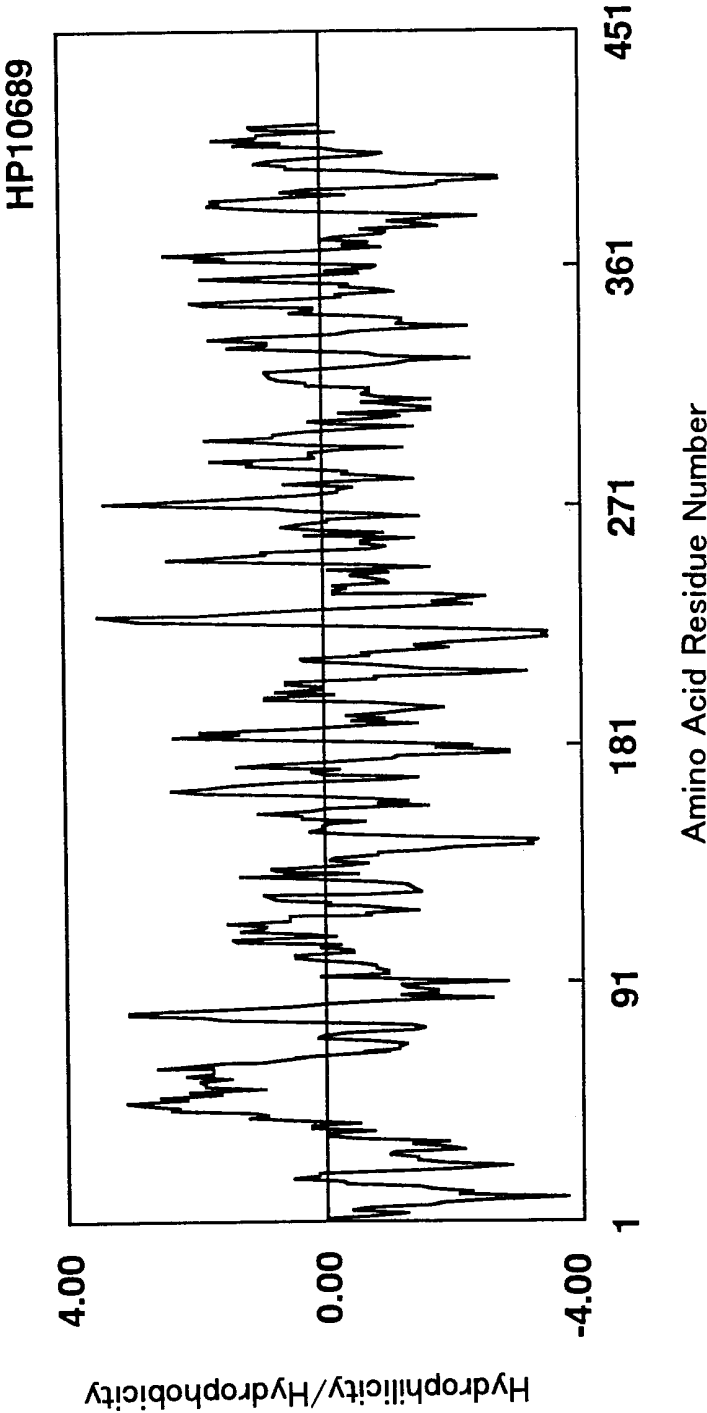


Fig.5

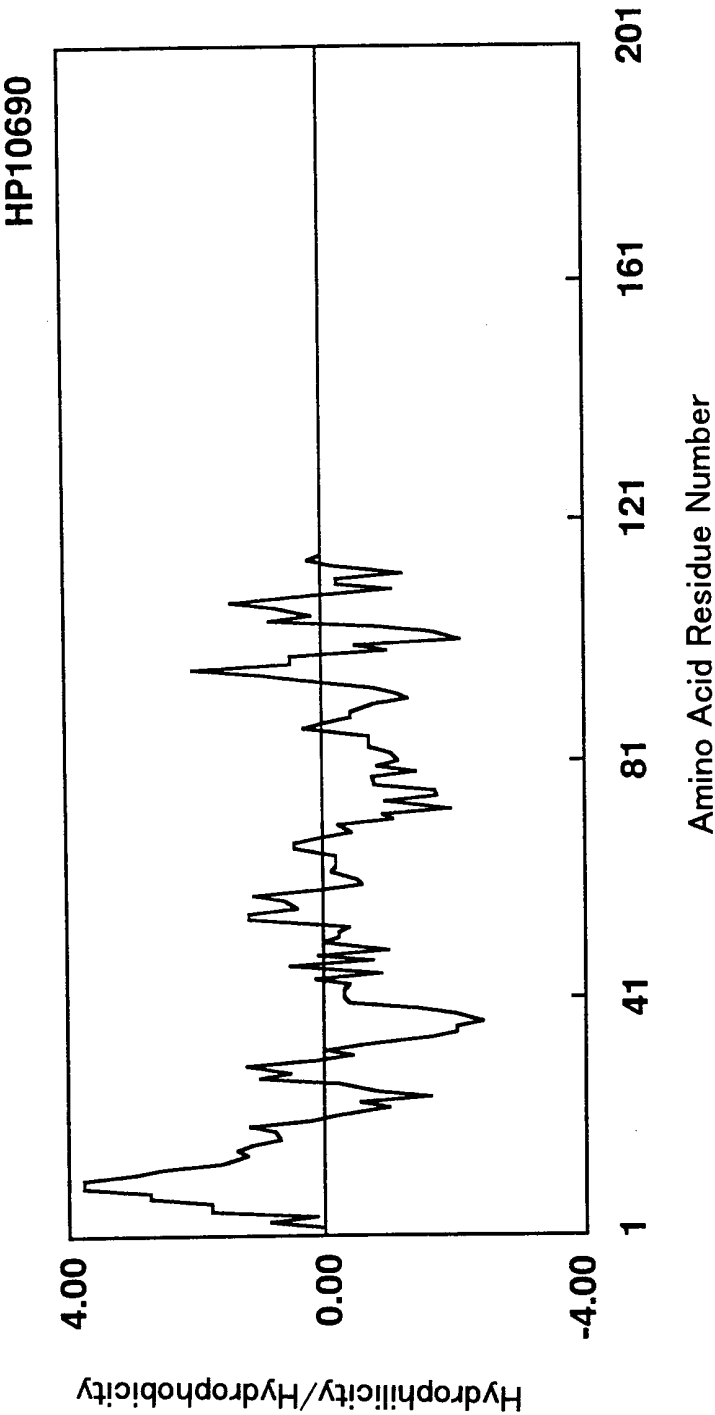


Fig.6

7/10

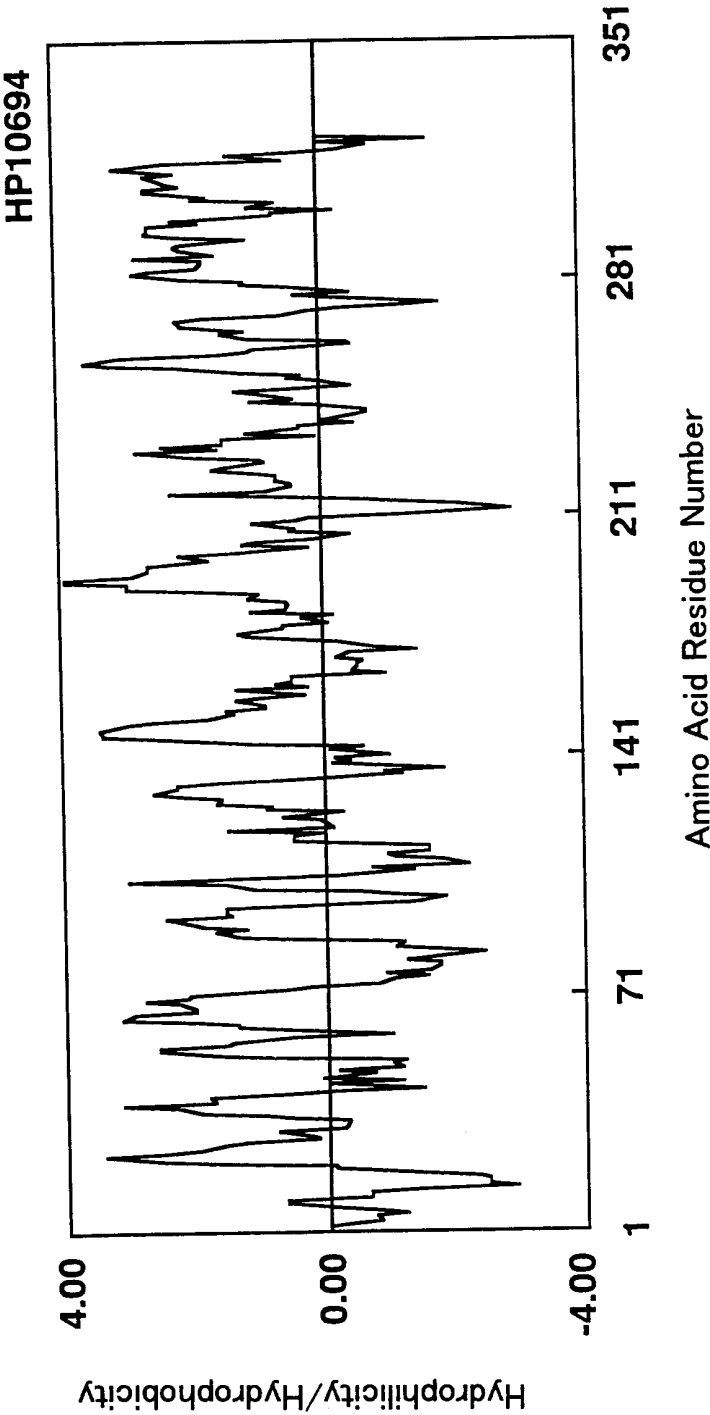


Fig.7

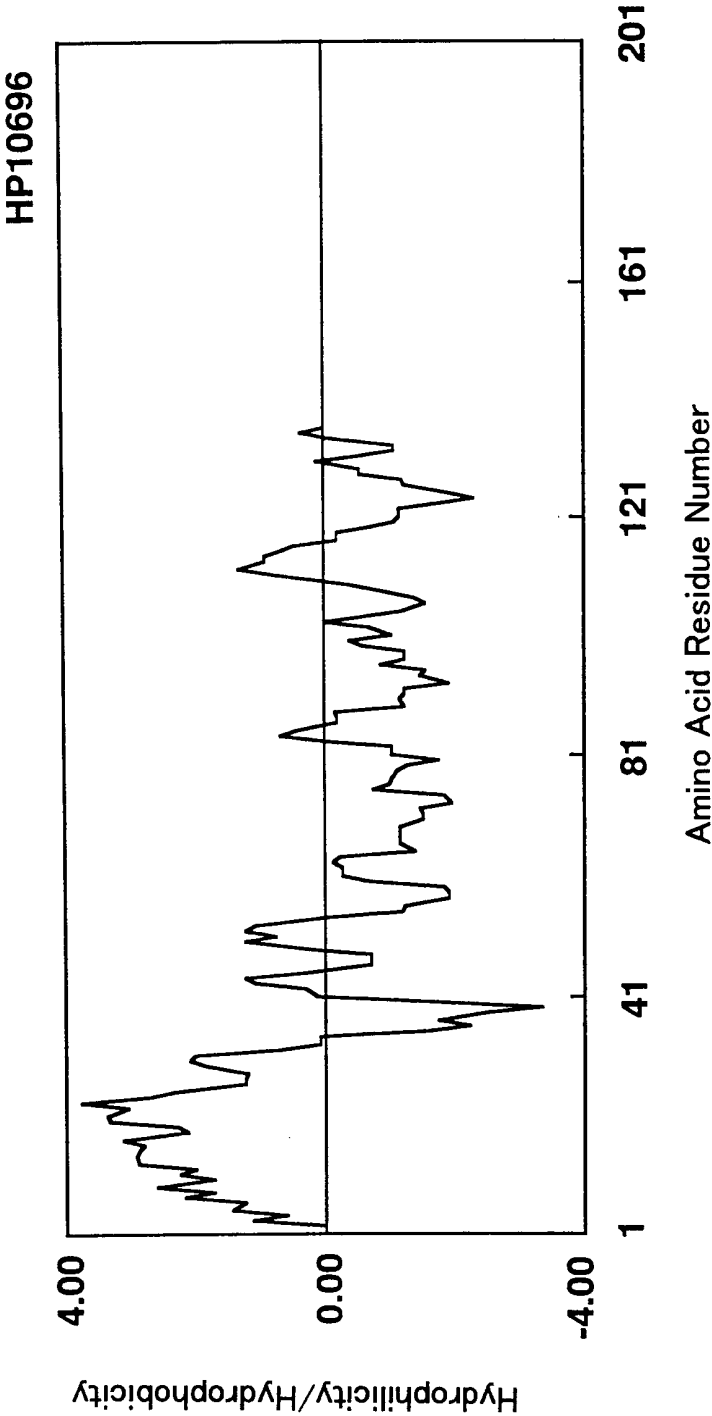


Fig.8

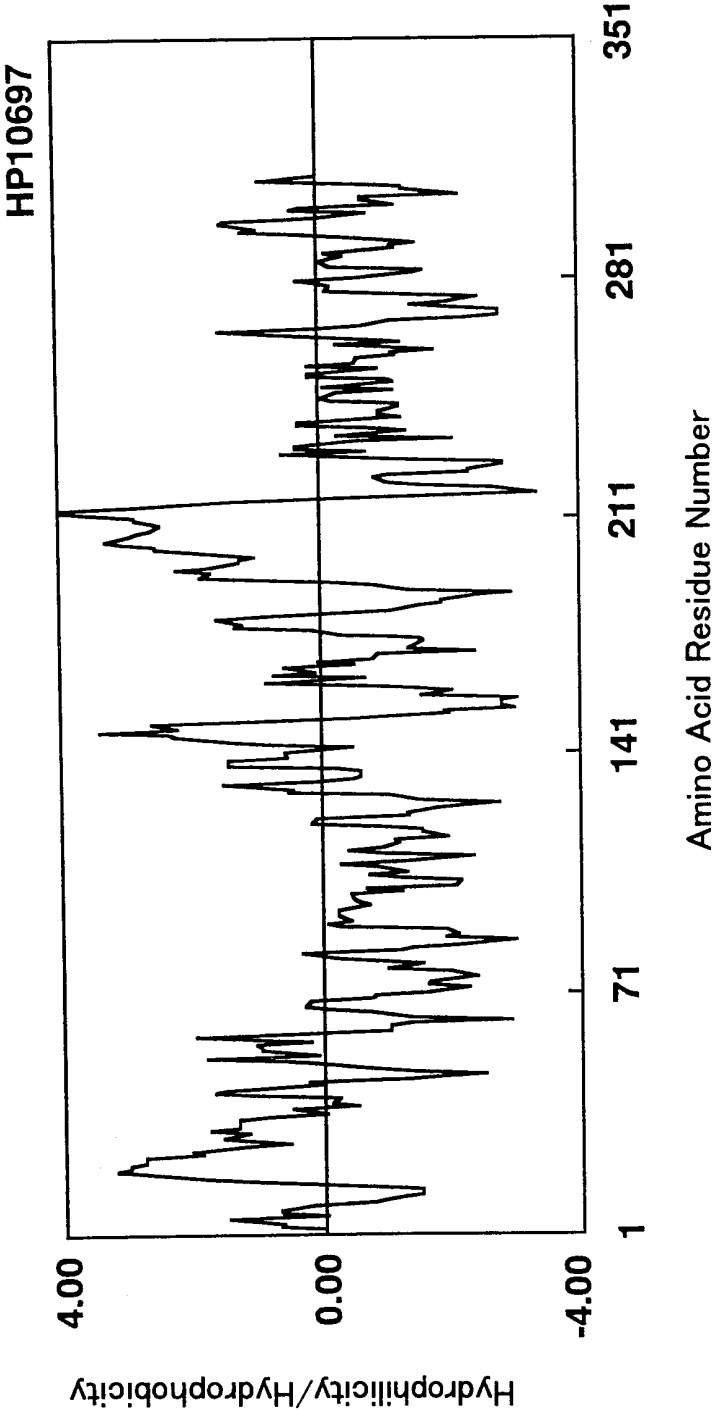


Fig.9

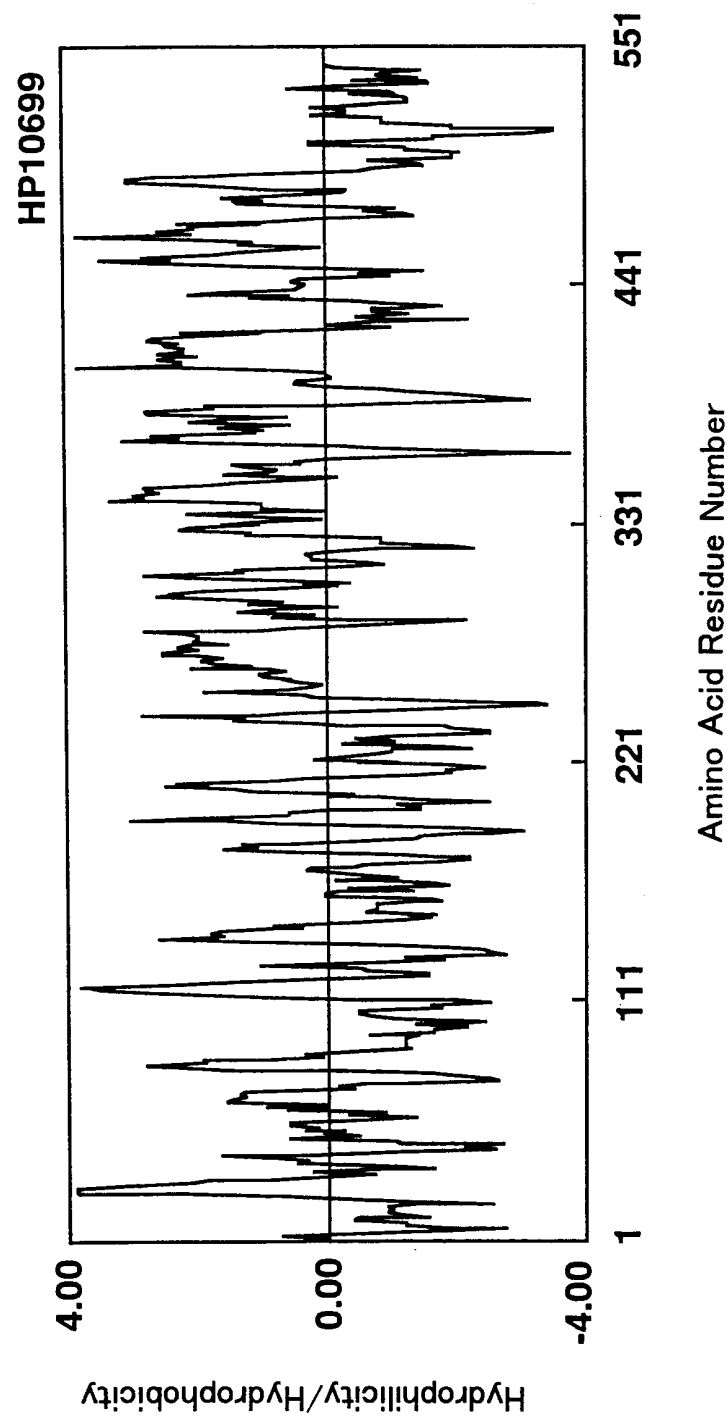


Fig.10

SEQUENCE LISTING

<110> Sagami Chemical Research Center,

Protegene Inc.

<120> Human proteins having hydrophobic domains and DNAs encoding these proteins

<130> 661926

<150> JP 11-194359

<151> 1999-07-08

<160> 30

<210> 1

<211> 339

<212> PRT

<213> Homo sapiens

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Met Ser Pro Ser Pro Thr Ala Leu Phe Cys Leu Gly Leu Cys Leu Gly

1

5

10

15

Arg Val Pro Ala Gln Ser Gly Pro Leu Pro Lys Pro Ser Leu Gln Ala

20

25

30

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

3

225 230 235 240
 Thr Glu Thr Ser Arg Ser Ile Thr Ala Ser Pro Lys Glu Ser Asp Ser
 245 250 255
 Pro Ala Gly Pro Ala Arg Gln Tyr Tyr Thr Lys Gly Asn Leu Val Arg
 260 265 270
 Ile Cys Leu Gly Ala Val Ile Leu Ile Ile Leu Ala Gly Phe Leu Ala
 275 280 285
 Glu Asp Trp His Ser Arg Arg Lys Arg Leu Arg His Arg Gly Arg Ala
 290 295 300
 Val Gln Arg Pro Leu Pro Pro Leu Pro Pro Leu Pro Leu Thr Arg Lys
 305 310 315 320
 Ser His Gly Gly Gln Asp Gly Gly Arg Gln Asp Val His Ser Arg Gly
 325 330 335
 Leu Cys Ser

<210> 2

<211> 487

<212> PRT

<213> Homo sapiens

<400> 2

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

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

420 425 430
 Gly Tyr Ser Met Thr Ala Phe Cys Leu Phe Thr Trp Asp Lys Trp Leu
 435 440 445
 Lys Val Tyr Lys Ser Ile Tyr Phe Leu Gly His Ile Phe Phe Leu Ser
