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Schiemann et al.

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(45) **Date of Patent: Apr. 17, 2012**

(54) **GENES AND PROTEINS ASSOCIATED WITH ANGIOGENESIS AND USES THEREOF**

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(65) **Prior Publication Data**

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Related U.S. Application Data

(60) Provisional application No. 60/772,694, filed on Sep. 30, 2005, provisional application No. 60/816,969, filed on Jun. 27, 2006.

(51) **Int. Cl.**
A61K 39/00 (2006.01)
A61K 38/16 (2006.01)
C12N 5/00 (2006.01)

(52) **U.S. Cl.** **424/9.1**; 424/227.1; 435/6; 435/32; 435/375; 514/8

(58) **Field of Classification Search** 424/277.1, 424/9.1; 435/6, 32, 375; 514/8
See application file for complete search history.

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(57) **ABSTRACT**

Disclosed is a panel of biomarkers associated with angiogenesis, and the use of such biomarkers (genes, proteins, homologues and analogs thereof) to regulate angiogenesis. Methods for identifying compounds useful for regulating angiogenesis and conditions related thereto are disclosed.

2 Claims, 14 Drawing Sheets

FIG. 1A

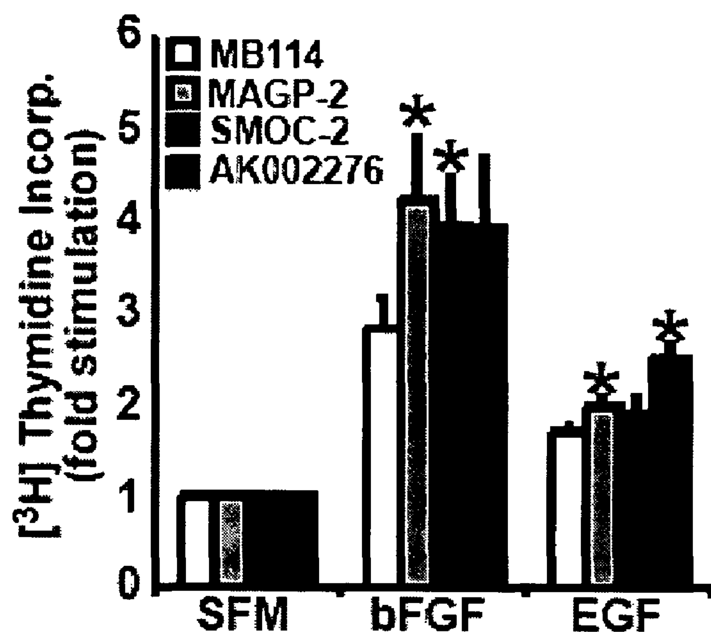


FIG. 1B

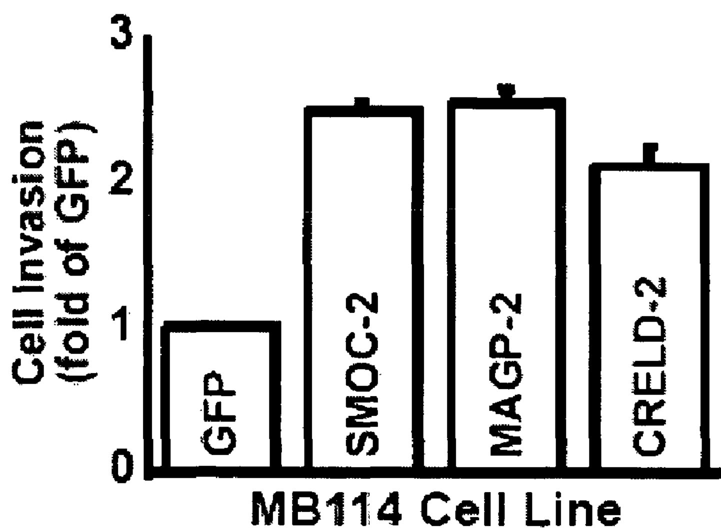


FIG. 1C

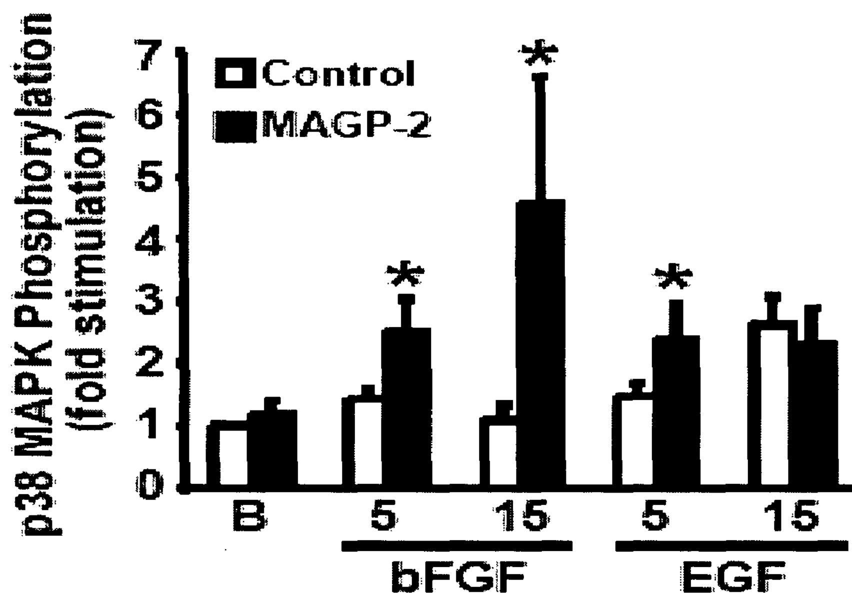


FIG. 1D

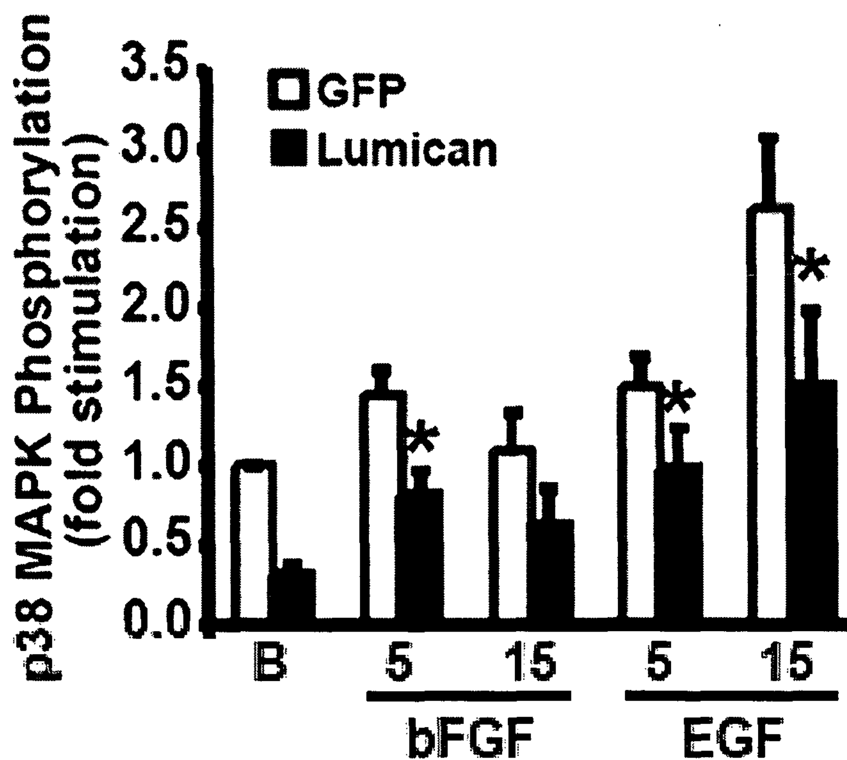


FIG. 1E

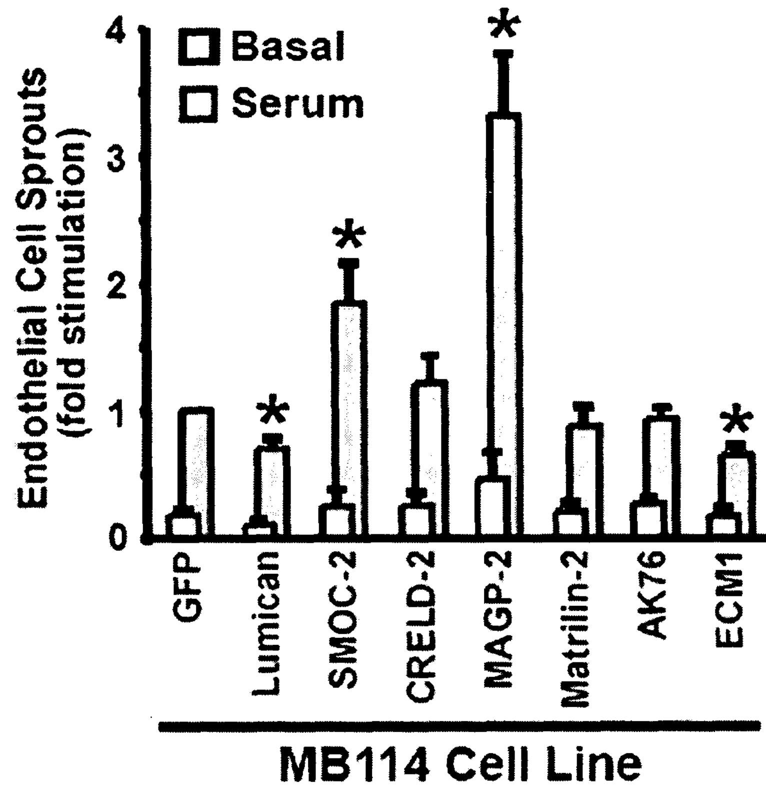


FIG. 2A

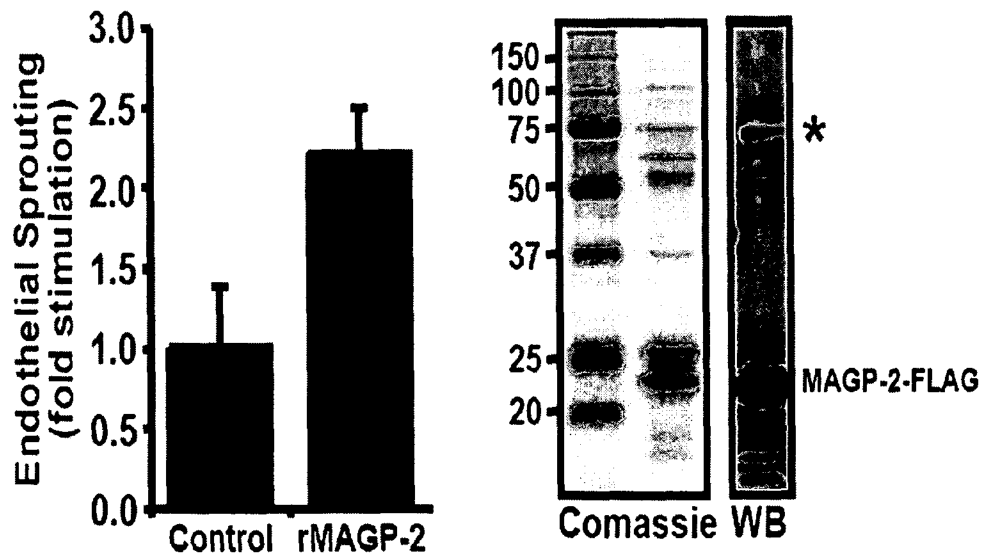


FIG. 2B

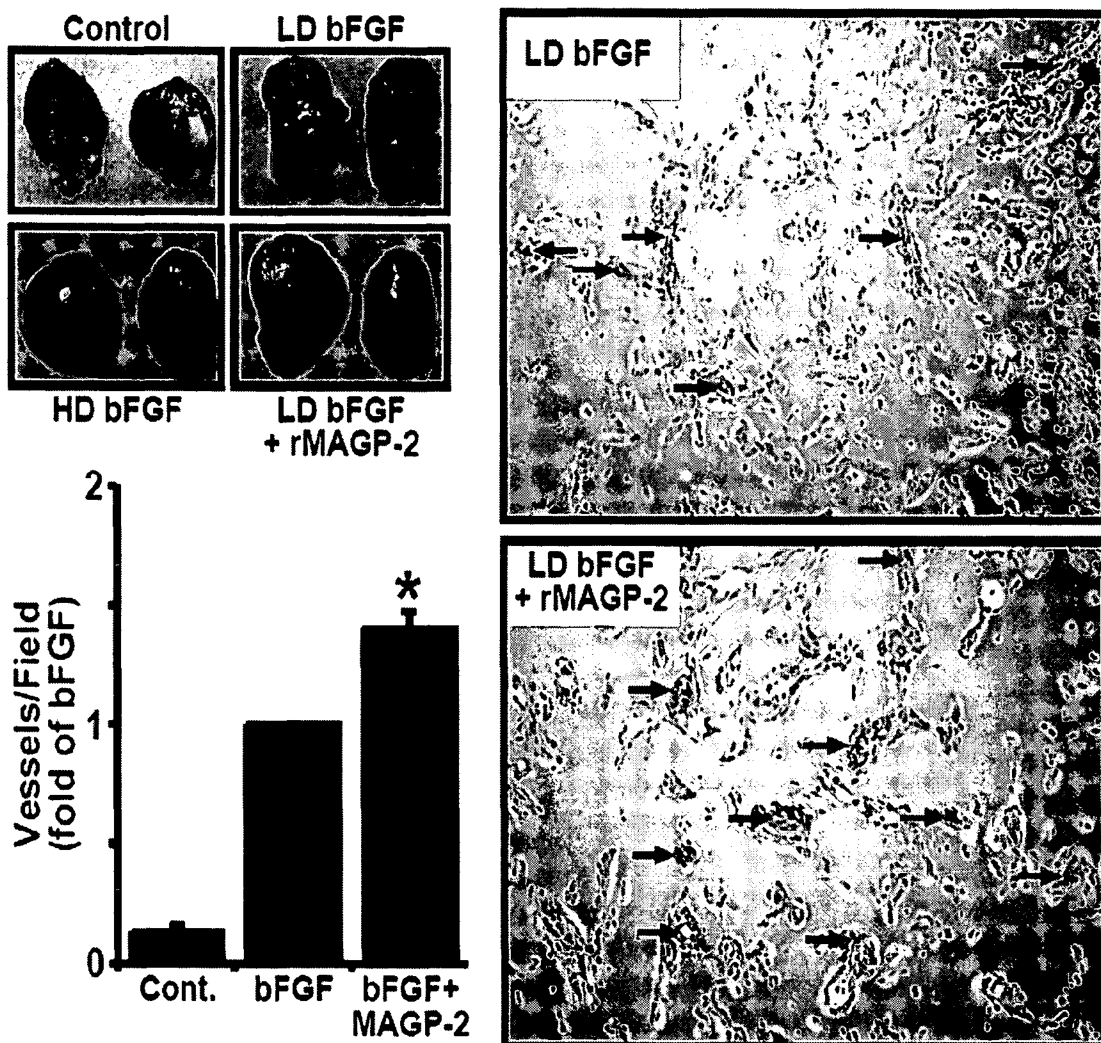


FIG. 3A

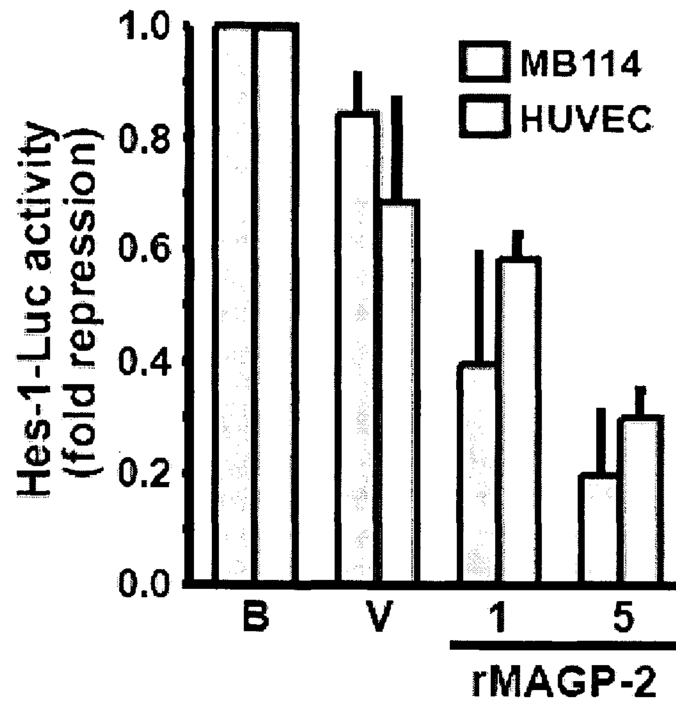


FIG. 3B

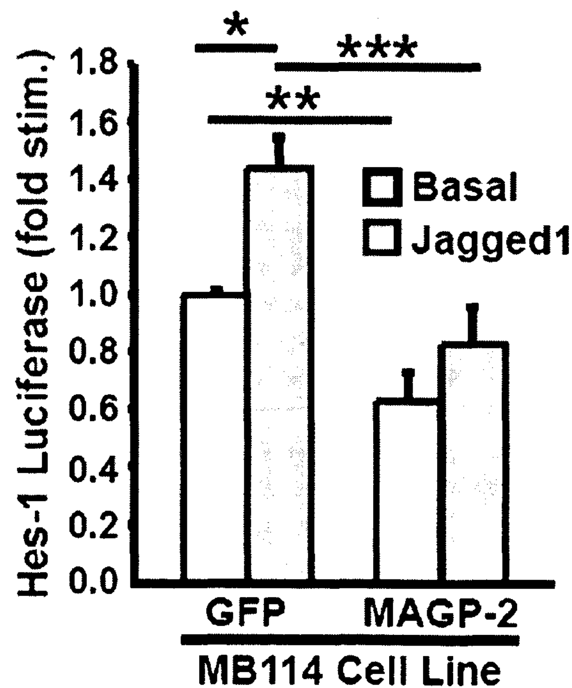
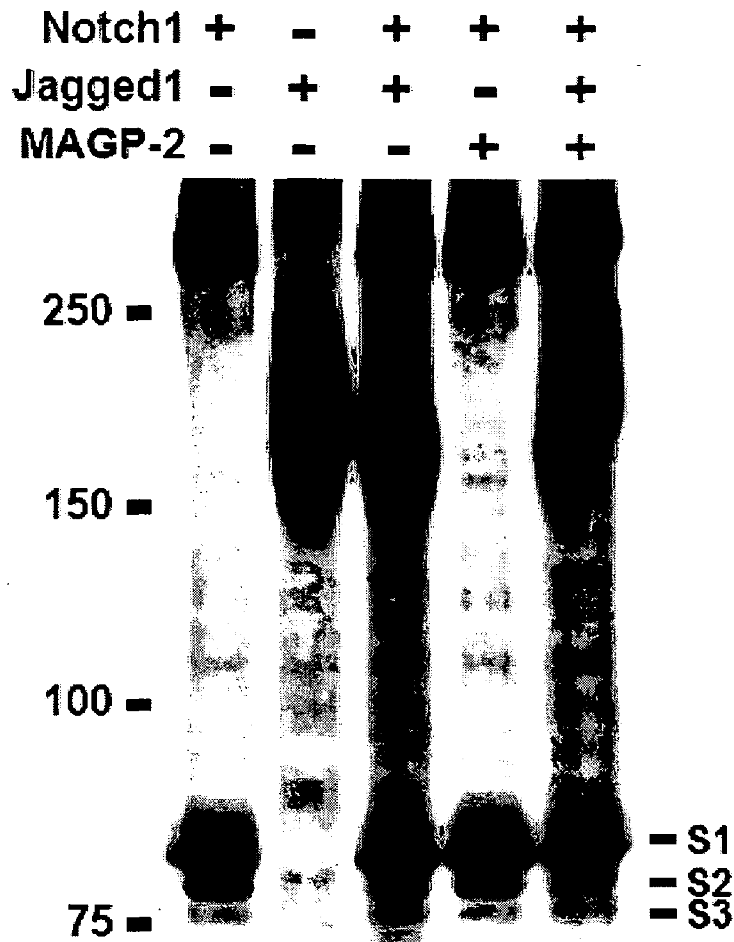


FIG. 4A



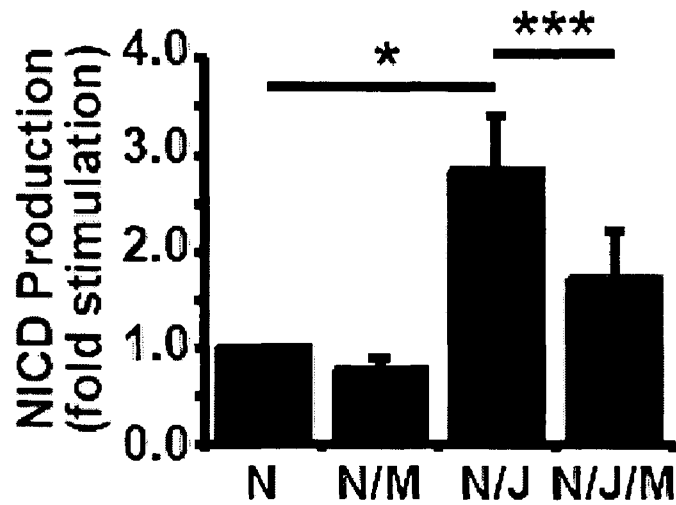


FIG. 4B

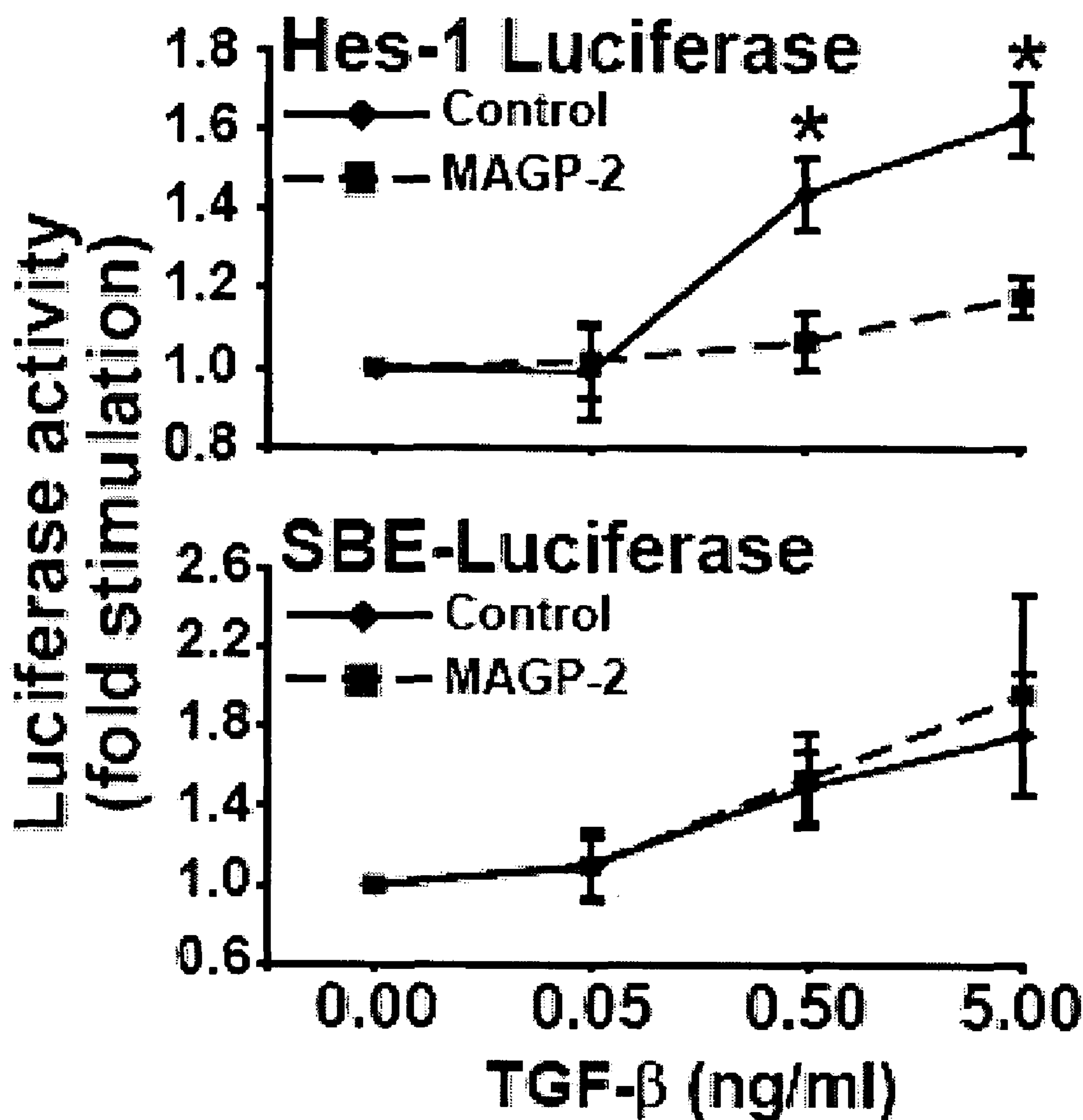


FIG. 5A

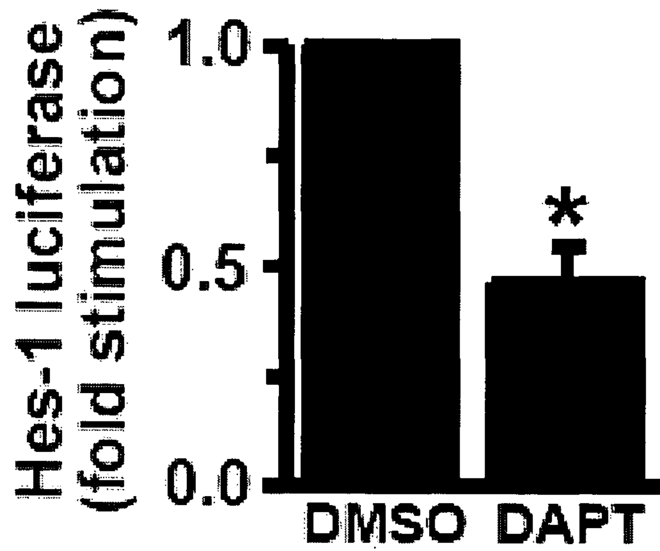


FIG. 5B

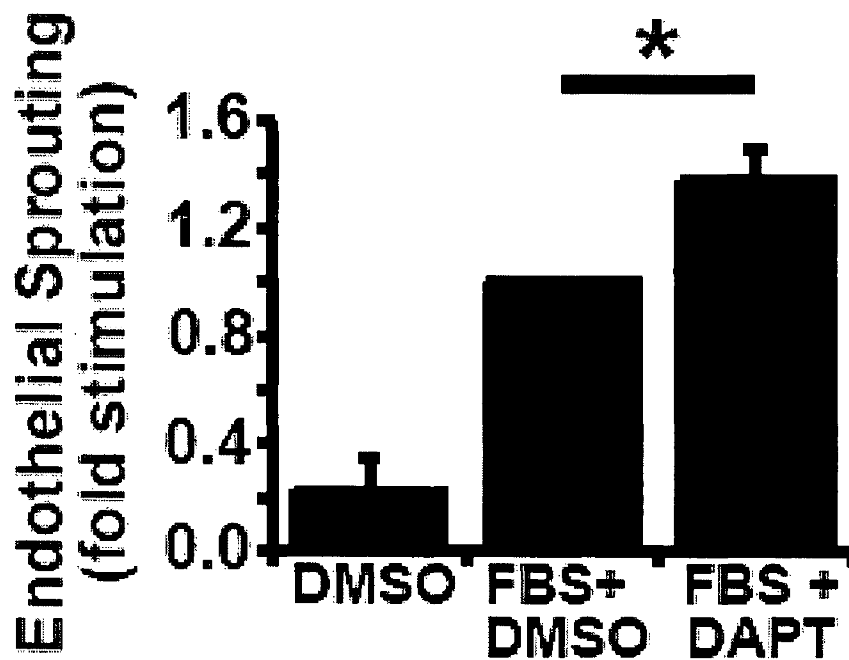


FIG. 5C

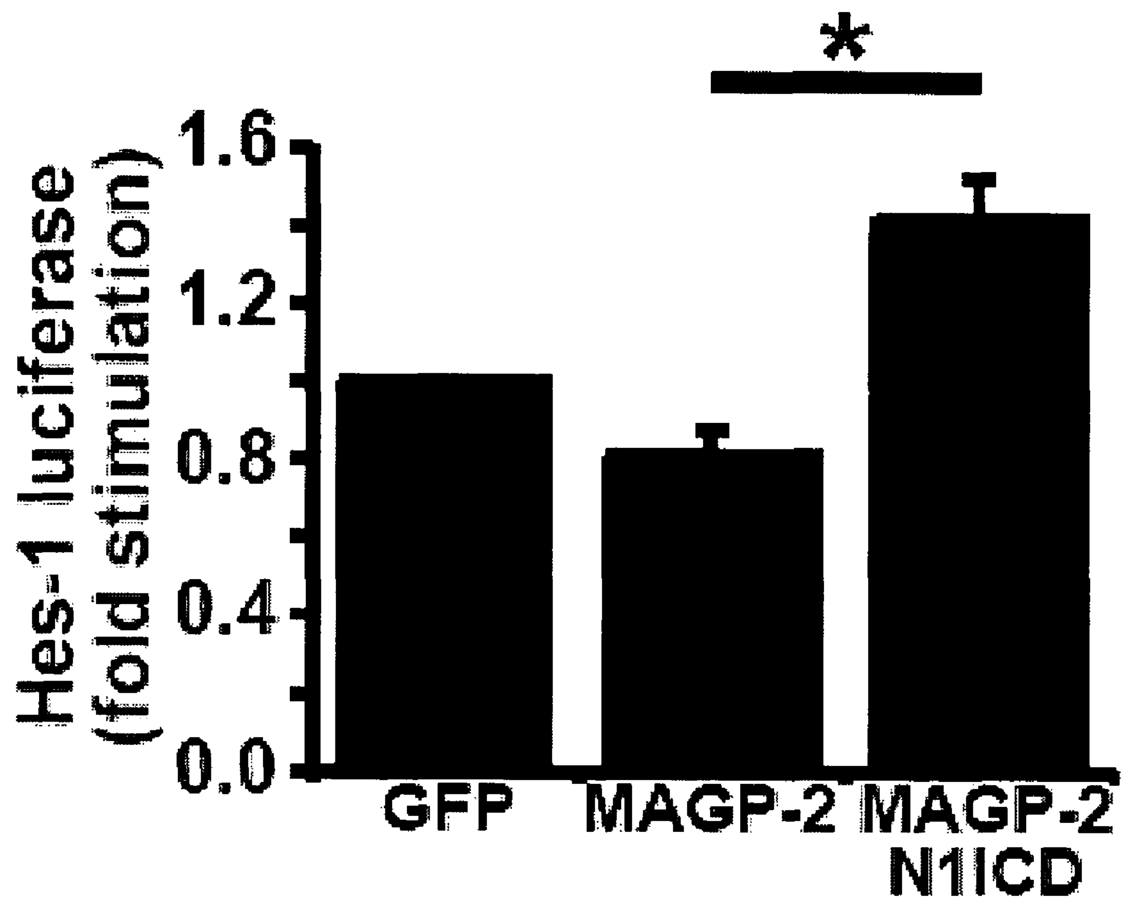
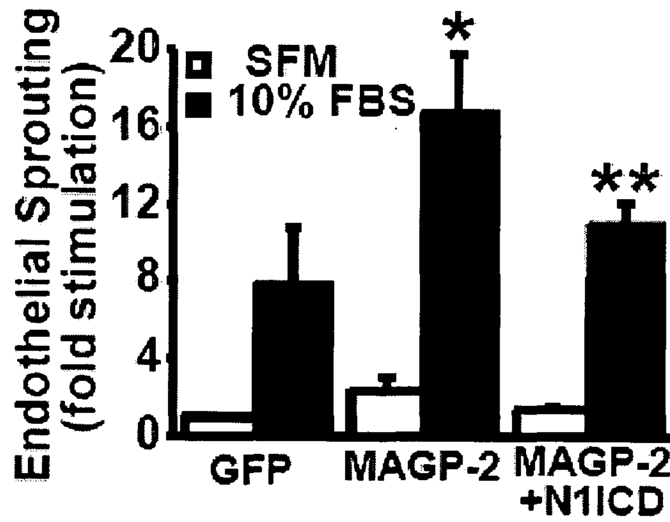


FIG. 5D



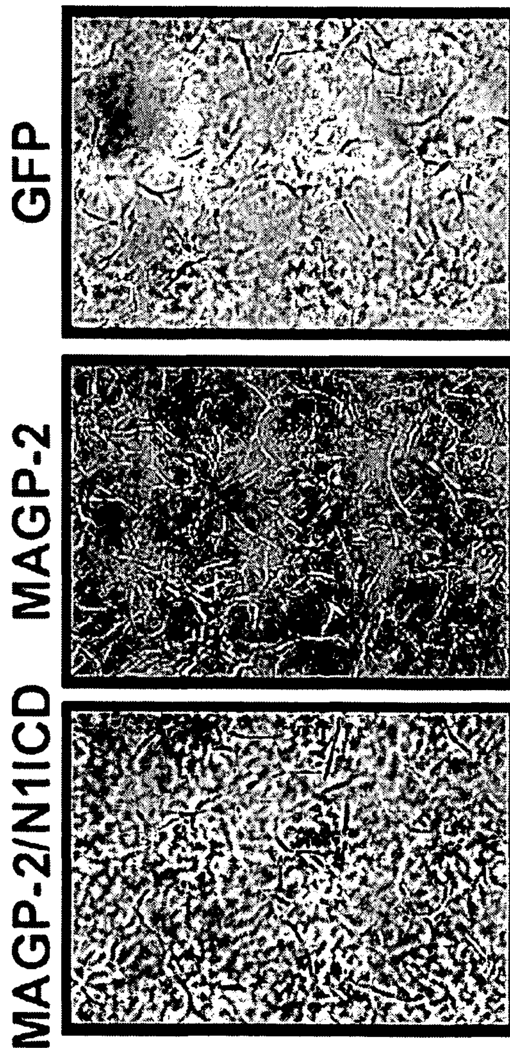


FIG. 6

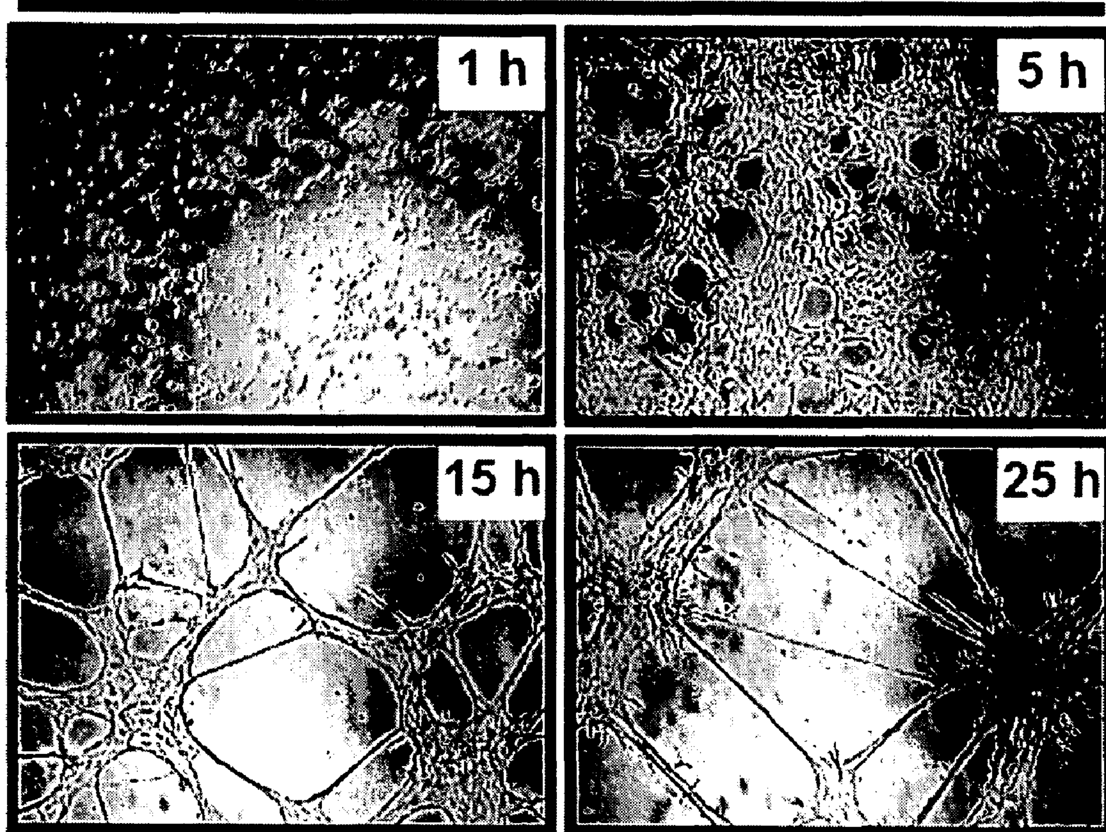


FIG. 7A

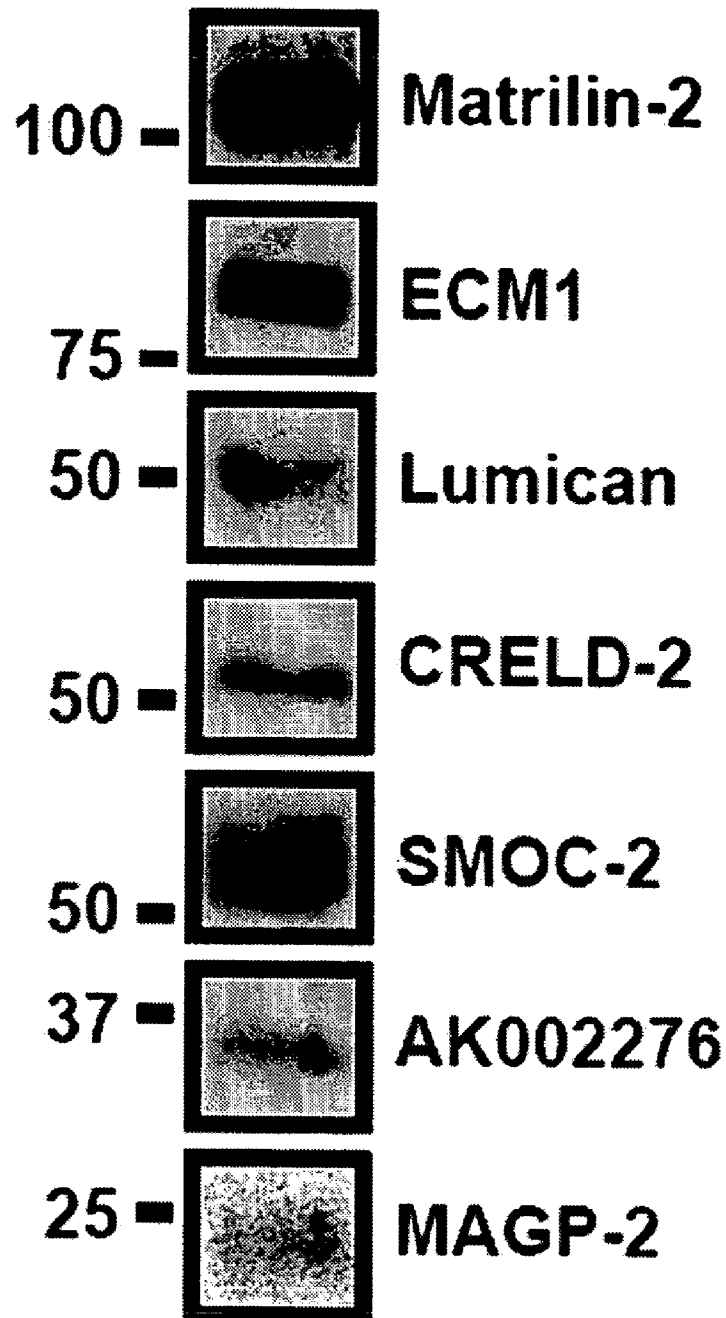


FIG. 7B

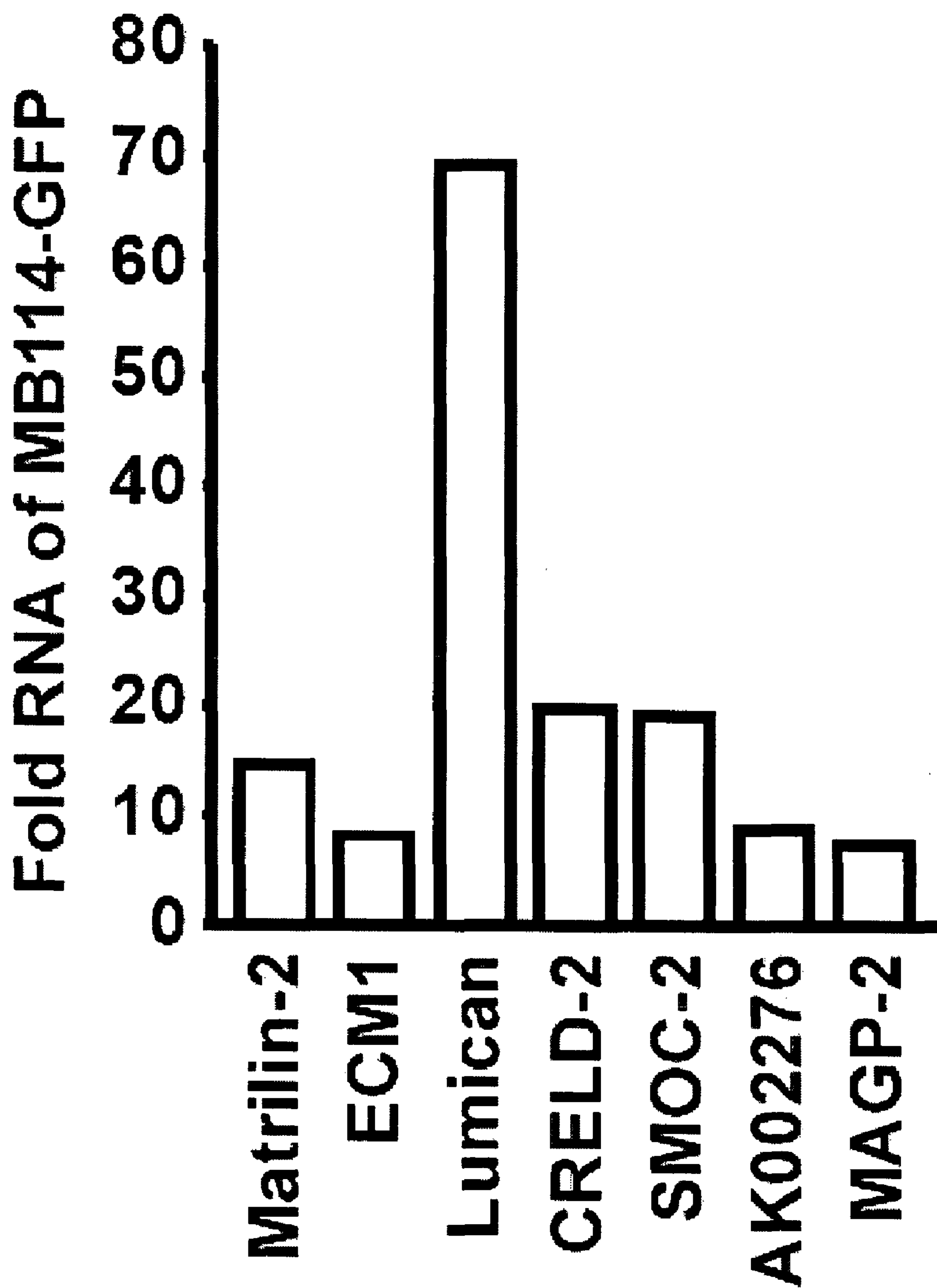
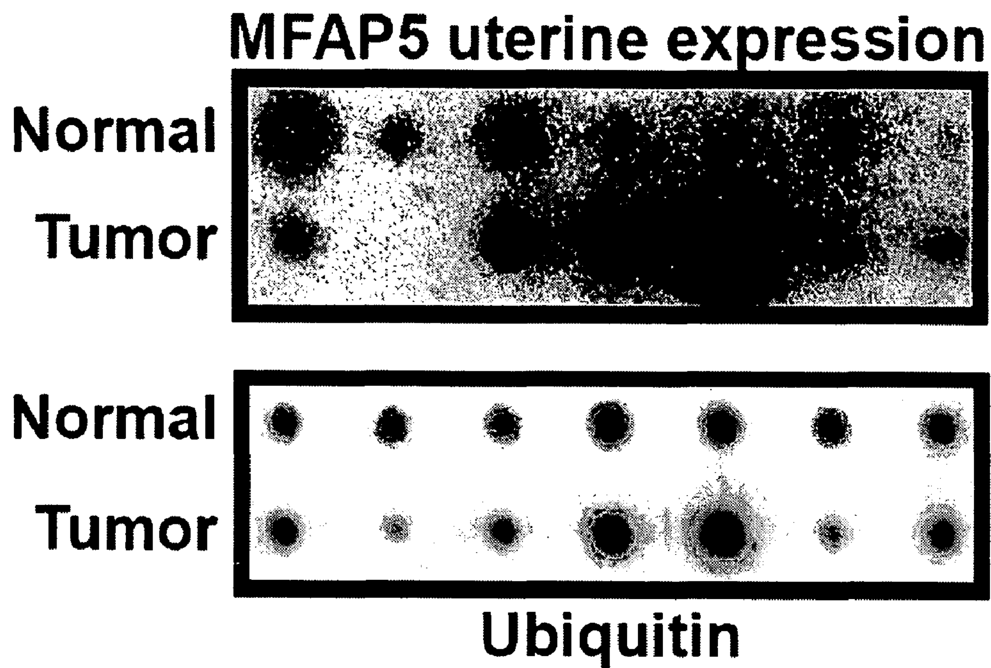


FIG. 8



MFAP5 expression in uterine tumors	
Altered	Increased
86%(6/7 cases)	67%(4/6 cases)

GENES AND PROTEINS ASSOCIATED WITH ANGIOGENESIS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority under 35 U.S.C. §119(e) from U.S. Provisional Application No. 60/722,694, filed Sep. 30, 2005 and from U.S. Provisional Application No. 60/816,969, filed Jun. 27, 2006. The entire disclosure of each of U.S. Provisional Application No. 60/722,694 and U.S. Provisional Application No. 60/816,969 is incorporated herein by reference in its entirety.

GOVERNMENT SUPPORT

This invention was made in part with government support under NIH Grant No. CA095519 and NIH Grant No. CA99321, each awarded by the National Institutes of Health. The government has certain rights to this invention.

REFERENCE TO SEQUENCE LISTING

This application contains a Sequence Listing submitted on a compact disc, in duplicate. Each of the two compact discs, which are identical to each other pursuant to 37 CFR §1.52 (e)(4), contains the following file: "Sequence Listing", having a size in bytes of 266 KB, recorded on 2 Oct. 2006. The information contained on the compact disc is hereby incorporated by reference in its entirety pursuant to 37 CFR §1.77 (b)(4).

FIELD OF THE INVENTION

The present invention generally relates to genes and proteins, including homologues and agonist or antagonist analogs thereof, as targets for regulating angiogenesis. The present invention also relates to methods to identify regulators of angiogenesis using such biomarkers, and methods related thereto.

BACKGROUND OF THE INVENTION

Angiogenesis is the process whereby new blood vessels are formed from preexisting vessels; it is a highly regulated event that encompasses a coordinated cascade of gene expression and repression, and one that is influenced by many factors, including a variety of environmental cues provided by the extracellular matrix (ECM) (Sottile, 2004; Stupack and Cheresh, 2002). Cancer cells play a vital role in eliciting many of these environmental cues in part via their ability to produce and secrete numerous angiogenic factors and proteases that create tumor microenvironments conductive to angiogenesis (Bissell et al, 2002; Pupa et al, 2002; Sottile, 2004). Although previously believed to be innocent bystanders during angiogenic reactions, it is becoming increasingly apparent that endothelial cells (ECs) also make important contributions to the activation and resolution of angiogenesis. Indeed, ECs generate a variety of environmental cues that shape and remodel tumor and vascular microenvironments, ultimately leading to altered vessel development (Davis and Senger, 2005; Sottile, 2004). Unfortunately, the molecular mechanisms whereby ECs and the molecules they secrete actively direct angiogenesis activation and resolution remain to be determined definitively. It is known that tumor angiogenesis depends upon the coordinated cooperation between cancer and endothelial cells (ECs), and results in the formation and infiltration of new vessels into tumor microenvironments, thereby providing developing tumors with a source of nutrients and oxygen, as well as a route for cancer cell metastasis (Carmeliet and Jain, 2000; Folkman and Shing, 1992). Failure to establish these cancer:EC connections prevents the development and progression of small, innocuous cancer growths, and as such, tumors remain in a dormant, benign state (Bergers and Benjamin, 2003; Hanahan and Folkman, 1996). Recently, significant inroads in understanding of the role of cancer cells in mediating tumor angiogenesis and EC activation have taken place. Indeed, cancer cells actively induce tumor angiogenesis via their ability to produce and secrete a variety of pro-angiogenic factors (Liotta and Kohn, 2001; Stupack and Cheresh, 2002), a process known as the angiogenic switch (Bergers and Benjamin, 2003; Hanahan and Folkman, 1996). In contrast, comparably little is known concerning the role of ECs during this process, particularly the functional consequences of their ability to remodel vascular and tumor microenvironments during angiogenesis. Although ECs are known to remodel their microenvironment by secreting various extracellular proteases, such as MMPs (matrix metalloproteases), ADAMs (a disintegrin and metalloprotease domain), and ADAMTS (a disintegrin and metalloprotease domain with thrombospondin motifs; Stupack and Cheresh, 2002), a thorough understanding of how these molecules and their stromal targets mediate angiogenesis activation or resolution remains incompletely understood. Thus, identifying and characterizing novel proteins secreted by angiogenic ECs will offer important insights into the role of the endothelium in mediating angiogenesis, as well as its potential to be targeted therapeutically to prevent tumor angiogenesis. Specifically, mapping and defining the EC secretome will significantly enhance understanding of angiogenesis, as well as identify novel therapeutic agents and/or targets that can be exploited to prevent tumor angiogenesis and metastasis in cancer patients.

SUMMARY OF THE INVENTION

One embodiment of the present invention relates to a method to regulate angiogenesis in cells or a tissue of a patient. The method comprises regulating the expression or biological activity in the cells or tissue of any one or more biomarkers selected from a biomarker represented in any one or more of Table I, Table IV, Table V, and/or Table VI.

In one aspect of this embodiment, the biomarkers are any one or more of the biomarkers in Table VI. In another aspect of this embodiment, the biomarkers are any one or more of the biomarkers selected from: ADAMts7, CRELD-2, Decorin, ECM1, Inhibin β-b, Integrin α-3, Integrin α-6, Lipocalin-7, Lox1-3, Lumican, MAGP-2, Matrilin-2, Nephronectin, SerpinE2, and/or SMOC-2.

In another aspect of this embodiment, the biomarkers are any one or more of the biomarkers selected from: 0610007C21Rik, apoptosis related protein APR-3, 1810014L12Rik, Cd14 (encoding CD14 antigen represented herein by SEQ ID NO:5 and SEQ ID NO:6), Cd38 (comprising a nucleic acid sequence represented herein by SEQ ID NO:7 and encoding CD38 antigen); Cd53 (encoding CD53 antigen represented herein by SEQ ID NO:8 and SEQ ID NO:9), Emp2 (encoding epithelial membrane protein represented herein by SEQ ID NO:10 and SEQ ID NO:11), Fcgrt (encoding Fc receptor (IgG, alpha chain transporter) represented herein by SEQ ID NO:12 and SEQ ID NO:13), Islr (encoding immunoglobulin superfamily containing leucine-rich repeat represented herein by SEQ ID NO:14 and SEQ ID NO:15); Lrp2 (comprising a nucleic acid sequence repre-

sented herein by SEQ ID NO:16 and SEQ ID NO:17 and encoding low density lipoprotein receptor-related protein 2); Ly6a (encoding lymphocyte antigen 6 complex, locus A represented herein by SEQ ID NO:18); P2rx4 (encoding purinergic receptor P2X, ligand-gated ion channel 4, represented herein by SEQ ID NO:19 and SEQ ID NO:20; Pcdhb9 (encoding protocadherin beta 9 represented herein by SEQ ID NO:21 and SEQ ID NO:22); Ptpre (encoding protein tyrosine phosphatase receptor type E represented herein by SEQ ID NO:23 and SEQ ID NO:24); Slc4a3 (encoding solute carrier family 4 (anion exchanger) member 3, represented herein by SEQ ID NO:25 and SEQ ID NO:26); and/or Tmc6 (encoding transmembrane channel-like gene family 6, represented herein by SEQ ID NO:27).

In another aspect of this embodiment, the biomarkers are any one or more of the biomarkers selected from: 9130213B05Rik (encoding a protein represented herein by SEQ ID NO:29); C1s (encoding complement component 1, s subcomponent, represented herein by SEQ ID NO:34 and SEQ ID NO:35); C3 (encoding complement component 3 represented herein by SEQ ID NO:30 and SEQ ID NO:31); Cfh (comprising a nucleic acid sequence represented herein by SEQ ID NO:32 and SEQ ID NO:33 and encoding complement component factor h); Col9a3 (comprising a nucleic acid sequence represented herein by SEQ ID NO:36 and SEQ ID NO:37 and encoding procollagen, type IX, alpha 3); Grem1 (encoding cysteine knot superfamily 1, BMP antagonist 1, represented herein by SEQ ID NO:38 and SEQ ID NO:39); Lox13 (encoding lysyl oxidase-like 3, represented herein by SEQ ID NO:40 and SEQ ID NO:41); MAGP-2 (comprising a nucleic acid sequence represented herein by SEQ ID NO:123 and SEQ ID NO:124 and encoding microfibrillar associated protein 5, represented herein by SEQ ID NO:42 and SEQ ID NO:43); Mglap (encoding matrix gamma-carboxyglutamate (gla) protein represented herein by SEQ ID NO:44 and SEQ ID NO:45); Naga (encoding N-acetyl galactosaminidase, alpha, represented herein by SEQ ID NO:46 and SEQ ID NO:47); Nbl1 (encoding neuroblastoma, suppression of tumorigenicity 1, represented herein by SEQ ID NO:48 and SEQ ID NO:49); Ngfb (encoding nerve growth factor, beta, represented herein by SEQ ID NO:50 and SEQ ID NO:51), Npnt (represented herein by SEQ ID NO:52 and SEQ ID NO:53 and encoding nephronectin); Olfm1 (encoding olfactomedin 1, represented herein by SEQ ID NO:54 and SEQ ID NO:55); and/or U90926 (encoding a protein represented herein by SEQ ID NO:56).

Any combinations of any of the above-identified biomarkers are included in the invention. In a preferred aspect of this embodiment, the biomarker is MAGP-2.

In one aspect, the step of regulating comprises contacting the cells or tissue of from the patient with an antagonist of the biomarker. In another aspect, the step of regulating comprises contacting the cells or tissue of from the patient with the biomarker or a biologically active homologue or agonist thereof. In another aspect, the step of regulating comprises expressing a recombinant nucleic acid molecule encoding the biomarker or a homologue thereof in the tissue of the patient.

In one aspect of this embodiment, angiogenesis is upregulated. Such an aspect of the invention can be used to treat a patient that has vascular deficiencies, cardiovascular disease, or would benefit from stimulation of endothelial cell activation and stabilization of newly formed microvessels or other vessels, such as in ischemia or stroke.

In another aspect of this embodiment angiogenesis is downregulated. Such an aspect of the invention can be used to treat conditions that are characterized or caused by abnormal or excessive angiogenesis, including, but are not limited to: cancer (e.g., activation of oncogenes, loss of tumor suppressors); infectious diseases (e.g., pathogens express angiogenic genes, enhance angiogenic programs); autoimmune disorders (e.g., activation of mast cells and other leukocytes); vascular malformations (e.g., Tie-2 mutation); DiGeorge syndrome (e.g., low VEGF and neuropilin-1 expression); HHT (e.g., mutations of endoglin or LK-1), cavernous hemangioma (e.g., loss of Cx37 and Cx40); atherosclerosis; transplant ateriopathy; obesity (e.g., angiogenesis induced by fatty diet, weight loss by angiogenesis inhibitors); psoriasis; warts; allergic dermatitis; scar keloids; pyogenic granulomas; blistering disease; Kaposi sarcoma in AIDS patients; persistent hyperplastic vitreous syndrome (e.g., loss of Ang-2 or VEGF164); diabetic retinopathy; retinopathy of prematurity; choroidal neovascularization (e.g., TIMP-3 mutation); primary pulmonary hypertension (e.g., germline BMPR-2 mutation, somatic EC mutation); asthma; nasal polyps; inflammatory bowel disease; periodontal disease; ascites; peritoneal adhesions; endometriosis; uterine bleeding; ovarian cysts; ovarian hyperstimulation; arthritis; synovitis; osteomyelitis; and/or osteophyte formation.

Another embodiment of the present invention relates to a method to reduce tumorigenicity in a patient, comprising regulating the expression or biological activity of any one or more biomarkers selected from a biomarker represented in any one or more of Table I, Table IV, Table V, and/or Table VI. In one aspect of this embodiment, the biomarkers are any one or more of the biomarkers in Table VI.

In another aspect of this embodiment, the biomarkers are any one or more of the biomarkers selected from: ADAMts7, CRELD-2, Decorin, ECM1, Inhibin β-b, Integrin α-3, Integrin α-6, Lipocalin-7, Lox1-3, Lumican, MAGP-2, Matrilin-2, Nephronectin, SerpinE2, and/or SMOC-2.

In another aspect of this embodiment, the biomarkers are any one or more of the biomarkers selected from: 0610007C21Rik, apoptosis related protein APR-3, 1810014L12Rik, Cd14 (encoding CD14 antigen represented herein by SEQ ID NO:5 and SEQ ID NO:6), Cd38 (comprising a nucleic acid sequence represented herein by SEQ ID NO:7 and encoding CD38 antigen); Cd53 (encoding CD53 antigen represented herein by SEQ ID NO:8 and SEQ ID NO:9), Emp2 (encoding epithelial membrane protein represented herein by SEQ ID NO:10 and SEQ ID NO:11), Fcgrt (encoding Fc receptor (IgG, alpha chain transporter) represented herein by SEQ ID NO:12 and SEQ ID NO:13), Islr (encoding immunoglobulin superfamily containing leucine-rich repeat represented herein by SEQ ID NO:14 and SEQ ID NO:15); Lrp2 (comprising a nucleic acid sequence represented herein by SEQ ID NO:16 and SEQ ID NO:17 and encoding low density lipoprotein receptor-related protein 2); Ly6a (encoding lymphocyte antigen 6 complex, locus A represented herein by SEQ ID NO:18); P2rx4 (encoding purinergic receptor P2X, ligand-gated ion channel 4, represented herein by SEQ ID NO:19 and SEQ ID NO:20; Pcdhb9 (encoding protocadherin beta 9 represented herein by SEQ ID NO:21 and SEQ ID NO:22); Ptpre (encoding protein tyrosine phosphatase receptor type E represented herein by SEQ ID NO:23 and SEQ ID NO:24); Slc4a3 (encoding solute carrier family 4 (anion exchanger) member 3, represented herein by SEQ ID NO:25 and SEQ ID NO:26); and/or Tmc6 (encoding transmembrane channel-like gene family 6, represented herein by SEQ ID NO:27).

In yet another aspect of this embodiment, the biomarkers are any one or more of the biomarkers selected from: 9130213B05Rik (encoding a protein represented herein by SEQ ID NO:29); C1s (encoding complement component 1, s subcomponent, represented herein by SEQ ID NO:34 and

SEQ ID NO:35); C3 (encoding complement component 3 represented herein by SEQ ID NO:30 and SEQ ID NO:31); Cfh (comprising a nucleic acid sequence represented herein by SEQ ID NO:32 and SEQ ID NO:33 and encoding complement component factor h); Col9a3 (comprising a nucleic acid sequence represented herein by SEQ ID NO:36 and SEQ ID NO:37 and encoding procollagen, type IX, alpha 3); Grem1 (encoding cysteine knot superfamily 1, BMP antagonist 1, represented herein by SEQ ID NO:38 and SEQ ID NO:39); Lox13 (encoding lysyl oxidase-like 3, represented herein by SEQ ID NO:40 and SEQ ID NO:41); MAGP-2 (comprising a nucleic acid sequence represented herein by SEQ ID NO:124 and SEQ ID NO:125 and encoding microfibrillar associated protein 5, represented herein by SEQ ID NO:42 and SEQ ID NO:43); Mglap (encoding matrix gamma-carboxyglutamate (gla) protein represented herein by SEQ ID NO:44 and SEQ ID NO:45); Naga (encoding N-acetyl galactosaminidase, alpha, represented herein by SEQ ID NO:46 and SEQ ID NO:47); Nbl1 (encoding neuroblastoma, suppression of tumorigenicity 1, represented herein by SEQ ID NO:48 and SEQ ID NO:49); Ngfb (encoding nerve growth factor, beta, represented herein by SEQ ID NO:50 and SEQ ID NO:51), Npnt (represented herein by SEQ ID NO:52 and SEQ ID NO:53 and encoding nephronectin); Olfm1 (encoding olfactomedin 1, represented herein by SEQ ID NO:54 and SEQ ID NO:55); and/or U90926 (encoding a protein represented herein by SEQ ID NO:56).

Any combinations of any of the above-identified biomarkers are included in the invention. In a preferred aspect of this embodiment, the biomarker is MAGP-2.

Another embodiment of the present invention relates to a method to identify a compound that regulates angiogenesis. The method includes the steps of: (a) detecting an initial level of the expression or activity of one or more biomarkers in a cell or soluble product derived therefrom, wherein the biomarker is a biomarker selected from a biomarker represented in any one or more of Table I, Table IV, Table V, and Table VI; (b) contacting the cell with a test compound; (c) detecting a level of the biomarker expression or activity in the cell or soluble product derived therefrom after contact of the cell with the compound; and, (d) selecting a compound that changes the level of biomarker expression or activity in the cell or soluble product therefrom, as compared to in the absence of the compound and/or as compared to the initial level of biomarker expression or activity, as a compound that regulates angiogenesis.

In one aspect of this embodiment, the biomarkers are any one or more of the biomarkers in Table VI.

In another aspect of this embodiment, the biomarkers are any one or more of the biomarkers selected from: ADAMts7, CRELD-2, Decorin, ECM1, Inhibin β-b, Integrin α-3, Integrin α-6, Lipocalin-7, Lox1-3, Lumican, MAGP-2, Matrilin-2, Nephronectin, SerpinE2, and/or SMOC-2.

In another aspect of this embodiment, the biomarkers are any one or more of the biomarkers selected from: 0610007C21Rik, apoptosis related protein APR-3, 1810014L12Rik, Cd14 (encoding CD14 antigen represented herein by SEQ ID NO:5 and SEQ ID NO:6), Cd38 (comprising a nucleic acid sequence represented herein by SEQ ID NO:7 and encoding CD38 antigen); Cd53 (encoding CD53 antigen represented herein by SEQ ID NO:8 and SEQ ID NO:9), Emp2 (encoding epithelial membrane protein represented herein by SEQ ID NO:10 and SEQ ID NO:11), Fcgrt (encoding Fc receptor (IgG, alpha chain transporter) represented herein by SEQ ID NO:12 and SEQ ID NO:13), Islr (encoding immunoglobulin superfamily containing leucine-rich repeat represented herein by SEQ ID NO:14 and SEQ ID NO:15); Lrp2 (comprising a nucleic acid sequence represented herein by SEQ ID NO:16 and SEQ ID NO:17 and encoding low density lipoprotein receptor-related protein 2); Ly6a (encoding lymphocyte antigen 6 complex, locus A represented herein by SEQ ID NO:18); P2rx4 (encoding purinergic receptor P2X, ligand-gated ion channel 4, represented herein by SEQ ID NO:19 and SEQ ID NO:20; Pcdhb9 (encoding protocadherin beta 9 represented herein by SEQ ID NO:21 and SEQ ID NO:22); Ptpre (encoding protein tyrosine phosphatase receptor type E represented herein by SEQ ID NO:23 and SEQ ID NO:24); Slc4a3 (encoding solute carrier family 4 (anion exchanger) member 3, represented herein by SEQ ID NO:25 and SEQ ID NO:26); and/or Tmc6 (encoding transmembrane channel-like gene family 6, represented herein by SEQ ID NO:27).

In yet another aspect of this embodiment, the biomarkers are any one or more of the biomarkers selected from: 9130213B05Rik (encoding a protein represented herein by SEQ ID NO:29); C1s (encoding complement component 1, s subcomponent, represented herein by SEQ ID NO:34 and SEQ ID NO:35); C3 (encoding complement component 3 represented herein by SEQ ID NO:30 and SEQ ID NO:31); Cfh (comprising a nucleic acid sequence represented herein by SEQ ID NO:32 and SEQ ID NO:33 and encoding complement component factor h); Col9a3 (comprising a nucleic acid sequence represented herein by SEQ ID NO:36 and SEQ ID NO:37 and encoding procollagen, type IX, alpha 3); Grem1 (encoding cysteine knot superfamily 1, BMP antagonist 1, represented herein by SEQ ID NO:38 and SEQ ID NO:39); Lox13 (encoding lysyl oxidase-like 3, represented herein by SEQ ID NO:40 and SEQ ID NO:41); MAGP-2 (comprising a nucleic acid sequence represented herein by SEQ ID NO:124 and SEQ ID NO:125 and encoding microfibrillar associated protein 5, represented herein by SEQ ID NO:42 and SEQ ID NO:43); Mglap (encoding matrix gamma-carboxyglutamate (gla) protein represented herein by SEQ ID NO:44 and SEQ ID NO:45); Naga (encoding N-acetyl galactosaminidase, alpha, represented herein by SEQ ID NO:46 and SEQ ID NO:47); Nbl1 (encoding neuroblastoma, suppression of tumorigenicity 1, represented herein by SEQ ID NO:48 and SEQ ID NO:49); Ngfb (encoding nerve growth factor, beta, represented herein by SEQ ID NO:50 and SEQ ID NO:51), Npnt (represented herein by SEQ ID NO:52 and SEQ ID NO:53 and encoding nephronectin); Olfm1 (encoding olfactomedin 1, represented herein by SEQ ID NO:54 and SEQ ID NO:55); and/or U90926 (encoding a protein represented herein by SEQ ID NO:56).

Any combinations of any of the above-identified biomarkers are included in the invention. In a preferred aspect of this embodiment, the biomarker is MAGP-2.

Another embodiment of the invention relates to a method to identify a compound useful for inhibition of tumor growth or malignancy. The method includes the steps of: (a) detecting an initial level of the expression or activity of one or more biomarkers in a cell or soluble product derived therefrom, wherein the biomarker is a biomarker represented in any one or more of Table I, Table IV, Table V, and Table VI; (b) contacting the tumor cell with a test compound; (c) detecting a level of biomarker expression or activity in the tumor cell or soluble product derived therefrom after contact of the tumor cell with the compound; and, (d) selecting a compound that changes the level of the biomarker expression or activity in the tumor cell or soluble product therefrom, as compared to the initial level of biomarker expression or activity, toward a baseline level of biomarker expression or activity established

from a non-tumor cell, wherein the selected compound is predicted to be useful for inhibition of tumor growth or malignancy.

Yet another embodiment of the present invention relates to a method for assessing the presence of tumor cells or potential therefore in a patient. The method includes the steps of: (a) detecting a level of expression or activity of the expression or activity of one or more biomarkers in a test sample from a patient to be diagnosed, wherein the biomarker is a biomarker represented in any one or more of Table I, Table IV, Table V, and Table VI; and (b) comparing the level of expression or activity of the biomarker in the test sample to a baseline level of biomarker expression or activity established from a control sample. Detection of a statistically significant difference in the biomarker expression or activity in the test sample, as compared to the baseline level of biomarker expression or biological activity, is an indicator of the presence of tumor cells or the potential therefore in the test sample as compared to cells in the control sample.

In one aspect of this embodiment, the step of detecting comprises detecting biomarker mRNA transcription by cells in the test sample. For example, such a step of detecting can be performed by a method selected from, but not limited to, polymerase chain reaction (PCR), reverse transcriptase-PCR (RT-PCR), in situ hybridization, Northern blot, sequence analysis, gene microarray analysis, and detection of a reporter gene. In one aspect, the step of detecting comprises detecting biomarker protein in the test sample. For example, such a step of detecting can be performed by a method selected from, but not limited to, immunoblot, enzyme-linked immunosorbant assay (ELISA), radioimmunoassay (RIA), immunoprecipitation, immunohistochemistry and immunofluorescence. In one aspect, the step of detecting comprises detecting biomarker biological activity in the test sample. For example, such a step of detecting can be performed by a method selected from, but not limited to, measuring proliferation of cells expressing the biomarker, measuring angiogenic sprouting of cells expressing the biomarker, and measuring migration and invasion ability of endothelial cells expressing the biomarker.

In one aspect of this embodiment, the test sample is from a source selected from the group consisting of: breast, kidney, ovary, colon, and uterus, in the patient. In another aspect, the test sample is from a patient being diagnosed for cancer and wherein the baseline level is established from a negative control sample that is established as non-tumorigenic.

In one aspect of this embodiment, the baseline level is established by a method selected from the group consisting of: (1) establishing a baseline level of biomarker expression or activity in an autologous control sample from the patient, wherein the autologous sample is from a same cell type, tissue type or bodily fluid type as the test sample of step (a); (2) establishing a baseline level of biomarker expression or activity from at least one previous detection of biomarker expression or activity in a previous test sample from the patient, wherein the previous test sample was of a same cell type, tissue type or bodily fluid type as the test sample of step (a); and, (3) establishing a baseline level of biomarker expression or activity from an average of control samples of a same cell type, tissue type or bodily fluid type as the test sample of step (a), the control samples having been obtained from a population of matched individuals.

