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(54) Title: COMPOSITIONS AND METHODS OF USE FOR ADAM12 ANTAGONISTS IN TREATING DISEASE

(57) Abstract: Microarray analysis, confirmed by RT-PCT, demonstrated that lung squamous cell carcinoma, colon/colorectal cancer, and breast carcinoma mRNA hybridizes specifically and preferentially to ADAM12L. Microarray analysis also demonstrated that RNA from malignant bladder, pancreas, and stomach tissue hybridizes specifically to ADAM12. ADAM12L is a transmembrane protein overexpressed on the surface of cancer cells compared to normal tissues and thus provides a therapeutic target for treating cancer. Modulators of ADAM12, highly expressed in cancerous as compared to normal tissues, are provided for the diagnosis and treatment of proliferative disorders such as cancer and psoriasis. The invention further provides methods of treating cancer with therapeutic agents directed toward ADAM12.



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**COMPOSITIONS AND METHODS OF USE FOR ADAM12
ANTAGONISTS IN TREATING DISEASE**

PRIORITY CLAIM

[001] This invention claims the benefit of provisional applications 60/591,527, filed in the United States Patent Office on July 27, 2004; and 60/674,700, filed in the United States Patent Office on April 26, 2005, which are both incorporated by reference in their entireties.

TECHNICAL FIELD

[002] This invention relates to human ADAM12 polynucleotides, and their encoded polypeptides, which are highly expressed in cancer tissues, such as lung cancer, including adenocarcinomas and squamous cell carcinomas, breast cancer, colorectal cancer, bladder cancer, pancreatic cancer, and stomach cancer. The invention also relates to modulators of such polynucleotides and polypeptides, for example, antibodies, that specifically bind to and/or interfere with the activity of these polypeptides, polynucleotides, their fragments, variants, and antagonists. The invention further relates to compositions containing such polypeptides, polynucleotides, or modulators thereof, and uses of such compositions in methods of treating proliferative disorders, including cancer and psoriasis. The invention additionally relates to methods of diagnosing proliferative disorders, such as cancer and psoriasis, by detecting these polynucleotides, polypeptides, or antibodies thereto in patient samples. The invention provides diagnostic tests which identify ADAM12 polypeptides and polynucleotides that correlate with particular disorders.

BACKGROUND ART

[003] The American Cancer Society estimates that approximately 1,400,000 new cases of cancer will have been diagnosed in the United States in 2004, and that approximately 570,000 cancer patients will have died of the disease. An estimated 173,000 of these new cases will be diagnosed as lung cancer, and an estimated 163,000 patients will have died of lung cancer in 2004. Lung cancer is the leading cause of cancer death in both men and women and carries an especially poor prognosis. While the 5 year survival rate for all cancers combined is 64%, the 5 year survival rate for lung cancer is only 15%. This is because most lung cancers are not detected until the disease has reached an advanced stage; tumor stage is the most significant determinant of survival. When lung cancer is detected at an early stage, the 5 year survival rate climbs to 49% (American Cancer Society (2005) Cancer

Facts & Figures. (<http://www.cancer.org/downloads/STT/CAFF2005f4PWSecured.pdf>)).

[004] An estimated 147,000 of the newly diagnosed cancers will be diagnosed as cancer of the colon or rectum (colorectal cancer) and an estimated 57,000 patients will have died of this disease in 2004. In its early stages, colorectal cancer usually also causes no symptoms. When it is detected at an early, localized, stage the 5 year survival rate is 90%; however, only 38% of colorectal cancers are discovered at this stage (American Cancer Society (2005) Cancer Facts & Figures. (<http://www.cancer.org/downloads/STT/CAFF2005f4PWSecured.pdf>)). Therefore, diagnostic markers for both early stage lung and colorectal cancer will have a significant impact on cancer morbidity and mortality.

[005] The ADAM (a disintegrin and metalloprotease) family of proteins largely comprises multidomain transmembrane proteins, and is characterized by the possession of a prodomain and metalloprotease, disintegrin, cysteine-rich, EGF-like, transmembrane, and cytoplasmic domains. ADAMs have been implicated in a variety of biologic processes involving cell-cell and cell-matrix interactions, including fertilization, muscle development, and neurogenesis (Wewer, U.M. (2003) ADAM12. *Handbook of Proteolytic Enzymes* 2nd edn. Barrett, A.J., Rawlings, N.D., Woessner, J.F. eds. Elsevier Academic Press).

[006] The ADAM12 gene has been mapped to human chromosome 10q26.3 (Gilpin, B.J., et al. (1998) *J. Biol. Chem.* 273:157-166). It can produce two isoforms of ADAM12, each arising from the differential use of alternatively spliced 3' exons. The longer isoform, ADAM12L, utilizes an exon encoding a transmembrane and intracellular domain, resulting in a type I transmembrane protein. The shorter isoform, ADAM12S, encodes a secreted protein lacking a transmembrane domain. ADAM12L is synthesized as a pro-protein which is proteolytically processed to yield a prodomain fragment and a mature protein fragment (Gilpin et al., 1998).

[007] ADAM12L can be expressed as a 909 amino acid transmembrane protein with a transmembrane and a cytoplasmic domain; it is designated NP_003465 in the National Center for Biotechnology Information (NCBI) database. Protein kinase C epsilon has been reported to induce regulated translocation of the transmembrane form to the cell surface from an intracellular storage site (Sundberg, C., et al. (2004) *J. Biol. Chem.* 279:51,601-51,611). ADAM12S can be expressed as a 738 amino acid secreted protein, designated NP_067673 by NCBI. Each of the

smaller and larger forms include a prodomain which is cleaved to produce a mature protein containing prometalloprotease, disintegrin, and cysteine-rich domains (Gilpin et al., 1998).

[008] ADAM12 has been implicated in developmental processes. It has been reported to be involved in the development of white adipose tissue, for example, by Masaki, M., et al. (2005) *Endocrinology* 146:1752; and Kawaguchi, N., et al. (2002) *Am. J. Pathol.* 160:1895-1903; the differentiation of myogenic precursor cells, for example, by Lafuste, P., et al. (2005) *Mol. Biol. Cell* 16:861-870; Cao, Y., et al. (2003) *Mol. Cell Biol.* 23:6725-6738; and in osteoclast differentiation, for example, by Bartholin, L., et al. (2005) *Biol. Cell.* 97:577.

[009] The invention provides ADAM12 compositions and methods for using ADAM12 to improve diagnostic, prognostic, and treatment procedures for proliferative diseases, such as cancer and psoriasis. The invention also provides modulators of ADAM12 with acceptable safety profiles that can be used in the diagnosis and treatment of proliferative diseases. These modulators may be, for example, antibodies.

SUMMARY

[010] The invention provides an isolated first nucleic acid molecule comprising a first polynucleotide sequence encoding a polypeptide, a complement thereof, or an isolated polypeptide encoded by a polynucleotide, wherein the polypeptide comprises an amino acid sequence chosen from the Tables, Figures, and Sequence Listing, or a biologically active fragment of any of these, wherein the polypeptide is other than a full-length ADAM12L, full-length ADAM12S, mature ADAM12L, mature ADAM12S, ADAM12 cysteine-rich domain, or the entire ADAM12 extracellular domain, as described in Figures 1 and 2. This polynucleotide may be chosen from a RNAi molecule, a ribozyme, and a nucleotide aptamer.

[011] The invention also provides a composition comprising a carrier and an isolated first nucleic acid molecule or polypeptide described above. In an embodiment the composition is a pharmaceutical composition and the carrier is a pharmaceutically acceptable carrier. In an embodiment, the invention provides a non-human animal injected with this polynucleotide and/or polypeptide.

[012] The invention further provides an isolated antibody that specifically recognizes, binds to, interferes with, and/or otherwise modulates the biological activity of at least one polypeptide and/or polynucleotide chosen from the Tables,

Sequence Listing, Figures, and a biologically active fragment of any of these, wherein the polypeptide is other than a full-length ADAM12L, a full-length ADAM12S, a mature ADAM12L, or mature ADAM12S polypeptide, as described in Figures 1 and 2, and wherein the antibody is not currently in the public domain. The antibody specificity may be directed to a non-transmembrane domain and/or an extracellular domain of a polypeptide chosen from the non-TM coordinates of Table 2. The antibody specificity may also be directed to a Pfam domain or a Prosite domain chosen from the functional domain coordinates of Table 3; the protein domain coordinates of Table 4; or a prodomain, a protease domain, a cysteine-rich domain, or an EGF-like domain, as described in Figures 1 and 2.

[013] In an embodiment, the invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and any of these antibodies. The antibodies of the invention may further comprise one or more cytotoxic component chosen from a radioisotope, a microbial toxin, a plant toxin, and a chemical compound.

[014] The invention yet further provides that any of the antibodies of the invention may have a function chosen from specifically inhibiting the binding of the polypeptide to a ligand, specifically inhibiting the binding of the polypeptide to a substrate, specifically inhibiting the binding of the polypeptide as a ligand, specifically inhibiting the binding of the polypeptide as a substrate, specifically inhibiting cofactor binding (zinc, for example), inducing apoptosis, inducing antibody-dependent cell cytotoxicity, inducing complement-dependent cytotoxicity, inhibiting protease activity, inhibiting adhesion, modulating ligand/receptor interaction, and modulating enzyme/substrate interaction.

[015] Antibodies of the invention may be chosen from one or more of a monoclonal antibody; a polyclonal antibody; a single chain antibody; an antibody comprising a backbone of a molecule with an Ig domain or a T cell receptor backbone; a targeting antibody; a neutralizing antibody; a stabilizing antibody; an enhancing antibody; an antibody agonist; an antibody antagonist; an antibody that promotes endocytosis of a target antigen; a cytotoxic antibody; an antibody that mediates antibody-dependent cell cytotoxicity; an antibody that mediates complement-dependent cytotoxicity; a human antibody; a non-human primate antibody; a non-primate animal antibody; a rabbit antibody; a mouse antibody; a rat antibody; a sheep antibody; a goat antibody; a horse antibody; a porcine antibody; a

cow antibody; a chicken antibody; a humanized antibody; a primatized antibody; a chimeric antibody; an antigen binding fragment; a fragment comprising a variable region of a heavy chain or a light chain of an immunoglobulin; a fragment comprising a complementarity determining region or a framework region of an immunoglobulin; and one or more active fragment, analogue, and/or antagonist of one or more of these antibodies.

[016] Antibodies of the invention may be produced in a plant, an animal, or a cell. For example, they may be produced in a bacterial cell, a fungal cell, a plant cell, an insect cell, and/or a mammalian cell. Suitable cells include, but are not limited to yeast cells, *Aspergillus* cells, SF9 cells, High Five cells, cereal plant cells, tobacco cells, tomato cells, 293 cells, myeloma cells, NS0 cells, PerC6 cells, and CHO cells. The invention provides an epitope of ADAM12, chosen from ARNYTG (SEQ ID NO: 375), RNYTGH (SEQ ID NO: 376), NYTGHC (SEQ ID NO: 377), YTGHCY (SEQ ID NO: 378), and TGHCCY (SEQ ID NO: 379). It also provides a bacteriophage displaying an antibody of the invention and/or a fragment thereof.

[017] The invention provides an isolated first nucleic acid molecule comprising a first polynucleotide sequence chosen from SEQ ID NOS.:341 and/or 342, a polynucleotide sequence encoding a polypeptide of SEQ ID NOS.:373, 374, and/or 375, and biologically active fragments of any of these, wherein the fragments comprise a polynucleotide sequence or an amino acid sequence encoded by a polynucleotide sequence comprising the splice sites utilized by CLN00575852. This nucleic acid molecule may be chosen from a cDNA molecule, a genomic DNA molecule, a cRNA molecule, a siRNA molecule, a RNAi molecule, and a mRNA molecule. The invention also provides a double-stranded isolated nucleic acid molecule comprising this first nucleic acid molecule and its complement.

[018] The invention further provides a second nucleic acid molecule comprising a second polynucleotide sequence complementary to the first nucleic acid molecule. This second nucleic acid molecule may be chosen from a RNAi molecule, an anti-sense molecule, and a ribozyme.

[019] The invention yet further provides an isolated polypeptide comprising an amino acid sequence chosen from SEQ ID NOS.:373, 374, 375, and biologically active fragments of any of these. This polypeptide may be present in a cell culture, for example, a bacterial cell culture, a mammalian cell culture, and/or an insect cell

culture. The isolated polypeptide may be encoded by the first nucleic acid molecule described above.

[020] In another aspect, the invention provides a method of modulating the biological activity of a first human or non-human animal host cell comprising providing an antibody of the invention and contacting the antibody with this first host cell, wherein the biological activity of the first host cell, and/or a second host cell, is modulated. This method may be performed such that the modulation of biological activity is chosen from inhibiting cell activity directly, inhibiting cell activity indirectly, inducing antibody-dependent cell cytotoxicity, and inducing complement-dependent cytotoxicity. The modulated biological cell activity may be chosen from signal transduction, transcription, and translation. It may result in cell death and/or inhibition of cell growth. In practicing the method, contacting the antibody with a first host cell may result in recruitment of at least one second host cell. The invention provides that the first host cell may be a cancer cell. The first or second host cell may be chosen from a T cell, B cell, NK cell, dendritic cell, antigen presenting cell, and macrophage.

[021] The invention also provides a method of identifying a modulator of the biological activity of a polypeptide comprising providing at least one polypeptide chosen from the sequences listed in the Tables, Figures, and Sequence Listing, and active fragments thereof, allowing at least one agent to contact the polypeptide, and selecting an agent that binds the polypeptide and/or affects the biological activity of the polypeptide. The modulator may be an antibody.

[022] The invention further provides a modulator composition comprising a pharmaceutically acceptable carrier and a modulator, wherein the modulator is obtainable by the method described above. The invention provides that the modulator composition may comprise a pharmaceutically acceptable carrier and a modulator, wherein the modulator is an antibody of the invention. The modulator composition may comprise a pharmaceutically acceptable carrier and a modulator, wherein the modulator is a soluble receptor that competes for ligand binding to an isolated polypeptide comprising an amino acid sequence chosen from the Tables, Figures, and Sequence Listing, and biologically active fragments thereof. In an embodiment, the modulator composition comprises a pharmaceutically acceptable carrier and a modulator, wherein the modulator is an extracellular fragment that competes for ligand binding to an isolated polypeptide comprising an amino acid sequence chosen

from the Tables, Figures, and Sequence Listing, and biologically active fragments thereof.

[023] In an embodiment, the modulator composition comprises a pharmaceutically acceptable carrier and a modulator, wherein the modulator is an RNAi molecule that inhibits the transcription or translation of an isolated polynucleotide or an isolated polypeptide comprising an amino acid sequence encoded by a polynucleotide chosen from the Tables, Figures, and Sequence Listing, and biologically active fragments thereof.

[024] In an embodiment, the modulator composition comprises a pharmaceutically acceptable carrier and a modulator, wherein the modulator is an antisense molecule that inhibits the transcription or translation of an isolated polynucleotide or an isolated polypeptide comprising an amino acid sequence encoded by a polynucleotide chosen from the Tables, Figures, and Sequence Listing, and biologically active fragments thereof.

[025] In an embodiment, the modulator composition comprises a pharmaceutically acceptable carrier and a modulator, wherein the modulator is a ribozyme that inhibits the transcription or translation of an isolated polynucleotide or an isolated polypeptide comprising an amino acid sequence encoded by a polynucleotide chosen from the Tables, Figures, and Sequence Listing, and biologically active fragments thereof.

[026] In an embodiment, the modulator composition comprises a pharmaceutically acceptable carrier and a modulator, wherein the modulator is an aptamer that inhibits the function of an isolated polynucleotide or an isolated polypeptide comprising an amino acid sequence encoded by a polynucleotide chosen from the Tables, Figures, and Sequence Listing, and biologically active fragments thereof.

[027] The invention provides a method of determining the presence of a polypeptide specifically binding to an antibody in a sample, comprising allowing an antibody of the invention to interact with the sample and determining whether interaction between the antibody and the polypeptide has occurred.

[028] The invention also provides a method of determining the presence of an antibody specifically binding to a polypeptide or a polynucleotide in a sample, comprising allowing an isolated polynucleotide encoding a polypeptide or an isolated polypeptide encoded by a polynucleotide, wherein the polypeptide comprises an

amino acid sequence chosen from the Tables, Figures, and Sequence Listing, and biologically active fragments thereof, to interact with the sample; and determining whether interaction between the antibody and the polypeptide or polynucleotide has occurred.

[029] The invention further provides a method of diagnosing cancer in a patient, comprising providing a polypeptide that specifically binds an antibody of the invention, allowing the polypeptide to contact a patient sample, and detecting specific binding between the polypeptide and any interacting molecule in the sample to determine whether the patient has cancer. This method may detect a cancer chosen from, for example, lung, colorectal, breast, bladder, pancreatic, and stomach cancer.

[030] The invention yet further provides a method of diagnosing cancer in a patient comprising providing an agent, for example, an antibody, that detects a prodomain region of ADAM12, providing a biological sample from the patient, and allowing the agent to react with the biological sample to determine the presence of the prodomain in the sample, for example, a blood sample. The invention provides a kit comprising an antibody of the invention and instructions for performing the diagnostic methods described above.

[031] The invention provides a method of treating uncontrolled proliferative cell growth in a patient comprising administering a modulator which binds to or interferes with the activity of an isolated polynucleotide encoding a polypeptide or an isolated polypeptide encoded by a polynucleotide, wherein the polypeptide comprises an amino acid sequence chosen from the Tables, Figures, and Sequence Listing, and biologically active fragments of any of these, to a patient. In an embodiment, the modulator is an antibody of the invention. In an embodiment, the uncontrolled proliferative growth is a tumor, for example, a tumor chosen from a lung tumor, a colorectal tumor, a breast tumor, a bladder tumor, a pancreatic tumor, and a stomach tumor.

[032] The invention also provides a method of treating a tumor in a patient comprising providing a modulator composition as described herein and administering the modulator composition to the patient. In an embodiment, the modulator is an antibody, which, for example, may specifically recognize, bind to, or modulate the biological activity of a polypeptide and wherein the polypeptide comprises an amino acid sequence chosen from the Tables, Figures, and Sequence Listing or is encoded

by a polynucleotide chosen from the Tables, Figures, and Sequence Listing, and biologically active fragments of any of these.

[033] The invention further provides a method of treating a lung, colorectal, breast, bladder, pancreatic, and/or stomach tumor in a patient comprising providing a modulator composition described herein and administering the modulator composition to the patient. In an embodiment, the modulator is an antibody, which, for example, may specifically recognize, bind to, or modulate the biological activity of a polypeptide and wherein the polypeptide comprises an amino acid sequence chosen from the Tables and Sequence Listing or is encoded by a polynucleotide chosen from the Tables and Sequence Listing, and biologically active fragments of any of these. The invention yet further provides a kit comprising one or more antibody of the invention and instructions for performing the methods of treatment described herein.

INDUSTRIAL APPLICABILITY

[034] ADAM12 polypeptides, polynucleotides, and modulators, for example, antibodies, find use in a number of diagnostic, prophylactic, and therapeutic applications relating to proliferative disorders, for example, cancer and psoriasis. These therapeutics include nucleic acid and polypeptide antibodies and vaccines, such as cancer vaccines, which may be administered alone, such as naked DNA, or may be facilitated, such as via viral vectors, microsomes, liposomes, or nanoparticles. Therapeutic antibodies include, for example, monoclonal antibodies or binding fragments. They may be administered alone or in combination with cytotoxic agents, such as radioactive or chemotherapeutic agents.

BRIEF DESCRIPTION OF THE TABLES AND FIGURES

Brief Description of the Tables

[035] Table 1 provides information regarding the sequences listed in the Sequence Listing. Column 1 shows an internally designated identification number (FP ID). Column 2 shows the nucleotide sequence ID number for the nucleic acid sequences of the Sequence Listing (SEQ. ID. NO. (N1)). Column 3 shows the amino acid sequence identification number for the polypeptide sequence (SEQ. ID. NO. (P1)). Column 4 shows the NCBI designation, clone identification, or probe or primer identification (Clone ID). Column 5 sets forth the amino acid sequences of the polypeptide fragments designated in column 3, or a description of the designated sequence (Notes).

[036] Table 2 lists polypeptides identified by hybridization to probe PRB102715_s_ at. Column 1 shows an internally designated identification number (FP ID). Column 2 shows the NCBI designation or clone identification number (Clone ID). Column 3 shows the predicted length of the polypeptide encoded by each clone (Pred Prot Len). Column 4 shows the result of an algorithm that predicts whether the predicted amino acid sequence is secreted (Tree vote). A Tree vote of 0 indicates a low probability that the protein is secreted. A Tree vote of 0.96 or 1.00 indicates a high probability that the protein is secreted. Column 5 shows the predicted signal peptide coordinates (Signal Peptide Coords). Column 6 shows the mature protein coordinates, which refer to the coordinates of the amino acid residues of the mature polypeptide after cleavage of the secretory leader or signal peptide sequence (Mature Protein Coords). Column 7 specifies the number of transmembrane domains (TM). Column 8 provides the coordinates of the transmembrane sequences of the polypeptides. Finally, column 9 provides a list of the Pfam and Prosite domains present in each of the identified clones (Domain). Coordinates are listed in terms of the amino acid residues beginning with "1" for the first amino acid residue at the N-terminus of the full-length polypeptide.

[037] Table 3 shows the coordinates of predicted Pfam and Prosite functional domains within ADAM12 polypeptides. Column 1 shows an internally designated identification number (FP ID). Column 2 shows the NCBI designation or clone identification of the polypeptide (Clone ID). Column 3 shows the name of the Pfam or Prosite functional domain (Func Dom). Column 4 shows the coordinates of the beginning and ending amino acid residues spanning the functional domain in the polypeptide (Coords).

[038] Table 4 shows the coordinates of predicted protein domains within ADAM12 polypeptides. Column 1 shows an internally designated identification number (FP ID). Column 2 shows the NCBI designation or clone identification of the polypeptide (Clone ID). Column 3 shows the designation of the protein domains (Prot Dom). Column 4 shows the coordinates of the beginning and ending amino acid residues spanning the protein domain (Coords).

Brief Description of the Figures

[039] Figure 1 compares the amino acid sequences of 37182874_ADAM12Sb (SEQ ID NO: 387), NP_067673_ADAM12Sa (SEQ ID NO: 21), CLN00575852_ADAM12Lb (SEQ ID NO: 373), 38173792_ADAM12Sc (SEQ ID

NO: 388), WO 01/68848_seq87.trans (SEQ ID NO: 399), CLN00575852_1-706 (SEQ ID NO: 374), and NP_003465_ADAM12La (SEQ ID NO: 380) by aligning them using clustal format for T-COFFEE Version_1.37 with the parameters CPU=0.00 sec, SCORE=94, Nseq=9, Len=909. The asterisks (*) indicate amino acid residues shared among all the sequences. The colons (:) indicate conservative amino acid changes. The dashes (-) indicate absent amino acids.

[040] Figure 2 compares the domain structures of the long transmembrane form (ADAM12L) and the short secreted form (ADAM12S) of ADAM12.

[041] Figure 3a shows an exon map of ADAM12L (A and E) and ADAM12S (C and F); the microarray hybridization probe location of PRB102715_s_at for ADAM12L (B) and PRB104353_at for ADAM12S (D); and the relative location of the RT-PCR primers and probes for ADAM12L and ADAM12S (E and F, respectively). A and C represent the complete exon map of ADAM12L and ADAM12S, respectively, including the 5'- and 3'-UTRs, while E and F represent the complete exon map of the open reading frames of ADAM12L and ADAM12S, respectively. The horizontal axis is a scaled version of the genome which considers all introns to have equal lengths (Relative Distance).

[042] Figure 3b and 3c show exon maps of ADAM12Lb (CLN00575852_ADAM12Lb), the ADAM12Lb sequence encoding amino acids 1-706 (CLN00575852_1-706), ADAM12La (NP_003465_ADAM12La), ADAM12Sa (NP_067673_ADAM12Sa), ADAM12Sc (38173792_ADAM12Sc), ADAM12Sb (37182874_ADAM12Sb), a Taqman probe directed to NP_003465 (NP_003465_taqman), a Taqman probe directed to NP_067673 (NP_067673_taqman), a hybridization probe directed to ADAM12L (PRB102715_s_at), and a hybridization probe directed to ADAM12S (PRB104353_at). The horizontal axis of Figure 3b represents a scaled version of the genome which considers all introns to have equal lengths (Relative Distance). The horizontal axis of Figure 3c represents relative distances between exons (Index).

[043] Figure 4 shows the expression level of ADAM12L as detected by PRB102715 (black bars) and ADAM12S as detected by PRB104353 (white bars) and measured by microarray hybridization, using a Five Prime chip, of 23 colorectal adenocarcinoma samples, and 22 normal human colorectal specimens. The results show that ADAM12L was expressed in three normal samples and ADAM12S was expressed in two normal samples. ADAM12L was expressed in 19 tumor samples

and ADAM12S was expressed in five tumor samples. High-level expression of ADAM12L, that is, expression in excess of the highest level of expression observed in a normal sample, was observed in about four of the tumor samples.

[044] Figure 5 shows the expression level of ADAM12L as detected by PRB102715 (black bars) and of ADAM12S as detected by PRB104353 (gray bars) and measured by microarray hybridization, using a Five Prime chip, to 19 lung squamous cell cancer samples, 19 human lung adenocarcinoma samples, and 24 normal lung samples. The results show that ADAM12L was expressed in all 19 lung squamous carcinoma samples, 11 of 19 lung adenocarcinoma samples, and six of 24 normal lung samples. ADAM12S was expressed in seven of 19 lung squamous carcinoma samples, one of 19 lung adenocarcinoma samples and five of 24 normal lung samples. High-level expression of ADAM12L was observed in about 15 of 19 lung squamous carcinoma samples and about 8 of 19 lung adenocarcinoma samples.

[045] Figure 6 shows the expression level of ADAM12L as detected by PRB102715 (black bars) and ADAM12S as detected by PRB104353 (grey bars) and measured by microarray hybridization, using a Five Prime chip, on normal tissue specimens. Figure 6a shows ADAM12 expression in normal adrenal, B-cell, bladder, bone marrow, breast, CD4T-cell, duodenum, fallopian tube, gallbladder, heart, and jejunum. Figure 6b shows ADAM12 expression in normal kidney, liver, lymph node, monocyte, endometrium, NK cell, omentum, ovary, pancreas, parotid gland, pituitary, and placenta. High-level expression of both ADAM12L and ADAM12S was observed in the placenta. Figure 6c shows ADAM12 expression in normal prostate, skeletal muscle, skin, small intestine, soft tissues, and white blood cells (WBC).

[046] Figure 7 shows the expression level of ADAM12L as detected by PRB102715 (black bars) and ADAM12S as detected by PRB104353 (grey bars) and measured by microarray hybridization, using a Five Prime chip, on breast ductal carcinoma specimens and normal breast specimens. The results show that ADAM12L was expressed in two of the three carcinoma samples but neither of the two normal breast samples. ADAM12S was not detected in any of the samples examined.

[047] Figure 8 shows the results of interrogating a proprietary oncology database from GeneLogic by probing an Affymetrix U133 chip with a probe corresponding to ADAM12 in order to determine the expression of the sequences in normal and malignant bladder tissues. ADAM12 was overexpressed in eight of the 12

malignant bladder tissues examined and none of the five normal bladder tissues examined.

[048] Figure 9 shows the results of interrogating the GeneLogic database as described in Figure 8. ADAM12 was overexpressed in three of the 18 malignant brain tissues examined and was not overexpressed in the normal brain specimen examined.

[049] Figure 10 shows the results of interrogating the GeneLogic database as described in Figure 8. ADAM12 was overexpressed in four of the 23 malignant endometrial tissues examined and four of the 109 normal endometrial tissues examined.

[050] Figure 11 shows the results of interrogating the GeneLogic database as described in Figure 8. ADAM12 was expressed at high levels in both normal and malignant skin tissue.

[051] Figure 12 shows the results of interrogating the GeneLogic database as described in Figure 8. ADAM12 was overexpressed in two of the 109 malignant kidney tissues examined and none of the 65 normal kidney tissues examined.

[052] Figure 13 shows the results of interrogating the GeneLogic database as described in Figure 8. ADAM12 was overexpressed in two of the 68 malignant liver tissues examined and none of the 48 normal liver tissues examined.

[053] Figure 14 shows the results of interrogating the GeneLogic database as described in Figure 8. ADAM12 was overexpressed in nine of the 120 malignant ovary tissues examined and five of the 89 normal ovary tissues examined.

[054] Figure 15 shows the results of interrogating the GeneLogic database as described in Figure 8. ADAM12 was overexpressed in 19 of the 79 malignant pancreas tissues examined and one of the 53 normal pancreas tissues examined.

[055] Figure 16 shows the results of interrogating the GeneLogic database as described in Figure 8. ADAM12 was not overexpressed in any of the 95 malignant prostate tissues examined, nor in any of the 56 normal prostate tissues examined.

[056] Figure 17 shows the results of interrogating the GeneLogic database as described in Figure 8. ADAM12 was overexpressed in malignant stomach, but not in normal stomach.

[057] Figure 18 shows the results of of interrogating the GeneLogic database as described in Figure 8. ADAM12 was overexpressed in one malignant thyroid tissue examined, and in none of the normal thyroid tissues examined.

[058] Figure 19 shows the specificity of real-time polymerase chain reaction (RT-PCR) primers/probes for ADAM12L and ADAM12S toward the membrane and secreted forms of ADAM12, respectively. These primers/probes were designed for use in RT-PCR to specifically detect ADAM12L and ADAM12S, and were used in a Taqman primer test. The results show that primer/probe S detected the soluble but not the membrane form, and primer/probe M detected the membrane but not the soluble form of ADAM12. The primers/probes detected their respective form of ADAM12 in a dose dependent manner.

[059] Figure 20 shows the relative expression of ADAM12L and ADAM12S in colon/colorectal cancer and normal adjacent RNA specimens, as determined by Taqman RT-PCR.

[060] Figure 21 shows the relative expression of ADAM12L and ADAM12S in lung squamous cell cancer and normal adjacent RNA specimens, as determined by Taqman RT-PCR.

[061] Figure 22 shows the relative expression of ADAM12L and ADAM12S in lung squamous cell cancer and RNA specimens from normal, non-adjacent tissues, including placenta, heart, lung, kidney, liver, adipose tissue, muscle, and adrenal gland, as determined by Taqman RT-PCR. The results show high-level expression of ADAM12L and ADAM12S in placenta, and high-level expression of ADAM12M in lung squamous cell carcinoma and adipose tissue.

DISCLOSURE OF THE INVENTION

[062] The invention provides target polynucleotides and polypeptides useful for diagnosing and treating proliferative disease. It provides the novel isoform ADAM12Lb and compositions comprising ADAM12Lb. It also provides probes that detect the overexpression of ADAM12 in cancer. It further provides modulators, such as antibodies, that may function as either agonists or antagonists, and/or may specifically bind to or interfere with the activity of ADAM12 or fragments of ADAM12. For example, polypeptides described herein can be used as immunogens to produce specific antibody modulators directed against the polypeptide targets. These antibodies can bind to and modulate polypeptides on cell surfaces, such as the extracellular or secreted domain of a transmembrane protein, for example, by inducing antibody-dependent cell cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC), carry a payload, such as a radioisotope or a cytotoxic molecule, or act as agonist or antagonist antibodies, for example by affecting ligand/receptor

interactions, affecting cofactor interactions, interfering with cell signaling, inducing an apoptotic factor, or blocking the action, production, or release of growth factors or survival factors, such as blocking the cleavage of heparin-bound EGF (HB-EGF) to inhibit release of EGF that signals through an EGF receptor, or the release of other growth factors which signal through one or more corresponding growth factor receptors. The modulators of the invention include not only antibodies, but also small molecule drugs, RNAi molecules, ribozymes, antisense molecules, soluble receptors, and extracellular fragments of receptors or transmembrane proteins.

[063] ADAM12 screening assays can identify modulators with a desired biologic or therapeutic effect. Modulators of the invention include therapeutic agents that can be used to treat proliferative diseases, including cancer and psoriasis. The polypeptides and polynucleotides herein are highly expressed in tumor tissues compared to normal tissue, especially normal tissues vulnerable to unwanted side effects of drugs. As shown below, microarray hybridization and real time PCR performed on normal tissue specimens demonstrated that the expression level of the two ADAM12 forms was very low in normal heart, kidney, lung, liver, and adrenal gland. Placenta expressed high levels of both forms of ADAM12, and adipose tissue preferentially expressed ADAM12L.

Definitions

[064] The terms used herein have their ordinary meanings, as set forth below, and can be further understood in the context of the specification.

[065] The terms "polynucleotide," "nucleotide," "nucleic acid," "nucleic acid molecule," "nucleic acid sequence," "polynucleotide sequence," and "nucleotide sequence" are used interchangeably herein to refer to polymeric forms of nucleotides of any length. The polynucleotides can contain deoxyribonucleotides, ribonucleotides, and/or their analogs or derivatives. Nucleotide sequences shown herein are listed in the 5' to 3' direction.

[066] The terms "polypeptide," "peptide," and "protein," used interchangeably herein, refer to a polymeric form of amino acids of any length, which can include naturally-occurring amino acids, coded and non-coded amino acids, chemically or biochemically modified, derivatized, or designer amino acids, amino acid analogs, peptidomimetics, and depsipeptides, and polypeptides having modified, cyclic, bicyclic, depsicyclic, or depsibicyclic peptide backbones. The term includes single chain protein as well as multimers. The term also includes conjugated proteins,

fusion proteins, including, but not limited to, glutathione S-transferase (GST) fusion proteins, fusion proteins with a heterologous amino acid sequence, fusion proteins with heterologous and homologous leader sequences, fusion proteins with or without N-terminal methionine residues, pegylated proteins, and immunologically tagged, or his-tagged proteins. The term also includes peptide aptamers.

[067] "Transmembrane proteins" extend into or through the cell membrane's lipid bilayer; they can span the membrane once, or more than once. Transmembrane proteins, having part of their molecules on either side of the bilayer, have many and widely variant biological functions. Transmembrane proteins are often involved in cell signaling events; they can comprise signaling molecules, or can interact with signaling molecules. Extracellular domains of transmembrane proteins may be cleaved to produce soluble receptors.

[068] "Secreted proteins" are generally capable of being directed to the endoplasmic reticulum (ER), secretory vesicles, or the extracellular space as a result of a secretory leader, signal peptide, or leader sequence. They may be released into the extracellular space, for example, by exocytosis or proteolytic cleavage, regardless of whether they comprise a signal sequence. A secreted protein may in some circumstances undergo processing to a mature polypeptide. Secreted proteins may comprise leader sequences of amino acid residues, located at the amino terminus of the polypeptide and extending to a cleavage site, which, upon proteolytic cleavage, result in the formation of a mature protein.

[069] A "leader sequence" comprises a sequence of amino acid residues, beginning at amino acid residue 1 located at the amino terminus of the polypeptide, and extending to a cleavage site, which, upon proteolytic cleavage, results in formation of a mature protein. Leader sequences are generally hydrophobic and have some positively charged residues. Leader sequences can be natural or synthetic, heterologous, or homologous with the protein to which they are attached. A "secretory leader" is a leader sequence that directs a protein to be secreted from the cell. A secretion signal sequence can be naturally occurring or it can be engineered.

[070] A "Pfam domain" is a protein or a portion of a protein with a tertiary structure. Pfams may have characteristic functional activities, such as enzymatic or binding activities. Multiple Pfam domains can be connected by flexible polypeptide regions within a protein. Pfam domains can comprise the N-terminus or the C-terminus of a protein, or can be situated at any point between.

[071] A "Prosites domain" is a protein or portion of a protein comprising one or more biologically meaningful motifs described as patterns or profiles. Prosites domains are linked to documentation related to the SWISS-PROT database.

[072] A "non-transmembrane domain" is a portion of a transmembrane protein that does not span the membrane. It may be extracellular, cytoplasmic, or luminal.

[073] A "soluble receptor" is a receptor that lacks a membrane anchor domain, such as a transmembrane domain, and may include naturally occurring splice variants of a wild-type transmembrane protein receptor in which the transmembrane domain is spliced out and the extracellular domains or any fragment of the extracellular domain of the transmembrane protein receptor. Soluble receptors can modulate a target protein. They can, for example, compete with wild-type receptors for ligand binding and participate in ligand/receptor interactions, thus modulating the activity of or the number of the receptors and/or the cellular activity downstream from the receptors. This modulation may trigger intracellular responses, for example, signal transduction events which activate cells, signal transduction events which inhibit cells, or events that modulate cellular growth, proliferation, differentiation, and/or death, or induce the production of other factors that, in turn, mediate such activities.

[074] A "biologically active" entity, or an entity having "biological activity," is one or more entity having structural, regulatory, or biochemical functions of a naturally occurring molecule or any function related to or associated with a metabolic or physiological process. Biologically active polynucleotide fragments are those exhibiting activity similar, but not necessarily identical, to an activity of a polynucleotide of the present invention. The biological activity can include an improved desired activity, or a decreased undesirable activity. For example, an entity demonstrates biological activity when it participates in a molecular interaction with another molecule, such as hybridization, when it has therapeutic value in alleviating a disease condition, when it has prophylactic value in inducing an immune response, when it has diagnostic value in determining the presence of a molecule, such as a biologically active fragment of a polynucleotide that can, for example, be detected as unique for the polynucleotide molecule, or that can be used as a primer in a polymerase chain reaction. A biologically active polypeptide or fragment thereof includes one that can participate in a biological reaction, for example, one that can

serve as an epitope or immunogen to stimulate an immune response, such as production of antibodies, or that can participate in stimulating or inhibiting signal transduction by binding to ligands receptors or other proteins, or nucleic acids; or activating enzymes or substrates.

[075] The terms "antibody" and "immunoglobulin" refer to a protein, for example, one generated by the immune system, synthetically, or recombinantly, that is capable of recognizing and binding to a specific antigen; antibodies are commonly known in the art. Antibodies may recognize polypeptide or polynucleotide antigens. The term includes active fragments, including for example, an antigen binding fragment of an immunoglobulin, a variable and/or constant region of a heavy chain, a variable and/or constant region of a light chain, a complementarity determining region (cdr), and a framework region. The terms include polyclonal and monoclonal antibody preparations, as well as preparations including hybrid antibodies, altered antibodies, chimeric antibodies, hybrid antibody molecules, F(ab')₂ and F(ab) fragments; Fv molecules (for example, noncovalent heterodimers), dimeric and trimeric antibody fragment constructs; minibodies, humanized antibody molecules, and any functional fragments obtained from such molecules, wherein such fragments retain specific binding.

[076] A "humanized" antibody is a non-human immunoglobulin that contains human immunoglobulin sequences. This term is generally used to refer to an immunoglobulin that has been modified to incorporate a human framework region with the hypervariable regions of a non-human immunoglobulin. The non-human regions of a humanized antibody may extend beyond the hypervariable regions into the variable regions and beyond the variable regions into the framework regions to achieve the desired antigen-binding properties.

[077] An "epitope" is a molecule to which an antibody binds, which may or may not be a contiguous sequence of amino acid residues in a polypeptide, and which may comprise sugars and/or molecules having other chemical structures.

[078] The term "antibody target" or "cancer target" refers to a polypeptide, polynucleotide, or carbohydrate that can be used as an immunogen in the production of antibodies that specifically bind to such a polypeptide, polynucleotide, or carbohydrate, or a small molecule drug that modulates the activity of such polypeptide, polynucleotide, or carbohydrate.

[079] "Antibody-dependent cell cytotoxicity" (ADCC) is a form of cell mediated cytotoxicity in which an effector cell, such as a lymphocyte, NK cell, granulocyte, neutrophil, eosinophil, basophil, mast cell, or macrophage, mediates the killing of a cell to which an antibody is attached. ADCC can involve humoral and/or cell-dependent mechanisms.

[080] "Complement-dependent cytotoxicity" (CDC) is an adverse effect on a cell that can result from activation of the complement pathway. It includes actions mediated through the classical complement pathway.

[081] The term "binds specifically," in the context of antibody binding, refers to high avidity and/or high affinity binding of an antibody to a specific epitope. Hence, an antibody that binds specifically to one epitope (a "first epitope") and not to another (a "second epitope") is a "specific antibody." An antibody specific to a first epitope may cross react with and bind to a second epitope if the two epitopes share homology or other similarity.

[082] The term "binds specifically," in the context of a polynucleotide, refers to hybridization under stringent conditions. Conditions that increase stringency of both DNA/DNA and DNA/RNA hybridization reactions are widely known and published in the art. See, for example, Sambrook, J., et al. (2000) *Molecular Cloning, A Laboratory Manual*. 3rd ed. Cold Spring Harbor Laboratory Press. The term "binds specifically," in the context of antibody binding, refers to high avidity and/or high affinity binding of an antibody to a specific epitope. Hence, an antibody that binds specifically to one epitope (a "first epitope") and not to another (a "second epitope") is a "specific antibody." An antibody specific to a first epitope may cross react with and bind to a second epitope if the two epitopes share homology or other similarity. The term "binds specifically," in the context of a polynucleotide, refers to hybridization under stringent conditions. Conditions that increase stringency of both DNA/DNA and DNA/RNA hybridization reactions are widely known and published in the art (*Curr. Prot. Molec. Biol.*, John Wiley & Sons (2001)).

[083] An "isolated," "purified," "substantially isolated," or "substantially purified" molecule (such as a polypeptide, polynucleotide, or antibody) is one that has been manipulated to exist in a higher concentration than in nature. For example, a subject antibody is isolated, purified, substantially isolated, or substantially purified when at least 10%, or 20%, or 40%, or 50%, or 70%, or 90% of non-subject-antibody materials with which it is associated in nature have been removed. As used herein, an

"isolated," "purified," "substantially isolated," or "substantially purified" molecule includes recombinant molecules.

[084] A "host cell" is an individual cell or cell culture which can be or has been a recipient of any recombinant vector(s) or isolated polynucleotide. Host cells include progeny of a single host cell, and the progeny may not necessarily be completely identical (in morphology or in total DNA complement) to the original parent cell due to natural, accidental, or deliberate mutation and/or change. A host cell includes cells transfected or infected *in vivo* or *in vitro* with a recombinant vector or a polynucleotide of the invention. A host cell which comprises a recombinant vector of the invention may be called a "recombinant host cell."

[085] "Patient," "individual," "host," and "subject" are used interchangeably herein to refer to mammals, including, but not limited to, rodents, simians, humans, felines, canines, equines, bovines, porcines, ovines, caprines, mammalian laboratory animals, mammalian farm animals, mammalian sport animals, and mammalian pets.