 450 455 460
 Leu Leu Phe Ile Leu Pro Tyr Ile His Lys Ala Met Val Pro Arg Lys
 465 470 475 480
 Glu Lys Leu Lys Lys Met Glu
 485

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<211> 262

<212> PRT

<213> Homo sapiens

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 20 25 30
 Gly Thr Gly Ala Arg Gly Ala Gly Ala Glu Gly Arg Glu Gly Glu Ala
 35 40 45
 Cys Gly Thr Val Gly Leu Leu Leu Glu His Ser Phe Glu Ile Asp Asp
 50 55 60
 Ser Ala Asn Phe Arg Lys Arg Gly Ser Leu Leu Trp Asn Gln Gln Asp

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

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<211> 166

<212> PRT

<213> Homo sapiens

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Gly Leu Ser Arg Arg Lys Lys Thr Ser Leu Trp Phe Val Gly Ser Leu

20 25 30

Leu Leu Val Ser Val Leu Ile Val Thr Val Gly Leu Ala Ala Thr Thr

35 40 45

Arg Thr Glu Asn Val Thr Val Gly Gly Tyr Tyr Pro Gly Ile Ile Leu

50 55 60

Gly Phe Gly Ser Phe Leu Gly Ile Ile Gly Ile Asn Leu Val Glu Asn

65 70 75 80

Arg Arg Gln Met Leu Val Ala Ala Ile Val Phe Ile Ser Phe Gly Val

85 90 95

Val Ala Ala Phe Cys Cys Ala Ile Val Asp Gly Val Phe Ala Ala Gln

100 105 110

His Ile Glu Pro Arg Pro Leu Thr Thr Gly Arg Cys Gln Phe Tyr Ser

115 120 125

Ser Gly Val Gly Tyr Leu Tyr Asp Val Tyr Gln Thr Glu Val Ser Arg

130 135 140

Ser Thr Glu Ile His Val Gly Phe Ala Gln Leu Thr Pro Pro Thr Pro

145 150 155 160

Arg Gly Phe Pro Cys Thr

165

<210> 5

<211> 416

<212> PRT

<213> Homo sapiens

<400> 5

Met Ser Glu Ala Asp Gly Leu Arg Gln Arg Arg Pro Leu Arg Pro Gln

1 5 10 15

Val Val Thr Asp Asp Asp Gly Gln Ala Pro Glu Ala Lys Asp Gly Ser

20 25 30