Yet another embodiment of the invention relates to an assay kit for assessing angiogenesis or the presence of tumor cells in a patient, comprising: (a) a reagent for detecting the expression or activity of a biomarker in a test sample, wherein the biomarker is a biomarker represented in any one or more of Table I, Table IV, Table V, and Table VI; and (b) a reagent for detecting a control marker characteristic of a cell or tissue type that is in the test sample or that is secreted into the test sample by the cell or tissue. In one aspect, the reagent of (a) is selected from the group consisting of: a hybridization probe of at least about 8 nucleotides that hybridizes under stringent hybridization conditions to a nucleic acid molecule encoding the biomarker or a fragment thereof; an oligonucleotide primer for amplification of mRNA encoding the biomarker or a fragment thereof; and an antibody that selectively binds to the biomarker. In one aspect, the reagent of (b) is selected from the group consisting of: a hybridization probe of at least about 8 nucleotides that hybridizes under stringent hybridization conditions to a nucleic acid molecule encoding the control marker or a fragment thereof; an oligonucleotide primer for amplification of mRNA encoding the control marker or a fragment thereof; and an antibody that selectively binds to the control marker. In one aspect, the reagents of (a) and (b) are suitable for use in a method of detection selected from the group consisting of immunohistochemistry and immunofluorescence.

Yet another embodiment of the invention relates to a method to reduce angiogenesis in cells or a tissue of a patient, comprising decreasing the expression or biological activity of Microfibril-associated glycoprotein-2 (MAGP-2) in the cells or tissue.

Another embodiment of the invention relates to a method to promote angiogenesis in cells or a tissue of a patient, comprising increasing the expression or biological activity of MAGP-2 in the cells or tissue.

Another embodiment of the invention relates to the use of MAGP-2 or a fragment or homologue thereof, or a nucleic acid molecule encoding MAGP-2 or a fragment or homologue thereof, or an agonist or antagonist of MAGP-2, in the preparation of a medicament for the regulation of angiogenesis.

BRIEF DESCRIPTION OF THE FIGURES OF THE INVENTION

FIG. **1**A is a bar graph shows DNA synthesis (determined by measuring [^{3}H]thymidine incorporation into cellular DNA) in serum-starved MB114 cells stably expressing either GFP or various putative angiogenic agents, stimulated in the absence or presence of either bFGF (50 ng/ml) or EGF (10 ng/ml) for 24 h at 37° C. (data are the mean (±SEM) of five independent experiments for MAGP-2 and SMOC-2, and of three independent experiments of CRELD-2; *, $p<0.05$; Student's T-Test).

FIG. **1**B is a bar graph showing the invasion of MB114 cells expressing either GFP or various putative angiogenic agents through synthetic basement membranes over 48 h using a modified Boyden-chamber assay (data are the mean (±SEM) of three independent experiments; *, $p<0.05$; Student's T-Test).

FIGS. **1**C and **1**D are bar graphs showing p38 MAPK phosphorylation in serum-starved MB114 cells expressing MAGP-2 (FIG. **1**C) or lumican (FIG. **1**D), stimulated with either bFGF (50 ng/ml) or EGF (10 ng/ml) 0-15 min (data are the mean (±SEM) of 5 independent experiments; *, $p<0.05$; Student's T-Test).

FIG. **1**E is a bar graph showing endothelial cell sprouting in MB114 cells expressing either GFP or various putative angiogenic agents (data are the mean (×SEM) of 5 independent experiments for lumican, SMOC-2, CRELD-2, MAGP-2, and Matrilin-2, and of three independent experiments for AK76 and ECM-1; *, $p<0.05$; Student's T-Test).

FIG. 2A shows that MAGP-2 (MAGP-2 purity was monitored by coomassie staining, and by immunoblotting with anti-FLAG M2 monoclonal antibodies (right panel)) promotes angiogenesis in vivo, as measured by angiogenic sprouting of quiescent MB114 cell monolayers (left panel) (data are the mean (±SEM) of two independent experiments; *, $p<0.05$; Student's T-Test).

FIG. 2B shows the results of subcutaneous injection of C57BL/6 female mice with Matrigel supplemented either with diluent (D), bFGF (50 ng/ml, LD; or 300 ng/ml, HD), or bFGF (50 ng/ml) in combination with MAGP-2 (1 μg/ml), where plugs were harvested and photographed (left panels), and then fixed, sectioned, and stained with Masson's trichrome to visualize infiltrating blood vessels (right panels; arrows denote blood vessels) (data are the mean (±SEM) of four independent experiments; *, **, ***, $p<0.05$; Student's Test).

FIG. 3A is a bar graph showing that MAGP-2 inhibits Hes-1 promoter activity in ECs (data are mean (±SEM) of 2 independent experiments).

FIG. 3B is a bar graph also showing that MAGP-2 inhibits Hes-1 promoter activity in ECs (data are the mean (±SEM) of four independent experiments; *, **, ***, $p<0.05$; Student's Test).

FIG. 4A shows Notch1 cleavage products (upper) and the densitometric analysis of Notch1 NICD production in response to experimental treatments (lower) in human 293T cells transiently transfected with cDNAs encoding Myc-tagged versions of Notch1, Jagged-1, and MAGP-2 in all combinations as indicated (data are the mean (±SEM) of four independent experiments; *, **, $p<0.05$; Student's T-Test; N, Notch1; N/M, Notch1 plus MAGP-2; N/J, Notch1 plus Jagged-1; N/J/M, Notch1, Jagged-1, and MAGP-2).

FIG. 4B shows luciferase activity after stimulation with TGF-β1 in GFP- and MAGP-2-expressing MB114 cells transiently transfected with either pHes1- or pSBE-luciferase, both together with pCMV-β-gal as indicated (data are the mean (±SEM) of 3 independent experiments; *, $p<0.05$; Student's T-Test).

FIG. 5A is a bar graph showing Hes-1 luciferase activity in MB114 cells transiently transfected with pHes1-luciferase and pCMV-β-gal cDNAs, incubated overnight in the absence or presence of DAPT (10 μM) (data are the mean (±SEM) of two independent experiments).

FIG. 5B is a bar graph showing endothelial angiogenic sprouting in quiescent MB114 cell monolayers induced to form angiogenic sprouts by addition of 10% FBS supplemented with or without DAPT (10 μM) (data are the mean (±SEM) of four independent experiment. (*, $p<0.05$; Student's T-Test)).

FIG. 5C is a bar graph showing Hes-1 luciferase activity in GFP-, MAGP-2-, and MAGP-2/N1ICD-expressing MB114 cells transiently transfected with pHes1-luciferase and pCMV-β-gal cDNAs (data are the mean (±SEM) of two independent experiments).

FIG. 5D is a bar graph showing endothelial angiogenic sprouting in quiescent monolayers of GFP-, MAGP-2-, and MAGP-2/N1ICD-expressing MB114 cells (bottom shows representative photomicrographs of angiogenic sprouts produced by GFP-, MAGP-2-, and MAGP-2N1ICD-expressing MB114 cells; data are the mean (±SEM) of four independent experiments; *, **, $p<0.05$; Student's T-Test).

FIG. 6 is a digitized image showing the time course of angiogenesis in vitro.

FIGS. 7A and 7B show retroviral expression of selected potential angiogenic proteins in MB114 cells via detergent-solubilized cell extracts (FIG. 7A) and semi-quantitative real-time PCR (FIG. 7B).

FIG. 8 is a digitized image showing that MAGP-2 is expressed aberrantly in a majority of human uterine tumors.

DETAILED DESCRIPTION OF THE INVENTION

The present invention generally relates to the discovery by the present inventor of several genes, and the proteins encoded thereby, that are associated with angiogenesis. More particularly, the present inventors used microarray analyses to monitor changes in the transcriptome of ECs undergoing angiogenesis when cultured onto tumor-derived basement membranes in vitro. In doing so, the inventors identified 308 genes whose expression was altered at least 3-fold during the angiogenic time course. Of these differentially-expressed genes, 63 encoded for EC secretory proteins and several were shown to mediate pro- or anti-angiogenic activities in vitro (e.g., SMOC-2, secreted MAGP-2 Promotes Angiogenesis modular calcium-binding protein-2; CRELD-2, cysteine-rich with EGF-like domains-1; MAGP-2, microfibril-associated glycoprotein-2; lumican; ECM-1, extracellular matrix protein-1). Expression of one of these genes, MAGP-2 (also known as Microfibrillar associated protein-5 (MFAP-5)), enhanced EC proliferation and p38 MAPK activation stimulated by bFGF, as well as stimulated EC invasion through synthetic basement membranes. The inventors have also demonstrated that MAGP-2 promoted EC sprouting in vitro, and as such, stimulated vessel formation and infiltration into Matrigel plugs implanted into genetically normal mice. Importantly, the inventors show herein that Notch1 activation prevented angiogenesis in vitro, a reaction that was overcome by MAGP-2-mediated antagonism of Notch1 signaling in ECs. Collectively, the inventors' findings have established MAGP-2 as a novel inducer of angiogenesis, doing so in part through its ability to antagonize Notch1 signaling in ECs. In addition, the inventors' findings have identified several additional targets for use in diagnostic, drug discovery and therapeutic applications related to the inhibition or promotion of angiogenesis.

More particularly, in order to increase the understanding of the role of ECs in mediating the remodeling of tumor and vascular microenvironments during pathological angiogenesis, the inventors cultured ECs on tumor-derived basement membranes to induce angiogenesis in vitro, and subsequently performed microarray analyses to identify alterations within the EC transcriptome that accompanied angiogenesis activation. In doing so, they focused specifically on genes that encoded secretory proteins or components of the ECM, which collectively comprised 20% (i.e., 63 out of 308 genes) of the differentially-expressed EC genes identified by the inventors (Table I). The analyses described herein also identified an additional 35 (~11%) membrane-spanning and/or membrane-associated genes, whose expression and activation likely mediate paracrine and/or autocrine signaling in angiogenic ECs. Thus, secreted molecules constituted a significant fraction (~31%) of all differentially regulated EC genes identified herein, thereby highlighting the importance of microenvironment remodeling during angiogenesis. The proportion of differentially-expressed EC genes classified as secretory proteins was similar to those observed in other recent EC transcriptome analyses (Aitkenhead et al, 2002; Bell et al, 2001; Kahn et al, 2000). However, unlike these profiling studies, the present inventors specifically investigated the inductive effect of tumor-derived basement membranes (i.e.,

Matrigel matrices) in regulating gene expression in tubulating ECs, and as such, numerous secretory proteins not previously associated with angiogenesis were identified (see Table I). Moreover, the inventors' identification of known angiogenic genes (Table I) validated this experimental design and gave credence to the notion that many of these newly identified genes may function as bone fide regulators of angiogenesis. Indeed, the present inventors' findings implicate ECM-1 and lumican as mediators of angiostasis, while CRELD-2 and SMOC-2 are proposed herein to function as novel mediators of angiogenesis (see discussion below). The ability of these EC secretory proteins to affect vessel development in vivo, as well as the molecular mechanisms whereby they mediate their pro- or anti-angiogenic activities in ECs can now be evaluated using the guidance provided herein.

An especially important finding of the present study was the inventors' identification of MAGP-2 as a novel mediator of angiogenesis. Indeed, the present inventors show for the first time that MAGP-2 expression stimulates EC proliferation, invasion, and angiogenic sprouting, as well as enhances EC activation of p38 MAPK in response to bFGF and EGF (FIG. **1**). Moreover, MAGP-2 is shown to enhance the ability of bFGF to promote neovascularization and vessel infiltration into Matrigel plugs implanted into genetically normal mice (FIG. **2**). Mechanistically, MAGP-2 is shown to induce angiogenesis through its ability to inhibit Notch1 processing and activation (FIGS. **3** and **4**), an inhibitory reaction that is rescued by constitutive expression of Notch1 NICD (FIG. **5**). Collectively, these findings have established MAGP-2 as a novel activator of angiogenesis, doing so in part via its ability to inhibit the Notch1 signaling pathway.

The precise mechanism whereby MAGP-2 antagonizes Notch1 signaling remains to be determined. Recent studies using heterologous cell expression systems have shown MAGP-2 to interact physically with Notch1 and its ligand, Jagged-1, resulting in their shedding from the cell surface (Miyamoto et al, 2006; Nehring et al, 2005). Although the inventors made no attempt to measure Notch1 and/or Jagged-1 extracellular domain shedding in response to MAGP-2, the production of such soluble Notch1 and Jagged-1 extracellular domains readily inhibits Notch signaling (Rebay et al, 1993; Small et al, 2001). In this fashion, MAGP-2 expression was observed to block the ability of Jagged-1 to stimulate Notch1 processing and the production of NICD, thereby preventing transactivation of the Hes1 promoter in ECs. Thus, MAGP-2 may promote angiogenesis in part by inducing Notch1 and/or Jagged-1 ectodomain shedding in ECs. In contrast to the present inventors' findings, Miyamoto et al (Miyamoto et al, 2006) recently found that MAGP-2 not only induces Notch1 ectodomain shedding in Cos-7 and NIH-3T3 cells, but also Notch1 processing and NICD production, leading to transcriptional activation of the Hes5 and CSL promoters. The reasons underlying this discrepancy are currently unknown, but most likely reflect differences in the cell types studied (i.e., ECs versus fibroblasts and kidney epithelial cells), as well as differences in microenvironmental factors that may influence the interactions between MAGP-2 and Notch1. In addition, cell-type specific expression of various Notch receptor and ligand combinations may also impact the ability of MAGP-2 to regulate, either positively or negatively, Notch signaling in responsive cells. Indeed, the present inventors, without being bound by theory, believe that MAGP-2 regulates angiogenesis in a context-specific manner via its ability to target both Notch signaling and elastin microfibril networks.

The present inventors' findings demonstrating the ability of MAGP-2 to stimulate angiogenesis by preventing Notch1 activation is intellectually credible in light of the established function of Notch in mediating angiostasis (Leong et al, 2002; Liu et al, 2006; Noseda et al, 2004; Williams et al, 2006; Zimrin et al, 1996). Moreover, the inventors recently observed MAGP-2 expression to be abnormally elevated in human uterine cancers (Example 6), and to significantly increase the growth and vascularization of MCA102 fibrosarcomas produced in mice (Albig and Schiemann, unpublished observation). It should be noted, however, that Notch activation also has been shown to stimulate angiogenesis (Leong and Karsan, 2005; Shawber and Kitajewski, 2004), and as such, it cannot yet be ascertained whether MAGP-2 promotes tumorigenesis by alleviating Notch1-mediated angiostasis, or by facilitating Notch1-mediated angiogenesis. The mechanisms whereby Notch mediates such disparate activities in ECs remains unclear, but may reflect a complex integration of cellular and environmental cues. Indeed, Notch signaling is subject to regulation by (i) the relative expression levels of various Notch receptors (Delaney et al, 2005; Duarte et al, 2004); (ii) the extent and form of Notch receptor glycosylation (Haines and Irvine, 2003); (iii) the availability of various Notch ligands within vascular microenvironments; and (iv) the activation of various Notch inhibitors, including MINT, Numb, NRARP, and proteolyzed ligands (Kadesch, 2004). The present inventors' findings herein and those by others (Miyamoto et al, 2006; Sakamoto et al, 2002) clearly show Notch signaling to be influenced by environmental cues, such as those produced by MAGP-2 (demonstrated herein).

Numerous additional EC secretory proteins were identified whose expression was also regulated by angiogenesis (Tables I and VI), suggesting that EC expression of these genes was obligatory for vessel development. Moreover, in vitro assays that modeled key steps in the angiogenic process showed that several these newly identified genes did indeed regulate EC activities-coupled to angiogenesis. For instance, lumican expression was found to inhibit MB114 cell proliferation (data not shown) and angiogenic sprouting (FIG. **1**), as well as reduce the ability of bFGF and EGF to activate p38 MAPK in MB114 cells (FIG. **1**). Lumican belongs the SLRP (small leucine-rich proteoglycan) family of ECM proteins, which also includes fibromodulin, biglycan, and the angiogenesis antagonist, decorin (Davies Cde et al, 2001; Kao et al, 2006; Sulochana et al, 2005). Genetic ablation of lumican in. mice indicates that this secreted proteoglycan functions in organizing collagen fibrils in the skin and cornea (Chakravarti et al, 1998). Additionally, lumican interacts physically with FasL (Fas-ligand), leading to enhanced Fas expression in and subsequent apoptosis of corneal fibroblasts (Vij et al, 2004; Vij et al, 2005). Recently, elevated lumican expression has been associated with cancers of the pancreas (Ping Lu et al, 2002), breast (Leygue et al, 1998), cervix (Naito et al, 2002), and colon (Lu et al, 2002), suggesting that lumican may promote tumorigenesis in these organs. In stark contrast, lumican expression also has been shown to inhibit the anchorage-independent growth and invasion of B16F1 melanoma cells in vitro, as well as their ability to form tumors in when implanted into mice (Vuillermoz et al, 2004). Thus, lumican also may function in suppressing cancer development and progression. Along these lines, the inventors have found that lumican antagonizes the development and infiltration of vessels in Matrigel plugs implanted into mice, as well as decreases the growth and blood vessel density of MCA102 fibrosarcomas produced in mice (Albig and Schiemann, unpublished observations).

The inventors further showed that ECM-1 is functionally similar to lumican and antagonized angiogenic sprouting by

MB114 cells (FIG. 1). ECM-1 is a broadly distributed glycoprotein that plays important roles in maintaining normal skin structure, function, and homeostasis (Chan, 2004). In humans, loss of function mutations in ECM-1 elicit a rare genetic skin disease called lipoid proteinosis (Chan, 2004; Hamada et al, 2002), whose clinicopathological features are phenocopied in patients with lichen sclerosus, an acquired inflammatory disorder of the skin and mucous membranes associated with the development self-reactive ECM-1 antibodies (Oyama et al, 2003). Interestingly, both skin conditions are characterized by the (i) abnormal development of cutaneous microvessels, and (ii) excessive deposition of basement membrane proteins, leading to thickened mucous and vascular basement membranes (Kowalewski et al, 2005). ECM-1 overexpression is observed in cancers of the breast, esophagus, thyroid, stomach, and colon (Han et al, 2001; Kebebew et al, 2005; Wang et al, 2003), and has been associated with the acquisition of angiogenic (Han et al, 2001) and metastatic phenotypes (Wang et al, 2003). Thus, ECM-1 is an important regulator of basement membrane protein secretion and deposition, and quite possibly, of microenvironment remodeling (Kowalewski et al, 2005; Mirancea et al, 2006). As such, aberrant ECM-1 production likely dysregulates normal microenvironment conditions operant in balancing pro- and anti-angiogenic signals, leading to altered vessel formation and disease development in humans.

In contrast to lumican and ECM-1, the inventors observed CRELD-2 expression to significantly increase MB114 cell invasion, and to promote a trend towards enhanced angiogenic sprouting (FIG. 1), indicating that this secreted EGF-like domain containing protein may serve to enhance angiogenesis. Along these lines, the inventors found SMOC-2 expression to enhance the proliferative response of MB114 cells to bFGF, and more importantly, to increase MB114 cell invasion and angiogenic cell sprouting (FIG. 1). SMOC-2 and its related molecule, SMOC-1, are widely expressed glycoproteins that localize predominantly to basement membranes, and to various ECM structures (Vannahme et al, 2003; Vannahme et al, 2002). Structurally, SMOCs are defined by a unique, centrally located SMOC domain that is flanked N-terminally by follistatin-like and thyroglobulin-like domains, and C-terminally by an extracellular calcium-binding (EC) domain reminiscent of that found in SPARC (Vannahme et al, 2003; Vannahme et al, 2002). Interestingly, proteolytic cleavage of SPARC results in the release of biologically active fragments that can induce angiogenesis (Funk and Sage, 1993; Sage et al, 2003). SPARC, however, also mediates angiostasis by interacting physically with VEGF via its EC domain (Jendraschak and Sage, 1996; Kupprion et al, 1998). Thus, given the functional and structural similarities between SMOC-2 and SPARC, it remains to be determined whether SMOC-2 also mediates pro- and anti-angiogenic activities, and if so, whether these disparate EC activities occur via direct or indirect mechanisms.

Collectively, the inventors' findings indicate that lumican and EMC-1 function as novel angiogenesis antagonists, while CRELD-2 and SMOC-2 function as novel angiogenesis agonists. The molecular mechanisms underlying their ability to impact the activation or resolution of angiogenesis can now be determined.

The present invention more particularly relates to genes, nucleic acid molecules derived therefrom, and proteins or fragments thereof encoded by such genes and nucleic acid molecules, as well as homologues of such genes and proteins and related agents (e.g., antibodies, agonists, antagonists), and the use or targeting of such genes, nucleic acids, proteins, homologues and/or related agents, and/or compositions or formulations comprising the same, in methods related to the inhibition or promotion of angiogenesis, including the inhibition of angiogenesis for the inhibition or treatment of cancer. As discussed above, the present inventors identified 308 genes whose expression in angiogenic ECs was altered ≧3-fold. Of these differentially-expressed genes, 63 genes (~20%) encoded EC secretory proteins (Table I), 35 genes (~11%) encoded transmembrane or membrane-associated proteins (Table V), and 210 genes encoded non-secretory proteins (Table IV). This approach identified several secretory proteins that were previously known to be associated with angiogenesis and/or microenvironment remodeling, including ADAMTS1 (Iruela-Arispe et al, 2003), CTGF (Brigstock, 2002), HGF (Gao and Vande Woude, 2005), MMPs 3 and 9 (Heissig et al, 2003), thrombospondins 1 and 2 (Armstrong and Bornstein, 2003), and TIMP3 (Qi et al, 2003) (Table I, bold type face). In addition, the inventors identified numerous secretory proteins not previously associated with angiogenesis (e.g., Table I, regular text face), all of which are encompassed by the present invention. The inventors verified the differential expression of 19 individual genes by semi-quantitative real-time PCR (see Materials and Methods). These analyses showed significant concordance in the expression profiles measured either by real-time PCR or microarray analyses (Table VI), indicating that these (and other) genes are indeed bona fide targets of angiogenic signaling systems in tubulating ECs.

Accordingly genes that are encompassed by the present invention (as well as nucleic acid molecules derived from or comprising at least a portion of the coding region and/or regulatory region of such genes and any proteins or fragments thereof encoded by such genes) include any of the genes or portions of genes (including ESTs) represented in Table I, Table IV, Table V, and/or Table VI. Preferred genes for use in the present invention include any of the genes presented in regular (non-bold)-type face in Table I or Table V and/or any of the genes in Table VI. The invention also includes the use of nucleic acid molecules derived from or comprising at least a portion of the coding region and/or regulatory region of such genes and any proteins or fragments thereof encoded by such genes. Particularly preferred genes for use in the present invention include any of the genes in Table VI. The invention also includes the use of nucleic acid molecules derived from or comprising at least a portion of the coding region and/or regulatory region of such genes and any proteins or fragments thereof encoded by such genes.

In one embodiment, the invention includes the use of genes encoding any one or more of the following proteins, the genes or nucleic acid sequences therein, or primers used to amplify and identify such genes being identified in Table I and/or Table III and/or Table VI:

murine ADAMts7 (encoded by a gene comprising the nucleic acid sequence found in GenBank Accession No. AL359939),

human ADAMts7 (encoded by a gene comprising the nucleic acid sequence found in GenBank Accession No. AF140675),

murine CRELD-2 or the human equivalent thereof (murine CRELD-2 encoded by a gene comprising the nucleic acid sequence found in GenBank Accession No. AK017880),

murine Decorin (encoded by a gene comprising the nucleic acid sequence found in GenBank Accession No. NM_007833),

human Decorin (encoded by a gene comprising the nucleic acid sequence found in GenBank Accession No. AH002681),

murine ECM1 (encoded by a gene comprising the nucleic acid sequence found in GenBank Accession No. NM_007899),

human ECM1 (encoded by a gene comprising the nucleic acid sequence found in GenBank Accession No. NP_001415),

murine Inhibin β-b (encoded by a gene comprising the nucleic acid sequence represented herein by SEQ ID NO:97 or SEQ ID NO:98)

human Inhibin β-b (encoded by a gene comprising the nucleic acid sequence found in GenBank Accession No. NM_002193),

murine Integrin α-3 (encoded by a gene comprising the nucleic acid sequence represented herein by SEQ ID NO:99 or SEQ ID NO:100),

human Integrin α-3 (encoded by a gene comprising the nucleic acid sequence found in GenBank Accession No. E16082),

murine Integrin α-6 (encoded by a gene comprising the nucleic acid sequence represented herein by SEQ ID NO:101 or SEQ ID NO:102),

human Integrin α-6 (encoded by a gene comprising the nucleic acid sequence found in, for example, GenBank Accession No. AH008066),

murine Lipocalin-7 (encoded by a gene comprising the nucleic acid sequence found in GenBank Accession No. BC005738 and represented herein by SEQ ID NO:103 or SEQ ID NO:104),

human Lipocalin-7 (encoded by a gene comprising the nucleic acid sequence found in GenBank Accession No. NM_022164),

murine Lox1-3 (encoded by a gene comprising the nucleic acid sequence found in GenBank Accession No. NM_013586, the amino acid sequence encoded by which is represented herein by SEQ ID NO:40),

human Lox1-3 (encoded by a gene comprising the nucleic acid sequence found in GenBank Accession No. AAH71865, the amino acid sequence encoded by which is represented herein by SEQ ID NO:41),

murine Lumican (encoded by a gene comprising the nucleic acid sequence found in GenBank Accession No. AK014312),

human Lumican (encoded by a gene comprising the nucleic acid sequence found in GenBank Accession No. AF239660),

murine MAGP-2 (encoded by a gene comprising the nucleic acid sequence found in GenBank Accession No. NM_015776 and represented herein by SEQ ID NO:123, the amino acid sequence encoded by which is represented herein by SEQ ID NO:42),

human MAGP-2 (encoded by a gene comprising the nucleic acid sequence found in GenBank Accession No. AAC83942 and represented herein by SEQ ID NO:124, the amino acid sequence encoded by which is represented herein by SEQ ID NO:43),

murine Matrilin-2 (encoded by a gene comprising the nucleic acid sequence found in GenBank Accession No. BC005429),

human Matrilin-2 (encoded by a gene comprising the nucleic acid sequence found in GenBank Accession No. BC010444),

murine Nephronectin (encoded by a gene comprising the nucleic acid sequence found in GenBank Accession No. AA223007 the amino acid sequence encoded by which is represented herein by SEQ ID NO:52),

human Nephronectin (encoded by a gene comprising the nucleic acid sequence found in GenBank Accession No. NM_001033047, the amino acid sequence encoded by which is represented herein by SEQ ID NO:53),

murine SerpinE2 (encoded by a gene comprising the nucleic acid sequence found in GenBank Accession No. NM_009255),

human SerpinE2 (encoded by a gene comprising the nucleic acid sequence found in GenBank Accession No. BC042628),

murine SMOC-2 (encoded by a gene comprising the nucleic acid sequence found in GenBank Accession No. NM_022315), and

human SMOC-2 (encoded by a gene comprising the nucleic acid sequence found in GenBank Accession No. NM_022138).

The invention also includes the use of nucleic acid molecules derived from or comprising at least a portion of the coding region and/or regulatory region of such genes and any proteins or fragments thereof encoded by such genes, as well as agonists and antagonists of any of such proteins or genes.

In another embodiment, the invention includes the use of genes from Table V encoding any one or more of the following proteins:

murine 0610007C21Rik (GenBank Accession No. AK002276; encoding a protein represented herein by SEQ ID NO:1);

human apoptosis related protein APR-3 (GenBank Accession No. AF144055; encoding a protein represented herein by SEQ ID NO:2);

murine 1810014L12Rik (GenBank Accession No. NM_133706; encoding a protein represented herein by SEQ ID NO:3);

human 1810014L12Rik (GenBank Accession No. NP_055388; encoding a protein represented herein by SEQ ID NO:4);

murine Cd14 (GenBank Accession No. NM_009841; encoding CD14 antigen represented herein by SEQ ID NO:5);

human Cd14 (GenBank Accession No. NP_000638; encoding CD14 antigen represented herein by SEQ ID NO:6);

murine Cd38 (GenBank Accession No. BB256012; comprising a nucleic acid sequence represented herein by SEQ ID NO:7 and encoding CD38 antigen);

murine Cd53 (GenBank Accession No. NM_007651; encoding CD53 antigen represented herein by SEQ ID NO:8);

human Cd53 (GenBank Accession No. NP_000551; encoding CD53 antigen represented herein by SEQ ID NO:9);

murine Emp2 (GenBank Accession No. AF083076; encoding epithelial membrane protein represented herein by SEQ ID NO:10);

human Emp2 (GenBank Accession No. NP_001415; encoding epithelial membrane protein represented herein by SEQ ID NO:11);

murine Fcgrt (GenBank Accession No. NM_010189; encoding Fc receptor (IgG, alpha chain transporter) represented herein by SEQ ID NO:12);

human Fcgrt (GenBank Accession No. NP_004098; encoding Fc receptor (IgG, alpha chain transporter) represented herein by SEQ ID NO:13);

murine Islr (GenBank Accession No. NM_012043; encoding immunoglobulin superfamily containing leucine-rich repeat represented herein by SEQ ID NO:14);

human Islr (GenBank Accession No. NP_005536; encoding immunoglobulin superfamily containing leucine-rich repeat represented herein by SEQ ID NO:15);

murine Lrp2 (GenBank Accession No. C80829; comprising a nucleic acid sequence represented herein by SEQ ID NO:16 and encoding low density lipoprotein receptor-related protein 2);

human Lrp2 (GenBank Accession No. NP_004516; comprising a nucleic acid sequence represented herein by SEQ ID NO:17 and encoding low density lipoprotein receptor-related protein 2);

murine Ly6a (GenBank Accession No. BC002070; encoding lymphocyte antigen 6 complex, locus A represented herein by SEQ ID NO:18);

murine P2rx4 (GenBank Accession No. AJ251462; encoding purinergic receptor P2X, ligand-gated ion channel 4, represented herein by SEQ ID NO:19);

human P2rx4 (GenBank Accession No. Q99571; encoding purinergic receptor P2X, ligand-gated ion channel 4, represented herein by SEQ ID NO:20);

murine Pcdhb9 (GenBank Accession No. NM_053134; encoding protocadherin beta 9 represented herein by SEQ ID NO:21);

human Pcdhb9 (GenBank Accession No. AA103495; encoding protocadherin beta 9 represented herein by SEQ ID NO:22);

murine Ptpre (GenBank Accession No. U35368; encoding protein tyrosine phosphatase receptor type E represented herein by SEQ ID NO:23);

human Ptpre (GenBank Accession No. NP_569119; encoding protein tyrosine phosphatase receptor type E represented herein by SEQ ID NO:24);

murine Slc4a3 (GenBank Accession No. NM_009208; encoding solute carrier family 4 (anion exchanger) member 3, represented herein by SEQ ID NO:25);

human Slc4a3 (GenBank Accession No. NP_005061; encoding solute carrier family 4 (anion exchanger) member 3, represented herein by SEQ ID NO:26);

murine Tmc6 (GenBank Accession No. BC004840; encoding transmembrane channel-like gene family 6 represented herein by SEQ ID NO:27).

and/or human Tmc6 (GenBank Accession No. AAH35648; encoding transmembrane channel-like gene family 6 represented herein by SEQ ID NO:28).

The invention also includes the use of nucleic acid molecules derived from or comprising at least a portion of the coding region and/or regulatory region of such genes and any proteins or fragments thereof encoded by such genes, as well as agonists and antagonists of any of such proteins or genes.

In another embodiment, the invention includes the use of genes from Table I encoding any one or more of the following proteins:

murine 9130213B05Rik (GenBank Accession No. BC006604; encoding a protein represented herein by SEQ ID NO:29);

murine C1s (GenBank Accession No. BC022123; encoding complement component 1, s subcomponent, represented herein by SEQ ID NO:34);

human C1s (GenBank Accession No. NM_001734; encoding complement component 1, s subcomponent, represented herein by SEQ ID NO:35);

murine C3 (GenBank Accession No. K02782; encoding complement component 3 represented herein by SEQ ID NO:30);

human C3 (GenBank Accession No. NP_000055; encoding complement component 3 represented herein by SEQ ID NO:31);

murine Cfh (GenBank Accession No. AI987976; comprising a nucleic acid sequence represented herein by SEQ ID NO:32 and encoding complement component factor h);

human Cfh (GenBank Accession No. CAA30403; comprising a nucleic acid sequence represented herein by SEQ ID NO:33 and encoding complement component factor h);

murine Col9a3 (GenBank Accession No. BG074456; comprising a nucleic acid sequence represented herein by SEQ ID NO:36 and encoding procollagen, type IX, alpha 3);

human Col9a3 (GenBank Accession No. Q14050; comprising a nucleic acid sequence represented herein by SEQ ID NO:37 and encoding procollagen, type IX, alpha 3);

murine Grem1 (GenBank Accession No. BC015293; encoding cysteine knot superfamily 1, BMP antagonist 1, represented herein by SEQ ID NO:38);

human Grem1 (GenBank Accession No. NP_037504; encoding cysteine knot superfamily 1, BMP antagonist 1, represented herein by SEQ ID NO:39);

murine Lox13 (GenBank Accession No. NM_013586; encoding lysyl oxidase-like 3, represented herein by SEQ ID NO:40);

human Lox13 (GenBank Accession No. AAH71865; encoding lysyl oxidase-like 3, represented herein by SEQ ID NO:41);

murine MAGP-2 (GenBank Accession No. NM_015776; comprising a nucleic acid sequence represented herein by SEQ ID NO:123 and encoding microfibril-associated glycoprotein-2 (also known as microfibrillar associated protein 5), represented herein by SEQ ID NO:42);

human MAGP-2 (GenBank Accession No. AAC83942; comprising a nucleic acid sequence represented herein by SEQ ID NO:124 and encoding microfibrillar associated protein 5, represented herein by SEQ ID NO:43);

murine Mglap (GenBank Accession No. NM_008597; encoding matrix gamma-carboxyglutamate (gla) protein represented herein by SEQ ID NO:44);

human Mglap (GenBank Accession No. AAP36640; encoding matrix gamma-carboxyglutamate (gla) protein represented herein by SEQ ID NO:45);

murine Naga (GenBank Accession No. BC021631; encoding N-acetyl galactosaminidase, alpha, represented herein by SEQ ID NO:46);

human Naga (GenBank Accession No. NP_000253; encoding N-acetyl galactosaminidase, alpha, represented herein by SEQ ID NO:47);

murine Nbl1 (GenBank Accession No. NM_008675; encoding neuroblastoma, suppression of tumorigenicity 1, represented herein by SEQ ID NO:48);

human Nbl1 (GenBank Accession No. AAL15440; encoding neuroblastoma, suppression of tumorigenicity 1, represented herein by SEQ ID NO:49);

murine Ngfb (GenBank Accession No. NM_013609; encoding nerve growth factor, beta, represented herein by SEQ ID NO:50);

human Ngfb (GenBank Accession No. AAH32517; encoding nerve growth factor, beta, represented herein by SEQ ID NO:51);

murine Npnt (GenBank Accession No. AA223007; encoding nephronectin and represented herein by SEQ ID NO:52);

human Npnt (GenBank Accession No. NM_001033047; encoding nephronectin and represented herein by SEQ ID NO:53);

murine Olfm1 (GenBank Accession No. C78264; encoding olfactomedin 1, represented herein by SEQ ID NO:54);

human Olfm1 (GenBank Accession No. Q99784; encoding olfactomedin 1, represented herein by SEQ ID NO:55);

and/or murine U90926 (GenBank Accession No. NM_020562; encoding a protein represented herein by SEQ ID NO:56).

The invention also includes the use of nucleic acid molecules derived from or comprising at least a portion of the coding region and/or regulatory region of such genes and any proteins or fragments thereof encoded by such genes.

The genes identified in the Tables herein are identified by name, by GenBank Accession numbers, and by description of the protein, when available. The amino acid sequence for several of the proteins encoded by the genes in the Tables herein are also provided herein. All information associated with the publicly available identifiers and accession numbers in any of the tables described herein, including the nucleic acid sequences of the genes and probes and the amino acid sequences of the proteins encoded thereby, is incorporated herein by reference in its entirety.

Genes and proteins identified in the present invention can also be referred to as "biomarkers". The term "biomarker" as used herein can refer to gene described herein or to the protein encoded by that gene, wherein the gene has been identified as being differentially regulated during angiogenesis. In addition, the term "biomarker" can be generally used to refer to any portion of such a gene or protein that can identify or correlate with the full-length gene or protein, for example, in an assay or other method of the invention.

Microfibril-associated glycoprotein-2 (MAGP-2) is a secreted glycoprotein (25 kDa) that incorporates into and organizes elastin fibril networks by interacting with tropoelastin, and with fibrillins 1 and 2; it also mediates cell adhesion by ligating integrins via its RGD integrin-binding motif (Gibson et al, 1998; Gibson et al, 1999). Abnormally elevated MAGP-2 expression is observed in the skin of systemic sclerosis patients, as well as in mouse models of systemic sclerosis that have associated MAGP-2 expression with excessive matrix deposition of type I collagen (Lemaire et al, 2004; Lemaire et al, 2005). Moreover, skin lesions in systemic sclerosis patients contain aberrant vessel morphologies characteristic of abnormal angiogenesis (Bodolay et al, 2002). In addition, MAGP-2 expression is induced in human T-47DE3 breast cancer cells when treated with progestin (Graham et al, 2005), and in human A549 lung adenocarcinoma cells when implanted into nude mice (Creighton et al, 2003). Most recently, MAGP-2 has been shown to interact physically with Notch1 (Miyamoto et al, 2006) and its ligand, Jagged-1 (Nehring et al, 2005), leading to the ectodomain shedding of both molecules from the cell surface.

Human MAGP-2 cDNA has been cloned and described, for example, in Faraco et al. (*Genomics*. 1995 Feb. 10; 25(3):630-7) and in Gibson et al. (J Biol Chem. 1996 Jan. 12; 271(2): 1096-103). The organization of the human MAGP-2 gene is described in Hatzinikolas and Gibson (*J Biol Chem.* 1998 Nov. 6; 273(45):29309-14). The organization of the mouse MAGP-2 gene has been described by Frankfater et al. (*Mamm Genome.* 2000 Mar.; 11(3):191-5). The nucleotide sequence encoding human MAGP-2 is described in the National Center for Biotechnology Information (NCBI) database Accession No. AH007047 (gi:3983462) and is represented herein by SEQ ID NO:124. The amino acid sequence for human MAGP-2 is represented herein as SEQ ID NO:43 and is also found in the NCBI database Accession No. AAC83942 (gi: 3983463). The nucleotide sequences encoding bovine and murine MAGP-2 are also known. The nucleotide sequence encoding murine MAGP-2 is described in NCBI database Accession No. BC025131 (gi: 19264044) and is represented herein by SEQ ID NO:123 and encodes the murine MAGP-2 protein, described in NCBI database Accession No. AAH25131 (gi:19264045), also represented herein by SEQ ID NO:42. The nucleotide sequence encoding bovine MAGP-2 is described in NCBI database Accession No. NM_174386 (gi:31342148) and encodes the bovine MAGP-2 protein, described in NCBI database Accession No. NP_776811 (gi:27805993). All of the information contained in the database accession numbers and in the publications referenced herein is incorporated herein by reference.

In accordance with the present invention, an isolated polynucleotide (also referred to as an isolated nucleic acid molecule) is a nucleic acid molecule that has been removed from its natural milieu (e.g., that has been subject to human manipulation), its natural milieu being the genome or chromosome in which the nucleic acid molecule is found in nature. As such, "isolated" does not necessarily reflect the extent to which the nucleic acid molecule has been purified, but indicates that the molecule does not include an entire genome or an entire chromosome in which the nucleic acid molecule is found in nature. The polynucleotides useful in the present invention are typically a portion of a gene (sense or non-sense strand) of the present invention that is suitable for use as a hybridization probe or PCR primer for the identification of a full-length gene (or portion thereof) in a given sample, to encode a protein or fragment thereof, or as a therapeutic reagent (e.g., antisense). An isolated nucleic acid molecule can include a gene or a portion of a gene (e.g., the regulatory region or promoter), for example, to produce a reporter construct according to the present invention. An isolated nucleic acid molecule that includes a gene is not a fragment of a chromosome that includes such gene, but rather includes the coding region and regulatory regions associated with the gene, but no additional genes naturally found on the same chromosome. An isolated nucleic acid molecule can also include a specified nucleic acid sequence flanked by (i.e., at the 5' and/or the 3' end of the sequence) additional nucleic acids that do not normally flank the specified nucleic acid sequence in nature (i.e., heterologous sequences). Isolated nucleic acid molecule can include DNA, RNA (e.g., mRNA), or derivatives of either DNA or RNA (e.g., cDNA). Although the phrase "nucleic acid molecule" primarily refers to the physical nucleic acid molecule and the phrase "nucleic acid sequence" primarily refers to the sequence of nucleotides on the nucleic acid molecule, the two phrases can be used interchangeably, especially with respect to a nucleic acid molecule, or a nucleic acid sequence, being capable of encoding a protein. Preferably, an isolated nucleic acid molecule of the present invention is produced using recombinant DNA technology (e.g., polymerase chain reaction (PCR) amplification, cloning) or chemical synthesis.

The minimum size of a nucleic acid molecule or polynucleotide of the present invention is a size sufficient to encode a protein having a desired biological activity, sufficient to form a probe or oligonucleotide primer that is capable of forming a stable hybrid with the complementary sequence of a nucleic acid molecule encoding the natural protein (e.g., under moderate, high or very high stringency conditions), or to otherwise be used as a target or agent in an assay or in any therapeutic method discussed herein. If the polynucleotide is an oligonucleotide probe or primer, the size of the polynucleotide can be dependent on nucleic acid composition and percent homology or identity between the nucleic acid molecule and a complementary sequence as well as upon hybridization conditions per se (e.g., temperature, salt concentration, and formamide concentration). The minimum size of a polynucleotide that is used as an oligonucleotide probe or primer is at least about 5 nucleotides in length, and preferably ranges from about 5 to about 50 or about 500 nucleotides or greater (1000, 2000, etc.), including any length in between, in whole number increments (i.e., 5, 6, 7, 8, 9, 10, . . . 33, 34, . . . 256, 257, . . . 500 . . . 1000 . . .), and more preferably from about

10 to about 40 nucleotides, and most preferably from about 15 to about 40 nucleotides in length. In one aspect, the oligonucleotide primer or probe is typically at least about 12 to about 15 nucleotides in length if the nucleic acid molecules are GC-rich and at least about 15 to about 18 bases in length if they are AT-rich. There is no limit, other than a practical limit, on the maximal size of a nucleic acid molecule of the present invention, in that the nucleic acid molecule can include a portion of a protein-encoding sequence or a nucleic acid sequence encoding a full-length protein.

According to the present invention, an oligonucleotide probe (or simply, probe) is a nucleic acid molecule which most typically ranges in size from about 8 nucleotides to several hundred nucleotides in length. Such a molecule is typically used to identify a target nucleic acid sequence in a sample by hybridizing to such target nucleic acid sequence under stringent hybridization conditions. As used herein, stringent hybridization conditions refer to standard hybridization conditions under which nucleic acid molecules are used to identify similar nucleic acid molecules. Such standard conditions are disclosed, for example, in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Labs Press, 1989. Sambrook et al., ibid., is incorporated by reference herein in its entirety (see specifically, pages 9.31-9.62). In addition, formulae to calculate the appropriate hybridization and wash conditions to achieve hybridization permitting varying degrees of mismatch of nucleotides are disclosed, for example, in Meinkoth et al., 1984, *Anal. Biochem.* 138, 267-284; Meinkoth et al., ibid., is incorporated by reference herein in its entirety.

More particularly, moderate stringency hybridization and washing conditions, as referred to herein, refer to conditions which permit isolation of nucleic acid molecules having at least about 70% nucleic acid sequence identity with the nucleic acid molecule being used to probe in the hybridization reaction (i.e., conditions permitting about 30% or less mismatch of nucleotides). High stringency hybridization and washing conditions, as referred to herein, refer to conditions which permit isolation of nucleic acid molecules having at least about 80% nucleic acid sequence identity with the nucleic acid molecule being used to probe in the hybridization reaction (i.e., conditions permitting about 20% or less mismatch of nucleotides). Very high stringency hybridization and washing conditions, as referred to herein, refer to conditions which permit isolation of nucleic acid molecules having at least about 90% nucleic acid sequence identity with the nucleic acid molecule being used to probe in the hybridization reaction (i.e., conditions permitting about 10% or less mismatch of nucleotides). As discussed above, one of skill in the art can use the formulae in Meinkoth et al., ibid. to calculate the appropriate hybridization and wash conditions to achieve these particular levels of nucleotide mismatch. Such conditions will vary, depending on whether DNA:RNA or DNA:DNA hybrids are being formed. Calculated melting temperatures for DNA:DNA hybrids are 10° C. less than for DNA:RNA hybrids. In particular embodiments, stringent hybridization conditions for DNA:DNA hybrids include hybridization at an ionic strength of 6×SSC (0.9 M Na^+) at a temperature of between about 20° C. and about 35° C. (lower stringency), more preferably, between about 28° C. and about 40° C. (more stringent), and even more preferably, between about 35° C. and about 45° C. (even more stringent), with appropriate wash conditions. In particular embodiments, stringent hybridization conditions for DNA:RNA hybrids include hybridization at an ionic strength of 6×SSC (0.9 M Na^+) at a temperature of between about 30° C. and about 45° C., more preferably, between about 38° C. and about 50° C., and even more preferably, between about 45° C. and about 55° C., with similarly stringent wash conditions. These values are based on calculations of a melting temperature for molecules larger than about 100 nucleotides, 0% formamide and a G+C content of about 40%. Alternatively, T_m can be calculated empirically as set forth in Sambrook et al., supra, pages 9.31 to 9.62. In general, the wash conditions should be as stringent as possible, and should be appropriate for the chosen hybridization conditions. For example, hybridization conditions can include a combination of salt and temperature conditions that are approximately 20-25° C. below the calculated T_m of a particular hybrid, and wash conditions typically include a combination of salt and temperature conditions that are approximately 12-20° C. below the calculated T_m of the particular hybrid. One example of hybridization conditions suitable for use with DNA:DNA hybrids includes a 2-24 hour hybridization in 6×SSC (50% formamide) at about 42° C., followed by washing steps that include one or more washes at room temperature in about 2×SSC, followed by additional washes at higher temperatures and lower ionic strength (e.g., at least one wash as about 37° C. in about 0.1×-0.5×SSC, followed by at least one wash at about 68° C. in about 0.1×-0.5×SSC).

PCR primers are also nucleic acid sequences, although PCR primers are typically oligonucleotides of fairly short length that are used in polymerase chain reactions. PCR primers and hybridization probes can readily be developed and produced by those of skill in the art, using sequence information from the target sequence. (See, for example, Sambrook et al., supra or Glick et al., supra).

Knowing the nucleic acid sequences of certain nucleic acid molecules of the present invention allows one skilled in the art to, for example, (a) make copies of those nucleic acid molecules and/or (b) obtain nucleic acid molecules including at least a portion of such nucleic acid molecules (e.g., nucleic acid molecules including full-length genes, full-length coding regions, regulatory control sequences, truncated coding regions). Such nucleic acid molecules can be obtained in a variety of ways including traditional cloning techniques using oligonucleotide probes to screen appropriate libraries or DNA and PCR amplification of appropriate libraries or DNA using oligonucleotide primers. Preferred libraries to screen or from which to amplify nucleic acid molecule include mammali7an genomic DNA libraries. Techniques to clone and amplify genes are disclosed, for example, in Sambrook et al., ibid.

As used herein, reference to an isolated protein or polypeptide in the present invention, including any of the proteins described particularly herein (e.g., any protein encoded by a gene or nucleic acid sequence referenced in Table I, Table IV, Table V, and/or Table VI), includes full-length proteins, fusion proteins, or any fragment or homologue of such a protein. Such a protein can include, but is not limited to, purified proteins, recombinantly produced proteins, membrane bound proteins, proteins complexed with lipids, soluble proteins and isolated proteins associated with other proteins. More specifically, an isolated protein, such as a MAGP-2 (MFAP-5) protein, by way of example, according to the present invention, is a protein (including a polypeptide or peptide) that has been removed from its natural milieu (i.e., that has been subject to human manipulation) and can include purified proteins, partially purified proteins, recombinantly produced proteins, and synthetically produced proteins, for example. As such, "isolated" does not reflect the extent to which the protein has been purified. Preferably, an isolated protein of the present invention is produced recombinantly. In addition, and again by way of example, a "human MAGP-2

protein" or a protein "derived from" a human MAGP-2 protein refers to a MAGP-2 protein (generally including a homologue of a naturally occurring MAGP-2 protein) from a human (*Homo sapiens*) or to a MAGP-2 protein that has been otherwise produced from the knowledge of the structure (e.g., sequence) and perhaps the function of a naturally occurring MAGP-2 protein from *Homo sapiens*. In other words, a human MAGP-2 protein includes any MAGP-2 protein that has substantially similar structure and function of a naturally occurring MAGP-2 protein from *Homo sapiens* or that is a biologically active (i.e., has biological activity) homologue of a naturally occurring MAGP-2 protein from *Homo sapiens* as described in detail herein. As such, a human MAGP-2 protein can include purified, partially purified, recombinant, mutated/modified and synthetic proteins. According to the present invention, the terms "modification" and "mutation" can be used interchangeably, particularly with regard to the modifications/mutations to the amino acid sequence of protein (or nucleic acid sequences) described herein. An isolated protein useful as an antagonist or agonist according to the present invention can be isolated from its natural source, produced recombinantly or produced synthetically.

As used herein, the term "homologue" is used to refer to a protein or peptide which differs from a naturally occurring protein or peptide (i.e., the "prototype" or "wild-type" protein) by minor modifications to the naturally occurring protein or peptide, but which maintains the basic protein and side chain structure of the naturally occurring form. Such changes include, but are not limited to: changes in one or a few amino acid side chains; changes one or a few amino acids, including deletions (e.g., a truncated version of the protein or peptide) insertions and/or substitutions; changes in stereochemistry of one or a few atoms; and/or minor derivatizations, including but not limited to: methylation, glycosylation, phosphorylation, acetylation, myristoylation, prenylation, palmitation, amidation and/or addition of glycosylphosphatidyl inositol. A homologue can have either enhanced, decreased, or substantially similar properties as compared to the naturally occurring protein or peptide. A homologue can include an agonist of a protein or an antagonist of a protein.

Homologues can be the result of natural allelic variation or natural mutation. A naturally occurring allelic variant of a nucleic acid encoding a protein is a gene that occurs at essentially the same locus (or loci) in the genome as the gene which encodes such protein, but which, due to natural variations caused by, for example, mutation or recombination, has a similar but not identical sequence. Allelic variants typically encode proteins having similar activity to that of the protein encoded by the gene to which they are being compared. One class of allelic variants can encode the same protein but have different nucleic acid sequences due to the degeneracy of the genetic code. Allelic variants can also comprise alterations in the 5' or 3' untranslated regions of the gene (e.g., in regulatory control regions). Allelic variants are well known to those skilled in the art.

Homologues can be produced using techniques known in the art for the production of proteins including, but not limited to, direct modifications to the isolated, naturally occurring protein, direct protein synthesis, or modifications to the nucleic acid sequence encoding the protein using, for example, classic or recombinant DNA techniques to effect random or targeted mutagenesis.

According to the present invention, an isolated protein, including a biologically active homologue or fragment thereof, has at least one characteristic of biological activity of activity the wild-type, or naturally occurring reference protein (which can vary depending on whether the homologue or fragment is an agonist or antagonist of the protein, or whether an agonist or antagonist mimetic of the protein is described). In general, the biological activity or biological action of a protein refers to any function(s) exhibited or performed by the protein that is ascribed to the naturally occurring form of the protein as measured or observed in vivo (i.e., in the natural physiological environment of the protein) or in vitro (i.e., under laboratory conditions). Modifications, activities or interactions which result in a decrease in protein expression or a decrease in the activity of the protein, can be referred to as inactivation (complete or partial), down-regulation, reduced action, or decreased action or activity of a protein. Similarly, modifications, activities or interactions which result in an increase in protein expression or an increase in the activity of the protein, can be referred to as amplification, overproduction, activation, enhancement, up-regulation or increased action of a protein. The biological activity of a protein according to the invention can be measured or evaluated using any assay for the biological activity of the protein as known in the art. Such assays can include, but are not limited to, binding assays, assays to determine internalization of the protein and/or associated proteins, enzyme assays, cell signal transduction assays (e.g., phosphorylation assays), and/or assays for determining downstream cellular events that result from activation or binding of the cell surface protein (e.g., expression of downstream genes, production of various biological mediators, etc.).

As used herein, reference to an "agonist" of a given protein refers to any compound that is characterized by the ability to agonize (e.g., stimulate, induce, increase, enhance, or mimic) the biological activity of the naturally occurring protein, and includes any homologue, binding protein (e.g., an antibody), agent that interacts with a protein or receptor bound by the protein, or any suitable product of drug/compound/peptide design or selection which is characterized by its ability to agonize (e.g., stimulate, induce, increase, enhance) the biological activity of the naturally occurring protein in a manner similar to the natural agonist, which is the reference protein.

Similarly, reference to an "antagonist" refers to any compound which inhibits (e.g., antagonizes, reduces, decreases, blocks, reverses, or alters) the effect of a given agonist of a protein (including the protein itself) as described above. More particularly, an antagonist is capable of acting in a manner relative to the activity of the protein, such that the biological activity of the natural agonist or reference protein, is decreased in a manner that is antagonistic (e.g., against, a reversal of, contrary to) to the natural action of the protein. Such antagonists can include, but are not limited to, a protein, peptide, or nucleic acid (including ribozymes, RNAi, aptamers, and antisense), antibodies and antigen binding fragments thereof, or product of drug/compound/peptide design or selection that provides the antagonistic effect.

As used herein, an anti-sense nucleic acid molecule is defined as an isolated nucleic acid molecule that reduces expression of a protein by hybridizing under high stringency conditions to a gene encoding the protein. Such a nucleic acid molecule is sufficiently similar to the gene encoding the protein that the molecule is capable of hybridizing under high stringency conditions to the coding or complementary strand of the gene or RNA encoding the natural protein. RNA interference (RNAi) is a process whereby double stranded RNA, and in mammalian systems, short interfering RNA (siRNA), is used to inhibit or silence expression of complementary genes. In the target cell, siRNA are unwound and associate with an RNA induced silencing complex (RISC), which is then guided to the mRNA sequences that are complementary to the siRNA, whereby the RISC cleaves the mRNA. A

ribozyme is an RNA segment that functions by binding to the target RNA moiety and inactivate it by cleaving the phosphodiester backbone at a specific cutting site. A ribozyme can serve as a targeting delivery vehicle for a nucleic acid molecule, or alternatively, the ribozyme can target and bind to RNA encoding the biomarker, for example, and thereby effectively inhibit the translation of the biomarker. Aptamers are short strands of synthetic nucleic acids (usually RNA but also DNA) selected from randomized combinatorial nucleic acid libraries by virtue of their ability to bind to a predetermined specific target molecule with high affinity and specificity. Aptamers assume a defined three-dimensional structure and are capable of discriminating between compounds with very small differences in structure.

Homologues of a given protein, including peptide and non-peptide agonists and antagonists (analogs), can be products of drug design or selection and can be produced using various methods known in the art. Such homologues can be referred to as mimetics. Various methods of drug design, useful to design or select mimetics or other therapeutic compounds useful in the present invention are disclosed in Maulik et al., 1997, *Molecular Biotechnology: Therapeutic Applications and Strategies*, Wiley-Liss, Inc., which is incorporated herein by reference in its entirety.

As used herein, a mimetic refers to any peptide or non-peptide compound that is able to mimic the biological action of a naturally occurring peptide, often because the mimetic has a basic structure that mimics the basic structure of the naturally occurring peptide and/or has the salient biological properties of the naturally occurring peptide. Mimetics can include, but are not limited to: peptides that have substantial modifications from the prototype such as no side chain similarity with the naturally occurring peptide (such modifications, for example, may decrease its susceptibility to degradation); anti-idiotypic and/or catalytic antibodies, or fragments thereof; non-proteinaceous portions of an isolated protein (e.g., carbohydrate structures); or synthetic or natural organic molecules, including nucleic acids and drugs identified through combinatorial chemistry, for example. Such mimetics can be designed, selected and/or otherwise identified using a variety of methods known in the art.

A mimetic can be obtained, for example, from molecular diversity strategies (a combination of related strategies allowing the rapid construction of large, chemically diverse molecule libraries), libraries of natural or synthetic compounds, in particular from chemical or combinatorial libraries (i.e., libraries of compounds that differ in sequence or size but that have the similar building blocks) or by rational, directed or random drug design. See for example, Maulik et al., supra.

In a molecular diversity strategy, large compound libraries are synthesized, for example, from peptides, oligonucleotides, carbohydrates and/or synthetic organic molecules, using biological, enzymatic and/or chemical approaches. The critical parameters in developing a molecular diversity strategy include subunit diversity, molecular size, and library diversity. The general goal of screening such libraries is to utilize sequential application of combinatorial selection to obtain high-affinity ligands for a desired target, and then to optimize the lead molecules by either random or directed design strategies. Methods of molecular diversity are described in detail in Maulik, et al., ibid.

In a rational drug design procedure, the three-dimensional structure of a regulatory compound can be analyzed by, for example, nuclear magnetic resonance (NMR) or X-ray crystallography. This three-dimensional structure can then be used to predict structures of potential compounds, such as potential regulatory agents by, for example, computer modeling. The predicted compound structure can be used to optimize lead compounds derived, for example, by molecular diversity methods. In addition, the predicted compound structure can be produced by, for example, chemical synthesis, recombinant DNA technology, or by isolating a mimetope from a natural source (e.g., plants, animals, bacteria and fungi).

Maulik et al. also disclose, for example, methods of directed design, in which the user directs the process of creating novel molecules from a fragment library of appropriately selected fragments; random design, in which the user uses a genetic or other algorithm to randomly mutate fragments and their combinations while simultaneously applying a selection criterion to evaluate the fitness of candidate ligands; and a grid-based approach in which the user calculates the interaction energy between three dimensional receptor structures and small fragment probes, followed by linking together of favorable probe sites.

In one embodiment, a homologue of a given protein comprises, consists essentially of, or consists of, an amino acid sequence that is at least about 45%, or at least about 50%, or at least about 55%, or at least about 60%, or at least about 65%, or at least about 70%, or at least about 75%, or at least about 80%, or at least about 85%, or at least about 90%, or at least about 95% identical, or at least about 95% identical, or at least about 96% identical, or at least about 97% identical, or at least about 98% identical, or at least about 99% identical (or any percent identity between 45% and 99%, in whole integer increments), to the amino acid sequence of the reference protein. In one embodiment, the homologue comprises, consists essentially of, or consists of, an amino acid sequence that is less than 100% identical, less than about 99% identical, less than about 98% identical, less than about 97% identical, less than about 96% identical, less than about 95% identical; and so on, in increments of 1%, to less than about 70% identical to the naturally occurring amino acid sequence of the reference protein.

As used herein, unless otherwise specified, reference to a percent (%) identity refers to an evaluation of homology which is performed using: (1) a BLAST 2.0 Basic BLAST homology search using blastp for amino acid searches and blastn for nucleic acid searches with standard default parameters, wherein the query sequence is filtered for low complexity regions by default (described in Altschul, S. F., Madden, T. L., Schääffer, A. A., Zhang, J., Zhang, Z., Miller, W. & Lipman, D. J. (1997) "Gapped BLAST and PSI-BLAST: a new generation of protein database search programs." Nucleic Acids Res. 25:3389-3402, incorporated herein by reference in its entirety); (2) a BLAST 2 alignment (using the parameters described below); (3) and/or PSI-BLAST with the standard default parameters (Position-Specific Iterated BLAST. It is noted that due to some differences in the standard parameters between BLAST 2.0 Basic BLAST and BLAST 2, two specific sequences might be recognized as having significant homology using the BLAST 2 program, whereas a search performed in BLAST 2.0 Basic BLAST using one of the sequences as the query sequence may not identify the second sequence in the top matches. In addition, PSI-BLAST provides an automated, easy-to-use version of a "profile" search, which is a sensitive way to look for sequence homologues. The program first performs a gapped BLAST database search. The PSI-BLAST program uses the information from any significant alignments returned to construct a position-specific score matrix, which replaces the query sequence for the next round of database searching. Therefore, it is to be understood that percent identity can be determined by using any one of these programs.

Two specific sequences can be aligned to one another using BLAST 2 sequence as described in Tatusova and Madden, (1999), "Blast 2 sequences—a new tool for comparing protein and nucleotide sequences", *FEMS Microbiol Lett.* 174: 247-250, incorporated herein by reference in its entirety. BLAST 2 sequence alignment is performed in blastp or blastn using the BLAST 2.0 algorithm to perform a Gapped BLAST search (BLAST 2.0) between the two sequences allowing for the introduction of gaps (deletions and insertions) in the resulting alignment. For purposes of clarity herein, a BLAST 2 sequence alignment is performed using the standard default parameters as follows.

For blastn, using 0 BLOSUM62 matrix:
Reward for match=1
Penalty for mismatch=−2
Open gap (5) and extension gap (2) penalties
gap x_dropoff (50) expect (10) word size (11) filter (on)
For blastp, using 0 BLOSUM62 matrix:
Open gap (11) and extension gap (1) penalties
gap x_dropoff (50) expect (10) word size (3) filter (on).

Also included in the present invention are antibodies and antigen binding fragments thereof that selectively bind to any of the proteins associated with angiogenesis described herein, as well as the use of such antibodies and antigen binding fragments thereof in any of the methods described herein. Antibodies that selectively bind to a protein can be produced using the structural information available for the protein (e.g., the amino acid sequence of at least a portion of the protein). More specifically, the phrase "selectively binds" refers to the specific binding of one protein to another (e.g., an antibody, fragment thereof, or binding partner to an antigen), wherein the level of binding, as measured by any standard assay (e.g., an immunoassay), is statistically significantly higher than the background control for the assay. For example, when performing an immunoassay, controls typically include a reaction well/tube that contain antibody or antigen binding fragment alone (i.e., in the absence of antigen), wherein an amount of reactivity (e.g., non-specific binding to the well) by the antibody or antigen binding fragment thereof in the absence of the antigen is considered to be background. Binding can be measured using a variety of methods standard in the art including enzyme immunoassays (e.g., ELISA), immunoblot assays, etc.). Antibodies useful in the assay kit and methods of the present invention can include polyclonal and monoclonal antibodies, divalent and monovalent antibodies, bi- or multi-specific antibodies, serum containing such antibodies, antibodies that have been purified to varying degrees, and any functional equivalents of whole antibodies. Isolated antibodies of the present invention can include serum containing such antibodies, or antibodies that have been purified to varying degrees. Whole antibodies of the present invention can be polyclonal or monoclonal. Alternatively, functional equivalents of whole antibodies, such as antigen binding fragments in which one or more antibody domains are truncated or absent (e.g., Fv, Fab, Fab', or $F(ab)_2$ fragments), as well as genetically-engineered antibodies or antigen binding fragments thereof, including single chain antibodies or antibodies that can bind to more than one epitope (e.g., bi-specific antibodies), or antibodies that can bind to one or more different antigens (e.g., bi- or multi-specific antibodies), may also be employed in the invention.

Genetically engineered antibodies include those produced by standard recombinant DNA techniques involving the manipulation and re-expression of DNA encoding antibody variable and/or constant regions. Particular examples include, chimeric antibodies, where the V_H and/or V_L domains of the antibody come from a different source to the remainder of the antibody, and CDR grafted antibodies (and antigen binding fragments thereof), in which at least one CDR sequence and optionally at least one variable region framework amino acid is (are) derived from one source and the remaining portions of the variable and the constant regions (as appropriate) are derived from a different source. Construction of chimeric and CDR-grafted antibodies are described, for example, in European Patent Applications: EP-A 0194276, EP-A 0239400, EP-A 0451216 and EP-A 0460617.

Generally, in the production of an antibody, a suitable experimental animal, such as, for example, but not limited to, a rabbit, a sheep, a hamster, a guinea pig, a mouse, a rat, or a chicken, is exposed to an antigen against which an antibody is desired. Typically, an animal is immunized with an effective amount of antigen that is injected into the animal. An effective amount of antigen refers to an amount needed to induce antibody production by the animal. The animal's immune system is then allowed to respond over a pre-determined period of time. The immunization process can be repeated until the immune system is found to be producing antibodies to the antigen. In order to obtain polyclonal antibodies specific for the antigen, serum is collected from the animal that contains the desired antibodies (or in the case of a chicken, antibody can be collected from the eggs). Such serum is useful as a reagent. Polyclonal antibodies can be further purified from the serum (or eggs) by, for example, treating the serum with ammonium sulfate.

Monoclonal antibodies may be produced according to the methodology of Kohler and Milstein (*Nature* 256:495-497, 1975). For example, B lymphocytes are recovered from the spleen (or any suitable tissue) of an immunized animal and then fused with myeloma cells to obtain a population of hybridoma cells capable of continual growth in suitable culture medium. Hybridomas producing the desired antibody are selected by testing the ability of the antibody produced by the hybridoma to bind to the desired antigen.

The invention also extends to non-antibody polypeptides, sometimes referred to as antigen binding partners or antigen binding peptides, that have been designed to bind selectively to the protein of interest. Examples of the design of such polypeptides, which possess a prescribed ligand specificity are given in Beste et al. (*Proc. Natl. Acad. Sci.* 96:1898-1903, 1999), incorporated herein by reference in its entirety.

One embodiment of the present invention relates to a method to identify a compound useful for the inhibition (reduction, decrease) of angiogenesis, which may also be applied to identifying agents useful for inhibition of tumor cell growth, presence, or malignancy. A similar method of the present invention can also be used to identify a compound useful for the promotion (increase, initiation, enhancement) of angiogenesis, which may also be applied to identifying agents useful for conditions in which angiogenesis may be desired (e.g., stroke, ischemia).

Either of such methods generally includes the steps of: (a) detecting an initial level of the expression or activity of one or more genes or proteins encoded thereby (biomarkers) that are associated with angiogenesis as described herein (e.g., any one or more of the genes or the proteins encoded by a gene or nucleic acid sequence referenced in Table I, Table IV, Table V, and/or Table VI, and/or any one or more of the genes or proteins specifically described herein by reference to a particular nucleic acid or amino acid sequence) in a cell or soluble sample or product derived from the cell (e.g., cell supernate); (b) contacting the cell with a test compound; (c) detecting a level of gene or protein expression or activity in the cell (or sample derived therefrom) after contact of the cell with the compound; and, (d) selecting a compound that regu-

lates the level of gene or protein expression or activity in the cell, as compared to prior to contact with the test compound. In one embodiment, the biomarker is a protein, or the gene encoding such protein, selected from: ADAMts7, CRELD-2, Decorin, ECM1, Inhibin β-b, Integrin α-3, Integrin α-6, Lipocalin-7, Lox1-3, Lumican, MAGP-2, Matrilin-2, Nephronectin, SerpinE2, and/or SMOC-2. These genes and proteins have been described in detail above.

In another embodiment, the biomarker is a gene, or the protein encoded by the gene, selected from: 0610007C21Rik, apoptosis related protein APR-3, 1810014L12Rik, Cd14 (encoding CD14 antigen represented herein by SEQ ID NO:5 and SEQ ID NO:6), Cd38 (comprising a nucleic acid sequence represented herein by SEQ ID NO:7 and encoding CD38 antigen); Cd53 (encoding CD53 antigen represented herein by SEQ ID NO:8 and SEQ ID NO:9), Emp2 (encoding epithelial membrane protein represented herein by SEQ ID NO:10 and SEQ ID NO:11), Fcgrt (encoding Fc receptor (IgG, alpha chain transporter) represented herein by SEQ ID NO:12 and SEQ ID NO:13), Islr (encoding immunoglobulin superfamily containing leucine-rich repeat represented herein by SEQ ID NO:14 and SEQ ID NO:15); Lrp2 (comprising a nucleic acid sequence represented herein by SEQ ID NO:16 and SEQ ID NO:17 and encoding low density lipoprotein receptor-related protein 2); Ly6a (encoding lymphocyte antigen 6 complex, locus A represented herein by SEQ ID NO:18); P2rx4 (encoding purinergic receptor P2X, ligand-gated ion channel 4, represented herein by SEQ ID NO:19 and SEQ ID NO:20; Pcdhb9 (encoding protocadherin beta 9 represented herein by SEQ ID NO:21 and SEQ ID NO:22); Ptpre (encoding protein tyrosine phosphatase receptor type E represented herein by SEQ ID NO:23 and SEQ ID NO:24); Slc4a3 (encoding solute carrier family 4 (anion exchanger) member 3, represented herein by SEQ ID NO:25 and SEQ ID NO:26); and/or Tmc6 (encoding transmembrane channel-like gene family 6, represented herein by SEQ ID NO:27).

In yet another embodiment, the biomarker is a gene, or the protein encoded by the gene, selected from: 9130213B05Rik (encoding a protein represented herein by SEQ ID NO:29); C1s (encoding complement component 1, s subcomponent, represented herein by SEQ ID NO:34 and SEQ ID NO:35); C3 (encoding complement component 3 represented herein by SEQ ID NO:30 and SEQ ID NO:31); Cfh (comprising a nucleic acid sequence represented herein by SEQ ID NO:32 and SEQ ID NO:33 and encoding complement component factor h); Col9a3 (comprising a nucleic acid sequence represented herein by SEQ ID NO:36 and SEQ ID NO:37 and encoding procollagen, type IX, alpha 3); Grem1 (encoding cysteine knot superfamily 1, BMP antagonist 1, represented herein by SEQ ID NO:38 and SEQ ID NO:39); Lox13 (encoding lysyl oxidase-like 3, represented herein by SEQ ID NO:40 and SEQ ID NO:41); MAGP-2 (comprising a nucleic acid sequence represented herein by SEQ ID NO:123 and SEQ ID NO:124 and encoding microfibril-associated glycoprotein-2, represented herein by SEQ ID NO:42 and SEQ ID NO:43); Mglap (encoding matrix gamma-carboxyglutamate (gla) protein represented herein by SEQ ID NO:44 and SEQ ID NO:45); Naga (encoding N-acetyl galactosaminidase, alpha, represented herein by SEQ ID NO:46 and SEQ ID NO:47); Nbl1 (encoding neuroblastoma, suppression of tumorigenicity 1, represented herein by SEQ ID NO:48 and SEQ ID NO:49); Ngfb (encoding nerve growth factor, beta, represented herein by SEQ ID NO:50 and SEQ ID NO:51), Npnt (represented herein by SEQ ID NO:52 and SEQ ID NO:53 and encoding nephronectin); Olfm1 (encoding olfactomedin 1, represented herein by SEQ ID NO:54 and SEQ ID NO:55); and/or U90926 (encoding a protein represented herein by SEQ ID NO:56).

In yet another embodiment, the biomarker is a gene, or the protein encoded by the gene, selected from any of the genes or proteins specifically identified by a sequence described herein.