[086] A "patient sample" is any biological specimen derived from a patient; the term includes, but is not limited to, biological fluids such as blood, serum, plasma, urine, cerebrospinal fluid, tears, saliva, lymph, dialysis fluid, lavage fluid, semen, and other liquid samples, as well as cell and tissues of biological origin. The term also includes cells or cells derived therefrom and the progeny thereof, including cells in culture, cell supernatants, and cell lysates. It further includes organ or tissue culture-derived fluids, tissue biopsy samples, tumor biopsy samples, stool samples, and fluids extracted from physiological tissues, as well as cells dissociated from solid tissues, tissue sections, and cell lysates. This definition encompasses samples that have been manipulated in any way after their procurement, such as by treatment with reagents, solubilization, or enrichment for certain components, such as polynucleotides or polypeptides. Also included in the term are derivatives and fractions of patient samples. A patient sample may be used in a diagnostic, prognostic, or other monitoring assay.

[087] The term "receptor" refers to a polypeptide that binds to a specific ligand. The ligand is usually an extracellular molecule which, upon binding to the receptor, usually initiates a cellular response such as initiation of a signal transduction pathway.

[088] The term "ligand" refers to a molecule that binds to a specific site on another molecule, usually a receptor.

[089] The term "modulate" refers to the production, either directly or indirectly, of an increase or a decrease, a stimulation, inhibition, interference, or blockage in a measured activity when compared to a suitable control. A "modulator" of a polypeptide or polynucleotide or an "agent" are terms used interchangeably herein to refer to a substance that affects, for example, increases, decreases, stimulates, inhibits, interferes with, or blocks a measured activity of the polypeptide or polynucleotide, when compared to a suitable control.

[090] The term "agonist" refers to a substance that mimics or enhances the function of an active molecule. Agonists include, but are not limited to, antibodies, growth factors, cytokines, lymphokines, small molecule drugs, hormones, and neurotransmitters, as well as analogues and fragments thereof.

[091] The term "antagonist" refers to a molecule that interferes with the activity or binding of another molecule such as an agonist, for example, by competing for the one or more binding sites of an agonist, but does not induce an active response.

[092] An "antibody modulator of a polypeptide" is a modulator that recognizes and binds specifically to the polypeptide. Such an antibody may, for example, induce ADCC, CDC, or apoptosis, or may block or otherwise interfere with the activity of a polypeptide.

[093] "Modulating a level of an active subject polypeptide" includes increasing or decreasing, blocking, or interfering with the expression or activity of a subject polypeptide, increasing or decreasing a level of an active polypeptide, and increasing or decreasing the level of mRNA encoding an active subject polypeptide. Modulation can occur directly or indirectly.

[094] "Treatment," as used herein, covers any administration or application of remedies for disease in a mammal, including a human, and includes inhibiting the disease, arresting its development, or relieving the disease, for example, by causing regression, or restoring or repairing a lost, missing, or defective function; or stimulating an inefficient process.

[095] "Prophylaxis," as used herein, includes preventing a disease from occurring or recurring in a subject that may be predisposed to the disease but is not currently symptomatic. Treatment and prophylaxis can be administered to an organism, or to a cell *in vivo*, *in vitro*, or *ex vivo*, and the cell subsequently administered to the subject.

[096] A "pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material, formulation auxiliary, or excipient of any conventional type. A pharmaceutically acceptable carrier is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation.

[097] A "composition" herein refers to a mixture that usually contains a carrier, such as a pharmaceutically acceptable carrier or excipient that is conventional in the art and which is suitable for administration into a subject for therapeutic, diagnostic, or prophylactic purposes. It may include a cell culture in which the polypeptide or polynucleotide is present in the cells or in the culture medium. For example, compositions for oral administration can form solutions, suspensions, tablets, pills, capsules, sustained release formulations, oral rinses, or powders.

[098] "Disease" refers to any condition, infection, disorder, or syndrome that requires medical intervention or for which medical intervention is desirable. Such medical intervention can include treatment, diagnosis, and/or prevention.

[099] "Cancer" is any abnormal cell or tissue growth, for example, a tumor, whether malignant, pre-malignant, or non-malignant. It is characterized by uncontrolled proliferation of cells that may or may not invade the surrounding tissue and, hence, may or may not metastasize to new body sites. Cancer encompasses carcinomas, which are cancers of epithelial cells; carcinomas include squamous cell carcinomas, adenocarcinomas, melanomas, and hepatomas. Cancer also encompasses sarcomas, which are tumors of mesenchymal origin; sarcomas include osteogenic sarcomas, leukemias, and lymphomas. Cancers may involve one or more neoplastic cell type.

Target Molecule ADAM12

[0100] The ADAM12 gene can produce five isoforms of ADAM12, each arising from the differential use of alternatively spliced 5' and 3' exons. The isoform ADAM12Lb is not represented in any public database. Two isoforms, ADAM12La and ADAM12Lb, encode the long form of ADAM12, a Type I transmembrane protein which includes a transmembrane and intracellular domain. The other three isoforms of ADAM12, ADAM12Sa, ADAM12Sb, and ADAM12Sc, encode a secreted short form which lacks the transmembrane domain.

[0101] The two isoforms ADAM12La and ADAM12Sa are the result of non-canonical splicing. The ADAM12La and ADAM12Sa amino acid sequences contain

the amino acid residues VIL following amino acid 113, as shown in Figure 1. This amino acid sequence is generated by the nucleotide sequence TAATTCTGG after nucleotide 340 (the first nucleotide being the initial A of the ATG start codon). When the nucleotide sequences are mapped to the genome, this TAATTCTGG sequence is predicted to span an exon/intron/exon boundary. Thus, TAATTCTG represents sequences at the end of exon 1, while G represents sequences at the beginning of exon 2. The donor/acceptor site is GC-AG, which occurs at a frequency of 0.70%.

[0102] ADAM12Lb, ADAM12Sb, and ADAM12Sc do not contain the amino acid residues VIL following amino acid 113, as shown in Figure 1. When their nucleotide sequences are mapped to the genome, the donor/acceptor site is not GC-AG but GT-AG, resulting in a deletion. This occurs at a frequency of 99.2%. ADAM12Sc has an additional canonical alternate splice site on the 3' exon, resulting in a six base pair (two amino acid) insertion.

[0103] The novel ADAM12Lb isoform comprises a full-length physical clone. It exhibits the same splicing pattern in the 5' region as ADAM12Sb and ADAM12Sc. ADAM12Lb differs from ADAM12Sb and ADAM12Sc in its use of different downstream exons, which result in the expression of different amino acids in the C-terminal region comprising the transmembrane and cytoplasmic regions. The ADAM12Lb transcript and polypeptide produced from the transcript are present in humans *in vivo* and are physiologically relevant, as described herein in further detail.

[0104] As shown in Figure 2, both the long transmembrane form (ADAM12L) and the short secreted form (ADAM12S) of ADAM12 have a signal peptide with 28 amino acids and a prodomain of 179 amino acids, which mediates trafficking and inhibits protease activity (Hougaard, S., et al. (2000) *Biochem. Biophys. Res. Commun.* 275:261-267). Both forms of ADAM12 also have a metalloprotease domain with latent protease activity that is activated by cleavage of the prodomain (Wewer, et al., 2003). The 209 amino acid metalloprotease domain mediates the proteolytic shedding of heparin-binding epidermal growth factor (HB-EGF) and the L1 adhesion molecule, as well as the proteolytic cleavage of insulin-like growth factor binding protein 3 (IGFbp3) (Loechel, F., et al. (2000) *Biochem. Biophys. Res. Comm.* 278:511-515; Gutwein, P., et al. (2000) *J. Biol. Chem.* 275:15,490-15,497). The metalloprotease activity depends on the presence of a divalent cation cofactor, such as zinc, magnesium, or manganese.

[0105] Both forms of ADAM12 also have a 96 amino acid disintegrin domain, a 140 amino acid cysteine-rich domain and a 36 amino acid EGF-like domain, which combine to form an adhesion domain that mediates binding to integrins, syndecans, and substrates of the metalloprotease domain (Zhao, Z., et al. (2004) *Exp. Cell Res.* 298:28-37; Thodeti, C.K., et al. (2003) *J. Biol. Chem.* 278:9576-9584; Kawaguchi, N., et al. (2003) *J. Cell Sci.* 16(Pt 19):3893-904; Epub Aug. 12, 2003). Specific to the long form is an approximately 23 amino acid transmembrane domain and a cytoplasmic tail of approximately 180 amino acids with multiple SH3-binding domains and binding sites for α -actinin, PI₃ kinase, Grb2, and src (Suzuki, A., et al. (2000) *Oncogene* 19:5842-5850).

[0106] Accordingly, the invention provides the novel isoform ADAM12Lb. It provides an isolated first nucleic acid molecule comprising a first polynucleotide sequence encoding a polypeptide, a complement thereof, an isolated polypeptide encoded by a polynucleotide, wherein the polypeptide comprises an amino acid sequence chosen from the Tables, Figures, and Sequence Listing, or a biologically active fragment thereof, wherein the polypeptide is other than a full-length ADAM12L, full-length ADAM12S, mature ADAM12L, mature ADAM12S, ADAM12 cysteine-rich domain, or the entire ADAM12 extracellular domain, as described in Figures 1 and 2.

[0107] The invention provides polynucleotide sequences of the open reading frames that encode polypeptides of the invention (SEQ. ID. NO. (N1)). SEQ. ID. NO.:1 represents the nucleotide sequence of ADAM12, identified as NP_067673:NM_021641 in the NCBI database. SEQ. ID. NO.:2 represents the nucleotide sequence of the extracellular domain of the long form of ADAM12. SEQ. ID. NOS.:341-342, 391, and 393 represent the nucleotide sequences of the novel ADAM12Lb clone and fragments of ADAM12Lb.

[0108] The invention also provides amino acid sequences of polypeptides of the invention (SEQ ID NO. (P1)). SEQ. ID. NO.:21 represents the amino acid sequence of ADAM12, identified as NP_067673:NM_021641 in the NCBI database. SEQ. ID. NOS.:22-338 represent the amino acid sequences of fragments of the long form of ADAM12, used as described herein. SEQ. ID. NO.:339 represents the amino acid sequence of the extracellular domain of ADAM12L. SEQ. ID. NOS.:373-379,

394, and 396 represent the amino acid sequence and fragments thereof, of novel ADAM12Lb.

[0109] The invention further provides the complete polynucleotide sequence of the ADAM12 (SEQ. ID. NO.:340), including both coding and non-coding regions, which is identified as NP_067673:NM_021641 in the NCBI database.

Microarray Hybridization

[0110] ADAM12 nucleic acid molecules and their encoded proteins, shown in the Tables, Figures, and Sequence Listing, may serve as antibody targets of the invention. They may also serve as target molecules for the production of modulators such as antibodies. As shown, for example, in Example 1 and Figures 4 -18 selected tumor tissues hybridized at higher intensities to ADAM12L probes than did normal tissues. Expression profiling analysis with the Five Prime chip revealed that ADAM12L RNA is overexpressed in lung squamous cell carcinoma compared to normal lung tissues, and in colon/colorectal cancer compared to normal colon/colorectal tissues. RNA from lung squamous cell carcinoma and from colon/colorectal cancer hybridized specifically and preferentially to probes representing the transmembrane isoform of ADAM12 (Figures 4-7). These RNAs did not hybridize or hybridized only weakly to probes specifically representing the secreted form of ADAM12, demonstrating that ADAM12L is specifically overexpressed in these cancers. ADAM12L RNA was also overexpressed in lung adenocarcinomas and lung squamous cell carcinoma samples compared to normal lung tissues, and in ductal breast carcinoma compared to normal breast tissues. Expression profiling analysis with the Affymetrix U133 chip revealed that ADAM12L RNA is overexpressed in bladder cancer, pancreatic cancer, and stomach cancer compared to normal bladder, pancreatic, and stomach tissue (Figures 8-18).

[0111] Microarray hybridization was performed under high stringency conditions. Examples of relevant conditions include (in order of increasing stringency): incubation temperatures of 25°C, 37°C, 50°C, and 68°C; buffer concentrations of 10X SSC, 6X SSC, 1X SSC, 0.1X SSC (where 1X SSC is 0.15 M NaCl and 15 mM citrate buffer); and their equivalents using other buffer systems; formamide concentrations of 0%, 25%, 50%, and 75%; incubation times from 5 minutes to 24 hours; 1, 2, or more washing steps; wash incubation times of 1, 2, or 15 minutes; and wash solutions of 6X SSC, 1X SSC, 0.1X SSC, or deionized water.

[0112] For example, high stringency conditions include hybridization in 50% formamide, 5X SSC, 0.2 µg/µl poly(dA), 0.2 µg/µl human cot1 DNA, and 0.5% SDS, in a humid oven at 42° C overnight, followed by successive washes in 1X SSC, 0.2% SDS at 55° C for 5 minutes, followed by washing at 0.1X SSC, 0.2% SDS at 55° C for 20 minutes. Further examples of high stringency conditions include hybridization at 50° C and 0.1X SSC (15 mM sodium chloride/1.5 mM sodium citrate); overnight incubation at 42° C in a solution containing 50% formamide, 1X SSC, 50 mM sodium phosphate (pH 7.6), 5X Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1X SSC at about 65° C. High stringency conditions also include aqueous hybridization (for example, free of formamide) in 6X SSC, 1% sodium dodecyl sulfate (SDS) at 65° C for about 8 hours (or more), followed by one or more washes in 0.2X SSC, 0.1% SDS at 65° C. Highly stringent hybridization conditions are hybridization conditions that are at least as stringent as any one of the above representative conditions. Other stringent hybridization conditions are known in the art and can also be employed to identify nucleic acids of this particular embodiment of the invention.

[0113] Conditions of reduced stringency, suitable for hybridization to molecules encoding structurally and functionally related proteins, or otherwise serving related or associated functions, are the same as those for high stringency conditions but with a reduction in temperature for hybridization and washing to lower temperatures (for example, room temperature or about 22° C to 25° C). For example, moderate stringency conditions include aqueous hybridization (for example, free of formamide) in 6X SSC, 1% SDS at 65° C for about 8 hours (or more), followed by one or more washes in 2X SSC, 0.1% SDS at room temperature. Low stringency conditions include, for example, aqueous hybridization at 50° C and 6X SSC and washing at 25° C in 1X SSC.

[0114] The specificity of a hybridization reaction allows any single-stranded sequence of nucleotides to be labeled with a radioisotope or chemical and used as a probe to find a complementary strand, even in a cell or cell extract that contains millions of different DNA and RNA sequences. Probes of this type are widely used to detect the nucleic acids corresponding to specific genes, both to facilitate the purification and characterization of the genes after cell lysis and to localize them in cells, tissues, and organisms.

Real Time PCR

[0115] The microarray hybridization results were validated and further characterized by quantitative real time-PCR, as set forth in Example 2. Specific primers and probes for each form were designed for the differentially spliced exons, as shown in Figure 3, specifically, the junction of exons 16 and 17 for ADAM12L and exon 17 for ADAM12S. In contrast to the microarray probes, which targeted the 3'-UTR non-coding region, the RT-PCR primer-probes targeted regions of the mRNA encoding amino acids present on the extracellular domain of either ADAM12S or ADAM12L. The results obtained from using these probes, shown in Example 2 and Figures 19-22, confirm that the expression observed by the microarray hybridizations can be extrapolated to the mRNA species that encodes the transmembrane form of ADAM12 (ADAM12L), and rules out the possibility that tumor cells produce the secreted form of ADAM12 (ADAM12S).

[0116] Quantitative RT-PCR (Taqman) analysis of lung squamous cell carcinoma, normal lung, colon/colorectal cancer, and normal colon samples confirmed the overexpression of ADAM12 in lung squamous cell carcinoma and in colon/colorectal cancer. ADAM12L was overexpressed in lung squamous cell carcinoma and colon/colorectal cancer compared to the corresponding normal tissues. ADAM12L expression in normal heart, lung, kidney, liver, skeletal muscle, and adrenal gland specimens by quantitative RT-PCR was directly compared to ADAM12L expression in lung squamous cell carcinoma and colon/colorectal cancer. Not only was ADAM12L overexpressed in lung squamous cell carcinoma and in colon/colorectal cancer compared to normal lung and colorectal tissues, but it was also overexpressed compared to normal heart, kidney, liver, skeletal muscle, and adrenal gland.

Antibody Targets

[0117] ADAM12 is an antibody target that corresponds to a probe that exhibited a "hit" when hybridized to the cRNA on a FivePrime microarray chip. The specific individual probe hit was identified as prb102715_s_at, and the fragment ID, also referred to as the chip ID, corresponding to the RNA (and its gene symbol) of the cloned tumor tissues or normal tissues was identified as 379507(53). It is predicted to function as a protease, based on the characteristics of gene cluster 199060, in which it was observed to be located. This cluster, (a group of human cDNA clones which

maps to a single locus on the human chromosome) is classified as comprising ADAM12 type 1 single transmembrane proteins.

[0118] ADAM12L is a therapeutic target for cancer, since it is a transmembrane protein overexpressed on the surface of cancer tissues compared to normal tissues. Antibodies are particularly suited to be used as therapeutic agents when their targets are transmembrane proteins expressed on the surface of cancer cells. Thus, in one aspect of the invention, the nucleic acids and proteins are antibody targets or markers or biomarkers identified by binding to an antibody. Among the antibody targets of the invention is the polypeptide encoded by the gene ADAM12 (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=Graphics&list_uids=8038). This gene encodes a disintegrin and metalloproteinase domain and has been implicated in a variety of biologic processes involving myogenesis and cell-cell and cell-matrix interactions, including fertilization and muscle development. Its expression has been reported to be associated with tumor aggressiveness and progression in hepatocellular carcinoma and liver metastasis of colon cancer (Le Pabic et al., *Hepatology* 37:1056 (2003)).

[0119] Antibodies binding to the extracellular domain of ADAM12L are therapeutic for cancers, including lung squamous cell carcinoma, lung adenocarcinoma, colon/colorectal cancer, bladder cancer, pancreatic cancer, and stomach cancer. Such antibodies can be used as monotherapy if they mediate ADCC or CDC, or if they modify the underlying function of the target molecule (in this case, ADAM12 function). Anti-ADAM12 antibodies can also be used in the form of antibody conjugates to directly deliver cancer agents with a lethal effect on the tumor. Such agents include radionuclides, toxins, and chemotherapeutics.

[0120] Anti-ADAM12 antibodies can also be used in combination with standard chemotherapeutic or radiation regimens to treat cancers. In this case, anti-ADAM12 antibodies can act to sensitize the cancer cells to chemotherapy or radiation, allowing for more efficient tumor killing. Alternatively, anti-ADAM12 antibodies can act in synergy with chemotherapy or radiation treatment, such that lower doses of either may be used, decreasing the overall toxicity to normal cells while maintaining equivalent efficacy in treating the tumor.

[0121] Antibodies having a therapeutic effect on cancers include those binding to ADAM12 amino acids sequences involved in ADAM12 function. Such

amino acid sequences include, for example, those containing the zinc binding active site in the metalloprotease domain, those containing the methionine turn in the metalloprotease domain including proline kink residue, those containing the upper rim of active site cleft; those containing residues located immediately cytoplasmic to the proline kink residue, those containing the metal coordinating cysteine outside the active site in the metalloprotease domain, those containing the integrin binding region of the disintegrin domain, those containing the disintegrin loop, those containing the IGFBP3 binding region of cys-rich domain, those containing the syndecan binding region of the cys-rich domain, those containing the fusion peptide region of cys-rich domain, and those containing the EGF-like region.

[0122] Such amino acids include those binding to ADAM12L amino acids 345-366, AVTLAHELGHNFGMNHDTLDRG (SEQ. ID. NO.:22), which comprise a zinc cofactor-binding active site in the metalloprotease domain. The invention provides antibodies that bind to this sequence and/or to any epitope of six or more consecutive amino acids contained within the sequence.

[0123] Such amino acids also include those binding to ADAM12L amino acids 373-392, VEKGGCIMNASTGYPPFPMVF (SEQ. ID. NO.:33), which comprise a methionine turn in the metalloprotease domain, including a proline kink residue. The invention provides antibodies that bind to this sequence and/or to any epitope of six or more consecutive amino acids contained within the sequence.

[0124] Such amino acids further include those binding to ADAM12L amino acids 311-328, FQGTITIGMAPIMSMCTAD (SEQ. ID. NO.:49), which comprises the upper rim of the active site cleft. The invention provides antibodies that bind to this sequence and/or any epitope of six or more consecutive amino acids contained within the sequence.

[0125] Such amino acids yet further include those binding to ADAM12L amino acids 388-401, FPMVFSSCSRKDLE (SEQ. ID. NO.:62), which comprises residues immediately cytoplasmic to the proline kink residue. The invention provides antibodies that bind to this sequence and/or to any epitope of six or more consecutive amino acids contained within the sequence.

[0126] Such amino acids include those binding to ADAM12L amino acids 263-284, GVEVWNDMDKCSVSQDPFTSLH (SEQ. ID. NO.:72), which comprises a metal coordinating cysteine outside the active site in the metalloprotease domain.

The invention provides antibodies that bind to this sequence and/or to any epitope of six or more consecutive amino acids contained within the sequence.

[0127] Such amino acids also include those binding to ADAM12L amino acids 477-500, PAGTACRDSSNSCDLPEFCTGASP (SEQ. ID. NO.:90), which comprises a disintegrin loop. The invention provides antibodies that bind to this sequence and/or to any epitope of six or more consecutive amino acids contained within the sequence.

[0128] Such amino acids further include those binding to ADAM12L amino acids 541-593, AKPAPGICFERVNSAGDPYGNCGKVKSSFAKCEMRDAKCGKI QCQGGASRPV (SEQ. ID. NO.:110), which comprises an IGFBP3 binding region of the cys-rich domain. The invention provides antibodies that bind to this sequence and/or to any epitope of six or more consecutive amino acids contained within the sequence.

[0129] Such amino acids further include those binding to ADAM12L amino acids 584-624, QCQGGASRPVIGTNAVSIETNIPLQQGGRILCRGTHVYLG (SEQ. ID. NO.:159), which comprises a fusion peptide region of cys-rich domain. The invention provides antibodies that bind to this sequence and/or to any epitope of six or more consecutive amino acids contained within the sequence.

[0130] Such amino acids yet further include those binding to amino acids 651-693, NISVFGVHECAMQCHGRGVCNNRKNCHCEAHWAPPFCDKFGFG (SEQ. ID. NO.:196), which comprises an EGF-like region of cys-rich domain. The invention provides antibodies that bind to this sequence and/or to any epitope of six or more consecutive amino acids contained within the sequence.

ADAM12 Protein Families and Domains

[0131] The ADAM12 sequences of the invention encompass a variety of different nucleic acids and polypeptides with different structures and functions, embodied in different molecular domains. They can encode or comprise polypeptides belonging to different protein families, for example, those described by the Pfam database and those having different biologically meaningful motifs, as described by the Prosite database. The Pfam system is an organization of protein sequence classification and analysis, based on conserved protein domains; it can be publicly accessed in a number of ways, for example, at <http://Pfam.wustl.edu>. Protein domains are portions of proteins that have a tertiary structure and sometimes have enzymatic or binding activities; multiple domains can be connected by flexible polypeptide regions

within a protein. Pfam domains can comprise the N-terminus or the C-terminus of a protein, or can be situated at any point in between. The Pfam system identifies protein families based on these domains and provides an annotated, searchable database that classifies proteins into families (Bateman, A., et al. (2000) *Nucleic Acids Research* 30:276-280).

[0132] Protein domains of ADAM12 have also been described, for example, by the Prosite system of classification. Prosite provides a collection of sequence motifs that are described as patterns or profiles, in conjunction with the SWISS-PROT protein database (Sigrist et al., 2002). It can be accessed publicly, for example, at <http://www.expasy.org/prosite> (Copyright© 2005 Oxford University Press).

[0133] Sequences of the invention can encode or be comprised of more than one Pfam or Prosite. Sequences encompassed by the invention include, but are not limited to, the polypeptide and polynucleotide sequences of the molecules shown in the Tables, Figures, and Sequence Listing and corresponding molecular sequences found at all developmental stages of an organism. Sequences of the invention can comprise genes or gene segments designated in the Tables, Figures, and Sequence Listing, and their RNA and polypeptide gene products. They also include variants of those presented in the Tables, Figures, and Sequence Listing that are present in the normal physiological state, for example, variant alleles such as SNPs, splice variants, as well as variants that are affected in pathological states, such as disease-related mutations or sequences with alterations that lead to pathology, and variants with conservative amino acid changes. Some sequences of the invention are categorized below with respect to one or more protein family. Any given sequence can belong to one or more than one category.

[0134] ADAM12L comprises several Pfam and Prosite domains, including, but not limited to, ADAM_MEPRO, disintegrin, reprotolysin, peptidase_M12B_propep, and EGF_3 (Tables 2 and 3). ADAM_MEPRO domains are ADAM-type metalloprotease domains; they generally resemble snake venom metalloproteases, which have a characteristic consensus active site (Wolfsberg, T.G., et al. (1995) *J. Cell Biol.* 131:275-278). Disintegrin domains are peptides of about 70 amino acid residues typically characterized by the presence of disulfide-bonded cysteines; they have been reported to bind to integrins (<http://www.sanger.ac.uk/cgi-bin/Pfam/getacc?PF00200>). Reprotolysin domains are zinc-dependent metalloproteases, also known as adamalysins; they are found, for example, in snake venom (<http://www>.

sanger.ac.uk/cgi-bin/Pfam/getacc?PF01421). The peptidase_M12B_propep domain corresponds to the propeptide of members of the reprotolysin family; it comprises a sequence motif similar to a matrixin cysteine switch, which has been reported to mediate cell-cell or cell-matrix interactions (<http://www.sanger.ac.uk/cgi-bin/Pfam/getacc?PF01562>). The EGF_3 domain is found in the extracellular or secreted region, closer to the C-terminus than the ADAM_MEPRO and disintegrin domains; it is characterized by an EGF-like domain (<http://www.expasy.org/cgi-bin/nicesite.pl?PS50026>).

Polypeptide Expression

[0135] The ADAM12 polypeptides described herein can be expressed using methods known in the art. Cell-based methods and cell-free methods are suitable for producing polypeptides of the invention. The use of the polymerase chain reaction has been described (Saiki et al., 1985) and current techniques have been reviewed (Sambrook et al., 2000; McPherson et al. 2000; Dieffenbach and Dveksler, 1995). Cell-based methods generally involve introducing a nucleic acid construct into a host cell *in vitro* and culturing the host cell under conditions suitable for expression, then harvesting the polypeptide, either from the culture medium or from the host cell, (for example, by disrupting the host cell), or both, as described in detail above. The invention also provides methods of producing a polypeptide using cell-free *in vitro* transcription/translation methods, which are well known in the art.

[0136] The ADAM12 polypeptides can be recovered and purified from recombinant cell cultures by well-known methods, including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography, and lectin chromatography, for example, as described by Deutscher, M.P., et al., eds. (1990) *Guide to Protein Purification: Methods in Enzymology*. (Methods in Enzymology Series, Vol 182). Acad. Press. High performance liquid chromatography (HPLC) can be employed for purification. ADAM12 polypeptides include products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may

be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

[0137] Typically, a heterologous polypeptide, whether modified or unmodified, may be expressed on its own, as described above, or as a fusion protein, and may include not only secretion signals, but also a secretory leader sequence. A secretory leader sequence of the invention may direct certain proteins to the ER. The ER separates the membrane-bound proteins from other proteins. Once localized to the ER, proteins can be further directed to the Golgi apparatus for distribution to vesicles; including secretory vesicles; the plasma membrane, lysosomes, and other organelles.

[0138] Proteins targeted to the ER by a secretory leader sequence can be released into the extracellular space as a secreted protein. For example, vesicles containing secreted proteins can fuse with the cell membrane and release their contents into the extracellular space in a process called exocytosis. Exocytosis can occur constitutively or in response to a triggering signal. In the latter case, the proteins may be stored in secretory vesicles (or secretory granules) until exocytosis is triggered. Similarly, proteins residing on the cell membrane can also be secreted into the extracellular space by proteolytic cleavage of a linker holding the protein to the membrane.

[0139] Additionally, peptide moieties and/or purification tags may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to polypeptides to engender secretion or excretion, to improve stability, and to facilitate purification, among other reasons, are familiar and routine techniques in the art. Suitable purification tags include, for example, V5, polyhistidines, avidin, and biotin.

[0140] Protein expression systems known in the art can produce fusion proteins that incorporate the polypeptides of the invention. ADAM12 fusion proteins

can facilitate production, secretion, and/or purification. They can confer a longer half-life when administered to an animal. Fusion partners suitable for use in the invention include, for example, fetuin, human serum albumin, Fc, and/or one or more of their fragments. Conjugated proteins, such as polyethylene glycol conjugates, are also provided. Such modified polypeptides can show, for example, enhanced activity or increased stability. In addition, they may be purified in higher yields and show better solubility than the corresponding natural polypeptide, at least under certain purification and storage conditions.

Kits

[0141] Detection of cancer cell-specific biomarkers provides an effective cancer screening strategy. Early detection provides not only early diagnosis, but also the ability to screen for polymorphism and detect post-operative residual tumor cells and occult metastases, an early indicator of tumor recurrence. Early detection of cancer cell-specific biomarkers can thus improve survival in patients before diagnosis, while undergoing treatment, and while in remission.

[0142] Mature ADAM12L and the ADAM12 prodomain are overexpressed in cancer patients. Since ADAM12L is not normally expressed at high levels in healthy, mature, non-pregnant adults, the presence of either the ADAM12 prodomain or mature ADAM12L can be used as a diagnostic or prognostic marker for cancer, such as in identifying a patient population appropriate for treatment. Diagnostic antibodies can be used in a number of ways, including but not limited to ELISA, Western blot, immunofluorescence, or immunohistochemistry, for these purposes.

[0143] Antibodies reactive with the prodomain can be used to detect ADAM12 prodomain in biological samples from cancer patients. Antibodies capable of detecting the prodomain in the serum include those binding to amino acids in the prodomain which are predicted to be solvent-exposed antibody epitopes. These include antibodies directed toward amino acids 29-44, RGVSLWNQGRADEVVVS (SEQ. ID. NO.:235); amino acids 64-92, HPEVLNIRLQRESKELIINLERNEGLIAS (SEQ. ID. NO.:246); amino acids 90-113, IASSFTETHYLQDGTDVSLARNYT (SEQ. ID. NO.:271); amino acids 115-128, ILGHCYYHGHVIRGY (SEQ. ID. NO.:291); amino acids 128-159, YSDSAVSLSTCSGLRGLIVFENESYVLEPMKS (SEQ. ID. NO.:301); amino acids 160-173, ATNRYKLFPKKLK (SEQ. ID. NO.:329); and/or directed toward any epitope of six or more consecutive amino acids contained within these sequences.

[0144] Microarrays comprising probes that detect overexpression of ADAM12 in cancer can provide a cancer diagnostic. Probes annotated as representing ADAM12 are currently present on the commercially available Affymetrix U133 microarray. However, none of the probe sets annotated as representing ADAM12 on the Affymetrix U133 microarray reveal overexpression of ADAM12 in either lung or colorectal cancers. Thus, probes that detect overexpression of ADAM12 in lung and/or colorectal cancers can improve the diagnosis of these cancers.

[0145] The invention provides methods for diagnosing disease states based on the detected presence and/or level of ADAM12 polynucleotides, polypeptides, or antibodies in a biological sample, and/or the detected presence and/or level of biological activity of the polynucleotide or polypeptide. These detection methods can be provided as part of a kit. Thus, the invention further provides kits for detecting the presence and/or a level of a polynucleotide, polypeptide, or antibody of interest in a biological sample.

[0146] Where the kit provides for polynucleotide detection, it can include one or more nucleotides that hybridize specifically to an ADAM12 nucleotide of interest. Where the kit provides for polypeptide detection, it can include one or more specific antibodies. In some embodiments, the antibody specific to the polypeptide of interest is detectably labeled. In other embodiments, the antibody specific to the polypeptide is not labeled; instead, a second, detectably labeled antibody is provided that binds to the specific antibody. The kit may further include blocking reagents, buffers, and reagents for developing and/or detecting the detectable marker. The kit may further include instructions for use, controls, and interpretive information.

[0147] The invention also provides for therapeutic kits with unit doses of an active agent. In some embodiments, the agent is provided in oral or injectable doses, as described in further detail below. Such kits can comprise containers containing the unit doses and an informational package insert describing the use and attendant benefits of the drugs in treating a condition of interest.

Gene Expression of the Target Molecules in Cancer

[0148] Genes that are uniquely or differentially expressed in cancerous cells or tissues may potentially serve as cancer cell markers in bodily fluids, for example, serum. A reliable marker must be specific to cancer, and expressed only when the patient has cancer. ADAM12L has been detected in breast cancer patient urine, and

increased urinary levels of this protein shown to correlate with breast cancer progression (Roy, R., et al. (2004) *J. Biol. Chem.* 279:51,323-51,330). The results of the bioinformatics, microarray hybridization, and quantitative PCR studies presented herein demonstrate that ADAM12, specifically ADAM12L, is a cancer cell marker useful for diagnosing cancer, including squamous cell lung carcinoma, colorectal carcinoma, breast carcinoma, bladder cancer, pancreatic cancer, and stomach cancer in patient samples.

[0149] ADAMs have been postulated to be involved in the adhesive and proteolytic properties of cancer cells by the actions of their cysteine-rich domain and metalloprotease domains, respectively (Iba, K., et al. (2000) *J. Cell Biol.* 149:1143-1156). ADAM12L has been reported to be highly expressed in human glioblastomas and postulated to play a role in their proliferation by shedding the glioblastoma cell's heparin-binding epidermal growth factor (Kodama, T., et al. (2004) *Am. J. Pathol.* 165:1743-1753).

[0150] ADAM12 has been associated with the transition from quiescent to activated state in rat hepatic stellate cells, a model of human liver cancer, and reported to be markedly increased in human livers with cirrhosis. ADAM12 expression was up-regulated by transforming growth factor beta. *In vivo*, the steady-state of ADAM12 mRNA levels was nearly undetectable in both normal livers and benign tumors and increased in hepatocellular carcinomas (up to 3- and 6-fold, respectively) and liver metastases from colonic carcinomas (up to 40- and 60-fold, respectively). The up-regulation of ADAM12 was correlated with an increase in matrix metalloproteinase 2 expression and activity. Thus, ADAM12 expression in liver cancers have been associated with tumor aggressiveness and progression (Le Pabic et al., 2003).

Active Agents (or Modulators)

[0151] The nucleic acid, polypeptide, and modulator compositions of the subject invention find use as therapeutic agents in situations where one wishes to modulate ADAM12 activity polypeptides, or to provide or inhibit ADAM12 activity at a particular anatomical site. The active agents of the invention are useful in the diagnosis and treatment of proliferative diseases, for example, lung, colorectal, breast, bladder, pancreatic, and stomach cancer; and psoriasis. Modulators of the invention include, for example, polypeptide variants, whether agonist or antagonist; aptamers, antibodies, whether agonist or antagonist, interfering or specific; soluble receptors,

usually antagonists; small molecule drugs, whether agonist or antagonist; RNAi, usually an antagonist; antisense molecules, usually antagonists; and ribozymes, usually antagonists.

[0152] In an embodiment, modulators of the invention bind to target ADAM12 molecules. They may directly modulate ADAM12 as a result of their binding. They may also indirectly modulate a biological process by interacting with ADAM12. Modulators of the invention may bind to ADAM12 in a manner that may or may not interfere with the function of the target ADAM12 molecule; the modulator may be therapeutically efficacious whether or not the modulator interferes with ADAM12 function. For example, a modulator may form a complex with ADAM12 and an effector molecule or effector cell.

[0153] In some embodiments, an agent is an ADAM12 polypeptide, where the ADAM12 polypeptide itself is administered to an individual. In some embodiments, an agent is an antibody specific for a subject target polypeptide. In some embodiments, an agent is a chemical compound, such as a small molecule, that may be useful as an orally available drug. Such modulation may include the recruitment of other molecules that directly effect the modulation. For example, an antibody that modulates the activity of a subject polypeptide that is a receptor on a cell surface may bind to the receptor and fix complement, activating the complement cascade and result in lysis of the cell. An agent which modulates a biological activity of a subject polypeptide or polynucleotide increases or decreases the activity or binding at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 50%, at least about 100%, or at least about 2-fold, at least about 5-fold, or at least about 10-fold or more when compared to a suitable control.

[0154] Inhibitors of ADAM12 may regulate growth and development. For example, inhibiting the metalloprotease activity of ADAM12 has been reported to inhibit the shedding of heparin-binding EGF receptors, and attenuate hypertrophic changes in cardiomyocytes induced by EGFR activation (Asakura, M., et al. (2002) *Nat. Med.* 8:35-40). The ADAM12 inhibitor KB-R7785 was reported to block receptor shedding and attenuate the hypertrophy (Askura et al., 2002).

[0155] The invention provides a method of identifying a modulator of the biological activity of a polypeptide of the invention by providing at least one polypeptide chosen from the sequences listed in the Tables, Figures, and Sequence Listing, and active fragments thereof; allowing at least one agent to contact the

polypeptide; and selecting an agent that binds the polypeptide or affects the biological activity of the polypeptide. In an embodiment, the modulator is an antibody.

[0156] The invention provides compositions comprising modulators obtained by this method and a pharmaceutically acceptable carrier. For example, the invention provides modulator compositions comprising a pharmaceutically acceptable carrier and a modulator, wherein the modulator is a soluble receptor that competes for ligand binding or cofactor binding to an isolated polypeptide comprising an amino acid sequence chosen from the Tables, Figures, and Sequence Listing, and biologically active fragments thereof. The invention also provides a modulator composition comprising a pharmaceutically acceptable carrier and a modulator, wherein the modulator is an extracellular fragment that competes for ligand binding or cofactor binding to an isolated polypeptide comprising an amino acid sequence chosen from the Tables, Figures, and Sequence Listing, and biologically active fragments thereof.

Antisense Oligonucleotides

[0157] In certain embodiments of the invention, the agent is an antisense molecule that modulates, and generally decreases or down regulates, polypeptide expression in a host (Agrawal, S., Crooke, S.T. eds. (1998) *Antisense Research and Application (Handbook of Experimental Pharmacology, Vol 131)*, Springer-Verlag New York, Inc.; Hartmann, G., et al., eds. (1999) *Manual of Antisense Methodology (Perspectives in Antisense Science. 1st ed. Kluwer Law International; Phillips, M.I., ed. (1999a) *Antisense Technology, Part A. Methods in Enzymology Vol. 313.* Academic Press, Inc.; Phillips, M.I., ed. (1999b) *Antisense Technology, Part B. Methods in Enzymology Vol. 314.* Academic Press, Inc.; Stein, C.A., et al., eds. (1998) *Applied Antisense Oligonucleotide Technology.* Wiley-Liss). Accordingly, the invention provides a modulator composition comprising a pharmaceutically acceptable carrier and a modulator, wherein the modulator is an antisense molecule that inhibits the transcription or translation of an isolated polynucleotide or an isolated polypeptide comprising an amino acid sequence encoded by a polynucleotide chosen from the Tables, Figures, and Sequence Listing, and biologically active fragments thereof. The invention also provides a modulator composition comprising a pharmaceutically acceptable carrier and a modulator, wherein the modulator is a ribozyme that inhibits the transcription or translation of an isolated polynucleotide or an isolated polypeptide comprising an amino acid sequence encoded by a*

polynucleotide chosen from the Tables, Figures, and Sequence Listing, and biologically active fragments thereof.

[0158] Antisense reagents of the invention include antisense oligonucleotides (ODN), for example, synthetic ODN having chemical modifications from native nucleic acids, or nucleic acid constructs that express such antisense molecules as RNA. The antisense sequence is complementary to the mRNA of the targeted ADAM12 gene, and inhibits expression of the targeted ADAM12 gene products. Antisense molecules inhibit ADAM12 gene expression through various mechanisms, for example, by reducing the amount of mRNA available for translation, through activation of RNase H, or steric hindrance. One or a combination of antisense molecules can be administered, where a combination can comprise multiple different sequences.

[0159] Antisense molecules can be produced by expression of all or a part of the ADAM12 gene sequence in an appropriate vector, where the transcriptional initiation is oriented such that an antisense strand is produced as an RNA molecule. Alternatively, the antisense molecule is a synthetic oligonucleotide. Antisense oligonucleotides can be chemically synthesized by methods known in the art (Wagner, R.W., et al. (1993) *Science* 260:1510-1513.; Milligan, J.F., et al. (1993) *J. Med. Chem.* 36:1923-1937). Antisense oligonucleotides will generally be at least about 7, at least about 12, or at least about 20 nucleotides in length, and not more than about 500, not more than about 50, or not more than about 35 nucleotides in length, where the length is governed by efficiency of inhibition, and specificity, including absence of cross-reactivity, and the like. Short oligonucleotides, of from about 7 to about 8 bases in length, can be strong and selective inhibitors of gene expression (Wagner, R.W., et al. (1996) *Nat. Biotechnol.* 14:840-844).

[0160] A specific region or regions of the endogenous sense strand ADAM12 mRNA sequence is chosen to be complemented by the antisense sequence. Selection of a specific sequence for the oligonucleotide can use an empirical method, where several candidate sequences are assayed for inhibition of expression of the target gene in an *in vitro* or animal model. As noted above, a combination of sequences can also be used, where several regions of the mRNA sequence are chosen for antisense complementation.

[0161] As an alternative to antisense inhibitors, catalytic nucleic acid compounds, for example, ribozymes, or antisense conjugates can be used to inhibit

gene expression. Ribozymes can be synthesized *in vitro* and administered to the patient, or can be encoded in an expression vector, from which the ribozyme is synthesized in the targeted cell (WO 9523225; Beigelman, L., et al. (1995) *Nucleic Acids Res.* 23:4434-4442). Examples of oligonucleotides with catalytic activity are described in WO 9506764. Conjugates of antisense ODN with a metal complex, for example, terpyridyl Cu(II), capable of mediating mRNA hydrolysis are described in Bashkin, J.K., et al. (1995) *Appl. Biochem. Biotechnol.* 54:43-56. Certain antisense modulators of ADAM12 were proposed by Ward et al., US2004/0002469A1.