Ser Phe Ser Gly Arg Val Phe Arg Val Thr Phe Leu Met Leu Ala Val

35 40 45

Ser Leu Thr Val Pro Leu Leu Gly Ala Met Met Leu Leu Glu Ser Pro

50 55 60

Ile Asp Pro Gln Pro Leu Ser Phe Lys Glu Pro Pro Leu Leu Leu Gly

65 70 75 80

Val Leu His Pro Asn Thr Lys Leu Arg Gln Ala Glu Arg Leu Phe Glu

85 90 95

Asn Gln Leu Val Gly Pro Glu Ser Ile Ala His Ile Gly Asp Val Met

100 105 110

Phe Thr Gly Thr Ala Asp Gly Arg Val Val Lys Leu Glu Asn Gly Glu
115 120 125

Ile Glu Thr Ile Ala Arg Phe Gly Ser Gly Pro Cys Lys Thr Arg Asp
130 135 140

Asp Glu Pro Val Cys Gly Arg Pro Leu Gly Ile Arg Ala Gly Pro Asn
145 150 155 160

Gly Thr Leu Phe Val Ala Asp Ala Tyr Lys Gly Leu Phe Glu Val Asn
165 170 175

Pro Trp Lys Arg Glu Val Lys Leu Leu Leu Ser Ser Glu Thr Pro Ile
180 185 190

Glu Gly Lys Asn Met Ser Phe Val Asn Asp Leu Thr Val Thr Gln Asp
195 200 205

Gly Arg Lys Ile Tyr Phe Thr Asp Ser Ser Ser Lys Trp Gln Arg Arg
210 215 220

Asp Tyr Leu Leu Leu Val Met Glu Gly Thr Asp Asp Gly Arg Leu Leu
225 230 235 240

Glu Tyr Asp Thr Val Thr Arg Glu Val Lys Val Leu Leu Asp Gln Leu
245 250 255

Arg Phe Pro Asn Gly Val Gln Leu Ser Pro Ala Glu Asp Phe Val Leu
260 265 270

Val Ala Glu Thr Thr Met Ala Arg Ile Arg Arg Val Tyr Val Ser Gly
275 280 285

Leu Met Lys Gly Gly Ala Asp Leu Phe Val Glu Asn Met Pro Gly Phe
290 295 300

Pro Asp Asn Ile Arg Pro Ser Ser Ser Gly Gly Tyr Trp Val Gly Met

11

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

<210> 6

<211> 117

<212> PRT

<213> Homo sapiens

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 1 5 10 15
 Ile Pro Gly Gly Leu Gly Asp Arg Ala Pro Leu Thr Ala Thr Ala Pro
 20 25 30
 Gln Leu Asp Asp Glu Glu Met Tyr Ser Ala His Met Pro Ala His Leu