Typically, compounds that regulate the expression or activity of the gene or protein in the presence of the compound in the manner that has been associated by the present inventors with angiogenesis can be selected as pro-angiogenic agents or anti-angiogenesis targets (agents that are targets for inhibition in order to inhibit angiogenesis), and compounds that regulate the expression or activity of the gene or protein in the presence of the compound in a manner that is opposite or contrary to the manner that has been associated by the present inventors with angiogenesis, can be selected as anti-angiogenic agents. The method can include a further step of detecting whether a compound selected in (d) has or regulates pro-angiogenic activity or anti-angiogenic activity, such as in a bioassay for angiogenesis described herein.

Detection of the regulation of the expression of a gene (or the protein encoded thereby) in the "manner" associated with the established level of expression for that gene during angiogenesis, at a minimum, refers to the detection of the regulation of a gene that has now been shown by the present inventors to be selectively regulated in during angiogenesis, in the same direction (i.e., upregulation or downregulation) and at a similar or comparable level, as compared to a normal control (the level of expression of the gene that has been or is established under normal, or non-angiogenic conditions). In other words, if "gene X" is upregulated during angiogenesis as compared to a normal control level of expression, then one determines whether the expression of gene X is upregulated in as compared to a normal control, or whether the expression of gene X is more similar to the level of expression of the normal control. In one aspect of the invention, a gene identified as being upregulated or downregulated as compared to a baseline control according to the invention is regulated in the same direction and to at least about 10%, and more preferably at least 20%, and more preferably at least 25%, and more preferably at least 30%, and more preferably at least 35%, and more preferably at least 40%, and more preferably at least 45%, and more preferably at least 50%, and preferably at least 55%, and more preferably at least 60%, and more preferably at least 65%, and more preferably at least 70%, and more preferably at least 75%, and more preferably at least 80%, and more preferably at least 85%, and more preferably at least 90%, and more preferably at least 95%, or even higher (e.g., above 100%) of the level of expression of the gene that has been established during angiogenesis. Statistical significance should be at least $p<0.05$, and more preferably, at least $p<0.01$, and more preferably, $p<0.005$, and even more preferably, $p<0.001$.

Steps (a) and (c) of the method of the present invention require detection of the biomarker (gene or protein encoded thereby) expression and/or biological activity in a cell or in a sample derived from the cell, such as a cellular extract or supernate. Detection of biomarker expression and/or biological activity can include, but is not limited to: detecting biomarker mRNA transcription (e.g., by polymerase chain reaction (PCR), reverse transcriptase-PCR (RT-PCR), in situ hybridization, Northern blot, sequence analysis or detection of a reporter gene); detecting biomarker translation (e.g., by immunoblot, enzyme-linked immunosorbant assay (ELISA), radioimmunoassay (RIA), immunoprecipitation, immunohistochemistry and immunofluorescence); and/or detecting

biomarker biological activity (e.g., by detecting any of the activities of the particular biomarker, such as enzyme activity, receptor binding, induction of a growth factor, a cell signal transduction event, etc.). The step of detection in step (a) is the control level of biomarker expression or biological activity for a cell to which the detection in step (c) is to be compared and evaluated. The step of detection in step (c) is the experimental level of biomarker expression or biological activity which indicates whether the test compound can change the level of biomarker expression or biological activity in the cell, as compared to the level determined in step (a). In other words, the assay determines whether a given compound is capable of regulating the expression or activity of the biomarker (up or down), and therefore can predicted to regulate angiogenesis.

One can use a tumor cell or a normal, non-tumor cell, such as an endothelial cell, or a sample derived therefrom, in this assay, in order to identify compounds that regulate biomarker-associated angiogenesis, including angiogenesis that is associated with tumor cells, or to identify compounds in order to screen for putative carcinogens.

A cell suitable for use in the present method is any cell which expresses or can be induced to express, a detectable level of the biomarker of interest. A detectable level of biomarker is a level which can be detected using any of the methods for biomarker detection described herein. Since the biomarkers identified herein are expressed by many mammalian cell types, a variety of cell types could be selected. However, it will be appreciated by those of skill in the art that some cell types are more suitable for use in an in vitro assay (e.g., easy to maintain in culture, easy to obtain), and that certain biomarkers may be more readily detectable in some cell types, and therefore, such cell types are preferable for use in the present invention. A preferred cell type to use in the method of the present invention is any cell type that has a high expression or low expression of the biomarker in a tumor cell as compared to a non-tumor cell of the same cell type, or has a high expression or low expression of the biomarker under angiogenic conditions as compared to non-angiogenic conditions, so that a change in biomarker expression or activity is readily detectable. As discussed above, one can also use a sample derived from such a cell, such as a cell extract or cell supernate. Some preferred cells to use in the method of the present invention include, but are not limited to: fibroblasts (and fibrosarcomas), epithelial cells, endothelial cells, and breast, colon, kidney, ovarian or uterine tumor cells and non-tumor cells that endogenously or recombinantly express the biomarker. In one embodiment, a cell suitable for use in any aspect the general assay method is a cell which has been transfected with a recombinant nucleic acid molecule encoding the biomarker and operatively linked to a transcription control sequence so that the biomarker is expressed by the cell. Methods and reagents for preparing recombinant cells are known in the art.

As used herein, the term "putative regulatory compound" refers to compounds having an unknown or previously unappreciated regulatory activity in a particular process. The above-described method for identifying a compound of the present invention includes a step of contacting a test cell with a compound being tested for its ability to regulate the expression or biological activity of the biomarker. For example, test cells can be grown in liquid culture medium or grown on solid medium in which the liquid medium or the solid medium contains the compound to be tested. In addition, as described above, the liquid or solid medium contains components necessary for cell growth, such as assimilable carbon, nitrogen and micronutrients.

The above-described methods, in one aspect, involve contacting cells with the compound being tested for a sufficient time to allow for interaction of the putative regulatory compound with an element that affects biomarker expression and/or biological activity in a cell. Such elements can include, but are not limited to: a nucleic acid molecule encoding the biomarker (including regulatory regions of such a molecule), the biomarker protein, biomarker inhibitors, biomarker stimulators, and biomarker substrates. The period of contact with the compound being tested can be varied depending on the result being measured, and can be determined by one of skill in the art. For example, for binding assays, a shorter time of contact with the compound being tested is typically suitable, than when activity or expression is assessed. As used herein, the term "contact period" refers to the time period during which cells are in contact with the compound being tested. The term "incubation period" refers to the entire time during which cells are allowed to grow prior to evaluation, and can be inclusive of the contact period. Thus, the incubation period includes all of the contact period and may include a further time period during which the compound being tested is not present but during which growth is continuing (in the case of a cell based assay) prior to scoring. The incubation time for growth of cells can vary but is sufficient to allow for the upregulation or downregulation of biomarker expression or biological activity in a cell. It will be recognized that shorter incubation times are preferable because compounds can be more rapidly screened. A preferred incubation time is between about 1 hour to about 48 hours.

The conditions under which the cell or cell lysate of the present invention is contacted with a putative regulatory compound, such as by mixing, are any suitable culture or assay conditions and includes an effective medium in which the cell can be cultured or in which the cell lysate can be evaluated in the presence and absence of a putative regulatory compound. Cells of the present invention can be cultured in a variety of containers including, but not limited to, tissue culture flasks, test tubes, microtiter dishes, and petri plates. Culturing is carried out at a temperature, pH and carbon dioxide content appropriate for the cell. Such culturing conditions are also within the skill in the art. Cells are contacted with a putative regulatory compound under conditions which take into account the number of cells per container contacted, the concentration of putative regulatory compound(s) administered to a cell, the incubation time of the putative regulatory compound with the cell, and the concentration of compound administered to a cell. Determination of effective protocols can be accomplished by those skilled in the art based on variables such as the size of the container, the volume of liquid in the container, conditions known to be suitable for the culture of the particular cell type used in the assay, and the chemical composition of the putative regulatory compound (i.e., size, charge etc.) being tested. A preferred amount of putative regulatory compound(s) comprises between about 1 nM to about 10 mM of putative regulatory compound(s) per well of a 96-well plate.

In one aspect, the present method also makes use of non-cell based assay systems to identify compounds that can regulate biomarker expression or biological activity and thereby are predicted to be useful for regulating cell growth. For example, biomarker proteins and nucleic acid molecules encoding the biomarker may be recombinantly expressed and utilized in non-cell based assays to identify compounds that bind to the protein or nucleic acid molecule, respectively. In non-cell based assays the recombinantly expressed biomarker or nucleic acid encoding the biomarker is attached to a

solid substrate such as a test tube, microtiter well or a column, by means well known to those in the art.

In one embodiment, DNA encoding a reporter molecule can be linked to a regulatory element of the biomarker gene (or a gene encoding a protein that directly regulates the biomarker) and used in appropriate intact cells, cell extracts or lysates to identify compounds that modulate biomarker gene expression, respectively. Appropriate cells or cell extracts are prepared from any cell type that normally expresses the biomarker, thereby ensuring that the cell extracts contain the transcription factors required for in vitro or in vivo transcription. The screen can be used to identify compounds that modulate the expression of the reporter construct. In such screens, the level of reporter gene expression is determined in the presence of the test compound and compared to the level of expression in the absence of the test compound.

Following steps (a), (b) and (c) of the method to identify a compound that regulates the biomarker is a step (d) of selecting a compound that regulates (up or down) the level of the biomarker expression or activity in the cell, as compared to in the absence of the compound. Compounds which cause a regulation (increase or decrease) in the level of biomarker expression or biological activity are selected by the present method as being compounds that are predicted to be useful as pro-angiogenesis agents or anti-angiogenesis agents (or targets for regulation of angiogenesis), depending on how the biomarker has been correlated with angiogenesis according to the description provided herein.

Preferably, compounds which are selected in step (d) are compounds for which, after the test cell was contacted with the compound in step (b), the level of biomarker expression or biological activity detected in step (c) was statistically significantly changed (i.e., with at least a 95% confidence level, or $p<0.05$) as compared to the initial level of biomarker expression or biological activity detected in step (a). Preferably, detection of at least about a 30% change in biomarker expression or biological activity in the cell as compared to initial level results in selection of the compound according to step (d). More preferably, detection of at least about a 50% change and more preferably at least about a 70% change, and more preferably at least about a 90% change, or any percentage change between 5% and higher in 1% increments (i.e., 5%, 6%, 7%, 8% . . .) in biomarker expression or biological activity in the cell as compared to the initial level results in selection of the compound according to step (d). In one embodiment, a 1.5 fold change in biomarker expression or biological activity in the cell as compared to the initial level results in selection of the compound according to step (d). More preferably, detection of at least about a 3 fold change, and more preferably at least about a 6 fold change, and even more preferably, at least about a 12 fold change, and even more preferably, at least about a 24 fold change, or any fold change from 1.5 up in increments of 0.5 fold (i.e., 1.5, 2.0, 2.5, 3.0 . . .) in biomarker expression or biological activity as compared to the initial level, results in selection of the compound according to step (d).

It is to be understood that either of steps (a) and (c) of detection in any of the methods to identify a compound described above can result in no detection, or no change in detection, of biomarker expression or biological activity. In addition, since the level of biomarker expression or biological activity in step (a) (i.e., the initial level) is one of the control levels of biomarker for the assay (i.e., in the absence of the test compound), if step (a) reveals no detectable biomarker expression or biological activity, then any detectable level of biomarker expression or biological activity in step (c) is considered to be a positive result and indicative of increased biomarker activity in the cell and the appropriate assessment associated with this result. If the initial level of biomarker expression or biological activity in step (a) is a detectable level, then the level of biomarker expression or biological activity detected in step (c) is evaluated to determine whether it is statistically significantly greater than or less than that of step (a). It is possible that the level of biomarker expression or biological activity in step (c) could be no detectable change, which would indicate that the compound did not increase or decrease biomarker activity. In this scenario, however, it should be determined that the test cell can display an increase or decrease in the particular biomarker expression or biological activity under some conditions (i.e., by contact with a compound known to increase the biomarker activity in the test cell), so that false negatives are not identified.

In one embodiment of this method to identify regulators of biomarkers of the present invention, the method further includes the step of detecting whether the compound selected in step (d) can inhibit tumor cell formation or a characteristic thereof. In this embodiment, the test cell is contacted with the compound as in step (b), and the growth characteristics of the cell before and after contact with the cell are evaluated. Evaluation of cell growth can be by any suitable method in the art, including, but not limited to, proliferation assays (e.g., by measuring uptake of [^{3}H]-thymidine, viewing cells morphologically) and/or evaluating markers of cell growth (e.g., measurement of changes in cell surface markers, measurement of intracellular indicators of cell growth). Such methods are known in the art and are exemplified in the attached examples.

Compounds suitable for testing and use in the methods of the present invention include any known or available proteins, nucleic acid molecules, as well as products of drug design, including peptides, oligonucleotides, carbohydrates and/or synthetic organic molecules. Such an agent can be obtained, for example, from molecular diversity strategies (a combination of related strategies allowing the rapid construction of large, chemically diverse molecule libraries), libraries of natural or synthetic compounds, in particular from chemical or combinatorial libraries (i.e., libraries of compounds that differ in sequence or size but that have the same building blocks) or by rational drug design. See for example, Maulik et al., 1997, supra. Candidate compounds initially identified by drug design methods can be screened for the ability to modulate the expression and/or biological activity of the biomarker using the methods described herein.

Compounds identified by the method described above can be used in a method to regulate angiogenesis, treat a condition or reduce a symptom of a condition in which inhibition of angiogenesis is desirable (e.g.,cancer), or treat a condition or reduce a symptom of a condition in which promotion of angiogenesis is desirable (e.g.,ischemia, stroke), as described herein and any such compounds are encompassed for use in the method described below.

More particularly, according to one embodiment of the present invention, administration of a compound or composition of the invention or targeting of a biomarker of the invention is useful to inhibit the tumorigenicity of a target cell or to inhibit angiogenesis in a tissue of a patient. Typically, it is desirable to inhibit the growth of a target cell (e.g., a tumor) to obtain a therapeutic benefit in the patient. In one embodiment, patients whom are suitable candidates for methods of the present invention include, but are not limited to, patients that have, or are at risk of developing (e.g., are predisposed to), cancer or a lymphoproliferative disease, or any condition in which regulation of angiogenesis might be beneficial. Particular conditions that are characterized or caused by abnor-

mal or excessive angiogenesis, and therefore may be treated using the methods and compositions of the invention include, but are not limited to: cancer (e.g., activation of oncogenes, loss of tumor suppressors); infectious diseases (e.g., pathogens express angiogenic genes, enhance angiogenic programs); autoimmune disorders (e.g., activation of mast cells and other leukocytes); vascular malformations (e.g., Tie-2 mutation); DiGeorge syndrome (e.g., low VEGF and neuropilin-1 expression); HHT (e.g., mutations of endoglin or LK-1), cavernous hemangioma (e.g., loss of Cx37 and Cx40); atherosclerosis; transplant ateriopathy; obesity (e.g., angiogenesis induced by fatty diet, weight loss by angiogenesis inhibitors); psoriasis; warts; allergic dermatitis; scar keloids; pyogenic granulomas; blistering disease; Kaposi sarcoma in AIDS patients; persistent hyperplastic vitreous syndrome (e.g., loss of Ang-2 or VEGF164); diabetic retinopathy; retinopathy of prematurity; choroidal neovascularization (e.g., TIMP-3 mutation); primary pulmonary hypertension (e.g., germline BMPR-2 mutation, somatic EC mutation); asthma; nasal polyps; inflammatory bowel disease; periodontal disease; ascites; peritoneal adhesions; endometriosis; uterine bleeding; ovarian cysts; ovarian hyperstimulation; arthritis; synovitis; osteomyelitis; and osteophyte formation.

In another embodiment of the invention, administration of a compound or composition of the invention or targeting of a biomarker of the invention is useful to promote angiogenesis. Patients whom are suitable candidates for such a method of the invention include, but are not limited to: patients with vascular deficiencies, cardiovascular disease, or patients in whom stimulation of endothelial cell activation and stabilization of newly formed microvessels or other vessels would be beneficial. For example, such conditions include, but are not limited to, stroke, ischemia and related conditions.

Therefore, yet another embodiment of the invention relates to methods to increase or decrease the expression or biological activity of any one or more of the biomarkers described herein (e.g., Table I, Table IV, Table V, and/or Table VI) in cells (e.g., isolated cells, cells of a tissue, cells in a patient) in order to achieve a goal. This goal can include, but is not limited to, reduction of angiogenesis in a tissue, decreased tumorigenicity of tumor cells, or reduction in the potential for development of tumor cells, enhancement or promotion of angiogenesis in a tissue, or treatment of a disease or condition in which enhanced angiogenesis would be desirable. Such methods generally include the step of increasing or decreasing the expression and/or biological activity of one or more biomarkers described herein, as required for a given cell type, in order to achieve the desired result (e.g., inhibition or promotion of angiogenesis, cancer inhibition, etc.). In one embodiment, the biomarker is a protein, or the gene encoding such protein, selected from: ADAMts7, CRELD-2, Decorin, ECM1, Inhibin β-b, Integrin α-3, Integrin α-6, Lipocalin-7, Lox1-3, Lumican, MAGP-2, Matrilin-2, Nephronectin, SerpinE2, and/or SMOC-2.

In another embodiment, the biomarker is a gene, or the protein encoded by the gene, selected from: 0610007C21Rik, apoptosis related protein APR-3, 1810014L12Rik, Cd14 (encoding CD14 antigen represented herein by SEQ ID NO:5 and SEQ ID NO:6), Cd38 (comprising a nucleic acid sequence represented herein by SEQ ID NO:7 and encoding CD38 antigen); Cd53 (encoding CD53 antigen represented herein by SEQ ID NO:8 and SEQ ID NO:9), Emp2 (encoding epithelial membrane protein represented herein by SEQ ID NO:10 and SEQ ID NO:11), Fcgrt (encoding Fc receptor (IgG, alpha chain transporter) represented herein by SEQ ID NO:12 and SEQ ID NO:13), Islr (encoding immunoglobulin superfamily containing leucine-rich repeat represented herein by SEQ ID NO:14 and SEQ ID NO:15); Lrp2 (comprising a nucleic acid sequence represented herein by SEQ ID NO:16 and SEQ ID NO:17 and encoding low density lipoprotein receptor-related protein 2); Ly6a (encoding lymphocyte antigen 6 complex, locus A represented herein by SEQ ID NO:18); P2rx4 (encoding purinergic receptor P2X, ligand-gated ion channel 4, represented herein by SEQ ID NO:19 and SEQ ID NO:20; Pcdhb9 (encoding protocadherin beta 9 represented herein by SEQ ID NO:21 and SEQ ID NO:22); Ptpre (encoding protein tyrosine phosphatase receptor type E represented herein by SEQ ID NO:23 and SEQ ID NO:24); Slc4a3 (encoding solute carrier family 4 (anion exchanger) member 3, represented herein by SEQ ID NO:25 and SEQ ID NO:26); and/or Tmc6 (encoding transmembrane channel-like gene family 6, represented herein by SEQ ID NO:27).

In yet another embodiment, the biomarker is a gene, or the protein encoded by the gene, selected from: 9130213B05Rik (encoding a protein represented herein by SEQ ID NO:29); C1s (encoding complement component 1, s subcomponent, represented herein by SEQ ID NO:34 and SEQ ID NO:35); C3 (encoding complement component 3 represented herein by SEQ ID NO:30 and SEQ ID NO:31); Cfh (comprising a nucleic acid sequence represented herein by SEQ ID NO:32 and SEQ ID NO:33 and encoding complement component factor h); Col9a3 (comprising a nucleic acid sequence represented herein by SEQ ID NO:36 and SEQ ID NO:37 and encoding procollagen, type IX, alpha 3); Grem1 (encoding cysteine knot superfamily 1, BMP antagonist 1, represented herein by SEQ ID NO:38 and SEQ ID NO:39); Lox13 (encoding lysyl oxidase-like 3, represented herein by SEQ ID NO:40 and SEQ ID NO:41); MAGP-2 (comprising a nucleic acid sequence represented herein by SEQ ID NO:123 and SEQ ID NO:124 and encoding microfibrillar associated protein 5, represented herein by SEQ ID NO:42 and SEQ ID NO:43); Mglap (encoding matrix gamma-carboxyglutamate (gla) protein represented herein by SEQ ID NO:44 and SEQ ID NO:45); Naga (encoding N-acetyl galactosaminidase, alpha, represented herein by SEQ ID NO:46 and SEQ ID NO:47); Nbl1 (encoding neuroblastoma, suppression of tumorigenicity 1, represented herein by SEQ ID NO:48 and SEQ ID NO:49); Ngfb (encoding nerve growth factor, beta, represented herein by SEQ ID NO:50 and SEQ ID NO:51), Npnt (represented herein by SEQ ID NO:52 and SEQ ID NO:53 and encoding nephronectin); Olfm1 (encoding olfactomedin 1, represented herein by SEQ ID NO:54 and SEQ ID NO:55); and/or U90926 (encoding a protein represented herein by SEQ ID NO:56).

In yet another embodiment, the biomarker is a gene, or the protein encoded by the gene, selected from any of the genes or proteins specifically identified by a sequence described herein.

In the method of the present invention wherein the goals are to reduce angiogenesis in a tissue, decrease tumorigenicity of tumor cells, decrease tumor burden, increase survival, or reduce the potential for the development of tumor cells, preferably, cells that are targeted by the method are cells which, prior to the application of the present method, are exhibiting inappropriate (malignant) cell growth or a potential therefore, or cells in a tissue where it is desirable to inhibit angiogenesis. Preferred cells to regulate according to this aspect of the present invention include tumor cells. Cells in which it is desirable to inhibit tumorigenicity or tissues in which inhibition of angiogenesis is desired can be identified, for example, using the method for assessing the presence of cancer cells or biomarker expression and activity of the present invention as described in detail above. Such methods are particularly use-

ful in patients where increased tumorigenicity (or simply tumor growth) or angiogenesis is, or is predicted to become, problematic. Therefore, such a method is particularly useful to treat patients that have, or are at a risk of developing, tumor cells (i.e., a cancer), or to treat any other patients having a condition characterized by undesirable cell growth (e.g., lymphoproliferative disorders). Other diseases and conditions in which inhibition of tumorigenicity or angiogenesis would be desirable will be apparent to those of skill in the art (many are discussed below) and are intended to be encompassed by the present invention.

Similarly, in the method of the present invention wherein the goals are to enhance or promote angiogenesis in a tissue, preferably, cells that are targeted by the method are cells in a tissue where it is desirable to promote angiogenesis. Preferred cells to regulate according to this aspect of the present invention include vascular endothelial cells. Such methods are particularly useful in patients where increased angiogenesis may be useful, such as in patients that have a vascular insufficiency or where the promotion of vascular stabilization and development is desired. Therefore, such a method is particularly useful to treat patients with vascular deficiencies, cardiovascular disease, or to stimulate endothelial cell activation and stabilization of newly formed microvessels or other vessels. Conditions in which promotion of angiogenesis would be desirable will be apparent to those of skill in the art and are intended to be encompassed by the present invention.

Accordingly, the method of the present invention includes a step of modulating (i.e., upregulating or downregulating) biomarker expression and/or biological activity in a patient that has, or is at risk of developing, inappropriate or unregulated cell growth (e.g., tumors) or angiogenesis, or a patient or subject that is in need of promotion of angiogenesis, depending on the goal of the therapy, as discussed above. Modulating biomarker expression or biological activity according to the present invention can be accomplished by directly affecting biomarker expression (transcription or translation) or biological activity, or by directly affecting the ability of a regulator (inhibitor or stimulator) of the biomarker to bind to the biomarker or to activate the biomarker. Preferably, the method of the present invention is targeted to a particular type of cell or tissue or region of the body in which inhibition of cell growth or regulation of angiogenesis is desired. A targeted cell, for example, could include a tumor cell, wherein the method does not substantially affect biomarker expression or biological activity in non-tumor cells, or in cells of a different type that the tumor cell type. Therefore, the method of the present invention, in one embodiment, is intended to be specifically targeted to biomarker expression and/or biological activity for the purpose of inhibiting or promoting cell growth, or inhibiting or promoting angiogenesis by modulating biomarker expression and/or biological activity.

An increase in biomarker expression and/or biological activity is defined herein as any measurable (detectable) increase (i.e., upregulation, stimulation, enhancement) of the expression or activity of the biomarker. As used herein, to increase biomarker expression and/or biological activity refers to any measurable increase in biomarker expression and/or biological activity by any suitable method of measurement. A decrease in biomarker expression and/or biological activity is defined herein as any measurable (detectable) decrease (i.e., downregulation, inhibition, reduction) of the expression or activity of biomarker. As used herein, to decrease biomarker expression and/or biological activity refers to any measurable decrease in the biomarker expression and/or biological activity by any suitable method of measurement.

Accordingly, one embodiment of the present invention includes the use of a variety of agents (i.e., regulatory compounds) which, by acting directly on the biomarker (or by being the biomarker gene encoding a protein or the biomarker protein itself) or by acting on inhibitors or stimulators of the biomarker or being an inhibitor or stimulator of the biomarker, modulate (regulate up or down) the expression and/or biological activity of the biomarker in a cell to produce a desired effect (e.g., inhibition of tumorigenesis or reduction of tumor burden or tumor stasis/increase of survival, inhibition or promotion of angiogenesis). Agents useful in the present invention include, for example, proteins, nucleic acid molecules, antibodies, and compounds that are products of rational drug design (i.e., drugs). Such compounds can be identified using the method of identifying compounds for regulating tumor cell growth and malignancy or for regulating angiogenesis as described above. Moreover, the expression or biological activity of the biomarker in a cell can be determined using the methods described above.

Therefore, in one embodiment, the method of the present invention increases the transcription and/or the translation of the biomarker by a cell that naturally expresses the biomarker and that is the target for growth regulation, or increases (stimulates, enhances) the biological activity of the biomarker. Methods for increasing the expression of a given biomarker include, but are not limited to, administering an agent that increases the expression or biological activity of the endogenous biomarker, administering biomarker protein or a homologue or analog (agonist) thereof to a subject, and/or overexpressing biomarker in target cells. In one aspect of this embodiment, the biomarker can be effectively overexpressed in a cell by increasing the activity of a promoter for the biomarker gene in the cell such that expression of endogenous biomarker in the cell is increased. For example, the activity of the biomarker gene promoter can be increased by methods which include, contacting the promoter with a transcriptional activator, inhibiting a biomarker promoter inhibitor, and increasing the activity of a biomarker promoter stimulator. Methods by which such compounds (e.g., transcriptional activators) can be administered to a cell are described below. In another embodiment, biomarker activity is increased by administering the biomarker or a homologue or analog (synthetic homologue or mimetic or compound) to the target cells or to the patient in an appropriate carrier or delivery vehicle.

In another embodiment, the method of the present invention decreases the transcription and/or the translation of the biomarker by a cell that naturally expresses the biomarker and that is the target for growth regulation, or inhibits the biological activity of biomarker. In this embodiment, it is desired to modify a target cell in order to decrease in biomarker gene expression, decrease the function of the gene, or decrease the function of the gene product (i.e., the protein encoded by the gene). Such methods can be referred to as inactivation (complete or partial), deletion, interruption, blockage or downregulation of a gene encoding the biomarker. In one embodiment, reduction in biomarker activity or expression is achieved by use of a biomarker antagonist, antagonists having been described above.

In one aspect of this embodiment of the present invention, the expression and/or biological activity of the biomarker is increased by overexpressing the biomarker in the cell in which angiogenesis is to be regulated. Overexpression of a biomarker refers to an increase in expression of the biomarker over a normal, endogenous level of biomarker expression. For some cell types, which do not express detectable levels of the biomarker under normal conditions, such expression can be any detectable level. For cell types which do express detect-

able levels of the biomarker under normal conditions, an overexpression is any statistically significant increase in expression of the biomarker ($p<0.05$) (or constitutive expression where expression is normally not constitutive) over endogenous levels of expression. One method by which biomarker overexpression can be achieved is by transfecting the cell with a recombinant nucleic acid molecule encoding the biomarker operatively linked to a transcription control sequence, wherein the recombinant biomarker is expressed by the cell. As discussed previously herein, the nucleic acid sequence encoding biomarker, vectors suitable for expressing such a molecule, and methods of transfection of a cell with such a molecule, including in vivo methods, are known and are described in detail below.

A recombinant nucleic acid molecule expressing the biomarker is a molecule that can include at least one of any nucleic acid sequence encoding a protein having the biomarker biological activity operatively linked to at least one of any transcription control sequence capable of effectively regulating expression of the nucleic acid molecule(s) in the cell to be transfected. Although the phrase "nucleic acid molecule" primarily refers to the physical nucleic acid molecule and the phrase "nucleic acid sequence" primarily refers to the sequence of nucleotides on the nucleic acid molecule, the two phrases can be used interchangeably, especially with respect to a nucleic acid molecule, or a nucleic acid sequence, being capable of encoding a protein. In addition, the phrase "recombinant molecule" primarily refers to a nucleic acid molecule operatively linked to a transcription control sequence, but can be used interchangeably with the phrase "nucleic acid molecule" which is administered to an animal.

Preferably, a recombinant nucleic acid molecule is produced using recombinant DNA technology (e.g., polymerase chain reaction (PCR) amplification, cloning). Suitable nucleic acid sequences encoding the biomarker for use in a recombinant nucleic acid molecule of the present invention include any nucleic acid sequence that encodes the biomarker protein having biological activity and suitable for use in the target host cell. For example, when the target host cell is a human cell, human biomarker-encoding nucleic acid sequences are preferably used, although the present invention is not limited to strict use of naturally occurring sequences or same-species sequences.

A recombinant nucleic acid molecule includes a recombinant vector, which is any nucleic acid sequence, typically a heterologous sequence, which is operatively linked to the isolated nucleic acid molecule encoding a biomarker protein, which is capable of enabling recombinant production of the biomarker protein, and which is capable of delivering the nucleic acid molecule into a host cell according to the present invention. Such a vector can contain nucleic acid sequences that are not naturally found adjacent to the isolated nucleic acid molecules to be inserted into the vector. The vector can be either RNA or DNA, either prokaryotic or eukaryotic, and preferably in the present invention, is a virus or a plasmid. Recombinant vectors can be used in the cloning, sequencing, and/or otherwise manipulating of nucleic acid molecules. Recombinant vectors are preferably used in the expression of nucleic acid molecules, and can also be referred to as expression vectors. Preferred recombinant vectors are capable of being expressed in a transfected host cell, and particularly, in a transfected mammalian host cell in vivo.

In a recombinant molecule of the present invention, nucleic acid molecules are operatively linked to expression vectors containing regulatory sequences such as transcription control sequences, translation control sequences, origins of replication, and other regulatory sequences that are compatible with the host cell and that control the expression of nucleic acid molecules of the present invention. In particular, recombinant molecules of the present invention include nucleic acid molecules that are operatively linked to one or more transcription control sequences. The phrase "operatively linked" refers to linking a nucleic acid molecule to a transcription control sequence in a manner such that the molecule is expressed when transfected (i.e., transformed, transduced or transfected) into a host cell.

Transcription control sequences are sequences that control the initiation, elongation, and termination of transcription. Particularly important transcription control sequences are those that control transcription initiation, such as promoter, enhancer, operator and repressor sequences. Suitable transcription control sequences include any transcription control sequence that can function in a host cell according to the present invention. A variety of suitable transcription control sequences are known to those skilled in the art. Preferred transcription control sequences include those which function in mammalian cells, with cell- or tissue-specific transcription control sequences being particularly preferred. Examples of preferred transcription control sequences include, but are not limited to, transcription control sequences useful for expression of a protein in epithelial cells and tumor cells and the naturally occurring biomarker promoter. Particularly preferred transcription control sequences include inducible promoters, cell-specific promoters, tissue-specific promoters (e.g., insulin promoters) and enhancers. Suitable promoters for these and other cell types will be easily determined by those of skill in the art. Transcription control sequences of the present invention can also include naturally occurring transcription control sequences naturally associated with the protein to be expressed prior to isolation. In one embodiment, a transcription control sequence includes an inducible promoter.

One type of recombinant vector useful in a recombinant nucleic acid molecule of the present invention is a recombinant viral vector. Such a vector includes a recombinant nucleic acid sequence encoding a biomarker protein of the present invention that is packaged in a viral coat that can be expressed in a host cell in an animal or ex vivo after administration. A number of recombinant viral vectors can be used, including, but not limited to, those based on alphaviruses, poxviruses, adenoviruses, herpesviruses, lentiviruses, adeno-associated viruses and retroviruses. Particularly preferred viral vectors are those based on adenoviruses and adeno-associated viruses. Viral vectors suitable for gene delivery are well known in the art and can be selected by the skilled artisan for use in the present invention. A detailed discussion of current viral vectors is provided in "Molecular Biotechnology," Second Edition, by Glick and Pasternak, ASM Press, Washington D.C., 1998, pp. 555-590, the entirety of which is incorporated herein by reference.

For example, a retroviral vector, which is useful when it is desired to have a nucleic acid sequence inserted into the host genome for long term expression, can be packaged in the envelope protein of another virus so that it has the binding specificity and infection spectrum that are determined by the envelope protein (e.g., a pseudotyped virus). In addition, the envelope gene can be genetically engineered to include a DNA element that encodes and amino acid sequence that binds to a cell receptor to create a recombinant retrovirus that infects a specific cell type. Expression of the biomarker gene can be further controlled by the use of a cell or tissue-specific promoter. Retroviral vectors have been successfully used to transfect cells with a gene which is expressed and maintained in a variety of ex vivo systems

An adenoviral vector is a preferred vector for use in the present method. An adenoviral vector infects a wide range of human cells and has been used extensively in live vaccines. Adenoviral vectors used in gene therapy do not integrate into the host genome, and therefore, gene therapy using this system requires periodic administration, although methods have been described which extend the expression time of adenoviral transferred genes, such as administration of antibodies directed against T cell receptors at the site of expression (Sawchuk et al., 1996, *Hum. Gene. Ther.* 7:499-506). The efficiency of adenovirus-mediated gene delivery can be enhanced by developing a virus that preferentially infects a particular target cell. For example, a gene for the attachment fibers of adenovirus can be engineered to include a DNA element that encodes a protein domain that binds to a cell-specific receptor. Examples of successful in vivo delivery of genes has been demonstrated and is discussed in more detail below.

Yet another type of viral vector is based on adeno-associated viruses, which are small, nonpathogenic, single-stranded human viruses. This virus can integrate into a specific site on chromosome 19. This virus can carry a cloned insert of about 4.5 kb, and has typically been successfully used to express proteins in vivo from 70 days to at least 5 months. Demonstrating that the art is quickly advancing in the area of gene therapy, however, a publication by Bennett et al. reported efficient and stable transgene expression by adeno-associated viral vector transfer in vivo for greater than 1 year (Bennett et al., 1999, *Proc. Natl. Acad. Sci. USA* 96:9920-9925).

Another type of viral vector that is suitable for use in the present invention is a herpes simplex virus vector. Herpes simplex virus type 1 infects and persists within nondividing neuronal cells, and is therefore a suitable vector for targeting and transfecting cells of the central and peripheral nervous system with a biomarker protein of the present invention. Preclinical trials in experimental animal models with such a vector has demonstrated that the vector can deliver genes to cells of both the brain and peripheral nervous system that are expressed and maintained for long periods of time.

Suitable host cells to transfect with a recombinant nucleic acid molecule according to the present invention include any mammalian cell that can be transfected. Host cells can be either untransfected cells or cells that are already transfected with at least one nucleic acid molecule. Host cells according to the present invention can be any cell capable of producing a biomarker protein as described herein or in which it is desired to produce the biomarker.

According to the present invention, a host cell can also be referred to as a target cell or a targeted cell in vivo, in which a recombinant nucleic acid molecule encoding a biomarker protein having the biological activity of the biomarker is to be expressed. As used herein, the term "target cell" or "targeted cell" refers to a cell to which a recombinant nucleic acid molecule of the present invention is selectively designed to be delivered. The term target cell does not necessarily restrict the delivery of a recombinant nucleic acid molecule only to the target cell and no other cell, but indicates that the delivery of the recombinant molecule, the expression of the recombinant molecule, or both, are specifically directed to a preselected host cell. Targeting delivery vehicles, including liposomes and viral vector systems are known in the art. For example, a liposome can be directed to a particular target cell or tissue by using a targeting agent, such as an antibody, soluble receptor or ligand, incorporated with the liposome, to target a particular cell or tissue to which the targeting molecule can bind. Targeting liposomes are described, for example, in Ho et al., 1986, *Biochemistry* 25: 5500-6; Ho et al., 1987a, *J Biol Chem* 262: 13979-84; Ho et al., 1987b, *J Biol Chem* 262: 13973-8; and U.S. Pat. No. 4,957,735 to Huang et al., each of which is incorporated herein by reference in its entirety). Ways in which viral vectors can be modified to deliver a nucleic acid molecule to a target cell have been discussed above. Alternatively, the route of administration, as discussed below, can be used to target a specific cell or tissue. For example, intracoronary administration of an adenoviral vector has been shown to be effective for the delivery of a gene cardiac myocytes (Maurice et al., 1999, *J Clin. Invest.* 104:21-29). Intravenous delivery of cholesterol-containing cationic liposomes has been shown to preferentially target pulmonary tissues (Liu et al., *Nature Biotechnology* 15:167, 1997), and effectively mediate transfer and expression of genes in vivo. Other examples of successful targeted in vivo delivery of nucleic acid molecules are known in the art. Finally, a recombinant nucleic acid molecule can be selectively (i.e., preferentially, substantially exclusively) expressed in a target cell by selecting a transcription control sequence, and preferably, a promoter, which is selectively induced in the target cell and remains substantially inactive in non-target cells.

According to the method of the present invention, a host cell is preferably transfected in vivo (i.e., in a mammal) as a result of administration to a mammal of a recombinant nucleic acid molecule, or ex vivo, by removing cells from a mammal and transfecting the cells with a recombinant nucleic acid molecule ex vivo. Transfection of a nucleic acid molecule into a host cell according to the present invention can be accomplished by any method by which a nucleic acid molecule administered into the cell in vivo, and includes, but is not limited to, transfection, electroporation, microinjection, lipofection, adsorption, viral infection, naked DNA injection and protoplast fusion. Methods of administration are discussed in detail below.

In one embodiment of the present invention, a recombinant nucleic acid molecule of the present invention is administered to a patient in a liposome delivery vehicle, whereby the nucleic acid sequence encoding the biomarker protein enters the host cell (i.e., the target cell) by lipofection. A liposome delivery vehicle contains the recombinant nucleic acid molecule and delivers the molecules to a suitable site in a host recipient. According to the present invention, a liposome delivery vehicle comprises a lipid composition that is capable of delivering a recombinant nucleic acid molecule of the present invention, including both plasmids and viral vectors, to a suitable cell and/or tissue in a patient. A liposome delivery vehicle of the present invention comprises a lipid composition that is capable of fusing with the plasma membrane of the target cell to deliver the recombinant nucleic acid molecule into a cell. A liposome delivery vehicle can also be used to deliver a protein, drug, or other regulatory compound to a patient.

A liposome delivery vehicle of the present invention can be modified to target a particular site in a mammal (i.e., a targeting liposome), thereby targeting and making use of a nucleic acid molecule of the present invention at that site. Suitable modifications include manipulating the chemical formula of the lipid portion of the delivery vehicle. Manipulating the chemical formula of the lipid portion of the delivery vehicle can elicit the extracellular or intracellular targeting of the delivery vehicle. For example, a chemical can be added to the lipid formula of a liposome that alters the charge of the lipid bilayer of the liposome so that the liposome fuses with particular cells having particular charge characteristics. Other targeting mechanisms include targeting a site by addition of exogenous targeting molecules (i.e., targeting agents) to a liposome (e.g., antibodies, soluble receptors or ligands).

A liposome delivery vehicle is preferably capable of remaining stable in a patient for a sufficient amount of time to deliver a nucleic acid molecule of the present invention to a preferred site in the patient (i.e., a target cell). A liposome delivery vehicle of the present invention is preferably stable in the patient into which it has been administered for at least about 30 minutes, more preferably for at least about 1 hour and even more preferably for at least about 24 hours. A preferred liposome delivery vehicle of the present invention is from about 0.01 microns to about 1 microns in size.

Suitable liposomes for use with the present invention include any liposome. Preferred liposomes of the present invention include those liposomes commonly used in, for example, gene delivery methods known to those of skill in the art. Preferred liposome delivery vehicles comprise multilamellar vesicle (MLV) lipids and extruded lipids. Methods for preparation of MLV's are well known in the art. According to the present invention, "extruded lipids" are lipids which are prepared similarly to MLV lipids, but which are subsequently extruded through filters of decreasing size, as described in Templeton et al., 1997, *Nature Biotech.,* 15:647-652, which is incorporated herein by reference in its entirety. Small unilamellar vesicle (SUV) lipids can also be used in the composition and method of the present invention. In one embodiment, liposome delivery vehicles comprise liposomes having a polycationic lipid composition (i.e., cationic liposomes) and/or liposomes having a cholesterol backbone conjugated to polyethylene glycol. In a preferred embodiment, liposome delivery vehicles useful in the present invention comprise one or more lipids selected from the group of DOTMA, DOTAP, DOTIM, DDAB, and cholesterol.

Preferably, the transfection efficiency of a nucleic acid: liposome complex of the present invention is at least about 1 picogram (pg) of protein expressed per milligram (mg) of total tissue protein per microgram (μg) of nucleic acid delivered. More preferably, the transfection efficiency of a nucleic acid:liposome complex of the present invention is at least about 10 pg of protein expressed per mg of total tissue protein per μg of nucleic acid delivered; and even more preferably, at least about 50 pg of protein expressed per mg of total tissue protein per μg of nucleic acid delivered; and most preferably, at least about 100 pg of protein expressed per mg of total tissue protein per μg of nucleic acid delivered.

Complexing a liposome with a nucleic acid molecule of the present invention can be achieved using methods standard in the art. A suitable concentration of a nucleic acid molecule of the present invention to add to a liposome includes a concentration effective for delivering a sufficient amount of recombinant nucleic acid molecule into a target cell of a patient such that the biomarker protein encoded by the nucleic acid molecule can be expressed in a an amount effective to inhibit the growth of the target cell or to inhibit or promote angiogenesis at a tissue site. Preferably, from about 0.1 μg to about 10 μg of nucleic acid molecule of the present invention is combined with about 8 nmol liposomes. In one embodiment, the ratio of nucleic acids to lipids (μg nucleic acid:nmol lipids) in a composition of the present invention is preferably at least from about 1:10 to about 6:1 nucleic acid:lipid by weight (i.e., 1:10=1 μg nucleic acid:10 nmol lipid).

According to the present invention, a regulatory compound for regulating the expression or biological activity of a biomarker, including a recombinant nucleic acid molecule encoding the biomarker, is typically administered to a patient in a composition. In addition to the recombinant nucleic acid molecule or other biomarker regulatory compound (i.e., a protein, antibody, carbohydrate, small molecule product of drug design), the composition can include, for example, a pharmaceutically acceptable carrier, which includes pharmaceutically acceptable excipients and/or delivery vehicles, for delivering the recombinant nucleic acid molecule or other regulatory compound to a patient (e.g., a liposome delivery vehicle). As used herein, a pharmaceutically acceptable carrier refers to any substance suitable for delivering a therapeutic composition useful in the method of the present invention to a suitable in vivo or ex vivo site. Preferred pharmaceutically acceptable carriers are capable of maintaining a recombinant nucleic acid molecule of the present invention in a form that, upon arrival of the nucleic acid molecule to a target cell, the nucleic acid molecule is capable of entering the cell and being expressed by the cell. Suitable excipients of the present invention include excipients or formularies that transport or help transport, but do not specifically target a nucleic acid molecule to a cell (also referred to herein as non-targeting carriers). Examples of pharmaceutically acceptable excipients include, but are not limited to water, phosphate buffered saline, Ringer's solution, dextrose solution, serum-containing solutions, Hank's solution, other aqueous physiologically balanced solutions, oils, esters and glycols. Aqueous carriers can contain suitable auxiliary substances required to approximate the physiological conditions of the recipient, for example, by enhancing chemical stability and isotonicity.

Suitable auxiliary substances include, for example, sodium acetate, sodium chloride, sodium lactate, potassium chloride, calcium chloride, and other substances used to produce phosphate buffer, Tris buffer, and bicarbonate buffer. Auxiliary substances can also include preservatives, such as thimerosal, m- or o-cresol, formalin and benzol alcohol. Compositions of the present invention can be sterilized by conventional methods and/or lyophilized.

One type of pharmaceutically acceptable carrier includes a controlled release formulation that is capable of slowly releasing a composition of the present invention into an animal. As used herein, a controlled release formulation comprises recombinant nucleic acid molecule or other biomarker regulatory compound of the present invention in a controlled release vehicle. Suitable controlled release vehicles include, but are not limited to, biocompatible polymers, other polymeric matrices, capsules, microcapsules, microparticles, bolus preparations, osmotic pumps, diffusion devices, liposomes, lipospheres, and transdermal delivery systems. Suitable delivery vehicles have been previously described herein, and include, but are not limited to liposomes, viral vectors or other delivery vehicles, including ribozymes. Natural lipid-containing delivery vehicles include cells and cellular membranes. Artificial lipid-containing delivery vehicles include liposomes and micelles. As discussed above, a delivery vehicle of the present invention can be modified to target to a particular site in a patient, thereby targeting and making use of a nucleic acid molecule at that site. Suitable modifications include manipulating the chemical formula of the lipid portion of the delivery vehicle and/or introducing into the vehicle a targeting agent capable of specifically targeting a delivery vehicle to a preferred site, for example, a preferred cell type. Other suitable delivery vehicles include gold particles, poly-L-lysine/DNA-molecular conjugates, and artificial chromosomes.

As discussed above, a composition of the present invention is administered to a patient in a manner effective to deliver the recombinant nucleic acid molecule comprising a nucleic acid sequence encoding a biomarker protein to a target cell, whereby the target cell is transfected by the recombinant molecule and whereby the biomarker protein is expressed in the target cell. When a biomarker regulatory compound is to

be delivered to a target cell in a patient, the composition is administered in a manner effective to deliver the biomarker regulatory compound to the target cell, whereby the compound can act on the cell (e.g., enter the cell and act on the biomarker or an inhibitor or stimulator thereof) so that the expression or biological activity of the biomarker is increased or decreased, depending on the isoform and the goal of the therapy. Suitable administration protocols include any in vivo or ex vivo administration protocol.

According to the present invention, an effective administration protocol (i.e., administering a composition of the present invention in an effective manner) comprises suitable dose parameters and modes of administration that result in transfection and expression of a recombinant nucleic acid molecule encoding a biomarker protein or another biomarker regulatory compound, in a target cell of a patient, and subsequent inhibition of the growth of the target cell or inhibition or promotion of angiogenesis, preferably so that the patient obtains some measurable, observable or perceived benefit from such administration. In some situations, where the target cell population is accessible for sampling, effective dose parameters can be determined using methods as described herein for assessment of tumor growth or using methods known in the art for the assessment of angiogenesis. Such methods include removing a sample of the target cell population from the patient prior to and after the recombinant nucleic acid molecule is administered, and measuring changes in biomarker expression or biological activity, as well as measuring inhibition of the cell or impact on angiogenesis of a suitable cell line. Alternatively, effective dose parameters can be determined by experimentation using in vitro cell cultures, in vivo animal models, and eventually, clinical trials if the patient is human. Effective dose parameters can be determined using methods standard in the art for a particular disease or condition that the patient has or is at risk of developing. Such methods include, for example, determination of survival rates, side effects (i.e., toxicity) and progression or regression of disease.

According to the present invention, suitable methods of administering a composition comprising a recombinant nucleic acid molecule of the present invention to a patient include any route of in vivo administration that is suitable for delivering a recombinant nucleic acid molecule into a patient. The preferred routes of administration will be apparent to those of skill in the art, depending on the type of delivery vehicle used, the target cell population, whether the compound is a protein, nucleic acid, or other compound (e.g., a drug) and the disease or condition experienced by the patient. Preferred methods of in vivo administration include, but are not limited to, intravenous administration, intraperitoneal administration, intramuscular administration, intracoronary administration, intraarterial administration (e.g., into a carotid artery), subcutaneous administration, transdermal delivery, intratracheal administration, subcutaneous administration, intraarticular administration, intraventricular administration, inhalation (e.g., aerosol), intracerebral, nasal, oral, pulmonary administration, impregnation of a catheter, and direct injection into a tissue. In an embodiment where the target cells are in or near a tumor, a preferred route of administration is by direct injection into the tumor or tissue surrounding the tumor. For example, when the tumor is a breast tumor, the preferred methods of administration include impregnation of a catheter, and direct injection into the tumor.

Intravenous, intraperitoneal, and intramuscular administrations can be performed using methods standard in the art. Aerosol (inhalation) delivery can also be performed using methods standard in the art (see, for example, Stribling et al., *Proc. Natl. Acad. Sci. USA* 189:11277-11281, 1992, which is incorporated herein by reference in its entirety). Oral delivery can be performed by complexing a therapeutic composition of the present invention to a carrier capable of withstanding degradation by digestive enzymes in the gut of an animal. Examples of such carriers, include plastic capsules or tablets, such as those known in the art.

One method of local administration is by direct injection. Direct injection techniques are particularly useful for administering a recombinant nucleic acid molecule to a cell or tissue that is accessible by surgery, and particularly, on or near the surface of the body. Administration of a composition locally within the area of a target cell refers to injecting the composition centimeters and preferably, millimeters from the target cell or tissue.

Various methods of administration and delivery vehicles disclosed herein have been shown to be effective for delivery of a nucleic acid molecule to a target cell, whereby the nucleic acid molecule transfected the cell and was expressed. In many studies, successful delivery and expression of a heterologous gene was achieved in preferred cell types and/or using preferred delivery vehicles and routes of administration of the present invention. All of the publications discussed below and elsewhere herein with regard to gene delivery and delivery vehicles are incorporated herein by reference in their entirety. For example, using liposome delivery, U.S. Pat. No. 5,705,151, issued Jan. 6, 1998, to Dow et al. demonstrated the successful in vivo intravenous delivery of a nucleic acid molecule encoding a superantigen and a nucleic acid molecule encoding a cytokine in a cationic liposome delivery vehicle, whereby the encoded proteins were expressed in tissues of the animal, and particularly in pulmonary tissues. Dow et al. also demonstrated successful in vivo delivery of a nucleic acid molecule by direct injection into a site of a tumor. As discussed above, Liu et al., 1997, ibid. demonstrated that intravenous delivery of cholesterol-containing cationic liposomes containing genes preferentially targets pulmonary tissues and effectively mediates transfer and expression of the genes in vivo. Several publications by Dzau and collaborators demonstrate the successful in vivo delivery and expression of a gene into cells of the heart, including cardiac myocytes and fibroblasts and vascular smooth muscle cells using both naked DNA and Hemagglutinating virus of Japan-liposome delivery, administered by both incubation within the pericardium and infusion into a coronary artery (intracoronary delivery) (See, for example, Aoki et al., 1997, *J Mol. Cell, Cardiol.* 29:949-959; Kaneda et al., 1997, *Ann N.Y. Acad. Sci.* 811:299-308; and von der Leyen et al., 1995, *Proc Natl Acad Sci USA* 92:1137-1141).

As discussed above, delivery of numerous nucleic acid sequences has been accomplished by administration of viral vectors encoding the nucleic acid sequences. Using such vectors, successful delivery and expression has been achieved using ex vivo delivery (See, of many examples, retroviral vector; Blaese et al., 1995, *Science* 270:475-480; Bordignon et al., 1995, *Science* 270:470-475), nasal administration (CFTR-adenovirus-associated vector), intracoronary administration (adenoviral vector and Hemagglutinating virus of Japan, see above), intravenous administration (adeno-associated viral vector; Koeberl et al., 1997, *Proc Natl Acad Sci USA* 94:1426-1431). A publication by Maurice et al., 1999, ibid. demonstrated that an adenoviral vector encoding a β2-adrenergic receptor, administered by intracoronary delivery, resulted in diffuse multichamber myocardial expression of the gene in vivo, and subsequent significant increases in hemodynamic function and other improved physiological parameters. Levine et al. describe in vitro, ex vivo and in vivo

delivery and expression of a gene to human adipocytes and rabbit adipocytes using an adenoviral vector and direct injection of the constructs into adipose tissue (Levine et al., 1998, *J. Nutr. Sci. Vitaminol.* 44:569-572).

In the area of neuronal gene delivery, multiple successful in vivo gene transfers have been reported. Millecamps et al. reported the targeting of adenoviral vectors to neurons using neuron restrictive enhancer elements placed upstream of the promoter for the transgene (phosphoglycerate promoter). Such vectors were administered to mice and rats intramuscularly and intracerebrally, respectively, resulting in successful neuronal-specific transfection and expression of the transgene in vivo (Millecamps et al., 1999, *Nat. Biotechnol.* 17:865-869). As discussed above, Bennett et al. reported the use of adeno-associated viral vector to deliver and express a gene by subretinal injection in the neural retina in vivo for greater than 1 year (Bennett, 1999, ibid.).

Gene delivery to synovial lining cells and articular joints has had similar successes. Oligino and colleagues report the use of a herpes simplex viral vector that is deficient for the immediate early genes, ICP4, 22 and 27, to deliver and express two different receptors in synovial lining cells in vivo (Oligino et al., 1999, *Gene Ther.* 6:1713-1720). The herpes vectors were administered by intraarticular injection. Kuboki et al. used adenoviral vector-mediated gene transfer and intraarticular injection to successfully and specifically express a gene in the temporomandibular joints of guinea pigs in vivo (Kuboki et al., 1999, *Arch. Oral. Biol.* 44:701-709). Apparailly and colleagues systemically administered adenoviral vectors encoding IL-10 to mice and demonstrated successful expression of the gene product and profound therapeutic effects in the treatment of experimentally induced arthritis (Apparailly et al., 1998, *J Immunol.* 160:5213-5220). In another study, murine leukemia virus-based retroviral vector was used to deliver (by intraarticular injection) and express a human growth hormone gene both ex vivo and in vivo (Ghivizzani et al., 1997, *Gene Ther.* 4:977-982). This study showed that expression by in vivo gene transfer was at least equivalent to that of the ex vivo gene transfer. As discussed above, Sawchuk et al. has reported successful in vivo adenoviral vector delivery of a gene by intraarticular injection, and prolonged expression of the gene in the synovium by pretreatment of the joint with anti-T cell receptor monoclonal antibody (Sawchuk et al., 1996, *ibid.* Finally, it is noted that ex vivo gene transfer of human interleukin-1 receptor antagonist using a retrovirus has produced high level intraarticular expression and therapeutic efficacy in treatment of arthritis, and is now entering FDA approved human gene therapy trials (Evans and Robbins, 1996, *Curr. Opin. Rheumatol.* 8:230-234). Therefore, the state of the art in gene therapy has led the FDA to consider human gene therapy an appropriate strategy for the treatment of at least arthritis. Taken together, all of the above studies in gene therapy indicate that delivery and expression of an biomarker-encoding recombinant nucleic acid molecule according to the present invention is feasible.

Another method of delivery of recombinant molecules is in a non-targeting carrier (e.g., as "naked" DNA molecules, such as is taught, for example in Wolff et al., 1990, *Science* 247, 1465-1468). Such recombinant nucleic acid molecules are typically injected by direct or intramuscular administration. Recombinant nucleic acid molecules to be administered by naked DNA administration include a nucleic acid molecule of the present invention, and preferably includes a recombinant molecule of the present invention that preferably is replication, or otherwise amplification, competent. A naked nucleic acid reagent of the present invention can comprise one or more nucleic acid molecule of the present invention in the form of, for example, a dicistronic recombinant molecule. Naked nucleic acid delivery can include intramuscular, subcutaneous, intradermal, transdermal, intranasal and oral routes of administration, with direct injection into the target tissue being most preferred. A preferred single dose of a naked nucleic acid vaccine ranges from about 1 nanogram (ng) to about 100 μg, depending on the route of administration and/or method of delivery, as can be determined by those skilled in the art. Suitable delivery methods include, for example, by injection, as drops, aerosolized and/or topically. In one embodiment, pure DNA constructs cover the surface of gold particles (1 to 3 μm in diameter) and are propelled into skin cells or muscle with a "gene gun."

In accordance with the present invention, a suitable single dose of a recombinant nucleic acid molecule encoding a biomarker protein as described herein is a dose that is capable of transfecting a host cell and being expressed in the host cell at a level sufficient, in the absence of the addition of any other factors or other manipulation of the host cell, to regulate angiogenesis and/or the tumorigenicity of the host cell when administered one or more times over a suitable time period. Doses can vary depending upon the cell type being targeted, the route of administration, the delivery vehicle used, and the disease or condition being treated.

In one embodiment, an appropriate single dose of a nucleic acid:liposome complex of the present invention is from about 0.1 μg to about 100 μg per kg body weight of the patient to which the complex is being administered. In another embodiment, an appropriate single dose is from about 1 μg to about 10 μg per kg body weight. In another embodiment, an appropriate single dose of nucleic acid:lipid complex is at least about 0.1 μg of nucleic acid, more preferably at least about 1 μg of nucleic acid, even more preferably at least about 10 μg of nucleic acid, even more preferably at least about 50 μg of nucleic acid, and even more preferably at least about 100 μg of nucleic acid.

Preferably, an appropriate single dose of a recombinant nucleic acid molecule encoding a biomarker protein of the present invention results in at least about 1 pg of protein expressed per mg of total tissue protein per μg of nucleic acid delivered. More preferably, an appropriate single dose is a dose which results in at least about 10 pg of protein expressed per mg of total tissue protein per μg of nucleic acid delivered; and even more preferably, at least about 50 pg of protein expressed per mg of total tissue protein per μg of nucleic acid delivered; and most preferably, at least about 100 pg of protein expressed per mg of total tissue protein per μg of nucleic acid delivered.

When the biomarker regulatory agent is a protein, small molecule (i.e., the products of drug design) or antibody, a preferred single dose of such a compound typically comprises between about 0.01 microgram×kilogram^{-1} and about 10 milligram×kilogram^{-1} body weight of an animal. A more preferred single dose of an agent comprises between about 1 microgram×kilogram^{-1} and about 10 milligram×kilograms^{-1} body weight of an animal. An even more preferred single dose of an agent comprises between about 5 microgram×kilograms^{-1} and about 7 milligram×kilograms^{-1} body weight of an animal. An even more preferred single dose of an agent comprises between about 10 microgram×kilogram^{-1} and about 5 milligram×kilograms^{-1} body weight of an animal. Another particularly preferred single dose of an agent comprises between about 0.1 microgram×kilograms^{-1} and about 10 microgram×kilograms^{-1} body weight of an animal, if the agent is delivered parenterally.

In another embodiment, a targeting vector can be used to deliver a particular nucleic acid molecule into a recombinant

host cell, wherein the nucleic acid molecule is used to delete or inactivate an endogenous gene (e.g., biomarker-encoding gene) within the host cell or microorganism (i.e., used for targeted gene disruption or knock-out technology). Such a vector may also be known in the art as a "knock-out" vector. In one aspect of this embodiment, a portion of the vector, but more typically, the nucleic acid molecule inserted into the vector (i.e., the insert), has a nucleic acid sequence that is homologous to a nucleic acid sequence of a target gene in the host cell (i.e., a gene which is targeted to be deleted or inactivated). The nucleic acid sequence of the vector insert is designed to bind to the target gene such that the target gene and the insert undergo homologous recombination, whereby the endogenous target gene is deleted, inactivated or attenuated (i.e., by at least a portion of the endogenous target gene being mutated or deleted).

Compositions of the present invention can be administered to any mammalian patient, and preferably to humans. According to the present invention, administration of a composition is useful to inhibit the tumorigenicity of a target cell or to treat cancer, or to inhibit angiogenesis in a tissue of a patient. Typically, it is desirable to inhibit the growth of a target cell, or to reduce tumor burden in the patient (tumor numbers and/or volume), or to prevent further growth of the tumor in the patient (tumor stasis), or to obtain any therapeutic benefit in the patient (e.g., increased survival). In one embodiment, patients whom are suitable candidates for the method of the present invention include, but are not limited to, patients that have, or are at risk of developing (e.g., are predisposed to), cancer or a lymphoproliferative disease, or any condition in which regulation of angiogenesis might be beneficial. In another embodiment, patients whom are suitable candidates for a method of the invention include, but are not limited to: patients with vascular deficiencies, cardiovascular disease, or patients in whom stimulation of endothelial cell activation and stabilization of newly formed microvessels or other vessels would be beneficial. Increasing or decreasing the expression or biological activity of various biomarkers to inhibit or promote angiogenesis in the absence of obtaining some therapeutic benefit is useful for the purposes of determining factors involved (or not involved) in a disease and preparing a patient to more beneficially receive another therapeutic composition. In a preferred embodiment, however, the methods of the present invention are directed to the inhibition of cancer or inhibition or promotion of angiogenesis in a tissue, which is useful in providing some therapeutic benefit to a patient.

As such, a therapeutic benefit is not necessarily a cure for a particular disease or condition, but rather, preferably encompasses a result which most typically includes alleviation of the disease or condition or increased survival, elimination of the disease or condition, reduction of a symptom associated with the disease or condition (e.g. reduced tumor burden), prevention or alleviation of a secondary disease or condition resulting from the occurrence of a primary disease or condition (e.g., metastatic tumor growth resulting from a primary cancer), and/or prevention of the disease or condition. As used herein, the phrase "protected from a disease" refers to reducing the symptoms of the disease; reducing the occurrence of the disease, and/or reducing the severity of the disease. Protecting a patient can refer to the ability of a composition of the present invention, when administered to a patient, to prevent a disease from occurring and/or to cure or to alleviate disease symptoms, signs or causes. As such, to protect a patient from a disease includes both preventing disease occurrence (prophylactic treatment) and treating a patient that has a disease (therapeutic treatment). In particular, protecting a patient from a disease is accomplished by inhibiting the tumorigenicity of a target cell in the patient or inhibiting or promoting angiogenesis in the cells or tissues of a patient by regulating biomarker expression or biological activity such that a beneficial effect is obtained. A beneficial effect can easily be assessed by one of ordinary skill in the art and/or by a trained clinician who is treating the patient. The term, "disease" refers to any deviation from the normal health of a mammal and includes a state when disease symptoms are present, as well as conditions in which a deviation (e.g., infection, gene mutation, genetic defect, etc.) has occurred, but symptoms are not yet manifested.

One embodiment of the present invention relates to a method (i.e., an assay) for diagnosing or assessing tumor cells (cancer) or the potential therefore in a patient. In one aspect of this embodiment, the method includes the steps of: (a) detecting a level of expression or activity of one or more biomarkers of the present invention in a test sample from a patient to be diagnosed; and (b) comparing the level of expression or activity of the biomarker(s) in the test sample to a normal level of biomarker expression or activity established from a control sample. For example, it is noted that the present inventor has determined that expression of MAGP-2 is upregulated in uterine tumor cells. According to the present invention, detection of the biomarker can be achieved by any method that detects the expression of the biomarker. Detection of a statistically significant difference in biomarker expression or activity in the test sample, as compared to the control level of biomarker expression or biological activity, is an indicator of a difference in the tumorigenicity or potential therefore of cells in the test sample as compared to cells in the control sample. The expression of the biomarker may be cell- and context-specific. Therefore, biomarker expression or activity could be either upregulated or downregulated in a cell as compared to the control. Typically, the biomarker is upregulated or downregulated in the manner associated with the expression of the biomarker during angiogenesis as represented in any one or more of the Tables or experiments described herein. The method of the present invention can be used for any type of tumor wherein the biomarker expression or activity is found to be statistically significantly changed in tumor cells as compared to the corresponding normal cells.

According to the present invention, the phrase "tumorigenicity" refers primarily to the tumor status of a cell or cells (e.g., the extent of neoplastic transformation of a cell, the malignancy of a cell, the propensity for a cell to form a tumor and/or have characteristics of a tumor, or simply the presence or absence of tumor cells in a patient or tissue/organ), which is reflective of a change of a cell or population of cells from a normal to malignant state. Tumorigenicity indicates that tumor cells are present in a sample, and/or that the transformation of cells from normal to tumor cells is in progress, as may be confirmed by any standard of measurement of tumor development. The change typically involves cellular proliferation at a rate which is more rapid than the growth observed for normal cells under the same conditions, and which is typically characterized by one or more of the following traits: continued growth even after the instigating factor (e.g., carcinogen, virus) is no longer present; a lack of structural organization and/or coordination with normal tissue, and typically, a formation of a mass of tissue, or tumor. A tumor, therefore, is most generally described as a proliferation of cells (e.g., a neoplasia, a growth, a polyp) resulting from neoplastic growth and is most typically a malignant tumor. In the case of a neoplastic transformation, a neoplasia is malignant or is predisposed to become malignant. Malignant tumors are typically characterized as being anaplastic (primi-

tive cellular growth characterized by a lack of differentiation), invasive (moves into and destroys surrounding tissues) and/or metastatic (spreads to other parts of the body). As used herein, reference to a "potential for neoplastic transformation", "potential for tumorigenicity" or a "potential for tumor cell growth" refers to an expectation or likelihood that, at some point in the future, a cell or population of cells will display characteristics of neoplastic transformation, including rapid cellular proliferation characterized by anaplastic, invasive and/or metastatic growth.

This method of the present invention has several different uses. First, the method can be used to diagnose tumorigenicity, or the potential for tumorigenicity, or simply the presence or absence of tumor cells, in a subject. The subject can be an individual who is suspected of having a tumor, or an individual who is presumed to be healthy, but who is undergoing a routine or diagnostic screening for the presence of a tumor (cancer). The subject can also be an individual who has previously been diagnosed with cancer and treated, and who is now under surveillance for recurring tumor growth. The terms "diagnose", "diagnosis", "diagnosing" and variants thereof refer to the identification of a disease or condition on the basis of its signs and symptoms. As used herein, a "positive diagnosis" indicates that the disease or condition, or a potential for developing the disease or condition, has been identified. In contrast, a "negative diagnosis" indicates that the disease or condition, or a potential for developing the disease or condition, has not been identified. Therefore, in the present invention, a positive diagnosis (i.e., a positive assessment) of tumor growth or tumorigenicity (i.e., malignant or inappropriate cell growth or neoplastic transformation), or the potential therefore, means that the indicators (e.g., signs, symptoms) of tumor presence and/or growth according to the present invention (i.e., a change in biomarker expression or biological activity as compared to a baseline control) have been identified in the sample obtained from the subject. Such a subject can then be prescribed treatment to reduce or eliminate the tumor growth. Similarly, a negative diagnosis (i.e., a negative assessment) for tumor growth or a potential therefore or the absence of tumor cells means that the indicators of tumor growth or tumor presence or a likelihood of developing tumors as described herein (i.e., a change in biomarker expression or biological activity as compared to a baseline control) have not been identified in the sample obtained from the subject. In this instance, the subject is typically not prescribed any treatment, but may be reevaluated at one or more timepoints in the future to again assess tumor growth. Baseline levels for this particular embodiment of the method of assessment of tumorigenicity of the present invention are typically based on a "normal" or "healthy" sample from the same bodily source as the test sample (i.e., the same tissue, cells or bodily fluid), as discussed in detail below.

In a second embodiment, the method of the present invention can be used more specifically to "stage" a tumor in a patient. Therefore, the patient can be diagnosed as having a tumor or. potential therefore by the method as discussed above, or by any other suitable method (e.g., physical exam, X-ray, CT scan, blood test for a tumor antigen, surgery), and then (or at the same time, when the present method is also used as a diagnostic), the method of the present invention can be used to determine the stage of progression of tumor growth in an individual. For most cancer types, standard staging criteria exist and are known in the art. For example, in breast tumors, there are five different general stages of tumor development which are known and acknowledged in the art as stages 0, I, II, III and IV (although these stages can be grouped into more complex subgroups based on more specific indicators). In this embodiment of the method of the present invention, the biomarker expression and/or biological activity in the patient sample is compared to a panel of several different "baseline" levels of biomarker expression or biological activity, wherein each baseline level represents a previously established level for a given stage of the cancer being diagnosed. The ability to "stage" a tumor in the method of the present invention allows the physician to more appropriately prescribe treatment for the patient.

In a third embodiment of this method of the present invention, the method is used to monitor the success, or lack thereof, of a treatment for cancer in a patient that has been diagnosed as having cancer. In this embodiment, the baseline or control level of biomarker expression or biological activity typically includes the previous level of biomarker expression or biological activity in a sample of the patient's tumor, so that a new level of biomarker expression or biological activity can be compared to determine whether tumor cell growth is decreasing, increasing, or substantially unchanged as compared to the previous, or first sample (i.e., the initial sample which presented a positive diagnosis). In addition, or alternatively, a baseline established as a "normal" or "healthy" level of biomarker expression or biological activity can be used in this embodiment, particularly to determine in what manner the biomarker expression is regulated in tumors for the given cell type. This embodiment allows the physician to monitor the success, or lack of success, of a treatment that the patient is receiving for cancer, and can help the physician to determine whether the treatment should be modified. In one embodiment of the present invention, the method includes additional steps of modifying cancer treatment for the patient based on whether an increase or decrease in tumor cell growth is indicated by evaluation of biomarker expression and/or biological activity in the patient.

The first step of the method of the present invention includes detecting biomarker expression or biological activity in a test sample from a patient. According to the present invention, the term "test sample" can be used generally to refer to a sample of any type which contains cells or products that have been secreted from cells (e.g., some biomarkers of the invention are secreted proteins and so one can evaluate a cell supemate, bodily fluid or other media into which such biomarkers may have been secreted by a cell) to be evaluated by the present method, including but not limited to, a sample of isolated cells, a tissue sample and/or a bodily fluid sample. According to the present invention, a sample of isolated cells is a specimen of cells, typically in suspension or separated from connective tissue which may have connected the cells within a tissue in vivo, which have been collected from an organ, tissue or fluid by any suitable method which results in the collection of a suitable number of cells for evaluation by the method of the present invention. The cells in the cell sample are not necessarily of the same type, although purification methods can be used to enrich for the type of cells that are preferably evaluated. Cells can be obtained, for example, by scraping of a tissue, processing of a tissue sample to release individual cells, or isolation from a bodily fluid. A tissue sample, although similar to a sample of isolated cells, is defined herein as a section of an organ or tissue of the body which typically includes several cell types and/or cytoskeletal structure which holds the cells together. One of skill in the art will appreciate that the term "tissue sample" may be used, in some instances, interchangeably with a "cell sample", although it is preferably used to designate a more complex structure than a cell sample. A tissue sample can be obtained by a biopsy, for example, including by cutting, slicing, or a punch. A bodily fluid sample, like the tissue sample, contains

the cells to be evaluated for biomarker expression or biological activity and/or contains the soluble biomarker secreted by cells, and is a fluid obtained by any method suitable for the particular bodily fluid to be sampled. Bodily fluids suitable for sampling include, but are not limited to, blood, mucous, seminal fluid, saliva, breast milk, bile and urine.