Interfering RNA

[0162] In some embodiments, the active agent is an interfering RNA (RNAi). RNA interference provides a method of silencing eukaryotic genes. Use of RNAi to reduce a level of a particular mRNA and/or protein is based on the interfering properties of RNA, e.g., double-stranded RNA (dsRNA), derived from the coding regions of a gene. The technique is an efficient high-throughput method for disrupting gene function (O'Neil, N.J., et al., (2001) *Am. J. Pharmacogenomics* 1:45-53). RNAi can also help identify the biochemical mode of action of a drug and to identify other genes encoding products that can respond or interact with specific compounds. Accordingly, the invention provides a modulator composition comprising a pharmaceutically acceptable carrier and a modulator, wherein the modulator is an RNAi molecule that inhibits the transcription or translation of an isolated polynucleotide or an isolated polypeptide comprising an amino acid sequence encoded by a polynucleotide chosen from the Tables, Figures, and Sequence Listing, and biologically active fragments thereof.

[0163] In one embodiment of the invention, complementary sense and antisense RNAs derived from a substantial portion of a polynucleotide encoding ADAM12 are synthesized *in vitro*. The resulting sense and antisense RNAs are annealed in an injection buffer, and the double-stranded RNA injected or otherwise introduced into the subject, for example, in food or by immersion in buffer containing the RNA (Gaudilliere, B., et al. (2002) *J. Biol. Chem.* 277:46,442-46,446.; O'Neil et al., 2001; WO99/32619). In an embodiment, dsRNA derived from an ADAM12 gene is generated *in vivo* by simultaneously expressing both sense and antisense RNA from appropriately positioned promoters operably linked to coding sequences in both sense and antisense orientations.

Aptamers

[0164] Another suitable agent for modulating an activity of a subject polypeptide is an aptamer. Aptamers of the invention include both nucleotide and peptide aptamers. Nucleotide aptamers of the invention include double stranded DNA and single stranded RNA molecules that bind to ADAM12 proteins or fragments thereof. Peptide aptamers are peptides or small polypeptides that act as dominant inhibitors of protein function. Peptide aptamers specifically bind to target proteins, blocking their functional ability (Kolonin, M.G., et al. (1998) *Proc. Natl. Acad. Sci.* 95:14,266-14,271). Due to the highly selective nature of peptide aptamers, they can be used not only to target a specific protein, but also to target specific functions of a given protein (for example, a signaling function). Further, peptide aptamers can be expressed in a controlled fashion by use of promoters which regulate expression in a temporal, spatial, or inducible manner. Peptide aptamers act dominantly, therefore, they can be used to analyze proteins for which loss-of-function mutants are not available. Aptamers of the invention may bind nucleotide cofactors (Latham, J.A., et al. (1994) *Nucl. Acids Res.* 22:2817-2822).

[0165] Peptide aptamers that bind with high affinity and specificity to a target protein can be isolated by a variety of techniques known in the art. Peptide aptamers can be isolated from random peptide libraries by yeast two-hybrid screens (Xu, C.W., et al. (1997) *Proc. Natl. Acad. Sci.* 94:12,473-12,478). They can also be isolated from phage libraries (Hoogenboom, H.R., et al. (1998) *Immunotechnology* 4:1-20) or chemically generated peptides/libraries.

Peptides and Modified Peptides

[0166] Polypeptides of the invention include full length proteins that include a signal peptide or leader sequence, if present, or a mature protein from which a signal peptide or leader sequence may have been cleaved, the signal peptide or leader sequence, or portions or fragments of the full length or mature protein. Also included in this term are biologically active variations of naturally occurring proteins, where such variations are homologous or substantially similar to the naturally occurring protein, as well as corresponding homologs from different species. Variants of polypeptide sequences may include insertions, additions, deletions, or substitutions compared with the subject polypeptides. Variants of polypeptide sequences include biologically active polymorphic variants.

[0167] In some embodiments of the present invention, the active agent is a peptide. Suitable peptides include peptides of from about 3 amino acids to about 50, from about 5 to about 30, or from about 10 to about 25 amino acids in length which may, but need not, correspond to the sequence of the naturally-occurring protein. In some embodiments, a peptide has a sequence of from about 7 amino acids to about 45, from about 9 to about 35, or from about 12 to about 25 amino acids of corresponding naturally-occurring protein. In some embodiments, a peptide exhibits one or more of the following activities: inhibits binding of a subject polypeptide to an interacting protein or other molecule; inhibits subject polypeptide binding to a second polypeptide molecule; inhibits a signal transduction activity of a subject polypeptide; inhibits an enzymatic activity of a subject polypeptide; or inhibits a DNA binding activity of a subject polypeptide.

[0168] Peptides of the invention can include naturally-occurring and non-naturally occurring amino acids. Peptides can comprise D-amino acids, a combination of D- and L-amino acids, and various "designer" or "synthetic" amino acids (for example, β -methyl amino acids, $\text{C}\alpha$ -methyl amino acids, and $\text{N}\alpha$ -methyl amino acids, etc.) to convey special properties. Additionally, peptides can be cyclic. Peptides can include non-classical amino acids in order to introduce particular conformational motifs. Any known non-classical amino acid can be used. Non-classical amino acids include, but are not limited to, 1,2,3,4-tetrahydroisoquinoline-3-carboxylate; (2S,3S)-methylphenylalanine, (2S,3R)-methyl-phenylalanine, (2R,3S)-methyl-phenylalanine and (2R,3R)-methyl-phenylalanine; 2-aminotetrahydro-naphthalene-2-carboxylic acid; hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate; β -carboline (D and L); HIC (histidine isoquinoline carboxylic acid); and HIC (histidine cyclic urea). Amino acid analogs and peptidomimetics can be incorporated into a peptide to induce or favor specific secondary structures, including, but not limited to, LL-Acp (LL-3-amino-2-propenidone-6-carboxylic acid), a β -turn inducing dipeptide analog; β -sheet inducing analogs; β -turn inducing analogs; α -helix inducing analogs; γ -turn inducing analogs; Gly-Ala turn analogs; amide bond isostere; or tetrazol, and the like.

[0169] An ADAM12 peptide of the invention can be a depsipeptide, which can be linear or cyclic (Kuisle, O., et al., (1999) *Tetrahedron Lett.* 40:1203-1206). Linear depsipeptides can comprise rings formed through S-S bridges, or through an hydroxy or a mercapto group of an hydroxy-, or mercapto-amino acid and the

carboxyl group of another amino- or hydroxy-acid but do not comprise rings formed only through peptide or ester links derived from hydroxy carboxylic acids. Cyclic depsipeptides contain at least one ring formed only through peptide or ester links, derived from hydroxy carboxylic acids.

[0170] ADAM12 peptides of the invention can be monocyclic or bicyclic. For example, the C-terminal carboxyl group or a C-terminal ester can be induced to cyclize by internal displacement of the (-OH) or the ester (-OR) of the carboxyl group or ester respectively with the N-terminal amino group to form a cyclic peptide. For example, after synthesis and cleavage to give the peptide acid, the free acid is converted to an activated ester by an appropriate carboxyl group activator such as dicyclohexylcarbodiimide (DCC) in solution, for example, in methylene chloride (CH_2Cl_2), dimethyl formamide (DMF) mixtures. The cyclic peptide is then formed by internal displacement of the activated ester with the N-terminal amine. Internal cyclization as opposed to polymerization can be enhanced by use of very dilute solutions. Methods for making cyclic peptides are well known in the art.

[0171] A desamino or descarboxy residue can be incorporated at the terminal ends of the peptide, so that there is no terminal amino or carboxyl group, to decrease susceptibility to proteases or to restrict conformation. C-terminal functional groups include amide, amide lower alkyl, amide di (lower alkyl), lower alkoxy, hydroxy, and carboxy, and the lower ester derivatives thereof, and the pharmaceutically acceptable salts thereof.

[0172] In addition to the foregoing N-terminal and C-terminal modifications, an ADAM12 peptide or peptidomimetic can be modified with or covalently coupled to one or more of a variety of hydrophilic polymers to increase solubility and circulation half-life of the peptide. Suitable nonproteinaceous hydrophilic polymers for coupling to a peptide include, but are not limited to, polyalkylethers as exemplified by polyethylene glycol and polypropylene glycol, polylactic acid, polyglycolic acid, polyoxyalkenes, polyvinylalcohol, polyvinylpyrrolidone, cellulose and cellulose derivatives, dextran, and dextran derivatives. Generally, such hydrophilic polymers have an average molecular weight ranging from about 500 to about 100,000 daltons, from about 2,000 to about 40,000 daltons, or from about 5,000 to about 20,000 daltons. The peptide can be derivatized with or coupled to such polymers using any of the methods set forth in Zallipsky, S. (1995) *Bioconjugate Chem.*, 6:150-165; Monfardini, C., et al. (1995) *Bioconjugate Chem.* 6:62-69; U.S.

Pat. Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192; 4,179,337, or WO 95/34326.

[0173] In an embodiment, peptide modulators of the invention can increase or decrease one or more biological activity of ADAM12L. For example, Oh, M., et al. (2004) *Bioorg. Med. Chem. Lett.* 14:6071-6074 have reported dipeptide analogs that inhibit the metalloprotease activity of ADAM12.

Small Molecules

[0174] Small molecule modulators such as those commonly used as therapeutic drugs, can be used as modulators in the invention. Small molecule agents include chemical compounds that bind the polypeptide and modulate activity of the polypeptide or cell containing the polypeptide. Small molecule modulators may permeate the cell, and/or may exert their action at the extracellular surface or on non-cellular structures, such as the extracellular matrix. Ichikawa, Y., et al. (2004) *Cardiovasc. Res.* 62:167-175 have reported that KB-R7785 is selective for ADAM12, but failed to demonstrate a physiologic relevance for this inhibition.

Antibodies

[0175] Modulators of the invention may be antibodies. The invention provides an isolated antibody that specifically recognizes, binds to, interferes with, and/or otherwise modulates the biological activity of at least one ADAM12 polypeptide of the Tables, Figures, and Sequence Listing or encoded by an ADAM12 nucleic acid molecule of the Tables, Figures, and Sequence Listing. For example, an antibody of the invention may be directed to a polypeptide comprising a non-transmembrane domain and/or an extracellular domain. An antibody of the invention may be directed to polypeptide comprising a part or all of a Pfam or Prosite domain, signal peptide, propeptide, metalloprotease domain, disintegrin domain, cysteine-rich domain, EGF-like domain, secreted tail, or cytoplasmic tail of ADAM12.

[0176] The production and use of antibodies is well-known in the art (Harlow, E., et al., eds. (1998) *Using Antibodies: A Laboratory Manual: Portable Protocol NO. I.* Cold Spring Harbor Laboratory; Harlow, E., Lane, D., eds. (1988) *Antibodies: A Laboratory Manual.* Cold Spring Harbor Laboratory; Howard, G.C., et al. (2000) *Basic Methods in Antibody Production and Characterization*, CRC Press). This antibody may be a monoclonal antibody; a polyclonal antibody; a single chain antibody; an antibody comprising a backbone of a molecule with an Ig domain or a T cell receptor backbone; a targeting antibody; a neutralizing antibody; a

stabilizing antibody; an enhancing antibody; an antibody agonist; an antibody antagonist; an antibody that promotes endocytosis of a target antigen; a cytotoxic antibody; an antibody that mediates antibody-dependent cell cytotoxicity; a human antibody; a non-human primate antibody; a non-primate animal antibody; an antibody that mediates complement-dependent cytotoxicity.

[0177] An antibody of the invention can be a human antibody, a non-human primate antibody, a non-primate animal antibody, a rabbit antibody, a mouse antibody, a rat antibody, a sheep antibody, a goat antibody, a horse antibody, a porcine antibody, a cow antibody, a chicken antibody, a humanized antibody, a primatized antibody, and/or a chimeric antibody. Antibodies of the invention can comprise a cytotoxic antibody with one or more cytotoxic component chosen from a radioisotope, a microbial toxin, a plant toxin, and a chemical compound. The chemical compound can, for example, be chosen from doxorubicin and cisplatin. Antibodies of the invention include antigen-binding fragments; fragments comprising a variable region of a heavy chain or a light chain of an immunoglobulin; fragments comprising a complementarity determining region or a framework region of an immunoglobulin; and one or more active fragments, analogues, and/or antagonists.

[0178] The isolated antibodies of the invention can be produced in a variety of cells. Host cells of the invention can be genetically modified to produce an antibody of the invention; these include bacterial cells, fungal cells, plant cells, insect cells, and mammalian cells. For example, isolated antibodies of the invention may be produced in yeast cells, *Aspergillus* cells, SF9 cells, High Five cells, cereal plant cells, tobacco cells, tomato cells, human kidney embryonic kidney 293 cells, myeloma cells, including mouse myeloma NS0 cells, human fetal Per C6 cells, and CHO cells.

[0179] In another aspect, the invention provides antibody targets. The ADAM12 polynucleotides and polypeptides described herein comprise nucleic acid and amino acid sequences that can be recognized by antibodies. A target sequence can be any polynucleotide or amino acid sequence of approximately eighteen or more contiguous nucleotides or approximately six or more amino acids. A variety of comparing means can be used to accomplish comparison of sequence information from a sample (for example, to analyze target sequences, target motifs, or relative expression levels) with the data storage means. A skilled artisan can readily recognize that any one of the publicly available homology search programs can be used as the search means for the computer based systems of the present invention to

accomplish comparison of target sequences and motifs. Computer programs to analyze expression levels in a sample and in controls are also known in the art. A target sequence includes an antibody target sequence, which refers to an amino acid sequence that can be used as an immunogen for injection into animals for production of antibodies or for screening against a phage display or antibody library for identification of binding partners.

[0180] The invention provides target structural motifs and target functional motifs, i.e., any rationally selected sequences or combination of sequences in which the sequence(s) are chosen based on a three-dimensional configuration formed upon the folding of the target motif, or on consensus sequences of regulatory or active sites. There are a variety of target motifs known in the art. Protein target motifs include, but are not limited to, enzyme active sites and signal sequences. Nucleic acid target motifs include, but are not limited to, hairpin structures, promoter sequences, and other expression elements, such as binding sites for transcription factors.

[0181] Antibodies of the invention bind specifically to their targets. Specific binding, in the context of antibody binding, refers to high avidity and/or high affinity binding of an antibody to a specific polypeptide, or more accurately, to an epitope of a specific polypeptide. Antibody binding to such an epitope on a polypeptide can be stronger than binding of the same antibody to any other epitopes, particularly other epitopes that can be present in molecules in association with, or in the same sample as the polypeptide of interest. For example, when an antibody binds more strongly to one epitope than to another, adjusting the binding conditions can result in antibody binding almost exclusively to the specific epitope and not to any other epitopes on the same polypeptide, and not to any other polypeptide, which does not comprise the epitope. Antibodies that bind specifically to a subject polypeptide may be capable of binding other polypeptides at a weak, yet detectable, level (for example, 10% or less of the binding shown to the polypeptide of interest). Such weak binding, or background binding, is readily discernible from the specific antibody binding to a subject polypeptide, for example, by use of appropriate controls. In general, antibodies of the invention bind to a specific polypeptide with a binding affinity of 10^7 M^{-1} or greater (for example, 10^8 M^{-1} , 10^9 M^{-1} , 10^{10} M^{-1} , 10^{11} M^{-1} , etc.).

[0182] The invention provides antibodies that can distinguish variant ADAM12 sequences from one another. These antibodies can distinguish polypeptides that differ by no more than one amino acid (U.S. Patent No. 6,656,467).

They have high affinity constants, which are in the range of approximately 10^{10} M^{-1} , and are produced, for example, by genetically engineering appropriate antibody gene sequences, according to the method described by Young et al., in U.S. Patent No. 6,656,467.

[0183] Antibodies of the invention can be provided as matrices, for example, as geometric networks of antibody molecules and their antigens, as found in immunoprecipitation and flocculation reactions. An antibody matrix can exist in solution or on a solid phase support.

[0184] Antibodies of the invention can be provided as a library of antibodies or fragments thereof, wherein at least one antibody or fragment thereof specifically binds to at least a portion of a polypeptide comprising an amino acid sequence or fragment thereof described in the Tables or Sequence Listing, and/or wherein at least one antibody or fragment thereof interferes with at least one activity of the polypeptide or fragment thereof. In certain embodiments, the antibody library comprises at least one antibody or fragment thereof that specifically inhibits the binding of an ADAM12 polypeptide to its ligand or substrate, or that specifically inhibits binding of an ADAM12 polypeptide as a substrate to another molecule. In certain embodiments, the antibody library comprises combinatorial complementarity determining regions, heavy chains, and light chains. The present invention also features corresponding polynucleotide libraries comprising at least one polynucleotide sequence that encodes an antibody or antibody fragment of the invention. In specific embodiments, the library is provided on a nucleic acid array or in computer-readable format.

[0185] The invention provides a method of making an antibody by introducing an antigen chosen from an isolated nucleic acid molecule comprising at least one polynucleotide sequence chosen from the Tables or Sequence Listing; sequences that hybridize to these sequences under high stringency conditions; sequences having at least 80% sequence identity to these sequences, or sequences that hybridize to them under high stringency conditions; complements of any of these sequences; or biologically active fragments of any of the above-listed sequences or an isolated polypeptide comprising an amino acid sequence, wherein the amino acid sequence is chosen from the Tables, Figures, or Sequence Listing, or a biologically active fragment thereof, or is encoded by a polynucleotide sequence chosen from the Tables, Figures, or Sequence Listing, or a biologically active fragment thereof, into an animal

in an amount sufficient to elicit generation of antibodies specific to the antigen, and recovering the antibodies therefrom.

[0186] The immunogen can comprise a nucleic acid, a complete protein, or fragments and derivatives thereof, or proteins expressed on cell surfaces. Protein domains, for example, Pfam domains, or extracellular, cytoplasmic, or luminal domains can be used as immunogens. Immunogens can comprise all or a part of one of the ADAM12 proteins, where these amino acids contain post-translational modifications, such as glycosylation, found on the native target protein. Immunogens comprising protein extracellular domains are produced in a variety of ways known in the art, for example, expression of cloned genes using conventional recombinant methods, or isolation from tumor cell culture supernatants, etc. The immunogen can also be expressed *in vivo* from a polynucleotide encoding the immunogenic peptide introduced into the host animal.

[0187] Polyclonal antibodies of the invention are prepared by conventional techniques. These include immunizing the host animal *in vivo* with the target protein (or immunogen) in substantially pure form, for example, comprising less than about 1% contaminant. The immunogen can comprise the complete target protein, fragments, or derivatives thereof. To increase the immune response of the host animal, the target protein can be combined with an adjuvant; suitable adjuvants include alum, dextran, sulfate, large polymeric anions, and oil and water emulsions, for example, Freund's adjuvant (complete or incomplete). The target protein can also be conjugated to synthetic carrier proteins or synthetic antigens. The target protein is administered to the host, usually intradermally, with an initial dosage followed by one or more, usually at least two, additional booster dosages. Following immunization, blood from the host is collected, followed by separation of the serum from blood cells. The immunoglobulin present in the resultant antiserum can be further fractionated using known methods, such as ammonium salt fractionation, or DEAE chromatography and the like.

[0188] Monoclonal antibodies of the invention are also produced by conventional techniques, such as fusing an antibody-producing plasma cell with an immortal cell to produce hybridomas. Suitable animals will be used, for example, to raise antibodies against a mouse polypeptide of the invention, the host animal will generally be a hamster, guinea pig, goat, chicken, or rabbit, or the like. Generally, the spleen and/or lymph nodes of an immunized host animal provide the source of plasma

cells, which are immortalized by fusion with myeloma cells to produce hybridoma cells. Culture supernatants from individual hybridomas are screened using standard techniques to identify clones producing antibodies with the desired specificity. The antibody can be purified from the hybridoma cell supernatants or from ascites fluid present in the host by conventional techniques, for example, affinity chromatography using antigen, for example, the subject protein, bound to an insoluble support, for example, protein A Sepharose[®], etc.

[0189] Cytokines can be used to help stimulate immune response. Cytokines act as chemical messengers, stimulating optimal responses from immune cells. An example of a cytokine is granulocyte-macrophage colony-stimulating factor (GM-CSF), which stimulates the proliferation of antigen-presenting cells, thus boosting an organism's response to a cancer vaccine. As with adjuvants, cytokines can be used in conjunction with the antibodies and vaccines disclosed herein. For example, they can be incorporated into the antigen-encoding plasmid or introduced via a separate plasmid, and in some embodiments, a viral vector can be engineered to display cytokines on its surface.

[0190] The antibody can be produced as a single chain, instead of the normal multimeric structure of the immunoglobulin molecule. Single chain antibodies have been previously described by Jost, C.R., et al. (1994) *J. Biol. Chem.* 269:26,267-26,273. DNA sequences encoding parts of the immunoglobulin, for example, the variable region of the heavy chain and the variable region of the light chain are ligated to a spacer, such as one encoding at least about four small neutral amino acids, such as glycine or serine. The protein encoded by this fusion allows the assembly of a functional variable region that retains the specificity and affinity of the original antibody.

[0191] The invention also provides intrabodies that are intracellularly expressed single-chain antibody molecules designed to specifically bind and inactivate target molecules inside cells. Intrabodies have been used in cell assays and in whole organisms (Chen, S.Y., et al. (1994) *Hum. Gene Ther.* 5:595-601; Hassanzadeh, G.H.G., et al. (1998) *FEBS Lett.* 437:75-80). Inducible expression vectors can be constructed with intrabodies that react specifically with a protein of the invention. These vectors can be introduced into host cells and model organisms.

[0192] The invention provides artificial antibodies - antibodies and antibody fragments produced and selected *in vitro*. In some embodiments, these antibodies, or

fragments thereof are displayed on the surface of a bacteriophage or other viral particle, as described above. Suitable fragments include single chain variable region antibodies. In other embodiments, artificial antibodies are present as fusion proteins with a viral or bacteriophage structural protein, including, but not limited to, M13 gene III protein. Methods of producing such artificial antibodies are well known in the art (U.S. Patent Nos. 5,516,637; 5,223,409; 5,658,727; 5,667,988; 5,498,538; 5,403,484; 5,571,698; and 5,625,033). The artificial antibodies, selected, for example, on the basis of phage binding to selected antigens, can be fused to a Fc fragment of an immunoglobulin for use as a therapeutic, as described, for example, in U.S. Patent No. 5,116,964 or WO 99/61630.

[0193] In an embodiment, artificial antibodies of the invention include genetically engineered antibodies. Single chain variable region antibodies are within the scope of such an embodiment. Engineered antibodies may incorporate non-antibody domains, including, for example, coiled coil domains for dimerization, linkers, or other such useful modifications. Genetically engineered antibodies of the invention include proteins with predetermined ligand specificity based on a known or predicted epitope, for example anticalins (Schlehuber, S., et al. (2001) *Biol. Chem.* 382:1335-1342), which are suitable for use in the invention when an immunogenic, cross-linking, or effector property of an antibody is undesirable.

[0194] For *in vivo* use, particularly for injection into humans, in some embodiments it is desirable to decrease the antigenicity of the antibody. An immune response of a recipient against the antibody may potentially decrease the period of time that the therapy is effective. Methods of humanizing antibodies are known in the art. The humanized antibody can be the product of an animal having transgenic human immunoglobulin genes, for example, constant region genes (for example, Grosveld, F., Kollias, G., eds. (1992) *Transgenic Animals*. 1st ed. Academic Press; Murphy, D., et al., eds. (1993) *Transgenesis Techniques: Principles and Protocols*. Humana Press; Pinkert, C.A., ed. (1994) *Transgenic Animal Technology: A Laboratory Handbook*. Academic Press; and International Patent Applications WO 90/10077 and WO 90/04036). Alternatively, the antibody of interest can be engineered by recombinant DNA techniques to substitute the CH1, CH2, CH3, hinge domains, and/or the framework domain with the corresponding human sequence (see, for example, WO 92/02190).

[0195] Thus, antibodies of the invention can be partially human or fully human antibodies. For example, xenogenic antibodies, which are produced in animals that are transgenic for human antibody genes, can be employed to make a fully human antibody. By xenogenic human antibodies is meant antibodies that are fully human antibodies, with the exception that they are produced in a non-human host that has been genetically engineered to express human antibodies (for example, WO 98/50433; WO 98/24893 and WO 99/53049).

[0196] Humanized antibodies can be produced by immunizing mice that make human antibodies. Abgenix's XenoMouse (for example, U.S. Patent Nos. 5,939,598; 6,075,181; 6,091,001; 6,114,598; 6,150,584; 6,162,963; 6,657,103; 6,673,986; 6,682,736) Medarex's mice (for example, U.S. Patent Nos. 5,922,845; 6,111,166; 6,410,690; 6,680,209) and Kirin's mice (for example, U.S. Patent Nos. 6,320,099; 6,632,976) are suitable for use in the invention. Humanized antibodies can be made, for example, using the technology of Protein Design Labs, Inc. (Fremont, CA) (for example, Coligan, J.E. et al., eds. (2002) *Current Protocols in Immunology*, vols. 1-4, including suppl.) John Wiley and Sons, Inc. New York, NY). Both polyclonal and monoclonal antibodies made in non-human animals may be humanized before administration to human subjects.

[0197] Chimeric immunoglobulin genes constructed with immunoglobulin cDNA are known in the art (Liu A.Y., et al. (1987a) *Proc. Natl. Acad. Sci.* 84:3439-3443; Liu, A.Y., et al. (1987b) *J. Immunol.* 139:3521-26.). Messenger RNA is isolated from a hybridoma or other cell producing the antibody and used to produce cDNA. The cDNA of interest can be amplified by the polymerase chain reaction using specific primers (U.S. Patent Nos. 4,683,195 and 4,683,202). Alternatively, a library is made and screened to isolate the sequence of interest. The DNA sequence encoding the variable region of the antibody is then fused to human constant region sequences. The sequences of human constant (C) regions genes are known in the art (Kabat, E.A., Wu T.T. (1991) *J. Immunol.* 147:1709-1719). Human C region genes are readily available from known clones. The choice of isotype will be guided by the desired effector functions, such as complement fixation, or antibody-dependent cellular cytotoxicity. IgG1, IgG2, IgG3, and IgG4 isotypes, and either of the kappa or lambda human light chain constant regions can be used. The chimeric, humanized antibody is then expressed by conventional methods.

[0198] Consensus sequences of heavy (H) and light (L) J regions can be used to design oligonucleotides for use as primers to introduce useful restriction sites into the J region for subsequent linkage of V region segments to human C region segments. C region cDNA can be modified by site-directed mutagenesis to place a restriction site at the analogous position in the human sequence.

[0199] A convenient expression vector for producing antibodies is one that encodes a functionally complete human CH or CL immunoglobulin sequence, with appropriate restriction sites engineered so that any VH or VL sequence can be easily inserted and expressed, such as plasmids, retroviruses, YACs, or EBV-derived episomes, and the like. In such vectors, splicing usually occurs between the splice donor site in the inserted J region and the splice acceptor site preceding the human C region, and also at the splice regions that occur within the human CH exons. Polyadenylation and transcription termination occur at native chromosomal sites downstream of the coding regions. The resulting chimeric antibody can be joined to any strong promoter, including retroviral LTRs, for example, SV-40 early promoter (Okayama, H., et al. (1983) *Mol. Cell. Biol.* 3:280-289), Rous sarcoma virus LTR (Gorman, C.M., et al. (1982) *Proc. Natl. Acad. Sci.* 79:6777-6781), and Moloney murine leukemia virus LTR (Grosschedl, R., Baltimore, D. (1985) *Cell* 41:885-897), or native immunoglobulin promoters.

[0200] Antibody fragments, such as Fv, F(ab')₂, and Fab can be prepared by cleavage of the intact protein, for example, by protease or chemical cleavage. These fragments can include heavy and light chain variable regions. Alternatively, a truncated gene can be designed, for example, a chimeric gene encoding a portion of the F(ab')₂ fragment that includes DNA sequences encoding the CH1 domain and hinge region of the H chain, followed by a translational stop codon.

[0201] Antibodies may be administered by injection systemically, such as by intravenous injection; or by injection or application to the relevant site, such as by direct injection into a tumor, or direct application to the site when the site is exposed in surgery; or by topical application, such as if the disorder is on the skin, for example.

[0202] The antibodies of the present invention may be administered alone or in combination with other molecules for use as a therapeutic, for example, by linking the antibody to cytotoxic agents or radioactive molecules. Radioactive antibodies and antibodies comprising a cytotoxic microbial, plant, or chemical compound that are

specific to a cancer cell, diseased cell, or other target cell may be able to deliver a sufficient dose of radioactivity or toxin to kill the cell.

[0203] Radiolabeled antibodies of the invention can be used clinically to detect tumor cells, including latent metastases. Radionuclide imaging can be performed according to well-known methods, including that described in Kufe et al., eds. (2003) *Cancer Medicine* 6th ed., B.C. Decker, Inc. *In vivo* diagnostic imaging methods of the invention include single photon and positron imaging, and may include the use of scanners and cameras, including, but not limited to computed tomography (CT) scanners and gamma cameras.

[0204] Antibodies of the invention can be used to modulate biological activity of cells, either directly or indirectly. An ADAM12 antibody can modulate the activity of a target cell, with which it has primary interaction, or it can modulate the activity of other cells by exerting secondary effects, for example in instances when the primary targets interact or communicate with other cells. An ADAM12 antibody can also modulate the activity of a target cell by primarily interacting with an antigen, which then exerts an effect, whether direct, or indirect, on a target cell. Antibodies of the invention may specifically inhibit the binding of an ADAM12 polypeptide to a ligand, specifically inhibit the binding of an ADAM12 polypeptide to a substrate, specifically inhibit the binding of an ADAM12 polypeptide as a ligand, specifically inhibit the binding of an ADAM12 polypeptide as a substrate, specifically inhibit cofactor binding, induce apoptosis, induce ADCC, induce CDC, inhibit protease activity, inhibit adhesion, inhibit ligand/receptor interaction, and/or inhibit enzyme/substrate interaction.

[0205] The invention provides a method of modulating the biological activity of a first human or non-human animal host cell by providing an antibody of the invention and contacting the antibody with the first host cell, wherein the activity of the first host cell, and/or a second host cell, is modulated. For example, the first host cell may be a cancer cell and the second host cell may be a lymphocyte, NK cell, granulocyte, neutrophil, eosinophil, basophil, mast cell, macrophage, dendritic cell, or antigen presenting cell. In an embodiment, the first host cell expresses a polypeptide and the second host cell is an effector. In an embodiment, the antibody modulator first binds to the first host cell. In an embodiment, the antibody modulator first binds to the second host cell. In an embodiment, contacting the antibody with the first host cell results in recruitment of at least one second host cell.

[0206] This method of modulation includes embodiments wherein the modulation of biological activity is chosen from inhibiting cell activity directly, inhibiting cell activity indirectly, inducing antibody-dependent cell cytotoxicity, and inducing complement-dependent cytotoxicity. The modulated cell activity can include signal transduction, transcription, and translation. The modulated activity may be cell mobility, cell metastasis, cell invasion, and/or cell adhesion. The modulation of cell activity may result in cell death and/or inhibition of cell growth.

[0207] The antibodies of the invention can be administered to mammals, and the present invention includes such administration, for example, for therapeutic and/or diagnostic purposes in humans. Accordingly, the invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an antibody of the invention.

[0208] The antibodies of the present invention can also be used in assays to detect ADAM12 polypeptides. In some embodiments, the assay is a binding assay that detects binding of a polypeptide with an antibody specific for the polypeptide; the subject polypeptide or antibody can be immobilized, while the subject polypeptide and/or antibody can be detectably labeled. For example, the antibody can be directly labeled or detected with a labeled secondary antibody. That is, suitable, detectable labels for antibodies include direct labels, which label the antibody to the protein of interest, and indirect labels, which label an antibody that recognizes the antibody to the protein of interest.

[0209] These labels include radioisotopes, including, but not limited to ^{64}Cu , ^{67}Cu , ^{90}Y , $^{99\text{m}}\text{Tc}$, ^{111}In , ^{124}I , ^{125}I , ^{131}I , ^{137}Cs , ^{186}Re , ^{211}At , ^{212}Bi , ^{213}Bi , ^{223}Ra , ^{241}Am , and ^{244}Cm ; enzymes having detectable products (for example, luciferase, peroxidase, alkaline phosphatase, β -galactosidase, and the like); fluorescers and fluorescent labels, for example, as provided herein; fluorescence emitting metals, for example, ^{152}Eu , or others of the lanthanide series, attached to the antibody through metal chelating groups such as EDTA; chemiluminescent compounds, for example, luminol, isoluminol, or acridinium salts; and bioluminescent compounds, for example, luciferin, or aequorin (green fluorescent protein), specific binding molecules, for example, magnetic particles, microspheres, nanospheres, and the like.

[0210] Alternatively, specific-binding pairs may be used, involving, for example, a second stage antibody or reagent that is detectably labeled and that can amplify the signal. For example, a primary antibody can be conjugated to biotin, and

horseradish peroxidase-conjugated streptavidin added as a second stage reagent. Digoxin and antidigoxin provide another such pair. In other embodiments, the secondary antibody can be conjugated to an enzyme such as peroxidase in combination with a substrate that undergoes a color change in the presence of the peroxidase. The absence or presence of antibody binding can be determined by various methods, including flow cytometry of dissociated cells, microscopy, radiography, or scintillation counting. Such reagents and their methods of use are well known in the art.

[0211] Antibodies of the invention can be provided in the form of arrays, which are collections of plural biological molecules having locatable addresses that may be separately detectable. Generally, a microarray encompasses use of submicrogram quantities of biological molecules. The antibodies may be affixed to a substrate or may be in solution or suspension. The substrate can be porous or solid, planar or non-planar, unitary or distributed, such as a glass slide, a 96 well plate, with or without the use of microbeads or nanobeads. Antibody microarrays of the invention include arrays of ADAM12 related antibodies obtained by purification, as fusion proteins, and or recombinantly, and can be used for specific binding studies (Zhu, H., et al. (2003) *Curr. Opin. Chem. Biol.* 7:55-63; Houseman, B.T., et al. (2002) *Nature Biotechnol.* 20:270-274; Schaeferling, M., et al. (2002) *Electrophoresis* 23:3097-3105; Weng, S., et al. (2002) *Proteomics* 2:48-57; Winssinger, N., et al. (2002) *Proc. Natl. Acad. Sci.* 99:11,139-11,144; Zhu, H., Bilgin, et al. (2001) *Science* 293:2101-2105; and MacBeath, G., et al. (2000) *Science* 289:1760-1763).

[0212] All of the immunogenic methods of the invention can be used alone or in combination with other conventional or unconventional therapies. For example, immunogenic molecules can be combined with other molecules that have a variety of antiproliferative effects, or with additional substances that help stimulate the immune response, for example, adjuvants or cytokines.

Vaccine Therapy

[0213] The mature form of ADAM12L is overexpressed at the surface of cancer cells and is not normally expressed at high levels in healthy, non-pregnant adults. The polypeptide, such as the extracellular domain of the mature form of ADAM12L (aa 208-706), or portions of it, can be formulated and administered as a vaccine. Such a vaccine can be used as to treat patients overexpressing ADAM12L at

the surface of cancer cells, inducing antibody or cell mediated immune responses against the cancer cells, including antibody-dependent cell cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC).

[0214] The invention also provides a method for prophylaxis or therapeutic treatment of a subject needing or desiring such treatment by providing a vaccine and administering the vaccine to the subject. The vaccine may comprise one or more of a polynucleotide, polypeptide, or modulator of the invention, for example an antibody vaccine composition, a polypeptide vaccine composition, or a polynucleotide vaccine composition. It may comprise a complement, biologically active fragment, or variant of any of these. For example, the vaccine can be a cancer vaccine, and the polypeptide can concomitantly be a cancer antigen. The vaccine can be administered with or without an adjuvant.

[0215] Vaccine therapy involves the use of polynucleotides, polypeptides, or agents of the invention as immunogens for tumor antigens (Machiels et al., 2002; Shinnick, T.M., et al. (1983) *Ann. Rev. Microbiol.* 37:425-446). For example, peptide-based vaccines of the invention include unmodified subject polypeptides, fragments thereof, and MHC class I and class II-restricted peptide (Knutson et al., 2001), comprising, for example, the disclosed sequences with universal, nonspecific MHC class II-restricted epitopes. Peptide-based vaccines comprising a tumor antigen can be given directly, either alone or in conjunction with other molecules. The vaccines can also be delivered orally by producing the antigens in transgenic plants that can be subsequently ingested (U.S. Patent No. 6,395,964).

[0216] In some embodiments, antibodies themselves can be used as antigens in anti-idiotypic vaccines. That is, administering an antibody to a tumor antigen can stimulate B cells to make antibodies to that antibody, which in turn recognize the tumor cells.

[0217] Nucleic acid-based vaccines can deliver tumor antigens as polynucleotide constructs encoding the antigen. Vaccines comprising genetic material, such as DNA or RNA, can be given directly, either alone or in conjunction with other molecules. Administration of a vaccine expressing a molecule of the invention, for example, as plasmid DNA, leads to persistent expression and release of the therapeutic immunogen over a period of time, helping to control unwanted tumor growth.

[0218] In some embodiments, nucleic acid-based vaccines encode subject antibodies. In such embodiments, the vaccines (for example, DNA vaccines) can include post-transcriptional regulatory elements, such as the post-transcriptional regulatory acting RNA element (WPRES) derived from Woodchuck Hepatitis Virus. These post-transcriptional regulatory elements can be used to target the antibody, or a fusion protein comprising the antibody and a co-stimulatory molecule, to the tumor microenvironment (Pertl et al., *Blood* 101:649 (2003)).

[0219] Besides stimulating anti-tumor immune responses by inducing humoral responses, vaccines of the invention can also induce cellular responses, including stimulating T-cells that recognize and kill tumor cells directly. For example, nucleotide-based vaccines of the invention encoding tumor antigens can be used to activate the CD8⁺ cytotoxic T lymphocyte arm of the immune system.

[0220] In some embodiments, the vaccines activate T-cells directly, and in others they enlist antigen-presenting cells to activate T-cells. Killer T-cells are primed, in part, by interacting with antigen-presenting cells, for example, dendritic cells. In some embodiments, plasmids comprising the nucleic acid molecules of the invention enter antigen-presenting cells, which in turn display the encoded tumor-antigens that contribute to killer T-cell activation. Again, the tumor antigens can be delivered as plasmid DNA constructs, either alone or with other molecules.

[0221] In further embodiments, RNA can be used. For example, antigen-presenting cells can be transfected or transduced with RNA encoding tumor antigens (Heiser et al., *J. Clin. Invest.* 109:409-417 (2002); Mitchell et al., *J. Clin. Invest.* 106:1065-1069 (2000)). This approach overcomes the limitations of obtaining sufficient quantities of tumor material, extending therapy to patients otherwise excluded from clinical trials. For example, a subject RNA molecule isolated from tumors can be amplified using RT-PCR. In some embodiments, the RNA molecule of the invention is directly isolated from tumors and transfected into antigen-presenting cells or dendritic cells with no intervening cloning steps.

[0222] In some embodiments, the molecules of the invention are altered such that the peptide antigens are more highly antigenic than in their native state. These embodiments address the need in the art to overcome the poor *in vivo* immunogenicity of most tumor antigens by enhancing tumor antigen immunogenicity via modification of epitope sequences (Yu et al., *J. Clin. Invest.* 110:289-294 (2002)).

[0223] Another recognized problem of cancer vaccines is the presence of preexisting neutralizing antibodies. Some embodiments of the present invention overcome this problem by using viral vectors from non-mammalian natural hosts, i.e., avian pox viruses. Alternative embodiments that also circumvent preexisting neutralizing antibodies include genetically engineered influenza viruses, and the use of "naked" plasmid DNA vaccines that contain DNA with no associated protein. (Yu and Restifo, 2002).

Carriers, Excipients and Formulations

[0224] In some embodiments, ADAM12-related compositions are provided in formulation with pharmaceutically acceptable excipients, a wide variety of which are known in the art (Gennaro, A.R. (2003) *Remington: The Science and Practice of Pharmacy with Facts and Comparisons: DrugfactsPlus*. 20th ed. Lippincott Williams & Williams; Ansel, H.C. et al., eds. (2004) *Pharmaceutical Dosage Forms and Drug Delivery Systems*. 8th ed. Lippincott Williams & Wilkins.; Kibbe, A.H., ed. (2000) *Handbook of Pharmaceutical Excipients*, 3rd ed. Pharmaceutical Press). Pharmaceutically acceptable excipients, such as vehicles, adjuvants, carriers, or diluents, are readily available to the public. Moreover, pharmaceutically acceptable auxiliary substances, such as pH adjusting and buffering agents, tonicity adjusting agents, stabilizers, wetting agents and the like, are readily available to the public.

[0225] Suitable carriers include, but are not limited to, water, dextrose, glycerol, saline, ethanol, and combinations thereof. The carrier can contain additional agents such as wetting or emulsifying agents, pH buffering agents, or adjuvants which enhance the effectiveness of the formulation. Topical carriers include liquid petroleum, isopropyl palmitate, polyethylene glycol, ethanol (95%), polyoxyethylene monolaurate (5%) in water, or sodium lauryl sulfate (5%) in water. Other materials such as anti-oxidants, humectants, viscosity stabilizers, and similar agents can be added as necessary. Percutaneous penetration enhancers such as Azone can also be included.

[0226] In pharmaceutical dosage forms, the compositions of the invention can be administered in the form of their pharmaceutically acceptable salts, or they can also be used alone or in appropriate association, as well as in combination, with other pharmaceutically active compounds. The subject compositions are formulated in accordance to the mode of potential administration. Administration of the agents can be achieved in various ways, including oral, buccal, nasal, rectal, parenteral,

intraperitoneal, intradermal, transdermal, subcutaneous, intravenous, intra-arterial, intracardiac, intraventricular, intracranial, intratracheal, and intrathecal administration, etc., or otherwise by implantation or inhalation. Thus, the subject compositions can be formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as tablets, capsules, powders, granules, ointments, solutions, suppositories, injections, inhalants and aerosols. The following methods and excipients are merely exemplary and are in no way limiting.

[0227] Compositions for oral administration can form solutions, suspensions, tablets, pills, granules, capsules, sustained release formulations, oral rinses, or powders. For oral preparations, the agents, polynucleotides, and polypeptides can be used alone or in combination with appropriate additives, for example, with conventional additives, such as lactose, mannitol, corn starch, or potato starch; with binders, such as crystalline cellulose, cellulose derivatives, acacia, corn starch, or gelatins; with disintegrators, such as corn starch, potato starch, or sodium carboxymethylcellulose; with lubricants, such as talc or magnesium stearate; and if desired, with diluents, buffering agents, moistening agents, preservatives, and flavoring agents.