12

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

<210> 7

<211> 324

<212> PRT

<213> Homo sapiens

<400> 7

Met Ser Val Glu Asp Gly Gly Met Pro Gly Leu Gly Arg Pro Arg Gln
 1 5 10 15
 Ala Arg Trp Thr Leu Met Leu Leu Leu Ser Thr Ala Met Tyr Gly Ala
 20 25 30
 His Ala Pro Leu Leu Ala Leu Cys His Val Asp Gly Arg Val Pro Phe
 35 40 45
 Arg Pro Ser Ser Ala Val Leu Leu Thr Glu Leu Thr Lys Leu Leu Leu

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

Val Leu Ser Gln Ala Leu Asn Gly Leu Leu Met Ser Ala Val Met Lys

260

265

270

His Gly Ser Ser Ile Thr Arg Leu Phe Val Val Ser Cys Ser Leu Val

275

280

285

Val Asn Ala Val Leu Ser Ala Val Leu Leu Arg Leu Gln Leu Thr Ala

290

295

300

Ala Phe Phe Leu Ala Thr Leu Leu Ile Gly Leu Ala Met Arg Leu Tyr

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310

315

320

Tyr Gly Ser Arg

<210> 8

<211> 137

<212> PRT

<213> Homo sapiens

<400> 8

Met Gly Phe Gly Ala Thr Leu Ala Val Gly Leu Thr Ile Phe Val Leu

1

5

10

15

Ser Val Val Thr Ile Ile Ile Cys Phe Thr Cys Ser Cys Cys Cys Leu

20

25

30

Tyr Lys Thr Cys Arg Arg Pro Arg Pro Val Val Thr Thr Thr Thr Ser

35

40

45

Thr Thr Val Val His Ala Pro Tyr Pro Gln Pro Pro Ser Val Pro Pro

50

55

60

Ser Tyr Pro Gly Pro Ser Tyr Gln Gly Tyr His Thr Met Pro Pro Gln

Met	Gly	Val	Pro	Thr	Ala	Leu	Glu	Ala	Gly	Ser	Trp	Arg	Trp	Gly	Ser
1				5					10					15	
Leu	Leu	Phe	Ala	Leu	Phe	Leu	Ala	Ala	Ser	Leu	Gly	Pro	Val	Ala	Ala
			20					25					30		
Phe	Lys	Val	Ala	Thr	Pro	Tyr	Ser	Leu	Tyr	Val	Cys	Pro	Glu	Gly	Gln
		35					40					45			
Asn	Val	Thr	Leu	Thr	Cys	Arg	Leu	Leu	Gly	Pro	Val	Asp	Lys	Gly	His
	50						55				60				
Asp	Val	Thr	Phe	Tyr	Lys	Thr	Trp	Tyr	Arg	Ser	Ser	Arg	Gly	Glu	Val

16

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

17

Glu Ser Gly Arg His Leu Leu Ser Glu Pro Ser Thr Pro Leu Ser Pro

275

280

285

Pro Gly Pro Gly Asp Val Phe Phe Pro Ser Leu Asp Pro Val Pro Asp

290

295

300

Ser Pro Asn Phe Glu Val Ile

305

310

<210> 10

<211> 543

<212> PRT

<213> Homo sapiens

<400> 10

Met Ala Val Ser Glu Arg Arg Gly Leu Gly Arg Gly Ser Pro Ala Glu

1

5

10

15

Trp Gly Gln Arg Leu Leu Leu Val Leu Leu Leu Gly Gly Cys Ser Gly

20

25

30

Arg Ile His Arg Leu Ala Leu Thr Gly Glu Lys Arg Ala Asp Ile Gln

35

40

45

Leu Asn Ser Phe Gly Phe Tyr Thr Asn Gly Ser Leu Glu Val Glu Leu

50

55

60

Ser Val Leu Arg Leu Gly Leu Arg Glu Ala Glu Glu Lys Ser Leu Leu

65

70

75

80

Val Gly Phe Ser Leu Ser Arg Val Arg Ser Gly Arg Val Arg Ser Tyr

85

90

95

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

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

Gln Pro Thr Gly Asn Asn Pro Tyr Leu Gln Leu Pro Gln Glu Asp Glu

500

505

510

Glu Asp Val Gln Met Glu Gln Val Met Thr Asp Ser Gly Phe Arg Glu

515

520

525

Gly Leu Ser Lys Val Asn Lys Thr Ala Ser Gly Arg Glu Leu Leu

530

535

540

<210> 11

<211> 1017

<212> DNA

<213> Homo sapiens

<400> 11

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<211> 498

<212> DNA

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<211> 1248

<212> DNA

<213> Homo sapiens

<400> 15

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<211> 351

<212> DNA

<213> Homo sapiens

<400> 16

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<211> 972

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<400> 17

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<212> DNA

<213> Homo sapiens

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<211> 933

<212> DNA

<213> Homo sapiens

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933

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<213> Homo sapiens

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Pro Gly Val Asp Leu Tyr Arg Leu Glu Lys Leu Ser Ser Ser Arg Tyr	
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10

15

20

25

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30

35

40

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Leu Arg Leu Ile Ile Ser Ile Phe Leu Gly Tyr Pro Phe Ala Leu Phe	
45 50 55	
tat cgg cat tac ctt ttc tac aag gag acc tac ctc atc cac ctc ttc	303
Tyr Arg His Tyr Leu Phe Tyr Lys Glu Thr Tyr Leu Ile His Leu Phe	
60 65 70	
cat acc ttt aca ggc ctc tca att gct tat ttt aac ttt gga aac cag	351
His Thr Phe Thr Gly Leu Ser Ile Ala Tyr Phe Asn Phe Gly Asn Gln	
75 80 85	
ctc tac cac tcc ctg ctg tgt att gtg ctt cag ttc ctc atc ctt cga	399
Leu Tyr His Ser Leu Leu Cys Ile Val Leu Gln Phe Leu Ile Leu Arg	
90 95 100 105	
cta atg ggc cgc acc atc act gcc gtc ctc act acc ttt tgc ttc cag	447
Leu Met Gly Arg Thr Ile Thr Ala Val Leu Thr Thr Phe Cys Phe Gln	
110 115 120	
atg gcc tac ctt ctg gct gga tac tat tac act gcc acc ggc aac tac	495
Met Ala Tyr Leu Leu Ala Gly Tyr Tyr Tyr Thr Ala Thr Gly Asn Tyr	
125 130 135	
gat atc aag tgg aca atg cca cat tgt gtt ctg act ttg aag ctg att	543
Asp Ile Lys Trp Thr Met Pro His Cys Val Leu Thr Leu Lys Leu Ile	
140 145 150	
ggt ttg gct gtt gac tac ttt gac gga ggg aaa gat cag aat tcc ttg	591
Gly Leu Ala Val Asp Tyr Phe Asp Gly Gly Lys Asp Gln Asn Ser Leu	
155 160 165	
tcc tct gag caa cag aaa tat gcc ata cgt ggt gtt cct tcc ctg ctg	639