In general, the sample type (i.e., cell, tissue or bodily fluid) is selected based on the accessibility and structure of the organ or tissue to be evaluated for tumor cell growth and/or on what type of cancer is to be evaluated. For example, if the organ/tissue to be evaluated is the breast, the sample can be a sample of epithelial cells from a biopsy (i.e., a cell sample) or a breast tissue sample from a biopsy (a tissue sample). The sample that is most useful in the present invention will be cells, tissues or bodily fluids isolated from a patient by a biopsy or surgery or routine laboratory fluid collection.

Once a sample is obtained from the patient, the sample is evaluated for detection of biomarker expression or biological activity in the cells of the sample. The phrase "biomarker expression" can generally refer to biomarker mRNA transcription or biomarker protein translation. Preferably, the method of detecting biomarker expression or biological activity in the patient is the same or qualitatively equivalent to the method used for detection of biomarker expression or biological activity in the sample used to establish the baseline level.

Methods suitable for detecting biomarker transcription include any suitable method for detecting and/or measuring mRNA levels from a cell or cell extract. Such methods include, but are not limited to: polymerase chain reaction (PCR), reverse transcriptase PCR (RT-PCR), in situ hybridization, Northern blot, sequence analysis, gene microarray analysis (gene chip analysis) and detection of a reporter gene. Such methods for detection of transcription levels are well known in the art, and many of such methods are described in detail in the attached examples, in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Labs Press, 1989 and/or in Glick et al., *Molecular Biotechnology: Principles and Applications of Recombinant DNA*, ASM Press, 1998; Sambrook et al., ibid., and Glick et al., ibid. are incorporated by reference herein in their entireties.

Measurement of biomarker transcription is suitable when the sample is a cell or tissue sample; therefore, when the sample is a bodily fluid sample containing cells or cellular extracts, the cells are typically isolated from the bodily fluid to perform the expression assay, or the fluid is evaluated for the presence of secreted biomarker protein.

Biomarker expression can also be identified by detection of biomarker translation (i.e., detection of biomarker protein in a sample). Methods suitable for the detection of biomarker protein include any suitable method for detecting and/or measuring proteins from a cell or cell extract. Such methods include, but are not limited to, immunoblot (e.g., Western blot), enzyme-linked immunosorbant assay (ELISA), radioimmunoassay (RIA), immunoprecipitation, immunohistochemistry and immunofluorescence. Particularly preferred methods for detection of proteins include any single-cell assay, including immunohistochemistry and immunofluorescence assays. Such methods are well known in the art. Furthermore, antibodies against certain of the biomarkers described herein are known in the art and are described in the public literature, and methods for production of antibodies that can be developed against biomarkers are well known in the art.

The method of the present invention includes a step of comparing the level of biomarker expression or biological activity detected in step (a) to a baseline level (also known as a control level) of biomarker expression or biological activity established from a control sample. According to the present invention, a "baseline level" is a control level, and in some embodiments (but not all embodiments, depending on the method), a normal level, of biomarker expression or activity against which a test level of biomarker expression or biological activity (i.e., in the test sample) can be compared. Therefore, it can be determined, based on the control or baseline level of biomarker expression or biological activity, whether a sample to be evaluated for tumor cell growth has a measurable increase, decrease, or substantially no change in biomarker expression or biological activity, as compared to the baseline level. As discussed above, the baseline level can be indicative of different states of cell tumorigenicity or lack thereof, depending on the primary use of the assay. For example, the baseline level can be indicative of the cell growth expected in a normal (i.e., healthy, negative control, non-tumor) cell sample. Therefore, the term "negative control" or "normal control" used in reference to a baseline level of biomarker expression or biological activity typically refers to a baseline level established in a sample from the patient or from a population of individuals which is believed to be normal (i.e., non-tumorous, not undergoing neoplastic transformation, not exhibiting inappropriate cell growth). For some biomarkers, the negative control may have a higher level of biomarker expression or activity than the tumor type. In another embodiment, a baseline can be indicative of a positive diagnosis of tumor cell growth. Such a baseline level, also referred to herein as a "positive control" baseline, refers to a level of biomarker expression or biological activity established in a cell sample from the patient, another patient, or a population of individuals, wherein the sample was believed, based on data for that cell sample, to be neoplastically transformed (i.e., tumorous, exhibiting inappropriate cell growth, cancerous). In one aspect, the baseline can be indicative of a particular stage of tumor cell growth, which will allow a patient's sample to be "staged" (i.e., the stage of the cancer in the patient can be identified). In yet another embodiment, the baseline level can be established from a previous sample from the patient being tested, so that the tumor growth of a patient can be monitored over time and/or so that the efficacy of a given therapeutic protocol can be evaluated over time. Methods for detecting biomarker expression or biological activity are described in detail above.

The method for establishing a baseline level of biomarker expression or activity is selected based on the sample type, the tissue or organ from which the sample is obtained, the status of the patient to be evaluated, and, as discussed above, the focus or goal of the assay (e.g., diagnosis, staging, monitoring). Preferably, the method is the same method that will be used to evaluate the sample in the patient. In a most preferred embodiment, the baseline level is established using the same cell type as the cell to be evaluated. Baseline levels can be established from an autologous control sample obtained from the patient. According to the present invention, and as used in the art, the term "autologous" means that the sample is obtained from the same patient from which the sample to be evaluated is obtained. The control sample should be of or from the same cell type and preferably, the control sample is obtained from the same organ, tissue or bodily fluid as the sample to be evaluated, such that the control sample serves as the best possible baseline for the sample to be evaluated. In one embodiment, when the goal of the assay is diagnosis of abnormal cell growth, it is desirable to take the control sample from a population of cells, a tissue or a bodily fluid which is believed to represent a "normal" cell, tissue, or bodily fluid, or at a minimum, a cell or tissue which is least likely to be

undergoing or potentially be predisposed to develop tumor cell growth. For example, if the sample to be evaluated is an area of apparently abnormal cell growth, such as a tumorous mass, the control sample is preferably obtained from a section of apparently normal tissue (i.e., an area other than and preferably a reasonable distance from the tumorous mass) in the tissue or organ where the tumorous mass is growing.

In another embodiment, when the goal is to monitor tumor cell growth in the patient, the autologous baseline sample is typically a previous sample from the patient which was taken from an apparent or confirmed tumorous mass, and/or from apparently normal (i.e., non-tumor) tissue in the patient (or a different type of baseline for normal can be used, as discussed below). Therefore, a second method for establishing a baseline level of biomarker expression or biological activity is to establish a baseline level of biomarker expression or biological activity from at least one measurement of biomarker expression or biological activity in a previous sample from the same patient. Such a sample is also an autologous sample, but is taken from the patient at a different time point than the sample to be tested. Preferably, the previous sample(s) were of a same cell type, tissue type or bodily fluid type as the sample to be presently evaluated. In one embodiment, the previous sample resulted in a negative diagnosis (i.e., no tumor cell growth, or potential therefore, was identified). In this embodiment, a new sample is evaluated periodically (e.g., at annual physicals), and as long as the patient is determined to be negative for tumor development, an average or other suitable statistically appropriate baseline of the previous samples can be used as a "negative control" for subsequent evaluations. For the first evaluation, an alternate control can be used, as described below, or additional testing may be performed to confirm an initial negative diagnosis, if desired, and the value for biomarker expression or biological activity can be used thereafter. This type of baseline control is frequently used in other clinical diagnosis procedures where a "normal" level may differ from patient to patient and/or where obtaining an autologous control sample at the time of diagnosis is not possible, not practical or not beneficial.

In another embodiment, the previous sample from the patient resulted in a positive diagnosis (i.e., tumor growth was positively identified). In this embodiment, the baseline provided by the previous sample is effectively a positive control for tumor growth, and the subsequent samplings of the patient are compared to this baseline to monitor the progress of the tumor growth and/or to evaluate the efficacy of a treatment that is being prescribed for the cancer. In this embodiment, it may also be beneficial to have a negative baseline level of biomarker expression or biological activity (i.e., a normal cell baseline control), so that a baseline for remission or regression of the tumor can be set. Monitoring of a patient's tumor growth can be used by the clinician to modify cancer treatment for the patient based on whether an increase or decrease in cell growth is indicated.

It will be clear to those of skill in the art that some samples to be evaluated will not readily provide an obvious autologous control sample, or it may be determined that collection of autologous control samples is too invasive and/or causes undue discomfort to the patient. In these instances, an alternate method of establishing a baseline level of biomarker expression or biological activity can be used.

Another method for establishing a baseline level of biomarker expression or biological activity is to establish a baseline level of biomarker expression or biological activity from control samples, and preferably control samples that were obtained from a population of matched individuals. It is preferred that the control samples are of the same sample type as the sample type to be evaluated for biomarker expression or biological activity (e.g., the same cell type, and preferably from the same tissue or organ). According to the present invention, the phrase "matched individuals" refers to a matching of the control individuals on the basis of one or more characteristics which are suitable for the type of cell or tumor growth to be evaluated. For example, control individuals can be matched with the patient to be evaluated on the basis of gender, age, race, or any relevant biological or sociological factor that may affect the baseline of the control individuals and the patient (e.g., preexisting conditions, consumption of particular substances, levels of other biological or physiological factors). For example, levels of biomarker expression in the uterine tissue of a normal individual (i.e., having uterine tissue that is not neoplastically transformed or predisposed to such transformation) may be lower or higher in individuals of a given classification (e.g., elderly vs. teenagers, smokers vs. non-smokers) (although such variation in groups is not currently known). To establish a control or baseline level of biomarker expression or biological activity, samples from a number of matched individuals are obtained and evaluated for biomarker expression or biological activity. The sample type is preferably of the same sample type and obtained from the same organ, tissue or bodily fluid as the sample type to be evaluated in the test patient. The number of matched individuals from whom control samples must be obtained to establish a suitable control level (e.g., a population) can be determined by those of skill in the art, but should be statistically appropriate to establish a suitable baseline for comparison with the patient to be evaluated (i.e., the test patient). The values obtained from the control samples are statistically processed using any suitable method of statistical analysis to establish a suitable baseline level using methods standard in the art for establishing such values.

It will be appreciated by those of skill in the art that a baseline need not be established for each assay as the assay is performed but rather, a baseline can be established by referring to a form of stored information regarding a previously determined baseline level of biomarker expression for a given control sample, such as a baseline level established by any of the above-described methods. Such a form of stored information can include, for example, but is not limited to, a reference chart, listing or electronic file of population or individual data regarding "normal" (negative control) or tumor positive (including staged tumors) biomarker expression; a medical chart for the patient recording data from previous evaluations; or any other source of data regarding baseline biomarker expression that is useful for the patient to be diagnosed.

After the level of biomarker expression or biological activity is detected in the sample to be evaluated for tumor cell growth, such level is compared to the established baseline level of biomarker expression or biological activity, determined as described above. Also, as mentioned above, preferably, the method of detecting used for the sample to be evaluated is the same or qualitatively and/or quantitatively equivalent to the method of detecting used to establish the baseline level, such that the levels of the test sample and the baseline can be directly compared. In comparing the test sample to the baseline control, it is determined whether the test sample has a measurable decrease or increase in biomarker expression or biological activity over the baseline level, or whether there is no statistically significant difference

between the test and baseline levels. After comparing the levels of biomarker expression or biological activity in the samples, the final step of making a diagnosis, monitoring, or staging of the patient can be performed as discussed above.

As discussed above, a positive diagnosis indicates that increased cell growth, and possibly tumor cell growth (neoplastic transformation), has occurred, is occurring, or is statistically likely to occur in the cells or tissue from which the sample was obtained. In order to establish a positive diagnosis, the level of biomarker activity is modulated as compared to the established baseline by an amount that is statistically significant (i.e., with at least a 95% confidence level, or $p<0.05$). Preferably, detection of at least about a 10% change in biomarker expression or biological activity in the sample as compared to the baseline level results in a positive diagnosis of cancer for said sample, as compared to the baseline. More preferably, detection of at least about a 30% change in biomarker expression or biological activity in the sample as compared to the baseline level results in a positive diagnosis of cancer for said sample, as compared to the baseline. More preferably, detection of at least about a 50% change, and more preferably at least about a 70% change, and more preferably at least about a 90% change, or any percentage change between 5% and higher in 1% increments (i.e., 5%, 6%, 7%, 8% . . .) in biomarker expression or biological activity in the sample as compared to the baseline level results in a positive diagnosis of cancer for said sample. In one embodiment, a 1.5 fold change in biomarker expression or biological activity in the sample as compared to the baseline level results in a positive diagnosis of cancer for said sample. More preferably, detection of at least about a 3 fold change, and more preferably at least about a 6 fold change, and even more preferably, at least about a 12 fold change, and even more preferably, at least about a 24 fold change, or any fold change from 1.5 up in increments of 0.5 fold (i.e., 1.5, 2.0, 2.5, 3.0 . . .) in biomarker expression or biological activity as compared to the baseline level, results in a positive diagnosis of cancer for said sample.

Once a positive diagnosis is made using the present method, the diagnosis can be substantiated, if desired, using any suitable alternate method of detection of tumor cells, including pathology screening, blood screening for tumor antigens, and surgery.

Included in the present invention are kits for assessing angiogenesis in cells or for diagnosing tumor cells (cancer) in a patient. The assay kit includes: (a) reagents for detecting biomarker expression or activity in a test sample (e.g., a probe that hybridizes under stringent hybridization conditions to a nucleic acid molecule encoding the biomarker or a fragment thereof; RT-PCR primers for amplification of mRNA encoding the biomarker or a fragment thereof; and/or an antibody, antigen-binding fragment thereof or other antigen-binding peptide that selectively binds to the biomarker); and (b) reagents for detecting a control marker characteristic of a cell type in the test sample (e.g., a probe that hybridizes under stringent hybridization conditions to a nucleic acid molecule encoding a protein marker; PCR primers which amplify such a nucleic acid molecule; and/or an antibody, antigen binding fragment thereof, or antigen binding peptide that selectively binds to the control marker in the sample).

The reagents for detecting of part (a) and or part (b) of the assay kit of the present invention can be conjugated to a detectable tag or detectable label. Such a tag can be any suitable tag which allows for detection of the reagents of part (a) or (b) and includes, but is not limited to, any composition or label detectable by spectroscopic, photochemical, biochemical, immunochemical, electrical, optical or chemical means. Useful labels in the present invention include biotin for staining with labeled streptavidin conjugate, magnetic beads (e.g., Dynabeads™), fluorescent dyes (e.g., fluorescein, texas red, rhodamine, green fluorescent protein, and the like), radiolabels (e.g., ^{3}H, ^{125}I, ^{35}S, ^{14}C, or ^{32}p), enzymes (e.g., horse radish peroxidase, alkaline phosphatase and others commonly used in an ELISA), and colorimetric labels such as colloidal gold or colored glass or plastic (e.g., polystyrene, polypropylene, latex, etc.) beads.

In addition, the reagents for detecting of part (a) and or part (b) of the assay kit of the present invention can be immobilized on a substrate. Such a substrate can include any suitable substrate for immobilization of a detection reagent such as would be used in any of the previously described methods of detection. Briefly, a substrate suitable for immobilization of a means for detecting includes any solid support, such as any solid organic, biopolymer or inorganic support that can form a bond with the means for detecting without significantly effecting the activity and/or ability of the detection means to detect the desired target molecule. Exemplary organic solid supports include polymers such as polystyrene, nylon, phenol-formaldehyde resins, acrylic copolymers (e.g., polyacrylamide), stabilized intact whole cells, and stabilized crude whole cell/membrane homogenates. Exemplary biopolymer supports include cellulose, polydextrans (e.g., Sephadex®), agarose, collagen and chitin. Exemplary inorganic supports include glass beads (porous and nonporous), stainless steel, metal oxides (e.g., porous ceramics such as ZrO_2, TiO_2, Al_2O_3, and NiO) and sand.

According to the present invention, the method and assay for assessing tumor cells in a patient, as well as other methods disclosed herein, are suitable for use in a patient that is a member of the Vertebrate class, Mammalia, including, without limitation, primates, livestock and domestic pets (e.g., a companion animal). Most typically, a patient will be a human patient.

The following examples are provided for the purpose of illustration and are not intended to limit the scope of the present invention. Each publication or other reference disclosed below and elsewhere herein is incorporated herein by reference in its entirety.

EXAMPLES

The following Materials and Methods were used in Examples 1-5 below.

Plasmids

All retroviral expression vectors encoding various putative angiogenic factors were generated by first PCR amplifying their full-length cDNAs from expressed sequence tags using oligonucleotides that facilitated their subsequent subcloning into the pcDNA3.1/Myc-His B vector (Invitrogen). The resulting full-length Myc-His_6-tagged cDNAs were PCR amplified using oligonucleotides that permitted their ligation into the bicistronic retroviral vector, pMSCV-IRES-YFP (Albig and Schiemann, 2005). Table II identifies all of the IMAGE clones and oligonucleotides used to synthesize these retroviral vectors. All putative angiogenic factor inserts were sequenced in their entirety on an Applied Biosystems 377A DNA sequencing machine.

TABLE II

Cloning oligonucleotides

Gene name	Image clone	Oligos for subcloning to pcDNA3.1/Myc-His	Oligos for subcloning to pMSCV-YFP
Matrilin-2	5063535	5'(NotI)GGCGGCGCGGCCGCATGGAGAAGATGTTGGTG SEQ ID NO: 57	5'(XhoI)GGCGGCCTCGAGATGGAGAAGATGTTGGTG SEQ ID NO: 59
		3'(SacII)GGCGGCCCGCGGTCTGTATTTTAGGCGATT SEQ ID NO: 58	3'(EcoRI)CCGGCCGAATTCTCAATGGTGATGGTGATGATGACC SEQ ID NO: 60
Lumican	5707371	5'(BamH1)GGCGCCGGATCCATGAATGTATGTGCGTTC SEQ ID NO: 61	5'(BgIII)GGCGCCAGATCTATGAATGTATGTGCGTTC SEQ ID NO: 63
		3'(NotI)GGCGCCGGATCCATGAATGTATGTGCGTTC SEQ ID NO: 62	3'(EcoRI)CCGGCCGAATTCTCAATGGTGATGGTGATGATGACC SEQ ID NO: 64
ECM1	5347298	5'(BamHI)GGCGGCGGATCCATGGGGACCGTATCCAGA SEQ ID NO: 65	5'(ECM1)GGCGCCAGATCTATGAATGTATGTGCGTTC SEQ ID NO: 67
		3'(SacII)GGCGGCCCGCGGTTCTTCCTTGGACCCAGG SEQ ID NO: 66	3'(HpaI)GGCCGGGTTAACTCAATGGTGATGGTGATGATG SEQ ID NO: 68
SMOC-2	3988177	5'(HindIII)GGCGGCAAGCTTATGCTGCCGCCACAGCTG SEQ ID NO: 69	5'(BgIII)GGCGGCCTCGAGATGTGGCCCCAACCACCC SEQ ID NO: 71
		3'(SacII)GGCGGCCCGCGGTCCTTGTTTCCTGGGCTG SEQ ID NO: 70	3'(EcoRI)CCGGCCGAATTCTCAATGGTGATGGTGATGATGACC SEQ ID NO: 72
MAGP-2	3469761	5'(HindIII)GGCGGCAAGCTTATGCTGTTCTTGGGGCAG SEQ ID NO: 73	5'(XhoI)GGCGGCCTCGAGATGTGGCCCCAACCACCC SEQ ID NO: 75
		3'(SacII)GGCGGCCCGCGGCAGACCATCGGGTCTCTG SEQ ID NO: 74	3'(EcoRI)CCGGCCGAATTCTCAATGGTGATGGTGATGATGACC SEQ ID NO: 76
AK002276	1481807	5'(HindIII)GGCGGCAAGCTTATGGCGTCTCGGGAGTCA SEQ ID NO: 77	5'(EcoRI)GGCGGCGAATTCATGGCGTCTCGGGAGTCA SEQ ID NO: 79
		3'(SacIII)GGCGGCCCGCGGTGAAGCCTTGGCTTTCCG SEQ ID NO: 78	3'(EcoRI)CCGGCCGAATTCTCAATGGTGATGGTGATGATGACC SEQ ID NO: 80
CRELD-2	6336331	5'(HindIII)GGCGGCCCGCGGTGAAGCCTTGGCTTTCCG SEQ ID NO: 81	5'(BgIII)GGCGGCAGATCTATGCACCTGCTGCTTGCA SEQ ID NO: 83
		3'(SacII)GGCGGCCCGCGGCAAATCCTCACGGGAGGG SEQ ID NO: 82	3'(XhoI)CCGGCCCTCGAGTCAATGGTGATGGTGATGATGACC SEQ ID NO: 84

The Myc-tagged mammalian expression vectors encoding murine Notch1 [pCS2+mN1FL6MT; (Mumm et al, 2000)] and Jagged-1 [pCS2+Jag1-6MT; (Mumm et al, 2000)] were kindly provided by Dr. Raphael Kopan (Washington University, St. Louis, Mo.). A retroviral Notch1 ICD vector was constructed by PCR amplifying the murine Notch1 ICD domain (amino acids 1744-2531 and contained in pCS2-mN1FL6MT) using a 5' oligonucleotide that contained a unique Xho I restriction site, a Kozak consensus sequence, and a start codon:

(5'GGCGGCCTCGAGGCCACCATGGTGCTGCTGTCCCGC; SEQ ID NO: 121)

and a 3'oligonucleotide that contained a unique Hpa I restriction site, a stop codon, and the C-terminal Myc-tag:

(5'GGCGGCGTTAACTCATGAATTCAAGTCCTCTTCAGA; SEQ ID NO: 122)

The resulting PCR product was ligated into identical restriction sites in the bicistronic retroviral vector, pMSCV-IRES-GFP (Albig and Schiemann, 2005). The pHes1-luciferase, pCMV-Hes1, and pCMV-NICD plasmids were kindly provided by Dr. Jan Jensen (University of Colorado Health Science Center, Denver, Colo.).

Cell Culture and Retroviral Infections

Retroviral supernatants were produced by EcoPack2 retroviral packaging cells (Clontech, Mountain View, Calif.) and used to infect MB114 cells as described previously (Albig et al, 2006; Albig and Schiemann, 2004). Infected cells were analyzed 48 h post-infection and the highest 10% of GFP-expressing cells were collected on a MoFlo cell sorter (Cytomation, Fort Collins, Colo.). Afterward, isolated cells were expanded to yield stable polyclonal populations that were ≧95% positive for transgene expression. Human kidney 293T cells were cultured in DMEM media supplemented with 10% fetal bovine serum (FBS), while human umbilical vein ECs (HUVEC; passages 3-6) were maintained in EGM-2 media (Cambrex Corp., East Rutherford, N.J.) supplemented with EC growth factors (Bullet Kit, Cambrex).

Recombinant MAGP-2 Protein Production

A bacterial MAGP-2 expression vector was synthesized by PCR amplifying the full-length MAGP-2 cDNA (less its signal sequence) using oligonucleotides that incorporated unique Nde I (N-terminus) and Bam HI (C-terminus). The resulting PCR fragment was ligated into identical sites in pSBET (Schenk et al, 1995), which appended a FLAG-tag to the C-terminus of MAGP-2. FLAG-tagged recombinant MAGP-2 protein was purified by passing TBS/0.1% Triton X-100-solubilized bacterial cell extracts over a column containing immobilized FLAG-M2 monoclonal antibodies (Sigma, St. Louis, Mo.). Bound proteins were washed ini-

tially with 10 column volumes of TBS/0.1% Triton X-100, followed by an additional 20 column volumes of TBS. Afterward, recombinant MAGP-2 was eluted by addition of 2.5 column volumes of FLAG M2 peptide (100 □g/ml), and subsequently was concentrated by centrifugation against PBS (5 kDa cutoff; Sartorius, Goettingen, Germany).

EC Activity Assays

The effect putative angiogenic agents had on MB114 cell activities were determined as follows: (i) cell proliferation using a [^{3}H]thymidine incorporation assay as described (Albig et al, 2006; Albig and Schiemann, 2004; Albig and Schiemann, 2005); (ii) cell invasion through Matrigel matrices using a modified Boyden-chamber assay as described (Albig et al, 2006; Albig and Schiemann, 2004; Albig and Schiemann, 2005); (iii) p38 MAPK phosphorylation using immunoblot analyses as described (Albig et al, 2006; Albig and Schiemann, 2004; Albig and Schiemann, 2005); (iv) angiogenic sprouting in rat tail collagen matrices as described (Albig et al, 2006; Albig and Schiemann, 2004); and (v) Hes1- and SBE-driven luciferase reporter gene assays as described (Albig et al, 2006; Albig and Schiemann, 2004; Albig and Schiemann, 2005).

Notch1 Processing Assay

To monitor the effects of MAGP-2 on the processing and S3 cleavage of Notch1, human kidney 293T cells were transiently transfected in 6-well plates with LT-1 liposomes containing 0.5 μg/well of Notch1 (pCS2+mN1FL6MT), 0.5 μg/well Jagged-1 (pCS2+Jag1-6MT), or 1.5 μg/well of MAGP-2 (pcDNA3.1-MAGP-2/Myc-His) in all combinations. Forty-eight h post-transfection, the cells were washed with ice-cold PBS, lysed immediately in Buffer H/1% Triton X-100 [500 μl/well; (Schiemann et al, 2002)], and incubated on ice for 30 min. Afterward, insoluble material was removed by microcentrifugation and 100 μl of the resulting clarified extract was fractionated through 6% SDS-PAGE gels. The fractionated proteins were transferred electrophoretically to nitrocellulose and probed with anti-Myc 9E10 monoclonal antibodies (Covance, Princeton, N.J.) to visual Notchi cleavage species.

Matrigel Plug Implantation Assay

The effect of MAGP-2 on vessel formation and infiltration into Matrigel plugs implanted into genetically normal mice was determined as described (Albig et al, 2006). Briefly, phenol red-free Matrigel (BD biosciences, Bedford, Mass.) was mixed with PBS (diluent), bFGF (50 or 300 ng/ml; R&D Systems, Minneapolis, Minn.), or recombinant MAGP-2 (1 μg/ml) together with bFGF (50 ng/ml), and the resulting mixtures were injected twice subcutaneously in the ventral groin area (400 μl/injection) of C57BL/6 mice. The mice were sacrificed 10 days post-implantation and the Matrigel plugs were dissected, fixed overnight in 10% formalin, and sectioned in the National Jewish Histology Laboratory. Afterward, Masson's trichrome staining was performed to visualize infiltrating vessels, which were quantified under a light microscope by determining the average number of vessels present in 5 random fields (200× magnification). Only those fields that contained at least one vessel in the area underlying the skin were tallied. Two mice were used per experimental condition and this experiment was performed three times in its entirety. All animal studies were performed according to protocol procedures approved by the Animal Care and Use Committee at National Jewish Medical and Research Center.

Semi-Quantitative Real-Time PCR

Semi-quantitative real-time PCR was performed as previously described (Albig et al, 2006; Albig and Schiemann, 2005). Briefly, MB114 cells were induced to tubulate on Matrigel matrices for 1-25 h, whereupon total RNA was isolated using the RNAqueous kit, followed by an additional round of phenol/chloroform extraction and ethanol precipitation as described above. Total RNA (1 μg) was reverse transcribed with random hexamers and iScript reverse transcriptase according to the manufacturer's recommendations (BioRad, Hercules, Calif.). The resulting cDNA reaction mixtures were diluted 40-fold in H_2O and employed in semi-quantitative real-time PCR reactions (25 μl) that used the SYBR Green PCR system (Applied Biosystems, Foster City, Calif.) supplemented with 10 μl of diluted cDNA and 0.1 μM of the oligonucleotide pairs listed in Table III. PCR reactions were performed and analyzed on an ABI 7000 sequence detection system (Applied Biosystems). Differences in RNA concentrations were controlled by normalizing individual gene signals to their corresponding GAPDH RNA signals.

TABLE III

Real-Time PCR oligonucleotides

Gene name	Real Time PCR Forward Oligonucleotide	Real-Time PCR Reverse Oligonucleotide
ADAMts1	5' AATGTTTGATGGACAAGCCCC SEQ ID NO: 85	5' TGCTTGGATTCCTCTCCGAA SEQ ID NO: 86
ADAMts7	5' ACCAGGAACGCCTACCTTTTC SEQ ID NO: 87	5' TCCAGTTTCCTACTTGCCAGC SEQ ID NO: 88
CTGF	5' CTGCCAGTGGAGTTCAAATGC SEQ ID NO: 89	5' TCATTGTCCCCAGGACAGTTG SEQ ID NO: 90
Decorin	5' GGCATTCAAACCTCTCGTGAA SEQ ID NO: 91	5' TCATGGACACGAAGTTCCTGG SEQ ID NO: 92
ECM1	5' CGGAGGAATTCGTGGAAAGA SEQ ID NO: 93	5' CCACTAAAGCCACGTTCCTCA SEQ ID NO: 94
Inhibin β-a	5' TCCCCAAGGCTAACAGAACCA SEQ ID NO: 95	5' CCCCTTTAAGCCCATTTCCTC SEQ ID NO: 96
Inhibin β-b	5' CAGACATCGCATCCGCAAA SEQ ID NO: 97	5' AATGATCCAGTCGTTCCAGCC SEQ ID NO: 98
Integrin α-3	5' AACCCCTTCAAACGGAACCA SEQ ID NO: 99	5' TCGACGTGGACAGCTGAAGAA SEQ ID NO: 100

TABLE III-continued

Real-Time PCR oligonucleotides		
Gene name	Real Time PCR Forward Oligonucleotide	Real-Time PCR Reverse Oligonucleotide
Integrin α-6	5' CTCGTTCTTCGTTCCAGGTTG SEQ ID NO: 101	5' AGCAGCAGCGGTGACATCTAT SEQ ID NO: 102
Lipocalin-7	5' GGACAACTGCAATCGATGCA SEQ ID NO: 103	5' GCCTCGGTTGATGGCTTTAAT SEQ ID NO: 104
LoxI-3	5' AAGTGTGACAGAATGCGCCTC SEQ ID NO: 105	5' ACTTGCAACTGATGCTCCACC SEQ ID NO: 106
Lumican	5' AGTGTGCCAATGGTTCCTCCT SEQ ID NO: 107	5' TGCAGGTCTGTGACGTTCTCA SEQ ID NO: 108
Matrilin-2	5' CACAGGCATCCTGATCTTTGC SEQ ID NO: 109	5' TGAAATTGGCCACCAGGAAG SEQ ID NO: 110
Nephronectin	5' GGTGATGGAGGACATGCGAAT SEQ ID NO: 111	5' TTGTTGGCTTGGAAGTAGGCC SEQ ID NO: 112
SerpinE-2	5' AATCTGATCGATGGTGCCCTT SEQ ID NO: 113	5' CGAATGTCCGTTTCTTTGTGC SEQ ID NO: 114
SMOC-2	5' CACCAAATGGAAGACCCATCA SEQ ID NO: 115	5' ATCATCTGCTTTCCCTGCTCC SEQ ID NO: 116
CRELD-2	5' GCAGAGGAACGAGACCCACAGCATC SEQ ID NO: 117	5' GTGCCCAGCCCACTTCACACTG SEQ ID NO: 118
MAGP-2	5' GCTTGTCTTGGCAGTCAGCATCCC SEQ ID NO: 119	5' GGTCGTCTGTGAATGTCTCAGGCAC SEQ ID NO: 120

Oligonucleotide Microarray Analysis

Murine brain microvascular MB114 ECs were cultured as previously described (Albig et al, 2006; Albig and Schiemann, 2004). To identify genes differentially expressed during angiogenesis, log phase-growing MB114 cells (2×10^6 cells/plate) were plated onto 10-cm plates that contained 4 ml of solidified Matrigel matrices [diluted 5:3 in serum-free media (SFM)]. Tubulogenesis was allowed to proceed for 1, 5, 15, or 25 h, at which point the cells were gently washed twice with ice-cold PBS, and subsequently were scraped, together with their Matrigel cushions, into 16 ml of lysis/binding buffer to isolate total RNA using the RNAqueous kit (Ambion, Austin, Tex.). Isolated total RNA samples were subjected to phenol:choloroform extraction and ethanol precipitation, followed by additional purification using the RNeasy kit (Qiagen, Valencia, Calif.). Afterward, the quality and integrity of purified total RNA (1.5 μg/lane) was analyzed on an Agilent 2100 Bioanalyzer (Agilent Technologies, Palo Alto, Calif.). Biotin-labeled cRNA probes were synthesized using 8 μg of total RNA that was primed with olido-dT and reverse transcribed with Superscript II (Invitrogen, Carlsbad, Calif.), and subsequently were fragmented and hybridized overnight to Affymetrix MOE430A GeneChips according to the manufacturer's recommendations (Affymetrix, Santa Clara, Calif.) in the University of Colorado Health Sciences Center Microarray Core Facility. The microarrays were scanned (2.5-3μ resolution) on a Affymetrix GeneChip Scanner 3000, and differentially expressed mRNAs were identified using GeneSpring 6.0 software (Agilent Technologies). In doing so, individual time points were first compiled into a single experiment that was filtered on flags (i.e., 6 out of 12 flags needed to pass filter). The remaining genes then were filtered by expression levels such that only those genes that were differentially regulated ≧3-fold≦ in at least one time point were considered significant.

Example 1

The following example describes the identification of secretory proteins differentially expressed in tubulating ECs.

To characterize the secretome of ECs undergoing tumor-induced angiogenesis, murine brain microvascular MB114 cells were cultured on tumor-derived basement membranes (i.e., Matrigel matrices) to stimulate angiogenesis activation and the formation of capillary-like structures in vitro. MB114 cells cultured onto Matrigel matrices for 0-25 hours as indicated in FIG. **6** spontaneously reorganized into elongated, capillary-like structures, a response that was readily detected by 5 h, and one that continued to develop over the next 20 h (FIG. **6**). Total RNA was isolated at various times after the initiation of tubulogenesis in MB114 cells, and subsequently was used to synthesize biotinylated cRNA probes that were hybridized to Affymetrix MOE430 GeneChips (see Materials and Methods). In doing so, 308 genes were identified whose expression in angiogenic ECs was altered ≧3-fold≦. Of these differentially-expressed genes, 63 genes (~20%) encoded EC secretory proteins (Table I), 35 genes (~11%) encoded transmembrane or membrane-associated proteins (Table V), and 210 genes encoded non-secretory proteins (Table IV). This approach identified several secretory proteins known to be associated with angiogenesis and/or microenvironment remodeling, including ADAMTS1 (Iruela-Arispe et al, 2003), CTGF (Brigstock, 2002), HGF (Gao and Vande Woude, 2005), MMPs 3 and 9 (Heissig et al, 2003), thrombospondins 1 and 2 (Armstrong and Bornstein, 2003), and TIMP3 (Qi et al, 2003) (Table I, bold type face). In addition, numerous secretory proteins not previously associated with angiogenesis were identified (Table I, regular text face). The differential expression of 19 individual genes was verified by semi-quantitative real-time PCR (see Materials and Methods). These analyses showed significant concor-

dance in the expression profiles measured either by real-time PCR or microarray analyses (Table VI), indicating that these (and other) genes are indeed bona fide targets of angiogenic. signaling systems in tubulating ECs.

TABLE I

Secreted proteins differentially regulated during MB114 tubulogenesis.

		Hours of tubulogenesis				
Name	GenBank #	1	5	15	25	Description
9130213B05Rik	BC006604	1.0	0.3	0.3	0.6	RIKEN cDNA 9130213B05 gene (has signal peptide)
Adamts1	**D67076**	**1.0**	**0.3**	**0.6**	**0.8**	**Adamts1**
Adamts7	AL359935	1.0	2.4	4.8	4.2	Adamts7
C1r	NM_023143	1.0	1.0	2.3	5.6	complement component 1, r subcomponent
C1s	BC022123	1.0	1.0	3.8	10.7	complement component 1, s subcomponent
C3	K02782	1.0	0.7	7.9	23.0	complement component 3
Ccl2	AF065933	1.0	0.7	0.2	0.1	chemokine (C-C motif) ligand 2
Ccl5	NM_013653	1.0	2.7	3.4	3.2	chemokine (C-C motif) ligand 5
Ccl7	AF128193	1.0	0.5	0.3	0.3	chemokine (C-C motif) ligand 7
Ccl8	NM_021443	1.0	1.1	2.8	4.9	chemokine (C-C motif) ligand 8
Cfh	AI987976	1	1.5	3.4	12.5	complement component factor h
Clu	**NM_013492**	**1.0**	**0.9**	**1.7**	**6.6**	**clusterin**
Col3a1	AW550625	1.0	1.3	3.0	3.9	procollagen, type III, alpha 1
Col9a3	BG074456	1.0	0.8	6.7	3.2	procollagen, type IX, alpha 3
Creld2	AK017880	1.0	3.1	1.0	1.1	cysteine-rich with EGF-like domains 2
Csf3	NM_009971	1.0	1.7	0.3	0.3	colony stimulating factor 3 (granulocyte)
Ctgf	**NM_010217**	**1.0**	**0.2**	**0.3**	**0.3**	**connective tissue growth factor**
Cxcl16	BC019961	1	3.9	3.4	3.0	chemokine (C-X-C motif) ligand 16
Cxcl2	NM_009140	1.0	1.2	0.2	0.1	chemokine (C-X-C motif) ligand 2
Cyr61	**NM_010516**	**1.0**	**0.5**	**0.3**	**0.2**	**cysteine rich protein 61**
Dcn	**NM_007833**	**1.0**	**2.1**	**6.9**	**11.0**	**decorin**
Ecm1	NM_007899	1.0	1.7	2.9	3.6	extracellular matrix protein 1
F3	BC024886	1.0	0.2	0.2	0.4	coagulation factor III
Grem1	BC015293	1.0	3.8	2.5	3.9	cysteine knot superfamily 1, BMP antagonist 1
Hgf	**AF042856**	**1.0**	**1.2**	**4.4**	**5.0**	**hepatocyte growth factor**
Igfbp4	BC019836	1.0	1.7	3.5	4.3	insulin-like growth factor binding protein 4
Igfbp5	NM_010518	1.0	0.9	3.8	5.2	insulin-like growth factor binding protein 5
Il6	**NM_031168**	**1.0**	**3.1**	**3.2**	**2.7**	**interleukin 6**
Inhba	**NM_008380**	**1.0**	**1.9**	**0.4**	**0.3**	**inhibin beta-A**
Lbp	NM_008489	1.0	0.7	2.3	5.2	lipopolysaccharide binding protein
Lcn2	X14607	1.0	1.3	24.7	97.3	lipocalin 2
Lcn7	BC005738	1.0	0.6	0.3	0.3	lipocalin 7
Lif	**AF065917**	**1.0**	**0.6**	**0.2**	**0.1**	**leukemia inhibitory factor**
Loxl3	NM_013586	1.0	1.2	4.0	4.7	lysyl oxidase-like 3
Lum	AK014312	1.0	1.1	1.8	3.2	lumican
MFAP5 (MAGP-2)	NM_015776	1.0	3.2	1.0	1.2	microfibrillar associated protein 5
Matn2	BC005429	1.0	1.4	6.4	9.9	Matrilin-2 matrix gamma-
Mglap	NM_008597	1.0	1.9	7.4	17.8	carboxyglutamate (gla) protein
Mmp10	**NM_019471**	**1.0**	**5.4**	**11.8**	**12.1**	**matrix metalloproteinase 10**
Mmp11	**NM_008606**	**1.0**	**1.4**	**4.9**	**9.4**	**matrix metalloproteinase 11**
Mmp19	**AF153199**	**1.0**	**1.9**	**5.7**	**9.4**	**matrix metalloproteinase 19**
Mmp3	**NM_010809**	**1.0**	**1.6**	**3.5**	**10.3**	**matrix metalloproteinase 3**
Mmp9	**NM_013599**	**1.0**	**4.4**	**5.7**	**3.6**	**matrix metalloproteinase 9**
Naga	BC021631	1.0	1.6	4.4	8.2	N-acetyl galactosaminidase, alpha
Nbl1	NM_008675	1.0	1.2	2.8	5.8	neuroblastoma, suppression of tumorigenicity 1
Ngfb	NM_013609	1.0	0.3	0.1	0.1	nerve growth factor, beta
Npnt	AA223007	1	0.6	0.2	0.2	Nephronectin
Npr3	NM_008728	1.0	0.6	0.2	0.2	natriuretic peptide receptor 3
Olfm1	D78264	1.0	1.5	3.6	3.2	olfactomedin 1
Plau	**NM_008873**	**1.0**	**0.9**	**0.2**	**0.3**	**plasminogen activator, urokinase**
Ptx3	**NM_008987**	**1.0**	**0.1**	**0.3**	**0.3**	**pentaxin related gene serine (or cysteine)**

TABLE I-continued

Secreted proteins differentially regulated during MB114 tubulogenesis.

Name	GenBank #	1	5	15	25	Description
		Hours of tubulogenesis				
Serpinb2	**NM_011111**	**1.0**	**1.8**	**1.4**	**1.9**	**proteinase inhibitor, clade B, member 2**
Serpine1	**NM_008871**	**1.0**	**0.6**	**0.2**	**0.1**	**serine (or cysteine) proteinase inhibitor, clade E, member 1**
Serpine2	NM_009255	1.0	3.6	16.3	29.5	serine (or cysteine) proteinase inhibitor, clade E, member 2
Sfrp2	NM_009144	1.0	0.8	4.1	5.5	secreted frizzled-related sequence protein 2
Slpi	NM_011414	1.0	1.2	3.7	6.9	secretory leukocyte protease inhibitor
Smoc2	NM_022315	1.0	7.2	10.6	5.5	Secreted modular calcium binding protein-2
Tgfb3	BC014690	1.0	5.4	2.2	2.8	transforming growth factor, beta 3
Thbs1	**AI385532**	**1.0**	**0.2**	**0.4**	**0.5**	**thrombospondin 1**
Thbs2	**NM_011581**	**1.0**	**0.9**	**3.6**	**6.6**	**thrombospondin 2**
Timp3	**BI111620**	**1.0**	**0.6**	**0.2**	**0.1**	**tissue inhibitor of metalloproteinase 3**
U90926	NM_020562	1.0	1.0	0.3	0.3	cDNA sequence U90926 (predicted signal peptide)
Wisp1	**NM_018865**	**1.0**	**0.9**	**0.4**	**0.2**	**WNT1 inducible signaling pathway protein 1**

Shown in Table I are differentially-expressed genes that encode for secretory proteins whose expression was altered at least 3-fold in at least one time point during the angiogenic timecourse. in tubulating ECs. Identified genes encoding known angiogenic regulators are shown in bold type face. Identified genes encoding putative angiogenic regulators are shown in regular text face.

TABLE IV

Non-secretory proteins differentially regulated during MB114 tubulogenesis

Name	GenBank #	1	5	15	25	Description
		Hours of Tubulogenesis				
Abca1	BB144704	1.0	1.6	4.8	5.4	ATP-binding cassette, sub-family A (ABC1), member 1
Abca7	NM_013850	1.0	1.2	3.4	4.1	ATP-binding cassette, sub-family A (ABC1), member 7
Abcb1a	M30697	1.0	3.6	4.1	2.7	ATP-binding cassette, sub-family B (MDR/TAP), member 1A
Abhd4	NM_134076	1.0	1.1	3.4	3.8	abhydrolase domain containing 4
Abtb1	NM_030251	1.0	1.9	5.0	5.4	ankyrin repeat and BTB (POZ) domain containing 1
Acta2	NM_007392	1.0	0.7	0.2	0.2	actin, alpha 2, smooth muscle, aorta
Actg2	NM_009610	1.0	0.7	0.3	0.3	actin, gamma 2, smooth muscle, enteric
Ahi1	BQ175532	1.0	3.2	3.4	2.5	Abelson helper integration site
Akr1c18	NM_134066	1.0	1.9	6.1	9.1	aldo-keto reductase family 1, member C18
Ampd3	D85596	1.0	1.0	3.7	3.7	AMP deaminase 3
Ankrd1	AK009959	1.0	0.3	0.3	0.2	ankyrin repeat domain 1 (cardiac muscle)
Aox1	NM_009676	1.0	1.0	6.7	11.8	aldehyde oxidase 1
Apbb3	BC024809	1.0	2.0	4.2	6.1	amyloid beta (A4) precursor protein-binding, family B, member 3
Aps	NM_018825	1.0	2.5	4.1	3.5	adaptor protein with pleckstrin homology and src
Arc	NM_018790	1.0	0.3	0.2	0.1	activity regulated cytoskeletal-associated protein
Arg2	NM_009705	1.0	1.4	4.1	5.2	arginase type II
Ass1	NM_007494	1.0	1.7	3.0	3.7	argininosuccinate synthetase 1
Bckdha	NM_007533	1.0	1.6	3.3	3.3	branched chain ketoacid dehydrogenase E1, alpha polypeptide
Atoh8	AK016909	1.0	8.5	9.3	6.8	atonal homolog 8 (*Drosophila*)
Bbs2	AF342737	1.0	1.8	3.6	4.2	Bardet-Biedl syndrome 2 homolog (human)
Bhlhb2	NM_011498	1.0	0.3	0.2	0.3	basic helix-loop-helix domain containing, class B2
Bst1	AI647987	1.0	1.4	3.9	5.9	bone marrow stromal cell antigen 1
Cbfa2t1h	X79989	1.0	0.4	4.7	8.4	CBFA2T1 identified gene homolog (human)
Cbr2	BC010758	1.0	1.1	5.3	18.0	carbonyl reductase 2
Ccnb1	AU015121	1.0	0.9	0.3	0.2	cyclin B1
Ccng2	U95826	1.0	1.7	3.4	3.1	cyclin G2
Cdc6	NM_011799	1.0	0.7	0.2	0.1	cell division cycle 6 homolog (*S. cerevisiae*)
Cdk5r	BB177836	1.0	0.5	0.2	0.2	cyclin-dependent kinase 5, regulatory subunit (p35)
Cdkn1a	AK007630	1.0	1.9	0.2	0.1	cyclin-dependent kinase inhibitor 1A (P21)
Cebpd	BB831146	1.0	3.6	6.5	8.8	CCAAT/enhancer binding protein (C/EBP), delta
Chc1	NM_133878	1.0	1.0	0.3	0.2	chromosome condensation 1

TABLE IV-continued

Non-secretory proteins differentially regulated during MB114 tubulogenesis						
Cit	AF086823	1.0	4.0	3.5	0.5	citron
Cte1	NM_012006	1.0	1.0	5.0	7.1	mitochondrial acyl-CoA thioesterase 1
Cyp51	NM_020010	1.0	0.5	0.2	0.3	cytochrome P450, 51
Cyp7b1	NM_007825	1.0	3.5	3.9	6.6	cytochrome P450, family 7, subfamily b, polypeptide 1
Dbp	BB550183	1.0	0.6	5.1	7.7	D site albumin promoter binding protein
Dck	BB030204	1.0	1.0	0.3	0.1	deoxycytidine kinase
Dcxr	BC012247	1.0	2.3	8.4	20.7	dicarbonyl L-xylulose reductase
Dhrs7	AK009385	1.0	1.8	3.5	5.6	dehydrogenase/reductase (SDR family) member 7
Dhrs8	NM_053262	1.0	0.9	4.8	5.4	dehydrogenase/reductase (SDR family) member 8
Diap3	NM_019670	1.0	0.5	0.2	0.1	diaphanous homolog 3 (*Drosophila*)
Dio2	AF177196	1.0	0.5	5.5	25.1	deiodinase, iodothyronine, type II
Dscr1	AF282255	1.0	0.5	0.2	0.2	Down syndrome critical region homolog 1 (human)
Dusp2	L11330	1.0	0.3	0.2	0.1	dual specificity phosphatase 2
Dusp9	AV295798	1.0	1.0	0.2	0.1	dual specificity phosphatase 9
Ech1	NM_016772	1.0	1.5	3.1	4.9	enoyl coenzyme A hydratase 1, peroxisomal
Egr1	NM_007913	1.0	0.2	0.3	0.3	early growth response 1
Egr2	X06746	1.0	0.2	0.2	0.2	early growth response 2
Erdr1	AJ007909	1.0	0.6	0.3	0.3	DNA segment, Chr 14, Wayne State University 89, expressed
Fabp5	BC002008	1.0	1.0	0.3	0.2	fatty acid binding protein 5, epidermal
Fbxo32	AF441120	1.0	1.4	9.3	16.4	F-box only protein 32
Fos	AV026617	1.0	0.2	0.2	0.3	FBJ osteosarcoma oncogene
Fosl1	U34245	1.0	0.8	0.2	0.2	fos-like antigen 1
Foxm1	NM_008021	1.0	0.6	0.3	0.0	forkhead box M1
Gabpb1	NM_010249	1.0	0.9	0.2	0.2	GA repeat binding protein, beta 1
Ggtl3	BC005772	1.0	2.4	3.3	4.1	gamma-glutamyltransferase-like 3
Gjb3	NM_008126	1.0	0.9	0.2	0.2	gap junction membrane channel protein beta 3
Gstt3	BC003903	1.0	1.3	3.7	3.6	glutathione S-transferase, theta 3
Hbp1	BC026853	1.0	1.1	3.0	3.5	high mobility group box transcription factor 1
Hdac11	BC016208	1.0	0.7	4.2	5.9	histone deacetylase 11
Hmgcr	BB123978	1.0	0.5	0.3	0.3	3-hydroxy-3-methylglutaryl-Coenzyme A reductase
Hmgcs1	BB705380	1.0	0.3	0.3	0.4	3-hydroxy-3-methylglutaryl-Coenzyme A synthase 1
Hnrpab	NM_010448	1.0	0.8	0.3	0.3	heterogeneous nuclear ribonucleoprotein A/B
Hs6st2	AW536432	1.0	0.5	0.3	0.3	heparan sulfate 6-O-sulfotransferase 2
Hsd17b7	NM_010476	1.0	0.4	0.2	0.3	hydroxysteroid (17-beta) dehydrogenase 7
Idi1	BC004801	1.0	0.5	0.2	0.3	isopentenyl-diphosphate delta isomerase
Ier2	NM_010499	1.0	0.5	0.3	0.3	immediate early response 2
Ier5	BF147705	1.0	0.5	0.3	0.3	immediate early response 5
Ifi203	M74124	1.0	8.5	8.4	7.2	interferon activated gene 205
Ifrd1	NM_013562	1.0	0.4	0.2	0.2	interferon-related developmental regulator 1
Junb	NM_008416	1.0	0.4	0.3	0.3	Jun-B oncogene
Kcnip1	NM_027398	1.0	0.8	0.2	0.1	Kv channel-interacting protein 1
Klf4	BG069413	1.0	0.5	0.2	0.2	Kruppel-like factor 4 (gut)
Kpnb1	NM_008379	1.0	0.6	0.3	0.3	karyopherin (importin) beta 1
Lhx1	AV335209	1.0	0.4	0.2	0.2	LIM homeobox protein 1
Lyar	NM_025281	1.0	1.0	0.3	0.2	Ly1 antibody reactive clone
Mafk	NM_010757	1.0	0.3	0.3	0.3	v-maf musculoaponeurotic fibrosarcoma oncogene family, protein K (avian)
Map3k5	NM_008580	1.0	3.4	4.2	4.2	mitogen activated protein kinase kinase kinase 5
Mark1	BM213279	1.0	1.7	8.6	18.7	MAP/microtubule affinity-regulating kinase 1
Mcm3	B1658327	1.0	0.8	0.3	0.1	minichromosome maintenance deficient 3 (*S. cerevisiae*)
Mgst2	AV066880	1.0	2.3	11.2	17.9	microsomal glutathione S-transferase 2
Mthfd2	BG076333	1.0	1.4	0.2	0.2	methylenetetrahydrofolate dehydrogenase (NAD+ dependent), methenyltetrahydrofolate cyclohydrolase
Mybl2	NM_008652	1.0	0.9	0.3	0.2	myeloblastosis oncogene-like 2
Myd116	NM_008654	1.0	0.4	0.3	0.3	myeloid differentiation primary response gene 116
Myl9	AK007972	1.0	0.6	0.1	0.3	myosin, light polypeptide 9, regulatory
Narg2	BE952805	1.0	4.1	3.7	2.8	NMDA receptor-regulated gene 2
Ndrg2	NM_013864	1.0	1.5	5.0	5.1	N-myc downstream regulated 2
Ndrg4	AV006122	1.0	1.5	3.8	3.4	N-myc downstream regulated 4
Nfatc4	BF227641	1.0	0.9	4.4	5.1	nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 4
Nfkbia	NM_010907	1.0	0.5	0.3	0.3	nuclear factor of kappa light chain gene enhancer in B-cells inhibitor, alpha
Nolc1	BM213850	1.0	0.8	0.3	0.2	nucleolar and coiled-body phosphoprotein 1
Nr4a2	NM_013613	1.0	1.7	4.3	4.1	nuclear receptor subfamily 4, group A, member 2
Nudt7	AK011172	1.0	2.2	3.1	4.1	nudix (nucleoside diphosphate linked moiety X)-type motif 7
Pa2g4	AA672939	1.0	0.8	0.3	0.2	proliferation-associated 2G4
Parc	BC026469	1.0	1.4	3.4	3.6	p53-associated parkin-like cytoplasmic protein
Paxip1	AW742928	1.0	0.8	0.3	0.3	PAX interacting (with transcription-activation domain) protein 1
Pdk2	NM_133667	1.0	0.9	3.7	4.6	pyruvate dehydrogenase kinase, isoenzyme 2
Pdzrn3	NM_018884	1.0	0.7	3.1	5.1	semaF cytoplasmic domain associated protein 3
Phyh	NM_010726	1.0	1.3	3.5	5.6	phytanoyl-CoA hydroxylase
Plk4	AI385771	1.0	0.7	0.3	0.1	polo-like kinase 4 (*Drosophila*)
Pprc1	BM199989	1.0	0.6	0.3	0.2	cDNA sequence BC013720
Ptp4a1	BC003761	1.0	0.4	0.3	0.3	protein tyrosine phosphatase 4a1

TABLE IV-continued

Non-secretory proteins differentially regulated during MB114 tubulogenesis						
Ptpre	U35368	1.0	1.0	0.3	0.3	protein tyrosine phosphatase, receptor type, E
Ran	AV090150	1.0	0.9	0.3	0.2	RAN, member RAS oncogene family
Rgs16	U94828	1.0	1.3	0.2	0.2	regulator of G-protein signaling 16
Rgs2	AF215668	1.0	2.4	7.9	12.4	regulator of G-protein signaling 2
Rgs5	NM_133736	1.0	2.0	4.8	6.5	regulator of G-protein signaling 5
Rin2	AK014548	1.0	2.1	3.4	4.5	Ras and Rab interactor 2
Rnase4	BC005569	1.0	1.0	5.0	9.2	RIKEN cDNA C730049F20 gene
Rps10	AV283093	1.0	0.7	0.3	0.3	RIKEN cDNA 2210402A09 gene
Sc4mol	AK005441	1.0	0.6	0.2	0.2	sterol-C4-methyl oxidase-like
Sdpr	BE197945	1.0	0.2	0.2	0.2	serum deprivation response
Sesn1	AV016566	1.0	1.2	3.3	3.4	sestrin 1
Shmt1	AF237702	1.0	1.0	0.3	0.1	serine hydroxymethyl transferase 1 (soluble)
Sil	BC004585	1.0	0.7	0.3	0.2	Tal1 interrupting locus
Snrpa1	BC013777	1.0	0.9	0.3	0.2	small nuclear ribonucleoprotein polypeptide A'
Socs3	BB241535	1.0	2.1	4.3	6.3	suppressor of cytokine signaling 3
Sox9	BC024958	1.0	0.4	0.3	0.3	SRY-box containing gene 9
Srm	NM_009272	1.0	0.9	0.3	0.3	spermidine synthase
T2bp	BB277065	1.0	1.2	4.9	7.1	Traf2 binding protein
Tagln	BB114067	1.0	0.9	0.2	0.1	transgelin
Tcofl	AW209012	1.0	0.8	0.3	0.2	Treacher Collins Franceschetti syndrome 1, homolog
Timm8a	W82151	1.0	1.1	0.2	0.2	translocase of inner mitochondrial membrane 8 homolog a (yeast)
Tiparp	BB707122	1.0	0.3	0.2	0.2	TCDD-inducible poly(ADP-ribose)polymerase
Tle2	AU067681	1.0	0.9	4.2	8.0	transducin-like enhancer of split 2, homolog of *Drosophila* E(spl)
Tle6	NM_053254	1.0	1.1	3.2	3.5	transducin-like enhancer of split 6, homolog of *Drosophila* E(spl)
Tnfaip3	NM_009397	1.0	0.4	0.1	0.1	tumor necrosis factor, alpha-induced protein 3
Tnnt2	NM_011619	1.0	10.6	9.1	1.4	troponin T2, cardiac
Tprt	AK011869	1.0	0.8	0.3	0.2	trans-prenyltransferase
Trib1	AV237242	1.0	0.5	0.2	0.3	tribbles homolog 1 (*Drosophila*)
Trip13	AK010336	1.0	1.0	0.3	0.1	thyroid hormone receptor interactor 13
Txnip	AF173681	1.0	2.8	4.3	4.9	thioredoxin interacting protein
Ugt1a2	BC019434	1.0	2.4	4.2	6.5	UDP glycosyltransferase 1 family, polypeptide A6
Uhrfl	BB702754	1.0	0.7	0.3	0.1	ubiquitin-like, containing PHD and RING finger domains, 1
Ung	BC004037	1.0	0.5	0.2	0.2	uracil-DNA glycosylase
Xdh	AV286265	1.0	1.1	9.2	27.5	xanthine dehydrogenase
Zfp36	X14678	1.0	0.3	0.3	0.3	TIS11 (AA 1-183); Mouse TPA-induced TIS11 mRNA.
Zfp36l2	BG094962	1.0	0.3	0.4	0.3	zinc finger protein 36, C3H type-like 2
Zfp60	NM_009560	1.0	4.5	6.2	4.2	zinc finger protein 60

ESTs

		Hours of Tubulogenesis			
Name	GenBank #	1	5	15	25
	AA223007	1.0	0.6	0.2	0.2
	AA414485	1.0	0.7	0.3	0.3
	AA672926	1.0	0.5	0.3	0.2
	AI324124	1.0	0.3	0.2	0.2
	AK009010	1.0	0.6	0.2	0.2
	AK011311	1.0	1.2	0.3	0.2
	AK012043	1.0	0.6	0.3	0.3
	AK014587	1.0	0.4	0.3	0.2
	AK015966	1.0	0.7	0.3	0.3
	AK017688	1.0	2.5	5.9	3.8
	AK018202	1.0	1.7	3.4	3.6
	AU017197	1.0	0.7	0.3	0.1
	AU018569	1.0	1.0	0.3	0.2
	AV167760	1.0	0.5	0.3	0.3
	AV171622	1.0	1.6	3.5	5.3
	AV171622	1.0	1.6	4.6	6.1
	AV171622	1.0	1.5	4.6	7.7
	AV209892	1.0	1.9	3.6	4.3
	AV221013	1.0	0.7	0.3	0.3
	AV232798	1.0	0.5	0.2	0.3
	AV371987	1.0	1.9	3.8	6.3
	AV374246	1.0	0.5	0.3	0.3
	AW488471	1.0	0.8	0.2	0.2
	AW554921	1.0	1.1	0.2	0.0
	AW744519	1.0	5.6	14.8	18.5
	AW744519	1.0	2.1	5.5	6.0
	AY029778	1.0	1.1	16.1	24.5
	BB010153	1.0	1.9	3.1	4.2
	BB042892	1.0	0.3	0.3	0.1
	BB230053	1.0	1.0	0.2	0.2
	BB332449	1.0	1.1	5.8	9.7

TABLE IV-continued

Non-secretory proteins differentially regulated during MB114 tubulogenesis				
BB371300	1.0	3.9	4.5	5.1
BB377340	1.0	1.2	3.3	4.8
BB407228	1.0	0.7	0.3	0.3
BB530223	1.0	1.3	5.0	4.7
BB550907	1.0	0.5	9.1	32.0
BB628049	1.0	1.3	3.2	3.5
BC006604	1.0	0.3	0.3	0.6
BC006717	1.0	1.8	4.8	5.6
BC011479	1.0	1.3	3.9	3.8
BC021353	1.0	0.2	0.2	0.2
BC021353	1.0	0.3	0.2	0.2
BC021353	1.0	0.3	0.3	0.3
BC021407	1.0	1.2	4.4	3.7
BC021429	1.0	0.9	0.3	0.3
BC021522	1.0	2.3	4.0	4.1
BC021842	1.0	1.8	4.5	6.6
BC022135	1.0	0.6	0.3	0.3
BC025169	1.0	0.7	0.2	0.1
BC026867	1.0	0.8	0.3	0.2
BF118393	1.0	0.7	0.3	0.2
BF578669	1.0	0.5	0.3	0.2
BG064632	1.0	10.2	14.7	16.6
BG066982	1.0	0.8	0.3	0.2
BG075321	1.0	0.7	3.7	5.0
BG080055	1.0	0.7	0.3	0.2
BG143461	1.0	0.5	0.3	0.2
BG868949	1.0	1.3	3.6	3.5
BG868949	1.0	1.3	4.4	4.3
BI251603	1.0	1.9	4.0	3.8
BI454991	1.0	2.0	3.7	4.2
BI466783	1.0	0.5	0.2	0.2
BI558298	1.0	1.1	0.3	0.2
BI660196	1.0	1.2	3.6	4.4
BM117243	1.0	1.4	3.3	4.1
BM117243	1.0	1.6	3.6	3.9
BM200151	1.0	1.0	0.3	0.3
BM213835	1.0	0.8	0.3	0.2
BM247465	1.0	0.5	0.2	0.1
C78203	1.0	2.5	3.7	3.4
NM_020562	1.0	1.0	0.3	0.3
NM_026235	1.0	1.3	3.1	7.2
NM_026839	1.0	0.7	0.3	0.2
NM_030697	1.0	0.5	3.4	5.0
NM_054098	1.0	2.1	15.0	24.3
NM_133706	1.0	1.0	0.3	0.2
NM_133775	1.0	1.8	3.2	4.3

Genes encoding non-secretory proteins that demonstrated at least 3-fold differential expression in at least one time-point over a 25 h angiogenesis timecourse.

TABLE V

Transmembrane proteins differentially regulated during MB114 tubulogenesis						
		Hours of tubulogenesis				
Name	GenBank	1	5	15	25	Description
0610007C21Rik	AK002276	1.0	1.5	2.1	3.3	Clone IMAGE: 1513950, mRNA (predicted transmembrane)
1810014L12Rik	NM_133706	1.0	1.0	0.3	0.2	RIKEN cDNA 1810014L12 gene (predicted transmembrane)
Alcam	U95030	1	3.4	4.2	2.6	activated leukocyte cell adhesion molecule
Anpep	NM_008486	1	3.5	7.0	9.3	alanyl (membrane) aminopeptidase
Areg	NM_009704	1	0.7	0.2	0.1	amphiregulin calcium channel, voltage-
Cacna2d1	NM_009784	1.0	2.3	3.9	4.3	dependent, alpha2/delta subunit 1
Cd14	NM_009841	1.0	2.0	4.0	6.4	CD14 antigen
Cd38	BB256012	1.0	4.5	4.8	5.1	CD38 antigen
Cd44	**X66083**	**1.0**	**1.2**	**0.3**	**0.2**	**CD44 antigen**
Cd53	NM_007651	1.0	2.0	9.6	10.4	CD53 antigen
Dtr	L07264	1.0	0.4	0.1	0.1	diphtheria toxin receptor
Emp2	AF083876	1	2.6	3.1	3.2	epithelial membrane protein 2

TABLE V-continued

Transmembrane proteins differentially regulated during MB114 tubulogenesis

Name	GenBank	Hours of tubulogenesis 1	5	15	25	Description
Epha2	**NM_010139**	**1.0**	**0.4**	**0.2**	**0.2**	**Eph receptor A2**
Fcgrt	NM_010189	1.0	1.1	2.5	6.1	Fc receptor, IgG, alpha chain transporter
Islr	NM_012043	1.0	1.2	2.4	4.2	immunoglobulin superfamily containing leucine-rich repeat
Itga3	NM_013565	1.0	0.9	0.3	0.2	integrin alpha 3
Itga6	BM935811	1.0	1.3	0.1	0.1	integrin alpha 6
Ldlr	AF425607	1.0	0.2	0.2	0.2	low density lipoprotein receptor
Lrp1	NM_008512	1.0	1.3	3.2	5.5	low density lipoprotein receptor-related protein 1
Lrp2	C80829	1.0	0.5	0.3	0.2	low density lipoprotein receptor-related protein 2
Ly6a	BC002070	1.0	0.7	2.3	4.8	lymphocyte antigen 6 complex, locus A
Npr3	NM_008728	1	0.5	0.2	0.2	natriuretic peptide receptor 3
P2rx4	AJ251462	1	1.1	3.2	5.2	purinergic receptor P2X, ligand-gated ion channel 4
Pcdh18	AK014140	1.0	0.2	0.3	0.3	protocadherin 18
Pcdhb9	NM_053134	1.0	1.1	3.2	4.7	protocadherin beta 9
Ptpre	U35368	1.0	1.0	0.3	0.3	protein tyrosine phosphatase, receptor type, E
Ramp1	NM_016894	1.0	1.3	4.0	5.9	receptor (calcitonin) activity modifying protein 1
Sele	**NM_011345**	**1.0**	**1.3**	**0.3**	**0.3**	**selectin, endothelial cell**
Slc4a3	NM_009208	1	1.7	3.1	4.5	solute carrier family 4 (anion exchanger), member 3
Slc7a5	BC026131	1	1.4	0.3	0.1	solute carrier family 7 (cationic amino acid transporter, y+ system), member 5
Tfrc	AK011596	1.0	1.1	0.3	0.3	transferrin receptor
Tm4sf12	BB072896	1.0	2.3	3.3	3.5	transmembrane 4 superfamily member 12
Tmc6	BC004840	1.0	2.1	3.4	3.3	transmembrane channel-like gene family 6

Genes encoding transmembrane or membrane-associated proteins that demonstrated at least 3-fold differential expression in at least one time-point over the 25 h angiogenesis timecourse. Identified genes encoding known angiogenic regulators are shown in bold type face. Identified genes encoding putative angiogenic regulators are shown in regular text face.

TABLE VI

Real-Time PCR analysis of select proteins

Name	Hrs. of Tubulogenesis 1	5	15	25
ADAMts1	1.0	0.4	1.6	2.4
ADAMts7	1.0	2.0	4.9	5.1
CRELD-2	1.0	11.4	5.8	10.0
CTGF	1.0	0.3	0.4	0.3
Decorin	1.0	3.6	8.4	16.6
ECM1	1.0	4.3	6.3	9.0
Inhibin β-a (Inhβ-a)	1.0	4.9	1.4	1.1
Inhibin β-b (Inhβ-b)	1.0	0.1	0.5	0.7
Integrin α-3	1.0	1.4	0.8	0.3
Integrin α-6	1.0	1.2	0.6	0.4
Lipocalin-7	1.0	0.9	0.6	0.6
Loxl-3	1.0	2.8	18.0	17.9
Lumican	1.0	0.4	0.9	1.7
MAGP-2	1.0	8.4	2.3	4.2
Matrilin-2	1.0	1.6	6.7	8.0
Nephronectin	1.0	0.9	0.5	0.5
SerpinE2	1.0	0.8	5.1	10.1
SMOC-2	1.0	21.5	58.3	13.1
TIMP-3	1.0	2.5	0.5	0.5

Real-time PCR analysis was conducted to confirm differential expression of selected genes from microarray analysis.

Example 2

The following example describes the effects of putative angiogenic gene expression on EC activities-coupled to angiogenesis.

The microarray analyses described in Example 1 identified numerous genes whose expression is regulated by angiogenesis, indicating that the expression of these genes is required during vessel formation. To test this hypothesis and to identify novel regulators of EC activities-coupled to angiogenesis, a series of in vitro assays was performed that modeled angiogenesis activation in ECs (Albig et al, 2006; Albig and Schiemann, 2004; Albig and Schiemann, 2005). In doing so, bicistronic retroviral transduction of MB114 cells was used to stably express six identified secretory proteins, namely matrilin-2, CRELD-2 (cysteine-rich with EGF-Like domains-2), MAGP-2, lumican, SMOC-2 (secreted modular calcium-binding protein-2), and ECM-1, (extracellular protein-1), and one putative transmembrane protein, AK002276. Immunoblotting and semi-quantitative real-time PCR analyses both showed that the expression of all individual transgenes were readily detected in MB114 cells (FIGS. **7**A and **7**B). In these experiments, MB114 cells were infected with retrovirus encoding either GFP (i.e., control) or various potential angiogenic agents as indicated. Afterward, infected cells were FACS-sorted by GFP expression (highest 10%) to establish stable polyclonal populations of transgenic MB114 cells.

Transgene expression was detected by immunoblotting nickel-captured secretory proteins with anti-Myc antibodies, except AK002276 which was captured from detergent-solubilized cell extracts (FIG. 7A) and by performing semi-quantitative real-time PCR (FIG. 7B).

FIG. 1A show results from an experiment in which serum-starved MB114 cells, stably expressing either GFP or various putative angiogenic agents, were stimulated in the absence or presence of either bFGF (50 ng/ml) or EGF (10 ng/ml) for 24 h at 37° C. Differences in MB114 cell DNA synthesis was determined by measuring [^{3}H]thymidine incorporation into cellular DNA. Functionally, MAGP-2 and SMOC-2 expression significantly enhanced the proliferative response of MB114 cells to bFGF, while MAGP-2 and AK002276 expression significantly enhanced that to EGF (FIG. 1A). In contrast, expression of all other transgenes failed to effect the proliferative response of MB114 cells to either bFGF or EGF (data not shown). FIG. 1B shows that SMOC-2, MAGP-2, and CRELD-2 expression all significantly induced MB114 cell invasion through synthetic basement membranes, a response that was not mimicked by expression of additional transgenes (data not shown). In this experiment, invasion of MB114 cells expressing either GFP or various putative angiogenic agents through synthetic basement membranes was determined over 48 h using a modified Boyden-chamber assay.