[0228] Suitable excipient vehicles are, for example, water, saline, dextrose, glycerol, ethanol, or the like, and combinations thereof. In addition, if desired, the vehicle can contain minor amounts of auxiliary substances such as wetting or emulsifying agents or pH buffering agents. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in the art (Gennaro, 2003). The composition or formulation to be administered will, in any event, contain a quantity of the agent adequate to achieve the desired state in the subject being treated.

[0229] The antibodies, other agents, polynucleotides, and polypeptides can be formulated into preparations for injection by dissolving, suspending or emulsifying them in an aqueous or nonaqueous solvent, such as vegetable or other similar oils, synthetic aliphatic acid glycerides, esters of higher aliphatic acids or propylene glycol; and if desired, with conventional additives such as solubilizers, isotonic agents, suspending agents, emulsifying agents, stabilizers, and preservatives. Other formulations for oral or parenteral delivery can also be used, as conventional in the art.

[0230] The antibodies, other agents, polynucleotides, and polypeptides can be utilized in aerosol formulation to be administered via inhalation. The compounds of

the present invention can be formulated into pressurized acceptable propellants such as dichlorodifluoromethane, propane, nitrogen, and the like. Further, the agent, polynucleotides, or polypeptide composition may be converted to powder form for administration intranasally or by inhalation, as conventional in the art.

[0231] Furthermore, the antibodies, other agents, polypeptides, and polynucleotides can be made into suppositories by mixing with a variety of bases such as emulsifying bases or water-soluble bases. The compounds of the present invention can be administered rectally via a suppository. The suppository can include vehicles such as cocoa butter, carbowaxes and polyethylene glycols, which melt at body temperature, yet are solidified at room temperature.

[0232] A polynucleotide, polypeptide, antibody, or other agent can also be introduced into tissues or host cells by other routes, such as viral infection, microinjection, or vesicle fusion. For example, expression vectors can be used to introduce nucleic acid compositions into a cell as described above. Further, jet injection can be used for intramuscular administration (Furth et al., 1992). The DNA can be coated onto gold microparticles, and delivered intradermally by a particle bombardment device, or "gene gun" as described in the literature (Tang, D.C., et al. (1992) *Nature* 356:152-154), where gold microprojectiles are coated with the DNA, then bombarded into skin cells.

[0233] The agents can be provided in unit dosage forms, which are, physically discrete units suitable as unitary dosages for human and animal subjects, each unit containing a predetermined quantity of compounds of the present invention calculated in an amount sufficient to produce the desired effect in association with a pharmaceutically acceptable diluent, carrier, or vehicle. The specifications for the novel unit dosage forms of the present invention depend on the particular compound employed and the effect to be achieved, and the pharmacodynamics associated with each compound in the host.

[0234] Unit dosage forms for oral or rectal administration such as syrups, elixirs, and suspensions can be provided wherein each dosage unit, for example, teaspoonful, tablespoonful, tablet, or suppository, contains a predetermined amount of the composition containing one or more agents. Similarly, unit dosage forms for injection or intravenous administration can comprise the agent(s) in a composition as a solution in sterile water, normal saline or another pharmaceutically acceptable carrier.

Therapeutic Applications

[0235] The invention provides various therapeutic methods. In some embodiments, methods of modulating, including increasing and inhibiting, a biological activity of ADAM12L are provided. In other embodiments, methods of modulating a signal transduction activity of ADAM12L are provided. In further embodiments, methods of modulating interaction of ADAM12L with another, interacting protein or other macromolecule (for example, DNA, carbohydrate, lipid), are provided.

[0236] Thus, in an embodiment, the therapeutic compositions herein are administered to subjects for treatment of a proliferative disease, such as a tumor or psoriasis. In an embodiment, the therapeutic compositions herein are administered to subjects for modulation of immune related diseases. In a further embodiment, the therapeutic compositions herein are administered to subjects for modulation of apoptosis-related diseases.

[0237] As mentioned above, an effective amount of an agent of the invention is administered to the host. In an embodiment, the agent is administered at a dosage sufficient to produce a desired result. In some embodiments, the desired result is at least a reduction in a given biological activity of a subject polypeptide as compared to a control. In other embodiments, the desired result is an increase in the level of the active subject polypeptide (in the individual, or in a localized anatomical site in the individual), as compared to a control. In some embodiments, the desired result is at least a reduction in enzymatic activity of a subject polypeptide as compared to a control. In other embodiments, the desired result is an increase in the level of enzymatically active subject polypeptide (in the individual, or in a localized anatomical site in the individual), as compared to a control.

[0238] Typically, the compositions of the instant invention will contain from less than 1% to about 95% of the active ingredient, in some embodiments, about 10% to about 50%. Generally, between about 100 mg and 500 mg of the compositions will be administered to a child and between about 500 mg and 5 grams will be administered to an adult. Administration is generally by injection and often by injection to a localized area. The frequency of administration will be determined by the care given based on patient responsiveness. Other effective dosages can be readily determined by one of ordinary skill in the art through trials establishing dose response curves.

[0239] In order to calculate the amount of therapeutic agent to be administered, those skilled in the art could use readily available information with respect to the amount of agent necessary to have the desired effect. The amount of an agent necessary to increase or decrease a level of active ADAM12 can be calculated from *in vitro* experimentation. The amount of agent will, of course, vary depending upon the particular agent used.

[0240] Other effective dosages can be readily determined by one of ordinary skill in the art through routine trials establishing dose response curves, for example, the amount of agent necessary to increase or decrease a level of active ADAM12 can be calculated from *in vitro* experimentation. Those of skill will readily appreciate that dose levels can vary as a function of the specific compound, the severity of the symptoms, and the susceptibility of the subject to side effects, and preferred dosages for a given compound are readily determinable by those of skill in the art by a variety of means. For example, in order to calculate the polypeptide, polynucleotide, or modulator dose, those skilled in the art can use readily available information with respect to the amount necessary to have the desired effect, depending upon the particular agent used.

Proliferative Conditions

[0241] In some embodiments, ADAM12 is involved in the control of cell proliferation, and an agent of the invention inhibits undesirable cell proliferation. Such agents are useful for treating disorders that involve abnormal cell proliferation, including, but not limited to, cancer. The polypeptides, polynucleotides, antibodies, and other agents of the invention are useful for treating colorectal cancer, as described below in the Examples and Figures 4 and 20. The polypeptides, polynucleotides, antibodies, and other agents of the invention are also useful for treating lung cancer, as described below in the Examples and Figures 5 and 21. The polypeptides, polynucleotides, antibodies, and other agents of the invention are further useful for treating breast cancer, as described below in the Examples and Figure 7. The polypeptides, polynucleotides, antibodies, and other agents of the invention are yet further useful for treating bladder cancer, as described below in the Examples and Figure 8. The polypeptides, polynucleotides, antibodies, and other agents of the invention are useful for treating pancreatic cancer, as described below in the Examples and Figure 15. The polypeptides, polynucleotides, antibodies, and other agents of the invention are also useful for treating stomach cancer, as described below

in the Examples and Figure 7. Whether a particular agent and/or therapeutic regimen of the invention is effective in reducing unwanted cellular proliferation, for example, in the context of treating cancer or psoriasis, can be determined using standard methods.

[0242] The therapeutic compositions and methods of the invention can be used in the treatment of cancer and/or any abnormal malignant cell or tissue growth, for example, a tumor. In an embodiment, the compositions and methods of the invention kill tumor cells. In an embodiment, they inhibit tumor development. Cancer is characterized by the proliferation of abnormal cells that tend to invade the surrounding tissue and metastasize to new body sites. The growth of cancer cells exceeds that of and is uncoordinated with the normal cells and tissues. In an embodiment, the compositions and methods of the invention inhibit the progression of premalignant lesions to malignant tumors.

[0243] Cancer encompasses carcinomas, which are cancers of epithelial cells, and are the most common forms of human cancer; carcinomas include squamous cell carcinoma, adenocarcinoma, melanomas, and hepatomas. Cancer also encompasses sarcomas, which are tumors of mesenchymal origin, and includes osteogenic sarcomas, leukemias, and lymphomas. Cancers can have one or more than one neoplastic cell type. Some characteristics that can, in some instances, apply to cancer cells are that they are morphologically different from normal cells, and may appear anaplastic; they have a decreased sensitivity to contact inhibition, and may be less likely than normal cells to stop moving when surrounded by other cells; and they have lost their dependence on anchorage for cell growth, and may continue to divide in liquid or semisolid surroundings, whereas normal cells must be attached to a solid surface to grow.

[0244] Treatment herein refers to obtaining a desired pharmacologic and/or physiologic effect, covering any treatment of a pathological condition or disorder in a mammal, including a human. The effect may be prophylactic in terms of completely or partially preventing a disorder or symptom thereof and/or may be therapeutic in terms of a partial or complete cure for a disorder and/or adverse affect attributable to the disorder. Thus, the invention provides both treatment and prophylaxis. It includes (1) preventing the disorder from occurring or recurring in a subject who may be predisposed to the disorder but is not yet symptomatic, (2) inhibiting the disorder, such as arresting its development, (3) stopping or terminating the disorder or at least

symptoms associated therewith, so that the host no longer suffers from the disorder or its symptoms, such as causing regression of the disorder or its symptoms, for example, by restoring or repairing a lost, missing or defective function, or stimulating an inefficient process, or (4) relieving, alleviating, or ameliorating the disorder, or symptoms associated therewith, where ameliorating is used in a broad sense to refer to at least a reduction in the magnitude of a parameter, such as inflammation, pain, and/or tumor size.

[0245] The polynucleotides, polypeptides, and antibodies described above can be used to treat cancer. In an embodiment, a fusion protein or conjugate can additionally comprise a tumor-targeting moiety. Suitable moieties include those that enhance delivery of an therapeutic molecule to a tumor. For example, compounds that selectively bind to cancer cells compared to normal cells, selectively bind to tumor vasculature, selectively bind to the tumor type undergoing treatment, or enhance penetration into a solid tumor are included in the invention. Tumor targeting moieties of the invention can be peptides. Nucleic acid and amino acid molecules of the invention can be used alone or as an adjunct to cancer treatment. For example, a nucleic acid or amino acid molecules of the invention may be added to a standard chemotherapy regimen. It may be combined with one or more of the wide variety of drugs that have been employed in cancer treatment, including, but are not limited to, cisplatin, taxol, etoposide, Novantrone (mitoxantrone), actinomycin D, camptothecin (or water soluble derivatives thereof), methotrexate, mitomycins (for example, mitomycin C), dacarbazine (DTIC), and anti-neoplastic antibiotics such as doxorubicin and daunomycin, or others, described, for example, in De Vita et al., 2001.

[0246] Drugs employed in cancer therapy may have a cytotoxic or cytostatic effect on cancer cells, or may reduce proliferation of the malignant cells. Drugs employed in cancer treatment can also be peptides. A nucleic acid or amino acid molecules of the invention can be combined with radiation therapy. A nucleic acid or amino acid molecules of the invention may be used adjunctively with therapeutic approaches described in De Vita, V.T., Jr., et al., eds. (2001) *Cancer: Principles & Practice of Oncology*. Lippincott Williams & Wilkins. For those combinations in which a nucleic acid or amino acid molecule of the invention and a second anti-cancer agent exert a synergistic effect against cancer cells, the dosage of the second agent may be reduced, compared to the standard dosage of the second agent when

administered alone. A method for increasing the sensitivity of cancer cells comprises co-administering a nucleic acid or amino acid molecule of the invention with an amount of a chemotherapeutic anti-cancer drug that is effective in enhancing sensitivity of cancer cells. Co-administration may be simultaneous or non-simultaneous administration. A nucleic acid or amino acid molecule of the invention may be administered along with other therapeutic agents, during the course of a treatment regimen. In one embodiment, administration of a nucleic acid or amino acid molecule of the invention and other therapeutic agents is sequential. An appropriate time course may be chosen by the physician, according to such factors as the nature of a patient's illness, and the patient's condition.

[0247] The invention also provides a method for prophylactic or therapeutic treatment of a subject needing or desiring such treatment by providing a vaccine that can be administered to the subject. The vaccine may comprise one or more agent of the invention, for example an antibody vaccine composition, a polypeptide vaccine composition, or a polynucleotide vaccine composition, useful for preventing or treating proliferative disorders, obesity, cardiac hypertrophy, or liver disease.

[0248] In some embodiments, ADAM12 is involved in the control of cell proliferation, and an agent of the invention inhibits undesirable cell proliferation. Such agents are useful for treating disorders that involve abnormal cell proliferation, including, but not limited to, lung, colorectal, breast, bladder, pancreatic, and stomach cancer. Whether a particular agent and/or therapeutic regimen of the invention is effective in reducing unwanted cellular proliferation, for example, in the context of treating cancer, can be determined using standard methods. For example, the number of cancer cells in a biological sample (for example, blood, a biopsy sample, and the like), can be determined. The tumor mass can be determined using standard radiological or biochemical methods.

[0249] Modulators of ADAM12 find use in immunotherapy of neoplastic, paraneoplastic, and hyperproliferative disorders, including cancer and psoriasis. That is, the subject molecules can correspond to tumor antigens, of which at least 1770 have been identified (Yu and Restifo, 2002). Immunotherapeutic approaches include passive immunotherapy and vaccine therapy and can accomplish both generic and antigen-specific cancer immunotherapy.

[0250] Passive immunity approaches involve antibodies of the invention that are directed toward specific tumor-associated antigens. Such antibodies can eradicate

systemic tumors at multiple sites, without eradicating normal cells. In some embodiments, the antibodies are combined with cytotoxic components, such as radioactive or chemotherapeutic components, as provided above, for example, combining the antibody's ability to specifically target tumors with the added lethality of the radioisotope to the tumor DNA.

[0251] Useful antibodies bind to or react with antigens comprising one or more discrete epitope or a combination of nested epitopes, for example, a 10-mer epitope and associated peptide multimers incorporating all potential 8-mers and 9-mers, or overlapping epitopes (Dutoit et al., *J. Clin. Invest.* 110:1813-1822 (2002)). Thus a single antibody can interact with one or more epitopes. Further, the antibody can be used alone or in combination with different antibodies that recognize either a single or multiple epitopes.

[0252] Neutralizing antibodies, described above, can provide therapy for cancer and proliferative disorders. Neutralizing antibodies that specifically recognize a protein or peptide of the invention can bind to the protein or peptide, for example, in a bodily fluid or the extracellular space, thereby modulating the biological activity of the protein or peptide. For example, neutralizing antibodies specific for proteins or peptides that play a role in stimulating the growth of cancer cells can be useful in modulating the growth of cancer cells. Similarly, neutralizing antibodies specific for proteins or peptides that play a role in the differentiation of cancer cells can be useful in modulating the differentiation of cancer cells.

Apoptosis and Cell Death

[0253] The control of cell numbers in mammals is believed to be determined, in part, by a balance between cell proliferation and cell death. One form of cell death, sometimes referred to as necrotic cell death, is typically characterized as pathologic, resulting from trauma or injury. In contrast, there is another physiologic form of cell death that usually proceeds in an orderly or controlled manner. This orderly or controlled form of cell death is often referred to as apoptosis (Barr, P.J., et al. (1994) *Bio/Technology* 12:487-493; Steller, H. (1995) *Science*, 267:1445-1449).

[0254] Apoptotic cell death naturally occurs in many physiological processes, including embryonic development and clonal selection in the immune system (Itoh, N., et al. (1991) *Cell* 66:233-243). Decreased levels of apoptotic cell death have been associated with a variety of pathological conditions, including cancer and immune disease (Thompson, C.B. (1995) *Science* 267:1456-1462). Antibodies

specific to ADAM12L can induce the apoptotic-induced death of cancer cells by binding to the extracellular domain.

[0255] Apoptosis can be assayed using any known method. Assays can be conducted on cell populations or an individual cell, and include morphological assays and biochemical assays. Procedures to detect cell death based on the TUNEL method are available commercially, for example, from Boehringer Mannheim (Cell Death Kit) and Oncor (Apoptag Plus).

Obesity

[0256] In some embodiments, ADAM12 is involved in the control of obesity, and an agent of the invention inhibits undesirable weight gain. The polypeptides, polynucleotides, antibodies, and other agents of the invention are useful for treating obesity. Whether a particular agent and/or therapeutic regimen of the invention is effective in reducing unwanted weight gain, for example, in the context of treating obesity, can be determined using standard methods.

[0257] In an embodiment, the compositions and methods of the invention inhibit adipogenesis. Obesity can be characterized by the proliferation of adipocytes. Increases in body weight, total fat body mass, and abdominal fat mass were observed in transgenic mice overexpressing ADAM12S, indicating that overexpression of ADAM12 is associated with an obese phenotype (Kawaguchi et al., *J. Cell Sci.* 16:3893 (2003)). Transgenic mice expressing a truncated form of ADAM12S lacking the prodomain and the metalloprotease domain did not display increased adipogenesis, suggesting that either or both of these domains is involved in ADAM12 mediated obesity (Kawaguchi et al., 2003). Conversely, mice deficient in ADAM12 were reported to resist weight gain induced by a high fat diet because they had fewer adipocytes than wild type mice (Masaki et al., *Endocrinology* 146:1752 (2005)).

Cardiac Hypertrophy

[0258] In some embodiments, ADAM12 is involved in the control of cardiac hypertrophy, and an agent of the invention inhibits undesirable cardiac hypertrophy. The polypeptides, polynucleotides, antibodies, and other agents of the invention are useful for treating cardiac hypertrophy. Whether a particular agent and/or therapeutic regimen of the invention is effective in reducing unwanted cardiac hypertrophy, for example, in the context of treating heart disease, can be determined using standard methods.

[0259] In an embodiment, the compositions and methods of the invention inhibit cardiac hypertrophy. Cardiac hypertrophy can be characterized by the abnormal growth of cardiomyocytes. Cardiomyocytes shed heparin-binding epidermal growth factor when they are stimulated by G-protein coupled receptor signaling; this shedding is mediated by metalloprotease activation and subsequent activation of the epidermal growth factor receptor. Mice deficient in ADAM12 were reported to have lower levels of heparin-binding epidermal growth factor shed from the cell surface in response to G-protein coupled receptor signaling than wild type mice (Asakura et al., *Nat. Med.* 8:35 (2002)).

Liver Fibrosis and Cirrhosis

[0260] In some embodiments, ADAM12 is involved in the control of liver fibrosis and liver cirrhosis, and an agent of the invention inhibits undesirable liver fibrosis and/or liver cirrhosis. The polypeptides, polynucleotides, antibodies, and other agents of the invention are useful for treating liver fibrosis and liver cirrhosis. Whether a particular agent and/or therapeutic regimen of the invention is effective in reducing unwanted liver fibrosis and/or liver cirrhosis, for example, in the context of treating liver disease, can be determined using standard methods.

[0261] In an embodiment, the compositions and methods of the invention inhibit liver fibrosis and/or liver cirrhosis. Liver fibrosis and cirrhosis can be characterized as a response of the liver to injury. Upon liver injury, hepatic stellate cells have been reported to become activated and express ADAM12 at high levels (Le Pabic et al., 2003). As a result, these cells have high levels of metalloprotease activity, and are active in liver tissue remodeling, including fibrogenesis. ADAM12 expression was reported to be mediated by transforming growth factor β in activated hepatic stellate cells and to be regulated by modulators of phosphatidylinositol 3-kinase and mitogen-activated protein kinase kinase (Le Pabic et al., 2003).

[0262] Additional objects and advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The objects and advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. Moreover, advantages described in the body of the specification, if not included in the claims, are not per se limitations to the claimed invention.

[0263] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed. Moreover, it must be understood that the invention is not limited to the particular embodiments described, as such may, of course, vary. Further, the terminology used to describe particular embodiments is not intended to be limiting, since the scope of the present invention will be limited only by the claims. The claims do not encompass embodiments in the public domain.

[0264] With respect to ranges of values, the invention encompasses each intervening value between the upper and lower limits of the range to at least a tenth of the lower limit's unit, unless the context clearly indicates otherwise. Further, the invention encompasses any other stated intervening values. Moreover, the invention also encompasses ranges excluding either or both of the upper and lower limits of the range, unless specifically excluded from the stated range.

[0265] Unless defined otherwise, the meanings of all technical and scientific terms used herein are those commonly understood by one of ordinary skill in the art to which this invention belongs. One of ordinary skill in the art will also appreciate that any methods and materials similar or equivalent to those described herein can also be used to practice or test the invention.

[0266] It must be noted that, as used herein and in the appended claims, the singular forms "a," "or," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a subject polypeptide" includes a plurality of such polypeptides and reference to "the agent" includes reference to one or more agents and equivalents thereof known to those skilled in the art, and so forth.

[0267] Further, all numbers expressing quantities of ingredients, reaction conditions, % purity, polypeptide and polynucleotide lengths, and so forth, used in the specification and claims, are modified by the term "about," unless otherwise indicated. Accordingly, the numerical parameters set forth in the specification and claims are approximations that may vary depending upon the desired properties of the present invention. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits, applying ordinary rounding techniques. Nonetheless, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical value,

however, inherently contains certain errors from the standard deviation of its experimental measurement.

[0268] The specification is most thoroughly understood in light of the references, all of which are hereby incorporated in their entireties. The disclosures of the patents and other references cited above are also hereby incorporated by reference. The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

Examples

[0269] The examples, which are intended to be purely exemplary of the invention and should therefore not be considered to limit the invention in any way, also describe and detail aspects and embodiments of the invention discussed above. The examples are not intended to represent that the experiments below are all or the only experiments performed. Efforts have been made to ensure accuracy with respect to numbers used (for example, amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1: ADAM12 Microarray Expression in Normal and Cancerous Tissues

[0270] The present invention utilized probes that were designed by and purchased from Affymetrix, Inc. (Santa Clara, CA) to identify specific ADAM12 targets. Eleven matching probes, each about 25 nucleotides in length, were designed to correspond to a target sequence for selected clones from tumor or normal tissues. Eleven other target probes were designed for each target sequence, each with a single nucleotide mismatch. These probes were spotted on a microarray chip designed by Five Prime Therapeutics, Inc. (South San Francisco, CA), with the nucleotide sequences of approximately 30,000 human genes ("the Five Prime chip") and hybridized to cRNA made complementary to RNA from tumor tissues or normal tissues.

[0271] The Five Prime chip contained specific probes for each of these two differentially spliced forms of ADAM12. Figure 3a shows the location of these two

probes in the context of ADAM12 exon maps. Figure 3a (A) shows the positions of the exons of ADAM12L. Figure 3a (B) shows the corresponding position of the Five Prime chip's probe specific for ADAM12L. Figure 3a (C) shows the positions of the exons of ADAM12S. Figure 3a (D) shows the corresponding position of the Five Prime chip's probe specific for ADAM12S.

[0272] After hybridization, using an Affymetrix protocol, the results were read, again using Affymetrix's equipment and protocol. Results were reported as being either present or absent on the chip and also as a value representing the intensity of the hybridization. A probe set was a "hit" when the probe set was "present" and when the intensity was high in tumor tissues and low in normal tissues. A probe set was a "hit" when the probes matching the designated sequence hybridized to the RNA and the mismatched probes did not hybridize.

[0273] RNA was prepared from tumor tissue resected from patients with colon cancer and lung squamous cell carcinoma, and from normal-appearing adjacent tissue resected from the same patients. RNA was also prepared from 99 other normal tissue specimens. Tissues were flash frozen in liquid nitrogen, transported on dry ice, and stored at minus 180° C in liquid nitrogen. Histology was performed on a sample of each frozen tissue specimen and reviewed by a pathologist to confirm the cancer diagnosis or the tissue's normality. Only confirmed specimens were used for microarray hybridization or real time PCR experiments.

[0274] RNA was isolated from the tissues by grinding them to a fine powder under liquid nitrogen with a pre-chilled mortar and pestle. Total RNA was extracted using TRIzol reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's protocol. It was treated with DNase in a final volume of 500 µl using 350 µg total RNA, 35 U DNase I, 50 µL DNase buffer and 280 U RNaseOUT (all from Invitrogen). Following incubation at 37° C for 30 min., 500 µl phenol:chloroform:isoamyl alcohol (Invitrogen) was added, and the mixture vortexed, centrifuged at 14,000 rpm for 5 min., and the aqueous phase transferred to a new 2 ml tube. The RNA was then ethanol precipitated by adding 80 µL 5 M NH₄OAc, 1.5 ml EtOH, incubated at -20° C for 30 min., then centrifuged at 14,000 rpm for 30 min. The pellet was washed with 75% EtOH and resuspended with 20 µL H₂O. The quality and concentration of the RNA were determined spectrophotometrically at 260 and 280 nm wavelengths and by agarose gel electrophoresis.

[0275] The resulting RNA was used as a template to prepare cDNA. First-strand cDNA synthesis was performed in a final volume of 20 μ l with 10 μ g total RNA, 5 μ M T7-linked oligo(dT)₂₄ primer, 4 μ l of 5X first-strand cDNA buffer, 10 mM DTT, 0.5 mM dNTP mix and 400 U Superscript II reverse transcriptase (all from Invitrogen). This mixture was incubated at 42° C for 80 min. Second-strand cDNA synthesis was performed in a final volume of 150 μ l using 20 μ l of the first strand synthesis mixture, 30 μ L 5X second-strand reaction buffer, 0.2 mM dNTP mix, 10 U *E. coli* DNA ligase, 40 U *E. coli* DNA polymerase I, and 2 U *E. coli* RNase H. This mixture was incubated at 16° C for 2 h. Then 20 U DNA polymerase was added and incubation at 16° C continued for an additional 5 min.

[0276] *In vitro* transcription was performed with biotinylated UTP and CTP (Enzo Life Sciences, Inc., Farmingdale, NY), resulting in an approximately 40-fold linear amplification of the RNA. Thirty-five micrograms of biotinylated RNA was fragmented to a size of approximately 50 to 150 nucleotides before overnight hybridization to a chip microarray designed by Five Prime Therapeutics, Inc. and custom built by Affymetrix. The array contained probe sets for approximately 30,000 human genes, including specific probes for the secreted form of ADAM12S (GenBank accession number NP_067673) and the membrane-bound form of ADAM12L (GenBank accession number NP_003465). Namely, probe PRB104353_at was designed to recognize the secreted form NP_067673 and probe PRB102715_s_at was designed to recognize the membrane-bound form NP_003465. After washing, arrays were stained with streptavidin-phycoerythrin (Molecular Probes) and scanned with an Affymetrix GeneChip 3000 high-resolution scanner. Intensity values were scaled such that overall intensity for each chip of the same type was equivalent. Intensity for each feature of the array was captured by using Genechip Software (GCOS) (Affymetrix, Santa Clara, CA), and a single raw expression level for each gene was derived from 11 probe pairs representing each gene by using a trimmed mean algorithm.

[0277] The sequence used to design the 11 probe pairs, each 25 nucleotides in length, for the membrane-bound form of ADAM12L (GenBank accession number NP_003465) was: >PRB102715_s_at:

AAGGTAAAATGCCATGATGCCTCTGTCTTCTGGACTGGTTTTCA
CATTAGAAGACAATTGACAACAGTTACATAATTCACCTCTGAGTGTTTTATG
AGAAAGCCTTCTTTTGGGGTCAACAGTTTTCCTATGCTTTGAAACAGAAAA

ATATGTACCAAGAATCTTGGTTTGCCTTCCAGAAAACAAAACCTGCATTTCA
 CTTTCCCGGTGTTCCCCACTGTATCTAGGCAACATAGTATTCATGACTATG
 GATAAACTAAACACGTGACACAAACACACACAAAAGGGAACCCAGCTCT
 AATACATTCCAACCTCGTATAGCATGCATCTGTTTATTCTATAGTTATTAAG
 TTCTTTAAATGTAAAGCCATGCTGGAAAATAATACTGCTGAGATACATA
 CAGAATTACTGTAAGTATTACACTTGGTAATTGTACTAAAGCCAAACAT
 ATATATACTATTAAAAAGGTTTACAGAATTTTATGGTGCATTACGTGGGCA
 TTGTCTTTTATAGATGCCCAAATCCT (SEQ ID NO.:347).

[0278] The sequence used to design the 11 probe pairs, each 25 nucleotides in length, for the membrane-bound form of ADAM12S (GenBank accession number NP_067673) was: >PRB104353_at:

CGACTTCCTGGTTGAGCTTCTGCTAAAACATGGACATGCTTCAGT
 GCTGCTCCTGAGAGAGTAGCAGGTTACCACTCTGGCAGGCCCCAGCCCTG
 CAGCAAGGAGGAAGAGGACTCAAAAGTCTGGCCTTTCCTGAGCCTCCAC
 AGCAGTGGGGGAGAAGCAAGGGTTGGGCCCAGTGTCCCCTTCCCCAGTG
 ACACCTCCGCCTTGGCAGCCCTGATGACTGGTCTCTGGCTGCAACTTAATG
 CTCTGATATGGCTTTTAGCATTTATTATATGAAAATAGCAGGGTTTTAGTT
 TTTAATTTATCAGAGACCCTGCCACCCATTCCATCTCCATCCAAGCAAAC
 GAATGGCATTGAAACAACTGGAGAAGAAGGTAGGAGAAAGGGCGGTGA
 ACTCTGGCTCTTTGCTGTGGACATGCGTGACCAGCAGTACTCAGGTTTGAG
 GGTTTGCAGAAAGCCAGGGAACCCACAGAGTCACCAACCCTTCATTTAAC
 AAGT (SEQ ID NO.:14).

Example 2: Expression of ADAM12 Quantified by Real-Time PCR

[0279] RNA was prepared from normal and cancerous tissues and a subset of these tissues were used to perform real time PCR. Complementary DNA was prepared by reverse transcription, performed in a final volume of 100 μ l with 2 μ g of the isolated RNA, 125 U Multiscribe reverse transcriptase, 10 μ L reverse transcription buffer, 22 μ L 25 mM $MgCl_2$, 20 μ L 10 mM dNTP, random hexamers, and oligo(dT)₁₆ at a final concentration of 2 mM each, and 40 U RNase inhibitor (all from Applied Biosystems, Foster City, CA, USA). This mixture was incubated at 25° C for 10 min. at 42° C for 60 min. then at 95° C for 5 min.

[0280] The Affymetrix U133 ADAM12 probesets and the FivePrime ADAM12 probesets fall in different locations on the ADAM12 gene. Bioinformatic analysis demonstrates that the Affymetrix U133 probesets do not necessarily

correspond to exon regions of the ADAM12 gene locus; some of the Affymetrix U133 probesets fall into intronic regions of the ADAM12 gene, for example. Such probesets do not detect ADAM12 RNA in expression profiling analyses. Five Prime PCR primers and probes were designed using Primer Express™ software (Applied Biosystems, Foster City, CA, USA). The sequences used for designing PCR primers and probes were limited to exons 16 and 17 of the open reading frame sequences of the secreted form of ADAM12S (NP_067673) and the membrane-bound form of ADAM12L (NP_003465). The locations of the PCR probes for ADAM12L and ADAM12S are shown in the context of the ADAM12 exon map, shown in Figure 3. Figure 3E shows that the probe for ADAM12L spans exons 16 and 17. Figure 3F shows that the probe for ADAM12S maps to exon 17.

[0281] The sequence of the forward primer for the secreted form (NP_067673) was GACAAGTTTGGCTTTGGAGGAA (SEQ. ID. NO.:397). The sequence of the reverse primer for the secreted form (NP_067673) was GCGCTCCCTGTTGGACTCT (SEQ. ID. NO.:398). The sequence of the probe for the secreted form (NP_067673) was CAGAAGCAAGGCAGGAA (SEQ. ID. NO.:17). The sequence of the forward primer for the membrane-bound form (NP_003465) was CCGGCAAGCAGATAAC CAA (SEQ. ID. NO.:18). The sequence of the reverse primer for the membrane-bound form (NP_003465) was ATCCTGTGTCTTCTTGCTGCC (SEQ. ID. NO.:19). The sequence of the probe for the membrane-bound form (NP_003465) was TTTAACCATAGGAATTCTG (SEQ. ID. NO.:20).

[0282] The primers and probes were used to quantitatively amplify ADAM12 in a polymerase chain reaction (PCR) performed on duplicate samples in a 25 µl reaction volume containing 2X TaqMan Universal PCR Master Mix (Applied Biosystems), primers at a final concentration of 900 nM each, 250 nM probe, water to a 20 µl final volume, and 5 µl of the cDNA. This PCR-based quantification analysis was performed with an ABI Prism 7000 Sequence Detection System (Applied Biosystems) using the following amplification parameters: 2 min. at 50 °C, 10 min. at 95 °C, 40 cycles of 15 sec. at 95 °C and 1 min. at 60 °C.

[0283] To confirm that the RT-PCR primer-probes were specific for each form, and did not cross react with the other form, each set of probes and primers was tested on cDNA plasmid clones that encoded each form. As shown in the left portion of Figure 19, when RT-PCR primer-probes for the secreted form (Primer-probe S)

reacted with clone-S, which encodes the secreted form, the resulting PCR signal was robust. This effect was dose-dependent; 1 ng clone S produced a stronger signal than 0.1 ng. In contrast, when these primer-probes were used to probe clone-M, which encodes the membrane form, no PCR signal was detected. As shown in the right portion of Figure 19, the primer-probes for the membrane form of ADAM12 detected clone-M, which encodes the membrane form, in a dose-dependent manner, but do not detect clone-S. Thus, the primer-probes designed to distinguish between the membrane and secreted forms of ADAM12 do not cross react and are specific to their intended form.

[0284] ADAM12 gene overexpression in colorectal cancer and lung squamous cell carcinomas was identified by hybridizing the RNA isolated from 30 colon/colorectal cancer specimens, 30 lung squamous cell carcinomas, 30 normal colon/colorectal specimens, and 30 normal lung adjacent tissue specimens on the Five Prime chip, with the purpose of identifying genes overexpressed in cancer when compared to normal adjacent tissues.

[0285] Probe PRB102715_s_at, which specifically detects the ADAM12L membrane-bound form, was expressed at a higher level to a significant degree in the colorectal cancer specimens compared to the normal colon/colorectal adjacent specimen (Figure 20, black bars). In contrast, there was no difference in expression on the ADAM12S secreted form probe PRB104353_at in colorectal cancer specimens when compared to the normal colorectal adjacent specimen (Figure 4, white bars). In addition, probe PRB102715_s_at was expressed at a much higher level in lung squamous cancer specimens and lung adenocarcinomas when compared to the lung normal adjacent specimens (Figure 21, dark bars). In contrast, there was no difference in the expression of PRB104353_at in lung squamous cancer and lung adenocarcinoma specimens when compared to normal lung adjacent specimens (Figure 21, white bars).

[0286] Data on the expression level of a variety of normal tissues contribute to informed decisions as to which antibody targets are best suited for development as cancer therapeutics, for cancer diagnostics, and for use as a vaccine target. These data are provided by microarray hybridization experiments performed on RNA isolated from a variety of normal tissues (Figure 22). Both the secreted and membrane-bound forms of ADAM12 were highly expressed in all three placenta RNA specimens examined; both were expressed in placenta at levels higher than in squamous cell lung

cancer and colorectal adenocarcinomas. Interestingly, the soluble form of ADAM12S was expressed at a level higher than that of the membrane form in several normal tissues, such as pancreas, skin, small intestine, spleen, testis, thymus, thyroid, uterus, white blood cells, duodenum, cardiomyopathic heart, jejunum, kidney, liver, CD4⁺ T-lymphocytes, adipose tissue, adrenal gland, bladder, B-lymphocytes, and bone marrow. The greater expression of the secreted form compared to the membrane forms in these normal tissues, and the low expression of both forms in these and other normal tissues makes ADAM12L a suitable target for a therapeutic antibody, a vaccine, and a suitable diagnostic marker.

[0287] To further characterize the expression levels of the secreted and the membrane forms of ADAM12, specific primers and probes for each form were designed, based on the differentially spliced exons of the ADAM12 gene, namely the junction of exons 16 and 17 of the membrane-bound form and exon 17 for the secreted form (Figure 3). This confirmed that the expression observed by microarray hybridization mapped to the locus of the mRNA encoding the extracellular domain, thus ruling out the possibility that the tumors examined produced truncated forms of ADAM12.

[0288] Real time PCR was performed on 16 colorectal cancer specimens, 10 normal colorectal adjacent tissue specimens, 11 lung squamous cell carcinomas, and 7 normal lung adjacent tissue specimens, using the specific probes and primers described above. Figure 21 shows that the relative expression of the membrane-bound form of ADAM12 was higher in lung squamous cell carcinoma specimens than in the normal adjacent lung specimens. Figure 21 also demonstrates that ADAM12L (dark bars) but not ADAM12S (light bars) was expressed in these lung tumor specimens. Figure 20 shows that the relative expression of the membrane-bound form of ADAM12 was higher in colon cancer specimens when compared to the normal adjacent colon specimens (black bars). The expression of the ADAM12 secreted form (white bars) was almost undetectable in the colon/colorectal cancer specimens and their respective normal adjacent tissue specimens.