Ser Ser Glu Gln Gln Lys Tyr Ala Ile Arg Gly Val Pro Ser Leu Leu
 170 175 180 185
 gaa gtt gct ggt ttc tcc tac ttc tat ggg gcc ttc ttg gta ggg ccc 687
 Glu Val Ala Gly Phe Ser Tyr Phe Tyr Gly Ala Phe Leu Val Gly Pro
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 cag ttc tca atg aat cac tac atg aag ctg gtg cag gga gag ctg att 735
 Gln Phe Ser Met Asn His Tyr Met Lys Leu Val Gln Gly Glu Leu Ile
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 Asp Ile Pro Gly Lys Ile Pro Asn Ser Ile Ile Pro Ala Leu Lys Arg
 220 225 230
 ctg agt ctg ggc ctt ttc tac cta gtg ggc tac aca ctg ctc agc ccc 831
 Leu Ser Leu Gly Leu Phe Tyr Leu Val Gly Tyr Thr Leu Leu Ser Pro
 235 240 245
 cac atc aca gaa gac tat ctc ctc act gaa gac tat gac aac cac ccc 879
 His Ile Thr Glu Asp Tyr Leu Leu Thr Glu Asp Tyr Asp Asn His Pro
 250 255 260 265
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 Phe Trp Phe Arg Cys Met Tyr Met Leu Ile Trp Gly Lys Phe Val Leu
 270 275 280
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 Tyr Lys Tyr Val Thr Cys Trp Leu Val Thr Glu Gly Val Cys Ile Leu
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 Thr Gly Leu Gly Phe Asn Gly Phe Glu Glu Lys Gly Lys Ala Lys Trp

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Asp Ala Cys Ala Asn Met Lys Val Trp Leu Phe Glu Thr Asn Pro Arg			
315	320	325	
ttc act ggc acc att gcc tca ttc aac atc aac acc aac gcc tgg gtg			1119
Phe Thr Gly Thr Ile Ala Ser Phe Asn Ile Asn Thr Asn Ala Trp Val			
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gcc cgc tac atc ttc aaa cga ctc aag ttc ctt gga aat aaa gaa ctc			1167
Ala Arg Tyr Ile Phe Lys Arg Leu Lys Phe Leu Gly Asn Lys Glu Leu			
350	355	360	
tct cag ggt ctc tcg ttg cta ttc ctg gcc ctc tgg cac ggc ctg cac			1215
Ser Gln Gly Leu Ser Leu Leu Phe Leu Ala Leu Trp His Gly Leu His			
365	370	375	
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Ser Gly Tyr Leu Val Cys Phe Gln Met Glu Phe Leu Ile Val Ile Val			
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Glu Arg Gln Ala Ala Arg Leu Ile Gln Glu Ser Pro Thr Leu Ser Lys			
395	400	405	
ctg gcc gcc att act gtc ctc cag ccc ttc tac tat ttg gtg caa cag			1359
Leu Ala Ala Ile Thr Val Leu Gln Pro Phe Tyr Tyr Leu Val Gln Gln			
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acc atc cac tgg ctc ttc atg ggt tac tcc atg act gcc ttc tgc ctc			1407
Thr Ile His Trp Leu Phe Met Gly Tyr Ser Met Thr Ala Phe Cys Leu			
430	435	440	

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<211> 1907

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<220>

<221> CDS

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Gly Ala Thr Arg Leu Leu Leu Leu Leu Met Ala Val Ala Ala Pro	
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agt cga gcc cgg ggc agc ggc tgc cgg gcc ggg act ggt gcg cga ggg	148
Ser Arg Ala Arg Gly Ser Gly Cys Arg Ala Gly Thr Gly Ala Arg Gly	
25 30 35	
gct ggg gcg gaa ggt cga gag ggc gag gcc tgt ggc acg gtg ggg ctg	196
Ala Gly Ala Glu Gly Arg Glu Gly Glu Ala Cys Gly Thr Val Gly Leu	
40 45 50	
ctg ctg gag cac tca ttt gag atc gat gac agt gcc aac ttc cgg aag	244
Leu Leu Glu His Ser Phe Glu Ile Asp Asp Ser Ala Asn Phe Arg Lys	
55 60 65 70	
cgg ggc tca ctg ctc tgg aac cag cag gat ggt acc ttg tcc ctg tca	292
Arg Gly Ser Leu Leu Trp Asn Gln Gln Asp Gly Thr Leu Ser Leu Ser	
75 80 85	

cag cgg cag ctc agc gag gag gag cgg ggc cga ctc cgg gat gtg gca	340
Gln Arg Gln Leu Ser Glu Glu Glu Arg Gly Arg Leu Arg Asp Val Ala	
90 95 100	
gcc ctg aat ggc ctg tac cgg gtc cgg atc cca agg cga ccc ggg gcc	388
Ala Leu Asn Gly Leu Tyr Arg Val Arg Ile Pro Arg Arg Pro Gly Ala	
105 110 115	
ctg gat ggc ctg gaa gct ggt ggc tat gtc tcc tcc ttt gtc cct gcg	436
Leu Asp Gly Leu Glu Ala Gly Gly Tyr Val Ser Ser Phe Val Pro Ala	
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tgc tcc ctg gtg gag tcg cac ctg tcg gac cag ctg acc ctg cac gtg	484
Cys Ser Leu Val Glu Ser His Leu Ser Asp Gln Leu Thr Leu His Val	
135 140 145 150	
gat gtg gcc ggc aac gtg gtg ggc gtg tcg gtg gtg acg cac ccc ggg	532
Asp Val Ala Gly Asn Val Val Gly Val Ser Val Val Thr His Pro Gly	
155 160 165	
ggc tgc cgg ggc cat gag gtg gag gac gtg gac ctg gag ctg ttc aac	580
Gly Cys Arg Gly His Glu Val Glu Asp Val Asp Leu Glu Leu Phe Asn	
170 175 180	
acc tcg gtg cag ctg cag ccg ccc acc aca gcc cca ggc cct gag acg	628
Thr Ser Val Gln Leu Gln Pro Pro Thr Thr Ala Pro Gly Pro Glu Thr	
185 190 195	
gcg gcc ttc att gag cgc ctg gag atg gaa cag gcc cag aag gcc aag	676
Ala Ala Phe Ile Glu Arg Leu Glu Met Glu Gln Ala Gln Lys Ala Lys	
200 205 210	
aac ccc cag gag cag aag tcc ttc ttc gcc aaa tac tgg atg tac atc	724

Asn	Pro	Gln	Gln	Lys	Ser	Phe	Phe	Ala	Lys	Tyr	Trp	Met	Tyr	Ile	
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Ile	Pro	Val	Val	Leu	Phe	Leu	Met	Met	Ser	Gly	Ala	Pro	Asp	Thr	Gly
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Gly	Gln	Gly	Gly	Gly	Gly	Gly	Gly	Gly	Gly	Gly	Gly	Gly	Ser	Gly	Arg
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tgattgaaat tcactgctca cttgatacgt tattcagaaa cccaaggaat ggctgtcccc															1840

41

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<211> 1727

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (20)... (520)

<400> 24

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 Leu Leu Asp Pro Ala Glu Gly Leu Ser Arg Arg Lys Lys Thr Ser Leu
 15 20 25
 tgg ttt gtg ggg tct ctg ctg ctg gtg tcc gtc ctc ata gtc acc gtc 145
 Trp Phe Val Gly Ser Leu Leu Leu Val Ser Val Leu Ile Val Thr Val
 30 35 40
 ggg ctg gct gcc acc acc agg acg gag aat gtg acc gtt ggg ggc tac 193
 Gly Leu Ala Ala Thr Thr Arg Thr Glu Asn Val Thr Val Gly Gly Tyr
 45 50 55

tac cca ggg atc att ctc ggc ttt gga tct ttc tta gga att att ggc	241
Tyr Pro Gly Ile Ile Leu Gly Phe Gly Ser Phe Leu Gly Ile Ile Gly	
60 65 70	
atc aac ttg gtg gag aat aga agg caa atg ctg gtg gca gcg atc gtg	289
Ile Asn Leu Val Glu Asn Arg Arg Gln Met Leu Val Ala Ala Ile Val	
75 80 85 90	
ttt atc agt ttt ggc gtg gtg gcc gcc ttc tgc tgc gcc atc gtg gac	337
Phe Ile Ser Phe Gly Val Val Ala Ala Phe Cys Cys Ala Ile Val Asp	
95 100 105	
ggc gta ttt gca gca cag cac att gaa ccg agg ccc ctc acc acg gga	385
Gly Val Phe Ala Ala Gln His Ile Glu Pro Arg Pro Leu Thr Thr Gly	
110 115 120	
aga tgc cag ttt tac tcc agt ggg gtg ggg tac ttg tac gat gtc tac	433
Arg Cys Gln Phe Tyr Ser Ser Gly Val Gly Tyr Leu Tyr Asp Val Tyr	
125 130 135	
cag aca gag gtg agc agg agc act gag att cat gtg ggt ttt gct cag	481
Gln Thr Glu Val Ser Arg Ser Thr Glu Ile His Val Gly Phe Ala Gln	
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Leu Thr Pro Pro Thr Pro Arg Gly Phe Pro Cys Thr	
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ccctgtgttt gggaccttga catttcgatg tgctgtattt cactctggag tcagagttct	650
ggacttgctt cattaaatca caacagtctc agagtgcacg tgtccagttc tgtatggctc	710
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<211> 2150