The inventors' previous studies have associated stimulation of p38 MAPK activity with angiogenesis of MB114 cells and, conversely, inhibition of p38 MAPK activity with angiostasis of MB114 cells (Albig et al, 2006; Albig and Schiemann, 2004; Albig and Schiemann, 2005). Serum-starved MB114 cells expressing MAGP-2 (FIG. 1C) or lumican (FIG. 1D) were stimulated with either bFGF (50 ng/ml) or EGF (10 ng/ml) 0-15 min as indicated in the figures. The phosphorylation status of p38 MAPK was determined by immunoblotting whole cell lysates with phospho-specific p38 MAPK antibodies (p38-P). Differences in protein loading were monitored by reprobing stripped membranes with anti-p38 MAPK polyclonal antibodies (p38). FIG. 1C shows that MAGP-2 expression significantly enhanced p38 MAPK phosphorylation in MB114 cells stimulated with either bFGF or EGF stimulation. In contrast, lumican expression significantly inhibited p38 MAPK activation in MB114 cells treated with either growth factor (FIG. 1D).

Finally, it was determined whether expression of these putative angiogenic factors could effect the angiogenic sprouting of quiescent MB114 cells monolayers. MB114 cells expressing either GFP or various putative angiogenic agents were grown to confluency, and subsequently were overlaid with rat tail collagen matrices. Angiogenic sprouting by quiescent EC monolayers was stimulated by inclusion of 10% FBS and allowed to proceed for 5 days. The quantity of invading angiogenic sprouts was determined by manual counting under a light microscope. FIG. 1E shows that expression of CRELD-2, matrillin-2, or AK002276 failed to significantly affect MB114 cell angiogenic sprouting in response to serum. In stark contrast, expression of MAGP-2 or SMOC-2 both significantly increased the sprouting of MB114 cells cell sprouting, while that of lumican and ECM-1 significantly decreased the ability of MB114 cells to form angiogenic sprouts in collagen matrices (FIG. 1E).

Collectively, these findings demonstrate that tubulating ECs upregulate expression of lumican and ECM-1 during the latter stages of angiogenesis, consistent with their involvement in mediating angiogenesis resolution. Accordingly, both proteins antagonized angiogenic sprouting in MB114 cells, and as such, the inventors propose lumican and ECM-1 as novel mediators of angiostasis. Conversely, tubulating ECs were observed to upregulate expression of MAGP-2 and SMOC-2 during the early stages of angiogenesis, implicating their involvement in mediating angiogenesis activation. Indeed, both proteins stimulated various angiogenic activities, including angiogenic sprouting in MB114 cells. Thus, it is proposed herein that MAGP-2 and SMOC-2 are novel mediators of angiogenesis. Because MAGP-2 was the only protein to exhibit angiogenic activity in all measured indices in vitro, the inventors chose to further characterize the molecular mechanisms whereby MAGP-2 induces angiogenesis in quiescent ECs.

Example 3

The following example demonstrates that MAGP-2 promotes angiogenesis in vivo.

The ability of MAGP-2 to stimulate EC activities coupled to angiogenesis in vitro indicated that MAGP-2 may function to induce vessel formation in vivo. The inventors tested this hypothesis by utilizing the Matrigel plug implantation assay, which monitors the ability of various angiogenic agents to alter vessel formation and infiltration into Matrigel plugs implanted subcutaneously into normal mice. In doing so, first, recombinant FLAG-tagged MAGP-2 (rMAGP-2) was expressed and purified from bacterial cells (FIG. 2A). More particularly, recombinant FLAG-tagged MAGP-2 (rMAGP-2) was purified from detergent-solubilized bacterial cell extracts by anti-FLAG chromatography. MAGP-2 purity was monitored by coomassie staining, and by immunoblotting with anti-FLAG M2 monoclonal antibodies (FIG. 2A; right panel). rMAGP-2 (1 μg/ml) stimulated angiogenic sprouting of quiescent MB114 cell monolayers (FIG. 2A; left panel). Similar to its constitutive expression in MB114 cells, purified rMAGP-2 protein (1 μg/ml) also was found to stimulate angiogenic sprouting of quiescent MB114 cells, thereby demonstrating that these rMAGP-2 preparations were biologically active (FIG. 2A). To further demonstrate that MAGP-2 promotes angiogenesis in vivo, C57BL/6 female mice were injected subcutaneously with Matrigel supplemented either with diluent (D), bFGF (50 ng/ml, LD; or 300 ng/ml, HD), or bFGF (50 ng/ml) in combination with MAGP-2 (1 μg/ml). Mice were sacrificed on day 10 and the plugs harvested and photographed (FIG. 2B; left panels). Afterward, the Matrigel plugs were fixed, sectioned, and stained with Masson's trichrome to visualize infiltrating blood vessels (FIG. 2B; right panels; arrows denote blood vessels), which were quantified by manual counting under a light microscope. FIG. 2B shows that bFGF dose-dependently stimulated significant vascularization of implanted Matrigel plugs. Importantly, rMAGP-2 administration (1 μg/ml) significantly increased the development and infiltration of vessels into Matrigel plugs supplemented with bFGF as compared to those solely containing bFGF (FIG. 2B). Collectively, these findings, together with the in vitro analyses, provide strong evidence implicating MAGP-2 as a bona fide promoter of angiogenesis.

Example 4

The following example demonstrates that MAGP-2 inhibits Notch1 signaling.

MAGP-2 can interact physically with Notch1 and its ligand, Jagged-1 (Miyamoto et al, 2006; Nehring et al, 2005), resulting in the ectodomain shedding of both molecules from the cell surface. Notch signaling also plays an essential role in regulating normal vessel development and angiogenesis in

mammals (Leong and Karsan, 2005; Shawber and Kitajewski, 2004). Given these two facts, the inventors hypothesized that MAGP-2 promotes angiogenesis by modulating Notch1 signaling. To test this hypothesis, first measured were changes in luciferase expression driven by a Hes1-luciferase reporter gene whose expression is induced by NotchI activation (Iso et al, 2003). MB114 and HUVEC cells were transiently transfected either with pHesI-luciferase, pCMV-β-gal, and MAGP-2 cDNAs, or with pHes1-luciferase and pCMV-β-gal cDNAs and subsequently stimulated with rMAGP-2 (1 or 5 μg/ml). Afterward, luciferase and β-gal activities contained in detergent-solubilized cell extracts were measured. In addition, GFP- and MAGP-2-expressing MB114 cells were transiently transfected with pHes1-luciferase and pCMV-β-gal cDNAs, together with or without Jagged-1 cDNA as indicated. Afterward, luciferase and β-gal activities were measured as above. FIG. 3A shows that MAGP-2 expression in or rMAGP-2 treatment of either MB114 or HUVEC cells repressed Hes1-driven luciferase activity. More importantly, MAGP-2 expression abrogated the ability of Jagged-1 to induce Hes1-luciferase activity in MB114 cells (FIG. 3B), suggesting that MAGP-2 functions to antagonize Jagged-1 and, consequently, Notch1 signaling in ECs.

Activation of Notch1 signaling involves three proteolytic processing events, termed S1, S2, and S3, that produce three distinct Notch1 fragments, termed TMIC, NEXT, and NICD, respectively (Mumm et al, 2000). NICD production is mediated by a gamma-secretase cleavage reaction that cuts Notch1 at a membrane proximal cytoplasmic site (Mumm et al, 2000), resulting in the release and subsequent translocation of NICD to the nucleus where it regulates the expression of Notch1-responsive genes, including Hes1 (Iso et al, 2003). The findings described above indicate that MAGP-2 antagonizes Notch1 signaling, and as such, indicate that MAGP-2 may do so by inhibiting Notch1 proteolytic processing. The inventors tested this possibility by transiently transfecting human 293T cells with cDNAs encoding Myc-tagged versions of Notch1, Jagged-1, and MAGP-2 in all combinations, and subsequently monitored changes in NICD production and accumulation by immunoblot analyses using anti-Myc monoclonal antibodies. As expected, Jagged-1 expression significantly enhanced Notch1 processing and the production of NICD as compared to cells solely expressing Notch1 (FIG. 4A). Importantly, the ability of Jagged-1 to induce Notch1 cleavage and NICD production in 293T cells was reduced significantly by co-expression of MAGP-2 (FIG. 4A). Thus, these findings indicate that MAGP-2 inhibits Notch1 signaling and Hes1 expression in part by preventing Notch1 processing and NICD production.

To further investigate the impact of MAGP-2 on Notch1 processing and NICD accumulation, the inventors took advantage of recent findings showing that the ability of TGF-β to induce Hes1 promoter activity requires Smad3 to interact physically with NICD (Blokzijl et al, 2003), a reaction that is dispensable for canonical Smad3-mediated signaling stimulated by TGF-β (Blokzijl et al, 2003). It was therefore reasoned that the ability of MAGP-2 to inhibit NICD production in ECs would reduce the capacity of TGF-β to induce luciferase expression driven by the Hes1 promoter, but not that driven by the synthetic Smad2/3-binding element (SBE). GFP- and MAGP-2-expressing MB114 cells were transiently transfected with either pHesI- or pSBE-luciferase, both together with pCMV-β-gal as indicated in FIG. 4B. Afterward, the resulting transfectants were stimulated overnight with increasing concentrations of TGF-β1 (0-5 ng/ml). MAGP-2 expression in MB114 cells significantly decreased the ability of TGF-β to stimulate Hes1-luciferase activity, but had no effect on its stimulation of SBE-luciferase activity (FIG. 4B). Similar effects of MAGP-2 on TGF-β-stimulated Hes1- and SBE-luciferase activities also were observed in HUVEC cells, indicating that MAGP-2-mediated inhibition of Notch1 processing and NICD production was not restricted solely to MB114 cells (data not shown). Collectively, these findings demonstrate that MAGP-2 antagonizes Notch1 signaling by preventing its cleavage and ultimate release of the Notch1 signaling fragment, NICD.

Example 5

The following examples shows that MAGP-2 promotes angiogenesis by antagonizing Notch signaling.

Based on the findings described in the Examples above, the inventors hypothesized that MAGP-2 promotes angiogenesis by antagonizing Notch1 signaling. To test this hypothesis, it was first determined whether inhibiting Notch signaling in MB114 cells would enhance their angiogenic sprouting. In doing so, MB114 cells were transiently transfected with the Hes1-luciferase reporter gene (and pCMV-β-gal cDNA as control), and subsequently were treated overnight with or without the highly specific gamma-secretase inhibitor, DAPT (Sastre et al, 2001), which inhibits S3-mediated cleavage of Notch1 and, consequently, NICD-mediated induction of Hes1 expression. Afterward, luciferase and β-gal activities were determined. As expected, DAPT administration (10 μM) significantly inhibited Hes1 promoter activity in MB114 cells (FIG. 5A). More importantly, MB114 cells treated with DAPT formed significantly more angiogenic sprouts than did their untreated counterparts (FIG. 5B). In this experiment, quiescent MB114 cell monolayers were overlaid with rat tail collagen matrices, and were induced to form angiogenic sprouts by addition of 10% FBS supplemented with or without DAPT (10 μM). Five days later the number of invading angiogenic spouts were quantified by manual counting on a light microscope. Based on these findings, the inventors conclude that Notch activation functions in mediating angiostasis in MB114 cells. This conclusion is bolstered further by the inventors' observation that the Notch ligands Jagged-1 and Delta-like-4, and the Hes1 transcription factor were all strongly downregulated in tubulating MB114 cells (Table VII). Collectively, these findings indicate that Notch1 signaling antagonizes angiogenic sprouting in MB114 cells, and that downregulation of Notch1 signaling components is necessary for angiogenesis activation in MB114 cells.

TABLE VII

Expression of Notch signaling components During Tubulogenesis

Name	Genbank	Hours of Tubulogenesis 1	5	15	25
DII1	NM_007865	1.0	0.9	1.3	1.1
DII3	AB013440	1.0	0.8	0.6	0.9
DII4	AK004739	1.0	1.2	0.3	0.4
Jag1	AA880220	1.0	0.7	0.2	0.2
Jag2	AV264681	1.0	0.4	0.7	1.3
Notch1	NM_008714	1.0	1.4	0.6	0.7
Notch2	D32210	1.0	1.1	1.1	1.2
Notch3	NM_008716	1.0	0.9	1.3	1.5
Notch4	NM_010929	1.0	1.1	1.1	1.1
Hes1	BC018375	1.0	0.5	0.2	0.1

Expression of various components of the Notch signaling pathway during MB114 cell tubulogenesis on Matrigel matrices.

Having shown that Notch1 signaling mediates angiostasis in MB114 cells, the inventors next asked whether MAGP-2 promotes angiogenesis in MB114 cells via its ability to antagonize Notch signaling. To do so, MAGP-2-expressing MB114 cells were engineered to constitutively express active Notch1 NICD fragment in an attempt to overcome the block of Notch processing mediated by MAGP-2. More particularly, GFP-, MAGP-2-, and MAGP-2/N1ICD-expressing MB114 cells were transiently transfected with pHes1-luciferase and pCMV-β-gal cDNAs. Luciferase and P-gal activities were determined 48 h post-transfection. As the inventors observed previously, MAGP-2 expression reduced Hes1-luciferase activity in MB114 cells (FIG. **5**C), a reaction that was bypassed by co-expression of NICD in these cells (FIG. **5**C). More importantly, the ability of MAGP-2 to promote angiogenic sprouting was prevented completely by constitutive N1ICD expression in MB114 cells (FIG. **5**D). In this experiment, quiescent monolayers of GFP-, MAGP-2-, and MAGP-2/N1ICD-expressing MB114 cells were overlaid with rat tail collagen matrices and incubated in the absence or presence of 10% FBS for 5 days. Afterward, the number of invading angiogenic sprouts were determined by manual counting under a light microscope. Taken together, these results demonstrate that Notch1 activation antagonizes angiogenesis in MB114 cells, and most notably, that MAGP-2 promotes angiogenesis in part via its ability to antagonize Notch1 processing and signaling in ECs.

Example 6

The following example shows that MAGP-2 is expressed aberrantly in the majority of human uterine tumors.

Radiolabeled cDNA probes corresponding to either murine MAGP-2 (FIG. **8**A; upper panel) or human ubiquitin (FIG. **8**A; lower panel) were hybridized to matched human normal:tumor cDNA array. The resulting phosphor-images depict MAGP-2 and ubiquitin expression in paired normal (upper spot) and malignant (bottom spot) uterine tissue. MAGP-2 expression was normalized to that of ubiquitin, followed by a determination of tumor:normal tissue MAGP-2 expression ratios. Ratios $\geqq 2$ or $\leqq 0.5$ were considered significant. The results showed that MAGP-2 is expressed aberrantly in the majority of human uterine tumors tested.

Each publication or other reference disclosed below and elsewhere herein is incorporated herein by reference in its entirety.

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U.S. Provisional Application No. 60/722,694
U.S. Provisional Application No. 60/816,969

While various embodiments of the present invention have been described in detail, it is apparent that modifications and adaptations of those embodiments will occur to those skilled in the art. It is to be expressly understood, however, that such modifications and adaptations are within the scope of the present invention, as set forth in the following claims.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 124

<210> SEQ ID NO 1
<211> LENGTH: 223
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 1

```
Met Ala Ser Arg Glu Ser Gly Gly Ser Arg Ala Ala Ala Leu Leu Leu
1               5                   10                  15

Val Leu Gly Val Glu Arg Ser Leu Ala Leu Pro Lys Ile Cys Thr Leu
            20                  25                  30

Cys Pro Gly Gly Met His Asn Leu Ser Arg Val Ala Ala Tyr Cys Glu
        35                  40                  45

Asp Thr Ser Lys Leu Met Gln Ala Arg Cys Cys Leu Asn Gln Lys Gly
    50                  55                  60

Pro Ile Leu Gly Leu Asn Leu Gln Asn Cys Ser Leu Lys Asp Pro Gly
65                  70                  75                  80

Pro Asn Phe Leu Gln Ala Tyr Thr Ala Ile Ile Ile Asp Leu Gln Ala
                85                  90                  95

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

Leu Gln Thr Leu Ile Leu Pro Gln Asp Val Pro Cys Pro Gly Gly Ser
        115                 120                 125

Asn Ala Trp Asp Asn Val Thr Ser Phe Lys Asp Lys Gln Ile Cys Gln
    130                 135                 140

Gly Gln Arg Asp Leu Cys Asn Ser Thr Gly Ser Pro Glu Met Cys Pro
145                 150                 155                 160

Glu Asn Gly Ser Cys Ala Ser Asp Gly Pro Gly Leu Leu Gln Cys Val
                165                 170                 175

Cys Ala Asp Gly Phe His Gly Tyr Lys Cys Met Arg Gln Gly Ser Phe
            180                 185                 190

Ser Leu Leu Met Phe Phe Gly Ile Leu Gly Ser Thr Thr Leu Ala Ile
        195                 200                 205

Ser Ile Leu Leu Trp Gly Thr Gln Arg Arg Lys Ala Lys Ala Ser
    210                 215                 220
```

<210> SEQ ID NO 2
<211> LENGTH: 229
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 2

```
Met Ala Pro His Gly Pro Gly Ser Leu Thr Thr Leu Val Pro Trp Ala
1               5                   10                  15

Ala Ala Leu Leu Leu Ala Leu Gly Val Glu Arg Ala Leu Ala Leu Pro
            20                  25                  30

Glu Ile Cys Thr Gln Cys Pro Gly Ser Val Gln Asn Leu Ser Lys Val
        35                  40                  45

Ala Phe Tyr Cys Lys Thr Thr Arg Glu Leu Met Leu His Ala Arg Cys
    50                  55                  60

Cys Leu Asn Gln Lys Gly Thr Ile Leu Gly Leu Asp Leu Gln Asn Cys
65                  70                  75                  80

Ser Leu Glu Asp Pro Gly Pro Asn Phe His Gln Ala His Thr Thr Val
                85                  90                  95
```

```
Ile Ile Asp Leu Gln Ala Asn Pro Leu Lys Gly Asp Leu Ala Asn Thr
            100                 105                 110

Phe Arg Gly Phe Thr Gln Leu Gln Thr Leu Ile Leu Pro Gln His Val
        115                 120                 125

Asn Cys Pro Gly Gly Ile Asn Ala Trp Asn Thr Ile Thr Ser Tyr Ile
    130                 135                 140

Asp Asn Gln Ile Cys Gln Gly Gln Lys Asn Leu Cys Asn Asn Thr Gly
145                 150                 155                 160

Asp Pro Glu Met Cys Pro Glu Asn Gly Ser Cys Val Pro Asp Gly Pro
                165                 170                 175

Gly Leu Leu Gln Cys Val Cys Ala Asp Gly Phe His Gly Tyr Lys Cys
            180                 185                 190

Met Arg Gln Gly Ser Phe Ser Leu Leu Met Phe Phe Gly Ile Leu Gly
        195                 200                 205

Ala Thr Thr Leu Ser Val Ser Ile Leu Leu Trp Ala Thr Gln Arg Arg
    210                 215                 220

Lys Ala Lys Thr Ser
225


<210> SEQ ID NO 3
<211> LENGTH: 176
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 3

Met Gly Ala Leu Ala Ala Arg Arg Cys Val Glu Trp Leu Leu Gly Leu
1               5                   10                  15

Tyr Phe Val Ser His Ile Pro Ile Thr Leu Phe Ile Asp Leu Gln Ala
            20                  25                  30

Val Leu Pro Pro Glu Leu Tyr Pro Gln Glu Phe Ser Asn Leu Leu Arg
        35                  40                  45

Trp Tyr Ser Lys Glu Phe Lys Asp Pro Leu Met Gln Glu Pro Pro Val
    50                  55                  60

Trp Phe Lys Ser Phe Leu Leu Cys Glu Leu Val Phe Gln Leu Pro Phe
65                  70                  75                  80

Phe Pro Ile Ala Ala Tyr Ala Phe Phe Lys Gly Ser Cys Arg Trp Ile
                85                  90                  95

Arg Ile Pro Ala Ile Ile Tyr Ala Ala His Thr Ile Thr Thr Leu Ile
            100                 105                 110

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

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

Gly Val Tyr Ala Pro Tyr Leu Ile Ile Pro Leu Ile Leu Leu Leu Phe
145                 150                 155                 160

Met Leu Arg Asn Pro Tyr Tyr Lys Tyr Glu Glu Lys Arg Lys Lys Lys
                165                 170                 175


<210> SEQ ID NO 4
<211> LENGTH: 176
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 4

Met Gly Ala Pro Ala Thr Arg Arg Cys Val Glu Trp Leu Leu Gly Leu
1               5                   10                  15

Tyr Phe Leu Ser His Ile Pro Ile Thr Leu Phe Met Asp Leu Gln Ala
```

```
            20                  25                  30

Val Leu Pro Arg Glu Leu Tyr Pro Val Glu Phe Arg Asn Leu Leu Lys
        35                  40                  45

Trp Tyr Ala Lys Glu Phe Lys Asp Pro Leu Leu Gln Glu Pro Pro Ala
    50                  55                  60

Trp Phe Lys Ser Phe Leu Phe Cys Glu Leu Val Phe Gln Leu Pro Phe
65                  70                  75                  80

Phe Pro Ile Ala Thr Tyr Ala Phe Leu Lys Gly Ser Cys Lys Trp Ile
                85                  90                  95

Arg Thr Pro Ala Ile Ile Tyr Ser Val His Thr Met Thr Thr Leu Ile
            100                 105                 110

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

Phe Lys Gly Gln Arg Pro Glu Thr Leu His Glu Arg Leu Thr Leu Val
    130                 135                 140

Ser Val Tyr Ala Pro Tyr Leu Leu Ile Pro Phe Ile Leu Leu Ile Phe
145                 150                 155                 160

Met Leu Arg Ser Pro Tyr Tyr Lys Tyr Glu Glu Lys Arg Lys Lys Lys
                165                 170                 175


<210> SEQ ID NO 5
<211> LENGTH: 366
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 5

Met Glu Arg Val Leu Gly Leu Leu Leu Leu Leu Leu Val His Ala Ser
1               5                   10                  15

Pro Ala Pro Pro Glu Pro Cys Glu Leu Asp Glu Glu Ser Cys Ser Cys
            20                  25                  30

Asn Phe Ser Asp Pro Lys Pro Asp Trp Ser Ser Ala Phe Asn Cys Leu
        35                  40                  45

Gly Ala Ala Asp Val Glu Leu Tyr Gly Gly Gly Arg Ser Leu Glu Tyr
    50                  55                  60

Leu Leu Lys Arg Val Asp Thr Glu Ala Asp Leu Gly Gln Phe Thr Asp
65                  70                  75                  80

Ile Ile Lys Ser Leu Ser Leu Lys Arg Leu Thr Val Arg Ala Ala Arg
                85                  90                  95

Ile Pro Ser Arg Ile Leu Phe Gly Ala Leu Arg Val Leu Gly Ile Ser
            100                 105                 110

Gly Leu Gln Glu Leu Thr Leu Glu Asn Leu Glu Val Thr Gly Thr Ala
        115                 120                 125

Pro Pro Pro Leu Leu Glu Ala Thr Gly Pro Asp Leu Asn Ile Leu Asn
    130                 135                 140

Leu Arg Asn Val Ser Trp Ala Thr Arg Asp Ala Trp Leu Ala Glu Leu
145                 150                 155                 160

Gln Gln Trp Leu Lys Pro Gly Leu Lys Val Leu Ser Ile Ala Gln Ala
                165                 170                 175

His Ser Leu Asn Phe Ser Cys Glu Gln Val Arg Val Phe Pro Ala Leu
            180                 185                 190

Ser Thr Leu Asp Leu Ser Asp Asn Pro Glu Leu Gly Glu Arg Gly Leu
        195                 200                 205

Ile Ser Ala Leu Cys Pro Leu Lys Phe Pro Thr Leu Gln Val Leu Ala
    210                 215                 220

Leu Arg Asn Ala Gly Met Glu Thr Pro Ser Gly Val Cys Ser Ala Leu
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225                 230                 235                 240

Ala Ala Ala Arg Val Gln Leu Gln Gly Leu Asp Leu Ser His Asn Ser
                245                 250                 255

Leu Arg Asp Ala Ala Gly Ala Pro Ser Cys Asp Trp Pro Ser Gln Leu
            260                 265                 270

Asn Ser Leu Asn Leu Ser Phe Thr Gly Leu Lys Gln Val Pro Lys Gly
        275                 280                 285

Leu Pro Ala Lys Leu Ser Val Leu Asp Leu Ser Tyr Asn Arg Leu Asp
    290                 295                 300

Arg Asn Pro Ser Pro Asp Glu Leu Pro Gln Val Gly Asn Leu Ser Leu
305                 310                 315                 320

Lys Gly Asn Pro Phe Leu Asp Ser Glu Ser His Ser Glu Lys Phe Asn
                325                 330                 335

Ser Gly Val Val Thr Ala Gly Ala Pro Ser Ser Gln Ala Val Ala Leu
            340                 345                 350

Ser Gly Thr Leu Ala Leu Leu Leu Gly Asp Arg Leu Phe Val
        355                 360                 365


<210> SEQ ID NO 6
<211> LENGTH: 374
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

Met Leu Ser Thr Ser Arg Ser Arg Phe Ile Arg Asn Thr Asn Glu Ser
1               5                   10                  15

Gly Glu Glu Val Thr Thr Phe Phe Asp Tyr Asp Tyr Gly Ala Pro Cys
            20                  25                  30

His Lys Phe Asp Val Lys Gln Ile Gly Ala Gln Leu Leu Pro Pro Leu
        35                  40                  45

Tyr Ser Leu Val Phe Ile Phe Gly Phe Val Gly Asn Met Leu Val Val
    50                  55                  60

Leu Ile Leu Ile Asn Cys Lys Lys Leu Lys Cys Leu Thr Asp Ile Tyr
65                  70                  75                  80

Leu Leu Asn Leu Ala Ile Ser Asp Leu Leu Phe Leu Ile Thr Leu Pro
                85                  90                  95

Leu Trp Ala His Ser Ala Ala Asn Glu Trp Val Phe Gly Asn Ala Met
            100                 105                 110

Cys Lys Leu Phe Thr Gly Leu Tyr His Ile Gly Tyr Phe Gly Gly Ile
        115                 120                 125

Phe Phe Ile Ile Leu Leu Thr Ile Asp Arg Tyr Leu Ala Ile Val His
    130                 135                 140

Ala Val Phe Ala Leu Lys Ala Arg Thr Val Thr Phe Gly Val Val Thr
145                 150                 155                 160

Ser Val Ile Thr Trp Leu Val Ala Val Phe Ala Ser Val Pro Gly Ile
                165                 170                 175

Ile Phe Thr Lys Cys Gln Lys Glu Asp Ser Val Tyr Val Cys Gly Pro
            180                 185                 190

Tyr Phe Pro Arg Gly Trp Asn Asn Phe His Thr Ile Met Arg Asn Ile
        195                 200                 205

Leu Gly Leu Val Leu Pro Leu Leu Ile Met Val Ile Cys Tyr Ser Gly
    210                 215                 220

Ile Leu Lys Thr Leu Leu Arg Cys Arg Asn Glu Lys Lys Arg His Arg
225                 230                 235                 240

Ala Val Arg Val Ile Phe Thr Ile Met Ile Val Tyr Phe Leu Phe Trp
```

```
                245                 250                 255

Thr Pro Tyr Asn Ile Val Ile Leu Leu Asn Thr Phe Gln Glu Phe Phe
            260                 265                 270

Gly Leu Ser Asn Cys Glu Ser Thr Ser Gln Leu Asp Gln Ala Thr Gln
        275                 280                 285

Val Thr Glu Thr Leu Gly Met Thr His Cys Cys Ile Asn Pro Ile Ile
    290                 295                 300

Tyr Ala Phe Val Gly Glu Lys Phe Arg Ser Leu Phe His Ile Ala Leu
305                 310                 315                 320

Gly Cys Arg Ile Ala Pro Leu Gln Lys Pro Val Cys Gly Gly Pro Gly
                325                 330                 335

Val Arg Pro Gly Lys Asn Val Lys Val Thr Thr Gln Gly Leu Leu Asp
            340                 345                 350

Gly Arg Gly Lys Gly Lys Ser Ile Gly Arg Ala Pro Glu Ala Ser Leu
        355                 360                 365

Gln Asp Lys Glu Gly Ala
    370


<210> SEQ ID NO 7
<211> LENGTH: 678
<212> TYPE: DNA
<213> ORGANISM: Mus musculus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (18)..(18)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 7

ttccctcatt gatttatnta atgagccctt agtctttatt ttagaaaata tagaaatttt      60

ttctagcatt ctggaatatc ttcagttttt tgaggcaaat gcttagacca ttgatatttc     120

agtctgtttt ctacacatgt actttaggat tctaggtttc tccctgagcc ctgctttcga     180

tgtaaccctg aatttctgta tgtctttact ggttagttac tttgatagtt tgtatatgct     240

tgacccagtg agtggcagga ttagaaggta tggccttgct ggaataggtg tgccactgtg     300

ggtgtagtct taagaccctt accctagctg cctggaggcc actattccac taacagcctt     360

caaatgaaaa tataaaactc tcagctctgc ctgtgccatg cctgcctgga tgctgccatg     420

ctcccacctt gatgataatg gactgaacct ctgaacctgt aagccagccc caatttgttg     480

tccttataaa agacttgctt tggtcatggt atctgttcac agcagaaaga acctaactaa     540

gacagttacc attcagttca aaataattct tgattttatt gttatttaga catgtgatat     600

ttacttttca acatctggag aattgtttag gttttttttt gtgtgtgtgt ctttagtagg     660

tattaataaa ctaaattg                                                   678


<210> SEQ ID NO 8
<211> LENGTH: 219
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 8

Met Gly Met Ser Ser Leu Lys Leu Leu Lys Tyr Val Leu Phe Ile Phe
1               5                   10                  15

Asn Leu Leu Phe Trp Val Cys Gly Cys Cys Ile Leu Gly Phe Gly Ile
            20                  25                  30

Tyr Phe Leu Val Gln Asn Thr Tyr Gly Val Leu Phe Arg Asn Leu Pro
        35                  40                  45

Phe Leu Thr Leu Gly Asn Ile Leu Val Ile Val Gly Ser Ile Ile Met
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50                  55                  60

Val Val Ala Phe Leu Gly Cys Met Gly Ser Ile Lys Glu Asn Lys Cys
65                  70                  75                  80

Leu Leu Met Ser Phe Phe Val Leu Leu Leu Ile Ile Leu Leu Ala Glu
                85                  90                  95

Val Thr Ile Ala Ile Leu Leu Phe Val Tyr Glu Gln Lys Leu Asn Thr
            100                 105                 110

Leu Val Ala Glu Gly Leu Asn Asp Ser Ile Gln His Tyr His Ser Asp
        115                 120                 125

Asn Ser Thr Met Lys Ala Trp Asp Phe Ile Gln Thr Gln Leu Gln Cys
    130                 135                 140

Cys Gly Val Asn Gly Ser Ser Asp Trp Thr Ser Gly Pro Pro Ser Ser
145                 150                 155                 160

Cys Pro Ser Gly Ala Asp Val Gln Gly Cys Tyr Asn Lys Ala Lys Ser
                165                 170                 175

Trp Phe His Ser Asn Phe Leu Tyr Ile Gly Ile Ile Thr Ile Cys Val
            180                 185                 190

Cys Val Ile Gln Val Leu Gly Met Ser Phe Ala Leu Thr Leu Asn Cys
        195                 200                 205

Gln Ile Asp Lys Thr Ser Gln Ala Leu Gly Leu
    210                 215


<210> SEQ ID NO 9
<211> LENGTH: 219
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 9

Met Gly Met Ser Ser Leu Lys Leu Leu Lys Tyr Val Leu Phe Phe Phe
1               5                   10                  15

Asn Leu Leu Phe Trp Ile Cys Gly Cys Cys Ile Leu Gly Phe Gly Ile
            20                  25                  30

Tyr Leu Leu Ile His Asn Asn Phe Gly Val Leu Phe His Asn Leu Pro
        35                  40                  45

Ser Leu Thr Leu Gly Asn Val Phe Val Ile Val Gly Ser Ile Ile Met
    50                  55                  60

Val Val Ala Phe Leu Gly Cys Met Gly Ser Ile Lys Glu Asn Lys Cys
65                  70                  75                  80

Leu Leu Met Ser Phe Phe Ile Leu Leu Leu Ile Ile Leu Leu Ala Glu
                85                  90                  95

Val Thr Leu Ala Ile Leu Leu Phe Val Tyr Glu Gln Lys Leu Asn Glu
            100                 105                 110

Tyr Val Ala Lys Gly Leu Thr Asp Ser Ile His Arg Tyr His Ser Asp
        115                 120                 125

Asn Ser Thr Lys Ala Ala Trp Asp Ser Ile Gln Ser Phe Leu Gln Cys
    130                 135                 140

Cys Gly Ile Asn Gly Thr Ser Asp Trp Thr Ser Gly Pro Pro Ala Ser
145                 150                 155                 160

Cys Pro Ser Asp Arg Lys Val Glu Gly Cys Tyr Ala Lys Ala Arg Leu
                165                 170                 175

Trp Phe His Ser Asn Phe Leu Tyr Ile Gly Ile Ile Thr Ile Cys Val
            180                 185                 190

Cys Val Ile Glu Val Leu Gly Met Ser Phe Ala Leu Thr Leu Asn Cys
        195                 200                 205

Gln Ile Asp Lys Thr Ser Gln Thr Ile Gly Leu
```

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    210                 215


<210> SEQ ID NO 10
<211> LENGTH: 172
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 10

Met Leu Val Ile Leu Ala Phe Ile Ile Val Phe His Ile Val Ser Thr
1               5                   10                  15

Ala Leu Leu Phe Ile Ser Thr Ile Asp Asn Ala Trp Trp Val Gly Asp
            20                  25                  30

Ser Phe Ser Ala Asp Leu Trp Arg Val Cys Thr Asn Ser Thr Asn Cys
        35                  40                  45

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

Val Met Gln Ala Val Gln Ala Thr Met Ile Leu Ser Thr Ile Leu Ser
65                  70                  75                  80

Cys Ile Ser Phe Leu Ile Phe Leu Leu Gln Leu Phe Arg Leu Lys Gln
                85                  90                  95

Gly Glu Arg Phe Val Leu Thr Ser Ile Ile Gln Leu Met Ser Cys Leu
            100                 105                 110

Cys Val Met Ile Gly Ala Ser Ile Tyr Thr Asp Arg Arg Gln Asp Leu
        115                 120                 125

His Gln Gln Asn Arg Lys Leu Tyr Tyr Leu Leu Gln Glu Gly Ser Tyr
    130                 135                 140

Gly Tyr Ser Phe Ile Leu Ala Trp Val Ala Phe Ala Phe Thr Phe Ile
145                 150                 155                 160

Ser Gly Leu Met Tyr Met Ile Leu Arg Lys Arg Lys
                165                 170


<210> SEQ ID NO 11
<211> LENGTH: 167
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11

Met Leu Val Leu Leu Ala Phe Ile Ile Ala Phe His Ile Thr Ser Ala
1               5                   10                  15

Ala Leu Leu Phe Ile Ala Thr Val Asp Asn Ala Trp Trp Val Gly Asp
            20                  25                  30

Glu Phe Phe Ala Asp Val Trp Arg Ile Cys Thr Asn Asn Thr Asn Cys
        35                  40                  45

Thr Val Ile Asn Asp Ser Phe Gln Glu Tyr Ser Thr Leu Gln Ala Val
    50                  55                  60

Gln Ala Thr Met Ile Leu Ser Thr Ile Leu Cys Cys Ile Ala Phe Phe
65                  70                  75                  80

Ile Phe Val Leu Gln Leu Phe Arg Leu Lys Gln Gly Glu Arg Phe Val
                85                  90                  95

Leu Thr Ser Ile Ile Gln Leu Met Ser Cys Leu Cys Val Met Ile Ala
            100                 105                 110

Ala Ser Ile Tyr Thr Asp Arg Arg Glu Asp Ile His Asp Lys Asn Ala
        115                 120                 125

Lys Phe Tyr Pro Val Thr Arg Glu Gly Ser Tyr Gly Tyr Ser Tyr Ile
    130                 135                 140

Leu Ala Trp Val Ala Phe Ala Cys Thr Phe Ile Ser Gly Met Met Tyr
145                 150                 155                 160
```

Leu Ile Leu Arg Lys Arg Lys
165

<210> SEQ ID NO 12
<211> LENGTH: 365
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 12

Met Gly Met Pro Leu Pro Trp Ala Leu Ser Leu Leu Leu Val Leu Leu
1 5 10 15

Pro Gln Thr Trp Gly Ser Glu Thr Arg Pro Pro Leu Met Tyr His Leu
20 25 30

Thr Ala Val Ser Asn Pro Ser Thr Gly Leu Pro Ser Phe Trp Ala Thr
35 40 45

Gly Trp Leu Gly Pro Gln Gln Tyr Leu Thr Tyr Asn Ser Leu Arg Gln
50 55 60

Glu Ala Asp Pro Cys Gly Ala Trp Val Trp Glu Asn Gln Val Ser Trp
65 70 75 80

Tyr Trp Glu Lys Glu Thr Thr Asp Leu Lys Ser Lys Glu Gln Leu Phe
85 90 95

Leu Glu Ala Leu Lys Thr Leu Glu Lys Ile Leu Asn Gly Thr Tyr Thr
100 105 110

Leu Gln Gly Leu Leu Gly Cys Glu Leu Ala Ser Asp Asn Ser Ser Val
115 120 125

Pro Thr Ala Val Phe Ala Leu Asn Gly Glu Glu Phe Met Lys Phe Asn
130 135 140

Pro Arg Ile Gly Asn Trp Thr Gly Glu Trp Pro Glu Thr Glu Ile Val
145 150 155 160

Ala Asn Leu Trp Met Lys Gln Pro Asp Ala Ala Arg Lys Glu Ser Glu
165 170 175

Phe Leu Leu Asn Ser Cys Pro Glu Arg Leu Leu Gly His Leu Glu Arg
180 185 190

Gly Arg Arg Asn Leu Glu Trp Lys Glu Pro Pro Ser Met Arg Leu Lys
195 200 205

Ala Arg Pro Gly Asn Ser Gly Ser Ser Val Leu Thr Cys Ala Ala Phe
210 215 220

Ser Phe Tyr Pro Pro Glu Leu Lys Phe Arg Phe Leu Arg Asn Gly Leu
225 230 235 240

Ala Ser Gly Ser Gly Asn Cys Ser Thr Gly Pro Asn Gly Asp Gly Ser
245 250 255

Phe His Ala Trp Ser Leu Leu Glu Val Lys Arg Gly Asp Glu His His
260 265 270

Tyr Gln Cys Gln Val Glu His Glu Gly Leu Ala Gln Pro Leu Thr Val
275 280 285

Asp Leu Asp Ser Ser Ala Arg Ser Ser Val Pro Val Val Gly Ile Val
290 295 300

Leu Gly Leu Leu Leu Val Val Val Ala Ile Ala Gly Gly Val Leu Leu
305 310 315 320

Trp Gly Arg Met Arg Ser Gly Leu Pro Ala Pro Trp Leu Ser Leu Ser
325 330 335

Gly Asp Asp Ser Gly Asp Leu Leu Pro Gly Gly Asn Leu Pro Pro Glu
340 345 350

Ala Glu Pro Gln Gly Ala Asn Ala Phe Pro Ala Thr Ser
355 360 365

<210> SEQ ID NO 13
<211> LENGTH: 365
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 13

```
Met Gly Val Pro Arg Pro Gln Pro Trp Ala Leu Gly Leu Leu Leu Phe
1               5                   10                  15

Leu Leu Pro Gly Ser Leu Gly Ala Glu Ser His Leu Ser Leu Leu Tyr
            20                  25                  30

His Leu Thr Ala Val Ser Ser Pro Ala Pro Gly Thr Pro Ala Phe Trp
        35                  40                  45

Val Ser Gly Trp Leu Gly Pro Gln Gln Tyr Leu Ser Tyr Asn Ser Leu
    50                  55                  60

Arg Gly Glu Ala Glu Pro Cys Gly Ala Trp Val Trp Glu Asn Gln Val
65                  70                  75                  80

Ser Trp Tyr Trp Glu Lys Glu Thr Thr Asp Leu Arg Ile Lys Glu Lys
                85                  90                  95

Leu Phe Leu Glu Ala Phe Lys Ala Leu Gly Gly Lys Gly Pro Tyr Thr
            100                 105                 110

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

Pro Thr Ala Lys Phe Ala Leu Asn Gly Glu Glu Phe Met Asn Phe Asp
    130                 135                 140

Leu Lys Gln Gly Thr Trp Gly Gly Asp Trp Pro Glu Ala Leu Ala Ile
145                 150                 155                 160

Ser Gln Arg Trp Gln Gln Gln Asp Lys Ala Ala Asn Lys Glu Leu Thr
                165                 170                 175

Phe Leu Leu Phe Ser Cys Pro His Arg Leu Arg Glu His Leu Glu Arg
            180                 185                 190

Gly Arg Gly Asn Leu Glu Trp Lys Glu Pro Pro Ser Met Arg Leu Lys
        195                 200                 205

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

Ser Phe Tyr Pro Pro Glu Leu Gln Leu Arg Phe Leu Arg Asn Gly Leu
225                 230                 235                 240

Ala Ala Gly Thr Gly Gln Gly Asp Phe Gly Pro Asn Ser Asp Gly Ser
                245                 250                 255

Phe His Ala Ser Ser Ser Leu Thr Val Lys Ser Gly Asp Glu His His
            260                 265                 270

Tyr Cys Cys Ile Val Gln His Ala Gly Leu Ala Gln Pro Leu Arg Val
        275                 280                 285

Glu Leu Glu Ser Pro Ala Lys Ser Ser Val Leu Val Val Gly Ile Val
    290                 295                 300

Ile Gly Val Leu Leu Leu Thr Ala Ala Ala Val Gly Gly Ala Leu Leu
305                 310                 315                 320

Trp Arg Arg Met Arg Ser Gly Leu Pro Ala Pro Trp Ile Ser Leu Arg
                325                 330                 335

Gly Asp Asp Thr Gly Val Leu Leu Pro Thr Pro Gly Glu Ala Gln Asp
            340                 345                 350

Ala Asp Leu Lys Asp Val Asn Val Ile Pro Ala Thr Ala
        355                 360                 365
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<210> SEQ ID NO 14

<211> LENGTH: 428
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 14

```
Met Arg Ala Leu Cys Leu Leu Cys Trp Ala Val Leu Leu Asn Leu Val
1               5                   10                  15

Arg Ala Cys Pro Glu Pro Cys Asp Cys Gly Glu Lys Tyr Gly Phe Gln
            20                  25                  30

Ile Ala Asp Cys Ala Tyr Arg Asp Leu Glu Gly Val Pro Pro Gly Phe
        35                  40                  45

Pro Ala Asn Val Thr Thr Leu Ser Leu Ser Ala Asn Arg Leu Pro Gly
    50                  55                  60

Leu Pro Glu Gly Ala Phe Arg Glu Val Pro Leu Leu Gln Ser Leu Trp
65                  70                  75                  80

Leu Ala His Asn Glu Ile Arg Ser Val Ala Ile Gly Ala Leu Ala Pro
                85                  90                  95

Leu Ser His Leu Lys Ser Leu Asp Leu Ser His Asn Leu Leu Ser Glu
            100                 105                 110

Phe Ala Trp Ser Asp Leu His Asn Leu Ser Ala Leu Gln Leu Leu Lys
        115                 120                 125

Met Asp Ser Asn Glu Leu Ala Phe Ile Pro Arg Asp Ala Phe Ser Ser
    130                 135                 140

Leu Ser Ala Leu Arg Ser Leu Gln Leu Asn His Asn Arg Leu His Ala
145                 150                 155                 160

Leu Ala Glu Gly Thr Phe Ala Pro Leu Thr Ala Leu Ser His Leu Gln
                165                 170                 175

Ile Asn Asp Asn Pro Phe Asp Cys Thr Cys Gly Ile Val Trp Phe Lys
            180                 185                 190

Thr Trp Ala Leu Ala Ser Ala Val Ser Ile Pro Glu Gln Asp Asn Ile
        195                 200                 205

Ala Cys Thr Thr Pro His Val Leu Lys Gly Ile Pro Leu Gly Arg Leu
    210                 215                 220

Pro Pro Leu Pro Cys Ser Ala Pro Ser Val Gln Leu Ser Tyr Gln Pro
225                 230                 235                 240

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

Cys Asp Val Asp Gly Gln Pro Val Pro Gln Leu His Trp His Ile His
            260                 265                 270

Thr Pro Gly Gly Thr Val Glu Ile Ala Ser Pro Asn Val Gly Thr Asp
        275                 280                 285

Gly Arg Ala Leu Pro Gly Ala Leu Ala Thr Ser Gly Gln Pro Arg Phe
    290                 295                 300

Gln Ala Phe Ala Asn Gly Ser Leu Leu Ile Pro Asp Phe Gly Lys Leu
305                 310                 315                 320

Glu Glu Gly Thr Tyr Ser Cys Leu Ala Thr Asn Glu Leu Gly Ser Ala
                325                 330                 335

Glu Ser Ser Val Asn Val Ala Leu Ala Thr Pro Gly Glu Gly Gly Glu
            340                 345                 350

Asp Ala Val Gly His Lys Phe His Gly Lys Ala Val Glu Gly Lys Gly
        355                 360                 365

Cys Tyr Thr Val Asp Asn Glu Val Gln Pro Ser Gly Pro Glu Asp Asn
    370                 375                 380

Val Val Ile Ile Tyr Leu Ser Arg Ala Gly Pro Pro Glu Ala Ala Ile
385                 390                 395                 400
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Ala Ala Asp Gly Arg Pro Ala Gln Gln Phe Ser Gly Ile Leu Leu Leu
                405                 410                 415

Gly Gln Ser Leu Leu Val Leu Ser Phe Phe Tyr Phe
            420                 425


<210> SEQ ID NO 15
<211> LENGTH: 428
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 15

Met Gln Glu Leu His Leu Leu Trp Trp Ala Leu Leu Leu Gly Leu Ala
1               5                   10                  15

Gln Ala Cys Pro Glu Pro Cys Asp Cys Gly Glu Lys Tyr Gly Phe Gln
            20                  25                  30

Ile Ala Asp Cys Ala Tyr Arg Asp Leu Glu Ser Val Pro Pro Gly Phe
        35                  40                  45

Pro Ala Asn Val Thr Thr Leu Ser Leu Ser Ala Asn Arg Leu Pro Gly
    50                  55                  60

Leu Pro Glu Gly Ala Phe Arg Glu Val Pro Leu Leu Gln Ser Leu Trp
65                  70                  75                  80

Leu Ala His Asn Glu Ile Arg Thr Val Ala Ala Gly Ala Leu Ala Ser
                85                  90                  95

Leu Ser His Leu Lys Ser Leu Asp Leu Ser His Asn Leu Ile Ser Asp
            100                 105                 110

Phe Ala Trp Ser Asp Leu His Asn Leu Ser Ala Leu Gln Leu Leu Lys
        115                 120                 125

Met Asp Ser Asn Glu Leu Thr Phe Ile Pro Arg Asp Ala Phe Arg Ser
    130                 135                 140

Leu Arg Ala Leu Arg Ser Leu Gln Leu Asn His Asn Arg Leu His Thr
145                 150                 155                 160

Leu Ala Glu Gly Thr Phe Thr Pro Leu Thr Ala Leu Ser His Leu Gln
                165                 170                 175

Ile Asn Glu Asn Pro Phe Asp Cys Thr Cys Gly Ile Val Trp Leu Lys
            180                 185                 190

Thr Trp Ala Leu Thr Thr Ala Val Ser Ile Pro Glu Gln Asp Asn Ile
        195                 200                 205

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

Pro Pro Leu Pro Cys Ser Ala Pro Ser Val Gln Leu Ser Tyr Gln Pro
225                 230                 235                 240

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

Cys Asp Val Asp Gly Gln Pro Ala Pro Gln Leu His Trp His Ile Gln
            260                 265                 270

Ile Pro Ser Gly Ile Val Glu Ile Thr Ser Pro Asn Val Gly Thr Asp
        275                 280                 285

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

Gln Ala Phe Ala Asn Gly Ser Leu Leu Ile Pro Asp Phe Gly Lys Leu
305                 310                 315                 320

Glu Glu Gly Thr Tyr Ser Cys Leu Ala Thr Asn Glu Leu Gly Ser Ala
                325                 330                 335

Glu Ser Ser Val Asp Val Ala Leu Ala Thr Pro Gly Glu Gly Gly Glu
            340                 345                 350
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```
Asp Thr Leu Gly Arg Arg Phe His Gly Lys Ala Val Glu Gly Lys Gly
        355                 360                 365

Cys Tyr Thr Val Asp Asn Glu Val Gln Pro Ser Gly Pro Glu Asp Asn
    370                 375                 380

Val Val Ile Ile Tyr Leu Ser Arg Ala Gly Asn Pro Glu Ala Ala Val
385                 390                 395                 400

Ala Glu Gly Val Pro Gly Gln Leu Pro Pro Gly Leu Leu Leu Leu Gly
                405                 410                 415

Gln Ser Leu Leu Leu Phe Phe Phe Leu Thr Ser Phe
            420                 425


<210> SEQ ID NO 16
<211> LENGTH: 580
<212> TYPE: DNA
<213> ORGANISM: Mus musculus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (327)..(327)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (336)..(336)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (350)..(350)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (353)..(353)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (364)..(364)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (487)..(487)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (502)..(502)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 16

aggcaaacag agaaaaatat atttttttat aaagtattga atgttaactt ctttttcatt      60

tgtctgtaaa aaatatatgt gcaaaagtga gtgtctaaat gttccctaga gagttggcaa     120

ggctatacat cagagtcttc cttcacaagg tttgcggtgt ctttaaaggt gtcttctgtg     180

gcagtgtagc ctggagtcga acttcttttt gaagctttag caggaagaga aggagatgga     240

gggggagcca cagccacagc ttccttttgc tcagtgtcca tctctgcata gattggattt     300

tcgaagtcgt gtctgctggg gttttcngtt tgaagnaatt ccatttgggn ccngagtttc     360

catnagctcc aggggaggct ggctttggct ctggaactat ctcagaaggt ctatggacct     420

tcctagttct ggttttccac attttctggt acagtcacct gtgagcttac tgacggtccc     480

tgcatgncag gcccactttg gnaatactgt cttggctgca tacattgggt ttcaaatatt     540

cacaggctgc ttgcctacct ccatgacgaa tgttcattca                           580


<210> SEQ ID NO 17
<211> LENGTH: 4655
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 17
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Met Asp Arg Gly Pro Ala Ala Val Ala Cys Thr Leu Leu Leu Ala Leu
1               5                   10                  15

Val Ala Cys Leu Ala Pro Ala Ser Gly Gln Glu Cys Asp Ser Ala His
            20                  25                  30

Phe Arg Cys Gly Ser Gly His Cys Ile Pro Ala Asp Trp Arg Cys Asp
        35                  40                  45

Gly Thr Lys Asp Cys Ser Asp Asp Ala Asp Glu Ile Gly Cys Ala Val
    50                  55                  60

Val Thr Cys Gln Gln Gly Tyr Phe Lys Cys Gln Ser Glu Gly Gln Cys
65                  70                  75                  80

Ile Pro Ser Ser Trp Val Cys Asp Gln Asp Gln Asp Cys Asp Asp Gly
                85                  90                  95

Ser Asp Glu Arg Gln Asp Cys Ser Gln Ser Thr Cys Ser Ser His Gln
            100                 105                 110

Ile Thr Cys Ser Asn Gly Gln Cys Ile Pro Ser Glu Tyr Arg Cys Asp
        115                 120                 125

His Val Arg Asp Cys Pro Asp Gly Ala Asp Glu Asn Asp Cys Gln Tyr
    130                 135                 140

Pro Thr Cys Glu Gln Leu Thr Cys Asp Asn Gly Ala Cys Tyr Asn Thr
145                 150                 155                 160

Ser Gln Lys Cys Asp Trp Lys Val Asp Cys Arg Asp Ser Ser Asp Glu
                165                 170                 175

Ile Asn Cys Thr Glu Ile Cys Leu His Asn Glu Phe Ser Cys Gly Asn
            180                 185                 190

Gly Glu Cys Ile Pro Arg Ala Tyr Val Cys Asp His Asp Asn Asp Cys
        195                 200                 205

Gln Asp Gly Ser Asp Glu His Ala Cys Asn Tyr Pro Thr Cys Gly Gly
    210                 215                 220

Tyr Gln Phe Thr Cys Pro Ser Gly Arg Cys Ile Tyr Gln Asn Trp Val
225                 230                 235                 240

Cys Asp Gly Glu Asp Asp Cys Lys Asp Asn Gly Asp Glu Asp Gly Cys
                245                 250                 255

Glu Ser Gly Pro His Asp Val His Lys Cys Ser Pro Arg Glu Trp Ser
            260                 265                 270

Cys Pro Glu Ser Gly Arg Cys Ile Ser Ile Tyr Lys Val Cys Asp Gly
        275                 280                 285

Ile Leu Asp Cys Pro Gly Arg Glu Asp Glu Asn Asn Thr Ser Thr Gly
    290                 295                 300

Lys Tyr Cys Ser Met Thr Leu Cys Ser Ala Leu Asn Cys Gln Tyr Gln
305                 310                 315                 320

Cys His Glu Thr Pro Tyr Gly Gly Ala Cys Phe Cys Pro Pro Gly Tyr
                325                 330                 335

Ile Ile Asn His Asn Asp Ser Arg Thr Cys Val Glu Phe Asp Asp Cys
            340                 345                 350

Gln Ile Trp Gly Ile Cys Asp Gln Lys Cys Glu Ser Arg Pro Gly Arg
        355                 360                 365

His Leu Cys His Cys Glu Glu Gly Tyr Ile Leu Glu Arg Gly Gln Tyr
    370                 375                 380

Cys Lys Ala Asn Asp Ser Phe Gly Glu Ala Ser Ile Ile Phe Ser Asn
385                 390                 395                 400

Gly Arg Asp Leu Leu Ile Gly Asp Ile His Gly Arg Ser Phe Arg Ile
                405                 410                 415

Leu Val Glu Ser Gln Asn Arg Gly Val Ala Val Gly Val Ala Phe His
            420                 425                 430
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Tyr His Leu Gln Arg Val Phe Trp Thr Asp Thr Val Gln Asn Lys Val
        435                 440                 445

Phe Ser Val Asp Ile Asn Gly Leu Asn Ile Gln Glu Val Leu Asn Val
    450                 455                 460

Ser Val Glu Thr Pro Glu Asn Leu Ala Val Asp Trp Val Asn Asn Lys
465                 470                 475                 480

Ile Tyr Leu Val Glu Thr Lys Val Asn Arg Ile Asp Met Val Asn Leu
                485                 490                 495

Asp Gly Ser Tyr Arg Val Thr Leu Ile Thr Glu Asn Leu Gly His Pro
            500                 505                 510

Arg Gly Ile Ala Val Asp Pro Thr Val Gly Tyr Leu Phe Phe Ser Asp
        515                 520                 525

Trp Glu Ser Leu Ser Gly Glu Pro Lys Leu Glu Arg Ala Phe Met Asp
    530                 535                 540

Gly Ser Asn Arg Lys Asp Leu Val Lys Thr Lys Leu Gly Trp Pro Ala
545                 550                 555                 560

Gly Val Thr Leu Asp Met Ile Ser Lys Arg Val Tyr Trp Val Asp Ser
                565                 570                 575

Arg Phe Asp Tyr Ile Glu Thr Val Thr Tyr Asp Gly Ile Gln Arg Lys
            580                 585                 590

Thr Val Val His Gly Gly Ser Leu Ile Pro His Pro Phe Gly Val Ser
        595                 600                 605

Leu Phe Glu Gly Gln Val Phe Phe Thr Asp Trp Thr Lys Met Ala Val
    610                 615                 620

Leu Lys Ala Asn Lys Phe Thr Glu Thr Asn Pro Gln Val Tyr Tyr Gln
625                 630                 635                 640

Ala Ser Leu Arg Pro Tyr Gly Val Thr Val Tyr His Ser Leu Arg Gln
                645                 650                 655

Pro Tyr Ala Thr Asn Pro Cys Lys Asp Asn Asn Gly Gly Cys Glu Gln
            660                 665                 670

Val Cys Val Leu Ser His Arg Thr Asp Asn Asp Gly Leu Gly Phe Arg
        675                 680                 685

Cys Lys Cys Thr Phe Gly Phe Gln Leu Asp Thr Asp Glu Arg His Cys
    690                 695                 700

Ile Ala Val Gln Asn Phe Leu Ile Phe Ser Ser Gln Val Ala Ile Arg
705                 710                 715                 720

Gly Ile Pro Phe Thr Leu Ser Thr Gln Glu Asp Val Met Val Pro Val
                725                 730                 735

Ser Gly Asn Pro Ser Phe Phe Val Gly Ile Asp Phe Asp Ala Gln Asp
            740                 745                 750

Ser Thr Ile Phe Phe Ser Asp Met Ser Lys His Met Ile Phe Lys Gln
        755                 760                 765

Lys Ile Asp Gly Thr Gly Arg Glu Ile Leu Ala Ala Asn Arg Val Glu
    770                 775                 780

Asn Val Glu Ser Leu Ala Phe Asp Trp Ile Ser Lys Asn Leu Tyr Trp
785                 790                 795                 800

Thr Asp Ser His Tyr Lys Ser Ile Ser Val Met Arg Leu Ala Asp Lys
                805                 810                 815

Thr Arg Arg Thr Val Val Gln Tyr Leu Asn Asn Pro Arg Ser Val Val
            820                 825                 830

Val His Pro Phe Ala Gly Tyr Leu Phe Phe Thr Asp Trp Phe Arg Pro
        835                 840                 845

Ala Lys Ile Met Arg Ala Trp Ser Asp Gly Ser His Leu Leu Pro Val
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    850                 855                 860

Ile Asn Thr Thr Leu Gly Trp Pro Asn Gly Leu Ala Ile Asp Trp Ala
865                 870                 875                 880

Ala Ser Arg Leu Tyr Trp Val Asp Ala Tyr Phe Asp Lys Ile Glu His
                885                 890                 895

Ser Thr Phe Asp Gly Leu Asp Arg Arg Arg Leu Gly His Ile Glu Gln
            900                 905                 910

Met Thr His Pro Phe Gly Leu Ala Ile Phe Gly Glu His Leu Phe Phe
        915                 920                 925

Thr Asp Trp Arg Leu Gly Ala Ile Ile Arg Val Arg Lys Ala Asp Gly
    930                 935                 940

Gly Glu Met Thr Val Ile Arg Ser Gly Ile Ala Tyr Ile Leu His Leu
945                 950                 955                 960

Lys Ser Tyr Asp Val Asn Ile Gln Thr Gly Ser Asn Ala Cys Asn Gln
                965                 970                 975

Pro Thr His Pro Asn Gly Asp Cys Ser His Phe Cys Phe Pro Val Pro
            980                 985                 990

Asn Phe Gln Arg Val Cys Gly Cys  Pro Tyr Gly Met Arg  Leu Ala Ser
        995                 1000                1005

Asn His  Leu Thr Cys Glu Gly  Asp Pro Thr Asn Glu  Pro Pro Thr
    1010                1015                1020

Glu Gln  Cys Gly Leu Phe Ser  Phe Pro Cys Lys Asn  Gly Arg Cys
    1025                1030                1035

Val Pro  Asn Tyr Tyr Leu Cys  Asp Gly Val Asp Asp  Cys His Asp
    1040                1045                1050

Asn Ser  Asp Glu Gln Leu Cys  Gly Thr Leu Asn Asn  Thr Cys Ser
    1055                1060                1065

Ser Ser  Ala Phe Thr Cys Gly  His Gly Glu Cys Ile  Pro Ala His
    1070                1075                1080

Trp Arg  Cys Asp Lys Arg Asn  Asp Cys Val Asp Gly  Ser Asp Glu
    1085                1090                1095

His Asn  Cys Pro Thr His Ala  Pro Ala Ser Cys Leu  Asp Thr Gln
    1100                1105                1110

Tyr Thr  Cys Asp Asn His Gln  Cys Ile Ser Lys Asn  Trp Val Cys
    1115                1120                1125

Asp Thr  Asp Asn Asp Cys Gly  Asp Gly Ser Asp Glu  Lys Asn Cys
    1130                1135                1140

Asn Ser  Thr Glu Thr Cys Gln  Pro Ser Gln Phe Asn  Cys Pro Asn
    1145                1150                1155

His Arg  Cys Ile Asp Leu Ser  Phe Val Cys Asp Gly  Asp Lys Asp
    1160                1165                1170

Cys Val  Asp Gly Ser Asp Glu  Val Gly Cys Val Leu  Asn Cys Thr
    1175                1180                1185

Ala Ser  Gln Phe Lys Cys Ala  Ser Gly Asp Lys Cys  Ile Gly Val
    1190                1195                1200

Thr Asn  Arg Cys Asp Gly Val  Phe Asp Cys Ser Asp  Asn Ser Asp
    1205                1210                1215

Glu Ala  Gly Cys Pro Thr Arg  Pro Pro Gly Met Cys  His Ser Asp
    1220                1225                1230

Glu Phe  Gln Cys Gln Glu Asp  Gly Ile Cys Ile Pro  Asn Phe Trp
    1235                1240                1245

Glu Cys  Asp Gly His Pro Asp  Cys Leu Tyr Gly Ser  Asp Glu His
    1250                1255                1260
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Asn Ala  Cys Val Pro Lys Thr  Cys Pro Ser Ser Tyr  Phe His Cys
    1265                 1270                 1275

Asp Asn  Gly Asn Cys Ile His  Arg Ala Trp Leu Cys  Asp Arg Asp
    1280                 1285                 1290

Asn Asp  Cys Gly Asp Met Ser  Asp Glu Lys Asp Cys  Pro Thr Gln
    1295                 1300                 1305

Pro Phe  Arg Cys Pro Ser Trp  Gln Trp Gln Cys Leu  Gly His Asn
    1310                 1315                 1320

Ile Cys  Val Asn Leu Ser Val  Val Cys Asp Gly Ile  Phe Asp Cys
    1325                 1330                 1335

Pro Asn  Gly Thr Asp Glu Ser  Pro Leu Cys Asn Gly  Asn Ser Cys
    1340                 1345                 1350

Ser Asp  Phe Asn Gly Gly Cys  Thr His Glu Cys Val  Gln Glu Pro
    1355                 1360                 1365

Phe Gly  Ala Lys Cys Leu Cys  Pro Leu Gly Phe Leu  Leu Ala Asn
    1370                 1375                 1380

Asp Ser  Lys Thr Cys Glu Asp  Ile Asp Glu Cys Asp  Ile Leu Gly
    1385                 1390                 1395

Ser Cys  Ser Gln His Cys Tyr  Asn Met Arg Gly Ser  Phe Arg Cys
    1400                 1405                 1410

Ser Cys  Asp Thr Gly Tyr Met  Leu Glu Ser Asp Gly  Arg Thr Cys
    1415                 1420                 1425

Lys Val  Thr Ala Ser Glu Ser  Leu Leu Leu Leu Val  Ala Ser Gln
    1430                 1435                 1440

Asn Lys  Ile Ile Ala Asp Ser  Val Thr Ser Gln Val  His Asn Ile
    1445                 1450                 1455

Tyr Ser  Leu Val Glu Asn Gly  Ser Tyr Ile Val Ala  Val Asp Phe
    1460                 1465                 1470

Asp Ser  Ile Ser Gly Arg Ile  Phe Trp Ser Asp Ala  Thr Gln Gly
    1475                 1480                 1485

Lys Thr  Trp Ser Ala Phe Gln  Asn Gly Thr Asp Arg  Arg Val Val
    1490                 1495                 1500

Phe Asp  Ser Ser Ile Ile Leu  Thr Glu Thr Ile Ala  Ile Asp Trp
    1505                 1510                 1515

Val Gly  Arg Asn Leu Tyr Trp  Thr Asp Tyr Ala Leu  Glu Thr Ile
    1520                 1525                 1530

Glu Val  Ser Lys Ile Asp Gly  Ser His Arg Thr Val  Leu Ile Ser
    1535                 1540                 1545

Lys Asn  Leu Thr Asn Pro Arg  Gly Leu Ala Leu Asp  Pro Arg Met
    1550                 1555                 1560

Asn Glu  His Leu Leu Phe Trp  Ser Asp Trp Gly His  His Pro Arg
    1565                 1570                 1575

Ile Glu  Arg Ala Ser Met Asp  Gly Ser Met Arg Thr  Val Ile Val
    1580                 1585                 1590

Gln Asp  Lys Ile Phe Trp Pro  Cys Gly Leu Thr Ile  Asp Tyr Pro
    1595                 1600                 1605

Asn Arg  Leu Leu Tyr Phe Met  Asp Ser Tyr Leu Asp  Tyr Met Asp
    1610                 1615                 1620

Phe Cys  Asp Tyr Asn Gly His  His Arg Arg Gln Val  Ile Ala Ser
    1625                 1630                 1635

Asp Leu  Ile Ile Arg His Pro  Tyr Ala Leu Thr Leu  Phe Glu Asp
    1640                 1645                 1650

Ser Val  Tyr Trp Thr Asp Arg  Ala Thr Arg Arg Val  Met Arg Ala
    1655                 1660                 1665
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Asn Lys  Trp His Gly Gly Asn  Gln Ser Val Val Met  Tyr Asn Ile
    1670                 1675                 1680

Gln Trp  Pro Leu Gly Ile Val  Ala Val His Pro Ser  Lys Gln Pro
    1685                 1690                 1695

Asn Ser  Val Asn Pro Cys Ala  Phe Ser Arg Cys Ser  His Leu Cys
    1700                 1705                 1710

Leu Leu  Ser Ser Gln Gly Pro  His Phe Tyr Ser Cys  Val Cys Pro
    1715                 1720                 1725

Ser Gly  Trp Ser Leu Ser Pro  Asp Leu Leu Asn Cys  Leu Arg Asp
    1730                 1735                 1740

Asp Gln  Pro Phe Leu Ile Thr  Val Arg Gln His Ile  Ile Phe Gly
    1745                 1750                 1755

Ile Ser  Leu Asn Pro Glu Val  Lys Ser Asn Asp Ala  Met Val Pro
    1760                 1765                 1770

Ile Ala  Gly Ile Gln Asn Gly  Leu Asp Val Glu Phe  Asp Asp Ala
    1775                 1780                 1785

Glu Gln  Tyr Ile Tyr Trp Val  Glu Asn Pro Gly Glu  Ile His Arg
    1790                 1795                 1800

Val Lys  Thr Asp Gly Thr Asn  Arg Thr Val Phe Ala  Ser Ile Ser
    1805                 1810                 1815

Met Val  Gly Pro Ser Met Asn  Leu Ala Leu Asp Trp  Ile Ser Arg
    1820                 1825                 1830

Asn Leu  Tyr Ser Thr Asn Pro  Arg Thr Gln Ser Ile  Glu Val Leu
    1835                 1840                 1845

Thr Leu  His Gly Asp Ile Arg  Tyr Arg Lys Thr Leu  Ile Ala Asn
    1850                 1855                 1860

Asp Gly  Thr Ala Leu Gly Val  Gly Phe Pro Ile Gly  Ile Thr Val
    1865                 1870                 1875

Asp Pro  Ala Arg Gly Lys Leu  Tyr Trp Ser Asp Gln  Gly Thr Asp
    1880                 1885                 1890

Ser Gly  Val Pro Ala Lys Ile  Ala Ser Ala Asn Met  Asp Gly Thr
    1895                 1900                 1905

Ser Val  Lys Thr Leu Phe Thr  Gly Asn Leu Glu His  Leu Glu Cys
    1910                 1915                 1920

Val Thr  Leu Asp Ile Glu Glu  Gln Lys Leu Tyr Trp  Ala Val Thr
    1925                 1930                 1935

Gly Arg  Gly Val Ile Glu Arg  Gly Asn Val Asp Gly  Thr Asp Arg
    1940                 1945                 1950

Met Ile  Leu Val His Gln Leu  Ser His Pro Trp Gly  Ile Ala Val
    1955                 1960                 1965

His Asp  Ser Phe Leu Tyr Tyr  Thr Asp Glu Gln Tyr  Glu Val Ile
    1970                 1975                 1980

Glu Arg  Val Asp Lys Ala Thr  Gly Ala Asn Lys Ile  Val Leu Arg
    1985                 1990                 1995

Asp Asn  Val Pro Asn Leu Arg  Gly Leu Gln Val Tyr  His Arg Arg
    2000                 2005                 2010

Asn Ala  Ala Glu Ser Ser Asn  Gly Cys Ser Asn Asn  Met Asn Ala
    2015                 2020                 2025

Cys Gln  Gln Ile Cys Leu Pro  Val Pro Gly Gly Leu  Phe Ser Cys
    2030                 2035                 2040

Ala Cys  Ala Thr Gly Phe Lys  Leu Asn Pro Asp Asn  Arg Ser Cys
    2045                 2050                 2055

Ser Pro  Tyr Asn Ser Phe Ile  Val Val Ser Met Leu  Ser Ala Ile
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    2060                2065                2070

Arg Gly  Phe Ser Leu Glu Leu  Ser Asp His Ser Glu  Thr Met Val
    2075                2080                2085

Pro Val  Ala Gly Gln Gly Arg  Asn Ala Leu His Val  Asp Val Asp
    2090                2095                2100

Val Ser  Ser Gly Phe Ile Tyr  Trp Cys Asp Phe Ser  Ser Ser Val
    2105                2110                2115

Ala Ser  Asp Asn Ala Ile Arg  Arg Ile Lys Pro Asp  Gly Ser Ser
    2120                2125                2130

Leu Met  Asn Ile Val Thr His  Gly Ile Gly Glu Asn  Gly Val Arg
    2135                2140                2145

Gly Ile  Ala Val Asp Trp Val  Ala Gly Asn Leu Tyr  Phe Thr Asn
    2150                2155                2160

Ala Phe  Val Ser Glu Thr Leu  Ile Glu Val Leu Arg  Ile Asn Thr
    2165                2170                2175

Thr Tyr  Arg Arg Val Leu Leu  Lys Val Thr Val Asp  Met Pro Arg
    2180                2185                2190

His Ile  Val Val Asp Pro Lys  Asn Arg Tyr Leu Phe  Trp Ala Asp
    2195                2200                2205

Tyr Gly  Gln Arg Pro Lys Ile  Glu Arg Ser Phe Leu  Asp Cys Thr
    2210                2215                2220

Asn Arg  Thr Val Leu Val Ser  Glu Gly Ile Val Thr  Pro Arg Gly
    2225                2230                2235

Leu Ala  Val Asp Arg Ser Asp  Gly Tyr Val Tyr Trp  Val Asp Asp
    2240                2245                2250

Ser Leu  Asp Ile Ile Ala Arg  Ile Arg Ile Asn Gly  Glu Asn Ser
    2255                2260                2265

Glu Val  Ile Arg Tyr Gly Ser  Arg Tyr Pro Thr Pro  Tyr Gly Ile
    2270                2275                2280

Thr Val  Phe Glu Asn Ser Ile  Ile Trp Val Asp Arg  Asn Leu Lys
    2285                2290                2295

Lys Ile  Phe Gln Ala Ser Lys  Glu Pro Glu Asn Thr  Glu Pro Pro
    2300                2305                2310

Thr Val  Ile Arg Asp Asn Ile  Asn Trp Leu Arg Asp  Val Thr Ile
    2315                2320                2325

Phe Asp  Lys Gln Val Gln Pro  Arg Ser Pro Ala Glu  Val Asn Asn
    2330                2335                2340

Asn Pro  Cys Leu Glu Asn Asn  Gly Gly Cys Ser His  Leu Cys Phe
    2345                2350                2355

Ala Leu  Pro Gly Leu His Thr  Pro Lys Cys Asp Cys  Ala Phe Gly
    2360                2365                2370

Thr Leu  Gln Ser Asp Gly Lys  Asn Cys Ala Ile Ser  Thr Glu Asn
    2375                2380                2385

Phe Leu  Ile Phe Ala Leu Ser  Asn Ser Leu Arg Ser  Leu His Leu
    2390                2395                2400

Asp Pro  Glu Asn His Ser Pro  Pro Phe Gln Thr Ile  Asn Val Glu
    2405                2410                2415

Arg Thr  Val Met Ser Leu Asp  Tyr Asp Ser Val Ser  Asp Arg Ile
    2420                2425                2430

Tyr Phe  Thr Gln Asn Leu Ala  Ser Gly Val Gly Gln  Ile Ser Tyr
    2435                2440                2445

Ala Thr  Leu Ser Ser Gly Ile  His Thr Pro Thr Val  Ile Ala Ser
    2450                2455                2460
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Gly Ile  Gly Thr Ala Asp Gly  Ile Ala Phe Asp Trp  Ile Thr Arg
    2465                 2470                 2475

Arg Ile  Tyr Tyr Ser Asp Tyr  Leu Asn Gln Met Ile  Asn Ser Met
    2480                 2485                 2490

Ala Glu  Asp Gly Ser Asn Arg  Thr Val Ile Ala Arg  Val Pro Lys
    2495                 2500                 2505

Pro Arg  Ala Ile Val Leu Asp  Pro Cys Gln Gly Tyr  Leu Tyr Trp
    2510                 2515                 2520

Ala Asp  Trp Asp Thr His Ala  Lys Ile Glu Arg Ala  Thr Leu Gly
    2525                 2530                 2535

Gly Asn  Phe Arg Val Pro Ile  Val Asn Ser Ser Leu  Val Met Pro
    2540                 2545                 2550

Ser Gly  Leu Thr Leu Asp Tyr  Glu Glu Asp Leu Leu  Tyr Trp Val
    2555                 2560                 2565

Asp Ala  Ser Leu Gln Arg Ile  Glu Arg Ser Thr Leu  Thr Gly Val
    2570                 2575                 2580

Asp Arg  Glu Val Ile Val Asn  Ala Ala Val His Ala  Phe Gly Leu
    2585                 2590                 2595

Thr Leu  Tyr Gly Gln Tyr Ile  Tyr Trp Thr Asp Leu  Tyr Thr Gln
    2600                 2605                 2610

Arg Ile  Tyr Arg Ala Asn Lys  Tyr Asp Gly Ser Gly  Gln Ile Ala
    2615                 2620                 2625

Met Thr  Thr Asn Leu Leu Ser  Gln Pro Arg Gly Ile  Asn Thr Val
    2630                 2635                 2640

Val Lys  Asn Gln Lys Gln Gln  Cys Asn Asn Pro Cys  Glu Gln Phe
    2645                 2650                 2655

Asn Gly  Gly Cys Ser His Ile  Cys Ala Pro Gly Pro  Asn Gly Ala
    2660                 2665                 2670

Glu Cys  Gln Cys Pro His Glu  Gly Asn Trp Tyr Leu  Ala Asn Asn
    2675                 2680                 2685

Arg Lys  His Cys Ile Val Asp  Asn Gly Glu Arg Cys  Gly Ala Ser
    2690                 2695                 2700

Ser Phe  Thr Cys Ser Asn Gly  Arg Cys Ile Ser Glu  Glu Trp Lys
    2705                 2710                 2715

Cys Asp  Asn Asp Asn Asp Cys  Gly Asp Gly Ser Asp  Glu Met Glu
    2720                 2725                 2730

Ser Val  Cys Ala Leu His Thr  Cys Ser Pro Thr Ala  Phe Thr Cys
    2735                 2740                 2745

Ala Asn  Gly Arg Cys Val Gln  Tyr Ser Tyr Arg Cys  Asp Tyr Tyr
    2750                 2755                 2760

Asn Asp  Cys Gly Asp Gly Ser  Asp Glu Ala Gly Cys  Leu Phe Arg
    2765                 2770                 2775

Asp Cys  Asn Ala Thr Thr Glu  Phe Met Cys Asn Asn  Arg Arg Cys
    2780                 2785                 2790

Ile Pro  Arg Glu Phe Ile Cys  Asn Gly Val Asp Asn  Cys His Asp
    2795                 2800                 2805

Asn Asn  Thr Ser Asp Glu Lys  Asn Cys Pro Asp Arg  Thr Cys Gln
    2810                 2815                 2820

Ser Gly  Tyr Thr Lys Cys His  Asn Ser Asn Ile Cys  Ile Pro Arg
    2825                 2830                 2835

Val Tyr  Leu Cys Asp Gly Asp  Asn Asp Cys Gly Asp  Asn Ser Asp
    2840                 2845                 2850

Glu Asn  Pro Thr Tyr Cys Thr  Thr His Thr Cys Ser  Ser Ser Glu
    2855                 2860                 2865
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Phe Gln  Cys Ala Ser Gly Arg  Cys Ile Pro Gln His  Trp Tyr Cys
    2870                 2875                 2880

Asp Gln  Glu Thr Asp Cys Phe  Asp Ala Ser Asp Glu  Pro Ala Ser
    2885                 2890                 2895

Cys Gly  His Ser Glu Arg Thr  Cys Leu Ala Asp Glu  Phe Lys Cys
    2900                 2905                 2910

Asp Gly  Gly Arg Cys Ile Pro  Ser Glu Trp Ile Cys  Asp Gly Asp
    2915                 2920                 2925

Asn Asp  Cys Gly Asp Met Ser  Asp Glu Asp Lys Arg  His Gln Cys
    2930                 2935                 2940

Gln Asn  Gln Asn Cys Ser Asp  Ser Glu Phe Leu Cys  Val Asn Asp
    2945                 2950                 2955

Arg Pro  Pro Asp Arg Arg Cys  Ile Pro Gln Ser Trp  Val Cys Asp
    2960                 2965                 2970

Gly Asp  Val Asp Cys Thr Asp  Gly Tyr Asp Glu Asn  Gln Asn Cys
    2975                 2980                 2985

Thr Arg  Arg Thr Cys Ser Glu  Asn Glu Phe Thr Cys  Gly Tyr Gly
    2990                 2995                 3000

Leu Cys  Ile Pro Lys Ile Phe  Arg Cys Asp Arg His  Asn Asp Cys
    3005                 3010                 3015

Gly Asp  Tyr Ser Asp Glu Arg  Gly Cys Leu Tyr Gln  Thr Cys Gln
    3020                 3025                 3030

Gln Asn  Gln Phe Thr Cys Gln  Asn Gly Arg Cys Ile  Ser Lys Thr
    3035                 3040                 3045

Phe Val  Cys Asp Glu Asp Asn  Asp Cys Gly Asp Gly  Ser Asp Glu
    3050                 3055                 3060

Leu Met  His Leu Cys His Thr  Pro Glu Pro Thr Cys  Pro Pro His
    3065                 3070                 3075

Glu Phe  Lys Cys Asp Asn Gly  Arg Cys Ile Glu Met  Met Lys Leu
    3080                 3085                 3090

Cys Asn  His Leu Asp Asp Cys  Leu Asp Asn Ser Asp  Glu Lys Gly
    3095                 3100                 3105

Cys Gly  Ile Asn Glu Cys His  Asp Pro Ser Ile Ser  Gly Cys Asp
    3110                 3115                 3120

His Asn  Cys Thr Asp Thr Leu  Thr Ser Phe Tyr Cys  Ser Cys Arg
    3125                 3130                 3135

Pro Gly  Tyr Lys Leu Met Ser  Asp Lys Arg Thr Cys  Val Asp Ile
    3140                 3145                 3150

Asp Glu  Cys Thr Glu Met Pro  Phe Val Cys Ser Gln  Lys Cys Glu
    3155                 3160                 3165

Asn Val  Ile Gly Ser Tyr Ile  Cys Lys Cys Ala Pro  Gly Tyr Leu
    3170                 3175                 3180

Arg Glu  Pro Asp Gly Lys Thr  Cys Arg Gln Asn Ser  Asn Ile Glu
    3185                 3190                 3195

Pro Tyr  Leu Ile Phe Ser Asn  Arg Tyr Tyr Leu Arg  Asn Leu Thr
    3200                 3205                 3210

Ile Asp  Gly Tyr Phe Tyr Ser  Leu Ile Leu Glu Gly  Leu Asp Asn
    3215                 3220                 3225

Val Val  Ala Leu Asp Phe Asp  Arg Val Glu Lys Arg  Leu Tyr Trp
    3230                 3235                 3240

Ile Asp  Thr Gln Arg Gln Val  Ile Glu Arg Met Phe  Leu Asn Lys
    3245                 3250                 3255

Thr Asn  Lys Glu Thr Ile Ile  Asn His Arg Leu Pro  Ala Ala Glu
```