Tables

Table 1. SEQ ID NOS.:1-396

FP ID	SEQ. ID. NO. (N1)	SEQ. ID. NO. (P1)	SEQ. ID. NO. (N0)	Clone ID	Notes
HG1019049	SEQ. ID. NO. 1	SEQ. ID. NO. 21	SEQ. ID. NO. 340	NP_067673:NM_021641	ADAM12Sa
HG1019050		SEQ. ID. NO. 22		ADAM12La_aa345-366_frag1	AVTLAHELGHNF MNHDTLDRG
HG1019051		SEQ. ID. NO. 23		ADAM12La_aa345-366_frag2	AVTLAH
HG1019052		SEQ. ID. NO. 24		ADAM12La_aa345-366_frag3	VTLAHE
HG1019053		SEQ. ID. NO. 25		ADAM12La_aa345-366_frag4	TLAHEL
HG1019054		SEQ. ID. NO. 26		ADAM12La_aa345-366_frag5	LAHELG
HG1019055		SEQ. ID. NO. 27		ADAM12La_aa345-366_frag6	AHELGH
HG1019056		SEQ. ID. NO. 28		ADAM12La_aa345-366_frag7	HELGHN
HG1019057		SEQ. ID. NO. 29		ADAM12La_aa345-366_frag8	ELGHNF
HG1019058		SEQ. ID. NO. 30		ADAM12La_aa345-366_frag9	LGHNF
HG1019059		SEQ. ID. NO. 31		ADAM12La_aa345-366_frag10	GHNF
HG1019060		SEQ. ID. NO. 32		ADAM12La_aa345-366_frag11	HNFGMN
HG1019061		SEQ. ID. NO. 33		ADAM12La_aa373-392_frag1	VEKGGCIMNASTGY PFP
HG1019062		SEQ. ID. NO. 34		ADAM12La_aa373-392_frag2	VEKGGC
HG1019063		SEQ. ID. NO. 35		ADAM12La_aa373-392_frag3	EKGGCI
HG1019064		SEQ. ID. NO. 36		ADAM12La_aa373-392_frag4	KGGCIM
HG1019065		SEQ. ID. NO. 37		ADAM12La_aa373-392_frag5	GGCIMN
HG1019066		SEQ. ID. NO. 38		ADAM12La_aa373-392_frag6	GCIMNA
HG1019067		SEQ. ID. NO. 39		ADAM12La_aa373-392_frag7	CIMNAS
HG1019068		SEQ. ID. NO. 40		ADAM12La_aa373-392_frag8	IMNAST
HG1019069		SEQ. ID. NO. 41		ADAM12La_aa373-392_frag9	MNASTG
HG1019070		SEQ. ID. NO. 42		ADAM12La_aa373-392_frag10	NASTGY
HG1019071		SEQ. ID. NO. 43		ADAM12La_aa373-392_frag11	ASTGYP
HG1019072		SEQ. ID. NO. 44		ADAM12La_aa373-392_frag12	STGYPF
HG1019073		SEQ. ID. NO. 45		ADAM12La_aa373-392_frag13	TGYPPF
HG1019074		SEQ. ID. NO. 46		ADAM12La_aa373-392_frag14	GYPFPM

FP ID	SEQ. ID. NO. (N1)	SEQ. ID. NO. (P1)	SEQ. ID. NO. (N0)	Clone ID	Notes
HG1019075		SEQ. ID. NO. 47		ADAM12La_aa373-392_frag15	YPFPMV
HG1019076		SEQ. ID. NO. 48		ADAM12La_aa373-392_frag16	PFPMPV
HG1019077		SEQ. ID. NO. 49		ADAM12La_aa311-328_frag1	FQGTIGMAPIMSM CTAD
HG1019078		SEQ. ID. NO. 50		ADAM12La_aa311-328_frag2	FQGTI
HG1019079		SEQ. ID. NO. 51		ADAM12La_aa311-328_frag3	QGTIG
HG1019080		SEQ. ID. NO. 52		ADAM12La_aa311-328_frag4	GTTIGM
HG1019081		SEQ. ID. NO. 53		ADAM12La_aa311-328_frag5	TTIGMA
HG1019082		SEQ. ID. NO. 54		ADAM12La_aa311-328_frag6	TIGMAP
HG1019083		SEQ. ID. NO. 55		ADAM12La_aa311-328_frag7	IGMAPI
HG1019084		SEQ. ID. NO. 56		ADAM12La_aa311-328_frag8	GMAPIM
HG1019085		SEQ. ID. NO. 57		ADAM12La_aa311-328_frag9	MAPIMS
HG1019086		SEQ. ID. NO. 58		ADAM12La_aa311-328_frag10	APIMSM
HG1019087		SEQ. ID. NO. 59		ADAM12La_aa311-328_frag11	PIMSMC
HG1019088		SEQ. ID. NO. 60		ADAM12La_aa311-328_frag12	IMSMCT
HG1019089		SEQ. ID. NO. 61		ADAM12La_aa311-328_frag13	MSMCTA
HG1019090		SEQ. ID. NO. 62		ADAM12La_aa388-401_frag1	FPMVFSSCSRKDLE
HG1019091		SEQ. ID. NO. 63		ADAM12La_aa388-401_frag2	FPMVFS
HG1019092		SEQ. ID. NO. 64		ADAM12La_aa388-401_frag3	PMVFSS
HG1019093		SEQ. ID. NO. 65		ADAM12La_aa388-401_frag4	MVFSSC
HG1019094		SEQ. ID. NO. 66		ADAM12La_aa388-401_frag5	VFSSCS
HG1019095		SEQ. ID. NO. 67		ADAM12La_aa388-401_frag6	FSSCSR
HG1019096		SEQ. ID. NO. 68		ADAM12La_aa388-401_frag7	SSCSRK
HG1019097		SEQ. ID. NO. 69		ADAM12La_aa388-401_frag8	SCSRKD
HG1019098		SEQ. ID. NO. 70		ADAM12La_aa388-401_frag9	CSRKDL
HG1019099		SEQ. ID. NO. 71		ADAM12La_aa388-401_frag10	SRKDLE
HG1019100		SEQ. ID. NO. 72		ADAM12La_aa263-284_frag1	GVEVWNDMDKCSV SQDPFTSLH
HG1019101		SEQ. ID. NO. 73		ADAM12La_aa263-284_frag2	GVEVWN
HG1019102		SEQ. ID. NO. 74		ADAM12La_aa263-284_frag3	VEVWND
HG1019103		SEQ. ID.		ADAM12La_aa263-284_frag4	EVWNDM

FP ID	SEQ. ID. NO. (N1)	SEQ. ID. NO. (P1)	SEQ. ID. NO. (N0)	Clone ID	Notes
		NO. 75			
HG1019104		SEQ. ID. NO. 76		ADAM12La_aa263-284_frag5	VWNDMD
HG1019105		SEQ. ID. NO. 77		ADAM12La_aa263-284_frag6	WNDMDK
HG1019106		SEQ. ID. NO. 78		ADAM12La_aa263-284_frag7	NDMDKC
HG1019107		SEQ. ID. NO. 79		ADAM12La_aa263-284_frag8	DMDKCS
HG1019108		SEQ. ID. NO. 80		ADAM12La_aa263-284_frag9	MDKCSV
HG1019109		SEQ. ID. NO. 81		ADAM12La_aa263-284_frag10	DKCSVS
HG1019110		SEQ. ID. NO. 82		ADAM12La_aa263-284_frag11	KCSVSQ
HG1019111		SEQ. ID. NO. 83		ADAM12La_aa263-284_frag12	CSVSQD
HG1019112		SEQ. ID. NO. 84		ADAM12La_aa263-284_frag13	SVSQDP
HG1019113		SEQ. ID. NO. 85		ADAM12La_aa263-284_frag14	VSQDPF
HG1019114		SEQ. ID. NO. 86		ADAM12La_aa263-284_frag15	SQDPFT
HG1019115		SEQ. ID. NO. 87		ADAM12La_aa263-284_frag16	QDPFTS
HG1019116		SEQ. ID. NO. 88		ADAM12La_aa263-284_frag17	DPFTSL
HG1019117		SEQ. ID. NO. 89		ADAM12La_aa263-284_frag18	PFTSLH
HG1019118		SEQ. ID. NO. 90		ADAM12La_aa477-500_frag1	PAGTACRDSSNSCD LPEFCTGASP
HG1019119		SEQ. ID. NO. 91		ADAM12La_aa477-500_frag2	PAGTAC
HG1019120		SEQ. ID. NO. 92		ADAM12La_aa477-500_frag3	AGTACR
HG1019121		SEQ. ID. NO. 93		ADAM12La_aa477-500_frag4	GTACRD
HG1019122		SEQ. ID. NO. 94		ADAM12La_aa477-500_frag5	TACRDS
HG1019123		SEQ. ID. NO. 95		ADAM12La_aa477-500_frag6	ACRDSS
HG1019124		SEQ. ID. NO. 96		ADAM12La_aa477-500_frag7	CRDSSN
HG1019125		SEQ. ID. NO. 97		ADAM12La_aa477-500_frag8	RDSSNS
HG1019126		SEQ. ID. NO. 98		ADAM12La_aa477-500_frag9	DSSNSC
HG1019127		SEQ. ID. NO. 99		ADAM12La_aa477-500_frag10	SSNSCD
HG1019128		SEQ. ID. NO. 100		ADAM12La_aa477-500_frag11	SNSCDL
HG1019129		SEQ. ID. NO. 101		ADAM12La_aa477-500_frag12	NSCDLP
HG1019130		SEQ. ID. NO. 102		ADAM12La_aa477-500_frag13	SCDLPE
HG1019131		SEQ. ID. NO. 103		ADAM12La_aa477-500_frag14	CDLPEF

FP ID	SEQ. ID. NO. (N1)	SEQ. ID. NO. (P1)	SEQ. ID. NO. (N0)	Clone ID	Notes
HG1019132		SEQ. ID. NO. 104		ADAM12La_aa477-500_frag15	DLPEFC
HG1019133		SEQ. ID. NO. 105		ADAM12La_aa477-500_frag16	LPEFCT
HG1019134		SEQ. ID. NO. 106		ADAM12La_aa477-500_frag17	PEFCTG
HG1019135		SEQ. ID. NO. 107		ADAM12La_aa477-500_frag18	EFCTGA
HG1019136		SEQ. ID. NO. 108		ADAM12La_aa477-500_frag19	FCTGAS
HG1019137		SEQ. ID. NO. 109		ADAM12La_aa477-500_frag20	CTGASP
HG1019138		SEQ. ID. NO. 110		ADAM12La_aa541-593_frag1	AKPAPGICFERVNSA GDPYGNCGKVS FAKCEMRDAKCGKI QCQGGASRPV
HG1019139		SEQ. ID. NO. 111		ADAM12La_aa541-593_frag2	AKPAPG
HG1019140		SEQ. ID. NO. 112		ADAM12La_aa541-593_frag3	KPAPGI
HG1019141		SEQ. ID. NO. 113		ADAM12La_aa541-593_frag4	PAPGIC
HG1019142		SEQ. ID. NO. 114		ADAM12La_aa541-593_frag5	APGICF
HG1019143		SEQ. ID. NO. 115		ADAM12La_aa541-593_frag6	PGICFE
HG1019144		SEQ. ID. NO. 116		ADAM12La_aa541-593_frag7	GICFER
HG1019145		SEQ. ID. NO. 117		ADAM12La_aa541-593_frag8	ICFERV
HG1019146		SEQ. ID. NO. 118		ADAM12La_aa541-593_frag9	CFERVN
HG1019147		SEQ. ID. NO. 119		ADAM12La_aa541-593_frag10	FERVNS
HG1019148		SEQ. ID. NO. 120		ADAM12La_aa541-593_frag11	ERVNSA
HG1019149		SEQ. ID. NO. 121		ADAM12La_aa541-593_frag12	RVNSAG
HG1019150		SEQ. ID. NO. 122		ADAM12La_aa541-593_frag13	VNSAGD
HG1019151		SEQ. ID. NO. 123		ADAM12La_aa541-593_frag14	NSAGDP
HG1019152		SEQ. ID. NO. 124		ADAM12La_aa541-593_frag15	SAGDPY
HG1019153		SEQ. ID. NO. 125		ADAM12La_aa541-593_frag16	AGDPYG
HG1019154		SEQ. ID. NO. 126		ADAM12La_aa541-593_frag17	GDPYGN
HG1019155		SEQ. ID. NO. 127		ADAM12La_aa541-593_frag18	DPYGNC
HG1019156		SEQ. ID. NO. 128		ADAM12La_aa541-593_frag19	PYGNCG
HG1019157		SEQ. ID. NO. 129		ADAM12La_aa541-593_frag20	YGNC GK
HG1019158		SEQ. ID. NO. 130		ADAM12La_aa541-593_frag21	GNC GK V
HG1019159		SEQ. ID.		ADAM12La_aa541-593_frag22	NCGKVS

FP ID	SEQ. ID. NO. (N1)	SEQ. ID. NO. (P1)	SEQ. ID. NO. (N0)	Clone ID	Notes
		NO. 131			
HG1019160		SEQ. ID. NO. 132		ADAM12La_aa541-593_frag23	CGKVSX
HG1019161		SEQ. ID. NO. 133		ADAM12La_aa541-593_frag24	GKVSXS
HG1019162		SEQ. ID. NO. 134		ADAM12La_aa541-593_frag25	KVSKSS
HG1019163		SEQ. ID. NO. 135		ADAM12La_aa541-593_frag26	VSKSSF
HG1019164		SEQ. ID. NO. 136		ADAM12La_aa541-593_frag27	SKSSFA
HG1019165		SEQ. ID. NO. 137		ADAM12La_aa541-593_frag28	KSSFAK
HG1019166		SEQ. ID. NO. 138		ADAM12La_aa541-593_frag29	SSFAKC
HG1019167		SEQ. ID. NO. 139		ADAM12La_aa541-593_frag30	SFAKCE
HG1019168		SEQ. ID. NO. 140		ADAM12La_aa541-593_frag31	FAKCEM
HG1019169		SEQ. ID. NO. 141		ADAM12La_aa541-593_frag32	AKCEMR
HG1019170		SEQ. ID. NO. 142		ADAM12La_aa541-593_frag33	KCEMRD
HG1019171		SEQ. ID. NO. 143		ADAM12La_aa541-593_frag34	CEMRDA
HG1019172		SEQ. ID. NO. 144		ADAM12La_aa541-593_frag35	EMRDAK
HG1019173		SEQ. ID. NO. 145		ADAM12La_aa541-593_frag36	MRDAKC
HG1019174		SEQ. ID. NO. 146		ADAM12La_aa541-593_frag37	RDACCG
HG1019175		SEQ. ID. NO. 147		ADAM12La_aa541-593_frag38	DAKCGK
HG1019176		SEQ. ID. NO. 148		ADAM12La_aa541-593_frag39	AKCGKI
HG1019177		SEQ. ID. NO. 149		ADAM12La_aa541-593_frag40	KCGKIQ
HG1019178		SEQ. ID. NO. 150		ADAM12La_aa541-593_frag41	CGKIQC
HG1019179		SEQ. ID. NO. 151		ADAM12La_aa541-593_frag42	GKIQCQ
HG1019180		SEQ. ID. NO. 152		ADAM12La_aa541-593_frag43	KIQCQG
HG1019181		SEQ. ID. NO. 153		ADAM12La_aa541-593_frag44	IQCQGG
HG1019182		SEQ. ID. NO. 154		ADAM12La_aa541-593_frag45	QCQGGA
HG1019183		SEQ. ID. NO. 155		ADAM12La_aa541-593_frag46	CQGGAS
HG1019184		SEQ. ID. NO. 156		ADAM12La_aa541-593_frag47	QGGASR
HG1019185		SEQ. ID. NO. 157		ADAM12La_aa541-593_frag48	GGASRP
HG1019186		SEQ. ID. NO. 158		ADAM12La_aa541-593_frag49	GASRPV
HG1019187		SEQ. ID. NO. 159		ADAM12La_aa584-624_frag1	QCQGGASRPVIGTN AVSIETNIPLQQGR

FP ID	SEQ. ID. NO. (N1)	SEQ. ID. NO. (P1)	SEQ. ID. NO. (N0)	Clone ID	Notes
					ILCRGTHVYLGD
HG1019188		SEQ. ID. NO. 160		ADAM12La_aa584-624_frag2	QCQGGA
HG1019189		SEQ. ID. NO. 161		ADAM12La_aa584-624_frag3	CQGGAS
HG1019190		SEQ. ID. NO. 162		ADAM12La_aa584-624_frag4	QGGASR
HG1019191		SEQ. ID. NO. 163		ADAM12La_aa584-624_frag5	GGASRP
HG1019192		SEQ. ID. NO. 164		ADAM12La_aa584-624_frag6	GASRPV
HG1019193		SEQ. ID. NO. 165		ADAM12La_aa584-624_frag7	ASRPVI
HG1019194		SEQ. ID. NO. 166		ADAM12La_aa584-624_frag8	SRPVIG
HG1019195		SEQ. ID. NO. 167		ADAM12La_aa584-624_frag9	RPVIGT
HG1019196		SEQ. ID. NO. 168		ADAM12La_aa584-624_frag10	PVIGTN
HG1019197		SEQ. ID. NO. 169		ADAM12La_aa584-624_frag11	VIGTNA
HG1019198		SEQ. ID. NO. 170		ADAM12La_aa584-624_frag12	IGTNAV
HG1019199		SEQ. ID. NO. 171		ADAM12La_aa584-624_frag13	GTNAVS
HG1019200		SEQ. ID. NO. 172		ADAM12La_aa584-624_frag14	TNAVSI
HG1019201		SEQ. ID. NO. 173		ADAM12La_aa584-624_frag15	NAVSIE
HG1019202		SEQ. ID. NO. 174		ADAM12La_aa584-624_frag16	AVSIET
HG1019203		SEQ. ID. NO. 175		ADAM12La_aa584-624_frag17	VSIETN
HG1019204		SEQ. ID. NO. 176		ADAM12La_aa584-624_frag18	SIETNI
HG1019205		SEQ. ID. NO. 177		ADAM12La_aa584-624_frag19	IETNIP
HG1019206		SEQ. ID. NO. 178		ADAM12La_aa584-624_frag20	ETNIPL
HG1019207		SEQ. ID. NO. 179		ADAM12La_aa584-624_frag21	TNIPLQ
HG1019208		SEQ. ID. NO. 180		ADAM12La_aa584-624_frag22	NIPLQQ
HG1019209		SEQ. ID. NO. 181		ADAM12La_aa584-624_frag23	IPLQQG
HG1019210		SEQ. ID. NO. 182		ADAM12La_aa584-624_frag24	PLQQGG
HG1019211		SEQ. ID. NO. 183		ADAM12La_aa584-624_frag25	LQQGGR
HG1019212		SEQ. ID. NO. 184		ADAM12La_aa584-624_frag26	QGGGRI
HG1019213		SEQ. ID. NO. 185		ADAM12La_aa584-624_frag27	QGGRIIL
HG1019214		SEQ. ID. NO. 186		ADAM12La_aa584-624_frag28	GGRILC
HG1019215		SEQ. ID.		ADAM12La_aa584-624_frag29	GRILCR

FP ID	SEQ. ID. NO. (N1)	SEQ. ID. NO. (P1)	SEQ. ID. NO. (N0)	Clone ID	Notes
		NO. 187			
HG1019216		SEQ. ID. NO. 188		ADAM12La_aa584-624_frag30	RILCRG
HG1019217		SEQ. ID. NO. 189		ADAM12La_aa584-624_frag31	ILCRGT
HG1019218		SEQ. ID. NO. 190		ADAM12La_aa584-624_frag32	LCRGTH
HG1019219		SEQ. ID. NO. 191		ADAM12La_aa584-624_frag33	CRGTHV
HG1019220		SEQ. ID. NO. 192		ADAM12La_aa584-624_frag34	RGTHVY
HG1019221		SEQ. ID. NO. 193		ADAM12La_aa584-624_frag35	GTHVYL
HG1019222		SEQ. ID. NO. 194		ADAM12La_aa584-624_frag36	THVYLG
HG1019223		SEQ. ID. NO. 195		ADAM12La_aa584-624_frag37	HVYLGD
HG1019224		SEQ. ID. NO. 196		ADAM12La_aa651-693_frag1	NISVFGVHECAMQC HGRGVCNNRKNCH CEAHWAPPFCDFKFG
HG1019225		SEQ. ID. NO. 197		ADAM12La_aa651-693_frag2	NISVFG
HG1019226		SEQ. ID. NO. 198		ADAM12La_aa651-693_frag3	ISVFGV
HG1019227		SEQ. ID. NO. 199		ADAM12La_aa651-693_frag4	SVFGVH
HG1019228		SEQ. ID. NO. 200		ADAM12La_aa651-693_frag5	VFGVHE
HG1019229		SEQ. ID. NO. 201		ADAM12La_aa651-693_frag6	FGVHEC
HG1019230		SEQ. ID. NO. 202		ADAM12La_aa651-693_frag7	GVHECA
HG1019231		SEQ. ID. NO. 203		ADAM12La_aa651-693_frag8	VHECAM
HG1019232		SEQ. ID. NO. 204		ADAM12La_aa651-693_frag9	HECAMQ
HG1019233		SEQ. ID. NO. 205		ADAM12La_aa651-693_frag10	ECAMQC
HG1019234		SEQ. ID. NO. 206		ADAM12La_aa651-693_frag11	CAMQCH
HG1019235		SEQ. ID. NO. 207		ADAM12La_aa651-693_frag12	AMQCHG
HG1019236		SEQ. ID. NO. 208		ADAM12La_aa651-693_frag13	MQCHGR
HG1019237		SEQ. ID. NO. 209		ADAM12La_aa651-693_frag14	QCHGRG
HG1019238		SEQ. ID. NO. 210		ADAM12La_aa651-693_frag15	CHGRGV
HG1019239		SEQ. ID. NO. 211		ADAM12La_aa651-693_frag16	HGRGVC
HG1019240		SEQ. ID. NO. 212		ADAM12La_aa651-693_frag17	GRGVCN
HG1019241		SEQ. ID. NO. 213		ADAM12La_aa651-693_frag18	RGVCNN
HG1019242		SEQ. ID. NO. 214		ADAM12La_aa651-693_frag19	GVCNNR

FP ID	SEQ. ID. NO. (N1)	SEQ. ID. NO. (P1)	SEQ. ID. NO. (N0)	Clone ID	Notes
HG1019243		SEQ. ID. NO. 215		ADAM12La_aa651-693_frag20	VCNNRK
HG1019244		SEQ. ID. NO. 216		ADAM12La_aa651-693_frag21	CNNRKN
HG1019245		SEQ. ID. NO. 217		ADAM12La_aa651-693_frag22	NNRKNC
HG1019246		SEQ. ID. NO. 218		ADAM12La_aa651-693_frag23	NRKNCH
HG1019247		SEQ. ID. NO. 219		ADAM12La_aa651-693_frag24	RKNCHC
HG1019248		SEQ. ID. NO. 220		ADAM12La_aa651-693_frag25	KNCHCE
HG1019249		SEQ. ID. NO. 221		ADAM12La_aa651-693_frag26	NCHCEA
HG1019250		SEQ. ID. NO. 222		ADAM12La_aa651-693_frag27	CHCEAH
HG1019251		SEQ. ID. NO. 223		ADAM12La_aa651-693_frag28	HCEAHW
HG1019252		SEQ. ID. NO. 224		ADAM12La_aa651-693_frag29	CEAHWA
HG1019253		SEQ. ID. NO. 225		ADAM12La_aa651-693_frag30	EAHWAP
HG1019254		SEQ. ID. NO. 226		ADAM12La_aa651-693_frag31	AHWAPP
HG1019255		SEQ. ID. NO. 227		ADAM12La_aa651-693_frag32	HWAPPF
HG1019256		SEQ. ID. NO. 228		ADAM12La_aa651-693_frag33	WAPPFC
HG1019257		SEQ. ID. NO. 229		ADAM12La_aa651-693_frag34	APPFCD
HG1019258		SEQ. ID. NO. 230		ADAM12La_aa651-693_frag35	PPFCDK
HG1019259		SEQ. ID. NO. 231		ADAM12La_aa651-693_frag36	PFCDKF
HG1019260		SEQ. ID. NO. 232		ADAM12La_aa651-693_frag37	FCDKFG
HG1019261		SEQ. ID. NO. 233		ADAM12La_aa651-693_frag38	CDKFGF
HG1019262		SEQ. ID. NO. 234		ADAM12La_aa651-693_frag39	DKFGFG
HG1019263		SEQ. ID. NO. 235		ADAM12La_aa29-44_frag1	RGVSLWNQGRADE VVS
HG1019264		SEQ. ID. NO. 236		ADAM12La_aa29-44_frag2	RGVSLW
HG1019265		SEQ. ID. NO. 237		ADAM12La_aa29-44_frag3	GVSLWN
HG1019266		SEQ. ID. NO. 238		ADAM12La_aa29-44_frag4	VSLWNQ
HG1019267		SEQ. ID. NO. 239		ADAM12La_aa29-44_frag5	SLWNQG
HG1019268		SEQ. ID. NO. 240		ADAM12La_aa29-44_frag6	LWNQGR
HG1019269		SEQ. ID. NO. 241		ADAM12La_aa29-44_frag7	WNQGRA
HG1019270		SEQ. ID. NO. 242		ADAM12La_aa29-44_frag8	NQGRAD
HG1019271		SEQ. ID.		ADAM12La_aa29-44_frag9	QGRADE

FP ID	SEQ. ID. NO. (N1)	SEQ. ID. NO. (P1)	SEQ. ID. NO. (N0)	Clone ID	Notes
		NO. 243			
HG1019272		SEQ. ID. NO. 244		ADAM12La_aa29-44_frag10	GRADEV
HG1019273		SEQ. ID. NO. 245		ADAM12La_aa29-44_frag11	RADEVV
HG1019274		SEQ. ID. NO. 246		ADAM12La_aa64-92_frag1	HPEVLNIRLQRESKE LIINLERNEGLIAS
HG1019275		SEQ. ID. NO. 247		ADAM12La_aa64-92_frag2	HPEVLN
HG1019276		SEQ. ID. NO. 248		ADAM12La_aa64-92_frag3	PEVLNI
HG1019277		SEQ. ID. NO. 249		ADAM12La_aa64-92_frag4	EVLNIR
HG1019278		SEQ. ID. NO. 250		ADAM12La_aa64-92_frag5	VLNIRL
HG1019279		SEQ. ID. NO. 251		ADAM12La_aa64-92_frag6	LNIRLQ
HG1019280		SEQ. ID. NO. 252		ADAM12La_aa64-92_frag7	NIRLQR
HG1019281		SEQ. ID. NO. 253		ADAM12La_aa64-92_frag8	IRLQRE
HG1019282		SEQ. ID. NO. 254		ADAM12La_aa64-92_frag9	RLQRES
HG1019283		SEQ. ID. NO. 255		ADAM12La_aa64-92_frag10	LQRESK
HG1019284		SEQ. ID. NO. 256		ADAM12La_aa64-92_frag11	QRESKE
HG1019285		SEQ. ID. NO. 257		ADAM12La_aa64-92_frag12	RESKEL
HG1019286		SEQ. ID. NO. 258		ADAM12La_aa64-92_frag13	ESKELI
HG1019287		SEQ. ID. NO. 259		ADAM12La_aa64-92_frag14	SKELII
HG1019288		SEQ. ID. NO. 260		ADAM12La_aa64-92_frag15	KELIIN
HG1019289		SEQ. ID. NO. 261		ADAM12La_aa64-92_frag16	ELIINL
HG1019290		SEQ. ID. NO. 262		ADAM12La_aa64-92_frag17	LIINLE
HG1019291		SEQ. ID. NO. 263		ADAM12La_aa64-92_frag18	IINLER
HG1019292		SEQ. ID. NO. 264		ADAM12La_aa64-92_frag19	INLERN
HG1019293		SEQ. ID. NO. 265		ADAM12La_aa64-92_frag20	NLERNE
HG1019294		SEQ. ID. NO. 266		ADAM12La_aa64-92_frag21	LERNEG
HG1019295		SEQ. ID. NO. 267		ADAM12La_aa64-92_frag22	ERNEGL
HG1019296		SEQ. ID. NO. 268		ADAM12La_aa64-92_frag23	RNEGLI
HG1019297		SEQ. ID. NO. 269		ADAM12La_aa64-92_frag24	NEGLIA
HG1019298		SEQ. ID. NO. 270		ADAM12La_aa64-92_frag25	EGLIAS
HG1019299		SEQ. ID. NO. 271		ADAM12La_aa90-113_frag1	IASSFTETHYLQDGT DVSLARNYT

FP ID	SEQ. ID. NO. (N1)	SEQ. ID. NO. (P1)	SEQ. ID. NO. (N0)	Clone ID	Notes
HG1019300		SEQ. ID. NO. 272		ADAM12La_aa90-113_frag2	IASSFT
HG1019301		SEQ. ID. NO. 273		ADAM12La_aa90-113_frag3	ASSFTE
HG1019302		SEQ. ID. NO. 274		ADAM12La_aa90-113_frag4	SSFTET
HG1019303		SEQ. ID. NO. 275		ADAM12La_aa90-113_frag5	SFTETH
HG1019304		SEQ. ID. NO. 276		ADAM12La_aa90-113_frag6	FTETHY
HG1019305		SEQ. ID. NO. 277		ADAM12La_aa90-113_frag7	TETHYL
HG1019306		SEQ. ID. NO. 278		ADAM12La_aa90-113_frag8	ETHYLQ
HG1019307		SEQ. ID. NO. 279		ADAM12La_aa90-113_frag9	THYLQD
HG1019308		SEQ. ID. NO. 280		ADAM12La_aa90-113_frag10	HYLQDG
HG1019309		SEQ. ID. NO. 281		ADAM12La_aa90-113_frag11	YLQDGT
HG1019310		SEQ. ID. NO. 282		ADAM12La_aa90-113_frag12	LQDGTD
HG1019311		SEQ. ID. NO. 283		ADAM12La_aa90-113_frag13	QDGTDV
HG1019312		SEQ. ID. NO. 283		ADAM12La_aa90-113_frag14	DGTDVS
HG1019313		SEQ. ID. NO. 285		ADAM12La_aa90-113_frag15	GTDVSL
HG1019314		SEQ. ID. NO. 286		ADAM12La_aa90-113_frag16	TDVSLA
HG1019315		SEQ. ID. NO. 287		ADAM12La_aa90-113_frag17	DVSLAR
HG1019316		SEQ. ID. NO. 288		ADAM12La_aa90-113_frag18	VSLARN
HG1019317		SEQ. ID. NO. 289		ADAM12La_aa90-113_frag19	SLARNY
HG1019318		SEQ. ID. NO. 290		ADAM12La_aa90-113_frag20	LARNYT
HG1019319		SEQ. ID. NO. 291		ADAM12La_aa115-128_frag1	ILGHCCYYHGHVIRGY
HG1019320		SEQ. ID. NO. 292		ADAM12La_aa115-128_frag2	LGHCCY
HG1019321		SEQ. ID. NO. 293		ADAM12La_aa115-128_frag3	GHCCYY
HG1019322		SEQ. ID. NO. 294		ADAM12La_aa115-128_frag4	HCCYYH
HG1019323		SEQ. ID. NO. 295		ADAM12La_aa115-128_frag5	CYYHGH
HG1019324		SEQ. ID. NO. 296		ADAM12La_aa115-128_frag6	YYHGH
HG1019325		SEQ. ID. NO. 297		ADAM12La_aa115-128_frag7	YHGHV
HG1019326		SEQ. ID. NO. 298		ADAM12La_aa115-128_frag8	HGHVR
HG1019327		SEQ. ID. NO. 299		ADAM12La_aa115-128_frag9	GHVRG
HG1019328		SEQ. ID.		ADAM12La_aa115-128_frag10	HVRGY

FP ID	SEQ. ID. NO. (N1)	SEQ. ID. NO. (P1)	SEQ. ID. NO. (N0)	Clone ID	Notes
		NO. 300			
HG1019329		SEQ. ID. NO. 301		ADAM12La_aa128-159_frag1	YSDSAVSLSTCSGLR GLIVFENESYVLEPM KS
HG1019330		SEQ. ID. NO. 302		ADAM12La_aa128-159_frag2	YSDSAV
HG1019331		SEQ. ID. NO. 303		ADAM12La_aa128-159_frag3	SDSAVS
HG1019332		SEQ. ID. NO. 304		ADAM12La_aa128-159_frag4	DSAVSL
HG1019333		SEQ. ID. NO. 305		ADAM12La_aa128-159_frag5	SAVSLS
HG1019334		SEQ. ID. NO. 306		ADAM12La_aa128-159_frag6	AVSLST
HG1019335		SEQ. ID. NO. 307		ADAM12La_aa128-159_frag7	VSLSTC
HG1019336		SEQ. ID. NO. 308		ADAM12La_aa128-159_frag8	SLSTCS
HG1019337		SEQ. ID. NO. 309		ADAM12La_aa128-159_frag9	LSTCSG
HG1019338		SEQ. ID. NO. 310		ADAM12La_aa128-159_frag10	STCSGL
HG1019339		SEQ. ID. NO. 311		ADAM12La_aa128-159_frag11	TCSGLR
HG1019340		SEQ. ID. NO. 312		ADAM12La_aa128-159_frag12	CSGLRG
HG1019341		SEQ. ID. NO. 313		ADAM12La_aa128-159_frag13	SGLRGL
HG1019342		SEQ. ID. NO. 314		ADAM12La_aa128-159_frag14	GLRGLI
HG1019343		SEQ. ID. NO. 315		ADAM12La_aa128-159_frag15	LRGLIV
HG1019344		SEQ. ID. NO. 316		ADAM12La_aa128-159_frag16	RGLIVF
HG1019345		SEQ. ID. NO. 317		ADAM12La_aa128-159_frag17	GLIVFE
HG1019346		SEQ. ID. NO. 318		ADAM12La_aa128-159_frag18	LIVFEN
HG1019347		SEQ. ID. NO. 319		ADAM12La_aa128-159_frag19	IVFENE
HG1019348		SEQ. ID. NO. 320		ADAM12La_aa128-159_frag20	VFENES
HG1019349		SEQ. ID. NO. 321		ADAM12La_aa128-159_frag21	FENESY
HG1019350		SEQ. ID. NO. 322		ADAM12La_aa128-159_frag22	ENESYV
HG1019351		SEQ. ID. NO. 323		ADAM12La_aa128-159_frag23	NESYVL
HG1019352		SEQ. ID. NO. 324		ADAM12La_aa128-159_frag24	ESYVLE
HG1019353		SEQ. ID. NO. 325		ADAM12La_aa128-159_frag25	SYVLEP
HG1019354		SEQ. ID. NO. 326		ADAM12La_aa128-159_frag26	YVLEPM
HG1019355		SEQ. ID. NO. 327		ADAM12La_aa128-159_frag27	VLEPMK
HG1019356		SEQ. ID.		ADAM12La_aa128-159_frag28	LEPMKS

FP ID	SEQ. ID. NO. (N1)	SEQ. ID. NO. (P1)	SEQ. ID. NO. (N0)	Clone ID	Notes
		NO. 328			
HG1019357		SEQ. ID. NO. 329		ADAM12La_aa160-173_frag1	ATNRYKLFPKKLK
HG1019358		SEQ. ID. NO. 330		ADAM12La_aa160-173_frag2	ATNRYK
HG1019359		SEQ. ID. NO. 331		ADAM12La_aa160-173_frag3	TNRYKL
HG1019360		SEQ. ID. NO. 332		ADAM12La_aa160-173_frag4	NRYKLF
HG1019361		SEQ. ID. NO. 333		ADAM12La_aa160-173_frag5	RYKLFP
HG1019362		SEQ. ID. NO. 334		ADAM12La_aa160-173_frag6	YKLFP
HG1019363		SEQ. ID. NO. 335		ADAM12La_aa160-173_frag7	KLFPK
HG1019364		SEQ. ID. NO. 336		ADAM12La_aa160-173_frag8	LFPKK
HG1019365		SEQ. ID. NO. 337		ADAM12La_aa160-173_frag9	FPAKKL
HG1019366		SEQ. ID. NO. 338		ADAM12La_aa160-173_frag10	PAKKLK
HG1019367	SEQ. ID. NO. 2	SEQ. ID. NO. 339		ADAM12La_extracellulardomain	
HG1019368	SEQ. ID. NO. 3			PRB104353_at:1	ATGCGTGACCAGC AGTACTCAGGTT
HG1019369	SEQ. ID. NO. 4			PRB104353_at:2	AGTAGCAGGTTAC CACTCTGGCAGG
HG1019370	SEQ. ID. NO. 5			PRB104353_at:3	ACTGGTCTCTGGCT GCAACTTAATG
HG1019371	SEQ. ID. NO. 6			PRB104353_at:4	ACATGGACATGCTT CAGTGCTGCTC
HG1019372	SEQ. ID. NO. 7			PRB104353_at:5	AACTCTGGCTCTTT GCTGTGGACAT
HG1019373	SEQ. ID. NO. 8			PRB104353_at:6	CGACTTCCTGGTTG AGCTTCTGCTA
HG1019374	SEQ. ID. NO. 9			PRB104353_at:7	GAAAGGGCGGTGA ACTCTGGCTCTT
HG1019375	SEQ. ID. NO. 10			PRB104353_at:8	GTCACCAACCCCTC ATTAAACAAGT
HG1019376	SEQ. ID. NO. 11			PRB104353_at:9	TCCATCTCCATCCA AGCAAAGTGA
HG1019377	SEQ. ID. NO. 12			PRB104353_at:10	TTAATTTATCAGAG ACCCTGCCACC
HG1019378	SEQ. ID. NO. 13			PRB104353_at:11	TTGGCAGCCCTGAT GACTGGTCTCT
HG1019379	SEQ. ID. NO. 14			PRB104353_at	
HG1019380	SEQ. ID. NO. 15			ADAM12S_primerF	CAAGTTTGGCTTTG GAGGAA
HG1019381	SEQ. ID. NO. 16			ADAM12S_primerR	GCGCTCCCTGTTGG ACTCT
HG1019382	SEQ. ID. NO. 17			ADAM12S_probe	CAGAAGCAAGGCA GGAA
HG1019383	SEQ. ID. NO. 18			ADAM12L_primerF	CCGGCAAGCAGAT AACCAA
HG1019384	SEQ. ID. NO. 19			ADAM12L_primerR	ATCCTGTGTCTTCT TGCTGCC

FP ID	SEQ. ID. NO. (N1)	SEQ. ID. NO. (P1)	SEQ. ID. NO. (N0)	Clone ID	Notes
HG1019385	SEQ. ID. NO. 20			ADAM12L_probe	TTTAACCATAGGAA TTCTG
HG1019509	SEQ. ID. NO. 341	SEQ. ID. NO. 373		CLN00575852	ADAM12Lb
HG1019510	SEQ. ID. NO. 342	SEQ. ID. NO. 374		CLN00575852_1-706	construct
HG1019511		SEQ. ID. NO. 375		CLN00575852_frag1	ARNYTG
HG1019512		SEQ. ID. NO. 376		CLN00575852_frag2	RNYTGH
HG1019513		SEQ. ID. NO. 377		CLN00575852_frag3	NYTGHC
HG1019514		SEQ. ID. NO. 378		CLN00575852_frag4	YTGHCY
HG1019515		SEQ. ID. NO. 379		CLN00575852_frag5	TGHCYY
HG1015830	SEQ. ID. NO. 343	SEQ. ID. NO. 380	SEQ. ID. NO. 384	NP_003465:NM_003474	ADAM12La
HG1016262	SEQ. ID. NO. 344	SEQ. ID. NO. 381		NP_003465:NM_003474. disintegrin.1	
HG1016263	SEQ. ID. NO. 345	SEQ. ID. NO. 382		NP_003465:NM_003474. Pep_M12B_propep.1	
HG1016264	SEQ. ID. NO. 346	SEQ. ID. NO. 383		NP_003465:NM_003474. Reprolysin.1	
HG1016397	SEQ. ID. NO. 347			PRB102715_s_at	
HG1017033	SEQ. ID. NO. 348			PRB102715_s_at:1	
HG1017034	SEQ. ID. NO. 349			PRB102715_s_at:10	
HG1017035	SEQ. ID. NO. 350			PRB102715_s_at:11	
HG1017036	SEQ. ID. NO. 351			PRB102715_s_at:2	
HG1017037	SEQ. ID. NO. 352			PRB102715_s_at:3	
HG1017038	SEQ. ID. NO. 353			PRB102715_s_at:4	
HG1017039	SEQ. ID. NO. 354			PRB102715_s_at:5	
HG1017040	SEQ. ID. NO. 355			PRB102715_s_at:6	
HG1017041	SEQ. ID. NO. 356			PRB102715_s_at:7	
HG1017042	SEQ. ID. NO. 357			PRB102715_s_at:8	
HG1017043	SEQ. ID. NO. 358			PRB102715_s_at:9	
HG1019516	SEQ. ID. NO. 359			204943_at	
HG1019517	SEQ. ID. NO. 360			241022_at	
HG1019518	SEQ. ID. NO. 361			242460_at	
HG1019519	SEQ. ID. NO. 362			215613_at	
HG1019520	SEQ. ID.			241026_at	

FP ID	SEQ. ID. NO. (N1)	SEQ. ID. NO. (P1)	SEQ. ID. NO. (N0)	Clone ID	Notes
	NO. 363				
HG1019521	SEQ. ID. NO. 364			232268_at	
HG1019524	SEQ. ID. NO. 365			NP_067673_taqman	
HG1019525	SEQ. ID. NO. 366			NP_003465_taqman	
HG1019526	SEQ. ID. NO. 367			NP_0067673_taqmanF	GACAAGTTTGGCTT TGGAGGAA
HG1019527	SEQ. ID. NO. 368			NP_0067673_taqmanR	GCGCTCCCTGTTGG ACTCT
HG1019528	SEQ. ID. NO. 369			NP_0067673_taqmanProbe	CAGAAGCAAGGCA GGAA
HG1019529	SEQ. ID. NO. 370			NP_003465_taqmanF	CCGGCAAGCAGAT AACCAA
HG1019530	SEQ. ID. NO. 371			NP_003465_taqmanR	GGCAGCAAGAAGA CACAGGAT
HG1019531	SEQ. ID. NO. 372			NP_003465_taqmanProbe	TTTAACCATAGGAA TTCTG
HG1019598	SEQ. ID. NO. 385	SEQ. ID. NO. 387	SEQ. ID. NO. 389	37182874:37182873	ADAM12Sb
HG1019599	SEQ. ID. NO. 386	SEQ. ID. NO. 388	SEQ. ID. NO. 390	38173792:38173791	ADAM12Sc
HG1019607	SEQ. ID. NO. 391	SEQ. ID. NO. 394		CLN00575852_prodomain	
HG1019608	SEQ. ID. NO. 392	SEQ. ID. NO. 395		NP_067673_prodomain	
HG1019609	SEQ. ID. NO. 393	SEQ. ID. NO. 396		CLN00575852_crd	

Table 2. Characterization of Polypeptides Identified by PRB102715_s_at

FP ID	Clone ID	Pred Pro Len	Tree-vote	Signal Peptide Coords	Mature Protein Coords	TM	TM Coords	Domain
HG1015830	NP_003465: NM_003474	909	0	(1-29)	(30-909)	1	(707-729)	Reprolysin EGF_2; Pep_M12B_propep; Disintegrin propeptide; Cys-rich-domain
HG1019049	NP_067673: NM_021641	738	0.96	(1-29)	(30-738)	0		Reprolysin EGF_2; Pep_M12B_propep; Disintegrin propeptide; Cys-rich-domain
HG1019509	CLN005758 52	906	0	(1-29)	(30-906)	1	(704-726)	Reprolysin EGF_2; Pep_M12B_propep; Disintegrin propeptide; Cys-rich-domain
HG1019510	CLN005758 52_1-706	703	0.96	(1-29)	(30-703)	0		Reprolysin EGF_2; Pep_M12B_propep; Disintegrin propeptide; Cys-rich-domain
HG1019598	37182874:37 182873	735	0.96	(1-29)	(30-735)	0		Reprolysin EGF_2; Pep_M12B_propep; Disintegrin propeptide; Cys-rich-domain
HG1019599	38173792:38 173791	737	0.95	(1-29)	(30-737)	0		Reprolysin EGF_2; Pep_M12B_propep; Disintegrin propeptide; Cys-rich-domain

Table 3. Pfam and ProSite Domain Coordinates

FP ID	Clone ID	Funct Dom	Coords
HG1015830	NP_003465:NM_003474	Pep_M12B_propep	(82-197)
HG1015830	NP_003465:NM_003474	EGF_2	(660-687)
HG1015830	NP_003465:NM_003474	Disintegrin	(433-508)
HG1015830	NP_003465:NM_003474	Reprolysin	(214-416)
HG1019049	NP_067673:NM_021641	Pep_M12B_propep	(82-197)
HG1019049	NP_067673:NM_021641	EGF_2	(660-687)
HG1019049	NP_067673:NM_021641	Disintegrin	(433-508)
HG1019049	NP_067673:NM_021641	Reprolysin	(214-416)
HG1019509	CLN00575852	Pep_M12B_propep	(82-194)
HG1019509	CLN00575852	EGF_2	(657-684)
HG1019509	CLN00575852	Disintegrin	(430-505)
HG1019509	CLN00575852	Reprolysin	(211-413)
HG1019510	CLN00575852_1-706	Pep_M12B_propep	(82-194)
HG1019510	CLN00575852_1-706	EGF_2	(657-684)
HG1019510	CLN00575852_1-706	Disintegrin	(430-505)
HG1019510	CLN00575852_1-706	Reprolysin	(211-413)
HG1019598	37182874:37182873	Pep_M12B_propep	(82-194)
HG1019598	37182874:37182873	EGF_2	(657-684)
HG1019598	37182874:37182873	Disintegrin	(430-505)
HG1019598	37182874:37182873	Reprolysin	(211-413)
HG1019599	38173792:38173791	Pep_M12B_propep	(82-194)
HG1019599	38173792:38173791	EGF_2	(657-684)
HG1019599	38173792:38173791	Disintegrin	(430-505)
HG1019599	38173792:38173791	Reprolysin	(211-413)

Table 4. Protein Domain Coordinates

FP ID	Clone ID	Prot Dom	Coords
HG1015830	NP_003465:NM_003474	sp	(1-28)
HG1015830	NP_003465:NM_003474	prodomain	(29-207)
HG1015830	NP_003465:NM_003474	metalloprotease	(208-416)
HG1015830	NP_003465:NM_003474	disintegrin	(417-512)
HG1015830	NP_003465:NM_003474	cys-rich	(513-652)
HG1015830	NP_003465:NM_003474	EGF-like	(653-688)
HG1019049	NP_067673:NM_021641	sp	(1-28)
HG1019049	NP_067673:NM_021641	prodomain	(29-207)
HG1019049	NP_067673:NM_021641	metalloprotease	(208-416)
HG1019049	NP_067673:NM_021641	disintegrin	(417-512)
HG1019049	NP_067673:NM_021641	cys-rich	(513-652)
HG1019049	NP_067673:NM_021641	EGF-like	(653-688)
HG1019509	CLN00575852	sp	(1-28)
HG1019509	CLN00575852	prodomain	(29-204)
HG1019509	CLN00575852	metalloprotease	(205-413)
HG1019509	CLN00575852	disintegrin	(414-509)
HG1019509	CLN00575852	cys-rich	(510-649)
HG1019509	CLN00575852	EGF-like	(650-685)
HG1019510	CLN00575852_1-706	sp	(1-28)
HG1019510	CLN00575852_1-706	prodomain	(29-204)
HG1019510	CLN00575852_1-706	metalloprotease	(205-413)
HG1019510	CLN00575852_1-706	disintegrin	(414-509)
HG1019510	CLN00575852_1-706	cys-rich	(510-649)
HG1019510	CLN00575852_1-706	EGF-like	(650-685)
HG1019598	37182874:37182873	sp	(1-28)
HG1019598	37182874:37182873	prodomain	(29-204)
HG1019598	37182874:37182873	metalloprotease	(205-413)
HG1019598	37182874:37182873	disintegrin	(414-509)
HG1019598	37182874:37182873	cys-rich	(510-649)
HG1019598	37182874:37182873	EGF-like	(650-685)
HG1019599	38173792:38173791	sp	(1-28)
HG1019599	38173792:38173791	prodomain	(29-204)
HG1019599	38173792:38173791	metalloprotease	(205-413)
HG1019599	38173792:38173791	disintegrin	(414-509)
HG1019599	38173792:38173791	cys-rich	(510-649)
HG1019599	38173792:38173791	EGF-like	(650-685)

SEQUENCE LISTING

[0289] The application includes a Sequence Listing provided in both electronic and paper format and a Statement Accompanying Sequence Listing.