<212> DNA

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44

<400> 25

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Arg Gln Arg Arg Pro Leu Arg Pro Gln Val Val Thr Asp Asp Asp Gly

10 15 20

cag gcc ccg gag gct aag gac ggc agc tcc ttt agc ggc aga gtt ttc 148

Gln Ala Pro Glu Ala Lys Asp Gly Ser Ser Phe Ser Gly Arg Val Phe

25 30 35

cga gtg acc ttc ttg atg ctg gct gtt tct ctc acc gtt ccc ctg ctt 196

Arg Val Thr Phe Leu Met Leu Ala Val Ser Leu Thr Val Pro Leu Leu

40 45 50 55

gga gcc atg atg ctg ctg gaa tct cct ata gat cca cag cct ctc agc 244

Gly Ala Met Met Leu Leu Glu Ser Pro Ile Asp Pro Gln Pro Leu Ser

60 65 70

ttc aaa gaa ccc ccg ctc ttg ctt ggt gtt ctg cat cca aat acg aag 292

Phe Lys Glu Pro Pro Leu Leu Leu Gly Val Leu His Pro Asn Thr Lys

75 80 85

ctg cga cag gca gaa agg ctg ttt gaa aat caa ctt gtt gga ccg gag 340

Leu Arg Gln Ala Glu Arg Leu Phe Glu Asn Gln Leu Val Gly Pro Glu

90 95 100

tcc ata gca cat att ggg gat gtg atg ttt act ggg aca gca gat ggc 388

Ser Ile Ala His Ile Gly Asp Val Met Phe Thr Gly Thr Ala Asp Gly

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Arg Val Val Lys Leu Glu Asn Gly Glu Ile Glu Thr Ile Ala Arg Phe			
120	125	130	135
ggt tcg ggc cct tgc aaa acc cga gat gat gag cct gtg tgt ggg aga			484
Gly Ser Gly Pro Cys Lys Thr Arg Asp Asp Glu Pro Val Cys Gly Arg			
	140	145	150
ccc ctg ggt atc cgt gca ggg ccc aat ggg act ctc ttt gtg gcc gat			532
Pro Leu Gly Ile Arg Ala Gly Pro Asn Gly Thr Leu Phe Val Ala Asp			
	155	160	165
gca tac aag gga cta ttt gaa gta aat ccc tgg aaa cgt gaa gtg aaa			580
Ala Tyr Lys Gly Leu Phe Glu Val Asn Pro Trp Lys Arg Glu Val Lys			
	170	175	180
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Leu Leu Leu Ser Ser Glu Thr Pro Ile Glu Gly Lys Asn Met Ser Phe			
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gtg aat gat ctt aca gtc act cag gat ggg agg aag att tat ttc acc			676
Val Asn Asp Leu Thr Val Thr Gln Asp Gly Arg Lys Ile Tyr Phe Thr			
200	205	210	215
gat tct agc agc aaa tgg caa aga cga gac tac ctg ctt ctg gtg atg			724
Asp Ser Ser Ser Lys Trp Gln Arg Arg Asp Tyr Leu Leu Leu Val Met			
	220	225	230
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Glu Gly Thr Asp Asp Gly Arg Leu Leu Glu Tyr Asp Thr Val Thr Arg			
	235	240	245

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Arg Tyr Ser Leu Val Leu Glu Leu Ser Asp Ser Gly Ala Phe Arg Arg	
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agc ctg cat gat ccc gat ggg ctg gtg gcc acc tac atc agc gag gtg	1204

Ser Leu His Asp Pro Asp Gly Leu Val Ala Thr Tyr Ile Ser Glu Val
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His Glu His Asp Gly His Leu Tyr Leu Gly Ser Phe Arg Ser Pro Phe
395 400 405
ctc tgc aga ctc agc ctc cag gct gtt tagccctccc agatagctgc c 1300
Leu Cys Arg Leu Ser Leu Gln Ala Val
410 415
cctgccacgc aggccaggag tttcacact caggcaccag gcctggtcca ggaggagctg 1360
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<213> Homo sapiens

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<221> CDS

<222> (28)... (381)

<400> 26

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Leu Leu Leu Leu Gly Ala Trp Ala Ile Pro Gly Gly Leu Gly Asp Arg

10

15

20

gcg cca ctc aca gcc aca gcc cca caa ctg gat gat gag gag atg tac 147

Ala Pro Leu Thr Ala Thr Ala Pro Gln Leu Asp Asp Glu Glu Met Tyr

25

30

35

40

tca gcc cac atg ccc gct cac ctg cgc tgt gat gcc tgc aga gct gtg 195

Ser Ala His Met Pro Ala His Leu Arg Cys Asp Ala Cys Arg Ala Val

45

50

55

gct tac cag gtg agt cct tca cca ctg tca ccc tgc cct gct cac acc 243

Ala Tyr Gln Val Ser Pro Ser Pro Leu Ser Pro Cys Pro Ala His Thr

60

65

70

cct tct caa gcc aga ccc ctc cac cca cct cac att cca cca ccg gcc 291

Pro Ser Gln Ala Arg Pro Leu His Pro Pro His Ile Pro Pro Pro Ala
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Phe Asp Pro Gln Ser Leu Pro Leu Gly Ile Lys Pro Gln Met Gln Pro
90 95 100
ttc ata tat tcc atg cct cag ttt acc cat ctg cct gcc ta 380
Phe Ile Tyr Ser Met Pro Gln Phe Thr His Leu Pro Ala
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 gtattctctc tggcaatgtt ccacggttc tcttctctgg gagctggctc cataacttga 180
 ttttcccaa acgtgttgca atccctgctg ccccttagcc acccagggtc ttgtgtgggt 240

atg agt gta gag gat ggg ggt atg cca ggc ctg ggc cgt ccc agg cag	288
Met Ser Val Glu Asp Gly Gly Met Pro Gly Leu Gly Arg Pro Arg Gln	
1 5 10 15	
gcc cgc tgg acc ctg atg cta ctc cta tcc act gcc atg tac ggt gcc	336
Ala Arg Trp Thr Leu Met Leu Leu Leu Ser Thr Ala Met Tyr Gly Ala	
20 25 30	
cat gcc cca ttg ctg gca ctg tgc cat gtg gac ggc cga gtg ccc ttc	384
His Ala Pro Leu Leu Ala Leu Cys His Val Asp Gly Arg Val Pro Phe	
35 40 45	
cgg ccc tcc tca gcc gtg ctg ctg act gag ctg acc aag cta ctg tta	432
Arg Pro Ser Ser Ala Val Leu Leu Thr Glu Leu Thr Lys Leu Leu Leu	
50 55 60	
tgc gcc ttc tcc ctt ctg gta ggc tgg caa gca tgg ccc cag ggg ccc	480
Cys Ala Phe Ser Leu Leu Val Gly Trp Gln Ala Trp Pro Gln Gly Pro	
65 70 75 80	
cca ccc tgg cgc cag gct gct ccc ttc gca cta tca gcc ctg ctc tat	528
Pro Pro Trp Arg Gln Ala Ala Pro Phe Ala Leu Ser Ala Leu Leu Tyr	
85 90 95	
ggc gct aac aac aac ctg gtg atc tat ctt cag cgt tac atg gac ccc	576
Gly Ala Asn Asn Asn Leu Val Ile Tyr Leu Gln Arg Tyr Met Asp Pro	
100 105 110	
agc acc tac cag gtg ctg agt aat ctc aag att gga agc aca gct gtg	624
Ser Thr Tyr Gln Val Leu Ser Asn Leu Lys Ile Gly Ser Thr Ala Val	
115 120 125	
ctc tac tgc ctc tgc ctc cgg cac cgc ctc tct gtg cgt cag ggg tta	672