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    3260                3265                3270

Ser Leu  Ala Val Asp Trp Val  Ser Arg Lys Leu Tyr  Trp Leu Asp
    3275                3280                3285

Ala Arg  Leu Asp Gly Leu Phe  Val Ser Asp Leu Asn  Gly Gly His
    3290                3295                3300

Arg Arg  Met Leu Ala Gln His  Cys Val Asp Ala Asn  Asn Thr Phe
    3305                3310                3315

Cys Phe  Asp Asn Pro Arg Gly  Leu Ala Leu His Pro  Gln Tyr Gly
    3320                3325                3330

Tyr Leu  Tyr Trp Ala Asp Trp  Gly His Arg Ala Tyr  Ile Gly Arg
    3335                3340                3345

Val Gly  Met Asp Gly Thr Asn  Lys Ser Val Ile Ile  Ser Thr Lys
    3350                3355                3360

Leu Glu  Trp Pro Asn Gly Ile  Thr Ile Asp Tyr Thr  Asn Asp Leu
    3365                3370                3375

Leu Tyr  Trp Ala Asp Ala His  Leu Gly Tyr Ile Glu  Tyr Ser Asp
    3380                3385                3390

Leu Glu  Gly His His Arg His  Thr Val Tyr Asp Gly  Ala Leu Pro
    3395                3400                3405

His Pro  Phe Ala Ile Thr Ile  Phe Glu Asp Thr Ile  Tyr Trp Thr
    3410                3415                3420

Asp Trp  Asn Thr Arg Thr Val  Glu Lys Gly Asn Lys  Tyr Asp Gly
    3425                3430                3435

Ser Asn  Arg Gln Thr Leu Val  Asn Thr Thr His Arg  Pro Phe Asp
    3440                3445                3450

Ile His  Val Tyr His Pro Tyr  Arg Gln Pro Ile Val  Ser Asn Pro
    3455                3460                3465

Cys Gly  Thr Asn Asn Gly Gly  Cys Ser His Leu Cys  Leu Ile Lys
    3470                3475                3480

Pro Gly  Gly Lys Gly Phe Thr  Cys Glu Cys Pro Asp  Asp Phe Arg
    3485                3490                3495

Thr Leu  Gln Leu Ser Gly Ser  Thr Tyr Cys Met Pro  Met Cys Ser
    3500                3505                3510

Ser Thr  Gln Phe Leu Cys Ala  Asn Asn Glu Lys Cys  Ile Pro Ile
    3515                3520                3525

Trp Trp  Lys Cys Asp Gly Gln  Lys Asp Cys Ser Asp  Gly Ser Asp
    3530                3535                3540

Glu Leu  Ala Leu Cys Pro Gln  Arg Phe Cys Arg Leu  Gly Gln Phe
    3545                3550                3555

Gln Cys  Ser Asp Gly Asn Cys  Thr Ser Pro Gln Thr  Leu Cys Asn
    3560                3565                3570

Ala His  Gln Asn Cys Pro Asp  Gly Ser Asp Glu Asp  Arg Leu Leu
    3575                3580                3585

Cys Glu  Asn His His Cys Asp  Ser Asn Glu Trp Gln  Cys Ala Asn
    3590                3595                3600

Lys Arg  Cys Ile Pro Glu Ser  Trp Gln Cys Asp Thr  Phe Asn Asp
    3605                3610                3615

Cys Glu  Asp Asn Ser Asp Glu  Asp Ser Ser His Cys  Ala Ser Arg
    3620                3625                3630

Thr Cys  Arg Pro Gly Gln Phe  Arg Cys Ala Asn Gly  Arg Cys Ile
    3635                3640                3645

Pro Gln  Ala Trp Lys Cys Asp  Val Asp Asn Asp Cys  Gly Asp His
    3650                3655                3660
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Ser Asp  Glu Pro Ile Glu Glu  Cys Met Ser Ser Ala  His Leu Cys
    3665                 3670                 3675

Asp Asn  Phe Thr Glu Phe Ser  Cys Lys Thr Asn Tyr  Arg Cys Ile
    3680                 3685                 3690

Pro Lys  Trp Ala Val Cys Asn  Gly Val Asp Asp Cys  Arg Asp Asn
    3695                 3700                 3705

Ser Asp  Glu Gln Gly Cys Glu  Glu Arg Thr Cys His  Pro Val Gly
    3710                 3715                 3720

Asp Phe  Arg Cys Lys Asn His  His Cys Ile Pro Leu  Arg Trp Gln
    3725                 3730                 3735

Cys Asp  Gly Gln Asn Asp Cys  Gly Asp Asn Ser Asp  Glu Glu Asn
    3740                 3745                 3750

Cys Ala  Pro Arg Glu Cys Thr  Glu Ser Glu Phe Arg  Cys Val Asn
    3755                 3760                 3765

Gln Gln  Cys Ile Pro Ser Arg  Trp Ile Cys Asp His  Tyr Asn Asp
    3770                 3775                 3780

Cys Gly  Asp Asn Ser Asp Glu  Arg Asp Cys Glu Met  Arg Thr Cys
    3785                 3790                 3795

His Pro  Glu Tyr Phe Gln Cys  Thr Ser Gly His Cys  Val His Ser
    3800                 3805                 3810

Glu Leu  Lys Cys Asp Gly Ser  Ala Asp Cys Leu Asp  Ala Ser Asp
    3815                 3820                 3825

Glu Ala  Asp Cys Pro Thr Arg  Phe Pro Asp Gly Ala  Tyr Cys Gln
    3830                 3835                 3840

Ala Thr  Met Phe Glu Cys Lys  Asn His Val Cys Ile  Pro Pro Tyr
    3845                 3850                 3855

Trp Lys  Cys Asp Gly Asp Asp  Asp Cys Gly Asp Gly  Ser Asp Glu
    3860                 3865                 3870

Glu Leu  His Leu Cys Leu Asp  Val Pro Cys Asn Ser  Pro Asn Arg
    3875                 3880                 3885

Phe Arg  Cys Asp Asn Asn Arg  Cys Ile Tyr Ser His  Glu Val Cys
    3890                 3895                 3900

Asn Gly  Val Asp Asp Cys Gly  Asp Gly Thr Asp Glu  Thr Glu Glu
    3905                 3910                 3915

His Cys  Arg Lys Pro Thr Pro  Lys Pro Cys Thr Glu  Tyr Glu Tyr
    3920                 3925                 3930

Lys Cys  Gly Asn Gly His Cys  Ile Pro His Asp Asn  Val Cys Asp
    3935                 3940                 3945

Asp Ala  Asp Asp Cys Gly Asp  Trp Ser Asp Glu Leu  Gly Cys Asn
    3950                 3955                 3960

Lys Gly  Lys Glu Arg Thr Cys  Ala Glu Asn Ile Cys  Glu Gln Asn
    3965                 3970                 3975

Cys Thr  Gln Leu Asn Glu Gly  Gly Phe Ile Cys Ser  Cys Thr Ala
    3980                 3985                 3990

Gly Phe  Glu Thr Asn Val Phe  Asp Arg Thr Ser Cys  Leu Asp Ile
    3995                 4000                 4005

Asn Glu  Cys Glu Gln Phe Gly  Thr Cys Pro Gln His  Cys Arg Asn
    4010                 4015                 4020

Thr Lys  Gly Ser Tyr Glu Cys  Val Cys Ala Asp Gly  Phe Thr Ser
    4025                 4030                 4035

Met Ser  Asp Arg Pro Gly Lys  Arg Cys Ala Ala Glu  Gly Ser Ser
    4040                 4045                 4050

Pro Leu  Leu Leu Leu Pro Asp  Asn Val Arg Ile Arg  Lys Tyr Asn
    4055                 4060                 4065
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Leu Ser  Ser Glu Arg Phe Ser  Glu Tyr Leu Gln Asp  Glu Glu Tyr
    4070                 4075                 4080

Ile Gln  Ala Val Asp Tyr Asp  Trp Asp Pro Lys Asp  Ile Gly Leu
    4085                 4090                 4095

Ser Val  Val Tyr Tyr Thr Val  Arg Gly Glu Gly Ser  Arg Phe Gly
    4100                 4105                 4110

Ala Ile  Lys Arg Ala Tyr Ile  Pro Asn Phe Glu Ser  Gly Arg Asn
    4115                 4120                 4125

Asn Leu  Val Gln Glu Val Asp  Leu Lys Leu Lys Tyr  Val Met Gln
    4130                 4135                 4140

Pro Asp  Gly Ile Ala Val Asp  Trp Val Gly Arg His  Ile Tyr Trp
    4145                 4150                 4155

Ser Asp  Val Lys Asn Lys Arg  Ile Glu Val Ala Lys  Leu Asp Gly
    4160                 4165                 4170

Arg Tyr  Arg Lys Trp Leu Ile  Ser Thr Asp Leu Asp  Gln Pro Ala
    4175                 4180                 4185

Ala Ile  Ala Val Asn Pro Lys  Leu Gly Leu Met Phe  Trp Thr Asp
    4190                 4195                 4200

Trp Gly  Lys Glu Pro Lys Ile  Glu Ser Ala Trp Met  Asn Gly Glu
    4205                 4210                 4215

Asp Arg  Asn Ile Leu Val Phe  Glu Asp Leu Gly Trp  Pro Thr Gly
    4220                 4225                 4230

Leu Ser  Ile Asp Tyr Leu Asn  Asn Asp Arg Ile Tyr  Trp Ser Asp
    4235                 4240                 4245

Phe Lys  Glu Asp Val Ile Glu  Thr Ile Lys Tyr Asp  Gly Thr Asp
    4250                 4255                 4260

Arg Arg  Val Ile Ala Lys Glu  Ala Met Asn Pro Tyr  Ser Leu Asp
    4265                 4270                 4275

Ile Phe  Glu Asp Gln Leu Tyr  Trp Ile Ser Lys Glu  Lys Gly Glu
    4280                 4285                 4290

Val Trp  Lys Gln Asn Lys Phe  Gly Gln Gly Lys Lys  Glu Lys Thr
    4295                 4300                 4305

Leu Val  Val Asn Pro Trp Leu  Thr Gln Val Arg Ile  Phe His Gln
    4310                 4315                 4320

Leu Arg  Tyr Asn Lys Ser Val  Pro Asn Leu Cys Lys  Gln Ile Cys
    4325                 4330                 4335

Ser His  Leu Cys Leu Leu Arg  Pro Gly Gly Tyr Ser  Cys Ala Cys
    4340                 4345                 4350

Pro Gln  Gly Ser Ser Phe Ile  Glu Gly Ser Thr Thr  Glu Cys Asp
    4355                 4360                 4365

Ala Ala  Ile Glu Leu Pro Ile  Asn Leu Pro Pro Pro  Cys Arg Cys
    4370                 4375                 4380

Met His  Gly Gly Asn Cys Tyr  Phe Asp Glu Thr Asp  Leu Pro Lys
    4385                 4390                 4395

Cys Lys  Cys Pro Ser Gly Tyr  Thr Gly Lys Tyr Cys  Glu Met Ala
    4400                 4405                 4410

Phe Ser  Lys Gly Ile Ser Pro  Gly Thr Thr Ala Val  Ala Val Leu
    4415                 4420                 4425

Leu Thr  Ile Leu Leu Ile Val  Val Ile Gly Ala Leu  Ala Ile Ala
    4430                 4435                 4440

Gly Phe  Phe His Tyr Arg Arg  Thr Gly Ser Leu Leu  Pro Ala Leu
    4445                 4450                 4455

Pro Lys  Leu Pro Ser Leu Ser  Ser Leu Val Lys Pro  Ser Glu Asn
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    4460                4465                4470

Gly Asn  Gly Val Thr Phe Arg  Ser Gly Ala Asp Leu  Asn Met Asp
    4475                4480                4485

Ile Gly  Val Ser Gly Phe Gly  Pro Glu Thr Ala Ile  Asp Arg Ser
    4490                4495                4500

Met Ala  Met Ser Glu Asp Phe  Val Met Glu Met Gly  Lys Gln Pro
    4505                4510                4515

Ile Ile  Phe Glu Asn Pro Met  Tyr Ser Ala Arg Asp  Ser Ala Val
    4520                4525                4530

Lys Val  Val Gln Pro Ile Gln  Val Thr Val Ser Glu  Asn Val Asp
    4535                4540                4545

Asn Lys  Asn Tyr Gly Ser Pro  Ile Asn Pro Ser Glu  Ile Val Pro
    4550                4555                4560

Glu Thr  Asn Pro Thr Ser Pro  Ala Ala Asp Gly Thr  Gln Val Thr
    4565                4570                4575

Lys Trp  Asn Leu Phe Lys Arg  Lys Ser Lys Gln Thr  Thr Asn Phe
    4580                4585                4590

Glu Asn  Pro Ile Tyr Ala Gln  Met Glu Asn Glu Gln  Lys Glu Ser
    4595                4600                4605

Val Ala  Ala Thr Pro Pro Pro  Ser Pro Ser Leu Pro  Ala Lys Pro
    4610                4615                4620

Lys Pro  Pro Ser Arg Arg Asp  Pro Thr Pro Thr Tyr  Ser Ala Thr
    4625                4630                4635

Glu Asp  Thr Phe Lys Asp Thr  Ala Asn Leu Val Lys  Glu Asp Ser
    4640                4645                4650

Glu Val
    4655


<210> SEQ ID NO 18
<211> LENGTH: 134
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 18

Met Asp Thr Ser His Thr Thr Lys Ser Cys Leu Leu Ile Leu Leu Val
1               5                   10                  15

Ala Leu Leu Cys Ala Glu Arg Ala Gln Gly Leu Glu Cys Tyr Gln Cys
            20                  25                  30

Tyr Gly Val Pro Phe Glu Thr Ser Cys Pro Ser Ile Thr Cys Pro Tyr
        35                  40                  45

Pro Asp Gly Val Cys Val Thr Gln Glu Ala Ala Val Ile Val Asp Ser
    50                  55                  60

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

Asn Ile Glu Ser Met Glu Ile Leu Gly Thr Lys Val Asn Val Lys Thr
                85                  90                  95

Ser Cys Cys Gln Glu Asp Leu Cys Asn Val Ala Val Pro Asn Gly Gly
            100                 105                 110

Ser Thr Trp Thr Met Ala Gly Val Leu Leu Phe Ser Leu Ser Ser Val
        115                 120                 125

Leu Leu Gln Thr Leu Leu
    130


<210> SEQ ID NO 19
<211> LENGTH: 339
<212> TYPE: PRT
```

<213> ORGANISM: Mus musculus

<400> SEQUENCE: 19

```
Met Ala Gly Cys Cys Ser Val Leu Gly Ser Phe Leu Phe Glu Tyr Asp
1               5                   10                  15

Thr Pro Arg Ile Val Leu Ile Arg Ser Arg Lys Val Gly Leu Met Asn
            20                  25                  30

Arg Val Val Gln Leu Leu Ile Leu Ala Tyr Val Ile Gly Trp Val Phe
        35                  40                  45

Val Trp Glu Lys Gly Tyr Gln Glu Thr Asp Ser Val Val Ser Ser Val
    50                  55                  60

Thr Thr Lys Ala Lys Gly Val Ala Val Thr Asn Thr Ser Gln Leu Gly
65                  70                  75                  80

Phe Arg Ile Trp Asp Val Ala Asp Tyr Val Val Pro Ala Gln Glu Glu
                85                  90                  95

Asn Ser Leu Phe Ile Met Thr Asn Met Ile Val Thr Val Asn Gln Thr
            100                 105                 110

Gln Gly Thr Cys Pro Glu Ile Pro Asp Lys Thr Ser Ile Cys Asp Ser
        115                 120                 125

Asp Ala Asn Cys Thr Leu Gly Ser Ser Asp Thr His Ser Ser Gly Ile
    130                 135                 140

Gly Thr Gly Arg Cys Val Pro Phe Asn Ala Ser Val Lys Thr Cys Glu
145                 150                 155                 160

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

Asn Ile Leu Pro Asn Ile Thr Thr Ser Tyr Leu Lys Ser Cys Ile Tyr
            180                 185                 190

Asn Ala Arg Thr Asp Pro Phe Cys Pro Ile Phe Arg Leu Gly Gln Ile
        195                 200                 205

Val Ala Asp Ala Gly His Ser Phe Gln Glu Met Ala Val Glu Gly Gly
    210                 215                 220

Ile Met Gly Ile Gln Ile Lys Trp Asp Cys Asn Leu Asp Arg Ala Ala
225                 230                 235                 240

Ser His Cys Leu Pro Arg Tyr Ser Phe Arg Arg Leu Asp Thr Arg Asp
                245                 250                 255

Leu Glu His Asn Val Ser Pro Gly Tyr Asn Phe Arg Phe Ala Lys Tyr
            260                 265                 270

Tyr Arg Asp Leu Ala Gly Asn Glu Gln Arg Thr Leu Thr Lys Ala Tyr
        275                 280                 285

Gly Ile Arg Phe Asp Ile Ile Val Phe Gly Lys Ala Thr Val Leu Cys
    290                 295                 300

Asp Val Ile Val Leu Tyr Cys Met Lys Lys Arg Tyr Tyr Tyr Arg Asp
305                 310                 315                 320

Lys Lys Tyr Lys Tyr Val Glu Asp Tyr Glu Gln Gly Leu Ser Gly Glu
                325                 330                 335

Met Asn Gln
```

<210> SEQ ID NO 20
<211> LENGTH: 388
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

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

Arg Ala Val Gln Leu Leu Ile Leu Ala Tyr Val Ile Gly Trp Val Phe
        35                  40                  45

Val Trp Glu Lys Gly Tyr Gln Glu Thr Asp Ser Val Val Ser Ser Val
    50                  55                  60

Thr Thr Lys Val Lys Gly Val Ala Val Thr Asn Thr Ser Lys Leu Gly
65                  70                  75                  80

Phe Arg Ile Trp Asp Val Ala Asp Tyr Val Ile Pro Ala Gln Glu Glu
                85                  90                  95

Asn Ser Leu Phe Val Met Thr Asn Val Ile Leu Thr Met Asn Gln Thr
            100                 105                 110

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

Asp Ala Ser Cys Thr Ala Gly Ser Ala Gly Thr His Ser Asn Gly Val
    130                 135                 140

Ser Thr Gly Arg Cys Val Ala Phe Asn Gly Ser Val Lys Thr Cys Glu
145                 150                 155                 160

Val Ala Ala Trp Cys Pro Val Glu Asp Asp Thr His Val Pro Gln Pro
                165                 170                 175

Ala Phe Leu Lys Ala Ala Glu Asn Phe Thr Leu Leu Val Lys Asn Asn
            180                 185                 190

Ile Trp Tyr Pro Lys Phe Asn Phe Ser Lys Arg Asn Ile Leu Pro Asn
        195                 200                 205

Ile Thr Thr Thr Tyr Leu Lys Ser Cys Ile Tyr Asp Ala Lys Thr Asp
    210                 215                 220

Pro Phe Cys Pro Ile Phe Arg Leu Gly Lys Ile Val Glu Asn Ala Gly
225                 230                 235                 240

His Ser Phe Gln Asp Met Ala Val Glu Gly Gly Ile Met Gly Ile Gln
                245                 250                 255

Val Asn Trp Asp Cys Asn Leu Asp Arg Ala Ala Ser Leu Cys Leu Pro
            260                 265                 270

Arg Tyr Ser Phe Arg Arg Leu Asp Thr Arg Asp Val Glu His Asn Val
        275                 280                 285

Ser Pro Gly Tyr Asn Phe Arg Phe Ala Lys Tyr Tyr Arg Asp Leu Ala
    290                 295                 300

Gly Asn Glu Gln Arg Thr Leu Ile Lys Ala Tyr Gly Ile Arg Phe Asp
305                 310                 315                 320

Ile Ile Val Phe Gly Lys Ala Gly Lys Phe Asp Ile Ile Pro Thr Met
                325                 330                 335

Ile Asn Ile Gly Ser Gly Leu Ala Leu Leu Gly Met Ala Thr Val Leu
            340                 345                 350

Cys Asp Ile Ile Val Leu Tyr Cys Met Lys Lys Arg Leu Tyr Tyr Arg
        355                 360                 365

Glu Lys Lys Tyr Lys Tyr Val Glu Asp Tyr Glu Gln Gly Leu Ala Ser
    370                 375                 380

Glu Leu Asp Gln
385


<210> SEQ ID NO 21
<211> LENGTH: 828
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 21
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```
Met Ser Asn Thr Val Lys Ile Pro Pro Lys Arg Glu Ser Glu Phe Ser
1               5                   10                  15

Val Ser Lys His Leu Glu Thr Ala Thr Gly Leu Asp Ala Ser Met His
            20                  25                  30

Phe Leu Ile Met Glu Lys Leu Gly Arg Ile His Leu Asn Arg Gln Val
        35                  40                  45

Met Ala Phe Ile Phe Met Met Val Leu Val Gln Val Cys Ser Glu Pro
    50                  55                  60

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

Ala His Leu Ala Lys Asp Leu Gly Leu Gly Ala Arg Glu Leu Ala Ala
                85                  90                  95

Arg Ser Ala Arg Val Leu Ser Asp Asp Tyr Lys Gln Arg Leu Leu Leu
            100                 105                 110

Asp Pro Glu Thr Gly Asp Leu Leu Leu Arg Glu Lys Val Asp Arg Glu
        115                 120                 125

Glu Val Cys Ser Thr Val Asp Pro Cys Val Leu His Phe Gln Val Thr
    130                 135                 140

Leu Glu Lys Pro Val Gln Tyr Phe Gln Arg Glu Leu Leu Ile Gln Asp
145                 150                 155                 160

Ile Asn Asp His Ala Pro Glu Phe Pro Asp Arg Glu Leu Leu Leu Arg
                165                 170                 175

Ile Pro Glu Asn Ser Gln Gln Gly Thr Gln Phe Ser Leu Asn Leu Ala
            180                 185                 190

Gln Asp Leu Asp Val Gly Ser Asn Gly Leu Gln Gln Tyr Thr Val Ser
        195                 200                 205

Pro Asn Pro Tyr Phe His Val Leu Thr Gln Asn Asn Ser Lys Gly Lys
    210                 215                 220

Lys Tyr Pro Glu Leu Val Gln Asp Arg Gly Leu Asp Arg Glu Glu Gln
225                 230                 235                 240

Ala Glu Leu Ser Leu Thr Leu Thr Ala Leu Asp Gly Gly Ser Pro Pro
                245                 250                 255

Arg Ser Gly Thr Ala Leu Val Arg Ile Leu Ile Met Asp Ile Asn Asp
            260                 265                 270

Asn Ala Pro Glu Phe Val Asn Ser Pro Tyr Glu Val Gln Val Leu Glu
        275                 280                 285

Ser Ser Pro Pro Asp Ser Pro Val Leu Thr Val Leu Ala Arg Asp Ala
    290                 295                 300

Asp Ala Gly Asn Phe Gly Arg Val Ser Tyr Gly Phe Phe Gln Ala Ser
305                 310                 315                 320

Asp Glu Ile Gln Gln Thr Phe Ser Ile Asn Ala Thr Ser Gly Asp Met
                325                 330                 335

Arg Leu Lys Lys Lys Leu Asp Phe Glu Lys Ile Lys Ser Tyr His Val
            340                 345                 350

Glu Ile Glu Ala Ile Asp Gly Gly Gly Leu Ser Gly Lys Gly Ser Val
        355                 360                 365

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

Ser Ser Leu Thr Ser Ser Val Pro Glu Asn Ala Pro Glu Thr Ile Ile
385                 390                 395                 400

Ser Ile Phe Arg Val Gly Asp Arg Asp Ser Gly Glu Asn Gly Lys Met
                405                 410                 415

Val Cys Ser Ile Pro Glu Asn Leu Pro Phe Ile Leu Lys Ser Thr Phe
            420                 425                 430
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Lys Asn Phe Tyr Thr Leu Val Thr Glu Ser Pro Leu Asp Arg Glu Ser
        435                 440                 445

Arg Ala Glu Tyr Asn Ile Thr Ile Met Val Ser Asp Met Gly Thr Pro
    450                 455                 460

Arg Leu Thr Thr Trp His Thr Ile Lys Val Gln Val Ser Asp Ile Asn
465                 470                 475                 480

Asp Asn Thr Pro Ala Phe Thr Gln Thr Ser Tyr Thr Met Phe Val Arg
                485                 490                 495

Glu Asn Asn Ser Pro Ala Leu His Ile Gly Thr Ile Ser Ala Thr Asp
            500                 505                 510

Ser Asp Ser Gly Ser Asn Ala His Ile Thr Tyr Ser Leu Leu Pro Pro
        515                 520                 525

His Asp Pro Glu Leu Ala Leu Ser Ser Leu Ile Ser Ile Asn Ala Asp
    530                 535                 540

Asn Gly Gln Leu Phe Ala Leu Arg Ala Leu Asp Tyr Glu Ala Leu Gln
545                 550                 555                 560

Val Phe Glu Phe His Val Gly Ala Thr Asp Gly Gly Ser Pro Pro Leu
                565                 570                 575

Ser Ser Gln Ala Leu Val Arg Val Val Val Leu Asp Asp Asn Asp Asn
            580                 585                 590

Ala Pro Phe Val Leu Tyr Pro Met Gln Asn Ala Ser Ala Pro Phe Thr
        595                 600                 605

Glu Leu Leu Pro Arg Ala Ala Glu Pro Gly Tyr Leu Val Thr Lys Val
    610                 615                 620

Val Ala Val Asp Arg Asp Ser Gly Gln Asn Ala Trp Leu Ser Phe Gln
625                 630                 635                 640

Leu Leu Lys Ala Thr Glu Pro Gly Leu Phe Ser Val Trp Ala His Asn
                645                 650                 655

Gly Glu Val Arg Thr Thr Arg Leu Leu Ser Glu Arg Asp Val Pro Lys
            660                 665                 670

His Arg Leu Leu Leu Val Val Lys Asp Asn Gly Glu Pro Gln Arg Ser
        675                 680                 685

Ala Ser Val Thr Leu Gln Val Leu Leu Val Asp Gly Phe Ser Gln Ser
    690                 695                 700

Tyr Leu Pro Leu Pro Glu Val Ala Arg Asp Pro Ala His Glu Asp Glu
705                 710                 715                 720

Asp Val Leu Thr Leu Tyr Leu Val Ile Ala Leu Ala Ser Val Ser Ser
                725                 730                 735

Leu Phe Leu Leu Ser Val Leu Leu Phe Val Gly Val Arg Leu Cys Arg
            740                 745                 750

Arg Ala Arg Glu Val Ser Leu Gly Gly Cys Ser Met Pro Gly Glu His
        755                 760                 765

Phe Pro Gly His Leu Val Asp Val Ser Gly Ala Gly Thr Leu Ser Gln
    770                 775                 780

Ser Tyr Gln Tyr Glu Val Cys Leu Arg Gly Asp Ser Gly Thr Gly Glu
785                 790                 795                 800

Phe Lys Phe Leu Lys Pro Met Ile Pro Asn Ala Gly Ile Glu Ile Met
                805                 810                 815

Glu Ser Pro His Cys Arg Asp Ser Phe Val Phe Asn
            820                 825
```

<210> SEQ ID NO 22
<211> LENGTH: 796
<212> TYPE: PRT

```
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

Lys Thr Arg Gly Phe Ser Phe Pro Arg Gln Arg Gln Val Leu Phe Leu
1               5                   10                  15

Phe Leu Phe Trp Gly Val Ser Leu Ala Gly Ser Gly Phe Gly Arg Tyr
            20                  25                  30

Ser Val Thr Glu Glu Thr Glu Lys Gly Ser Phe Val Val Asn Leu Ala
        35                  40                  45

Lys Asp Leu Gly Leu Ala Glu Gly Glu Leu Ala Ala Arg Gly Thr Arg
    50                  55                  60

Val Val Ser Asp Asp Asn Lys Gln Tyr Leu Leu Leu Asp Ser His Thr
65                  70                  75                  80

Gly Asn Leu Leu Thr Asn Glu Lys Leu Asp Arg Glu Lys Leu Cys Gly
                85                  90                  95

Pro Lys Glu Pro Cys Met Leu Tyr Phe Gln Ile Leu Met Asp Asp Pro
            100                 105                 110

Phe Gln Ile Tyr Arg Ala Glu Leu Arg Val Arg Asp Ile Asn Asp His
        115                 120                 125

Ser Pro Val Phe Arg His Lys Glu Met Val Leu Lys Ile Ser Glu Asn
    130                 135                 140

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

Glu Gly His Asn Ser Ile Gln Asn Tyr Thr Ile Ser Ser Asn Ser Phe
                165                 170                 175

Phe His Ile Lys Ile Ser Gly Ser Asp Glu Gly Met Ile Tyr Pro Glu
            180                 185                 190

Leu Val Leu Asp Lys Ala Leu Asp Arg Glu Glu Gln Glu Glu Leu Ser
        195                 200                 205

Leu Thr Leu Thr Ala Leu Asp Gly Gly Ser Pro Ser Arg Ser Gly Thr
    210                 215                 220

Ser Thr Ile Arg Ile Val Val Leu Asp Val Asn Asp Asn Ala Pro Gln
225                 230                 235                 240

Phe Ala Gln Ala Leu Tyr Glu Thr Gln Ala Pro Glu Asn Ser Pro Val
                245                 250                 255

Gly Ser Leu Ile Val Lys Val Ser Ala Gly Asp Ala Asp Ser Gly Val
            260                 265                 270

Asn Ala Glu Val Ser Tyr Ser Phe Phe Asp Ala Ser Glu Asp Ile Leu
        275                 280                 285

Thr Thr Phe Gln Ile Asn Pro Phe Ser Gly Glu Ile Phe Leu Arg Glu
    290                 295                 300

Leu Leu Asp Tyr Glu Leu Val Asn Ser Tyr Lys Ile Asn Ile Gln Ala
305                 310                 315                 320

Met Asp Gly Gly Gly Leu Ser Ala Arg Cys Thr Val Leu Ile Lys Val
                325                 330                 335

Leu Asp Ser Asn Asp Asn Pro Pro Glu Leu Ile Ile Ser Ser Leu Ser
            340                 345                 350

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

Ile Lys Asp Arg Asp Ser Gly Glu Asn Gly Lys Thr Ile Cys Tyr Val
    370                 375                 380

Gln Asp Asn Leu Pro Phe Phe Leu Lys Pro Ser Val Asp Asn Phe Tyr
385                 390                 395                 400

Ile Leu Met Thr Glu Gly Ala Leu Asp Arg Glu Ser Lys Ala Glu Tyr
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```
                405                 410                 415

Asn Ile Thr Ile Thr Val Thr Asp Leu Gly Thr Pro Arg Leu Lys Thr
            420                 425                 430

Glu His Ser Ile Thr Leu Gln Val Ser Asp Val Asn Asp Asn Ala Pro
        435                 440                 445

Ala Phe Thr Gln Thr Ser Tyr Thr Leu Phe Val Arg Glu Asn Asn Ser
    450                 455                 460

Pro Ala Leu His Ile Gly Ser Val Ser Ala Thr Asp Arg Asp Ser Gly
465                 470                 475                 480

Thr Asn Ala Gln Val Thr Tyr Ser Leu Leu Pro Pro Gln Asp Pro His
                485                 490                 495

Leu Pro Leu Ala Ser Leu Val Ser Ile Asn Ala Asp Asn Gly His Leu
            500                 505                 510

Phe Ala Leu Arg Ser Leu Asp Tyr Glu Ala Leu Gln Ala Phe Asp Phe
        515                 520                 525

Arg Val Gly Ala Ser Asp Arg Gly Ser Pro Ala Leu Ser Ser Glu Ala
    530                 535                 540

Leu Val Arg Val Leu Val Leu Asp Ala Asn Asp Asn Ser Pro Phe Val
545                 550                 555                 560

Leu Tyr Pro Leu Gln Asn Gly Ser Ala Pro Cys Thr Glu Leu Val Pro
                565                 570                 575

Arg Ala Ala Glu Pro Gly Tyr Leu Val Thr Lys Val Val Ala Val Asp
            580                 585                 590

Gly Asp Ser Gly Gln Asn Ala Trp Leu Ser Tyr Gln Leu Leu Lys Ala
        595                 600                 605

Thr Glu Pro Gly Leu Phe Gly Val Trp Ala His Asn Gly Glu Val Arg
    610                 615                 620

Thr Ala Arg Leu Leu Ser Glu Arg Asp Ala Ala Lys His Arg Leu Val
625                 630                 635                 640

Val Leu Val Lys Asp Asn Gly Glu Pro Pro Arg Ser Ala Thr Ala Thr
                645                 650                 655

Leu His Val Leu Leu Val Asp Gly Phe Ser Gln Pro Tyr Leu Pro Leu
            660                 665                 670

Pro Glu Ala Ala Pro Ala Gln Ala Gln Ala Asp Leu Leu Thr Val Tyr
        675                 680                 685

Pro Val Val Ala Leu Ala Ser Val Ser Ser Leu Phe Leu Leu Ser Val
    690                 695                 700

Leu Leu Phe Val Ala Val Arg Leu Cys Arg Arg Ser Arg Ala Ala Ser
705                 710                 715                 720

Val Gly Arg Cys Ser Val Pro Glu Gly Pro Phe Pro Gly His Leu Val
                725                 730                 735

Asp Val Ser Gly Thr Gly Thr Leu Phe Gln Ser Tyr Gln Tyr Glu Val
            740                 745                 750

Cys Leu Thr Gly Gly Ser Glu Thr Gly Glu Phe Lys Phe Leu Lys Pro
        755                 760                 765

Ile Thr Pro His Leu Pro Pro His Arg Gly Gly Lys Glu Ile Glu Glu
    770                 775                 780

Asn Ser Thr Leu Pro Asn Ser Phe Gly Phe Asn Tyr
785                 790                 795
```