CLAIMS

1. An isolated first nucleic acid molecule comprising a first polynucleotide sequence encoding a polypeptide; a complement thereof; an isolated polypeptide encoded by a polynucleotide, wherein the polypeptide comprises an amino acid sequence chosen from the Tables, Figures, and Sequence Listing; or a biologically active fragment of any of these, wherein the polypeptide is other than a full-length ADAM12L, full-length ADAM12S, mature ADAM12L, mature ADAM12S, ADAM12 cysteine-rich domain, or the entire ADAM12 extracellular domain, as described in Figures 1 and 2.
2. The polynucleotide of claim 1, wherein the polynucleotide is chosen from a RNAi molecule, a ribozyme, and a nucleotide aptamer.
3. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the polynucleotide or polypeptide of claim 1.
4. A non-human animal injected with the polynucleotide and/or polypeptide of claim 1.
5. An isolated antibody specifically recognizing, binding to, interfering with, and/or otherwise modulating the biological activity of at least one polypeptide and/or polynucleotide chosen from the Tables, Sequence Listing, Figures, and a biologically active fragment of any of these, wherein the polypeptide is other than a full-length ADAM12L, a full-length ADAM12S, a mature ADAM12L, or mature ADAM12S polypeptide, as described in Figures 1 and 2, and wherein the antibody is not currently in the public domain.
6. The antibody of claim 5, wherein the polypeptide comprises a non-transmembrane domain and/or an extracellular domain chosen from the non-TM coordinates of Table 2.
7. The antibody of claim 5, wherein the polypeptide comprises a Pfam domain or a Prosite domain chosen from the functional domain coordinates of Table 3; the protein domain coordinates of Table 4; or a prodomain, a protease domain, a cysteine-rich domain, or an EGF-like domain, as described in Figures 1 and 2.
8. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the antibody of claim 5.

9. The antibody of claim 5, further comprising one or more cytotoxic component chosen from a radioisotope, a microbial toxin, a plant toxin, and a chemical compound.

10. The antibody of claim 5, wherein the antibody has a function chosen from specifically inhibiting the binding of the polypeptide to a ligand, specifically inhibiting the binding of the polypeptide to a substrate, specifically inhibiting the binding of the polypeptide as a ligand, specifically inhibiting the binding of the polypeptide as a substrate, specifically inhibiting cofactor binding, inducing apoptosis, inducing antibody-dependent cell cytotoxicity, inducing complement-dependent cytotoxicity, inhibiting protease activity, inhibiting adhesion, modulating ligand/receptor interaction, and modulating enzyme/substrate interaction.

11. The antibody of claim 10, wherein the cofactor is zinc.

12. The antibody of claim 5, chosen from one or more of a monoclonal antibody; a polyclonal antibody; a single chain antibody; an antibody comprising a backbone of a molecule with an Ig domain or a T cell receptor backbone; a targeting antibody; a neutralizing antibody; a stabilizing antibody; an enhancing antibody; an antibody agonist; an antibody antagonist; an antibody that promotes endocytosis of a target antigen; a cytotoxic antibody; an antibody that mediates antibody-dependent cell cytotoxicity; an antibody that mediates complement-dependent cytotoxicity; a human antibody; a non-human primate antibody; a non-primate animal antibody; a rabbit antibody; a mouse antibody; a rat antibody; a sheep antibody; a goat antibody; a horse antibody; a porcine antibody; a cow antibody; a chicken antibody; a humanized antibody; a primatized antibody; a chimeric antibody; an antigen-binding fragment; a fragment comprising a variable region of a heavy chain or a light chain of an immunoglobulin; a fragment comprising a complementarity determining region or a framework region of an immunoglobulin; and one or more active fragments, analogues, and/or antagonists of one or more of these antibodies.

13. The antibody of claim 12, wherein the antibody is a monoclonal antibody.

14. The antibody of claim 12, wherein the antibody is an antigen-binding fragment of an immunoglobulin.

15. The antibody of claim 12, wherein the antibody is produced in a plant, an animal, or a cell.
16. The antibody of claim 15, wherein the cell is chosen from a bacterial cell, a fungal cell, a plant cell, an insect cell, and a mammalian cell.
17. The antibody of claim 15, wherein the cell is chosen from a yeast cell, an *Aspergillus* cell, an SF9 cell, a High Five cell, a cereal plant cell, a tobacco cell, a tomato cell, a 293 cell, a myeloma cell, a NS0 cell, a PerC6 cell, and a CHO cell.
18. An epitope of ADAM12 chosen from ARNYTG (SEQ ID NO: 375), RNYTGH (SEQ ID NO: 376), NYTGHC (SEQ ID NO: 377), YTGHCY (SEQ ID NO: 378), and TGHCYY (SEQ ID NO: 379).
19. A host cell genetically modified to produce the antibody of claim 15.
20. A bacteriophage displaying the antibody of claim 5 and/or a fragment thereof.
21. An isolated first nucleic acid molecule comprising a first polynucleotide sequence chosen from (A) SEQ ID NOS.:341 and/or 342, (B) a polynucleotide sequence encoding a polypeptide of SEQ ID NOS.:373, 374, 375, and/or 379, and (C) biologically active fragments of any of these, wherein the fragments comprise a polynucleotide sequence or an amino acid sequence encoded by a polynucleotide sequence comprising the splice sites utilized by CLN00575852.
22. The first nucleic acid molecule of claim 21, wherein the nucleic acid molecule is chosen from a cDNA molecule, a genomic DNA molecule, a cRNA molecule, a siRNA molecule, a RNAi molecule, and a mRNA molecule.
23. A double-stranded isolated nucleic acid molecule comprising the first nucleic acid molecule of claim 21 and its complement.
24. A second nucleic acid molecule comprising a second polynucleotide sequence complementary to the first nucleic acid molecule of claim 21.
25. The second nucleic acid molecule of claim 24, chosen from a RNAi molecule, an anti-sense molecule, and a ribozyme.
26. An isolated polypeptide comprising an amino acid sequence chosen from SEQ ID NOS.:373, 374, 375, and biologically active fragments of any of these.

27. The polypeptide of claim 26, wherein the polypeptide is present in a cell culture.
28. The polypeptide of claim 27, wherein the cell culture is chosen from a bacterial cell culture, a mammalian cell culture, and an insect cell culture.
29. An isolated polypeptide encoded by the first nucleic acid molecule of claim 21.
30. A method of modulating the biological activity of a first human or non-human animal host cell comprising:
- (a) providing the antibody of claim 5; and
 - (b) contacting the antibody with the first host cell, wherein the activity of the first host cell, and a second host cell, is modulated.
31. The method of claim 30, wherein the modulation of biological activity is chosen from inhibiting cell activity directly, inhibiting cell activity indirectly, inducing antibody-dependent cell cytotoxicity, and inducing complement-dependent cytotoxicity.
32. The method of claim 30, wherein the modulated cell activity is chosen from signal transduction, transcription, and translation.
33. The method of claim 30, wherein the modulation of cell activity results in cell death and/or inhibition of cell growth.
34. The method of claim 30, wherein contacting the antibody with a first host cell results in recruitment of at least one second host cell.
35. The method of claim 30, wherein the first host cell is a cancer cell.
36. The method of claim 30, wherein the first or second host cell is chosen from a T cell, B cell, NK cell, dendritic cell, antigen presenting cell, and macrophage.
37. A method of identifying a modulator of the biological activity of a polypeptide comprising:
- (a) providing at least one polypeptide chosen from the sequences listed in the Tables, Figures, and Sequence Listing, and active fragments thereof;
 - (b) allowing at least one agent to contact the polypeptide; and
 - (c) selecting an agent that binds the polypeptide and/or affects the biological activity of the polypeptide.

38. The method of claim 37, wherein the modulator is an antibody.
39. A modulator composition comprising a pharmaceutically acceptable carrier and a modulator, wherein the modulator is obtainable by the method of claim 37.
40. A modulator composition comprising a pharmaceutically acceptable carrier and a modulator, wherein the modulator is the antibody of claim 5.
41. A modulator composition comprising a pharmaceutically acceptable carrier and a modulator, wherein the modulator is a soluble receptor that competes for ligand binding to an isolated polypeptide comprising an amino acid sequence chosen from the Tables, Figures, and Sequence Listing, and biologically active fragments thereof.
42. A modulator composition comprising a pharmaceutically acceptable carrier and a modulator, wherein the modulator is an extracellular fragment that competes for ligand binding to an isolated polypeptide comprising an amino acid sequence chosen from the Tables, Figures, and Sequence Listing, and biologically active fragments thereof.
43. A modulator composition comprising a pharmaceutically acceptable carrier and a modulator, wherein the modulator is an RNAi molecule that inhibits the transcription or translation of an isolated polynucleotide or an isolated polypeptide comprising an amino acid sequence encoded by a polynucleotide chosen from the Tables, Figures, and Sequence Listing, and biologically active fragments thereof.
44. A modulator composition comprising a pharmaceutically acceptable carrier and a modulator, wherein the modulator is an antisense molecule that inhibits the transcription or translation of an isolated polynucleotide or an isolated polypeptide comprising an amino acid sequence encoded by a polynucleotide chosen from the Tables, Figures, and Sequence Listing, and biologically active fragments thereof.
45. A modulator composition comprising a pharmaceutically acceptable carrier and a modulator, wherein the modulator is a ribozyme that inhibits the transcription or translation of an isolated polynucleotide or an isolated polypeptide comprising an amino acid sequence encoded by a polynucleotide chosen from the Tables, Figures, and Sequence Listing, and biologically active fragments thereof.

46. A modulator composition comprising a pharmaceutically acceptable carrier and a modulator, wherein the modulator is an aptamer that inhibits the function of an isolated polynucleotide or an isolated polypeptide comprising an amino acid sequence encoded by a polynucleotide chosen from the Tables, Figures, and Sequence Listing, and biologically active fragments thereof.

47. A method of determining the presence of a polypeptide specifically binding to an antibody in a sample, comprising:

- (a) allowing the antibody of claim 5 to interact with the sample; and
- (b) determining whether interaction between the antibody and the polypeptide has occurred.

48. A method of determining the presence of an antibody specifically binding to a polypeptide or a polynucleotide in a sample, comprising:

- (a) allowing an isolated polynucleotide encoding a polypeptide or an isolated polypeptide, wherein the polypeptide comprises an amino acid sequence chosen from the Tables, Figures, and Sequence Listing, and biologically active fragments thereof, to interact with the sample; and
- (b) determining whether interaction between the antibody and the polypeptide or polynucleotide has occurred.

49. A method of diagnosing cancer in a patient, comprising:

- (a) providing a polypeptide that specifically binds the antibody of claim 5;
- (b) allowing the polypeptide to contact a patient sample; and
- (c) detecting specific binding between the polypeptide and any interacting molecule in the sample to determine whether the patient has cancer.

50. The method of claim 49, wherein the cancer is chosen from lung, colorectal, breast, bladder, pancreatic, and stomach cancer.

51. A method of diagnosing cancer in a patient comprising:

- (a) providing an agent that detects a region of ADAM12 chosen from a prodomain, prometalloprotease domain, disintegrin domain, cysteine-rich domain, EGF-like domain, transmembrane domain, and cytoplasmic tail domain;
- (b) providing a biological sample from the patient; and

(c) allowing the agent to react with the biological sample to determine the presence of the prodomain in the sample.

52. The method of claim 51, wherein the sample is a blood sample.

53. The method of claim 51, wherein the agent is an antibody.

54. A kit comprising the antibody of claim 5 and instructions for performing the method of claim 39.

55. A method of treating uncontrolled proliferative growth in a patient comprising administering a modulator which binds to or interferes with the activity of an isolated polynucleotide encoding a polypeptide or an isolated polypeptide encoded by a polynucleotide, wherein the polypeptide comprises an amino acid sequence chosen from the Tables, Figures, and Sequence Listing, and biologically active fragments of any of these, to a patient.

56. The method of claim 55, wherein the modulator is the antibody of claim 5.

57. The method of claim 55, wherein the uncontrolled proliferative growth is a tumor.

58. The method of claim 57, wherein the tumor is chosen from a lung tumor, a colorectal tumor, a breast tumor, a bladder tumor, a pancreatic tumor, and a stomach tumor.

59. A method of treating a tumor in a patient comprising:

- (a) providing the modulator composition of claim 43; and
- (b) administering the modulator composition to the patient.

60. The method of claim 59, wherein the modulator is an antibody.

61. The method of claim 60, wherein the antibody specifically recognizes, binds to, or modulates the biological activity of a polypeptide and wherein the polypeptide comprises an amino acid sequence chosen from the Tables, Figures, and Sequence Listing or is encoded by a polynucleotide chosen from the Tables, Figures, and Sequence Listing, and biologically active fragments of any of these.

62. A method of treating a lung tumor in a patient comprising:

- (a) providing the modulator composition of claim 39; and
- (b) administering the modulator composition to the patient.

63. The method of claim 62, wherein the modulator is an antibody.
64. The method of claim 63, wherein the antibody specifically recognizes, binds to, and/or modulates the biological activity of a polypeptide and wherein the polypeptide comprises an amino acid sequence or is encoded by a polynucleotide chosen from the Tables, Figures, and Sequence Listing and biologically active fragments of any of these.
65. A method of treating a colorectal tumor in a patient comprising:
- (a) providing the modulator composition of claim 39; and
 - (b) administering the modulator composition to the patient.
66. The method of claim 65, wherein the modulator is an antibody.
67. The method of claim 66, wherein the antibody specifically recognizes, binds to, and/or modulates the biological activity of a polypeptide and wherein the polypeptide comprises an amino acid sequence or is encoded by a polynucleotide chosen from the Tables, Figures, and Sequence Listing and biologically active fragments of any of these.
68. A method of treating a breast tumor in a patient comprising:
- (a) providing the modulator composition of claim 39; and
 - (b) administering the modulator composition to the patient.
69. The method of claim 68, wherein the modulator is an antibody.
70. The method of claim 69, wherein the antibody specifically recognizes, binds to, and/or modulates the biological activity of a polypeptide and wherein the polypeptide comprises an amino acid sequence or is encoded by a polynucleotide chosen from the Tables, Figures, and Sequence Listing and biologically active fragments of any of these.
71. A method of treating a bladder tumor in a patient comprising:
- (a) providing the modulator composition of claim 39; and
 - (b) administering the modulator composition to the patient.
72. The method of claim 71, wherein the modulator is an antibody.
73. The method of claim 72, wherein the antibody specifically recognizes, binds to, and/or modulates the biological activity of a polypeptide and wherein the polypeptide comprises an amino acid sequence or is encoded by a polynucleotide

chosen from the Tables, Figures, and Sequence Listing and biologically active fragments of any of these.

74. A method of treating a pancreatic tumor in a patient comprising:

- (a) providing the modulator composition of claim 39; and
- (b) administering the modulator composition to the patient.

75. The method of claim 74, wherein the modulator is an antibody.

76. The method of claim 75, wherein the antibody specifically recognizes, binds to, and/or modulates the biological activity of a polypeptide and wherein the polypeptide comprises an amino acid sequence or is encoded by a polynucleotide chosen from the Tables, Figures, and Sequence Listing and biologically active fragments of any of these.

77. A method of treating a stomach tumor in a patient comprising:

- (a) providing the modulator composition of claim 39; and
- (b) administering the modulator composition to the patient.

78. The method of claim 77, wherein the modulator is an antibody.

79. The method of claim 78, wherein the antibody specifically recognizes, binds to, and/or modulates the biological activity of a polypeptide and wherein the polypeptide comprises an amino acid sequence or is encoded by a polynucleotide chosen from the Tables, Figures, and Sequence Listing and biologically active fragments of any of these.

80. A kit comprising the antibody of claim 79 and instructions for performing the method of any of claims 55-79.

81. A method for prophylaxis or therapeutic treatment of a subject, comprising:

- (a) providing a vaccine; and
- (b) administering the vaccine to the subject;

wherein the vaccine comprises a polynucleotide or a polypeptide chosen from at least one sequence according to SEQ ID NO.:1-396 or a complement, biologically active fragment, or variant thereof.

82. The method of claim 81, wherein the vaccine is a cancer vaccine.

MAARPLVSPARALLLALAGALLAPCEARGVSLWNQGRADEVVVSASVRSGDLWIPVKSFD	60
MAARPLVSPARALLLALAGALLAPCEARGVSLWNQGRADEVVVSASVRSGDLWIPVKSFD	60
MAARPLVSPARALLLALAGALLAPCEARGVSLWNQGRADEVVVSASVRSGDLWIPVKSFD	60
MAARPLVSPARALLLALAGALLAPCEARGVSLWNQGRADEVVVSASVRSGDLWIPVKSFD	60
MAARPLVSPARALLLALAGALLAPCEARGVSLWNQGRADEVVVSASVRSGDLWIPVKSFD	60
MAARPLVSPARALLLALAGALLAPCEARGVSLWNQGRADEVVVSASVRSGDLWIPVKSFD	60
MAARPLVSPARALLLALAGALLAPCEARGVSLWNQGRADEVVVSASVRSGDLWIPVKSFD	60
MAARPLVSPARALLLALAGALLAPCEARGVSLWNQGRADEVVVSASVRSGDLWIPVKSFD	60
*****;*****	
SKNHPEVINIRLORESKELIINLERNEGLIASSFTETHYLODGTVDVSLARNYT---GHCY	117
SKNHPEVINIRLORESKELIINLERNEGLIASSFTETHYLODGTVDVSLARNYT---GHCY	120
SKNHPEVINIRLORESKELIINLERNEGLIASSFTETHYLODGTVDVSLARNYT---GHCY	117
SKNHPEVINIRLORESKELIINLERNEGLIASSFTETHYLODGTVDVSLARNYT---GHCY	117
SKNHPEVINIRLORESKELIINLERNEGLIASSFTETHYLODGTVDVSLARNYT---GHCY	117
SKNHPEVINIRLORESKELIINLERNEGLIASSFTETHYLODGTVDVSLARNYT---GHCY	117
SKNHPEVINIRLORESKELIINLERNEGLIASSFTETHYLODGTVDVSLARNYT---GHCY	117

YGHVVRGYSDSAVSLSTCSGLRGLIIVFENESVYLEPMKSATNRYKLPAPAKLKSVRSGCG	177
YGHVVRGYSDSAVSLSTCSGLRGLIIVFENESVYLEPMKSATNRYKLPAPAKLKSVRSGCG	180
YGHVVRGYSDSAVSLSTCSGLRGLIIVFENESVYLEPMKSATNRYKLPAPAKLKSVRSGCG	177
YGHVVRGYSDSAVSLSTCSGLRGLIIVFENESVYLEPMKSATNRYKLPAPAKLKSVRSGCG	177
YGHVVRGYSDSAVSLSTCSGLRGLIIVFENESVYLEPMKSATNRYKLPAPAKLKSVRSGCG	177
YGHVVRGYSDSAVSLSTCSGLRGLIIVFENESVYLEPMKSATNRYKLPAPAKLKSVRSGCG	177
YGHVVRGYSDSAVSLSTCSGLRGLIIVFENESVYLEPMKSATNRYKLPAPAKLKSVRSGCG	180

SHHNTPNLAAKNVPPPPSQTWARRHKKRETLKATKYVELIVADNREFORQGDLEKVKQR	237
SHHNTPNLAAKNVPPPPSQTWARRHKKRETLKATKYVELIVADNREFORQGDLEKVKQR	240
SHHNTPNLAAKNVPPPPSQTWARRHKKRETLKATKYVELIVADNREFORQGDLEKVKQR	237
SHHNTPNLAAKNVPPPPSQTWARRHKKRETLKATKYVELIVADNREFORQGDLEKVKQR	237
SHHNTPNLAAKNVPPPPSQTWARRHKKRETLKATKYVELIVADNREFORQGDLEKVKQR	237
SHHNTPNLAAKNVPPPPSQTWARRHKKRETLKATKYVELIVADNREFORQGDLEKVKQR	237
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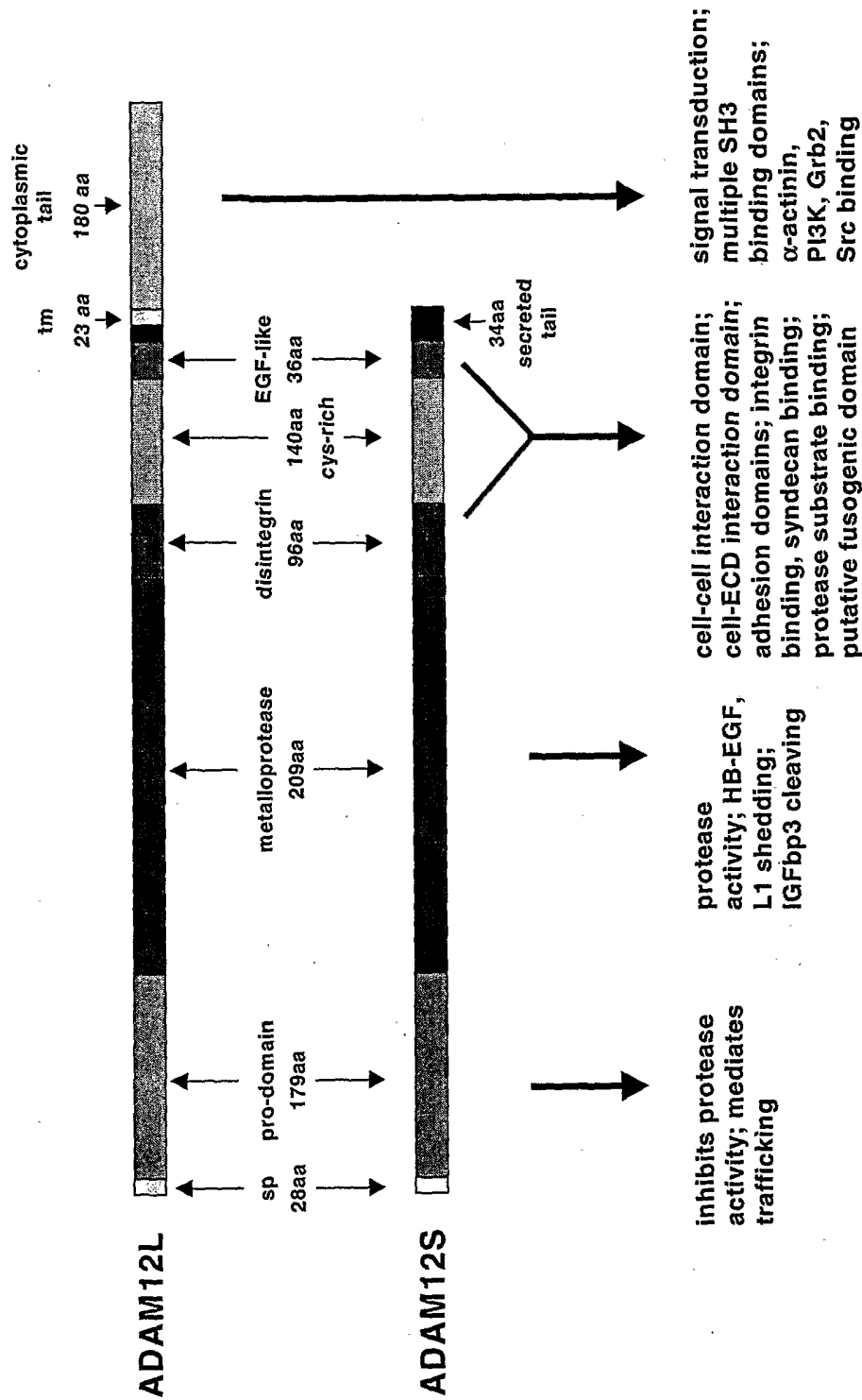


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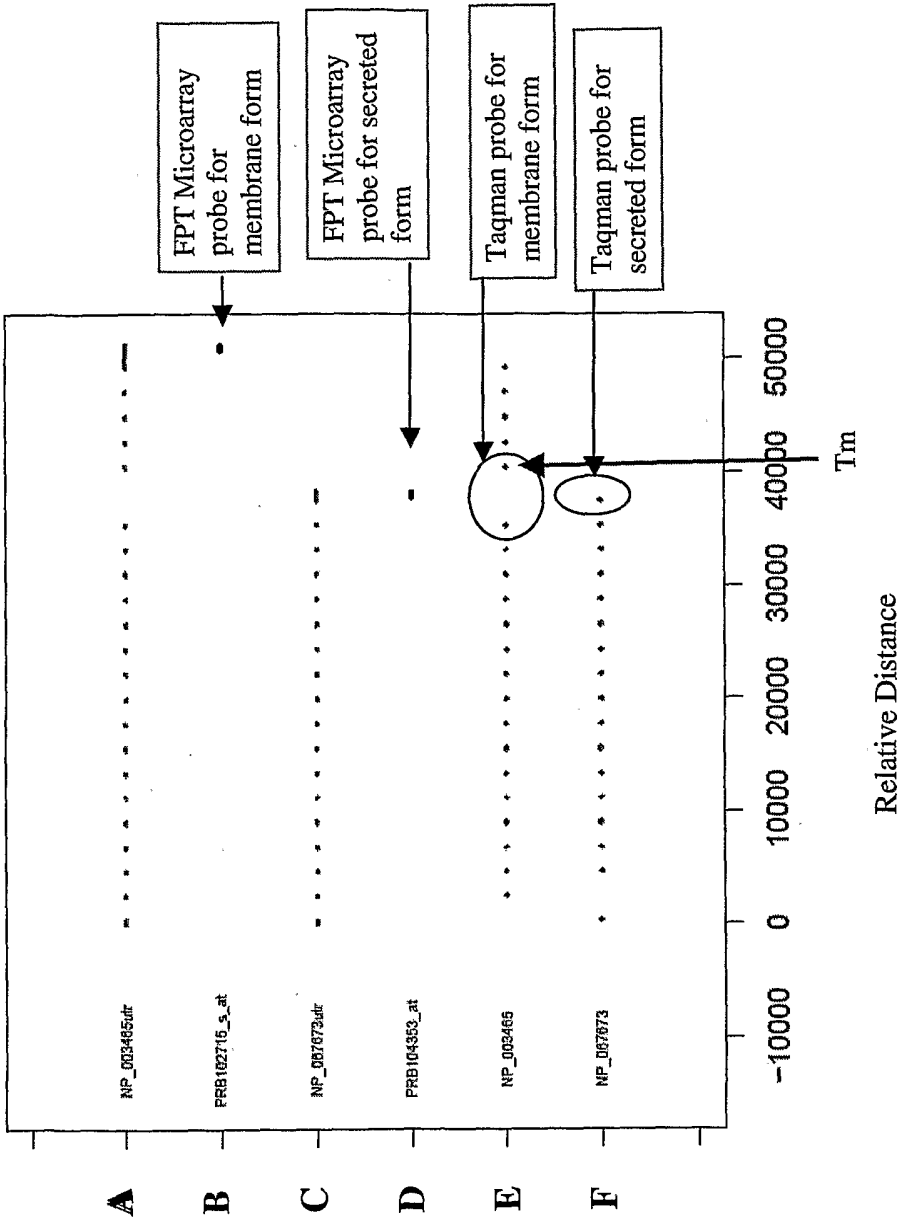


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ADAM12

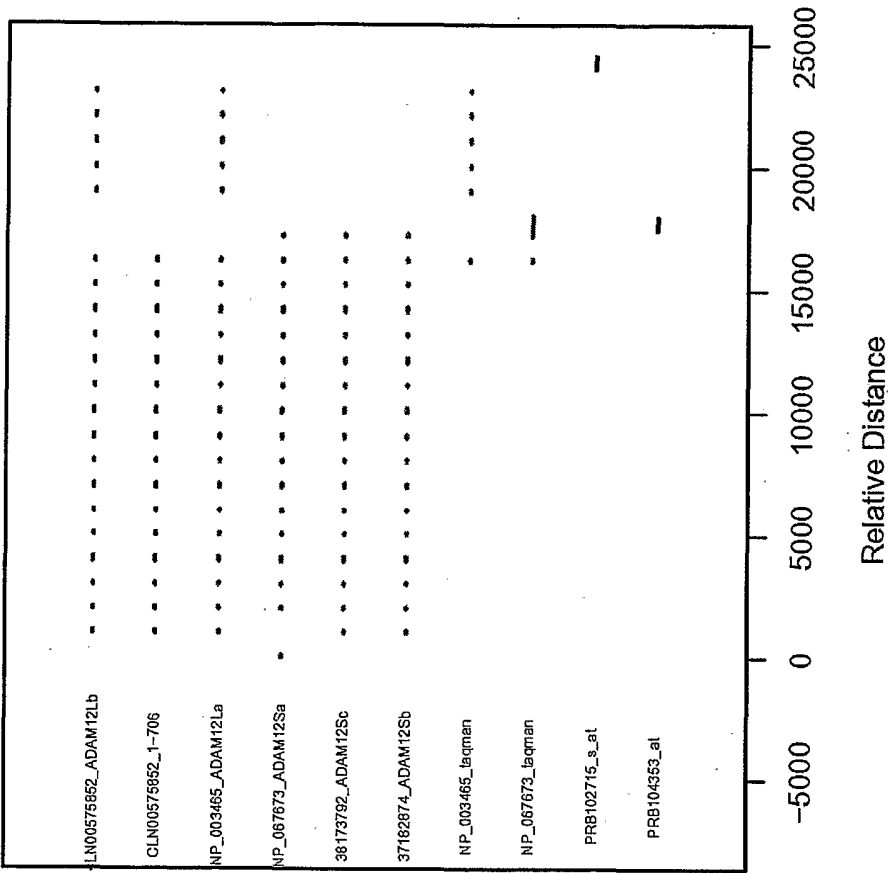


Figure 3b

[illegible]

Figure 3c

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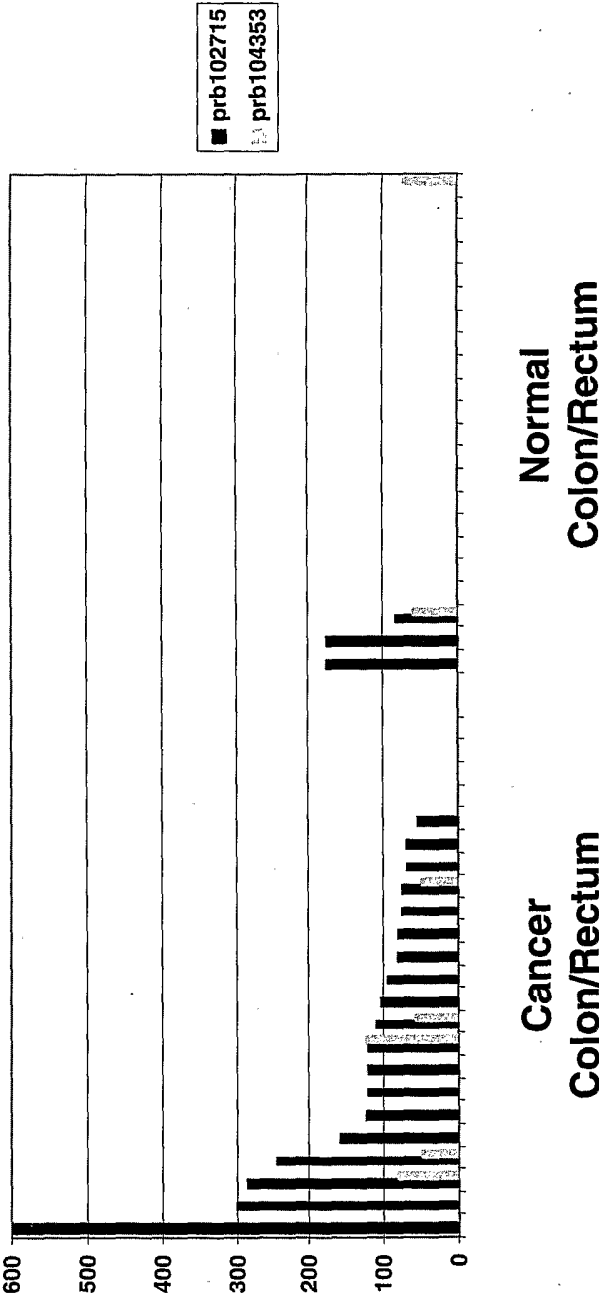


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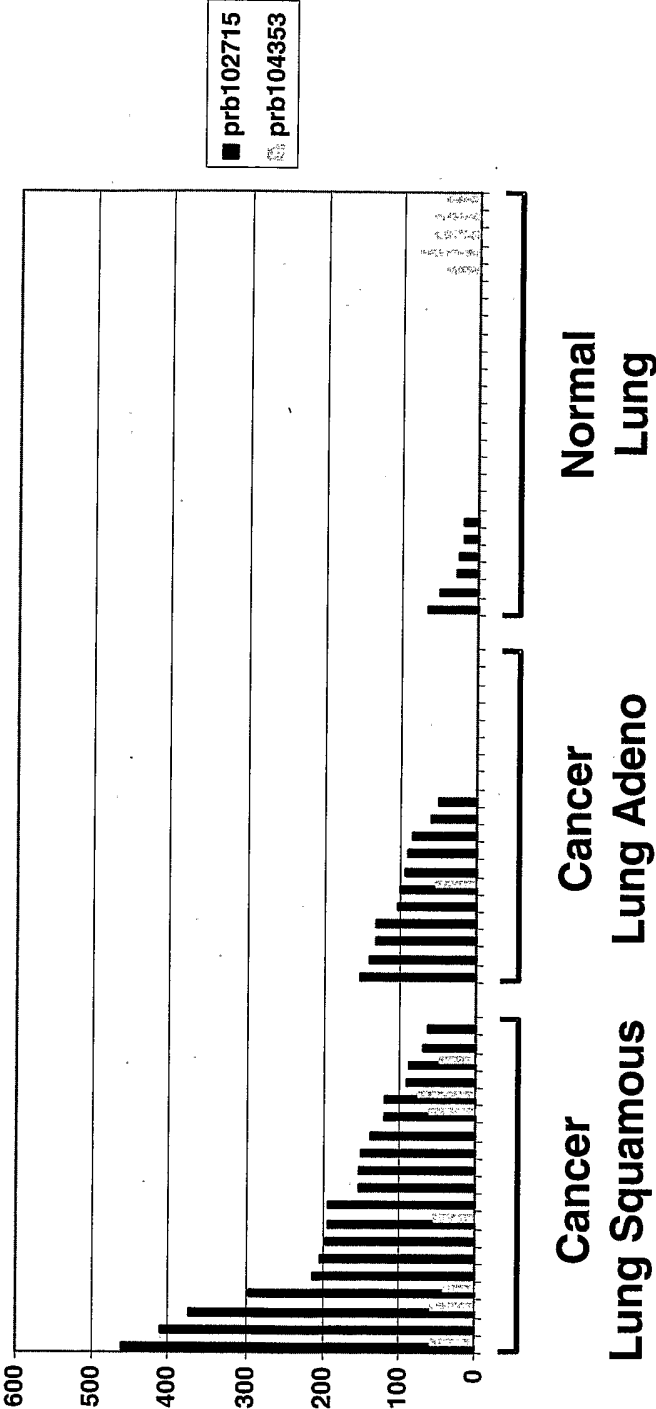


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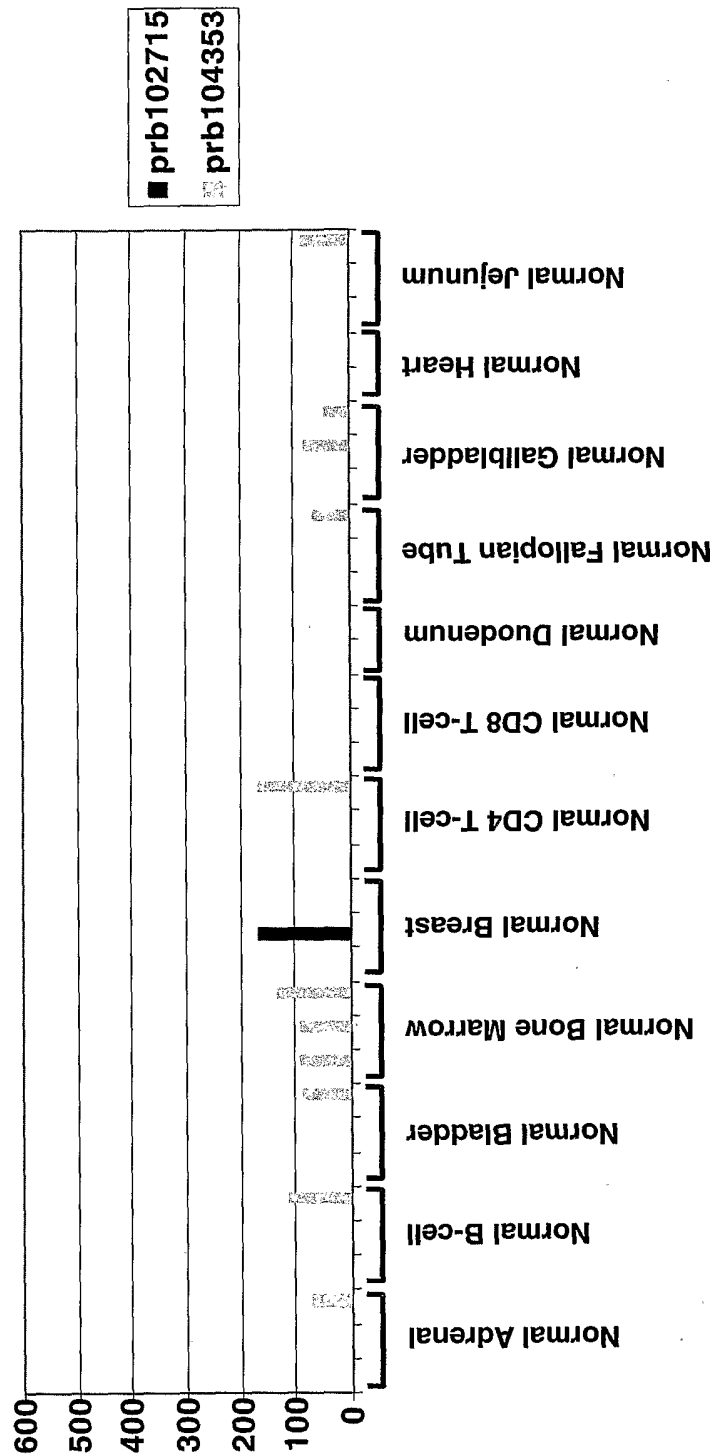


Figure 6a

12/29

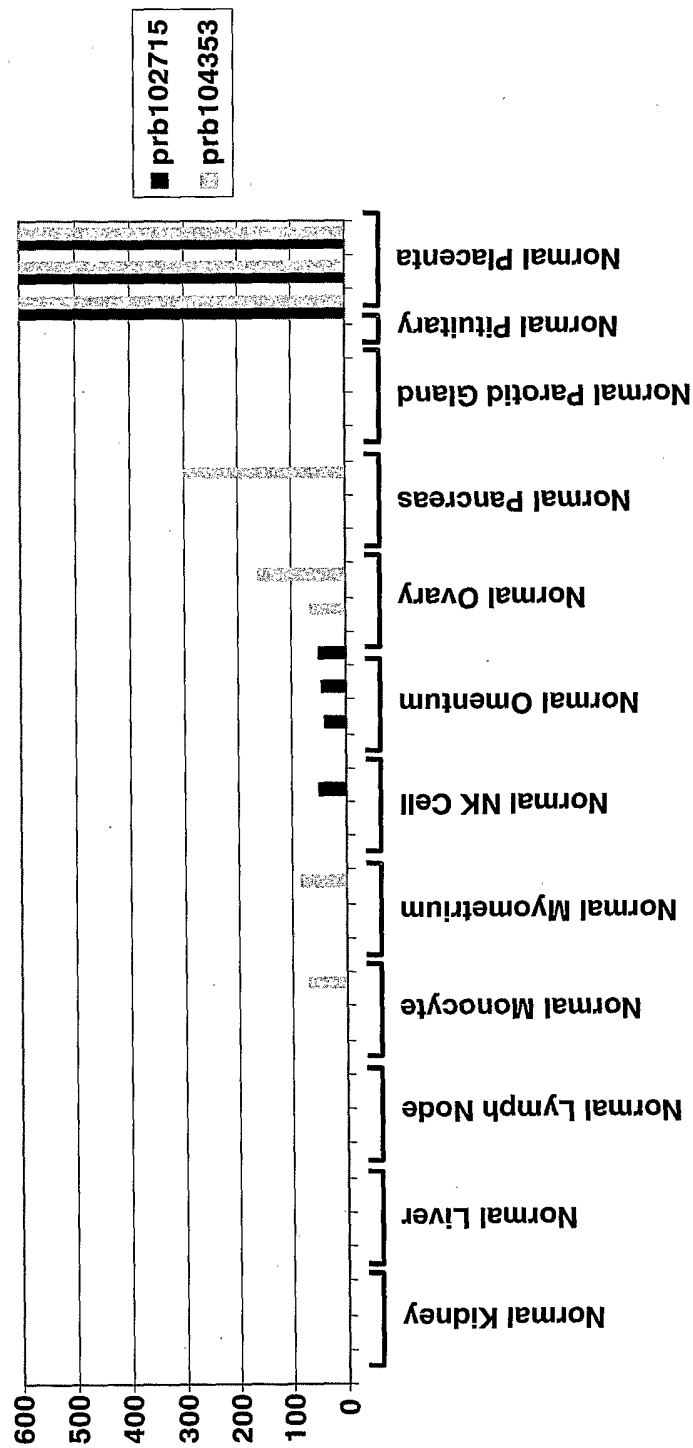


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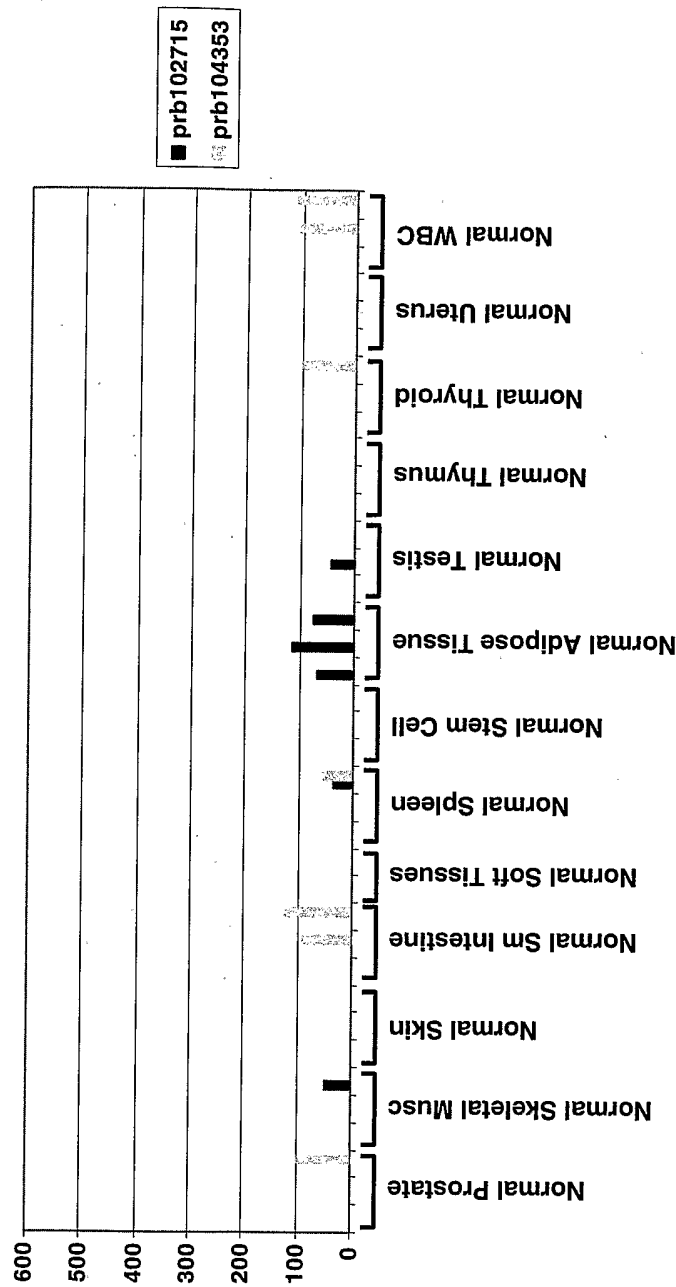