Leu Tyr Cys Leu Cys Leu Arg His Arg Leu Ser Val Arg Gln Gly Leu
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 Ala Leu Leu Leu Leu Met Ala Ala Gly Ala Cys Tyr Ala Ala Gly Gly
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 ctt caa gtt ccc ggg aac acc ctt ccc agt ccc cct cca gca gct gct 768
 Leu Gln Val Pro Gly Asn Thr Leu Pro Ser Pro Pro Pro Ala Ala Ala
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 gcc agc ccc atg ccc ctg cat atc act ccg cta ggc ctg ctg ctc ctc 816
 Ala Ser Pro Met Pro Leu His Ile Thr Pro Leu Gly Leu Leu Leu Leu
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 att ctg tac tgc ctc atc tca ggc ttg tgc tca gtg tac aca gag ctg 864
 Ile Leu Tyr Cys Leu Ile Ser Gly Leu Ser Ser Val Tyr Thr Glu Leu
 195 200 205
 ctc atg aag cga cag cgg ctg ccc ctg gca ctt cag aac ctc ttc ctc 912
 Leu Met Lys Arg Gln Arg Leu Pro Leu Ala Leu Gln Asn Leu Phe Leu
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 tac act ttt ggt gtg ctt ctg aat cta ggt ctg cat gct ggc ggc ggc 960
 Tyr Thr Phe Gly Val Leu Leu Asn Leu Gly Leu His Ala Gly Gly Gly
 225 230 235 240
 tct ggc cca ggc ctc ctg gaa ggt ttc tca gga tgg gca gca ctc gtg 1008
 Ser Gly Pro Gly Leu Leu Glu Gly Phe Ser Gly Trp Ala Ala Leu Val
 245 250 255
 gtg ctg agc cag gca cta aat gga ctg ctc atg tct gct gtc atg aag 1056
 Val Leu Ser Gln Ala Leu Asn Gly Leu Leu Met Ser Ala Val Met Lys

260	265	270	
cat ggc agc agc atc aca cgc ctc ttt gtg gtg tcc tgc tcg ctg gtg			1104
His Gly Ser Ser Ile Thr Arg Leu Phe Val Val Ser Cys Ser Leu Val			
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gtc aac gcc gtg ctc tca gca gtc ctg cta cgg ctg cag ctc aca gcc			1152
Val Asn Ala Val Leu Ser Ala Val Leu Leu Arg Leu Gln Leu Thr Ala			
290	295	300	
gcc ttc ttc ctg gcc aca ttg ctc att ggc ctg gcc atg cgc ctg tac			1200
Ala Phe Phe Leu Ala Thr Leu Leu Ile Gly Leu Ala Met Arg Leu Tyr			
305	310	315	320
tat ggc agc cgc tagtccctga caacttccac cctgattccg gaccctgt			1250
Tyr Gly Ser Arg			
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<212> DNA

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<221> CDS

<222> (95)... (508)

<400> 28

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Met Gly Phe Gly Ala Thr

1

5

ttg gcc gtt ggc ctg acc atc ttt gtg ctg tct gtc gtc act atc atc 160
 Leu Ala Val Gly Leu Thr Ile Phe Val Leu Ser Val Val Thr Ile Ile

10

15

20

atc tgc ttc acc tgc tcc tgc tgc tgc ctt tac aag acg tgc cgc cga 208
 Ile Cys Phe Thr Cys Ser Cys Cys Cys Leu Tyr Lys Thr Cys Arg Arg

25

30

35

55

cca cgt ccg gtt gtc acc acc acc aca tcc acc act gtg gtg cat gcc 256
 Pro Arg Pro Val Val Thr Thr Thr Thr Ser Thr Thr Val Val His Ala
 40 45 50

cct tat cct cag cct cca agt gtg ccg ccc agc tac cct gga cca agc 304
 Pro Tyr Pro Gln Pro Pro Ser Val Pro Pro Ser Tyr Pro Gly Pro Ser
 55 60 65 70

tac cag ggc tac cac acc atg ccg cct cag cca ggg atg cca gca gca 352
 Tyr Gln Gly Tyr His Thr Met Pro Pro Gln Pro Gly Met Pro Ala Ala
 75 80 85

ccc tac cca atg cag tac cca cca cct tac cca gcc cag ccc atg ggc 400
 Pro Tyr Pro Met Gln Tyr Pro Pro Pro Tyr Pro Ala Gln Pro Met Gly
 90 95 100

cca ccg gcc tac cac gag acc ctg gct gga gga gca gcc gcg ccc tac 448
 Pro Pro Ala Tyr His Glu Thr Leu Ala Gly Gly Ala Ala Ala Pro Tyr
 105 110 115

ccc gcc agc cag cct cct tac aac ccg gcc tac atg gat gcc ccg aag 496
 Pro Ala Ser Gln Pro Pro Tyr Asn Pro Ala Tyr Met Asp Ala Pro Lys
 120 125 130

gcg gcc ctc tgagcattcc ctggcctctc tggtgccac ttggttatgt tgtgt 550
 Ala Ala Leu
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gtgtgcgtga gtggtgtgca ggcgcggttc cttacgcccc atgtgtgctg tgtgtgtcca 610
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catggctcgt ccccgagtt ggggggtaccc gttgcagagc cagggacatg atgcaggcga     1030
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<210> 29

<211> 1930

<212> DNA

<213> Homo sapiens

<220>

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<222> (82)... (1017)

<400> 29

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      Met Gly Val Pro Thr Ala Leu Glu Ala Gly
              1              5              10
agc tgg cgc tgg gga tcc ctg ctc ttc gct ctc ttc ctg gct gcg tcc      159
Ser Trp Arg Trp Gly Ser Leu Leu Phe Ala Leu Phe Leu Ala Ala Ser
              15              20              25
cta ggt ccg gtg gca gcc ttc aag gtc gcc acg ccg tat tcc ctg tat      207
Leu Gly Pro Val Ala Ala Phe Lys Val Ala Thr Pro Tyr Ser Leu Tyr
              30              35              40
gtc tgt ccc gag ggg cag aac gtc acc ctc acc tgc agg ctc ttg ggc      255
Val Cys Pro Glu Gly Gln Asn Val Thr Leu Thr Cys Arg Leu Leu Gly
              45              50              55
cct gtg gac aaa ggg cac gat gtg acc ttc tac aag acg tgg tac cgc      303
Pro Val Asp Lys Gly His Asp Val Thr Phe Tyr Lys Thr Trp Tyr Arg
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agc tcg agg ggc gag gtg cag acc tgc tca gag cgc cgg ccc atc cgc      351
Ser Ser Arg Gly Glu Val Gln Thr Cys Ser Glu Arg Arg Pro Ile Arg
              75              80              85              90
aac ctc acg ttc cag gac ctt cac ctg cac cat gga ggc cac cag gct      399
Asn Leu Thr Phe Gln Asp Leu His Leu His His Gly Gly His Gln Ala
              95              100              105
gcc aac acc agc cac gac ctg gct cag cgc cac ggg ctg gag tcg gcc      447

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Ala Asn Thr Ser His Asp Leu Ala Gln Arg His Gly Leu Glu Ser Ala
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Ser Asp His His Gly Asn Phe Ser Ile Thr Met Arg Asn Leu Thr Leu
125 130 135
ctg gat agc ggc ctc tac tgc tgc ctg gtg gtg gag atc agg cac cac 543
Leu Asp Ser Gly Leu Tyr Cys Cys Leu Val Val Glu Ile Arg His His
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His Ser Glu His Arg Val His Gly Ala Met Glu Leu Gln Val Gln Thr
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Gly Lys Asp Ala Pro Ser Asn Cys Val Val Tyr Pro Ser Ser Ser Gln
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Glu Ser Glu Asn Ile Thr Ala Ala Ala Leu Ala Thr Gly Ala Cys Ile
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gta gga atc ctc tgc ctc ccc ctc atc ctg ctc ctg gtc tac aag caa 735
Val Gly Ile Leu Cys Leu Pro Leu Ile Leu Leu Leu Val Tyr Lys Gln
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agg cag gca gcc tcc aac cgc cgt gcc cag gag ctg gtg cgg atg gac 783
Arg Gln Ala Ala Ser Asn Arg Arg Ala Gln Glu Leu Val Arg Met Asp
220 225 230
agc aac att caa ggg att gaa aac ccc ggc ttt gaa gcc tca cca cct 831
Ser Asn Ile Gln Gly Ile Glu Asn Pro Gly Phe Glu Ala Ser Pro Pro