<210> SEQ ID NO 23
<211> LENGTH: 699
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 23

```
Met Glu Pro Phe Cys Pro Leu Leu Leu Ala Ser Phe Ser Leu Ser Leu
1               5                   10                  15

Ala Arg Ala Gly Gln Gly Asn Asp Thr Thr Pro Thr Glu Ser Asn Trp
            20                  25                  30

Thr Ser Thr Thr Ala Gly Pro Pro Asp Pro Gly Ala Ser Gln Pro Leu
        35                  40                  45

Leu Thr Trp Leu Leu Leu Pro Leu Leu Leu Leu Leu Phe Leu Leu Ala
    50                  55                  60

Ala Tyr Phe Phe Arg Phe Arg Lys Gln Arg Lys Ala Val Val Ser Ser
65                  70                  75                  80

Asn Asp Lys Lys Met Pro Asn Gly Ile Leu Glu Glu Gln Glu Gln Gln
                85                  90                  95

Arg Val Met Leu Leu Ser Arg Ser Pro Ser Gly Pro Lys Lys Phe Phe
            100                 105                 110

Pro Ile Pro Val Glu His Leu Glu Glu Glu Ile Arg Val Arg Ser Ala
        115                 120                 125

Asp Asp Cys Lys Arg Phe Arg Glu Glu Phe Asn Ser Leu Pro Ser Gly
    130                 135                 140

His Ile Gln Gly Thr Phe Glu Leu Ala Asn Lys Glu Glu Asn Arg Glu
145                 150                 155                 160

Lys Asn Arg Tyr Pro Asn Ile Leu Pro Asn Asp His Cys Arg Val Ile
                165                 170                 175

Leu Ser Gln Val Asp Gly Ile Pro Cys Ser Asp Tyr Ile Asn Ala Ser
            180                 185                 190

Tyr Ile Asp Gly Tyr Lys Glu Lys Asn Lys Phe Ile Ala Ala Gln Gly
        195                 200                 205

Pro Lys Gln Glu Thr Val Asn Asp Phe Trp Arg Met Val Trp Glu Gln
    210                 215                 220

Arg Ser Ala Thr Ile Val Met Leu Thr Asn Leu Lys Glu Arg Lys Glu
225                 230                 235                 240

Glu Lys Cys Tyr Gln Tyr Trp Pro Asp Gln Gly Cys Trp Thr Tyr Gly
                245                 250                 255

Asn Ile Arg Val Cys Val Glu Asp Cys Val Val Leu Val Asp Tyr Thr
            260                 265                 270

Ile Arg Lys Phe Cys Ile His Pro Gln Leu Pro Asp Ser Cys Lys Ala
        275                 280                 285

Pro Arg Leu Val Ser Gln Leu His Phe Thr Ser Trp Pro Asp Phe Gly
    290                 295                 300

Val Pro Phe Thr Pro Ile Gly Met Leu Lys Phe Leu Lys Lys Val Lys
305                 310                 315                 320

Thr Leu Asn Pro Ser His Ala Gly Pro Ile Val Val His Cys Ser Ala
                325                 330                 335

Gly Val Gly Arg Thr Gly Thr Phe Ile Val Ile Asp Ala Met Met Asp
            340                 345                 350

Met Ile His Ser Glu Gln Lys Val Asp Val Phe Glu Phe Val Ser Arg
        355                 360                 365

Ile Arg Asn Gln Arg Pro Gln Met Val Gln Thr Asp Val Gln Tyr Thr
    370                 375                 380

Phe Ile Tyr Gln Ala Leu Leu Glu Tyr Tyr Leu Tyr Gly Asp Thr Glu
385                 390                 395                 400

Leu Asp Val Ser Ser Leu Glu Arg His Leu Gln Thr Leu His Ser Thr
                405                 410                 415
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```
Ala Thr His Phe Asp Lys Ile Gly Leu Glu Glu Glu Phe Arg Lys Leu
            420                 425                 430

Thr Asn Val Arg Ile Met Lys Glu Asn Met Arg Thr Gly Asn Leu Pro
        435                 440                 445

Ala Asn Met Lys Lys Ala Arg Val Ile Gln Ile Ile Pro Tyr Asp Phe
    450                 455                 460

Asn Arg Val Ile Leu Ser Met Lys Arg Gly Gln Glu Phe Thr Asp Tyr
465                 470                 475                 480

Ile Asn Ala Ser Phe Ile Asp Gly Tyr Arg Gln Lys Asp Tyr Phe Met
                485                 490                 495

Ala Thr Gln Gly Pro Leu Ala His Thr Gly Glu Asp Phe Trp Arg Met
            500                 505                 510

Val Trp Glu Trp Lys Ser His Thr Ile Val Met Leu Thr Glu Val Gln
        515                 520                 525

Glu Arg Glu Gln Asp Lys Cys Tyr Gln Tyr Trp Pro Thr Glu Gly Ser
    530                 535                 540

Val Thr His Gly Asp Ile Thr Ile Glu Ile Lys Ser Asp Thr Leu Ser
545                 550                 555                 560

Glu Ala Ile Ser Val Arg Asp Phe Leu Val Thr Phe Lys Gln Pro Leu
                565                 570                 575

Ala Arg Gln Glu Glu Gln Val Arg Met Val Arg Gln Phe His Phe His
            580                 585                 590

Gly Trp Pro Glu Val Gly Ile Pro Ala Glu Gly Lys Gly Ile Ile Asp
        595                 600                 605

Leu Ile Ala Ala Val Gln Lys Gln Gln Gln Gln Thr Gly Asn His Pro
    610                 615                 620

Ile Thr Val His Cys Ser Ala Gly Ala Gly Arg Thr Gly Thr Phe Ile
625                 630                 635                 640

Ala Leu Ser Asn Ile Leu Glu Arg Val Lys Ala Glu Gly Leu Leu Asp
                645                 650                 655

Val Phe Gln Ala Val Lys Ser Leu Arg Leu Gln Arg Pro His Met Val
            660                 665                 670

Gln Thr Leu Glu Gln Tyr Glu Phe Cys Tyr Lys Val Val Gln Asp Phe
        675                 680                 685

Ile Asp Ile Phe Ser Asp Tyr Ala Asn Phe Lys
    690                 695


<210> SEQ ID NO 24
<211> LENGTH: 642
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24

Met Ser Asn Arg Ser Ser Phe Ser Arg Leu Thr Trp Phe Arg Lys Gln
1               5                   10                  15

Arg Lys Ala Val Val Ser Thr Ser Asp Lys Lys Met Pro Asn Gly Ile
            20                  25                  30

Leu Glu Glu Gln Glu Gln Gln Arg Val Met Leu Leu Ser Arg Ser Pro
        35                  40                  45

Ser Gly Pro Lys Lys Tyr Phe Pro Ile Pro Val Glu His Leu Glu Glu
    50                  55                  60

Glu Ile Arg Ile Arg Ser Ala Asp Asp Cys Lys Gln Phe Arg Glu Glu
65                  70                  75                  80

Phe Asn Ser Leu Pro Ser Gly His Ile Gln Gly Thr Phe Glu Leu Ala
                85                  90                  95
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-continued

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Asn Lys Glu Glu Asn Arg Glu Lys Asn Arg Tyr Pro Asn Ile Leu Pro
            100                 105                 110

Asn Asp His Ser Arg Val Ile Leu Ser Gln Leu Asp Gly Ile Pro Cys
        115                 120                 125

Ser Asp Tyr Ile Asn Ala Ser Tyr Ile Asp Gly Tyr Lys Glu Lys Asn
    130                 135                 140

Lys Phe Ile Ala Ala Gln Gly Pro Lys Gln Glu Thr Val Asn Asp Phe
145                 150                 155                 160

Trp Arg Met Val Trp Glu Gln Lys Ser Ala Thr Ile Val Met Leu Thr
                165                 170                 175

Asn Leu Lys Glu Arg Lys Glu Glu Lys Cys His Gln Tyr Trp Pro Asp
            180                 185                 190

Gln Gly Cys Trp Thr Tyr Gly Asn Ile Arg Val Cys Val Glu Asp Cys
        195                 200                 205

Val Val Leu Val Asp Tyr Thr Ile Arg Lys Phe Cys Ile Gln Pro Gln
    210                 215                 220

Leu Pro Asp Gly Cys Lys Ala Pro Arg Leu Val Ser Gln Leu His Phe
225                 230                 235                 240

Thr Ser Trp Pro Asp Phe Gly Val Pro Phe Thr Pro Ile Gly Met Leu
                245                 250                 255

Lys Phe Leu Lys Lys Val Lys Thr Leu Asn Pro Val His Ala Gly Pro
            260                 265                 270

Ile Val Val His Cys Ser Ala Gly Val Gly Arg Thr Gly Thr Phe Ile
        275                 280                 285

Val Ile Asp Ala Met Met Ala Met Met His Ala Glu Gln Lys Val Asp
    290                 295                 300

Val Phe Glu Phe Val Ser Arg Ile Arg Asn Gln Arg Pro Gln Met Val
305                 310                 315                 320

Gln Thr Asp Met Gln Tyr Thr Phe Ile Tyr Gln Ala Leu Leu Glu Tyr
                325                 330                 335

Tyr Leu Tyr Gly Asp Thr Glu Leu Asp Val Ser Ser Leu Glu Lys His
            340                 345                 350

Leu Gln Thr Met His Gly Thr Thr Thr His Phe Asp Lys Ile Gly Leu
        355                 360                 365

Glu Glu Glu Phe Arg Lys Leu Thr Asn Val Arg Ile Met Lys Glu Asn
    370                 375                 380

Met Arg Thr Gly Asn Leu Pro Ala Asn Met Lys Lys Ala Arg Val Ile
385                 390                 395                 400

Gln Ile Ile Pro Tyr Asp Phe Asn Arg Val Ile Leu Ser Met Lys Arg
                405                 410                 415

Gly Gln Glu Tyr Thr Asp Tyr Ile Asn Ala Ser Phe Ile Asp Gly Tyr
            420                 425                 430

Arg Gln Lys Asp Tyr Phe Ile Ala Thr Gln Gly Pro Leu Ala His Thr
        435                 440                 445

Val Glu Asp Phe Trp Arg Met Ile Trp Glu Trp Lys Ser His Thr Ile
    450                 455                 460

Val Met Leu Thr Glu Val Gln Glu Arg Glu Gln Asp Lys Cys Tyr Gln
465                 470                 475                 480

Tyr Trp Pro Thr Glu Gly Ser Val Thr His Gly Glu Ile Thr Ile Glu
                485                 490                 495

Ile Lys Asn Asp Thr Leu Ser Glu Ala Ile Ser Ile Arg Asp Phe Leu
            500                 505                 510

Val Thr Leu Asn Gln Pro Gln Ala Arg Gln Glu Glu Gln Val Arg Val
        515                 520                 525
```

```
Val Arg Gln Phe His Phe His Gly Trp Pro Glu Ile Gly Ile Pro Ala
    530                 535                 540

Glu Gly Lys Gly Met Ile Asp Leu Ile Ala Ala Val Gln Lys Gln Gln
545                 550                 555                 560

Gln Gln Thr Gly Asn His Pro Ile Thr Val His Cys Ser Ala Gly Ala
                565                 570                 575

Gly Arg Thr Gly Thr Phe Ile Ala Leu Ser Asn Ile Leu Glu Arg Val
            580                 585                 590

Lys Ala Glu Gly Leu Leu Asp Val Phe Gln Ala Val Lys Ser Leu Arg
        595                 600                 605

Leu Gln Arg Pro His Met Val Gln Thr Leu Glu Gln Tyr Glu Phe Cys
    610                 615                 620

Tyr Lys Val Val Gln Asp Phe Ile Asp Ile Phe Ser Asp Tyr Ala Asn
625                 630                 635                 640

Phe Lys


<210> SEQ ID NO 25
<211> LENGTH: 1227
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 25

Met Ala Asn Gly Val Ile Pro Pro Pro Gly Gly Ala Ser Pro Leu Pro
1               5                   10                  15

Gln Val Arg Val Pro Leu Glu Glu Pro Pro Leu Gly Pro Asp Val Glu
            20                  25                  30

Glu Glu Asp Asp Asp Leu Gly Lys Thr Leu Ala Val Ser Arg Phe Gly
        35                  40                  45

Asp Leu Ile Ser Lys Thr Pro Ala Trp Asp Pro Glu Lys Pro Ser Arg
    50                  55                  60

Ser Tyr Ser Glu Arg Asp Phe Glu Phe His Arg His Thr Ser His His
65                  70                  75                  80

Thr His His Pro Leu Ser Ala Arg Leu Pro Pro Pro His Lys Leu Arg
                85                  90                  95

Arg Pro Pro Pro Thr Ser Ala Arg His Thr Arg Arg Lys Arg Lys Lys
            100                 105                 110

Glu Lys Thr Ser Ala Pro Pro Ser Glu Gly Thr Pro Pro Ile Gln Glu
        115                 120                 125

Glu Gly Gly Ala Gly Ala Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu
    130                 135                 140

Glu Gly Glu Ser Glu Ala Glu Pro Val Glu Pro Leu Pro Pro Gly Pro
145                 150                 155                 160

Pro Gln Lys Ala Lys Phe Ser Ile Gly Ser Asp Glu Asp Asp Ser Pro
                165                 170                 175

Gly Leu Pro Val Lys Ala Pro Cys Ala Lys Ala Leu Pro Ser Val Gly
            180                 185                 190

Leu Gln Ser Asp Gln Ser Pro Gln Arg Ser Gly Ser Ser Pro Ser Pro
        195                 200                 205

Arg Ala Arg Ala Ser Arg Ile Ser Thr Glu Lys Ser Arg Pro Trp Ser
    210                 215                 220

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

Leu Gly Asn Pro Gly Pro Glu Gln Arg Val Pro Thr Asp Glu Ala Glu
                245                 250                 255
```

```
Ala Gln Met Leu Gly Ser Ala Asp Leu Asp Asp Met Lys Ser His Arg
            260                 265                 270

Leu Glu Asp Asn Pro Gly Val Arg Arg His Leu Val Lys Lys Pro Ser
        275                 280                 285

Arg Ile Gln Gly Gly Arg Gly Ser Pro Ser Gly Leu Ala Pro Ile Leu
    290                 295                 300

Arg Arg Lys Lys Lys Lys Lys Lys Leu Asp Arg Arg Pro His Glu Val
305                 310                 315                 320

Phe Val Glu Leu Asn Glu Leu Met Leu Asp Arg Ser Gln Glu Pro His
                325                 330                 335

Trp Arg Glu Thr Ala Arg Trp Ile Lys Phe Glu Glu Asp Val Glu Glu
            340                 345                 350

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

Ser Leu Leu Glu Leu Arg Arg Thr Ile Ala Gln Gly Ala Ala Leu Leu
    370                 375                 380

Asp Leu Glu Gln Thr Thr Leu Pro Gly Ile Ala His Leu Val Val Glu
385                 390                 395                 400

Thr Met Ile Val Ser Asp Gln Ile Arg Pro Glu Asp Arg Ala Ser Val
                405                 410                 415

Leu Arg Thr Leu Leu Leu Lys His Ser His Pro Asn Asp Asp Lys Asp
            420                 425                 430

Ser Gly Phe Phe Pro Arg Asn Pro Ser Ser Ser Ser Val Asn Ser Val
        435                 440                 445

Leu Gly Asn His His Pro Thr Pro Ser His Gly Pro Asp Gly Ala Val
    450                 455                 460

Pro Thr Met Ala Asp Asp Gln Gly Glu Pro Ala Pro Leu Trp Pro His
465                 470                 475                 480

Asp Pro Asp Ala Lys Glu Lys Pro Leu His Met Pro Gly Gly Asp Gly
                485                 490                 495

His Arg Gly Lys Ser Leu Lys Leu Leu Glu Lys Ile Pro Glu Asp Ala
            500                 505                 510

Glu Ala Thr Val Val Leu Val Gly Cys Val Pro Phe Leu Glu Gln Pro
        515                 520                 525

Ala Gly Ala Phe Val Arg Leu Ser Glu Ala Val Leu Leu Glu Ser Val
    530                 535                 540

Leu Glu Val Pro Val Pro Val Arg Phe Leu Phe Val Met Leu Gly Pro
545                 550                 555                 560

Ser His Thr Ser Thr Asp Tyr His Glu Leu Gly Arg Ser Ile Ala Thr
                565                 570                 575

Leu Met Ser Asp Lys Leu Phe His Glu Ala Ala Tyr Gln Ala Asp Asp
            580                 585                 590

Arg Gln Asp Leu Leu Gly Ala Ile Ser Glu Phe Leu Asp Gly Ser Ile
        595                 600                 605

Val Ile Pro Pro Ser Glu Val Glu Gly Arg Asp Leu Leu Arg Ser Val
    610                 615                 620

Ala Ala Phe Gln Arg Glu Leu Leu Arg Lys Arg Arg Glu Arg Glu Gln
625                 630                 635                 640

Thr Lys Val Glu Met Thr Thr Arg Gly Gly Tyr Ala Ala Pro Gly Lys
                645                 650                 655

Glu Leu Ser Leu Glu Met Gly Gly Ser Glu Ala Thr Ser Glu Asp Asp
            660                 665                 670

Pro Leu Gln Arg Thr Gly Ser Val Phe Gly Gly Leu Val Arg Asp Val
        675                 680                 685
```

```
Lys Arg Arg Tyr Pro His Tyr Pro Ser Asp Leu Arg Asp Ala Leu His
    690                 695                 700

Ser Gln Cys Val Ala Ala Val Leu Phe Ile Tyr Phe Ala Ala Leu Ser
705                 710                 715                 720

Pro Ala Ile Thr Phe Gly Gly Leu Leu Gly Glu Lys Thr Glu Gly Leu
                725                 730                 735

Met Gly Val Ser Glu Leu Ile Val Ser Thr Ala Val Leu Gly Val Leu
            740                 745                 750

Phe Ser Leu Leu Gly Ala Gln Pro Leu Leu Val Val Gly Phe Ser Gly
        755                 760                 765

Pro Leu Leu Val Phe Glu Glu Ala Phe Phe Lys Phe Cys Arg Ala Gln
    770                 775                 780

Asp Leu Glu Tyr Leu Thr Gly Arg Val Trp Val Gly Leu Trp Leu Val
785                 790                 795                 800

Val Phe Val Leu Ala Leu Val Ala Ala Glu Gly Thr Phe Leu Val Arg
                805                 810                 815

Tyr Ile Ser Pro Phe Thr Gln Glu Ile Phe Ala Phe Leu Ile Ser Leu
            820                 825                 830

Ile Phe Ile Tyr Glu Thr Phe His Lys Leu Tyr Lys Val Phe Thr Glu
        835                 840                 845

His Pro Leu Leu Pro Phe Tyr Pro Pro Asp Glu Ala Leu Glu Thr Gly
    850                 855                 860

Leu Glu Leu Asn Ser Ser Ala Leu Pro Pro Thr Glu Gly Pro Pro Gly
865                 870                 875                 880

Pro Arg Asn Gln Pro Asn Thr Ala Leu Leu Ser Leu Ile Leu Met Leu
                885                 890                 895

Gly Thr Phe Leu Ile Ala Phe Phe Leu Arg Lys Phe Arg Asn Ser Arg
            900                 905                 910

Phe Leu Gly Gly Lys Ala Arg Arg Ile Ile Gly Asp Phe Gly Ile Pro
        915                 920                 925

Ile Ser Ile Leu Val Met Val Leu Val Asp Tyr Ser Ile Thr Asp Thr
    930                 935                 940

Tyr Thr Gln Lys Leu Thr Val Pro Thr Gly Leu Ser Val Thr Ser Pro
945                 950                 955                 960

His Lys Arg Thr Trp Phe Ile Pro Pro Leu Gly Ser Ala Arg Pro Phe
                965                 970                 975

Pro Pro Trp Met Met Val Ala Ala Ala Val Pro Ala Leu Leu Val Leu
            980                 985                 990

Ile Leu Ile Phe Met Glu Thr Gln  Ile Thr Ala Leu Ile  Val Ser Gln
        995                 1000                1005

Lys Ala  Arg Arg Leu Leu Lys  Gly Ser Gly Phe His  Leu Asp Leu
    1010                1015                1020

Leu Leu  Ile Gly Ser Leu Gly  Gly Leu Cys Gly Leu  Phe Gly Leu
    1025                1030                1035

Pro Trp  Leu Thr Ala Ala Thr  Val Arg Ser Val Thr  His Val Asn
    1040                1045                1050

Ala Leu  Thr Val Met Arg Thr  Ala Ile Ala Pro Gly  Asp Lys Pro
    1055                1060                1065

Gln Ile  Gln Glu Val Arg Glu  Gln Arg Val Thr Gly  Val Leu Ile
    1070                1075                1080

Ala Ser  Leu Val Gly Leu Ser  Ile Val Met Gly Ala  Val Leu Arg
    1085                1090                1095

Arg Ile  Pro Leu Ala Val Leu  Phe Gly Ile Phe Leu  Tyr Met Gly
```

```
    1100                1105                1110

Val Thr  Ser Leu Ser Gly Ile  Gln Leu Ser Gln Arg  Leu Leu Leu
    1115                1120                1125

Ile Phe  Met Pro Ala Lys His  His Pro Glu Gln Pro  Tyr Val Thr
    1130                1135                1140

Lys Val  Lys Thr Trp Arg Ile  Asp Leu Phe Thr Cys  Ile Gln Leu
    1145                1150                1155

Gly Cys  Ile Ala Leu Leu Trp  Val Val Lys Ser Thr  Ala Ala Ser
    1160                1165                1170

Leu Ala  Phe Pro Phe Leu Leu  Leu Leu Thr Val Pro  Leu Ser Gly
    1175                1180                1185

Cys Leu  Leu Pro Arg Leu Phe  Gln Asp Arg Glu Leu  Gln Ala Leu
    1190                1195                1200

Asp Ser  Glu Asp Ala Glu Pro  Asn Phe Asp Glu Asp  Gly Gln Asp
    1205                1210                1215

Glu Tyr  Asn Glu Leu His Met  Pro Val
    1220                1225


<210> SEQ ID NO 26
<211> LENGTH: 1232
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

Met Ala Asn Gly Val Ile Pro Pro Pro Gly Gly Ala Ser Pro Leu Pro
1               5                   10                  15

Gln Val Arg Val Pro Leu Glu Glu Pro Pro Leu Ser Pro Asp Val Glu
            20                  25                  30

Glu Glu Asp Asp Asp Leu Gly Lys Thr Leu Ala Val Ser Arg Phe Gly
        35                  40                  45

Asp Leu Ile Ser Lys Pro Pro Ala Trp Asp Pro Glu Lys Pro Ser Arg
    50                  55                  60

Ser Tyr Ser Glu Arg Asp Phe Glu Phe His Arg His Thr Ser His His
65                  70                  75                  80

Thr His His Pro Leu Ser Ala Arg Leu Pro Pro Pro His Lys Leu Arg
                85                  90                  95

Arg Leu Pro Pro Thr Ser Ala Arg His Thr Arg Arg Lys Arg Lys Lys
            100                 105                 110

Glu Lys Thr Ser Ala Pro Pro Ser Glu Gly Thr Pro Pro Ile Gln Glu
        115                 120                 125

Glu Gly Gly Ala Gly Val Asp Glu Glu Glu Glu Glu Glu Glu Glu Glu
    130                 135                 140

Glu Gly Glu Ser Glu Ala Glu Pro Val Glu Pro Pro Pro Ser Gly Thr
145                 150                 155                 160

Pro Gln Lys Ala Lys Phe Ser Ile Gly Ser Asp Glu Asp Asp Ser Pro
                165                 170                 175

Gly Leu Pro Gly Arg Ala Ala Val Thr Lys Pro Leu Pro Ser Val Gly
            180                 185                 190

Pro His Thr Asp Lys Ser Pro Gln His Ser Ser Ser Ser Pro Ser Pro
        195                 200                 205

Arg Ala Arg Ala Ser Arg Leu Ala Gly Glu Lys Ser Arg Pro Trp Ser
    210                 215                 220

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

Leu Gly Asn Pro Gly Gly Pro Glu Gln Gln Val Pro Thr Asp Glu Ala
```

```
                245                 250                 255

Glu Ala Gln Met Leu Gly Ser Ala Asp Leu Asp Asp Met Lys Ser His
            260                 265                 270

Arg Leu Glu Asp Asn Pro Gly Val Arg Arg His Leu Val Lys Lys Pro
        275                 280                 285

Ser Arg Thr Gln Gly Gly Arg Gly Ser Pro Ser Gly Leu Ala Pro Ile
    290                 295                 300

Leu Arg Arg Lys Lys Lys Lys Lys Lys Leu Asp Arg Arg Pro His Glu
305                 310                 315                 320

Val Phe Val Glu Leu Asn Glu Leu Met Leu Asp Arg Ser Gln Glu Pro
                325                 330                 335

His Trp Arg Glu Thr Ala Arg Trp Ile Lys Phe Glu Glu Asp Val Glu
            340                 345                 350

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

Arg Ser Leu Leu Glu Leu Arg Arg Thr Ile Ala His Gly Ala Ala Leu
    370                 375                 380

Leu Asp Leu Glu Gln Thr Thr Leu Pro Gly Ile Ala His Leu Val Val
385                 390                 395                 400

Glu Thr Met Ile Val Ser Asp Gln Ile Arg Pro Glu Asp Arg Ala Ser
                405                 410                 415

Val Leu Arg Thr Leu Leu Leu Lys His Ser His Pro Asn Asp Asp Lys
            420                 425                 430

Asp Ser Gly Phe Phe Pro Arg Asn Pro Ser Ser Ser Ser Met Asn Ser
        435                 440                 445

Val Leu Gly Asn His His Pro Thr Pro Ser His Gly Pro Asp Gly Ala
    450                 455                 460

Val Pro Thr Met Ala Asp Asp Leu Gly Glu Pro Ala Pro Leu Trp Pro
465                 470                 475                 480

His Asp Pro Asp Ala Lys Glu Lys Pro Leu His Met Pro Gly Gly Asp
                485                 490                 495

Gly His Arg Gly Lys Ser Leu Lys Leu Leu Glu Lys Ile Pro Glu Asp
            500                 505                 510

Ala Glu Ala Thr Val Val Leu Val Gly Cys Val Pro Phe Leu Glu Gln
        515                 520                 525

Pro Ala Ala Ala Phe Val Arg Leu Asn Glu Ala Val Leu Leu Glu Ser
    530                 535                 540

Val Leu Glu Val Pro Val Pro Val Arg Phe Leu Phe Val Met Leu Gly
545                 550                 555                 560

Pro Ser His Thr Ser Thr Asp Tyr His Glu Leu Gly Arg Ser Ile Ala
                565                 570                 575

Thr Leu Met Ser Asp Lys Leu Phe His Glu Ala Ala Tyr Gln Ala Asp
            580                 585                 590

Asp Arg Gln Asp Leu Leu Ser Ala Ile Ser Glu Phe Leu Asp Gly Ser
        595                 600                 605

Ile Val Ile Pro Pro Ser Glu Val Glu Gly Arg Asp Leu Leu Arg Ser
    610                 615                 620

Val Ala Ala Phe Gln Arg Glu Leu Leu Arg Lys Arg Arg Glu Arg Glu
625                 630                 635                 640

Gln Thr Lys Val Glu Met Thr Thr Arg Gly Gly Tyr Thr Ala Pro Gly
                645                 650                 655

Lys Glu Leu Ser Leu Glu Leu Gly Gly Ser Glu Ala Thr Pro Glu Asp
            660                 665                 670
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Asp Pro Leu Leu Arg Thr Gly Ser Val Phe Gly Gly Leu Val Arg Asp
        675                 680                 685

Val Arg Arg Arg Tyr Pro His Tyr Pro Ser Asp Leu Arg Asp Ala Leu
    690                 695                 700

His Ser Gln Cys Val Ala Ala Val Leu Phe Ile Tyr Phe Ala Ala Leu
705                 710                 715                 720

Ser Pro Ala Ile Thr Phe Gly Gly Leu Leu Gly Glu Lys Thr Glu Gly
                725                 730                 735

Leu Met Gly Val Ser Glu Leu Ile Val Ser Thr Ala Val Leu Gly Val
            740                 745                 750

Leu Phe Ser Leu Leu Gly Ala Gln Pro Leu Leu Val Val Gly Phe Ser
        755                 760                 765

Gly Pro Leu Leu Val Phe Glu Glu Ala Phe Phe Lys Phe Cys Arg Ala
    770                 775                 780

Gln Asp Leu Glu Tyr Leu Thr Gly Arg Val Trp Val Gly Leu Trp Leu
785                 790                 795                 800

Val Val Phe Val Leu Ala Leu Val Ala Ala Glu Gly Ser Phe Leu Val
                805                 810                 815

Arg Tyr Ile Ser Pro Phe Thr Gln Glu Ile Phe Ala Phe Leu Ile Ser
            820                 825                 830

Leu Ile Phe Ile Tyr Glu Thr Phe Tyr Lys Leu Tyr Lys Val Phe Thr
        835                 840                 845

Glu His Pro Leu Leu Pro Phe Tyr Pro Pro Glu Gly Ala Leu Glu Gly
    850                 855                 860

Ser Leu Ala Ala Gly Leu Glu Pro Asn Gly Ser Ala Leu Pro Pro Thr
865                 870                 875                 880

Glu Gly Pro Pro Ser Pro Arg Asn Gln Pro Asn Thr Ala Leu Leu Ser
                885                 890                 895

Leu Ile Leu Met Leu Gly Thr Phe Phe Ile Ala Phe Phe Leu Arg Lys
            900                 905                 910

Phe Arg Asn Ser Arg Phe Leu Gly Gly Lys Ala Arg Arg Ile Ile Gly
        915                 920                 925

Asp Phe Gly Ile Pro Ile Ser Ile Leu Val Met Val Leu Val Asp Tyr
    930                 935                 940

Ser Ile Thr Asp Thr Tyr Thr Gln Lys Leu Thr Val Pro Thr Gly Leu
945                 950                 955                 960

Ser Val Thr Ser Pro Asp Lys Arg Ser Trp Phe Ile Pro Pro Leu Gly
                965                 970                 975

Ser Ala Arg Pro Phe Pro Pro Trp Met Met Val Ala Ala Ala Val Pro
            980                 985                 990

Ala Leu Leu Val Leu Ile Leu Ile  Phe Met Glu Thr Gln  Ile Thr Ala
        995                 1000                1005

Leu Ile  Val Ser Gln Lys Ala  Arg Arg Leu Leu Lys  Gly Ser Gly
    1010                1015                1020

Phe His  Leu Asp Leu Leu Leu  Ile Gly Ser Leu Gly  Gly Leu Cys
    1025                1030                1035

Gly Leu  Phe Gly Leu Pro Trp  Leu Thr Ala Ala Thr  Val Arg Ser
    1040                1045                1050

Val Thr  His Val Asn Ala Leu  Thr Val Met Arg Thr  Ala Ile Ala
    1055                1060                1065

Pro Gly  Asp Lys Pro Gln Ile  Gln Glu Val Arg Glu  Gln Arg Val
    1070                1075                1080

Thr Gly  Val Leu Ile Ala Ser  Leu Val Gly Leu Ser  Ile Val Met
    1085                1090                1095
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Gly Ala  Val Leu Arg Arg Ile  Pro Leu Ala Val Leu  Phe Gly Ile
    1100                 1105                 1110

Phe Leu  Tyr Met Gly Val Thr  Ser Leu Ser Gly Ile  Gln Leu Ser
    1115                 1120                 1125

Gln Arg  Leu Leu Leu Ile Leu  Met Pro Ala Lys His  His Pro Glu
    1130                 1135                 1140

Gln Pro  Tyr Val Thr Lys Val  Lys Thr Trp Arg Met  His Leu Phe
    1145                 1150                 1155

Thr Cys  Ile Gln Leu Gly Cys  Ile Ala Leu Leu Trp  Val Val Lys
    1160                 1165                 1170

Ser Thr  Ala Ala Ser Leu Ala  Phe Pro Phe Leu Leu  Leu Leu Thr
    1175                 1180                 1185

Val Pro  Leu Arg His Cys Leu  Leu Pro Arg Leu Phe  Gln Asp Arg
    1190                 1195                 1200

Glu Leu  Gln Ala Leu Asp Ser  Glu Asp Ala Glu Pro  Asn Phe Asp
    1205                 1210                 1215

Glu Asp  Gly Gln Asp Glu Tyr  Asn Glu Leu His Met  Pro Val
    1220                 1225                 1230


<210> SEQ ID NO 27
<211> LENGTH: 810
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 27

Met Ala Gln Ser Leu Ala Leu Ala Leu Asp Val Pro Glu Thr Thr Gly
1               5                   10                  15

Asp Glu Gly Leu Glu Pro Ser Pro Tyr Glu Glu Ser Glu Val His Asp
            20                  25                  30

Ser Phe His Gln Leu Ile Gln Glu Gln Ser Leu Arg Val Ala Glu Glu
        35                  40                  45

Gly Leu Glu Leu Leu Pro Leu Gly Leu Gly Arg Gly Asp Gln Thr Leu
    50                  55                  60

Pro Gly Leu Glu Gly Ala Pro Ala Leu Ser Ser Ala Thr Leu Arg Ile
65                  70                  75                  80

Leu Ala Ser Met Pro Ser Arg Thr Ile Gly Arg Ser Arg Gly Ala Ile
                85                  90                  95

Ile Ser Gln Tyr Tyr Asn Arg Thr Val Arg Leu Arg Arg Arg Ser Ser
            100                 105                 110

Arg Pro Leu Leu Gly Asn Val Val Pro Ser Ala Arg Pro Ser Leu Arg
        115                 120                 125

Leu Tyr Asp Leu Glu Leu Asp Ser Thr Ile Leu Glu Glu Asp Glu Lys
    130                 135                 140

Arg Ser Leu Leu Val Lys Glu Leu Gln Gly Leu Ser Ala Ala Gln Arg
145                 150                 155                 160

Asp His Met Val Arg Asn Met Pro Leu Ser Leu Gly Glu Lys Arg Cys
                165                 170                 175

Leu Arg Glu Lys Ser Trp Ser Pro Lys Gly Lys Arg Arg His Leu Gln
            180                 185                 190

Gly Arg Ser Gly Ala Phe Ser Cys Cys Ser Arg Leu Arg Tyr Thr Cys
        195                 200                 205

Met Leu Ala Leu His Ser Leu Gly Leu Ala Leu Leu Ser Gly Leu Tyr
    210                 215                 220

Ala Ala Arg Pro Trp Arg Tyr Ala Leu Lys Gln Ile Gly Gly Gln Phe
225                 230                 235                 240
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Gly Ser Ser Val Leu Ser Tyr Phe Leu Phe Leu Lys Thr Leu Leu Ala
                245                 250                 255

Phe Asn Ala Leu Met Leu Leu Pro Leu Leu Ala Phe Leu Val Gly Val
            260                 265                 270

Gln Ala Ala Phe Pro Pro Asp Pro Ala Gly Pro Val Pro Thr Phe Ser
        275                 280                 285

Gly Leu Glu Leu Leu Thr Gly Gly Gly Arg Phe Thr His Thr Val Met
    290                 295                 300

Tyr Tyr Gly Tyr Tyr Ser Asn Ser Thr Leu Ser Pro Ser Cys Asp Ala
305                 310                 315                 320

Pro Arg Glu Gly Gly Gln Cys Ser Pro Arg Leu Gly Ser Leu Pro Tyr
                325                 330                 335

Asn Met Pro Leu Ala Tyr Leu Phe Thr Met Gly Ala Thr Phe Phe Leu
            340                 345                 350

Thr Cys Ile Ile Leu Val Tyr Ser Met Ser His Ser Phe Gly Glu Ser
        355                 360                 365

Tyr Arg Val Gly Ser Thr Lys Gly Ile His Ala Leu Thr Val Phe Cys
    370                 375                 380

Ser Trp Asp Tyr Lys Val Thr Gln Lys Arg Ala Ser Arg Val Gln Gln
385                 390                 395                 400

Asp Ser Ile Cys Thr Gln Leu Lys Glu Leu Leu Ala Glu Trp His Leu
                405                 410                 415

Arg Lys Arg Pro Arg Ser Val Cys Gly Gln Leu Arg Gln Val Val Val
            420                 425                 430

Leu Gly Leu Gly Trp Leu Leu Cys Leu Gly Ser Thr Met Gly Cys Thr
        435                 440                 445

Val Ala Val Leu Thr Phe Ser Glu Val Met Ile Gln Arg Pro Ala Ser
    450                 455                 460

Gly Gly Gln Gly Val Glu Ala Leu Ala Leu Pro Leu Val Val Ser Val
465                 470                 475                 480

Leu Asn Leu Gly Ala Ser Tyr Leu Phe Arg Gly Leu Ala Thr Leu Glu
                485                 490                 495

Arg His Asp Ser Pro Val Leu Glu Val Tyr Met Ala Ile Cys Arg Asn
            500                 505                 510

Leu Ile Leu Lys Met Ala Val Leu Gly Val Leu Cys Tyr His Trp Leu
        515                 520                 525

Gly Arg Arg Val Ala Thr Leu Gln Gly Gln Cys Trp Glu Asp Phe Val
    530                 535                 540

Gly Gln Glu Leu Tyr Arg Phe Met Val Val Asp Phe Ile Phe Met Leu
545                 550                 555                 560

Leu Asp Ser Leu Phe Gly Glu Leu Val Trp Arg Leu Ile Ser Glu Lys
                565                 570                 575

Lys Leu Lys Arg Gly Gln Lys Pro Glu Phe Asp Ile Ala Arg Asn Val
            580                 585                 590

Leu Asp Leu Ile Tyr Gly Gln Thr Leu Thr Trp Leu Gly Val Leu Phe
        595                 600                 605

Ser Pro Leu Leu Pro Ala Val Gln Ile Leu Arg Leu Leu Phe Leu Phe
    610                 615                 620

His Ile Lys Lys Ala Ser Leu Met Ala Asn Cys Gln Ala Pro Arg Arg
625                 630                 635                 640

Pro Trp Leu Ala Ser His Met Ser Thr Val Phe Leu Thr Leu Leu Cys
                645                 650                 655

Phe Pro Ser Phe Leu Gly Ala Ala Val Phe Leu Cys Tyr Ala Val Trp
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            660                 665                 670

Gln Val Arg Pro Ser Ser Thr Cys Gly Pro Phe Arg Thr Leu Asn Thr
        675                 680                 685

Met Tyr Glu Ala Gly Thr Val Trp Val Arg Arg Leu Glu His Ala Gly
    690                 695                 700

Ser Gly Ala Ser Trp Leu Pro Trp Leu His His Phe Leu Val Glu Asn
705                 710                 715                 720

Thr Phe Phe Leu Phe Leu Ala Ser Ala Leu Leu Leu Ala Val Ile Tyr
                725                 730                 735

Phe Asn Ile Gln Val Val Lys Gly Gln Arg Lys Val Ile Cys Leu Leu
            740                 745                 750

Lys Glu Gln Ile Arg Asn Glu Gly Glu Asp Lys Ile Phe Leu Ile Asn
        755                 760                 765

Lys Leu His Ser Val Tyr Glu Glu Glu Gly Arg Ser Arg Pro Gly Arg
    770                 775                 780

Thr Gln Asp Ala Thr Glu Pro Pro Ala Trp His Glu Asp Gly Gly Asp
785                 790                 795                 800

Gln Lys Glu Pro Cys Asn Pro Arg Ser Pro
                805                 810


<210> SEQ ID NO 28
<211> LENGTH: 444
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

Met Ala His Ser Phe Gly Glu Ser Tyr Arg Val Gly Ser Thr Ser Gly
1               5                   10                  15

Ile His Ala Ile Thr Val Phe Cys Ser Trp Asp Tyr Lys Val Thr Gln
            20                  25                  30

Lys Arg Ala Ser Arg Leu Gln Gln Asp Asn Ile Arg Thr Arg Leu Lys
        35                  40                  45

Glu Leu Leu Ala Glu Trp Gln Leu Arg His Ser Pro Arg Ser Val Cys
    50                  55                  60

Gly Arg Leu Arg Gln Ala Ala Val Leu Gly Leu Val Trp Leu Leu Cys
65                  70                  75                  80

Leu Gly Thr Ala Leu Gly Cys Ala Val Ala Val His Val Phe Ser Glu
                85                  90                  95

Phe Met Ile Gln Ser Pro Glu Ala Ala Gly Gln Glu Ala Val Leu Leu
            100                 105                 110

Val Leu Pro Leu Val Val Gly Leu Leu Asn Leu Gly Ala Pro Tyr Leu
        115                 120                 125

Cys Arg Val Leu Ala Ala Leu Glu Pro His Asp Ser Pro Val Leu Glu
    130                 135                 140

Val Tyr Val Ala Ile Cys Arg Asn Leu Ile Leu Lys Leu Ala Ile Leu
145                 150                 155                 160

Gly Thr Leu Cys Tyr His Trp Leu Gly Arg Arg Val Gly Val Leu Gln
                165                 170                 175

Gly Gln Cys Trp Glu Asp Phe Val Gly Gln Glu Leu Tyr Arg Phe Leu
            180                 185                 190

Val Met Asp Phe Val Leu Met Leu Leu Asp Thr Leu Phe Gly Glu Leu
        195                 200                 205

Val Trp Arg Ile Ile Ser Glu Lys Lys Leu Lys Arg Arg Arg Lys Pro
    210                 215                 220

Glu Phe Asp Ile Ala Arg Asn Val Leu Glu Leu Ile Tyr Gly Gln Thr
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225                 230                 235                 240

Leu Thr Trp Leu Gly Val Leu Phe Ser Pro Leu Leu Pro Ala Val Gln
                245                 250                 255

Ile Ile Lys Leu Leu Leu Val Phe Tyr Val Lys Lys Thr Ser Leu Leu
            260                 265                 270

Ala Asn Cys Gln Ala Pro Arg Arg Pro Trp Leu Ala Ser His Met Ser
        275                 280                 285

Thr Val Phe Leu Thr Leu Leu Cys Phe Pro Ala Phe Leu Gly Ala Ala
    290                 295                 300

Val Phe Leu Cys Tyr Ala Val Trp Gln Val Lys Pro Ser Ser Thr Cys
305                 310                 315                 320

Gly Pro Phe Arg Thr Leu Asp Thr Met Tyr Glu Ala Gly Arg Val Trp
                325                 330                 335

Val Arg His Leu Glu Ala Ala Gly Pro Arg Val Ser Trp Leu Pro Trp
            340                 345                 350

Val His Arg Tyr Leu Met Glu Asn Thr Phe Phe Val Phe Leu Val Ser
        355                 360                 365

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

Gln Arg Lys Val Ile Cys Leu Leu Lys Glu Gln Ile Ser Asn Glu Gly
385                 390                 395                 400

Glu Asp Lys Ile Phe Leu Ile Asn Lys Leu His Ser Ile Tyr Glu Arg
                405                 410                 415

Lys Glu Arg Glu Glu Arg Ser Arg Val Gly Thr Thr Glu Glu Ala Ala
            420                 425                 430

Ala Pro Pro Ala Leu Leu Thr Asp Glu Gln Asp Ala
        435                 440


<210> SEQ ID NO 29
<211> LENGTH: 296
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 29

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

Arg Val Gln Gly Ser Pro Thr Val Pro Leu Pro Val Ser Leu Met Thr
            20                  25                  30

Lys Ser Ser Ala Pro Val Ala Thr Trp Thr Thr Ser Ala Pro His Thr
        35                  40                  45

Ala Arg Ala Thr Thr Pro Val Ala Ser Ala Thr His Asn Ala Ser Val
    50                  55                  60

Leu Arg Thr Thr Ala Ala Ser Leu Thr Ser Gln Leu Pro Thr Asp His
65                  70                  75                  80

Arg Glu Glu Ala Val Thr Ser Pro Pro Leu Lys Arg Asp Val Asn Ser
                85                  90                  95

Thr Asp Ser Ser Pro Ala Gly Phe Pro Ser Thr Ser Ser Asp Gly His
            100                 105                 110

Leu Ala Pro Thr Pro Glu Glu His Ser Leu Gly Ser Pro Glu Ala Thr
        115                 120                 125

Val Pro Ala Thr Gly Ser Gln Ser Pro Met Leu Leu Ser Ser Gln Ala
    130                 135                 140

Pro Thr Ser Ala Thr Thr Ser Pro Ala Thr Ser Leu Ser Glu Ser Leu
145                 150                 155                 160

Ser Ala Ser Val Thr Ser Ser His Asn Ser Thr Val Ala Asn Ile Gln
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                165                 170                 175

Pro Thr Glu Ala Pro Met Ala Pro Ala Ser Pro Thr Glu Glu His Ser
            180                 185                 190

Ser Ser His Thr Pro Thr Ser His Val Thr Ala Glu Pro Val Pro Lys
        195                 200                 205

Glu Lys Ser Pro Gln Asp Thr Glu Pro Gly Lys Val Ile Cys Glu Ser
    210                 215                 220

Glu Thr Thr Thr Pro Phe Leu Ile Met Gln Glu Val Glu Asn Ala Leu
225                 230                 235                 240

Ser Ser Gly Ser Ile Ala Ala Ile Thr Val Thr Val Ile Ala Val Val
                245                 250                 255

Leu Leu Val Phe Gly Gly Ala Ala Tyr Leu Lys Ile Arg His Ser Ser
            260                 265                 270

Tyr Gly Arg Leu Leu Asp Asp His Asp Tyr Gly Ser Trp Gly Asn Tyr
        275                 280                 285

Asn Asn Pro Leu Tyr Asp Asp Ser
    290                 295


<210> SEQ ID NO 30
<211> LENGTH: 1663
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 30

Met Gly Pro Ala Ser Gly Ser Gln Leu Leu Val Leu Leu Leu Leu Leu
1               5                   10                  15

Ala Ser Ser Pro Leu Ala Leu Gly Ile Pro Met Tyr Ser Ile Ile Thr
            20                  25                  30

Pro Asn Val Leu Arg Leu Glu Ser Glu Glu Thr Ile Val Leu Glu Ala
        35                  40                  45

His Asp Ala Gln Gly Asp Ile Pro Val Thr Val Thr Val Gln Asp Phe
    50                  55                  60

Leu Lys Arg Gln Val Leu Thr Ser Glu Lys Thr Val Leu Thr Gly Ala
65                  70                  75                  80

Ser Gly His Leu Arg Ser Val Ser Ile Lys Ile Pro Ala Ser Lys Glu
                85                  90                  95

Phe Asn Ser Asp Lys Glu Gly His Lys Tyr Val Thr Val Val Ala Asn
            100                 105                 110

Phe Gly Glu Thr Val Val Glu Lys Ala Val Met Val Ser Phe Gln Ser
        115                 120                 125

Gly Tyr Leu Phe Ile Gln Thr Asp Lys Thr Ile Tyr Thr Pro Gly Ser
    130                 135                 140

Thr Val Leu Tyr Arg Ile Phe Thr Val Asp Asn Asn Leu Leu Pro Val
145                 150                 155                 160

Gly Lys Thr Val Val Ile Leu Ile Glu Thr Pro Asp Gly Ile Pro Val
                165                 170                 175

Lys Arg Asp Ile Leu Ser Ser Asn Asn Gln His Gly Ile Leu Pro Leu
            180                 185                 190

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

Ala Phe Tyr Glu His Ala Pro Lys Gln Ile Phe Ser Ala Glu Phe Glu
    210                 215                 220

Val Lys Glu Tyr Val Leu Pro Ser Phe Glu Val Arg Val Glu Pro Thr
225                 230                 235                 240

Glu Thr Phe Tyr Tyr Ile Asp Asp Pro Asn Gly Leu Glu Val Ser Ile
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                245                 250                 255

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

Ile Phe Gly Val Gln Asp Gly Asp Lys Lys Ile Ser Leu Ala His Ser
        275                 280                 285

Leu Thr Arg Val Val Ile Glu Asp Gly Val Gly Asp Ala Val Leu Thr
    290                 295                 300

Arg Lys Val Leu Met Glu Gly Val Arg Pro Ser Asn Ala Asp Ala Leu
305                 310                 315                 320

Val Gly Lys Ser Leu Tyr Val Ser Val Thr Val Ile Leu His Ser Gly
                325                 330                 335

Ser Asp Met Val Glu Ala Glu Arg Ser Gly Ile Pro Ile Val Thr Ser
            340                 345                 350

Pro Tyr Gln Ile His Phe Thr Lys Thr Pro Lys Phe Phe Lys Pro Ala
        355                 360                 365

Met Pro Phe Asp Leu Met Val Phe Val Thr Asn Pro Asp Gly Ser Pro
    370                 375                 380

Ala Ser Lys Val Leu Val Val Thr Gln Gly Ser Asn Ala Lys Ala Leu
385                 390                 395                 400

Thr Gln Asp Asp Gly Val Ala Lys Leu Ser Ile Asn Thr Pro Asn Ser
                405                 410                 415

Arg Gln Pro Leu Thr Ile Thr Val Arg Thr Lys Lys Asp Thr Leu Pro
            420                 425                 430

Glu Ser Arg Gln Ala Thr Lys Thr Met Glu Ala His Pro Tyr Ser Thr
        435                 440                 445

Met His Asn Ser Asn Asn Tyr Leu His Leu Ser Val Ser Arg Met Glu
    450                 455                 460

Leu Lys Pro Gly Asp Asn Leu Asn Val Asn Phe His Leu Arg Thr Asp
465                 470                 475                 480

Pro Gly His Glu Ala Lys Ile Arg Tyr Tyr Thr Tyr Leu Val Met Asn
                485                 490                 495

Lys Gly Lys Leu Leu Lys Ala Gly Arg Gln Val Arg Glu Pro Gly Gln
            500                 505                 510

Asp Leu Val Val Leu Ser Leu Pro Ile Thr Pro Glu Phe Ile Pro Ser
        515                 520                 525

Phe Arg Leu Val Ala Tyr Tyr Thr Leu Ile Gly Ala Ser Gly Gln Arg
    530                 535                 540

Glu Val Val Ala Asp Ser Val Trp Val Asp Val Lys Asp Ser Cys Ile
545                 550                 555                 560

Gly Thr Leu Val Val Lys Gly Asp Pro Arg Asp Asn His Leu Ala Pro
                565                 570                 575

Gly Gln Gln Thr Thr Leu Arg Ile Glu Gly Asn Gln Gly Ala Arg Val
            580                 585                 590

Gly Leu Val Ala Val Asp Lys Gly Val Phe Val Leu Asn Lys Lys Asn
        595                 600                 605

Lys Leu Thr Gln Ser Lys Ile Trp Asp Val Val Glu Lys Ala Asp Ile
    610                 615                 620

Gly Cys Thr Pro Gly Ser Gly Lys Asn Tyr Ala Gly Val Phe Met Asp
625                 630                 635                 640

Ala Gly Leu Ala Phe Lys Thr Ser Gln Gly Leu Gln Thr Glu Gln Arg
                645                 650                 655

Ala Asp Leu Glu Cys Thr Lys Pro Ala Ala Arg Arg Arg Arg Ser Val
            660                 665                 670
```

```
Gln Leu Met Glu Arg Arg Met Asp Lys Ala Gly Gln Tyr Thr Asp Lys
        675                 680                 685

Gly Leu Arg Lys Cys Cys Glu Asp Gly Met Arg Asp Ile Pro Met Arg
    690                 695                 700

Tyr Ser Cys Gln Arg Arg Ala Arg Leu Ile Thr Gln Gly Glu Asn Cys
705                 710                 715                 720

Ile Lys Ala Phe Ile Asp Cys Cys Asn His Ile Thr Lys Leu Arg Glu
                725                 730                 735

Gln His Arg Arg Asp His Val Leu Gly Leu Ala Arg Ser Glu Leu Glu
            740                 745                 750

Glu Asp Ile Ile Pro Glu Glu Asp Ile Ile Ser Arg Ser His Phe Pro
        755                 760                 765

Gln Ser Trp Leu Trp Thr Ile Glu Glu Leu Lys Glu Pro Glu Lys Asn
    770                 775                 780

Gly Ile Ser Thr Lys Val Met Asn Ile Phe Leu Lys Asp Ser Ile Thr
785                 790                 795                 800

Thr Trp Glu Ile Leu Ala Val Ser Leu Ser Asp Lys Lys Gly Ile Cys
                805                 810                 815

Val Ala Asp Pro Tyr Glu Ile Arg Val Met Gln Asp Phe Phe Ile Asp
            820                 825                 830

Leu Arg Leu Pro Tyr Ser Val Val Arg Asn Glu Gln Val Glu Ile Arg
        835                 840                 845

Ala Val Leu Phe Asn Tyr Arg Glu Gln Gln Glu Leu Lys Val Arg Val
    850                 855                 860

Glu Leu Leu His Asn Pro Ala Phe Cys Ser Met Ala Thr Ala Lys Asn
865                 870                 875                 880

Arg Tyr Phe Gln Thr Ile Lys Ile Pro Pro Lys Ser Ser Val Ala Val
                885                 890                 895

Pro Tyr Val Ile Val Pro Leu Lys Ile Gly Gln Gln Glu Val Glu Val
            900                 905                 910

Lys Ala Ala Val Phe Asn His Phe Ile Ser Asp Gly Val Lys Lys Thr
        915                 920                 925

Leu Lys Val Val Pro Glu Gly Met Arg Ile Asn Lys Thr Val Ala Ile
    930                 935                 940

His Thr Leu Asp Pro Glu Lys Leu Gly Gln Gly Gly Val Gln Lys Val
945                 950                 955                 960

Asp Val Pro Ala Ala Asp Leu Ser Asp Gln Val Pro Asp Thr Asp Ser
                965                 970                 975

Glu Thr Arg Ile Ile Leu Gln Gly Ser Pro Val Val Gln Met Ala Glu
            980                 985                 990

Asp Ala Val Asp Gly Glu Arg Leu  Lys His Leu Ile Val  Thr Pro Ala
        995                 1000                1005

Gly Cys  Gly Glu Gln Asn Met  Ile Gly Met Thr Pro  Thr Val Ile
    1010                1015                1020

Ala Val  His Tyr Leu Asp Gln  Thr Glu Gln Trp Glu  Lys Phe Gly
    1025                1030                1035

Ile Glu  Lys Arg Gln Glu Ala  Leu Glu Leu Ile Lys  Lys Gly Tyr
    1040                1045                1050

Thr Gln  Gln Leu Ala Phe Lys  Gln Pro Ser Ser Ala  Tyr Ala Ala
    1055                1060                1065

Phe Asn  Asn Arg Pro Pro Ser  Thr Trp Leu Thr Ala  Tyr Val Val
    1070                1075                1080

Lys Val  Phe Ser Leu Ala Ala  Asn Leu Ile Ala Ile  Asp Ser His
    1085                1090                1095
```

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Val Leu  Cys Gly Ala Val Lys  Trp Leu Ile Leu Glu  Lys Gln Lys
    1100                1105                1110

Pro Asp  Gly Val Phe Gln Glu  Asp Gly Pro Val Ile  His Gln Glu
    1115                1120                1125

Met Ile  Gly Gly Phe Arg Asn  Ala Lys Glu Ala Asp  Val Ser Leu
    1130                1135                1140

Thr Ala  Phe Val Leu Ile Ala  Leu Gln Glu Ala Arg  Asp Ile Cys
    1145                1150                1155

Glu Gly  Gln Val Asn Ser Leu  Pro Gly Ser Ile Asn  Lys Ala Gly
    1160                1165                1170

Glu Tyr  Ile Glu Ala Ser Tyr  Met Asn Leu Gln Arg  Pro Tyr Thr
    1175                1180                1185

Val Ala  Ile Ala Gly Tyr Ala  Leu Ala Leu Met Asn  Lys Leu Glu
    1190                1195                1200

Glu Pro  Tyr Leu Gly Lys Phe  Leu Asn Thr Ala Lys  Asp Arg Asn
    1205                1210                1215

Arg Trp  Glu Glu Pro Asp Gln  Gln Leu Tyr Asn Val  Glu Ala Thr
    1220                1225                1230

Ser Tyr  Ala Leu Leu Ala Leu  Leu Leu Leu Lys Asp  Phe Asp Ser
    1235                1240                1245

Val Pro  Pro Val Val Arg Trp  Leu Asn Glu Gln Arg  Tyr Tyr Gly
    1250                1255                1260

Gly Gly  Tyr Gly Ser Thr Gln  Ala Thr Phe Met Val  Phe Gln Ala
    1265                1270                1275

Leu Ala  Gln Tyr Gln Thr Asp  Val Pro Asp His Lys  Asp Leu Asn
    1280                1285                1290

Met Asp  Val Ser Phe His Leu  Pro Ser Arg Ser Ser  Ala Thr Thr
    1295                1300                1305

Phe Arg  Leu Leu Trp Glu Asn  Gly Asn Leu Leu Arg  Ser Glu Glu
    1310                1315                1320

Thr Lys  Gln Asn Glu Ala Phe  Ser Leu Thr Ala Lys  Gly Lys Gly
    1325                1330                1335

Arg Gly  Thr Leu Ser Val Val  Ala Val Tyr His Ala  Lys Leu Lys
    1340                1345                1350

Ser Lys  Val Thr Cys Lys Lys  Phe Asp Leu Arg Val  Ser Ile Arg
    1355                1360                1365

Pro Ala  Pro Glu Thr Ala Lys  Lys Pro Glu Glu Ala  Lys Asn Thr
    1370                1375                1380

Met Phe  Leu Glu Ile Cys Thr  Lys Tyr Leu Gly Asp  Val Asp Ala
    1385                1390                1395

Thr Met  Ser Ile Leu Asp Ile  Ser Met Met Thr Gly  Phe Ala Pro
    1400                1405                1410

Asp Thr  Lys Asp Leu Glu Leu  Leu Ala Ser Gly Val  Asp Arg Tyr
    1415                1420                1425

Ile Ser  Lys Tyr Glu Met Asn  Lys Ala Phe Ser Asn  Lys Asn Thr
    1430                1435                1440

Leu Ile  Ile Tyr Leu Glu Lys  Ile Ser His Thr Glu  Glu Asp Cys
    1445                1450                1455

Leu Thr  Phe Lys Val His Gln  Tyr Phe Asn Val Gly  Leu Ile Gln
    1460                1465                1470

Pro Gly  Ser Val Lys Val Tyr  Ser Tyr Tyr Asn Leu  Glu Glu Ser
    1475                1480                1485

Cys Thr  Arg Phe Tyr His Pro  Glu Lys Asp Asp Gly  Met Leu Ser
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    1490                1495                1500

Lys Leu  Cys His Ser Glu Met  Cys Arg Cys Ala Glu  Glu Asn Cys
    1505                1510                1515

Phe Met  Gln Gln Ser Gln Glu  Lys Ile Asn Leu Asn  Val Arg Leu
    1520                1525                1530

Asp Lys  Ala Cys Glu Pro Gly  Val Asp Tyr Val Tyr  Lys Thr Glu
    1535                1540                1545

Leu Thr  Asn Ile Lys Leu Leu  Asp Asp Phe Asp Glu  Tyr Thr Met
    1550                1555                1560

Thr Ile  Gln Gln Val Ile Lys  Ser Gly Ser Asp Glu  Val Gln Ala
    1565                1570                1575

Gly Gln  Gln Arg Lys Phe Ile  Ser His Ile Lys Cys  Arg Asn Ala
    1580                1585                1590

Leu Lys  Leu Gln Lys Gly Lys  Lys Tyr Leu Met Trp  Gly Leu Ser
    1595                1600                1605

Ser Asp  Leu Trp Gly Glu Lys  Pro Asn Thr Ser Tyr  Ile Ile Gly
    1610                1615                1620

Lys Asp  Thr Trp Val Glu His  Trp Pro Glu Ala Glu  Glu Cys Gln
    1625                1630                1635

Asp Gln  Lys Tyr Gln Lys Gln  Cys Glu Glu Leu Gly  Ala Phe Thr
    1640                1645                1650

Glu Ser  Met Val Val Tyr Gly  Cys Pro Asn
    1655                1660


&lt;210&gt; SEQ ID NO 31
&lt;211&gt; LENGTH: 1663
&lt;212&gt; TYPE: PRT
&lt;213&gt; ORGANISM: Homo sapiens

&lt;400&gt; SEQUENCE: 31

Met Gly Pro Thr Ser Gly Pro Ser Leu Leu Leu Leu Leu Leu Thr His
1               5                   10                  15

Leu Pro Leu Ala Leu Gly Ser Pro Met Tyr Ser Ile Ile Thr Pro Asn
            20                  25                  30

Ile Leu Arg Leu Glu Ser Glu Glu Thr Met Val Leu Glu Ala His Asp
        35                  40                  45

Ala Gln Gly Asp Val Pro Val Thr Val Thr Val His Asp Phe Pro Gly
    50                  55                  60

Lys Lys Leu Val Leu Ser Ser Glu Lys Thr Val Leu Thr Pro Ala Thr
65                  70                  75                  80

Asn His Met Gly Asn Val Thr Phe Thr Ile Pro Ala Asn Arg Glu Phe
                85                  90                  95

Lys Ser Glu Lys Gly Arg Asn Lys Phe Val Thr Val Gln Ala Thr Phe
            100                 105                 110

Gly Thr Gln Val Val Glu Lys Val Val Leu Val Ser Leu Gln Ser Gly
        115                 120                 125

Tyr Leu Phe Ile Gln Thr Asp Lys Thr Ile Tyr Thr Pro Gly Ser Thr
    130                 135                 140

Val Leu Tyr Arg Ile Phe Thr Val Asn His Lys Leu Leu Pro Val Gly
145                 150                 155                 160

Arg Thr Val Met Val Asn Ile Glu Asn Pro Glu Gly Ile Pro Val Lys
                165                 170                 175

Gln Asp Ser Leu Ser Ser Gln Asn Gln Leu Gly Val Leu Pro Leu Ser
            180                 185                 190

Trp Asp Ile Pro Glu Leu Val Asn Met Gly Gln Trp Lys Ile Arg Ala
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        195                 200                 205

Tyr Tyr Glu Asn Ser Pro Gln Gln Val Phe Ser Thr Glu Phe Glu Val
    210                 215                 220

Lys Glu Tyr Val Leu Pro Ser Phe Glu Val Ile Val Glu Pro Thr Glu
225                 230                 235                 240

Lys Phe Tyr Tyr Ile Tyr Asn Glu Lys Gly Leu Glu Val Thr Ile Thr
                245                 250                 255

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

Phe Gly Ile Gln Asp Gly Glu Gln Arg Ile Ser Leu Pro Glu Ser Leu
        275                 280                 285

Lys Arg Ile Pro Ile Glu Asp Gly Ser Gly Glu Val Val Leu Ser Arg
    290                 295                 300

Lys Val Leu Leu Asp Gly Val Gln Asn Pro Arg Ala Glu Asp Leu Val
305                 310                 315                 320

Gly Lys Ser Leu Tyr Val Ser Ala Thr Val Ile Leu His Ser Gly Ser
                325                 330                 335

Asp Met Val Gln Ala Glu Arg Ser Gly Ile Pro Ile Val Thr Ser Pro
            340                 345                 350

Tyr Gln Ile His Phe Thr Lys Thr Pro Lys Tyr Phe Lys Pro Gly Met
        355                 360                 365

Pro Phe Asp Leu Met Val Phe Val Thr Asn Pro Asp Gly Ser Pro Ala
    370                 375                 380

Tyr Arg Val Pro Val Ala Val Gln Gly Glu Asp Thr Val Gln Ser Leu
385                 390                 395                 400

Thr Gln Gly Asp Gly Val Ala Lys Leu Ser Ile Asn Thr His Pro Ser
                405                 410                 415

Gln Lys Pro Leu Ser Ile Thr Val Arg Thr Lys Lys Gln Glu Leu Ser
            420                 425                 430

Glu Ala Glu Gln Ala Thr Arg Thr Met Gln Ala Leu Pro Tyr Ser Thr
        435                 440                 445

Val Gly Asn Ser Asn Asn Tyr Leu His Leu Ser Val Leu Arg Thr Glu
    450                 455                 460

Leu Arg Pro Gly Glu Thr Leu Asn Val Asn Phe Leu Leu Arg Met Asp
465                 470                 475                 480

Arg Ala His Glu Ala Lys Ile Arg Tyr Tyr Thr Tyr Leu Ile Met Asn
                485                 490                 495

Lys Gly Arg Leu Leu Lys Ala Gly Arg Gln Val Arg Glu Pro Gly Gln
            500                 505                 510

Asp Leu Val Val Leu Pro Leu Ser Ile Thr Thr Asp Phe Ile Pro Ser
        515                 520                 525

Phe Arg Leu Val Ala Tyr Tyr Thr Leu Ile Gly Ala Ser Gly Gln Arg
    530                 535                 540

Glu Val Val Ala Asp Ser Val Trp Val Asp Val Lys Asp Ser Cys Val
545                 550                 555                 560

Gly Ser Leu Val Val Lys Ser Gly Gln Ser Glu Asp Arg Gln Pro Val
                565                 570                 575

Pro Gly Gln Gln Met Thr Leu Lys Ile Glu Gly Asp His Gly Ala Arg
            580                 585                 590

Val Val Leu Val Ala Val Asp Lys Gly Val Phe Val Leu Asn Lys Lys
        595                 600                 605

Asn Lys Leu Thr Gln Ser Lys Ile Trp Asp Val Val Glu Lys Ala Asp
    610                 615                 620
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Ile Gly Cys Thr Pro Gly Ser Gly Lys Asp Tyr Ala Gly Val Phe Ser
625                 630                 635                 640

Asp Ala Gly Leu Thr Phe Thr Ser Ser Ser Gly Gln Gln Thr Ala Gln
                645                 650                 655

Arg Ala Glu Leu Gln Cys Pro Gln Pro Ala Ala Arg Arg Arg Arg Ser
            660                 665                 670

Val Gln Leu Thr Glu Lys Arg Met Asp Lys Val Gly Lys Tyr Pro Lys
        675                 680                 685

Glu Leu Arg Lys Cys Cys Glu Asp Gly Met Arg Glu Asn Pro Met Arg
    690                 695                 700

Phe Ser Cys Gln Arg Arg Thr Arg Phe Ile Ser Leu Gly Glu Ala Cys
705                 710                 715                 720

Lys Lys Val Phe Leu Asp Cys Cys Asn Tyr Ile Thr Glu Leu Arg Arg
                725                 730                 735

Gln His Ala Arg Ala Ser His Leu Gly Leu Ala Arg Ser Asn Leu Asp
            740                 745                 750

Glu Asp Ile Ile Ala Glu Glu Asn Ile Val Ser Arg Ser Glu Phe Pro
        755                 760                 765

Glu Ser Trp Leu Trp Asn Val Glu Asp Leu Lys Glu Pro Pro Lys Asn
    770                 775                 780

Gly Ile Ser Thr Lys Leu Met Asn Ile Phe Leu Lys Asp Ser Ile Thr
785                 790                 795                 800

Thr Trp Glu Ile Leu Ala Val Ser Met Ser Asp Lys Lys Gly Ile Cys
                805                 810                 815

Val Ala Asp Pro Phe Glu Val Thr Val Met Gln Asp Phe Phe Ile Asp
            820                 825                 830

Leu Arg Leu Pro Tyr Ser Val Val Arg Asn Glu Gln Val Glu Ile Arg
        835                 840                 845

Ala Val Leu Tyr Asn Tyr Arg Gln Asn Gln Glu Leu Lys Val Arg Val
    850                 855                 860

Glu Leu Leu His Asn Pro Ala Phe Cys Ser Leu Ala Thr Thr Lys Arg
865                 870                 875                 880

Arg His Gln Gln Thr Val Thr Ile Pro Pro Lys Ser Ser Leu Ser Val
                885                 890                 895

Pro Tyr Val Ile Val Pro Leu Lys Thr Gly Leu Gln Glu Val Glu Val
            900                 905                 910

Lys Ala Ala Val Tyr His His Phe Ile Ser Asp Gly Val Arg Lys Ser
        915                 920                 925

Leu Lys Val Val Pro Glu Gly Ile Arg Met Asn Lys Thr Val Ala Val
    930                 935                 940

Arg Thr Leu Asp Pro Glu Arg Leu Gly Arg Glu Gly Val Gln Lys Glu
945                 950                 955                 960

Asp Ile Pro Pro Ala Asp Leu Ser Asp Gln Val Pro Asp Thr Glu Ser
                965                 970                 975

Glu Thr Arg Ile Leu Leu Gln Gly Thr Pro Val Ala Gln Met Thr Glu
            980                 985                 990

Asp Ala Val Asp Ala Glu Arg Leu  Lys His Leu Ile Val  Thr Pro Ser
        995                 1000                1005

Gly Cys  Gly Glu Gln Asn Met  Ile Gly Met Thr Pro  Thr Val Ile
    1010                1015                1020

Ala Val  His Tyr Leu Asp Glu  Thr Glu Gln Trp Glu  Lys Phe Gly
    1025                1030                1035

Leu Glu  Lys Arg Gln Gly Ala  Leu Glu Leu Ile Lys  Lys Gly Tyr
    1040                1045                1050
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Thr Gln  Gln Leu Ala Phe Arg  Gln Pro Ser Ser Ala  Phe Ala Ala
    1055                 1060                 1065

Phe Val  Lys Arg Ala Pro Ser  Thr Trp Leu Thr Ala  Tyr Val Val
    1070                 1075                 1080

Lys Val  Phe Ser Leu Ala Val  Asn Leu Ile Ala Ile  Asp Ser Gln
    1085                 1090                 1095

Val Leu  Cys Gly Ala Val Lys  Trp Leu Ile Leu Glu  Lys Gln Lys
    1100                 1105                 1110

Pro Asp  Gly Val Phe Gln Glu  Asp Ala Pro Val Ile  His Gln Glu
    1115                 1120                 1125

Met Ile  Gly Gly Leu Arg Asn  Asn Asn Glu Lys Asp  Met Ala Leu
    1130                 1135                 1140

Thr Ala  Phe Val Leu Ile Ser  Leu Gln Glu Ala Lys  Asp Ile Cys
    1145                 1150                 1155

Glu Glu  Gln Val Asn Ser Leu  Pro Gly Ser Ile Thr  Lys Ala Gly
    1160                 1165                 1170

Asp Phe  Leu Glu Ala Asn Tyr  Met Asn Leu Gln Arg  Ser Tyr Thr
    1175                 1180                 1185

Val Ala  Ile Ala Gly Tyr Ala  Leu Ala Gln Met Gly  Arg Leu Lys
    1190                 1195                 1200

Gly Pro  Leu Leu Asn Lys Phe  Leu Thr Thr Ala Lys  Asp Lys Asn
    1205                 1210                 1215

Arg Trp  Glu Asp Pro Gly Lys  Gln Leu Tyr Asn Val  Glu Ala Thr
    1220                 1225                 1230

Ser Tyr  Ala Leu Leu Ala Leu  Leu Gln Leu Lys Asp  Phe Asp Phe
    1235                 1240                 1245

Val Pro  Pro Val Val Arg Trp  Leu Asn Glu Gln Arg  Tyr Tyr Gly
    1250                 1255                 1260

Gly Gly  Tyr Gly Ser Thr Gln  Ala Thr Phe Met Val  Phe Gln Ala
    1265                 1270                 1275

Leu Ala  Gln Tyr Gln Lys Asp  Ala Pro Asp His Gln  Glu Leu Asn
    1280                 1285                 1290

Leu Asp  Val Ser Leu Gln Leu  Pro Ser Arg Ser Ser  Lys Ile Thr
    1295                 1300                 1305

His Arg  Ile His Trp Glu Ser  Ala Ser Leu Leu Arg  Ser Glu Glu
    1310                 1315                 1320

Thr Lys  Glu Asn Glu Gly Phe  Thr Val Thr Ala Glu  Gly Lys Gly
    1325                 1330                 1335

Gln Gly  Thr Leu Ser Val Val  Thr Met Tyr His Ala  Lys Ala Lys
    1340                 1345                 1350

Asp Gln  Leu Thr Cys Asn Lys  Phe Asp Leu Lys Val  Thr Ile Lys
    1355                 1360                 1365

Pro Ala  Pro Glu Thr Glu Lys  Arg Pro Gln Asp Ala  Lys Asn Thr
    1370                 1375                 1380

Met Ile  Leu Glu Ile Cys Thr  Arg Tyr Arg Gly Asp  Gln Asp Ala
    1385                 1390                 1395

Thr Met  Ser Ile Leu Asp Ile  Ser Met Met Thr Gly  Phe Ala Pro
    1400                 1405                 1410

Asp Thr  Asp Asp Leu Lys Gln  Leu Ala Asn Gly Val  Asp Arg Tyr
    1415                 1420                 1425

Ile Ser  Lys Tyr Glu Leu Asp  Lys Ala Phe Ser Asp  Arg Asn Thr
    1430                 1435                 1440

Leu Ile  Ile Tyr Leu Asp Lys  Val Ser His Ser Glu  Asp Asp Cys
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    1445                1450                1455

Leu Ala  Phe Lys Val His Gln  Tyr Phe Asn Val Glu  Leu Ile Gln
    1460                1465                1470

Pro Gly  Ala Val Lys Val Tyr  Ala Tyr Tyr Asn Leu  Glu Glu Ser
    1475                1480                1485

Cys Thr  Arg Phe Tyr His Pro  Glu Lys Glu Asp Gly  Lys Leu Asn
    1490                1495                1500

Lys Leu  Cys Arg Asp Glu Leu  Cys Arg Cys Ala Glu  Glu Asn Cys
    1505                1510                1515

Phe Ile  Gln Lys Ser Asp Asp  Lys Val Thr Leu Glu  Glu Arg Leu
    1520                1525                1530

Asp Lys  Ala Cys Glu Pro Gly  Val Asp Tyr Val Tyr  Lys Thr Arg
    1535                1540                1545

Leu Val  Lys Val Gln Leu Ser  Asn Asp Phe Asp Glu  Tyr Ile Met
    1550                1555                1560

Ala Ile  Glu Gln Thr Ile Lys  Ser Gly Ser Asp Glu  Val Gln Val
    1565                1570                1575

Gly Gln  Gln Arg Thr Phe Ile  Ser Pro Ile Lys Cys  Arg Glu Ala
    1580                1585                1590

Leu Lys  Leu Glu Glu Lys Lys  His Tyr Leu Met Trp  Gly Leu Ser
    1595                1600                1605

Ser Asp  Phe Trp Gly Glu Lys  Pro Asn Leu Ser Tyr  Ile Ile Gly
    1610                1615                1620

Lys Asp  Thr Trp Val Glu His  Trp Pro Glu Glu Asp  Glu Cys Gln
    1625                1630                1635

Asp Glu  Glu Asn Gln Lys Gln  Cys Gln Asp Leu Gly  Ala Phe Thr
    1640                1645                1650

Glu Ser  Met Val Val Phe Gly  Cys Pro Asn
    1655                1660

<210> SEQ ID NO 32
<211> LENGTH: 705
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 32

Thr Ala Thr Ala Gly Asn Ala Ala Thr Thr Ala Ala Thr Thr Gly Gly
1               5                   10                  15

Gly Thr Gly Cys Ala Thr Thr Ala Gly Thr Cys Ala Thr Ala Thr Ala
            20                  25                  30

Ala Thr Ala Thr Ala Thr Gly Ala Thr Ala Gly Thr Thr Thr Gly Gly
        35                  40                  45

Thr Thr Gly Thr Thr Ala Cys Ala Thr Gly Cys Thr Thr Thr Gly Gly
    50                  55                  60

Gly Ala Ala Ala Thr Cys Ala Thr Ala Thr Thr Ala Ala Gly Gly Gly
65                  70                  75                  80

Gly Ala Ala Gly Ala Ala Thr Cys Ala Gly Thr Cys Ala Ala Thr Ala
                85                  90                  95

Thr Ala Thr Cys Cys Thr Thr Thr Ala Thr Cys Cys Ala Cys Thr Gly
            100                 105                 110

Thr Ala Ala Ala Thr Cys Ala Gly Gly Ala Cys Cys Thr Thr Ala Cys
        115                 120                 125

Ala Thr Cys Ala Ala Ala Ala Gly Gly Thr Ala Thr Cys Cys Ala Gly
    130                 135                 140

Gly Ala Ala Ala Ala Thr Cys Thr Gly Ala Gly Ala Ala Ala Gly Thr
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145                 150                 155                 160

Thr Cys Thr Gly Ala Ala Thr Ala Gly Ala Ala Ala Cys Ala Gly Ala
                165                 170                 175

Thr Gly Thr Thr Gly Ala Ala Gly Ala Ala Cys Thr Thr Ala Cys Ala
            180                 185                 190

Thr Cys Thr Ala Cys Thr Thr Thr Cys Thr Thr Gly Ala Thr Thr Gly
        195                 200                 205

Ala Ala Ala Thr Ala Gly Thr Thr Thr Gly Thr Cys Cys Thr Thr Gly
    210                 215                 220

Gly Ala Cys Ala Thr Ala Thr Cys Ala Thr Ala Thr Thr Thr Thr Ala
225                 230                 235                 240

Gly Ala Thr Thr Ala Gly Gly Ala Gly Thr Thr Thr Thr Gly Ala Ala
                245                 250                 255

Thr Thr Ala Cys Thr Gly Cys Thr Thr Thr Thr Gly Cys Ala Thr Thr
            260                 265                 270

Thr Thr Gly Gly Cys Ala Ala Thr Ala Gly Thr Thr Thr Thr Thr Ala
        275                 280                 285

Ala Ala Gly Thr Thr Ala Cys Ala Ala Ala Thr Thr Ala Ala Thr Cys
    290                 295                 300

Ala Cys Cys Ala Thr Ala Thr Ala Ala Cys Ala Ala Ala Ala Ala Thr
305                 310                 315                 320

Gly Thr Thr Thr Ala Thr Ala Thr Thr Thr Ala Thr Gly Ala Gly Ala
                325                 330                 335

Ala Gly Ala Cys Ala Thr Gly Ala Gly Thr Thr Ala Ala Ala Cys Ala
            340                 345                 350

Ala Thr Ala Cys Thr Thr Cys Ala Ala Thr Gly Cys Ala Ala Ala Thr
        355                 360                 365

Thr Gly Ala Ala Ala Gly Thr Ala Thr Ala Thr Thr Ala Gly Thr Cys
    370                 375                 380

Ala Cys Ala Thr Gly Cys Ala Thr Gly Thr Gly Cys Cys Thr Thr Thr
385                 390                 395                 400

Cys Thr Ala Ala Ala Cys Ala Ala Thr Ala Ala Ala Ala Thr Cys Ala
                405                 410                 415

Ala Cys Thr Ala Ala Thr Ala Ala Ala Thr Gly Thr Ala Thr Thr Ala
            420                 425                 430

Thr Gly Ala Thr Thr Thr Thr Ala Thr Ala Cys Ala Cys Ala Ala Gly
        435                 440                 445

Thr Gly Gly Gly Ala Thr Ala Ala Thr Thr Gly Ala Thr Gly Gly Thr
    450                 455                 460

Gly Cys Cys Ala Thr Thr Ala Ala Thr Gly Cys Ala Cys Thr Thr Thr
465                 470                 475                 480

Gly Thr Ala Cys Gly Ala Ala Ala Thr Gly Gly Cys Gly Gly Thr Gly
                485                 490                 495

Ala Ala Thr Cys Thr Cys Thr Thr Gly Cys Thr Thr Thr Ala Thr Ala
            500                 505                 510

Ala Thr Ala Thr Cys Cys Ala Thr Ala Thr Thr Thr Ala Cys Ala Thr
        515                 520                 525

Cys Cys Ala Ala Ala Thr Thr Cys Ala Ala Thr Ala Thr Cys Cys Thr
    530                 535                 540

Cys Cys Cys Cys Thr Gly Ala Ala Thr Gly Gly Gly Ala Ala Thr Ala
545                 550                 555                 560

Ala Ala Thr Cys Thr Thr Thr Thr Cys Ala Gly Thr Gly Thr Gly Thr
                565                 570                 575
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Cys Thr Cys Cys Ala Thr Thr Thr Gly Ala Gly Ala Ala Thr Thr Ala
            580                 585                 590

Thr Ala Thr Thr Gly Thr Gly Thr Gly Ala Thr Cys Cys Cys Ala Thr
        595                 600                 605

Ala Ala Thr Gly Thr Thr Thr Thr Cys Thr Gly Gly Thr Ala Thr Thr
    610                 615                 620

Ala Cys Ala Cys Ala Thr Gly Cys Ala Thr Gly Thr Ala Ala Gly Cys
625                 630                 635                 640

Ala Thr Gly Thr Thr Gly Thr Gly Gly Cys Thr Cys Ala Gly Ala Cys
                645                 650                 655

Cys Ala Cys Thr Thr Cys Cys Ala Thr Thr Thr Cys Thr Ala Cys Ala
            660                 665                 670

Thr Gly Thr Ala Thr Gly Thr Cys Thr Cys Thr Thr Cys Cys Cys Thr
        675                 680                 685

Thr Ala Ala Gly Ala Gly Ala Thr Ala Thr Ala Cys Thr Thr Cys Thr
    690                 695                 700

Gly
705


<210> SEQ ID NO 33
<211> LENGTH: 449
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 33

Met Arg Leu Leu Ala Lys Ile Ile Cys Leu Met Leu Trp Ala Ile Cys
1               5                   10                  15

Val Ala Glu Asp Cys Asn Glu Leu Pro Pro Arg Arg Asn Thr Glu Ile
            20                  25                  30

Leu Thr Gly Ser Trp Ser Asp Gln Thr Tyr Pro Glu Gly Thr Gln Ala
        35                  40                  45

Ile Tyr Lys Cys Arg Pro Gly Tyr Arg Ser Leu Gly Asn Val Ile Met
    50                  55                  60

Val Cys Arg Lys Gly Glu Trp Val Ala Leu Asn Pro Leu Arg Lys Cys
65                  70                  75                  80

Gln Lys Arg Pro Cys Gly His Pro Gly Asp Thr Pro Phe Gly Thr Phe
                85                  90                  95

Thr Leu Thr Gly Gly Asn Val Phe Glu Tyr Gly Val Lys Ala Val Tyr
            100                 105                 110

Thr Cys Asn Glu Gly Tyr Gln Leu Leu Gly Glu Ile Asn Tyr Arg Glu
        115                 120                 125

Cys Asp Thr Asp Gly Trp Thr Asn Asp Ile Pro Ile Cys Glu Val Val
    130                 135                 140

Lys Cys Leu Pro Val Thr Ala Pro Glu Asn Gly Lys Ile Val Ser Ser
145                 150                 155                 160

Ala Met Glu Pro Asp Arg Glu Tyr His Phe Gly Gln Ala Val Arg Phe
                165                 170                 175

Val Cys Asn Ser Gly Tyr Lys Ile Glu Gly Asp Glu Glu Met His Cys
            180                 185                 190

Ser Asp Asp Gly Phe Trp Ser Lys Glu Lys Pro Lys Cys Val Glu Ile
        195                 200                 205

Ser Cys Lys Ser Pro Asp Val Ile Asn Gly Ser Pro Ile Ser Gln Lys
    210                 215                 220

Ile Ile Tyr Lys Glu Asn Glu Arg Phe Gln Tyr Lys Cys Asn Met Gly
225                 230                 235                 240
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Tyr Glu Tyr Ser Glu Arg Gly Asp Ala Val Cys Thr Glu Ser Gly Trp
                245                 250                 255

Arg Pro Leu Pro Ser Cys Glu Glu Lys Ser Cys Asp Asn Pro Tyr Ile
            260                 265                 270

Pro Asn Gly Asp Tyr Ser Pro Leu Arg Ile Lys His Arg Thr Gly Asp
        275                 280                 285

Glu Ile Thr Tyr Gln Cys Arg Asn Gly Phe Tyr Pro Ala Thr Arg Gly
    290                 295                 300

Asn Thr Ala Lys Cys Thr Ser Thr Gly Trp Ile Pro Ala Pro Arg Cys
305                 310                 315                 320

Thr Leu Lys Pro Cys Asp Tyr Pro Asp Ile Lys His Gly Gly Leu Tyr
                325                 330                 335

His Glu Asn Met Arg Arg Pro Tyr Phe Pro Val Ala Val Gly Lys Tyr
            340                 345                 350

Tyr Ser Tyr Tyr Cys Asp Glu His Phe Glu Thr Pro Ser Gly Ser Tyr
        355                 360                 365

Trp Asp His Ile His Cys Thr Gln Asp Gly Trp Ser Pro Ala Val Pro
    370                 375                 380

Cys Leu Arg Lys Cys Tyr Phe Pro Tyr Leu Glu Asn Gly Tyr Asn Gln
385                 390                 395                 400

Asn Tyr Gly Arg Lys Phe Val Gln Gly Lys Ser Ile Asp Val Ala Cys
                405                 410                 415

His Pro Gly Tyr Ala Leu Pro Lys Ala Gln Thr Thr Val Thr Cys Met
            420                 425                 430

Glu Asn Gly Trp Ser Pro Thr Pro Arg Cys Ile Arg Val Ser Phe Thr
        435                 440                 445

Leu


<210> SEQ ID NO 34
<211> LENGTH: 694
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 34

Met Gly Lys Ser Pro Gly Met Trp Cys Leu Val Leu Phe Ser Leu Leu
1               5                   10                  15

Ala Ser Phe Ser Ala Glu Pro Thr Met His Gly Glu Ile Leu Ser Pro
            20                  25                  30

Asn Tyr Pro Gln Ala Tyr Pro Asn Asp Val Val Lys Ser Trp Asp Ile
        35                  40                  45

Glu Val Pro Glu Gly Phe Gly Ile His Leu Tyr Phe Thr His Val Asp
    50                  55                  60

Ile Glu Pro Ser Glu Ser Cys Ala Tyr Asp Ser Val Gln Ile Ile Ser
65                  70                  75                  80

Gly Gly Ile Glu Glu Gly Arg Leu Cys Gly Gln Lys Thr Ser Lys Ser
                85                  90                  95

Pro Asn Ser Pro Ile Ile Glu Glu Phe Gln Phe Pro Tyr Asn Lys Leu
            100                 105                 110

Gln Val Val Phe Thr Ser Asp Phe Ser Asn Glu Glu Arg Phe Thr Gly
        115                 120                 125

Phe Ala Ala Tyr Tyr Thr Ala Ile Asp Ile Asn Glu Cys Thr Asp Phe
    130                 135                 140

Thr Asp Val Pro Cys Ser His Phe Cys Asn Asn Phe Ile Gly Gly Tyr
145                 150                 155                 160

Phe Cys Ser Cys Pro Pro Glu Tyr Phe Leu His Asp Asp Met Arg Asn
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                165                 170                 175

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

Ile Ser Ser Pro Asn Tyr Pro Asn Pro Tyr Pro Glu Asn Ser Arg Cys
        195                 200                 205

Glu Tyr Gln Ile Gln Leu Gln Glu Gly Phe Gln Val Val Val Thr Met
    210                 215                 220

Gln Arg Glu Asp Phe Asp Val Glu Pro Ala Asp Ser Glu Gly Asn Cys
225                 230                 235                 240

Pro Asp Ser Leu Thr Phe Ala Ser Lys Asn Gln Gln Phe Gly Pro Tyr
                245                 250                 255

Cys Gly Asn Gly Phe Pro Gly Pro Leu Thr Ile Arg Thr Gln Ser Asn
            260                 265                 270

Thr Leu Gly Ile Val Phe Gln Thr Asp Leu Met Gly Gln Lys Lys Gly
        275                 280                 285

Trp Lys Leu Arg Tyr His Gly Asp Pro Ile Ser Cys Ala Lys Lys Ile
    290                 295                 300

Thr Ala Asn Ser Thr Trp Glu Pro Asp Lys Ala Lys Tyr Val Phe Lys
305                 310                 315                 320

Asp Val Val Lys Ile Thr Cys Val Asp Gly Phe Glu Val Val Glu Gly
                325                 330                 335

His Val Ser Ser Thr Ser Tyr Tyr Ser Thr Cys Gln Ser Asp Gly Gln
            340                 345                 350

Trp Ser Asn Ser Gly Leu Lys Cys Gln Pro Val Tyr Cys Gly Ile Pro
        355                 360                 365

Asp Pro Ile Ala Asn Gly Lys Val Glu Glu Pro Glu Asn Ser Val Phe
    370                 375                 380

Gly Thr Val Val His Tyr Thr Cys Glu Glu Pro Tyr Tyr Tyr Met Glu
385                 390                 395                 400

His Glu Glu Gly Gly Glu Tyr Arg Cys Ala Ala Asn Gly Arg Trp Val
                405                 410                 415

Asn Asp Gln Leu Gly Ile Glu Leu Pro Arg Cys Ile Pro Ala Cys Gly
            420                 425                 430

Val Pro Thr Glu Pro Phe Gln Val His Gln Arg Ile Phe Gly Gly Gln
        435                 440                 445

Pro Ala Lys Ile Glu Asn Phe Pro Trp Gln Val Phe Phe Asn His Pro
    450                 455                 460

Arg Ala Ser Gly Ala Leu Ile Asn Glu Tyr Trp Val Leu Thr Ala Ala
465                 470                 475                 480

His Val Leu Glu Lys Ile Ser Asp Pro Leu Met Tyr Val Gly Thr Met
                485                 490                 495

Ser Val Arg Thr Thr Leu Leu Glu Asn Ala Gln Arg Leu Tyr Ser Lys
            500                 505                 510

Arg Val Phe Ile His Pro Ser Trp Lys Lys Glu Asp Asp Pro Asn Thr
        515                 520                 525

Arg Thr Asn Phe Asp Asn Asp Ile Ala Leu Val Gln Leu Lys Asp Pro
    530                 535                 540

Val Lys Met Gly Pro Lys Val Ser Pro Ile Cys Leu Pro Gly Thr Ser
545                 550                 555                 560

Ser Glu Tyr Asn Val Ser Pro Gly Asp Met Gly Leu Ile Ser Gly Trp
                565                 570                 575

Gly Ser Thr Glu Lys Lys Val Phe Val Ile Asn Leu Arg Gly Ala Lys
            580                 585                 590
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```
Val Pro Val Thr Ser Leu Glu Thr Cys Lys Gln Val Lys Glu Glu Asn
        595                 600                 605

Pro Thr Val Arg Pro Glu Asp Tyr Val Phe Thr Asp Asn Met Ile Cys
    610                 615                 620

Ala Gly Glu Lys Gly Val Asp Ser Cys His Gly Asp Ser Gly Gly Ala
625                 630                 635                 640

Phe Ala Phe Gln Val Pro Asn Val Thr Val Pro Lys Phe Tyr Val Ala
                645                 650                 655

Gly Leu Val Ser Trp Gly Lys Arg Cys Gly Thr Tyr Gly Val Tyr Thr
            660                 665                 670

Lys Val Lys Asn Tyr Val Asp Trp Ile Leu Lys Thr Met Gln Glu Asn
        675                 680                 685

Ser Gly Pro Arg Lys Asp
    690


<210> SEQ ID NO 35
<211> LENGTH: 688
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35

Met Trp Cys Ile Val Leu Phe Ser Leu Leu Ala Trp Val Tyr Ala Glu
1               5                   10                  15

Pro Thr Met Tyr Gly Glu Ile Leu Ser Pro Asn Tyr Pro Gln Ala Tyr
            20                  25                  30

Pro Ser Glu Val Glu Lys Ser Trp Asp Ile Glu Val Pro Glu Gly Tyr
        35                  40                  45

Gly Ile His Leu Tyr Phe Thr His Leu Asp Ile Glu Leu Ser Glu Asn
    50                  55                  60

Cys Ala Tyr Asp Ser Val Gln Ile Ile Ser Gly Asp Thr Glu Glu Gly
65                  70                  75                  80

Arg Leu Cys Gly Gln Arg Ser Ser Asn Asn Pro His Ser Pro Ile Val
                85                  90                  95

Glu Glu Phe Gln Val Pro Tyr Asn Lys Leu Gln Val Ile Phe Lys Ser
            100                 105                 110

Asp Phe Ser Asn Glu Glu Arg Phe Thr Gly Phe Ala Ala Tyr Tyr Val
        115                 120                 125

Ala Thr Asp Ile Asn Glu Cys Thr Asp Phe Val Asp Val Pro Cys Ser
    130                 135                 140

His Phe Cys Asn Asn Phe Ile Gly Gly Tyr Phe Cys Ser Cys Pro Pro
145                 150                 155                 160

Glu Tyr Phe Leu His Asp Asp Met Lys Asn Cys Gly Val Asn Cys Ser
                165                 170                 175

Gly Asp Val Phe Thr Ala Leu Ile Gly Glu Ile Ala Ser Pro Asn Tyr
            180                 185                 190

Pro Lys Pro Tyr Pro Glu Asn Ser Arg Cys Glu Tyr Gln Ile Arg Leu
        195                 200                 205

Glu Lys Gly Phe Gln Val Val Val Thr Leu Arg Arg Glu Asp Phe Asp
    210                 215                 220

Val Glu Ala Ala Asp Ser Ala Gly Asn Cys Leu Asp Ser Leu Val Phe
225                 230                 235                 240

Val Ala Gly Asp Arg Gln Phe Gly Pro Tyr Cys Gly His Gly Phe Pro
                245                 250                 255

Gly Pro Leu Asn Ile Glu Thr Lys Ser Asn Ala Leu Asp Ile Ile Phe
            260                 265                 270
```

```
Gln Thr Asp Leu Thr Gly Gln Lys Lys Gly Trp Lys Leu Arg Tyr His
        275                 280                 285

Gly Asp Pro Met Pro Cys Pro Lys Glu Asp Thr Pro Asn Ser Val Trp
    290                 295                 300

Glu Pro Ala Lys Ala Lys Tyr Val Phe Arg Asp Val Val Gln Ile Thr
305                 310                 315                 320

Cys Leu Asp Gly Phe Glu Val Val Glu Gly Arg Val Gly Ala Thr Ser
                325                 330                 335

Phe Tyr Ser Thr Cys Gln Ser Asn Gly Lys Trp Ser Asn Ser Lys Leu
            340                 345                 350

Lys Cys Gln Pro Val Asp Cys Gly Ile Pro Glu Ser Ile Glu Asn Gly
        355                 360                 365

Lys Val Glu Asp Pro Glu Ser Thr Leu Phe Gly Ser Val Ile Arg Tyr
    370                 375                 380

Thr Cys Glu Glu Pro Tyr Tyr Tyr Met Glu Asn Gly Gly Gly Gly Glu
385                 390                 395                 400

Tyr His Cys Ala Gly Asn Gly Ser Trp Val Asn Glu Val Leu Gly Pro
                405                 410                 415

Glu Leu Pro Lys Cys Val Pro Val Cys Gly Val Pro Arg Glu Pro Phe
            420                 425                 430

Glu Glu Lys Gln Arg Ile Ile Gly Gly Ser Asp Ala Asp Ile Lys Asn
        435                 440                 445

Phe Pro Trp Gln Val Phe Phe Asp Asn Pro Trp Ala Gly Gly Ala Leu
    450                 455                 460

Ile Asn Glu Tyr Trp Val Leu Thr Ala Ala His Val Val Glu Gly Asn
465                 470                 475                 480

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

Leu Ala Lys Ser Lys Met Leu Thr Pro Glu His Val Phe Ile His Pro
            500                 505                 510

Gly Trp Lys Leu Leu Glu Val Pro Glu Gly Arg Thr Asn Phe Asp Asn
        515                 520                 525

Asp Ile Ala Leu Val Arg Leu Lys Asp Pro Val Lys Met Gly Pro Thr
    530                 535                 540

Val Ser Pro Ile Cys Leu Pro Gly Thr Ser Ser Asp Tyr Asn Leu Met
545                 550                 555                 560

Asp Gly Asp Leu Gly Leu Ile Ser Gly Trp Gly Arg Thr Glu Lys Arg
                565                 570                 575

Asp Arg Ala Val Arg Leu Lys Ala Ala Arg Leu Pro Val Ala Pro Leu
            580                 585                 590

Arg Lys Cys Lys Glu Val Lys Val Glu Lys Pro Thr Ala Asp Ala Glu
        595                 600                 605

Ala Tyr Val Phe Thr Pro Asn Met Ile Cys Ala Gly Gly Glu Lys Gly
    610                 615                 620

Met Asp Ser Cys Lys Gly Asp Ser Gly Gly Ala Phe Ala Val Gln Asp
625                 630                 635                 640

Pro Asn Asp Lys Thr Lys Phe Tyr Ala Ala Gly Leu Val Ser Trp Gly
                645                 650                 655

Pro Gln Cys Gly Thr Tyr Gly Leu Tyr Thr Arg Val Lys Asn Tyr Val
            660                 665                 670