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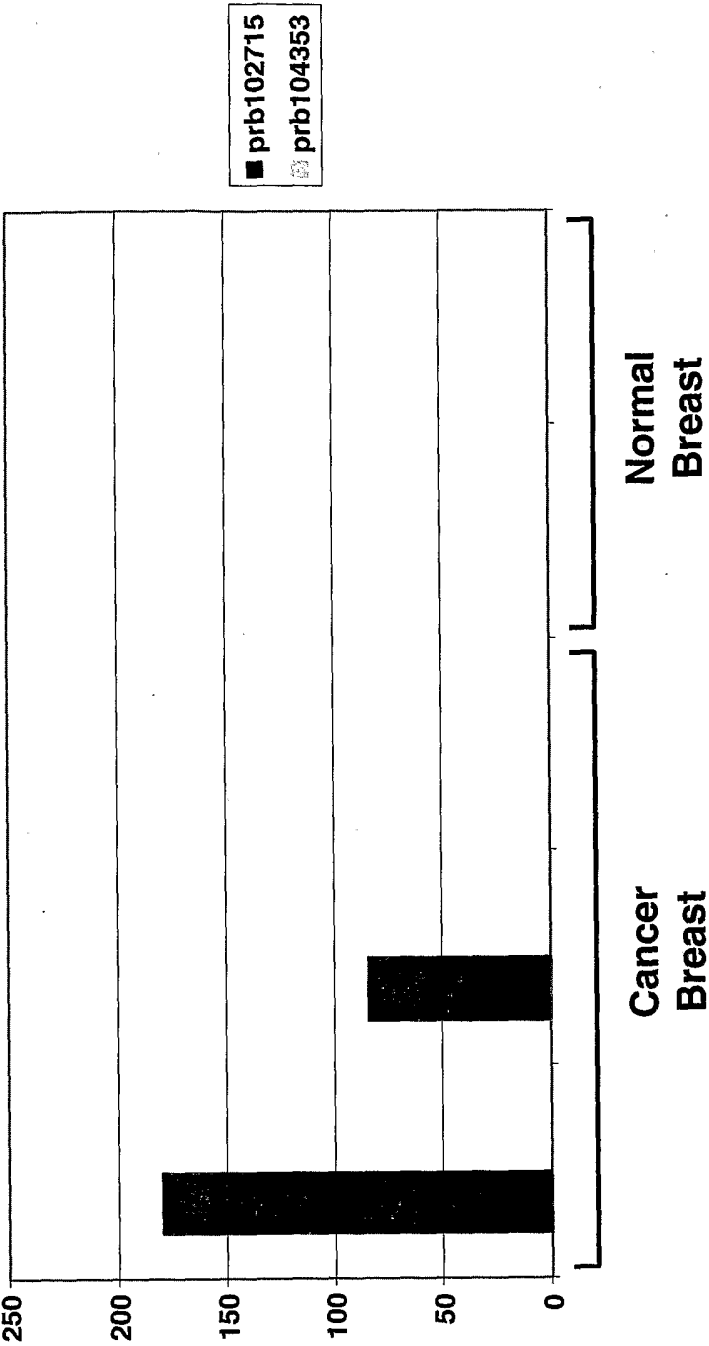
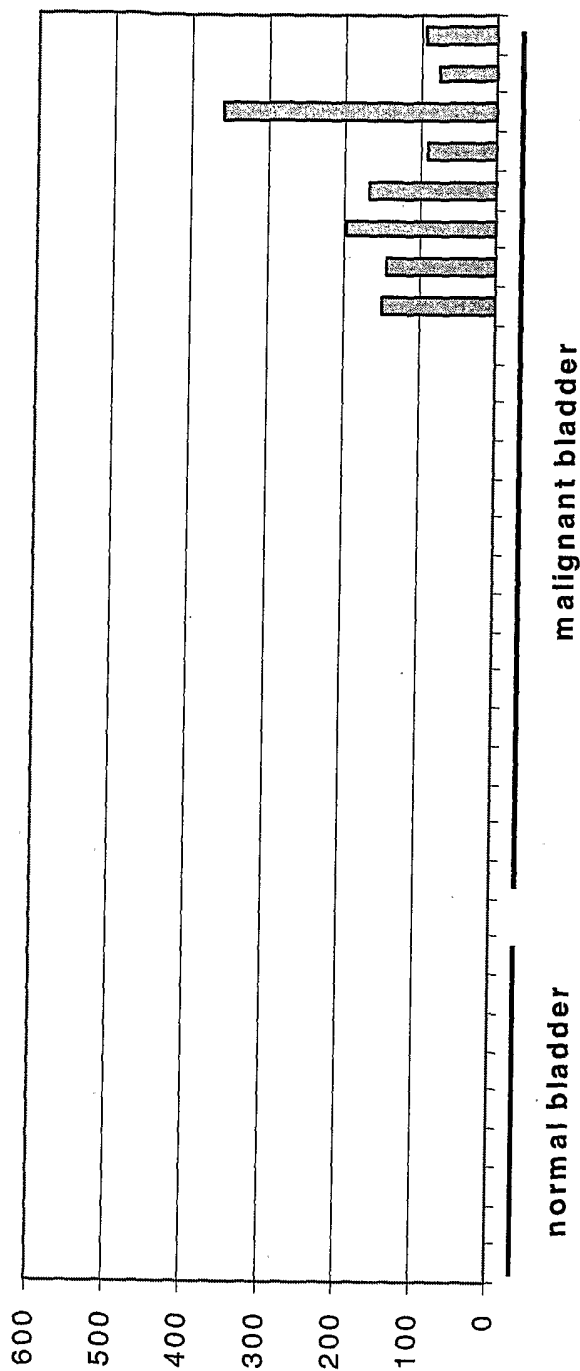


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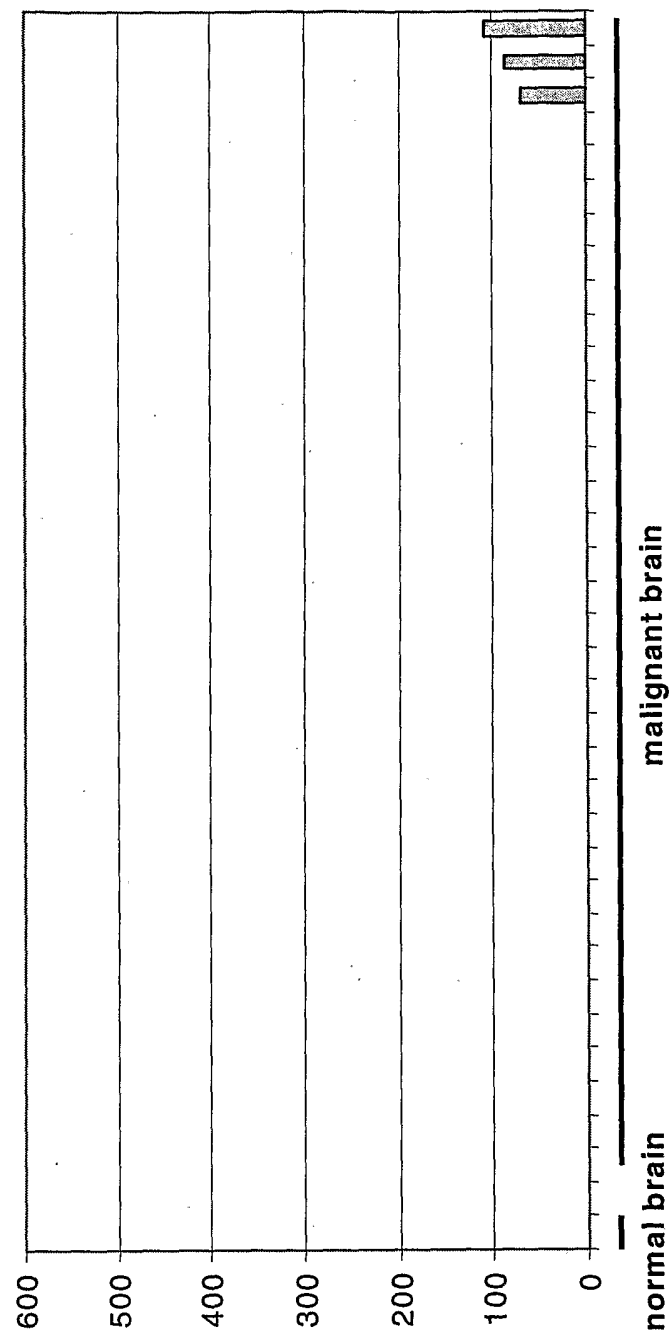


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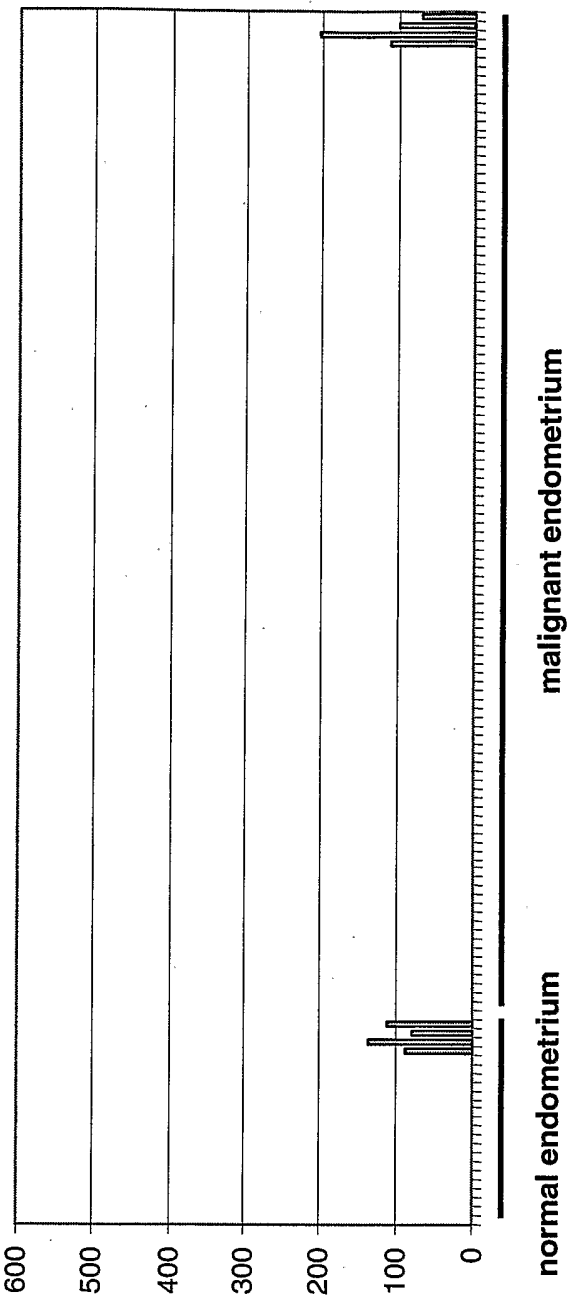


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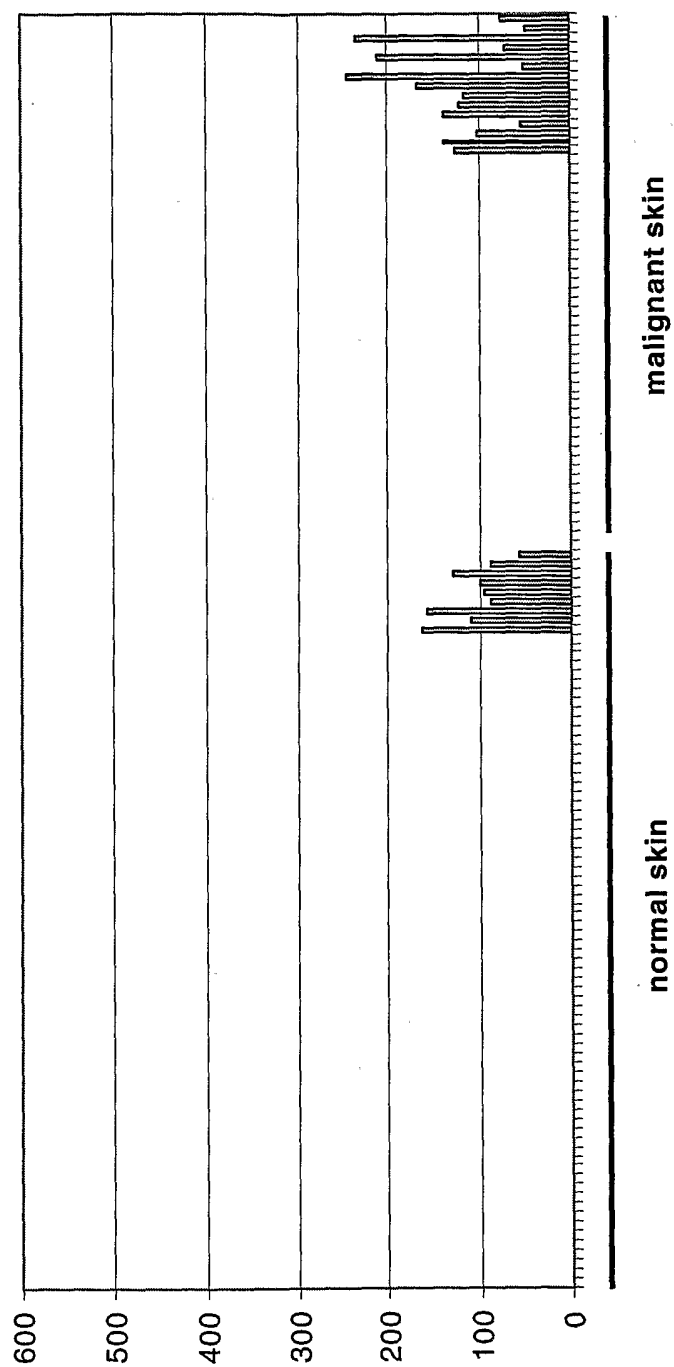


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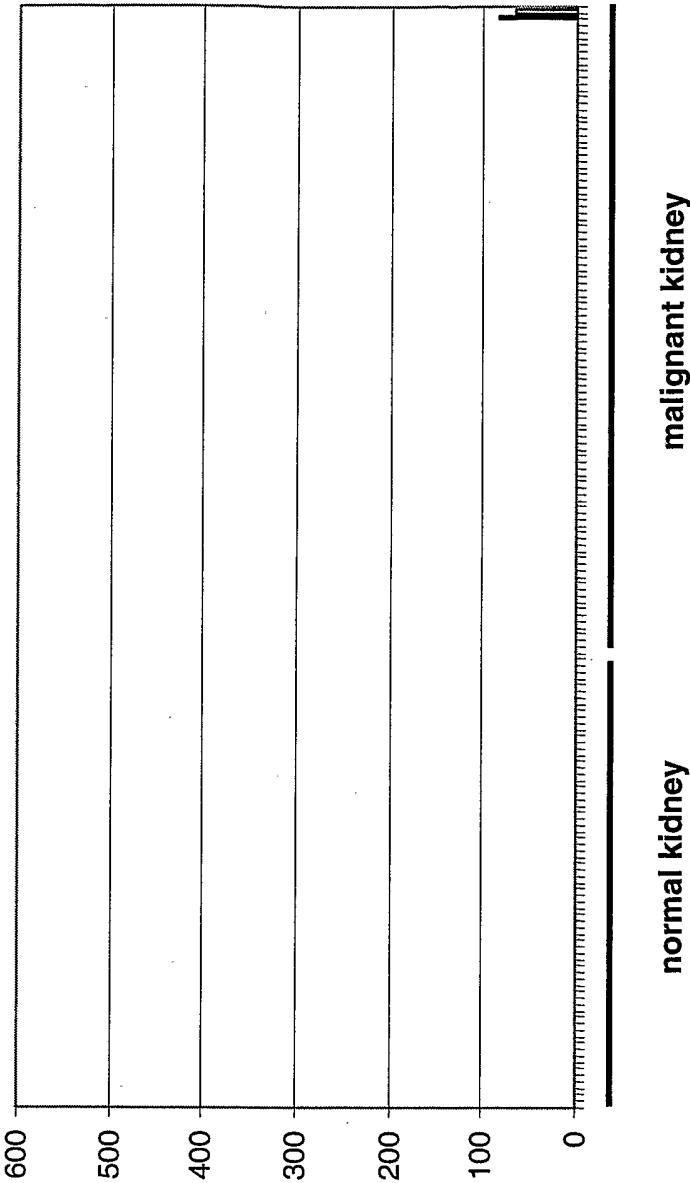


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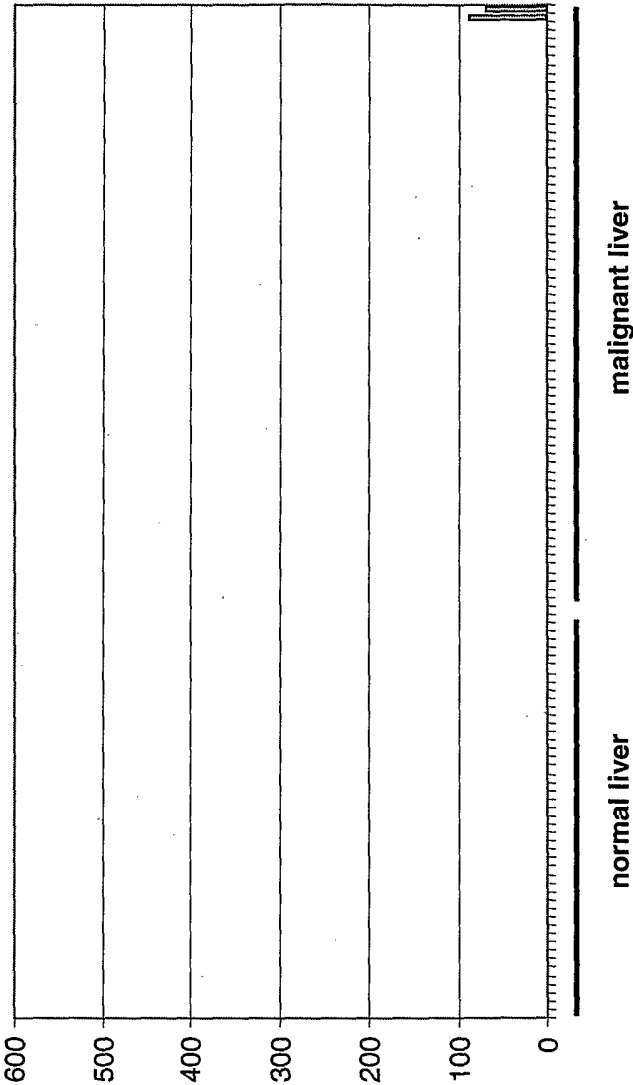


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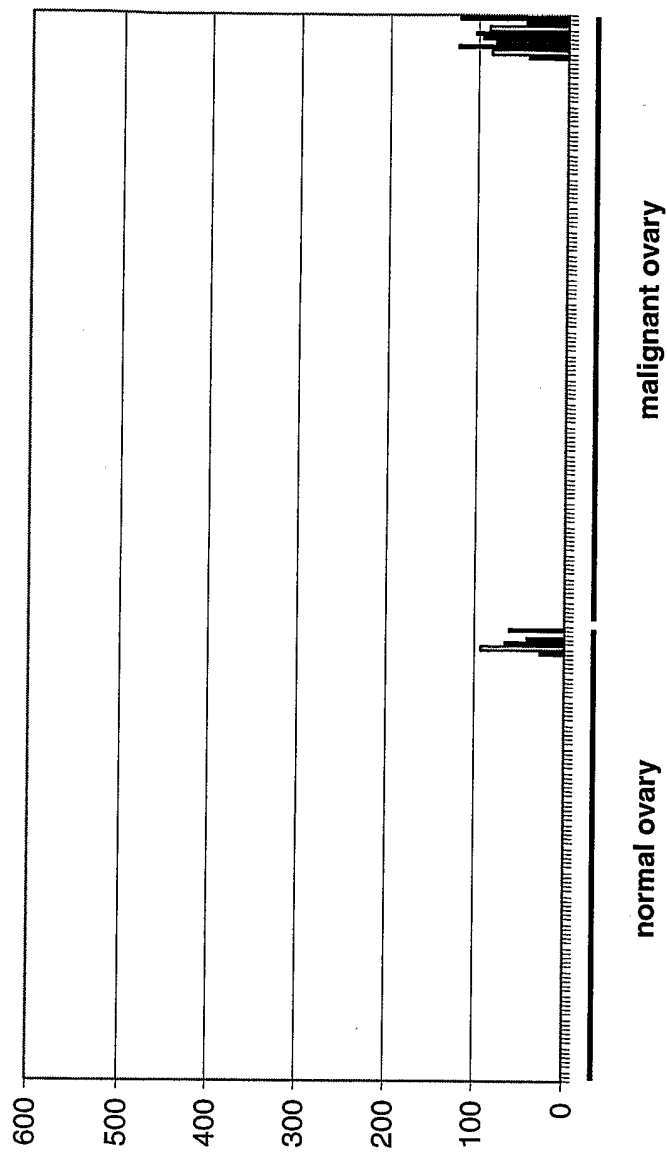


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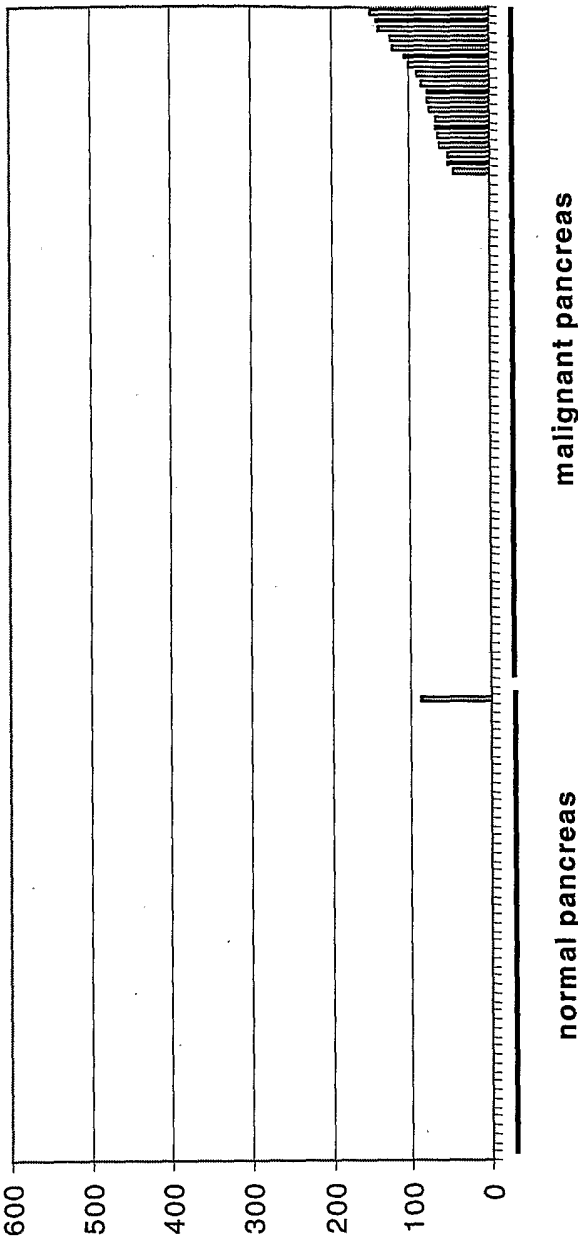


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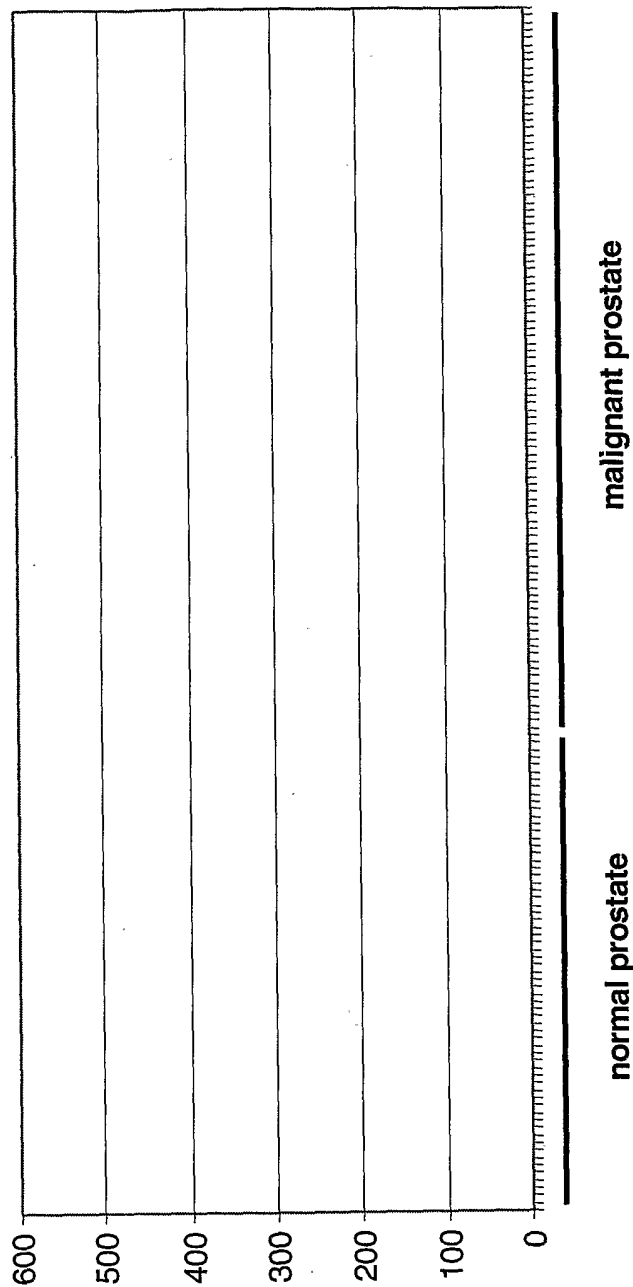


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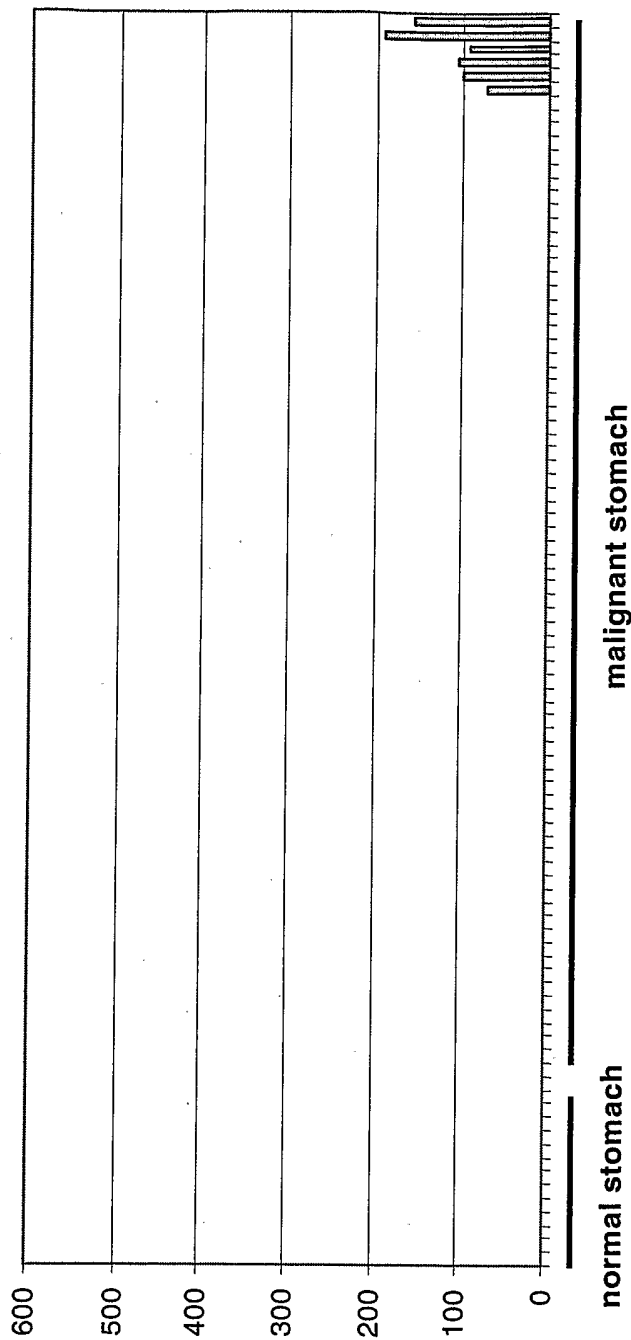


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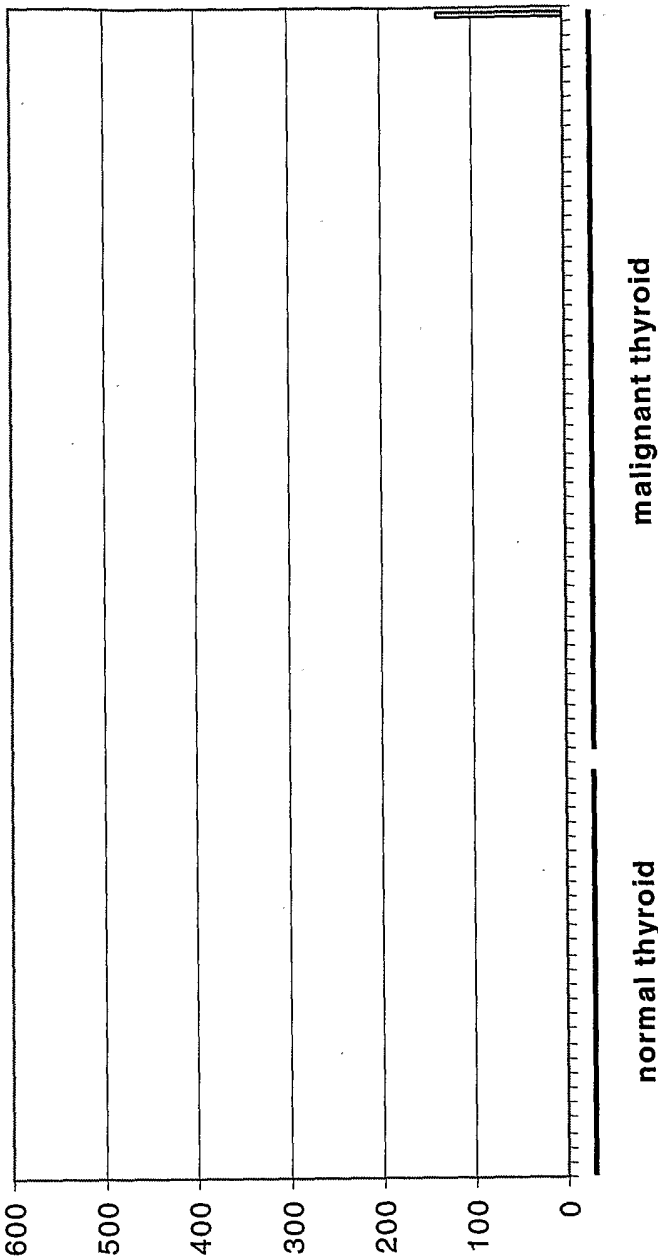


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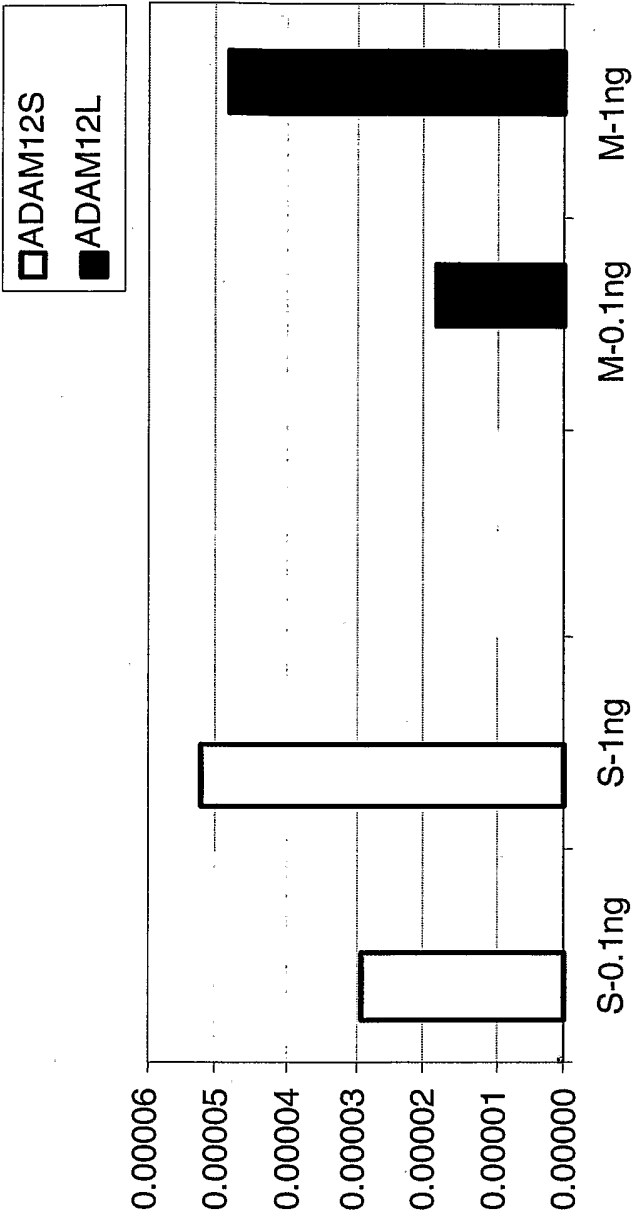


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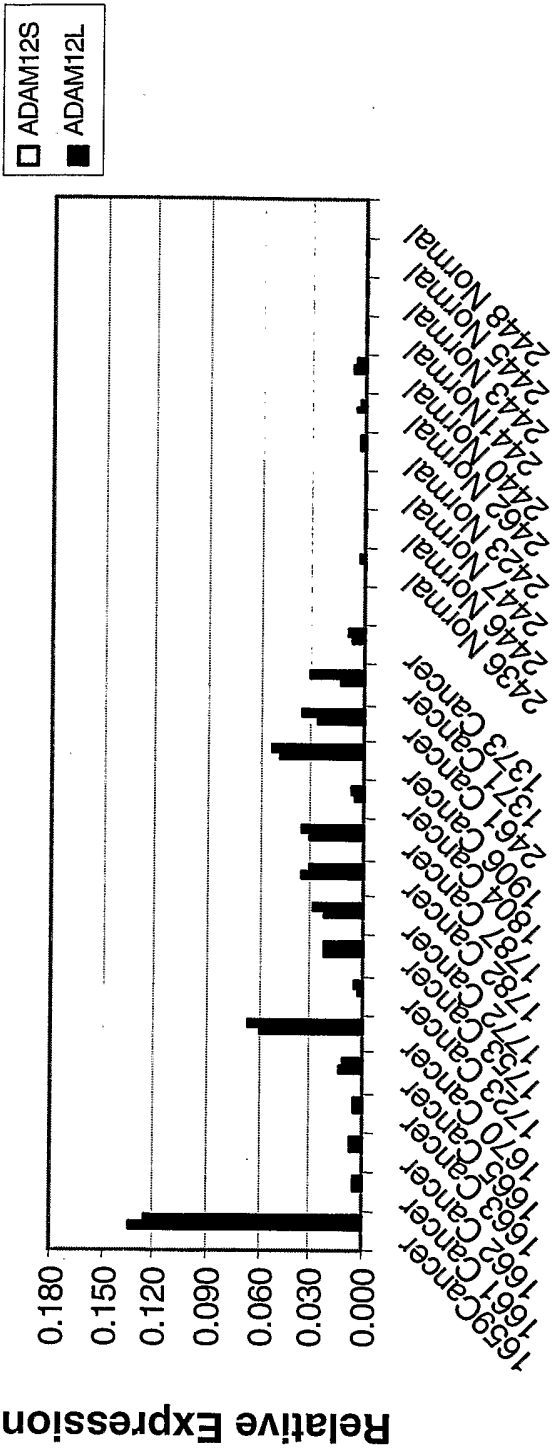


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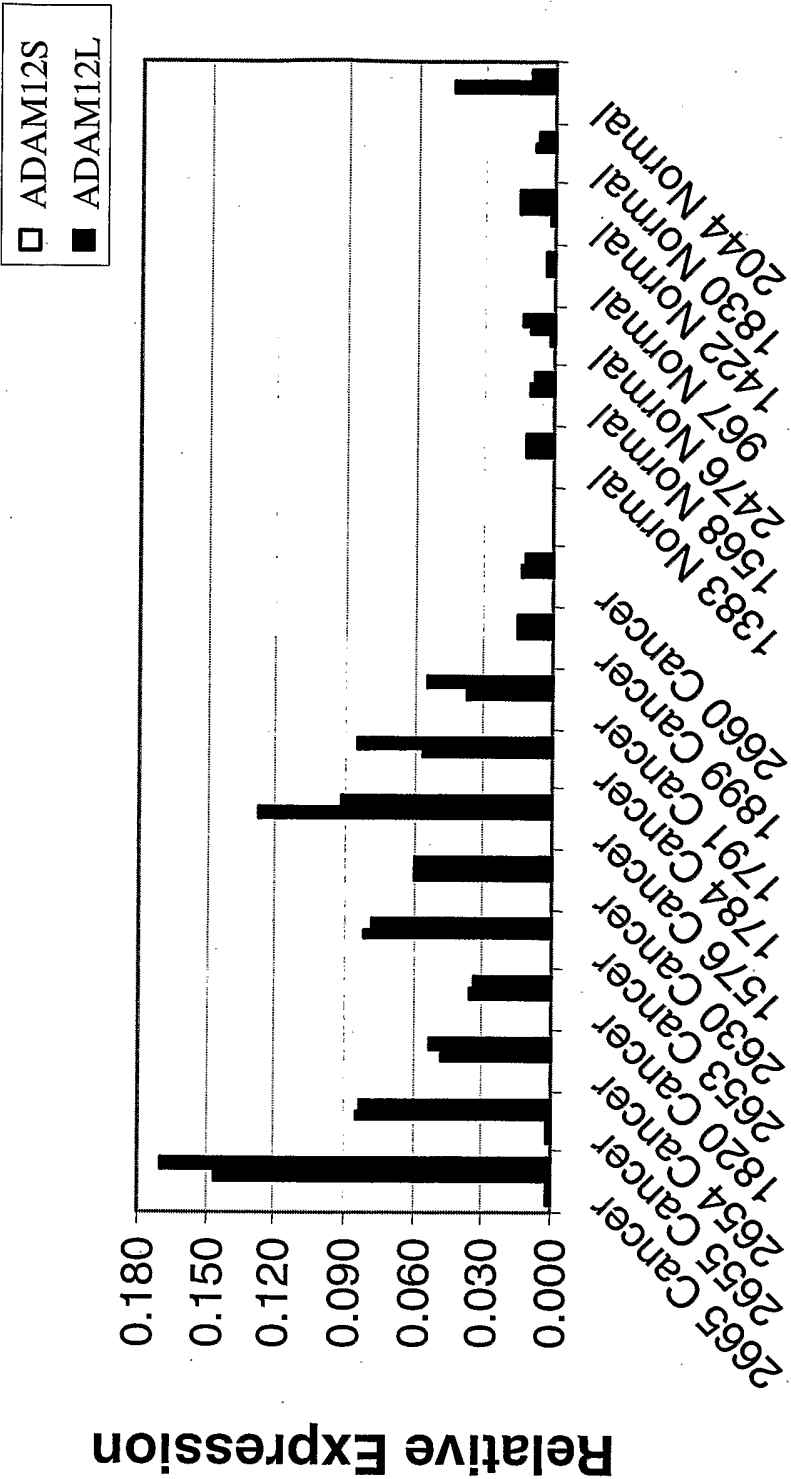