235	240	245	250	
gcc cag ggg ata ccc gag gcc aaa gtc agg cac ccc ctg tcc tat gtg				879
Ala Gln Gly Ile Pro Glu Ala Lys Val Arg His Pro Leu Ser Tyr Val				
	255	260	265	
gcc cag cgg cag cct tct gag tct ggg cgg cat ctg ctt tcg gag ccc				927
Ala Gln Arg Gln Pro Ser Glu Ser Gly Arg His Leu Leu Ser Glu Pro				
	270	275	280	
agc acc ccc ctg tct cct cca ggc ccc gga gac gtc ttc ttc cca tcc				975
Ser Thr Pro Leu Ser Pro Pro Gly Pro Gly Asp Val Phe Phe Pro Ser				
	285	290	295	
ctg gac cct gtc cct gac tct cca aac ttt gag gtc atc tagccc				1020
Leu Asp Pro Val Pro Asp Ser Pro Asn Phe Glu Val Ile				
300	305	310		
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<211> 1892

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (5)... (1636)

<400> 30

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 Glu Trp Gly Gln Arg Leu Leu Leu Val Leu Leu Leu Gly Gly Cys Ser
 20 25 30
 ggg cgc atc cac cgg ctg gcg ctg acg ggg gag aag cga gcg gac atc 145
 Gly Arg Ile His Arg Leu Ala Leu Thr Gly Glu Lys Arg Ala Asp Ile
 35 40 45
 cag ctg aac agc ttc ggt ttc tac acc aat ggc tct ctg gag gtg gag 193

Gln Leu Asn Ser Phe Gly Phe Tyr Thr Asn Gly Ser Leu Glu Val Glu
 50 55 60
 ttg agc gtc ctg cgg ctg ggc ctc cgg gag gca gaa gag aag tcc ctg 241
 Leu Ser Val Leu Arg Leu Gly Leu Arg Glu Ala Glu Glu Lys Ser Leu
 65 70 75
 ctg gtg ggg ttc agt ctc agc cgg gtt cgg tct ggc aga gtt cgc tcc 289
 Leu Val Gly Phe Ser Leu Ser Arg Val Arg Ser Gly Arg Val Arg Ser
 80 85 90 95
 tat tca acc cgg gat ttc cag gac tgc cct ctc cag aaa aac agt agc 337
 Tyr Ser Thr Arg Asp Phe Gln Asp Cys Pro Leu Gln Lys Asn Ser Ser
 100 105 110
 agt ttc ctg gtc ctg ttc ctc atc aac acc aag gat ctg cag gtc cag 385
 Ser Phe Leu Val Leu Phe Leu Ile Asn Thr Lys Asp Leu Gln Val Gln
 115 120 125
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 Val Arg Lys Tyr Gly Glu Gln Lys Thr Leu Phe Ile Phe Pro Gly Leu
 130 135 140
 ctc ccg gaa gca ccc tcc aaa cca ggg ctc ccg aag cca cag gcc aca 481
 Leu Pro Glu Ala Pro Ser Lys Pro Gly Leu Pro Lys Pro Gln Ala Thr
 145 150 155
 gtc ccc cgc aag gtg gat ggc gga ggg acc tct gca gcc agc aag ccc 529
 Val Pro Arg Lys Val Asp Gly Gly Gly Thr Ser Ala Ala Ser Lys Pro
 160 165 170 175
 aag tca aca ccc gca gtg att cag ggt cct agt ggg aag gac aag gac 577
 Lys Ser Thr Pro Ala Val Ile Gln Gly Pro Ser Gly Lys Asp Lys Asp

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Leu Val Leu Gly Leu Ser His Leu Asn Asn Ser Tyr Asn Phe Ser Phe			
195	200	205	
cac gtg gtg atc ggc tct cag gcg gaa gaa ggc cag tac agc ctg aac			673
His Val Val Ile Gly Ser Gln Ala Glu Glu Gly Gln Tyr Ser Leu Asn			
210	215	220	
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Phe His Asn Cys Asn Asn Ser Val Pro Gly Lys Glu His Pro Phe Asp			
225	230	235	
atc acg gtg atg atc cgg gag aag aac ccc gat ggc ttc ctg tgc gca			769
Ile Thr Val Met Ile Arg Glu Lys Asn Pro Asp Gly Phe Leu Ser Ala			
240	245	250	255
gcg gag atg ccc ctt ttc aag ctc tac atg gtc atg tcc gcc tgc ttc			817
Ala Glu Met Pro Leu Phe Lys Leu Tyr Met Val Met Ser Ala Cys Phe			
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Leu Ala Ala Gly Ile Phe Trp Val Ser Ile Leu Cys Arg Asn Thr Tyr			
275	280	285	
agc gtc ttc aag atc cac tgg ctc atg gcg gcc ttg gcc ttc acc aag			913
Ser Val Phe Lys Ile His Trp Leu Met Ala Ala Leu Ala Phe Thr Lys			
290	295	300	
agc atc tct ctc ctc ttc cac agc atc aac tac tac ttc atc aac agc			961
Ser Ile Ser Leu Leu Phe His Ser Ile Asn Tyr Tyr Phe Ile Asn Ser			
305	310	315	

cag ggc cac ccc atc gaa ggc ctt gcc gtc atg tac tac atc gca cac	1009
Gln Gly His Pro Ile Glu Gly Leu Ala Val Met Tyr Tyr Ile Ala His	
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ctg ctg aag ggc gcc ctc ctc ttc atc acc atc gcc ctg att ggc tca	1057
Leu Leu Lys Gly Ala Leu Leu Phe Ile Thr Ile Ala Leu Ile Gly Ser	
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ggc tgg gcc ttc atc aag tac gtc ctg tgc gat aag gag aag aag gtc	1105
Gly Trp Ala Phe Ile Lys Tyr Val Leu Ser Asp Lys Glu Lys Lys Val	
355 360 365	
ttt ggg atc gtg atc ccc atg cag gtc ctg gcc aac gtg gcc tac atc	1153
Phe Gly Ile Val Ile Pro Met Gln Val Leu Ala Asn Val Ala Tyr Ile	
370 375 380	
atc atc gag tcc cgc gag gaa ggc gcc agc gac tac gtg ctg tgg aag	1201
Ile Ile Glu Ser Arg Glu Glu Gly Ala Ser Asp Tyr Val Leu Trp Lys	
385 390 395	
gag att ttg ttc ctg gtg gac ctc atc tgc tgt ggt gcc atc ctg ttc	1249
Glu Ile Leu Phe Leu Val Asp Leu Ile Cys Cys Gly Ala Ile Leu Phe	
400 405 410 415	
ccc gta gtc tgg tcc atc cgg cat ctc cag gat gcg tct ggc aca gac	1297
Pro Val Val Trp Ser Ile Arg His Leu Gln Asp Ala Ser Gly Thr Asp	
420 425 430	
ggg aag gtg gca gtg aac ctg gcc aag ctg aag ctg ttc cgg cat tac	1345
Gly Lys Val Ala Val Asn Leu Ala Lys Leu Lys Leu Phe Arg His Tyr	
435 440 445	
tat gtc atg gtc atc tgc tac gtc tac ttc acc cgc atc atc gcc atc	1393

Tyr Val Met Val Ile Cys Tyr Val Tyr Phe Thr Arg Ile Ile Ala Ile
 450 455 460
 ctg ctg cag gtg gct gtg ccc ttt cag tgg cag tgg ctg tac cag ctc 1441
 Leu Leu Gln Val Ala Val Pro Phe Gln Trp Gln Trp Leu Tyr Gln Leu
 465 470 475
 ttg gtg gag ggc tcc acc ctg gcc ttc ttc gtg ctc acg ggc tac aag 1489
 Leu Val Glu Gly Ser Thr Leu Ala Phe Phe Val Leu Thr Gly Tyr Lys
 480 485 490 495
 ttc cag ccc aca ggg aac aac ccg tac ctg cag ctg ccc cag gag gac 1537
 Phe Gln Pro Thr Gly Asn Asn Pro Tyr Leu Gln Leu Pro Gln Glu Asp
 500 505 510
 gag gag gat gtt cag atg gag caa gta atg acg gac tct ggg ttc cgg 1585
 Glu Glu Asp Val Gln Met Glu Gln Val Met Thr Asp Ser Gly Phe Arg
 515 520 525
 gaa ggc ctc tcc aaa gtc aac aaa aca gcc agc ggg cgg gaa ctg tta 1633
 Glu Gly Leu Ser Lys Val Asn Lys Thr Ala Ser Gly Arg Glu Leu Leu
 530 535 540
 tgatcac ctccacatct cagaccaaag ggctgctctc cccagcatt tctcactct 1690
 gcccttcttc cacagcgtat gtggggaggt ggaggggggtc catgtggacc aggcgccag 1750
 ctccccggga ccccggttcc cggacaagcc catttggaag aagagtcctt tcctccccc 1810
 aaatattggg cagccctgtc cttaccccg gaccaccct cccttcagc tatgtgtaca 1870
 ataatgacca atctgtttgg ct 1892