Asp Trp Ile Met Lys Thr Met Gln Glu Asn Ser Thr Pro Arg Glu Asp
        675                 680                 685
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<210> SEQ ID NO 36

```
<211> LENGTH: 573
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 36

aagggttaga agatcacttt attggtagtc tatcataggc tttatataaa tgttatgtaa     60

acaagtctct tgagtgtttt tatctcatgg aattgtacaa aactcttaga taacaccatc    120

cctcccagat gctgggttta aagtctccat ccctaaggcc tgtgtctgag gtattgggct    180

gccataaatc ttggagatgg gacagtgaca gtgctgccaa tagatgttct tggggccaag    240

cagcaggcca tgaaggacca actgtagcca gccactgtcc atttctgtcc atagccacac    300

cgctcatccc tgctgcctgc tggagtgctc tcgtatttca gtaggaaata tggagccatt    360

tcctactgaa gtccttgttt tatgagctcc gaggacccga cttttcccca cctcccccta    420

acacagctcc ttggcaggct gaagtgtcgc agatccctgg ggtaccctga gcaccagcag    480

ctccaggaag gccaggatca ccgggaaggc caggctcacc atgagcacca tctcgaccat    540

ctttgctgat gccaggtaca ccttgaggcc ctt                                 573


<210> SEQ ID NO 37
<211> LENGTH: 684
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 37

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

Gly Glu Leu Leu Ala Ala Ala Gly Ala Gln Arg Val Gly Leu Pro Gly
            20                  25                  30

Pro Pro Gly Pro Pro Gly Pro Pro Gly Lys Pro Gly Gln Asp Gly Ile
        35                  40                  45

Asp Gly Glu Ala Gly Pro Pro Gly Leu Pro Gly Pro Pro Gly Pro Lys
    50                  55                  60

Gly Ala Pro Gly Lys Pro Gly Lys Pro Gly Glu Ala Gly Leu Pro Gly
65                  70                  75                  80

Leu Pro Gly Val Asp Gly Leu Thr Gly Arg Asp Gly Pro Pro Gly Pro
                85                  90                  95

Lys Gly Ala Pro Gly Glu Arg Gly Ser Leu Gly Pro Pro Gly Pro Pro
            100                 105                 110

Gly Leu Gly Gly Lys Gly Leu Pro Gly Pro Pro Gly Glu Ala Gly Val
        115                 120                 125

Ser Gly Pro Pro Gly Gly Ile Gly Leu Arg Gly Pro Pro Gly Pro Ser
    130                 135                 140

Gly Leu Pro Gly Leu Pro Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly
145                 150                 155                 160

His Pro Gly Val Leu Pro Glu Gly Ala Thr Asp Leu Gln Cys Pro Ser
                165                 170                 175

Ile Cys Pro Pro Gly Pro Pro Gly Pro Pro Gly Met Pro Gly Phe Lys
            180                 185                 190

Gly Pro Thr Gly Tyr Lys Gly Glu Gln Gly Glu Val Gly Lys Asp Gly
        195                 200                 205

Glu Lys Gly Asp Pro Gly Pro Pro Gly Pro Ala Gly Leu Pro Gly Ser
    210                 215                 220

Val Gly Leu Gln Gly Pro Arg Gly Leu Arg Gly Leu Pro Gly Pro Leu
225                 230                 235                 240

Gly Pro Pro Gly Asp Arg Gly Pro Ile Gly Phe Arg Gly Pro Pro Gly
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                245                 250                 255

Ile Pro Gly Ala Pro Gly Lys Ala Gly Asp Arg Gly Glu Arg Gly Pro
            260                 265                 270

Glu Gly Phe Arg Gly Pro Lys Gly Asp Leu Gly Arg Pro Gly Pro Lys
        275                 280                 285

Gly Thr Pro Gly Val Ala Gly Pro Ser Gly Glu Pro Gly Met Pro Gly
    290                 295                 300

Lys Asp Gly Gln Asn Gly Val Pro Gly Leu Asp Gly Gln Lys Gly Glu
305                 310                 315                 320

Ala Gly Arg Asn Gly Ala Pro Gly Glu Lys Gly Pro Asn Gly Leu Pro
                325                 330                 335

Gly Leu Pro Gly Arg Ala Gly Ser Lys Gly Glu Lys Gly Glu Arg Gly
            340                 345                 350

Arg Ala Gly Glu Leu Gly Glu Ala Gly Pro Ser Gly Glu Pro Gly Val
        355                 360                 365

Pro Gly Asp Ala Gly Met Pro Gly Glu Arg Gly Glu Ala Gly His Arg
    370                 375                 380

Gly Ser Ala Gly Ala Leu Gly Pro Gln Gly Pro Pro Gly Ala Pro Gly
385                 390                 395                 400

Val Arg Gly Phe Gln Gly Gln Lys Gly Ser Met Gly Asp Pro Gly Leu
                405                 410                 415

Pro Gly Pro Gln Gly Leu Arg Gly Asp Val Gly Asp Arg Gly Pro Gly
            420                 425                 430

Gly Ala Ala Gly Pro Lys Gly Asp Gln Gly Ile Ala Gly Ser Asp Gly
        435                 440                 445

Leu Pro Gly Asp Lys Gly Glu Leu Gly Pro Ser Gly Leu Val Gly Pro
    450                 455                 460

Lys Gly Glu Ser Gly Ser Arg Gly Glu Leu Gly Pro Lys Gly Thr Gln
465                 470                 475                 480

Gly Pro Asn Gly Thr Ser Gly Val Gln Gly Val Pro Gly Pro Pro Gly
                485                 490                 495

Pro Leu Gly Leu Gln Gly Val Pro Gly Val Pro Gly Ile Thr Gly Lys
            500                 505                 510

Pro Gly Val Pro Gly Lys Glu Ala Ser Glu Gln Arg Ile Arg Glu Leu
        515                 520                 525

Cys Gly Gly Met Ile Ser Glu Gln Ile Ala Gln Leu Ala Ala His Leu
    530                 535                 540

Arg Lys Pro Leu Ala Pro Gly Ser Ile Gly Arg Pro Gly Pro Ala Gly
545                 550                 555                 560

Pro Pro Gly Pro Pro Gly Pro Pro Gly Ser Ile Gly His Pro Gly Ala
                565                 570                 575

Arg Gly Pro Pro Gly Tyr Arg Gly Pro Thr Gly Glu Leu Gly Asp Pro
            580                 585                 590

Gly Pro Arg Gly Asn Gln Gly Asp Arg Gly Asp Lys Gly Ala Ala Gly
        595                 600                 605

Ala Gly Leu Asp Gly Pro Glu Gly Asp Gln Gly Pro Gln Gly Pro Gln
    610                 615                 620

Gly Val Pro Gly Thr Ser Lys Asp Gly Gln Asp Gly Ala Pro Gly Glu
625                 630                 635                 640

Pro Gly Pro Pro Gly Asp Pro Gly Leu Pro Gly Ala Ile Gly Ala Gln
                645                 650                 655

Gly Thr Pro Gly Ile Cys Asp Thr Ser Ala Cys Gln Gly Ala Val Leu
            660                 665                 670
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Gly Gly Val Gly Glu Lys Ser Gly Ser Arg Ser Ser
        675                 680


<210> SEQ ID NO 38
<211> LENGTH: 184
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 38

Met Asn Arg Thr Ala Tyr Thr Val Gly Ala Leu Leu Leu Leu Leu Gly
1               5                   10                  15

Thr Leu Leu Pro Thr Ala Glu Gly Lys Lys Lys Gly Ser Gln Gly Ala
            20                  25                  30

Ile Pro Pro Pro Asp Lys Ala Gln His Asn Asp Ser Glu Gln Thr Gln
        35                  40                  45

Ser Pro Pro Gln Pro Gly Ser Arg Thr Arg Gly Arg Gly Gln Gly Arg
    50                  55                  60

Gly Thr Ala Met Pro Gly Glu Glu Val Leu Glu Ser Ser Gln Glu Ala
65                  70                  75                  80

Leu His Val Thr Glu Arg Lys Tyr Leu Lys Arg Asp Trp Cys Lys Thr
                85                  90                  95

Gln Pro Leu Lys Gln Thr Ile His Glu Glu Gly Cys Asn Ser Arg Thr
            100                 105                 110

Ile Ile Asn Arg Phe Cys Tyr Gly Gln Cys Asn Ser Phe Tyr Ile Pro
        115                 120                 125

Arg His Ile Arg Lys Glu Glu Gly Ser Phe Gln Ser Cys Ser Phe Cys
    130                 135                 140

Lys Pro Lys Lys Phe Thr Thr Met Met Val Thr Leu Asn Cys Pro Glu
145                 150                 155                 160

Leu Gln Pro Pro Thr Lys Lys Lys Arg Val Thr Arg Val Lys Gln Cys
                165                 170                 175

Arg Cys Ile Ser Ile Asp Leu Asp
            180


<210> SEQ ID NO 39
<211> LENGTH: 184
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 39

Met Ser Arg Thr Ala Tyr Thr Val Gly Ala Leu Leu Leu Leu Leu Gly
1               5                   10                  15

Thr Leu Leu Pro Ala Ala Glu Gly Lys Lys Lys Gly Ser Gln Gly Ala
            20                  25                  30

Ile Pro Pro Pro Asp Lys Ala Gln His Asn Asp Ser Glu Gln Thr Gln
        35                  40                  45

Ser Pro Gln Gln Pro Gly Ser Arg Asn Arg Gly Arg Gly Gln Gly Arg
    50                  55                  60

Gly Thr Ala Met Pro Gly Glu Glu Val Leu Glu Ser Ser Gln Glu Ala
65                  70                  75                  80

Leu His Val Thr Glu Arg Lys Tyr Leu Lys Arg Asp Trp Cys Lys Thr
                85                  90                  95

Gln Pro Leu Lys Gln Thr Ile His Glu Glu Gly Cys Asn Ser Arg Thr
            100                 105                 110

Ile Ile Asn Arg Phe Cys Tyr Gly Gln Cys Asn Ser Phe Tyr Ile Pro
        115                 120                 125

Arg His Ile Arg Lys Glu Glu Gly Ser Phe Gln Ser Cys Ser Phe Cys
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    130                 135                 140

Lys Pro Lys Lys Phe Thr Thr Met Met Val Thr Leu Asn Cys Pro Glu
145                 150                 155                 160

Leu Gln Pro Pro Thr Lys Lys Lys Arg Val Thr Arg Val Lys Gln Cys
                165                 170                 175

Arg Cys Ile Ser Ile Asp Leu Asp
            180


<210> SEQ ID NO 40
<211> LENGTH: 754
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 40

Met Arg Ala Val Ser Val Trp Tyr Cys Cys Pro Trp Gly Leu Leu Leu
1               5                   10                  15

Leu His Cys Leu Cys Ser Phe Ser Val Gly Ser Pro Ser Pro Ser Ile
            20                  25                  30

Ser Pro Glu Lys Lys Val Gly Ser Gln Gly Leu Arg Phe Arg Leu Ala
        35                  40                  45

Gly Phe Pro Arg Lys Pro Tyr Glu Gly Arg Val Glu Ile Gln Arg Ala
    50                  55                  60

Gly Glu Trp Gly Thr Ile Cys Asp Asp Asp Phe Thr Leu Gln Ala Ala
65                  70                  75                  80

His Val Leu Cys Arg Glu Leu Gly Phe Thr Glu Ala Thr Gly Trp Thr
                85                  90                  95

His Ser Ala Lys Tyr Gly Pro Gly Thr Gly Arg Ile Trp Leu Asp Asn
            100                 105                 110

Leu Ser Cys Arg Gly Thr Glu Gly Ser Val Thr Glu Cys Ala Ser Arg
        115                 120                 125

Gly Trp Gly Asn Ser Asp Cys Thr His Asp Glu Asp Ala Gly Val Ile
    130                 135                 140

Cys Lys Asp Gln Arg Leu Pro Gly Phe Ser Asp Ser Asn Val Ile Glu
145                 150                 155                 160

Val Glu His Gln Leu Gln Val Glu Glu Val Arg Leu Arg Pro Ala Val
                165                 170                 175

Glu Trp Gly Arg Arg Pro Leu Pro Val Thr Glu Gly Leu Val Glu Val
            180                 185                 190

Arg Leu Pro Glu Gly Trp Ser Gln Val Cys Asp Lys Gly Trp Ser Ala
        195                 200                 205

His Asn Ser His Val Val Cys Gly Met Leu Gly Phe Pro Gly Glu Lys
    210                 215                 220

Arg Val Asn Met Ala Phe Tyr Arg Met Leu Ala Gln Lys Lys Gln His
225                 230                 235                 240

Ser Phe Gly Leu His Ser Val Ala Cys Val Gly Thr Glu Ala His Leu
                245                 250                 255

Ser Leu Cys Ser Leu Glu Phe Tyr Arg Ala Asn Asp Thr Thr Arg Cys
            260                 265                 270

Ser Gly Gly Asn Pro Ala Val Val Ser Cys Val Leu Gly Pro Leu Tyr
        275                 280                 285

Ala Thr Phe Thr Gly Gln Lys Lys Gln Gln His Ser Lys Pro Gln Gly
    290                 295                 300

Glu Ala Arg Val Arg Leu Lys Gly Gly Ala His Gln Gly Glu Gly Arg
305                 310                 315                 320

Val Glu Val Leu Lys Ala Gly Thr Trp Gly Thr Val Cys Asp Arg Lys
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                325                 330                 335

Trp Asp Leu Gln Ala Ala Ser Val Val Cys Arg Glu Leu Gly Phe Gly
            340                 345                 350

Thr Ala Arg Glu Ala Leu Ser Gly Ala Arg Met Gly Gln Gly Met Gly
        355                 360                 365

Ala Ile His Leu Ser Glu Val Arg Cys Ser Gly Gln Glu Pro Ser Leu
    370                 375                 380

Trp Arg Cys Pro Ser Lys Asn Ile Thr Ala Glu Asp Cys Ser His Ser
385                 390                 395                 400

Gln Asp Ala Gly Val Arg Cys Asn Leu Pro Tyr Thr Gly Val Glu Thr
                405                 410                 415

Lys Ile Arg Leu Ser Gly Gly Arg Ser Arg Tyr Glu Gly Arg Val Glu
            420                 425                 430

Val Gln Ile Gly Ile Pro Gly His Leu Arg Trp Gly Leu Ile Cys Gly
        435                 440                 445

Asp Asp Trp Gly Thr Leu Glu Ala Met Val Ala Cys Arg Gln Leu Gly
    450                 455                 460

Leu Gly Tyr Ala Asn His Gly Leu Gln Glu Thr Trp Tyr Trp Asp Ser
465                 470                 475                 480

Gly Asn Val Thr Glu Val Val Met Ser Gly Val Arg Cys Thr Gly Ser
                485                 490                 495

Glu Leu Ser Leu Asn Gln Cys Ala His His Ser Ser His Ile Thr Cys
            500                 505                 510

Lys Lys Thr Gly Thr Arg Phe Thr Ala Gly Val Ile Cys Ser Glu Thr
        515                 520                 525

Ala Ser Asp Leu Leu Leu His Ser Ala Leu Val Gln Glu Thr Ala Tyr
    530                 535                 540

Ile Glu Asp Arg Pro Leu His Met Leu Tyr Cys Ala Ala Glu Glu Asn
545                 550                 555                 560

Cys Leu Ala Ser Ser Ala Arg Ser Ala Asn Trp Pro Tyr Gly His Arg
                565                 570                 575

Arg Leu Leu Arg Phe Ser Ser Gln Ile His Asn Leu Gly Arg Ala Asp
            580                 585                 590

Phe Arg Pro Lys Ala Gly Arg His Ser Trp Val Trp His Glu Cys His
        595                 600                 605

Gly His Tyr His Ser Met Asp Ile Phe Thr His Tyr Asp Ile Leu Thr
    610                 615                 620

Pro Asn Gly Thr Lys Val Ala Glu Gly His Lys Ala Ser Phe Cys Leu
625                 630                 635                 640

Glu Asp Thr Glu Cys Gln Glu Asp Val Ser Lys Arg Tyr Glu Cys Ala
                645                 650                 655

Asn Phe Gly Glu Gln Gly Ile Thr Val Gly Cys Trp Asp Leu Tyr Arg
            660                 665                 670

His Asp Ile Asp Cys Gln Trp Ile Asp Ile Thr Asp Val Lys Pro Gly
        675                 680                 685

Asn Tyr Ile Leu Gln Val Val Ile Asn Pro Asn Phe Glu Val Ala Glu
    690                 695                 700

Ser Asp Phe Thr Asn Asn Ala Met Lys Cys Asn Cys Lys Tyr Asp Gly
705                 710                 715                 720

His Arg Ile Trp Val His Asn Cys His Ile Gly Asp Ala Phe Ser Glu
                725                 730                 735

Glu Ala Asn Arg Arg Phe Glu Arg Tyr Pro Gly Gln Thr Ser Asn Gln
            740                 745                 750
```

Ile Val

<210> SEQ ID NO 41
<211> LENGTH: 608
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 41

```
Met Arg Pro Val Ser Val Trp Gln Trp Ser Pro Trp Gly Leu Leu Leu
1               5                   10                  15

Cys Leu Leu Cys Ser Ser Cys Leu Gly Ser Pro Ser Pro Ser Thr Gly
            20                  25                  30

Pro Glu Lys Lys Ala Gly Ser Gln Gly Leu Arg Phe Arg Leu Ala Gly
        35                  40                  45

Phe Pro Arg Lys Pro Tyr Glu Gly Arg Val Glu Ile Gln Arg Ala Gly
    50                  55                  60

Glu Trp Gly Thr Ile Cys Asp Asp Asp Phe Thr Leu Gln Ala Ala His
65                  70                  75                  80

Ile Leu Cys Arg Glu Leu Gly Phe Thr Glu Ala Thr Gly Trp Thr His
                85                  90                  95

Ser Ala Lys Tyr Gly Pro Gly Thr Gly Arg Ile Trp Leu Asp Asn Leu
            100                 105                 110

Ser Cys Ser Gly Thr Glu Gln Ser Val Thr Glu Cys Ala Ser Arg Gly
        115                 120                 125

Trp Gly Asn Ser Asp Cys Thr His Asp Glu Asp Ala Gly Val Ile Cys
    130                 135                 140

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

Arg Val Arg Leu Lys Gly Gly Ala His Pro Gly Glu Gly Arg Val Glu
                165                 170                 175

Val Leu Lys Ala Ser Thr Trp Gly Thr Val Cys Asp Arg Lys Trp Asp
            180                 185                 190

Leu His Ala Ala Ser Val Val Cys Arg Glu Leu Gly Phe Gly Ser Ala
        195                 200                 205

Arg Glu Ala Leu Ser Gly Ala Arg Met Gly Gln Gly Met Gly Ala Ile
    210                 215                 220

His Leu Ser Glu Val Arg Cys Ser Gly Gln Glu Leu Ser Leu Trp Lys
225                 230                 235                 240

Cys Pro His Lys Asn Ile Thr Ala Glu Asp Cys Ser His Ser Gln Asp
                245                 250                 255

Ala Gly Val Arg Cys Asn Leu Pro Tyr Thr Gly Ala Glu Thr Arg Ile
            260                 265                 270

Arg Leu Ser Gly Gly Arg Ser Gln His Glu Gly Arg Val Glu Val Gln
        275                 280                 285

Ile Gly Gly Pro Gly Pro Leu Arg Trp Gly Leu Ile Cys Gly Asp Asp
    290                 295                 300

Trp Gly Thr Leu Glu Ala Met Val Ala Cys Arg Gln Leu Gly Leu Gly
305                 310                 315                 320

Tyr Ala Asn His Gly Leu Gln Glu Thr Trp Tyr Trp Asp Ser Gly Asn
                325                 330                 335

Ile Thr Glu Val Val Met Ser Gly Val Arg Cys Thr Gly Thr Glu Leu
            340                 345                 350

Ser Leu Asp Gln Cys Ala His His Gly Thr His Ile Thr Cys Lys Arg
        355                 360                 365

Thr Gly Thr Arg Phe Thr Ala Gly Val Ile Cys Ser Glu Thr Ala Ser
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    370                 375                 380

Asp Leu Leu Leu His Ser Ala Leu Val Gln Glu Thr Ala Tyr Ile Glu
385                 390                 395                 400

Asp Arg Pro Leu His Met Leu Tyr Cys Ala Ala Glu Glu Asn Cys Leu
                405                 410                 415

Ala Ser Ser Ala Arg Ser Ala Asn Trp Pro Tyr Gly His Arg Arg Leu
            420                 425                 430

Leu Arg Phe Ser Ser Gln Ile His Asn Leu Gly Arg Ala Asp Phe Arg
        435                 440                 445

Pro Lys Ala Gly Arg His Ser Trp Val Trp His Glu Cys His Gly His
    450                 455                 460

Tyr His Ser Met Asp Ile Phe Thr His Tyr Asp Ile Leu Thr Pro Asn
465                 470                 475                 480

Gly Thr Lys Val Ala Glu Gly His Lys Ala Ser Phe Cys Leu Glu Asp
                485                 490                 495

Thr Glu Cys Gln Glu Asp Val Ser Lys Arg Tyr Glu Cys Ala Asn Phe
            500                 505                 510

Gly Glu Gln Gly Ile Thr Val Gly Cys Trp Asp Leu Tyr Arg His Asp
        515                 520                 525

Ile Asp Cys Gln Trp Ile Asp Ile Thr Asp Val Lys Pro Gly Asn Tyr
    530                 535                 540

Ile Leu Gln Val Val Ile Asn Pro Asn Phe Glu Val Ala Glu Ser Asp
545                 550                 555                 560

Phe Thr Asn Asn Ala Met Lys Cys Asn Cys Lys Tyr Asp Gly His Arg
                565                 570                 575

Ile Trp Val His Asn Cys His Ile Gly Asp Ala Phe Ser Glu Glu Ala
            580                 585                 590

Asn Arg Arg Phe Glu Arg Tyr Pro Gly Gln Thr Ser Asn Gln Ile Ile
        595                 600                 605


<210> SEQ ID NO 42
<211> LENGTH: 164
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 42

Met Leu Phe Leu Gly Gln Lys Ala Leu Leu Leu Val Leu Ala Ile Ser
1               5                   10                  15

Ile Pro Ser Asp Trp Leu Pro Leu Gly Val Ser Gly Gln Arg Gly Asp
            20                  25                  30

Asp Val Pro Glu Thr Phe Thr Asp Asp Pro Asn Leu Val Asn Asp Pro
        35                  40                  45

Ser Thr Asp Asp Thr Ala Leu Ala Asp Ile Thr Pro Ser Thr Asp Asp
    50                  55                  60

Leu Ala Gly Asp Lys Asn Ala Thr Ala Glu Cys Arg Asp Glu Lys Phe
65                  70                  75                  80

Ala Cys Thr Arg Leu Tyr Ser Val His Arg Pro Val Arg Gln Cys Val
                85                  90                  95

His Gln Ser Cys Phe Thr Ser Leu Arg Arg Met Tyr Ile Ile Asn Asn
            100                 105                 110

Glu Ile Cys Ser Arg Leu Val Cys Lys Glu His Glu Ala Met Lys Asp
        115                 120                 125

Glu Leu Cys Arg Gln Met Ala Gly Leu Pro Pro Arg Arg Leu Arg Arg
    130                 135                 140

Ser Asn Tyr Phe Arg Leu Pro Pro Cys Glu Asn Met Asn Leu Gln Arg
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145                 150                 155                 160

Pro Asp Gly Leu


<210> SEQ ID NO 43
<211> LENGTH: 173
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 43

Met Ser Leu Leu Gly Pro Lys Val Leu Leu Phe Leu Ala Ala Phe Ile
1               5                   10                  15

Ile Thr Ser Asp Trp Ile Pro Leu Gly Val Asn Ser Gln Arg Gly Asp
            20                  25                  30

Asp Val Thr Gln Ala Thr Pro Glu Thr Phe Thr Glu Asp Pro Asn Leu
        35                  40                  45

Val Asn Asp Pro Ala Thr Asp Glu Thr Val Leu Ala Val Leu Ala Asp
    50                  55                  60

Ile Ala Pro Ser Thr Asp Asp Leu Ala Ser Leu Ser Glu Lys Asn Thr
65                  70                  75                  80

Thr Ala Glu Cys Trp Asp Glu Lys Phe Thr Cys Thr Arg Leu Tyr Ser
                85                  90                  95

Val His Arg Pro Val Lys Gln Cys Ile His Gln Leu Cys Phe Thr Ser
            100                 105                 110

Leu Arg Arg Met Tyr Ile Val Asn Lys Glu Ile Cys Ser Arg Leu Val
        115                 120                 125

Cys Lys Glu His Glu Ala Met Lys Asp Glu Leu Cys Arg Gln Met Ala
    130                 135                 140

Gly Leu Pro Pro Arg Arg Leu Arg Arg Ser Asn Tyr Phe Arg Leu Pro
145                 150                 155                 160

Pro Cys Glu Asn Val Asp Leu Gln Arg Pro Asn Gly Leu
                165                 170


<210> SEQ ID NO 44
<211> LENGTH: 104
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 44

Met Lys Ser Leu Leu Pro Leu Ala Ile Leu Ala Ala Leu Ala Val Ala
1               5                   10                  15

Thr Leu Cys Tyr Glu Ser His Glu Ser Met Glu Ser Tyr Glu Ile Ser
            20                  25                  30

Pro Phe Ile Asn Arg Arg Asn Ala Asn Thr Phe Met Ser Pro Gln Gln
        35                  40                  45

Arg Trp Arg Ala Lys Ala Gln Lys Arg Val Gln Glu Arg Asn Lys Pro
    50                  55                  60

Ala Tyr Glu Ile Asn Arg Glu Ala Cys Asp Asp Tyr Lys Leu Cys Glu
65                  70                  75                  80

Arg Tyr Ala Met Val Tyr Gly Tyr Asn Ala Ala Tyr Asn Arg Tyr Phe
                85                  90                  95

Arg Gln Arg Arg Gly Ala Lys Tyr
            100


<210> SEQ ID NO 45
<211> LENGTH: 103
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
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<400> SEQUENCE: 45

Met Lys Ser Leu Ile Leu Leu Ala Ile Leu Ala Ala Leu Ala Val Val
1               5                   10                  15

Thr Leu Cys Tyr Glu Ser His Glu Ser Met Glu Ser Tyr Glu Leu Asn
            20                  25                  30

Pro Phe Ile Asn Arg Arg Asn Ala Asn Thr Phe Ile Ser Pro Gln Gln
        35                  40                  45

Arg Trp Arg Ala Lys Val Gln Glu Arg Ile Arg Glu Arg Ser Lys Pro
    50                  55                  60

Val His Glu Leu Asn Arg Glu Ala Cys Asp Asp Tyr Arg Leu Cys Glu
65                  70                  75                  80

Arg Tyr Ala Met Val Tyr Gly Tyr Asn Ala Ala Tyr Asn Arg Tyr Phe
                85                  90                  95

Arg Lys Arg Arg Gly Ala Lys
            100


<210> SEQ ID NO 46
<211> LENGTH: 415
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 46

Met Leu Gln Lys Thr Val Leu Leu Leu Ala Leu Val Ala Gln Val Leu
1               5                   10                  15

Met Leu Glu Asn Gly Leu Leu Arg Thr Pro Pro Met Gly Trp Leu Ala
            20                  25                  30

Trp Glu Arg Phe Arg Cys Asn Ile Asp Cys Val Glu Asp Pro Lys Asn
        35                  40                  45

Cys Ile Ser Glu Arg Leu Phe Met Glu Met Ala Asp Arg Leu Ala Gln
    50                  55                  60

Asp Gly Trp Arg Asp Leu Gly Tyr Val Tyr Leu Asn Ile Asp Asp Cys
65                  70                  75                  80

Trp Ile Gly Gly Arg Asp Ala Ser Gly Arg Leu Ile Pro Asp Pro Lys
                85                  90                  95

Arg Phe Pro His Gly Ile Ala Phe Leu Ala Asp Tyr Ala His Ser Leu
            100                 105                 110

Gly Leu Lys Leu Gly Ile Tyr Glu Asp Met Gly Lys Met Thr Cys Met
        115                 120                 125

Gly Tyr Pro Gly Thr Thr Leu Asp Lys Val Glu Leu Asp Ala Glu Thr
    130                 135                 140

Phe Ala Glu Trp Lys Val Asp Met Leu Lys Leu Asp Gly Cys Phe Ser
145                 150                 155                 160

Ser Ser Arg Glu Arg Ala Glu Gly Tyr Pro Lys Met Ala Ala Ala Leu
                165                 170                 175

Asn Ala Thr Gly Arg Pro Ile Ala Phe Ser Cys Ser Trp Pro Ala Tyr
            180                 185                 190

Glu Gly Gly Leu Pro Pro Lys Val Asn Tyr Thr Glu Val Ser Arg Val
        195                 200                 205

Cys Asn Leu Trp Arg Asn Tyr Lys Asp Ile Gln Asp Ser Trp Lys Ser
    210                 215                 220

Val Leu Ser Ile Leu Asp Trp Phe Val Arg His Gln Asp Val Pro Gln
225                 230                 235                 240

Pro Val Ala Gly Pro Gly His Trp Asn Asp Pro Asp Met Leu Leu Ile
                245                 250                 255

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

Trp Thr Val Leu Ala Ala Pro Leu Leu Met Ser Thr Asp Leu Arg Thr
        275                 280                 285

Ile Ser Pro Gln Asn Met Asp Ile Leu Gln Asn Pro Leu Met Ile Lys
    290                 295                 300

Ile Asn Gln Asp Pro Leu Gly Ile Gln Gly Arg Arg Ile Leu Lys Ser
305                 310                 315                 320

Lys Ser His Ile Glu Val Phe Lys Arg Tyr Leu Ser Asn Gln Ala Ser
                325                 330                 335

Ala Leu Val Phe Phe Ser Arg Arg Thr Asp Met Pro Phe Arg Phe His
            340                 345                 350

Cys Ser Leu Leu Glu Leu Asn Tyr Pro Lys Gly Arg Val Tyr Glu Gly
        355                 360                 365

Gln Asn Val Phe Thr Gly Asp Ile Phe Ser Gly Leu Gln Thr Glu Val
    370                 375                 380

Asn Phe Thr Val Ile Ile Asn Pro Ser Gly Val Val Met Trp Tyr Leu
385                 390                 395                 400

Tyr Pro Ile Lys Asp Leu Gly Ile Ser Thr Met Met Ser His Trp
                405                 410                 415


<210> SEQ ID NO 47
<211> LENGTH: 411
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 47

Met Leu Leu Lys Thr Val Leu Leu Leu Gly His Val Ala Gln Val Leu
1               5                   10                  15

Met Leu Asp Asn Gly Leu Leu Gln Thr Pro Pro Met Gly Trp Leu Ala
            20                  25                  30

Trp Glu Arg Phe Arg Cys Asn Ile Asn Cys Asp Glu Asp Pro Lys Asn
        35                  40                  45

Cys Ile Ser Glu Gln Leu Phe Met Glu Met Ala Asp Arg Met Ala Gln
    50                  55                  60

Asp Gly Trp Arg Asp Met Gly Tyr Thr Tyr Leu Asn Ile Asp Asp Cys
65                  70                  75                  80

Trp Ile Gly Gly Arg Asp Ala Ser Gly Arg Leu Met Pro Asp Pro Lys
                85                  90                  95

Arg Phe Pro His Gly Ile Pro Phe Leu Ala Asp Tyr Val His Ser Leu
            100                 105                 110

Gly Leu Lys Leu Gly Ile Tyr Ala Asp Met Gly Asn Phe Thr Cys Met
        115                 120                 125

Gly Tyr Pro Gly Thr Thr Leu Asp Lys Val Val Gln Asp Ala Gln Thr
    130                 135                 140

Phe Ala Glu Trp Lys Val Asp Met Leu Lys Leu Asp Gly Cys Phe Ser
145                 150                 155                 160

Thr Pro Glu Glu Arg Ala Gln Gly Tyr Pro Lys Met Ala Ala Ala Leu
                165                 170                 175

Asn Ala Thr Gly Arg Pro Ile Ala Phe Ser Cys Ser Trp Pro Ala Tyr
            180                 185                 190

Glu Gly Gly Leu Pro Pro Arg Val Asn Tyr Ser Leu Leu Ala Asp Ile
        195                 200                 205

Cys Asn Leu Trp Arg Asn Tyr Asp Asp Ile Gln Asp Ser Trp Trp Ser
    210                 215                 220

Val Leu Ser Ile Leu Asn Trp Phe Val Glu His Gln Asp Ile Leu Gln
```

```
225                 230                 235                 240

Pro Val Ala Gly Pro Gly His Trp Asn Asp Pro Asp Met Leu Leu Ile
                245                 250                 255

Gly Asn Phe Gly Leu Ser Leu Glu Gln Ser Arg Ala Gln Met Ala Leu
            260                 265                 270

Trp Thr Val Leu Ala Ala Pro Leu Leu Met Ser Thr Asp Leu Arg Thr
        275                 280                 285

Ile Ser Ala Gln Asn Met Asp Ile Leu Gln Asn Pro Leu Met Ile Lys
    290                 295                 300

Ile Asn Gln Asp Pro Leu Gly Ile Gln Gly Arg Arg Ile His Lys Glu
305                 310                 315                 320

Lys Ser Leu Ile Glu Val Tyr Met Arg Pro Leu Ser Asn Lys Ala Ser
                325                 330                 335

Ala Leu Val Phe Phe Ser Cys Arg Thr Asp Met Pro Tyr Arg Tyr His
            340                 345                 350

Ser Ser Leu Gly Gln Leu Asn Phe Thr Gly Ser Val Ile Tyr Glu Ala
        355                 360                 365

Gln Asp Val Tyr Ser Gly Asp Ile Ile Ser Gly Leu Arg Asp Glu Thr
    370                 375                 380

Asn Phe Thr Val Ile Ile Asn Pro Ser Gly Val Val Met Trp Tyr Leu
385                 390                 395                 400

Tyr Pro Ile Lys Asn Leu Glu Met Ser Gln Gln
                405                 410


<210> SEQ ID NO 48
<211> LENGTH: 178
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 48

Met Leu Trp Val Leu Val Gly Ala Val Leu Pro Val Met Leu Leu Ala
1               5                   10                  15

Ala Pro Pro Pro Ile Asn Lys Leu Ala Leu Phe Pro Asp Lys Ser Ala
            20                  25                  30

Trp Cys Glu Ala Lys Asn Ile Thr Gln Ile Val Gly His Ser Gly Cys
        35                  40                  45

Glu Ala Lys Ser Ile Gln Asn Arg Ala Cys Leu Gly Gln Cys Phe Ser
    50                  55                  60

Tyr Ser Val Pro Asn Thr Phe Pro Gln Ser Thr Glu Ser Leu Val His
65                  70                  75                  80

Cys Asp Ser Cys Met Pro Ala Gln Ser Met Trp Glu Ile Val Thr Leu
                85                  90                  95

Glu Cys Pro Asp His Glu Glu Val Pro Arg Val Asp Lys Leu Val Glu
            100                 105                 110

Lys Ile Val His Cys Ser Cys Gln Ala Cys Gly Lys Glu Pro Ser His
        115                 120                 125

Glu Gly Leu Asn Val Tyr Val Gln Gly Glu Asp Ser Pro Gly Ser Gln
    130                 135                 140

Pro Gly Pro His Ser His Ala His Pro His Pro Gly Gly Gln Thr Pro
145                 150                 155                 160

Glu Pro Glu Glu Pro Pro Gly Ala Pro Gln Val Glu Glu Glu Gly Ala
                165                 170                 175

Glu Asp


<210> SEQ ID NO 49
```

<211> LENGTH: 181
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 49

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

Ala Ala Pro Pro Pro Ile Asn Lys Leu Ala Leu Phe Pro Asp Lys Ser
            20                  25                  30

Ala Trp Cys Glu Ala Lys Asn Ile Thr Gln Ile Val Gly His Ser Gly
        35                  40                  45

Cys Glu Ala Lys Ser Ile Gln Asn Arg Ala Cys Leu Gly Gln Cys Phe
    50                  55                  60

Ser Tyr Ser Val Pro Asn Thr Phe Pro Gln Ser Thr Glu Ser Leu Val
65                  70                  75                  80

His Cys Asp Ser Cys Met Pro Ala Gln Ser Met Trp Glu Ile Val Thr
                85                  90                  95

Leu Glu Cys Pro Gly His Glu Glu Val Pro Arg Val Asp Lys Leu Val
            100                 105                 110

Glu Lys Ile Leu His Cys Ser Cys Gln Ala Cys Gly Lys Glu Pro Ser
        115                 120                 125

His Glu Gly Leu Ser Val Tyr Val Gln Gly Glu Asp Gly Pro Gly Ser
    130                 135                 140

Gln Pro Gly Thr His Pro His Pro His Pro His Pro His Pro Gly Gly
145                 150                 155                 160

Gln Thr Pro Glu Pro Glu Asp Pro Pro Gly Ala Pro His Thr Glu Glu
                165                 170                 175

Glu Gly Ala Glu Asp
            180
```

<210> SEQ ID NO 50
<211> LENGTH: 307
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 50

```
Met Leu Cys Leu Lys Pro Val Lys Leu Gly Ser Leu Glu Val Gly His
1               5                   10                  15

Gly Gln His Gly Gly Val Leu Ala Cys Gly Arg Ala Val Gln Gly Ala
            20                  25                  30

Gly Trp His Ala Gly Pro Lys Leu Thr Ser Val Ser Gly Pro Asn Lys
        35                  40                  45

Gly Phe Ala Lys Asp Ala Ala Phe Tyr Thr Gly Arg Ser Glu Val His
    50                  55                  60

Ser Val Met Ser Met Leu Phe Tyr Thr Leu Ile Thr Ala Phe Leu Ile
65                  70                  75                  80

Gly Val Gln Ala Glu Pro Tyr Thr Asp Ser Asn Val Pro Glu Gly Asp
                85                  90                  95

Ser Val Pro Glu Ala His Trp Thr Lys Leu Gln His Ser Leu Asp Thr
            100                 105                 110

Ala Leu Arg Arg Ala Arg Ser Ala Pro Thr Ala Pro Ile Ala Ala Arg
        115                 120                 125

Val Thr Gly Gln Thr Arg Asn Ile Thr Val Asp Pro Arg Leu Phe Lys
    130                 135                 140

Lys Arg Arg Leu His Ser Pro Arg Val Leu Phe Ser Thr Gln Pro Pro
145                 150                 155                 160
```

```
Pro Thr Ser Ser Asp Thr Leu Asp Leu Asp Phe Gln Ala His Gly Thr
                165                 170                 175

Ile Pro Phe Asn Arg Thr His Arg Ser Lys Arg Ser Ser Thr His Pro
            180                 185                 190

Val Phe His Met Gly Glu Phe Ser Val Cys Asp Ser Val Ser Val Trp
        195                 200                 205

Val Gly Asp Lys Thr Thr Ala Thr Asp Ile Lys Gly Lys Glu Val Thr
    210                 215                 220

Val Leu Ala Glu Val Asn Ile Asn Asn Ser Val Phe Arg Gln Tyr Phe
225                 230                 235                 240

Phe Glu Thr Lys Cys Arg Ala Ser Asn Pro Val Glu Ser Gly Cys Arg
                245                 250                 255

Gly Ile Asp Ser Lys His Trp Asn Ser Tyr Cys Thr Thr Thr His Thr
            260                 265                 270

Phe Val Lys Ala Leu Thr Thr Asp Glu Lys Gln Ala Ala Trp Arg Phe
        275                 280                 285

Ile Arg Ile Asp Thr Ala Cys Val Cys Val Leu Ser Arg Lys Ala Thr
    290                 295                 300

Arg Arg Gly
305


<210> SEQ ID NO 51
<211> LENGTH: 299
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 51

Gly Arg Val Gly Ala Gly Ser Arg Arg Gly Ala Gln Arg Val Leu Ala
1               5                   10                  15

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

Ser Ser Ala Ser Gly Pro Asn Asn Ser Phe Thr Lys Gly Ala Ala Phe
        35                  40                  45

Tyr Pro Gly His Thr Glu Val His Ser Val Met Ser Met Leu Phe Tyr
    50                  55                  60

Thr Leu Ile Thr Ala Phe Leu Ile Gly Ile Gln Ala Glu Pro His Ser
65                  70                  75                  80

Glu Ser Asn Val Pro Ala Gly His Thr Ile Pro Gln Val His Trp Thr
                85                  90                  95

Lys Leu Gln His Ser Leu Asp Thr Ala Leu Arg Arg Ala Arg Ser Ala
            100                 105                 110

Pro Ala Ala Ala Ile Ala Ala Arg Val Ala Gly Gln Thr Arg Asn Ile
        115                 120                 125

Thr Val Asp Pro Arg Leu Phe Lys Lys Arg Arg Leu Arg Ser Pro Arg
    130                 135                 140

Val Leu Phe Ser Thr Gln Pro Pro Arg Glu Ala Ala Asp Thr Gln Asp
145                 150                 155                 160

Leu Asp Phe Glu Val Gly Gly Ala Ala Pro Phe Asn Arg Thr His Arg
                165                 170                 175

Ser Lys Arg Ser Ser Ser His Pro Ile Phe His Arg Gly Glu Phe Ser
            180                 185                 190

Val Cys Asp Ser Val Ser Val Trp Val Gly Asp Lys Thr Thr Ala Thr
        195                 200                 205

Asp Ile Lys Gly Lys Glu Val Met Val Leu Gly Glu Val Asn Ile Asn
    210                 215                 220
```

```
Asn Ser Val Phe Lys Gln Tyr Phe Phe Glu Thr Lys Cys Arg Asp Pro
225                 230                 235                 240

Asn Pro Val Asp Ser Gly Cys Arg Gly Ile Asp Ser Lys His Trp Asn
                245                 250                 255

Ser Tyr Cys Thr Thr Thr His Thr Phe Val Lys Ala Leu Thr Met Asp
            260                 265                 270

Gly Lys Gln Ala Ala Trp Arg Phe Ile Arg Ile Asp Thr Ala Cys Val
        275                 280                 285

Cys Val Leu Ser Arg Lys Ala Val Arg Arg Ala
    290                 295


<210> SEQ ID NO 52
<211> LENGTH: 592
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 52

Met Ala Val Leu Leu Ala Ala Val Leu Ala Ser Ser Leu Tyr Leu Gln
1               5                   10                  15

Val Ala Ala Asp Phe Asp Gly Arg Trp Pro Arg Gln Ile Val Ser Ser
            20                  25                  30

Ile Gly Leu Cys Arg Tyr Gly Gly Arg Ile Asp Cys Cys Trp Gly Trp
        35                  40                  45

Ala Arg Gln Ser Trp Gly Gln Cys Gln Pro Val Cys Gln Pro Gln Cys
    50                  55                  60

Lys His Gly Glu Cys Val Gly Pro Asn Lys Cys Lys Cys His Pro Gly
65                  70                  75                  80

Phe Ala Gly Lys Thr Cys Asn Gln Asp Glu Ser Phe His Pro Thr Pro
                85                  90                  95

Leu Asp Gln Gly Ser Glu Gln Pro Leu Phe Gln Pro Pro Asp His Gln
            100                 105                 110

Ala Thr Asn Val Pro Ser Arg Asp Leu Asn Glu Cys Gly Leu Lys Pro
        115                 120                 125

Arg Pro Cys Lys His Arg Cys Met Asn Thr Phe Gly Ser Tyr Lys Cys
    130                 135                 140

Tyr Cys Leu Asn Gly Tyr Met Leu Leu Pro Asp Gly Ser Cys Ser Ser
145                 150                 155                 160

Ala Leu Ser Cys Ser Met Ala Asn Cys Gln Tyr Gly Cys Asp Val Val
                165                 170                 175

Lys Gly Gln Val Arg Cys Gln Cys Pro Ser Pro Gly Leu Gln Leu Ala
            180                 185                 190

Pro Asp Gly Arg Thr Cys Val Asp Ile Asp Glu Cys Ala Thr Gly Arg
        195                 200                 205

Val Ser Cys Pro Arg Phe Arg Gln Cys Val Asn Thr Phe Gly Ser Tyr
    210                 215                 220

Ile Cys Lys Cys His Thr Gly Phe Asp Leu Met Tyr Ile Gly Gly Lys
225                 230                 235                 240

Tyr Gln Cys His Asp Ile Asp Glu Cys Ser Leu Gly Gln His Gln Cys
                245                 250                 255

Ser Ser Tyr Ala Arg Cys Tyr Asn Ile His Gly Ser Tyr Lys Cys Gln
            260                 265                 270

Cys Arg Asp Gly Tyr Glu Gly Asp Gly Leu Asn Cys Val Tyr Ile Pro
        275                 280                 285

Lys Val Met Ile Glu Pro Ser Gly Pro Ile His Met Pro Glu Arg Asn
    290                 295                 300
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```
Gly Thr Ile Ser Lys Gly Asp Gly Gly His Ala Asn Arg Ile Pro Asp
305                 310                 315                 320

Ala Gly Ser Thr Arg Trp Pro Leu Lys Thr Pro Tyr Ile Pro Pro Val
                325                 330                 335

Ile Thr Asn Arg Pro Thr Ser Lys Pro Thr Thr Arg Pro Thr Pro Asn
            340                 345                 350

Pro Thr Pro Gln Pro Thr Pro Pro Pro Pro Pro Pro Leu Pro Thr Glu
        355                 360                 365

Pro Arg Thr Thr Pro Leu Pro Pro Thr Pro Glu Arg Pro Ser Thr Arg
    370                 375                 380

Pro Thr Thr Ile Ala Pro Ala Thr Ser Thr Thr Thr Arg Val Ile Thr
385                 390                 395                 400

Val Asp Asn Arg Ile Gln Thr Asp Pro Gln Lys Pro Arg Gly Asp Val
                405                 410                 415

Phe Ile Pro Arg Gln Pro Thr Asn Asp Leu Phe Glu Ile Phe Glu Ile
            420                 425                 430

Glu Arg Gly Val Ser Ala Asp Glu Glu Val Lys Asp Asp Pro Gly Ile
        435                 440                 445

Leu Ile His Ser Cys Asn Phe Asp His Gly Leu Cys Gly Trp Ile Arg
    450                 455                 460

Glu Lys Asp Ser Asp Leu His Trp Glu Thr Ala Arg Asp Pro Ala Gly
465                 470                 475                 480

Gly Gln Tyr Leu Thr Val Ser Ala Ala Lys Ala Pro Gly Gly Lys Ala
                485                 490                 495

Ala Arg Leu Val Leu Arg Leu Gly His Leu Met His Ser Gly Asp Leu
            500                 505                 510

Cys Leu Ser Phe Arg His Lys Val Thr Gly Leu His Ser Gly Thr Leu
        515                 520                 525

Gln Val Phe Val Arg Lys His Gly Thr His Gly Ala Ala Leu Trp Gly
    530                 535                 540

Arg Asn Gly Gly His Gly Trp Arg Gln Thr Gln Ile Thr Leu Arg Gly
545                 550                 555                 560

Ala Asp Val Lys Ser Val Ile Phe Lys Gly Glu Lys Arg Arg Gly His
                565                 570                 575

Thr Gly Glu Ile Gly Leu Asp Asp Val Ser Leu Lys Arg Gly Arg Cys
            580                 585                 590


<210> SEQ ID NO 53
<211> LENGTH: 565
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 53

Met Asp Phe Leu Leu Ala Leu Val Leu Val Ser Ser Leu Tyr Leu Gln
1               5                   10                  15

Ala Ala Ala Glu Phe Asp Gly Arg Trp Pro Arg Gln Ile Val Ser Ser
            20                  25                  30

Ile Gly Leu Cys Arg Tyr Gly Gly Arg Ile Asp Cys Cys Trp Gly Trp
        35                  40                  45

Ala Arg Gln Ser Trp Gly Gln Cys Gln Pro Val Cys Gln Pro Arg Cys
    50                  55                  60

Lys His Gly Glu Cys Ile Gly Pro Asn Lys Cys Lys Cys His Pro Gly
65                  70                  75                  80

Tyr Ala Gly Lys Thr Cys Asn Gln Asp Leu Asn Glu Cys Gly Leu Lys
                85                  90                  95
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Pro Arg Pro Cys Lys His Arg Cys Met Asn Thr Tyr Gly Ser Tyr Lys
            100                 105                 110

Cys Tyr Cys Leu Asn Gly Tyr Met Leu Met Pro Asp Gly Ser Cys Ser
        115                 120                 125

Ser Ala Leu Thr Cys Ser Met Ala Asn Cys Gln Tyr Gly Cys Asp Val
    130                 135                 140

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

Ala Pro Asp Gly Arg Thr Cys Val Asp Val Asp Glu Cys Ala Thr Gly
                165                 170                 175

Arg Ala Ser Cys Pro Arg Phe Arg Gln Cys Val Asn Thr Phe Gly Ser
            180                 185                 190

Tyr Ile Cys Lys Cys His Lys Gly Phe Asp Leu Met Tyr Ile Gly Gly
        195                 200                 205

Lys Tyr Gln Cys His Asp Ile Asp Glu Cys Ser Leu Gly Gln Tyr Gln
    210                 215                 220

Cys Ser Ser Phe Ala Arg Cys Tyr Asn Ile Arg Gly Ser Tyr Lys Cys
225                 230                 235                 240

Lys Cys Lys Glu Gly Tyr Gln Gly Asp Gly Leu Thr Cys Val Tyr Ile
                245                 250                 255

Pro Lys Val Met Ile Glu Pro Ser Gly Pro Ile His Val Pro Lys Gly
            260                 265                 270

Asn Gly Thr Ile Leu Lys Gly Asp Thr Gly Asn Asn Asn Trp Ile Pro
        275                 280                 285

Asp Val Gly Ser Thr Trp Trp Pro Pro Lys Thr Pro Tyr Ile Pro Pro
    290                 295                 300

Ile Ile Thr Asn Arg Pro Thr Ser Lys Pro Thr Thr Arg Pro Thr Pro
305                 310                 315                 320

Lys Pro Thr Pro Ile Pro Thr Pro Pro Pro Pro Pro Pro Leu Pro Thr
                325                 330                 335

Glu Leu Arg Thr Pro Leu Pro Pro Thr Thr Pro Glu Arg Pro Thr Thr
            340                 345                 350

Gly Leu Thr Thr Ile Ala Pro Ala Ala Ser Thr Pro Pro Gly Gly Ile
        355                 360                 365

Thr Val Asp Asn Arg Val Gln Thr Asp Pro Gln Lys Pro Arg Gly Asp
    370                 375                 380

Val Phe Ile Pro Arg Gln Pro Ser Asn Asp Leu Phe Glu Ile Phe Glu
385                 390                 395                 400

Ile Glu Arg Gly Val Ser Ala Asp Asp Glu Ala Lys Asp Asp Pro Gly
                405                 410                 415

Val Leu Val His Ser Cys Asn Phe Asp His Gly Leu Cys Gly Trp Ile
            420                 425                 430

Arg Glu Lys Asp Asn Asp Leu His Trp Glu Pro Ile Arg Asp Pro Ala
        435                 440                 445

Gly Gly Gln Tyr Leu Thr Val Ser Ala Ala Lys Ala Pro Gly Gly Lys
    450                 455                 460

Ala Ala Arg Leu Val Leu Pro Leu Gly Arg Leu Met His Ser Gly Asp
465                 470                 475                 480

Leu Cys Leu Ser Phe Arg His Lys Val Thr Gly Leu His Ser Gly Thr
                485                 490                 495

Leu Gln Val Phe Val Arg Lys His Gly Ala His Gly Ala Ala Leu Trp
            500                 505                 510

Gly Arg Asn Gly Gly His Gly Trp Arg Gln Thr Gln Ile Thr Leu Arg
        515                 520                 525
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```
Gly Ala Asp Ile Lys Ser Val Val Phe Lys Gly Glu Lys Arg Arg Gly
    530                 535                 540

His Thr Gly Glu Ile Gly Leu Asp Asp Val Ser Leu Lys Lys Gly His
545                 550                 555                 560

Cys Ser Glu Glu Arg
                565


<210> SEQ ID NO 54
<211> LENGTH: 457
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 54

Met Gln Pro Ala Arg Lys Leu Leu Ser Leu Leu Val Leu Leu Val Met
1               5                   10                  15

Gly Thr Glu Leu Thr Gln Val Leu Pro Thr Asn Pro Glu Glu Ser Trp
            20                  25                  30

Gln Val Tyr Ser Ser Ala Gln Asp Ser Glu Gly Arg Cys Ile Cys Thr
        35                  40                  45

Val Val Ala Pro Gln Gln Thr Met Cys Ser Arg Asp Ala Arg Thr Lys
    50                  55                  60

Gln Leu Arg Gln Leu Leu Glu Lys Val Gln Asn Met Ser Gln Ser Ile
65                  70                  75                  80

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

Met Glu Asn Gln Met Lys Gly Leu Glu Thr Lys Phe Lys Gln Val Glu
            100                 105                 110

Glu Ser His Lys Gln His Leu Ala Arg Gln Phe Lys Ala Ile Lys Ala
        115                 120                 125

Lys Met Asp Glu Leu Arg Pro Leu Ile Pro Val Leu Glu Glu Tyr Lys
    130                 135                 140

Ala Asp Ala Lys Leu Val Leu Gln Phe Lys Glu Glu Val Gln Asn Leu
145                 150                 155                 160

Thr Ser Val Leu Asn Glu Leu Gln Glu Glu Ile Gly Ala Tyr Asp Tyr
                165                 170                 175

Asp Glu Leu Gln Ser Arg Val Ser Asn Leu Glu Glu Arg Leu Arg Ala
            180                 185                 190

Cys Met Gln Lys Leu Ala Cys Gly Lys Leu Thr Gly Ile Ser Asp Pro
        195                 200                 205

Val Thr Val Lys Thr Ser Gly Ser Arg Phe Gly Ser Trp Met Thr Asp
    210                 215                 220

Pro Leu Ala Pro Glu Gly Asp Asn Arg Val Trp Tyr Met Asp Gly Tyr
225                 230                 235                 240

His Asn Asn Arg Phe Val Arg Glu Tyr Lys Ser Met Val Asp Phe Met
                245                 250                 255

Asn Thr Asp Asn Phe Thr Ser His Arg Leu Pro His Pro Trp Ser Gly
            260                 265                 270

Thr Gly Gln Val Val Tyr Asn Gly Ser Ile Tyr Phe Asn Lys Phe Gln
        275                 280                 285

Ser His Ile Ile Ile Arg Phe Asp Leu Lys Thr Glu Ala Ile Leu Lys
    290                 295                 300

Thr Arg Ser Leu Asp Tyr Ala Gly Tyr Asn Asn Met Tyr His Tyr Ala
305                 310                 315                 320

Trp Gly Gly His Ser Asp Ile Asp Leu Met Val Asp Glu Asn Gly Leu
                325                 330                 335
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Trp Ala Val Tyr Ala Thr Asn Gln Asn Ala Gly Asn Ile Val Ile Ser
            340                 345                 350

Lys Leu Asp Pro Val Ser Leu Gln Ile Leu Gln Thr Trp Asn Thr Ser
        355                 360                 365

Tyr Pro Lys Arg Ser Ala Gly Glu Ala Phe Ile Ile Cys Gly Thr Leu
    370                 375                 380

Tyr Val Thr Asn Gly Tyr Ser Gly Gly Thr Lys Val His Tyr Ala Tyr
385                 390                 395                 400

Gln Thr Asn Ala Ser Thr Tyr Glu Tyr Ile Asp Ile Pro Phe Gln Asn
                405                 410                 415

Lys Tyr Ser His Ile Ser Met Leu Asp Tyr Asn Pro Lys Asp Arg Ala
            420                 425                 430

Leu Tyr Ala Trp Asn Asn Gly His Gln Thr Leu Tyr Asn Val Thr Leu
        435                 440                 445

Phe His Val Ile Arg Ser Asp Glu Leu
    450                 455


<210> SEQ ID NO 55
<211> LENGTH: 485
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 55

Met Ser Val Pro Leu Leu Lys Ile Gly Val Val Leu Ser Thr Met Ala
1               5                   10                  15

Met Ile Thr Asn Trp Met Ser Gln Thr Leu Pro Ser Leu Val Gly Leu
            20                  25                  30

Asn Thr Thr Arg Leu Ser Ala Ala Ser Gly Gly Thr Leu Asp Arg Ser
        35                  40                  45

Thr Gly Val Leu Pro Thr Asn Pro Glu Glu Ser Trp Gln Val Tyr Ser
    50                  55                  60

Ser Ala Gln Asp Ser Glu Gly Arg Cys Ile Cys Thr Val Val Ala Pro
65                  70                  75                  80

Gln Gln Thr Met Cys Ser Arg Asp Ala Arg Thr Lys Gln Leu Arg Gln
                85                  90                  95

Leu Leu Glu Lys Val Gln Asn Met Ser Gln Ser Ile Glu Val Leu Asp
            100                 105                 110

Arg Arg Thr Gln Arg Asp Leu Gln Tyr Val Glu Lys Met Glu Asn Gln
        115                 120                 125

Met Lys Gly Leu Glu Ser Lys Phe Lys Gln Val Glu Glu Ser His Lys
    130                 135                 140

Gln His Leu Ala Arg Gln Phe Lys Ala Ile Lys Ala Lys Met Asp Glu
145                 150                 155                 160

Leu Arg Pro Leu Ile Pro Val Leu Glu Glu Tyr Lys Ala Asp Ala Lys
                165                 170                 175

Leu Val Leu Gln Phe Lys Glu Glu Val Gln Asn Leu Thr Ser Val Leu
            180                 185                 190

Asn Glu Leu Gln Glu Glu Ile Gly Ala Tyr Asp Tyr Asp Glu Leu Gln
        195                 200                 205

Ser Arg Val Ser Asn Leu Glu Glu Arg Leu Arg Ala Cys Met Gln Lys
    210                 215                 220

Leu Ala Cys Gly Lys Leu Thr Gly Ile Ser Asp Pro Val Thr Val Lys
225                 230                 235                 240

Thr Ser Gly Ser Arg Phe Gly Ser Trp Met Thr Asp Pro Leu Ala Pro
                245                 250                 255
```

```
Glu Gly Asp Asn Arg Val Trp Tyr Met Asp Gly Tyr His Asn Asn Arg
            260                 265                 270

Phe Val Arg Glu Tyr Lys Ser Met Val Asp Phe Met Asn Thr Asp Asn
        275                 280                 285

Phe Thr Ser His Arg Leu Pro His Pro Trp Ser Gly Thr Gly Gln Val
    290                 295                 300

Val Tyr Asn Gly Ser Ile Tyr Phe Asn Lys Phe Gln Ser His Ile Ile
305                 310                 315                 320

Ile Arg Phe Asp Leu Lys Thr Glu Thr Ile Leu Lys Thr Arg Ser Leu
                325                 330                 335

Asp Tyr Ala Gly Tyr Asn Asn Met Tyr His Tyr Ala Trp Gly Gly His
            340                 345                 350

Ser Asp Ile Asp Leu Met Val Asp Glu Ser Gly Leu Trp Ala Val Tyr
        355                 360                 365

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

Val Ser Leu Gln Thr Leu Gln Thr Trp Asn Thr Ser Tyr Pro Lys Arg
385                 390                 395                 400

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

Gly Tyr Ser Gly Gly Thr Lys Val His Tyr Ala Tyr Gln Thr Asn Ala
            420                 425                 430

Ser Thr Tyr Glu Tyr Ile Asp Ile Pro Phe Gln Asn Lys Tyr Ser His
        435                 440                 445

Ile Ser Met Leu Asp Tyr Asn Pro Lys Asp Arg Ala Leu Tyr Ala Trp
    450                 455                 460

Asn Asn Gly His Gln Ile Leu Tyr Asn Val Thr Leu Phe His Val Ile
465                 470                 475                 480

Arg Ser Asp Glu Leu
                485


<210> SEQ ID NO 56
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 56

Met Lys Val Val Ile Leu Met Ala Leu Leu Val Leu Thr Ala His Cys
1               5                   10                  15

Val Pro Val Ser Arg Phe Pro Gly Lys Ile Phe Leu Tyr Cys Pro Phe
            20                  25                  30

Phe Asn Arg Lys His Cys Gln Arg Phe Cys Glu Phe Phe Lys Ile Cys
        35                  40                  45

Arg Lys Pro Pro Leu Ser Arg Arg Thr Thr Val Val Pro Ser Phe Pro
    50                  55                  60

Leu Thr Thr Glu Ala Asp Leu Ser Leu Thr Gly Gly Pro Leu Thr Pro
65                  70                  75                  80

Thr Gly Gly Glu Ile Gln Asp Ser Arg Val Pro His Ser Pro Glu Lys
                85                  90                  95

Pro Leu Pro Pro His Ser Ala His Ala Thr Val Gly Ser Cys Phe Gln
            100                 105                 110

Leu Leu Pro Ala Pro Gln
        115


<210> SEQ ID NO 57
```

<211> LENGTH: 32
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 57

ggcggcgcgg ccgcatggag aagatgttgg tg 32

<210> SEQ ID NO 58
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 58

ggcggcccgc ggtctgtatt ttaggcgatt 30

<210> SEQ ID NO 59
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 59

ggcggcctcg agatggagaa gatgttggtg 30

<210> SEQ ID NO 60
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 60

ccggccgaat tctcaatggt gatggtgatg atgacc 36

<210> SEQ ID NO 61
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 61

ggcgccggat ccatgaatgt atgtgcgttc 30

<210> SEQ ID NO 62
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 62

ggcgccggat ccatgaatgt atgtgcgttc 30

<210> SEQ ID NO 63
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 63

ggcgccagat ctatgaatgt atgtgcgttc 30

<210> SEQ ID NO 64
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 64

ccggccgaat tctcaatggt gatggtgatg atgacc 36

<210> SEQ ID NO 65
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 65

ggcggcggat ccatggggac cgtatccaga 30

<210> SEQ ID NO 66
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<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 66

ggcggcccgc ggttcttcct tggacccagg 30

<210> SEQ ID NO 67
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 67

ggcgccagat ctatgaatgt atgtgcgttc 30

<210> SEQ ID NO 68
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 68

ggccgggtta actcaatggt gatggtgatg atg 33

<210> SEQ ID NO 69
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<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 69

ggcggcaagc ttatgctgcc gccacagctg 30

<210> SEQ ID NO 70
<211> LENGTH: 30
<212> TYPE: DNA
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<223> OTHER INFORMATION: primer

<400> SEQUENCE: 70

ggcggcccgc ggtccttgtt tcctgggctg 30

<210> SEQ ID NO 71
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<212> TYPE: DNA
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<400> SEQUENCE: 71

ggcggcctcg agatgtggcc ccaaccaccc 30

<210> SEQ ID NO 72
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<400> SEQUENCE: 72

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<210> SEQ ID NO 76
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<212> TYPE: DNA
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<210> SEQ ID NO 77

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ggcggcaagc ttatggcgtc tcgggagtca 30

<210> SEQ ID NO 78
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<212> TYPE: DNA
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ggcggcccgc ggtgaagcct tggctttccg 30

<210> SEQ ID NO 79
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<400> SEQUENCE: 79

ggcggcgaat tcatggcgtc tcgggagtca 30

<210> SEQ ID NO 80
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<212> TYPE: DNA
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<210> SEQ ID NO 81
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ggcggcccgc ggtgaagcct tggctttccg 30

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ggcggcccgc ggcaaatcct cacgggaggg 30

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ggcggcagat ctatgcacct gctgcttgca 30

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ccggccctcg agtcaatggt gatggtgatg atgacc 36

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aatgtttgat ggacaagccc c 21

<210> SEQ ID NO 86
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tgcttggatt cctctccgaa 20

<210> SEQ ID NO 87
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accaggaacg cctacctttt c 21

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tccagtttcc tacttgccag c 21

<210> SEQ ID NO 89
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<212> TYPE: DNA
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ctgccagtgg agttcaaatg c 21

<210> SEQ ID NO 90
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<212> TYPE: DNA
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<223> OTHER INFORMATION: primer

<400> SEQUENCE: 90

tcattgtccc caggacagtt g 21

<210> SEQ ID NO 91
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<212> TYPE: DNA
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<400> SEQUENCE: 91

ggcattcaaa cctctcgtga a 21

<210> SEQ ID NO 92
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<212> TYPE: DNA
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<400> SEQUENCE: 92

tcatggacac gaagttcctg g 21

<210> SEQ ID NO 93
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<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 93

cggaggaatt cgtggaaaga 20

<210> SEQ ID NO 94
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<212> TYPE: DNA
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: primer

<400> SEQUENCE: 94

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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 95

tccccaaggc taacagaacc a 21

<210> SEQ ID NO 96
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<212> TYPE: DNA
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<400> SEQUENCE: 96

cccctttaag cccatttcct c 21

<210> SEQ ID NO 97

<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 97

cagacatcgc atccgcaaa 19

<210> SEQ ID NO 98
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 98

aatgatccag tcgttccagc c 21

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<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 99

aacccсttca aacggaacca 20

<210> SEQ ID NO 100
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<212> TYPE: DNA
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tcgacgtgga cagctgaaga a 21

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<212> TYPE: DNA
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<400> SEQUENCE: 101

ctcgttcttc gttccaggtt g 21

<210> SEQ ID NO 102
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<212> TYPE: DNA
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<400> SEQUENCE: 102

agcagcagcg gtgacatcta t 21

<210> SEQ ID NO 103
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<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 103

ggacaactgc aatcgatgca 20

<210> SEQ ID NO 104
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 104

gcctcggttg atggctttaa t 21

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aagtgtgaca gaatgcgcct c 21

<210> SEQ ID NO 106
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<212> TYPE: DNA
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<400> SEQUENCE: 106

acttgcaact gatgctccac c 21

<210> SEQ ID NO 107
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 107

agtgtgccaa tggttcctcc t 21

<210> SEQ ID NO 108
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<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 108

tgcaggtctg tgacgttctc a 21

<210> SEQ ID NO 109
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial
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cacaggcatc ctgatctttg c 21

<210> SEQ ID NO 110
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<212> TYPE: DNA
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<223> OTHER INFORMATION: primer

<400> SEQUENCE: 110

tgaaattggc caccaggaag 20

<210> SEQ ID NO 111
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 111

ggtgatggag gacatgcgaa t 21

<210> SEQ ID NO 112
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<212> TYPE: DNA
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: primer

<400> SEQUENCE: 112

ttgttggctt ggaagtaggc c 21

<210> SEQ ID NO 113
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<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 113

aatctgatcg atggtgccct t 21

<210> SEQ ID NO 114
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<212> TYPE: DNA
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<400> SEQUENCE: 114

cgaatgtccg tttctttgtg c 21

<210> SEQ ID NO 115
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<220> FEATURE:
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caccaaatgg aagacccatc a 21

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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 116

atcatctgct ttccctgctc c 21

<210> SEQ ID NO 117

<211> LENGTH: 25
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: primer

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gcagaggaac gagacccaca gcatc 25

<210> SEQ ID NO 118
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<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 118

gtgcccagcc cacttcacac tg 22

<210> SEQ ID NO 119
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 119

gcttgtcttg gcagtcagca tccc 24

<210> SEQ ID NO 120
<211> LENGTH: 25
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 120

ggtcgtctgt gaatgtctca ggcac 25

<210> SEQ ID NO 121
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 121

ggcggcctcg aggccaccat ggtgctgctg tcccgc 36

<210> SEQ ID NO 122
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 122

ggcggcgtta actcatgaat tcaagtcctc ttcaga 36

<210> SEQ ID NO 123
<211> LENGTH: 773
<212> TYPE: DNA
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gctaccccta ggggtcagtg gtcaacgtgg agatgatgtg cctgagacat tcacagacga    180

ccctaatctg gtgaacgatc cctctacaga cgatacagct ctggctgata tcacaccttc    240

cacggacgac ctagctgatg acaaaaatgc tactgcagag tgccgggatg agaagtttgc    300

ttgtacaaga ctgtactctg tccatcggcc agtcagacag tgtgtgcacc agtcctgctt    360

caccagttta cggcgcatgt acatcatcaa taatgagatc tgttcccgac tcgtctgtaa    420

agaacatgaa gctatgaaag atgagctttg ccggcagatg gcaggcctgc ctccaaggcg    480

actccggcgc tccaactact tccgacttcc tccctgtgaa aatatgaatt tgcagagacc    540

cgatggtctg tgatcaccaa ggaagaaaga agaaaatgtg gatgaaggaa tcgaaaattc    600

tttctccttc aacccctgcc atctgtcccg tagacatgta tttttaaact aagccctttg    660

caatgccccg gcttcctacc ctactctaat tttcactggt gctggtaacg tttgtctcat    720

tttgcggtac tgacaataca ttgtctatat tgtgaaaaaa aaaaaaaaaa aaa           773
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<210> SEQ ID NO 124
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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 124

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aaaatcctgg atcagagaaa gtgttatcta cacattatat gatctaagga aaaatattgg    120

tagaaaatga ggcaagcata ataaccttgc ctttcaattt tctttgggca tctgattgca    180

ttttatcctt aagagcccag aaacccagat tcttagttaa gctcaaacaa agccaaaaga    240

caaagtaagg ctggcacccc tttcacagag cttctctaca tttgaaaatg atttggagag    300

ttctgaaaag ttcctcaact ttttataacc ctaaggtagc cagccttcct cttggacaaa    360

actcataagg tatctgtgtt cgcttggttg tgagaataca taggatattc caaggggaaa    420

aaaaacaaga agagtctaaa tgtgtaggtc aagaaagagg cagagatgaa aaagaaatac    480

aggaataaaa agaaatttgt tagtgctgaa gagacgaata ttgaaaaaga aagtgagaaa    540

gaaggatgaa ggaatgattc aaatatggaa tataaggagg ctgaggcagg ataattgctt    600

gaactcagga ggcggaggtt gcagtgagcc aagatcacat cattgcactc cagcctgggt    660

gacaggagca aaactctgtc ttaaaaaaaa aaaacaaaaa acaaagaaga agaagatagc    720

cagagagaga gaaacagcat ctataatgtg cattaaaaca caccaaggag gagacggaac    780

ttttcggtaa gaaagaaccc aaggaacaaa ggggagctgg gaccagatcg tgagaggagg    840

gaaaataggc taatggaaga aaggcaatac atgagctggg gccaacactt ccagggagca    900

gcaagagctc tcaccagtgt agtcataaca tttggaatga gggtgtgagc aactgcaaat    960

tcccatctcc cttctcattc cagcctcatt gtaacacaca ttctacgcct agcctggctt   1020

tcttgctctc cctcatctca ttgtttcagc ggaggccaaa tctgaagtcc tttccaggga   1080

gtggctctgt tcatcttatt cgccagccaa agtaggaaca gcgtaagagg agagagacac   1140

attcagcagc caaaggactc ggtggaaaga gcagaacacc atagacagtg agttatttga   1200

ttacctgaaa ccctaaagag acagagggaa tgtgtgtatg                         1240
```

What is claimed is:

1. A method to promote angiogenesis in cells or a tissue of a patient that has, or is at risk of developing, a condition selected from stroke or ischemia, comprising contacting the cells or tissue from the patient with an effective amount of a MAGP-2 protein having the amino acid sequence of SEQ ID NO:43.

2. The method of claim **1**, wherein the MAGP-2 protein is encoded by a nucleic acid molecule comprising the nucleic acid sequence of SEQ ID NO:124.

* * * * *