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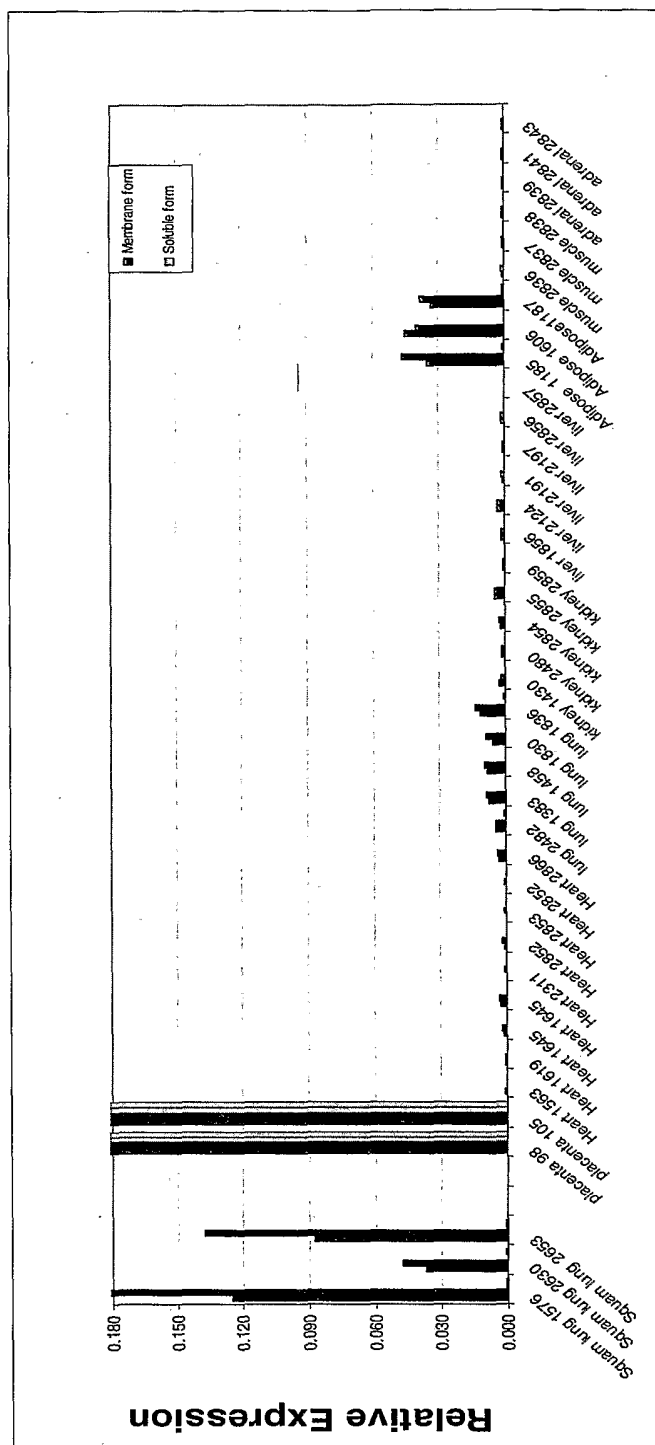


Figure 22

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cgacttcctg gttgagcttc tgcta 25

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gaaagggcgg tgaactctgg ctctt 25

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<400> 10
gtcaccaacc cttcatttaa caagt 25

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<400> 12
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<400> 13
ttggcagccc tgatgactgg totct 25

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gtagcagggt accactctgg caggccccag ccctgcagca aggaggaaga ggactcaaaa 120
gtctggcctt tctagagcc tccacagcag tgggggagaa gcaaggggtg ggcccagtgt 180
cccctttccc cagtgcaccc tccgccttgg cagccctgat gactgggtctc tggctgcaac 240
ttaatgctct gatatggctt ttagcattta ttatatgaaa atagcagggt tttagttttt 300
aatattatcag agaccctgcc acccattcca tctccatcca agcaaactga atggcattga 360
aacaactgg agaagaagg aggagaaagg gcggtgaact ctggctcttt gctgtggaca 420
tgcgtgacca gcagtactca ggtttgaggg tttgcagaaa gccaggaac ccacagagtc 480
accaaccctt catttaacaa gt 502

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gcgctccctg ttggactct 19

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cagaagcaag gcaggaa 17

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ccggcaagca gataaccaa 19

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atcctgtgtc ttcttgctgc c 21

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

Leu Trp Asn Glu Gly Arg Ala Asp Glu Val Val Ser Ala Ser Val Arg
 35 40 45

Ser Gly Asp Leu Trp Ile Pro Val Lys Ser Phe Asp Ser Lys Asn His
 50 55 60

Pro Glu Val Leu Asn Ile Arg Leu Gln Arg Glu Ser Lys Glu Leu Ile
 65 70 75 80

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

Thr His Tyr Leu Gln Asp Gly Thr Asp Val Ser Leu Ala Arg Asn Tyr
 100 105 110

Thr Val Ile Leu Gly His Cys Tyr Tyr His Gly His Val Arg Gly Tyr
 115 120 125

Ser Asp Ser Ala Val Ser Leu Ser Thr Cys Ser Gly Leu Arg Gly Leu
 130 135 140

Ile Val Phe Glu Asn Glu Ser Tyr Val Leu Glu Pro Met Lys Ser Ala
 145 150 155 160

Thr Asn Arg Tyr Lys Leu Phe Pro Ala Lys Lys Leu Lys Ser Val Arg
 165 170 175

Gly Ser Cys Gly Ser His His Asn Thr Pro Asn Leu Ala Ala Lys Asn
 180 185 190

Val Phe Pro Pro Pro Ser Gln Thr Trp Ala Arg Arg His Lys Arg Glu
 195 200 205

Thr Leu Lys Ala Thr Lys Tyr Val Glu Leu Val Ile Val Ala Asp Asn
 210 215 220

Arg Glu Phe Gln Arg Gln Gly Lys Asp Leu Glu Lys Val Lys Gln Arg
 225 230 235 240

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Leu Ile Glu Ile Ala Asn His Val Asp Lys Phe Tyr Arg Pro Leu Asn
 245 250 255

Ile Arg Ile Val Leu Val Gly Val Glu Val Trp Asn Asp Met Asp Lys
 260 265 270

Cys Ser Val Ser Gln Asp Pro Phe Thr Ser Leu His Glu Phe Leu Asp
 275 280 285

Trp Arg Lys Met Lys Leu Leu Pro Arg Lys Ser His Asp Asn Ala Gln
 290 295 300

Leu Val Ser Gly Val Tyr Phe Gln Gly Thr Thr Ile Gly Met Ala Pro
 305 310 315 320

Ile Met Ser Met Cys Thr Ala Asp Gln Ser Gly Gly Ile Val Met Asp
 325 330 335

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

Gly His Asn Phe Gly Met Asn His Asp Thr Leu Asp Arg Gly Cys Ser
 355 360 365

Cys Gln Met Ala Val Glu Lys Gly Gly Cys Ile Met Asn Ala Ser Thr
 370 375 380

Gly Tyr Pro Phe Pro Met Val Phe Ser Ser Cys Ser Arg Lys Asp Leu
 385 390 395 400

Glu Thr Ser Leu Glu Lys Gly Met Gly Val Cys Leu Phe Asn Leu Pro
 405 410 415

Glu Val Arg Glu Ser Phe Gly Gly Gln Lys Cys Gly Asn Arg Phe Val
 420 425 430

Glu Glu Gly Glu Glu Cys Asp Cys Gly Glu Pro Glu Glu Cys Met Asn
 435 440 445

Arg Cys Cys Asn Ala Thr Thr Cys Thr Leu Lys Pro Asp Ala Val Cys
 450 455 460

Ala His Gly Leu Cys Cys Glu Asp Cys Gln Leu Lys Pro Ala Gly Thr
 465 470 475 480

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Ala Cys Arg Asp Ser Ser Asn Ser Cys Asp Leu Pro Glu Phe Cys Thr
 485 490 495

Gly Ala Ser Pro His Cys Pro Ala Asn Val Tyr Leu His Asp Gly His
 500 505 510

Ser Cys Gln Asp Val Asp Gly Tyr Cys Tyr Asn Gly Ile Cys Gln Thr
 515 520 525

His Glu Gln Gln Cys Val Thr Leu Trp Gly Pro Gly Ala Lys Pro Ala
 530 535 540

Pro Gly Ile Cys Phe Glu Arg Val Asn Ser Ala Gly Asp Pro Tyr Gly
 545 550 555 560

Asn Cys Gly Lys Val Ser Lys Ser Ser Phe Ala Lys Cys Glu Met Arg
 565 570 575

Asp Ala Lys Cys Gly Lys Ile Gln Cys Gln Gly Gly Ala Ser Arg Pro
 580 585 590

Val Ile Gly Thr Asn Ala Val Ser Ile Glu Thr Asn Ile Pro Leu Gln
 595 600 605

Gln Gly Gly Arg Ile Leu Cys Arg Gly Thr His Val Tyr Leu Gly Asp
 610 615 620

Asp Met Pro Asp Pro Gly Leu Val Leu Ala Gly Thr Lys Cys Ala Asp
 625 630 635 640

Gly Lys Ile Cys Leu Asn Arg Gln Cys Gln Asn Ile Ser Val Phe Gly
 645 650 655

Val His Glu Cys Ala Met Gln Cys His Gly Arg Gly Val Cys Asn Asn
 660 665 670

Arg Lys Asn Cys His Cys Glu Ala His Trp Ala Pro Pro Phe Cys Asp
 675 680 685

Lys Phe Gly Phe Gly Gly Ser Thr Asp Ser Gly Pro Ile Arg Gln Ala
 690 695 700

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Glu Ala Arg Gln Glu Ala Ala Glu Ser Asn Arg Glu Arg Gly Gln Gly
705 710 715 720

Gln Glu Pro Val Gly Ser Gln Glu His Ala Ser Thr Ala Ser Leu Thr
725 730 735

Leu Ile

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1 5 10 15

Asp Thr Leu Asp Arg Gly
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Ala Val Thr Leu Ala His
1 5

<210> 24
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<400> 24
Val Thr Leu Ala His Glu
1 5

<210> 25
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<400> 25
Thr Leu Ala His Glu Leu
1 5

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<210> 26
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<400> 26
Leu Ala His Glu Leu Gly
1 5

<210> 27
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<400> 27
Ala His Glu Leu Gly His
1 5

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<400> 28
His Glu Leu Gly His Asn
1 5

<210> 29
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<400> 29
Glu Leu Gly His Asn Phe
1 5

<210> 30
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<400> 30
Leu Gly His Asn Phe Gly
1 5

<210> 31
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<400> 31
Gly His Asn Phe Gly Met
1 5

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<210> 32
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<400> 32
His Asn Phe Gly Met Asn
1 5

<210> 33
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1 5 10 15

Pro Met Val Phe
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Val Glu Lys Gly Gly Cys
1 5

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Glu Lys Gly Gly Cys Ile
1 5

<210> 36
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<400> 36
Lys Gly Gly Cys Ile Met
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13/124

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<400> 37
Gly Gly Cys Ile Met Asn
1 5

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<400> 38
Gly Cys Ile Met Asn Ala
1 5

<210> 39
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<400> 39
Cys Ile Met Asn Ala Ser
1 5

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Ile Met Asn Ala Ser Thr
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Met Asn Ala Ser Thr Gly
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Asn Ala Ser Thr Gly Tyr
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Thr Gly Tyr Pro Phe Pro
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<400> 47
Tyr Pro Phe Pro Met Val
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<210> 48
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Gly Thr Thr Ile Gly Met
1 5

<210> 53
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<400> 53
Thr Thr Ile Gly Met Ala
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16/124

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Gly Met Ala Pro Ile Met
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Met Ala Pro Ile Met Ser
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<400> 58
Ala Pro Ile Met Ser Met
1 5

<210> 59
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<400> 59

Pro Ile Met Ser Met Cys
1 5

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Ile Met Ser Met Cys Thr
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<213> Homo sapiens

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Phe Pro Met Val Phe Ser Ser Cys Ser Arg Lys Asp Leu Glu
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<400> 63

Phe Pro Met Val Phe Ser
1 5

<210> 64

<211> 6

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Pro Met Val Phe Ser Ser
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18/124

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<210> 66
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Val Phe Ser Ser Cys Ser
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<400> 67
Phe Ser Ser Cys Ser Arg
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<210> 68
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<400> 69
Ser Cys Ser Arg Lys Asp
1 5

<210> 70
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Cys Ser Arg Lys Asp Leu
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19/124

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<400> 71
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<210> 72
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Pro Phe Thr Ser Leu His
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Gly Val Glu Val Trp Asn
1 5

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Val Glu Val Trp Asn Asp
1 5

<210> 75
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Glu Val Trp Asn Asp Met
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20/124

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Trp Asn Asp Met Asp Lys
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Asp Met Asp Lys Cys Ser
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Met Asp Lys Cys Ser Val
1 5

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<400> 81
Asp Lys Cys Ser Val Ser
1 5

21/124

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Lys Cys Ser Val Ser Gln
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Cys Ser Val Ser Gln Asp
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Ser Val Ser Gln Asp Pro
1 5

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Val Ser Gln Asp Pro Phe
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<213> Homo sapiens

<400> 86
Ser Gln Asp Pro Phe Thr
1 5

<210> 87
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<400> 87

Gln Asp Pro Phe Thr Ser
1 5

<210> 88

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<213> Homo sapiens

<400> 88

Asp Pro Phe Thr Ser Leu
1 5

<210> 89

<211> 6

<212> PRT

<213> Homo sapiens

<400> 89

Pro Phe Thr Ser Leu His
1 5

<210> 90

<211> 24

<212> PRT

<213> Homo sapiens

<400> 90

Pro Ala Gly Thr Ala Cys Arg Asp Ser Ser Asn Ser Cys Asp Leu Pro
1 5 10 15

Glu Phe Cys Thr Gly Ala Ser Pro
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<212> PRT

<213> Homo sapiens

<400> 91

Pro Ala Gly Thr Ala Cys
1 5

<210> 92

<211> 6

<212> PRT

<213> Homo sapiens

<400> 92

Ala Gly Thr Ala Cys Arg
1 5

23/124

<210> 93
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<400> 93
Gly Thr Ala Cys Arg Asp
1 5

<210> 94
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<400> 94
Thr Ala Cys Arg Asp Ser
1 5

<210> 95
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Ala Cys Arg Asp Ser Ser
1 5

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Cys Arg Asp Ser Ser Asn
1 5

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<400> 97
Arg Asp Ser Ser Asn Ser
1 5

<210> 98
<211> 6
<212> PRT
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<400> 98
Asp Ser Ser Asn Ser Cys
1 5

<210> 99
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<400> 99
Ser Ser Asn Ser Cys Asp
1 5

<210> 100
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Ser Asn Ser Cys Asp Leu
1 5

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Asn Ser Cys Asp Leu Pro
1 5

<210> 102
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<400> 102
Ser Cys Asp Leu Pro Glu
1 5

<210> 103
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<400> 103
Cys Asp Leu Pro Glu Phe
1 5

25/124

<210> 104
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<400> 104
Asp Leu Pro Glu Phe Cys
1 5

<210> 105
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Leu Pro Glu Phe Cys Thr
1 5

<210> 106
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Pro Glu Phe Cys Thr Gly
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<400> 107
Glu Phe Cys Thr Gly Ala
1 5

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<400> 108
Phe Cys Thr Gly Ala Ser
1 5

<210> 109
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<400> 109
Cys Thr Gly Ala Ser Pro
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26/124

<210> 110
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Ala Lys Pro Ala Pro Gly Ile Cys Phe Glu Arg Val Asn Ser Ala Gly
1 5 10 15

Asp Pro Tyr Gly Asn Cys Gly Lys Val Ser Lys Ser Ser Phe Ala Lys
20 25 30

Cys Glu Met Arg Asp Ala Lys Cys Gly Lys Ile Gln Cys Gln Gly Gly
35 40 45

Ala Ser Arg Pro Val
50

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1 5

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Lys Pro Ala Pro Gly Ile
1 5

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<400> 113
Pro Ala Pro Gly Ile Cys
1 5

<210> 114
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<400> 114
Ala Pro Gly Ile Cys Phe
1 5

<210> 115
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Pro Gly Ile Cys Phe Glu
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Gly Ile Cys Phe Glu Arg
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Ile Cys Phe Glu Arg Val
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<400> 118
Cys Phe Glu Arg Val Asn
1 5

<210> 119
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Phe Glu Arg Val Asn Ser
1 5

28/124

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<400> 120
Glu Arg Val Asn Ser Ala
1 5

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Arg Val Asn Ser Ala Gly
1 5

<210> 122
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Val Asn Ser Ala Gly Asp
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Ser Ala Gly Asp Pro Tyr
1 5

<210> 125
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Ala Gly Asp Pro Tyr Gly
1 5

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Gly Asp Pro Tyr Gly Asn
1 5

<210> 127
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Asp Pro Tyr Gly Asn Cys
1 5

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Pro Tyr Gly Asn Cys Gly
1 5

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Tyr Gly Asn Cys Gly Lys
1 5

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<400> 130
Gly Asn Cys Gly Lys Val
1 5

<210> 131
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Asn Cys Gly Lys Val Ser
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<400> 132
Cys Gly Lys Val Ser Lys
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Gly Lys Val Ser Lys Ser
1 5

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Lys Val Ser Lys Ser Ser
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Val Ser Lys Ser Ser Phe
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Ser Lys Ser Ser Phe Ala
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34/124

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35 40

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39/124

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41/124

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35 40

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42/124

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43/124

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Met Gln Cys His Gly Arg
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44/124

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46/124

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Glu Ala His Trp Ala Pro
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48/124

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49/124

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Pro Glu Val Leu Asn Ile
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51/124

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53/124

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<210> 265
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Asn Leu Glu Arg Asn Glu
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54/124

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<210> 271
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1 5 10 15

Val Ser Leu Ala Arg Asn Tyr Thr
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Ala Ser Ser Phe Thr Glu
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Ser Phe Thr Glu Thr His
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<210> 276

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Phe Thr Glu Thr His Tyr
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1 5

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1 5

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Gly His Cys Tyr Tyr
1 5

59/124

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<400> 298
His Gly His Val Arg
1 5

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60/124

<400> 299

Gly His Val Arg Gly
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His Val Arg Gly Tyr
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<211> 32

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<400> 301

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Tyr Ser Asp Ser Ala Val
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Ser Asp Ser Ala Val Ser
1 5

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<400> 304

Asp Ser Ala Val Ser Leu
1 5

61/124

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Ser Ala Val Ser Leu Ser
1 5

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Ser Leu Ser Thr Cys Ser
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Leu Ser Thr Cys Ser Gly
1 5

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1 5

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Cys Ser Gly Leu Arg Gly
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Ser Gly Leu Arg Gly Leu
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Leu Arg Gly Leu Ile Val
1 5

63/124

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64/124

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1 5

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65/124

<400> 327

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Leu Glu Pro Met Lys Ser
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Ala Thr Asn Arg Tyr Lys
1 5

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Thr Asn Arg Tyr Lys Leu
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Asn Arg Tyr Lys Leu Phe
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66/124

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Phe Pro Ala Lys Lys Leu
1 5

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Pro Ala Lys Lys Leu Lys
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67/124

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<400> 339

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Arg Leu Ile Glu Ile Ala Asn His Val Asp Lys Phe Tyr Arg Pro Leu
35 40 45

Asn Ile Arg Ile Val Leu Val Gly Val Glu Val Trp Asn Asp Met Asp
50 55 60

Lys Cys Ser Val Ser Gln Asp Pro Phe Thr Ser Leu His Glu Phe Leu
65 70 75 80

Asp Trp Arg Lys Met Lys Leu Leu Pro Arg Lys Ser His Asp Asn Ala
85 90 95

Gln Leu Val Ser Gly Val Tyr Phe Gln Gly Thr Thr Ile Gly Met Ala
100 105 110

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

Asp His Ser Asp Asn Pro Leu Gly Ala Ala Val Thr Leu Ala His Glu
130 135 140

Leu Gly His Asn Phe Gly Met Asn His Asp Thr Leu Asp Arg Gly Cys
145 150 155 160

Ser Cys Gln Met Ala Val Glu Lys Gly Gly Cys Ile Met Asn Ala Ser
165 170 175

Thr Gly Tyr Pro Phe Pro Met Val Phe Ser Ser Cys Ser Arg Lys Asp
180 185 190

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

Pro Glu Val Arg Glu Ser Phe Gly Gly Gln Lys Cys Gly Asn Arg Phe
 210 215 220

Val Glu Glu Gly Glu Glu Cys Asp Cys Gly Glu Pro Glu Glu Cys Met
 225 230 235 240

Asn Arg Cys Cys Asn Ala Thr Thr Cys Thr Leu Lys Pro Asp Ala Val
 245 250 255

Cys Ala His Gly Leu Cys Cys Glu Asp Cys Gln Leu Lys Pro Ala Gly
 260 265 270

Thr Ala Cys Arg Asp Ser Ser Asn Ser Cys Asp Leu Pro Glu Phe Cys
 275 280 285

Thr Gly Ala Ser Pro His Cys Pro Ala Asn Val Tyr Leu His Asp Gly
 290 295 300

His Ser Cys Gln Asp Val Asp Gly Tyr Cys Tyr Asn Gly Ile Cys Gln
 305 310 315 320

Thr His Glu Gln Gln Cys Val Thr Leu Trp Gly Pro Gly Ala Lys Pro
 325 330 335

Ala Pro Gly Ile Cys Phe Glu Arg Val Asn Ser Ala Gly Asp Pro Tyr
 340 345 350

Gly Asn Cys Gly Lys Val Ser Lys Ser Ser Phe Ala Lys Cys Glu Met
 355 360 365

Arg Asp Ala Lys Cys Gly Lys Ile Gln Cys Gln Gly Gly Ala Ser Arg
 370 375 380

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

Gln Gln Gly Gly Arg Ile Leu Cys Arg Gly Thr His Val Tyr Leu Gly
 405 410 415

Asp Asp Met Pro Asp Pro Gly Leu Val Leu Ala Gly Thr Lys Cys Ala
 420 425 430

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Asp Gly Lys Ile Cys Leu Asn Arg Gln Cys Gln Asn Ile Ser Val Phe
 435 440 445

Gly Val His Glu Cys Ala Met Gln Cys His Gly Arg Gly Val Cys Asn
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Asn Arg Lys Asn Cys His Cys Glu Ala His Trp Ala Pro Pro Phe Cys
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Asp Lys Phe Gly Phe Gly Gly Ser Thr Asp Ser Gly Pro Ile Arg Gln
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Ala Asp Asn

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<213> Homo sapiens

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<213> Homo sapiens

<400> 341

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<211> 2109

<212> DNA

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<213> Homo sapiens

<400> 343

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tccaagaatc atccagaagt gctgaatatt cgactacaac gggaaagcaa agaactgatc 240
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ctcaggggac ttattgtgtt tgaaaatgaa agctatgtct tagaaccaat gaaaagtgca 480
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ttggtaggag tggaagtgtg gaatgacatg gacaaatgct ctgtaagtca ggaccattc 840
accagcctcc atgaatttct ggactggagg aagatgaagc ttctacctcg caaatcccat 900
gacaatgcgc agcttgtcag tggggtttat ttccaaggga ccaccatcg catggcccca 960

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gcacttaggc	aggcccaggg	gaacctgtaag	ccaaaccccc	ctcagaagcc	tctgcctgca	2580
gatcctctgg	ccagaacaac	tgggtcact	catgccttgg	ccaggacccc	aggacaatgg	2640
gagactgggc	tccgctggc	acccctcaga	cctgctccac	aatatccaca	ccaagtgcc	2700

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2730

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tgccagctga agcctgcagg aacagcgtgc agggactcca gcaactcctg tgacctcca 180

gagttctgca cagggggccag ccctcactgc ccagccaacg tgtacctg 228

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<211> 348

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catggacatg tacggggata ttctgattca gcagtcagtc tcagcacgtg ttctgggtctc 180

aggggactta ttgtgtttga aatgaaagc tatgtcttag aaccaatgaa aagtgcaacc 240

aacagataca aactcttccc agcgaagaag ctgaaaagcg tccggggatc atgtggatca 300

catcacaaca caccaaacct cgctgcaaag aatgtgtttc caccaccc 348

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<211> 609

<212> DNA

<213> Homo sapiens

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ccactgaaca ttcggtatcgt gttggtaggc gtggaagtgt ggaatgacat ggacaaatgc 180

tctgtaagtc aggaccatt caccagcctc catgaatttc tggactggag gaagatgaag 240

cttctacctc gcaaatacca tgacaatgcg cagcttgtca gtgggggttta tttccaaggg 300

accaccatcg gcatggcccc aatcatgagc atgtgcacgg cagaccagtc tgggggaatt 360

gtcatggacc attcagacaa tccccttggc gcagccgtga ccctggcaca tgagctgggc 420

77/124

cacaatttcg ggatgaatca tgacacactg gacaggggct gtagctgtca aatggcggtt 480
 gagaaaggag gctgcatcat gaacgcttcc accgggtacc catttcccat ggtgttcagc 540
 agttgcagca ggaaggactt ggagaccagc ctggagaaag gaatgggggt gtgcctgttt 600
 aacctgccg 609

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 <211> 524
 <212> DNA
 <213> Homo sapiens

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 gttttcctat gctttgaaac agaaaaatat gtaccaagaa tcttggtttg ccttccagaa 180
 aacaaaactg catttcactt tcccggtgtt cccactgta tctaggcaac atagtattca 240
 tgactatgga taaactaaac acgtgacaca aacacacaca aaagggaacc cagctctaatt 300
 acattccaac tcgtatagca tgcattctgtt tattctatag ttattaagtt ctttaaaatg 360
 taaagccatg ctggaaaata atactgctga gatacataga gaattactgt aactgattac 420
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gcatgcatct gtttattcta tagtt 25

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<400> 356
gggtcaacag ttttcctatg ctttg 25

79/124

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<400> 358
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<210> 359
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 cagtggggga gaagcaaggg ttgggccag tgtcccttt cccagtgac acctccgctt 180
 tggcagccct gatgactggc ctctggctgc aacttaatgc tctgatatgg ctttttagcat 240
 ttattatatg aaaatagcag ggtttttagt tttaatttat cagagaccct gccaccatt 300
 ccatctccat ccaagcaaac tgaatggcat tgaaacaaac tggagaagaa ggtaggagaa 360
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 gggtttgcag aaagccaggg aaccacaga gtcaccaacc cttcatttaa caagtaagaa 480
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 aaaat 545

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 cattagaaag tattagctta aaacattcta caccaaaatg aagtacattc acatattttg 180
 tgctgcatct tacaggctt ctagtacctt ctatcccctt ctatgattgg tcgtacacat 240

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agtacgtaag agcctcttcc catatagaag aagggggaaa gctaagctgc tttcagctat 300

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81/124

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ttgtcactcc cntcctcctg ctggctgcag aaatgacctc agcccaggcc agagacccca 180
gctctggcaa ggnccctcttg tggtcgncca ggncccagnn tgaaagccaa gcagaatcag 240
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83/124

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cntnagctga ggaagccctg tccacccctgt ggtttcanan nactgggnatc ctttaaccag 180

agtacctcac ggntnccctg ctgtctnctt aaccctcttg ctaccctggg gaattacagc 240

tagagttcat tctaatagtt cttccccacc gagtttttct gatgtacca caagaattct 300

tgaatattga acttagtcaa caagagtcca aattataaca gtgaacaaga ttggtgtnaa 360

aaaaaataag tgattgaaaa atcattgctg catatgcagt aggcaataaa ctgttttaac 420

tcccttgatc caaaaaacgc aaagggtggg gctccaagga ggaggctgcc attccaata 480

agctttaccc ctgctcgtcc ccaaagggtg aaccataagc gagaacggct ttgtgtggta 540

gccaaaagca catcttcat 559

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84/124

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cacnggacta tnagttactt gaaagctgag gcttggtaga gggctggagc caattgcgtt 180
aaactaacta acattattgc aaaatatatt ctagggcttt tactctaata aaaatgactc 240
ctggaactgc agtactatat tcttggaacc ccaagaaacc aggtgacaac ccataaattt 300
accatcactt ttcagatgag gaaggcaaat ctggaaggcc aaattacttg tccaaag 357

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taaacttaac tatatgttta ctttttttcc tttttatttc ctctaccctc attttaaaact 180
tttgaagtga ttttagccta aatgagtaaa aattcaattg gggaatgaaa tgactccttc 240
taaaacagag ctacacttct gcaactacaa aggcaaaaaa aaacaacaac aacaacaaac 300
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tgaacttggt tattttattt acatccacaa tggatagttt cagtggtttg atgaaaatca 420
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<213> Homo sapiens

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gaagctgcag agtccaacag ggagcgcggc cagggccagg agcccgtagg atcgaggag 180
catgctgcta ctgcctcact gacactcatc tgagccctcc catgacatgg agaccgtgac 240
cagtgtgctg gcagaggagg tcacgcgtcc ccaaggcctc ctgtgactgg cagcattgac 300
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ctttcactga gcctccacag cagtggggga gaagcaaggg ttggggccag tgtccccttt 600
ccccagtgac acctcagcct tggcagccct gatgactggg ctctggctgc aacttaatgc 660

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cagagaccct gccacccatt ccatctccat ccaagcaaac tgaatggcaa tgaaacaaac	780
tggagaagaa ggtaggagaa agggcggtga actctggctc tttgctgtgg acatgcgtga	840
ccagcagtac tcaggtttga gggtttgcag aaagccaggg aaccacaga gtcaccaacc	900
cttcatttaa caagtaagaa tgttaaaaag tgaaaacaat gtaagagcct aactccatcc	960
cccgtggcca ttactgcata aaatagagtg catttgaaat	1000

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<211> 726

<212> DNA

<213> Homo sapiens

<400> 366

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ttaaccatag gaattctggt gaccatcctg tgtcttcttg ctgccggatt tgtggtttat	180
ctcaaaagga agaccttgat acgactgctg tttaaaaata agaagaccac cattgaaaaa	240
ctaagggtgtg tgcgcccttc ccggccaccc cgtggcttcc aacctgtca ggctcacctc	300
ggccaccttg gaaaaggcct gatgaggaag ccgccagatt cctaccacc gaaggacaat	360
cccaggagat tgctgcagtg tcagaatgtt gacatcagca gaccctcaa cggcctgaat	420
gtccctcagc ccagtcacac tcagcgagtg cttcctcccc tccaccgggc tccacgtgca	480
cctagcgtcc ctgccagacc cctgccagcc aagcctgcac ttaggcaggc ccaggggacc	540
tgtaagccaa accccctca gaagcctctg cctgcagatc ctctggccag aacaactcgg	600
ctcactcatg ccttggccag gacccagga caatgggaga ctgggctccg cctggcacc	660
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aagtga	726

<210> 367

<211> 22

<212> DNA

<213> Homo sapiens

<400> 367

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<211> 17
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ggcagcaaga agacacagga t 21

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<212> DNA
<213> Homo sapiens

<400> 372
tttaaccata ggaattctg 19

<210> 373
<211> 906
<212> PRT
<213> Homo sapiens

<400> 373
Met Ala Ala Arg Pro Leu Pro Val Ser Pro Ala Arg Ala Leu Leu Leu
1 5 10 15

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

88/124

Leu Trp Asn Gln Gly Arg Ala Asp Glu Val Val Ser Ala Ser Val Arg
 35 40 45

Ser Gly Asp Leu Trp Ile Pro Val Lys Ser Phe Asp Ser Lys Asn His
 50 55 60

Pro Glu Val Leu Asn Ile Arg Leu Gln Arg Glu Ser Lys Glu Leu Ile
 65 70 75 80

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

Thr His Tyr Leu Gln Asp Gly Thr Asp Val Ser Leu Ala Arg Asn Tyr
 100 105 110

Thr Gly His Cys Tyr Tyr His Gly His Val Arg Gly Tyr Ser Asp Ser
 115 120 125

Ala Val Ser Leu Ser Thr Cys Ser Gly Leu Arg Gly Leu Ile Val Phe
 130 135 140

Glu Asn Glu Ser Tyr Val Leu Glu Pro Met Lys Ser Ala Thr Asn Arg
 145 150 155 160

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

Gly Ser His His Asn Thr Pro Asn Leu Ala Ala Lys Asn Val Phe Pro
 180 185 190

Pro Pro Ser Gln Thr Trp Ala Arg Arg His Lys Arg Glu Thr Leu Lys
 195 200 205

Ala Thr Lys Tyr Val Glu Leu Val Ile Val Ala Asp Asn Arg Glu Phe
 210 215 220

Gln Arg Gln Gly Lys Asp Leu Glu Lys Val Lys Gln Arg Leu Ile Glu
 225 230 235 240

Ile Ala Asn His Val Asp Lys Phe Tyr Arg Pro Leu Asn Ile Arg Ile
 245 250 255

89/124

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

90/124

Pro His Cys Pro Ala Asn Val Tyr Leu His Asp Gly His Ser Cys Gln
 500 505 510

Asp Val Asp Gly Tyr Cys Tyr Asn Gly Ile Cys Gln Thr His Glu Gln
 515 520 525

Gln Cys Val Thr Leu Trp Gly Pro Gly Ala Lys Pro Ala Pro Gly Ile
 530 535 540

Cys Phe Glu Arg Val Asn Ser Ala Gly Asp Pro Tyr Gly Asn Cys Gly
 545 550 555 560

Lys Val Ser Lys Ser Ser Phe Ala Lys Cys Glu Met Arg Asp Ala Lys
 565 570 575

Cys Gly Lys Ile Gln Cys Gln Gly Gly Ala Ser Arg Pro Val Ile Gly
 580 585 590

Thr Asn Ala Val Ser Ile Glu Thr Asn Ile Pro Leu Gln Gln Gly Gly
 595 600 605

Arg Ile Leu Cys Arg Gly Thr His Val Tyr Leu Gly Asp Asp Met Pro
 610 615 620

Asp Pro Gly Leu Val Leu Ala Gly Thr Lys Cys Ala Asp Gly Lys Ile
 625 630 635 640

Cys Leu Asn Arg Gln Cys Gln Asn Ile Ser Val Phe Gly Val His Glu
 645 650 655

Cys Ala Met Gln Cys His Gly Arg Gly Val Cys Asn Asn Arg Lys Asn
 660 665 670

Cys His Cys Glu Ala His Trp Ala Pro Pro Phe Cys Asp Lys Phe Gly
 675 680 685

Phe Gly Gly Ser Thr Asp Ser Gly Pro Ile Arg Gln Ala Asp Asn Gln
 690 695 700

Gly Leu Thr Ile Gly Ile Leu Val Thr Ile Leu Cys Leu Leu Ala Ala
 705 710 715 720

Gly Phe Val Val Tyr Leu Lys Arg Lys Thr Leu Ile Arg Leu Leu Phe
725 730 735

Thr Asn Lys Lys Thr Thr Ile Glu Lys Leu Arg Cys Val Arg Pro Ser
740 745 750

Arg Pro Pro Arg Gly Phe Gln Pro Cys Gln Ala His Leu Gly His Leu
755 760 765

Gly Lys Gly Leu Met Arg Lys Pro Pro Asp Ser Tyr Pro Pro Lys Asp
770 775 780

Asn Pro Arg Arg Leu Leu Gln Cys Gln Asn Val Asp Ile Ser Arg Pro
785 790 795 800

Leu Asn Gly Leu Asn Val Pro Gln Pro Gln Ser Thr Gln Arg Val Leu
805 810 815

Pro Pro Leu His Arg Ala Pro Arg Ala Pro Ser Val Pro Ala Arg Pro
820 825 830

Leu Pro Ala Lys Pro Ala Leu Arg Gln Ala Gln Gly Thr Cys Lys Pro
835 840 845

Asn Pro Pro Gln Lys Pro Leu Pro Ala Asp Pro Leu Ala Arg Thr Thr
850 855 860

Arg Leu Thr His Ala Leu Ala Arg Thr Pro Gly Gln Trp Glu Ile Gly
865 870 875 880

Leu Arg Leu Ala Pro Leu Arg Pro Ala Pro Gln Tyr Pro His Gln Val
885 890 895

Pro Arg Ser Thr His Thr Ala Tyr Ile Lys
900 905

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<210> 374
<211> 703
<212> PRT
<213> Homo sapiens
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<400> 374
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92/124

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

Leu Trp Asn Gln Gly Arg Ala Asp Glu Val Val Ser Ala Ser Val Arg
 35 40 45

Ser Gly Asp Leu Trp Ile Pro Val Lys Ser Phe Asp Ser Lys Asn His
 50 55 60

Pro Glu Val Leu Asn Ile Arg Leu Gln Arg Glu Ser Lys Glu Leu Ile
 65 70 75 80

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

Thr His Tyr Leu Gln Asp Gly Thr Asp Val Ser Leu Ala Arg Asn Tyr
 100 105 110

Thr Gly His Cys Tyr Tyr His Gly His Val Arg Gly Tyr Ser Asp Ser
 115 120 125

Ala Val Ser Leu Ser Thr Cys Ser Gly Leu Arg Gly Leu Ile Val Phe
 130 135 140

Glu Asn Glu Ser Tyr Val Leu Glu Pro Met Lys Ser Ala Thr Asn Arg
 145 150 155 160

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

Gly Ser His His Asn Thr Pro Asn Leu Ala Ala Lys Asn Val Phe Pro
 180 185 190

Pro Pro Ser Gln Thr Trp Ala Arg Arg His Lys Arg Glu Thr Leu Lys
 195 200 205

Ala Thr Lys Tyr Val Glu Leu Val Ile Val Ala Asp Asn Arg Glu Phe
 210 215 220

Gln Arg Gln Gly Lys Asp Leu Glu Lys Val Lys Gln Arg Leu Ile Glu
 225 230 235 240

Ile Ala Asn His Val Asp Lys Phe Tyr Arg Pro Leu Asn Ile Arg Ile
 245 250 255

93/124

Val Leu Val Gly Val Glu Val Trp Asn Asp Met Asp Lys Cys Ser Val
 260 265 270

Ser Gln Asp Pro Phe Thr Ser Leu His Glu Phe Leu Asp Trp Arg Lys
 275 280 285

Met Lys Leu Leu Pro Arg Lys Ser His Asp Asn Ala Gln Leu Val Ser
 290 295 300

Gly Val Tyr Phe Gln Gly Thr Thr Ile Gly Met Ala Pro Ile Met Ser
 305 310 315 320

Met Cys Thr Ala Asp Gln Ser Gly Gly Ile Val Met Asp His Ser Asp
 325 330 335

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

Phe Gly Met Asn His Asp Thr Leu Asp Arg Gly Cys Ser Cys Gln Met
 355 360 365

Ala Val Glu Lys Gly Gly Cys Ile Met Asn Ala Ser Thr Gly Tyr Pro
 370 375 380

Phe Pro Met Val Phe Ser Ser Cys Ser Arg Lys Asp Leu Glu Thr Ser
 385 390 395 400

Leu Glu Lys Gly Met Gly Val Cys Leu Phe Asn Leu Pro Glu Val Arg
 405 410 415

Glu Ser Phe Gly Gly Gln Lys Cys Gly Asn Arg Phe Val Glu Glu Gly
 420 425 430

Glu Glu Cys Asp Cys Gly Glu Pro Glu Glu Cys Met Asn Arg Cys Cys
 435 440 445

Asn Ala Thr Thr Cys Thr Leu Lys Pro Asp Ala Val Cys Ala His Gly
 450 455 460

Leu Cys Cys Glu Asp Cys Gln Leu Lys Pro Ala Gly Thr Ala Cys Arg
 465 470 475 480

94/124

Asp Ser Ser Asn Ser Cys Asp Leu Pro Glu Phe Cys Thr Gly Ala Ser
 485 490 495

Pro His Cys Pro Ala Asn Val Tyr Leu His Asp Gly His Ser Cys Gln
 500 505 510

Asp Val Asp Gly Tyr Cys Tyr Asn Gly Ile Cys Gln Thr His Glu Gln
 515 520 525

Gln Cys Val Thr Leu Trp Gly Pro Gly Ala Lys Pro Ala Pro Gly Ile
 530 535 540

Cys Phe Glu Arg Val Asn Ser Ala Gly Asp Pro Tyr Gly Asn Cys Gly
 545 550 555 560

Lys Val Ser Lys Ser Ser Phe Ala Lys Cys Glu Met Arg Asp Ala Lys
 565 570 575

Cys Gly Lys Ile Gln Cys Gln Gly Gly Ala Ser Arg Pro Val Ile Gly
 580 585 590

Thr Asn Ala Val Ser Ile Glu Thr Asn Ile Pro Leu Gln Gln Gly Gly
 595 600 605

Arg Ile Leu Cys Arg Gly Thr His Val Tyr Leu Gly Asp Asp Met Pro
 610 615 620

Asp Pro Gly Leu Val Leu Ala Gly Thr Lys Cys Ala Asp Gly Lys Ile
 625 630 635 640

Cys Leu Asn Arg Gln Cys Gln Asn Ile Ser Val Phe Gly Val His Glu
 645 650 655

Cys Ala Met Gln Cys His Gly Arg Gly Val Cys Asn Asn Arg Lys Asn
 660 665 670

Cys His Cys Glu Ala His Trp Ala Pro Pro Phe Cys Asp Lys Phe Gly
 675 680 685

Phe Gly Gly Ser Thr Asp Ser Gly Pro Ile Arg Gln Ala Asp Asn
 690 695 700

95/124

<210> 375
<211> 6
<212> PRT
<213> Homo sapiens

<400> 375
Ala Arg Asn Tyr Thr Gly
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<210> 376
<211> 6
<212> PRT
<213> Homo sapiens

<400> 376
Arg Asn Tyr Thr Gly His
1 5

<210> 377
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<213> Homo sapiens

<400> 377
Asn Tyr Thr Gly His Cys
1 5

<210> 378
<211> 6
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<213> Homo sapiens

<400> 378
Tyr Thr Gly His Cys Tyr
1 5

<210> 379
<211> 6
<212> PRT
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<400> 379
Thr Gly His Cys Tyr Tyr
1 5

<210> 380
<211> 909
<212> PRT
<213> Homo sapiens

<400> 380
Met Ala Ala Arg Pro Leu Pro Val Ser Pro Ala Arg Ala Leu Leu Leu
1 5 10 15

96/124

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

Leu Trp Asn Gln Gly Arg Ala Asp Glu Val Val Ser Ala Ser Val Arg
 35 40 45

Ser Gly Asp Leu Trp Ile Pro Val Lys Ser Phe Asp Ser Lys Asn His
 50 55 60

Pro Glu Val Leu Asn Ile Arg Leu Gln Arg Glu Ser Lys Glu Leu Ile
 65 70 75 80

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

Thr His Tyr Leu Gln Asp Gly Thr Asp Val Ser Leu Ala Arg Asn Tyr
 100 105 110

Thr Val Ile Leu Gly His Cys Tyr Tyr His Gly His Val Arg Gly Tyr
 115 120 125

Ser Asp Ser Ala Val Ser Leu Ser Thr Cys Ser Gly Leu Arg Gly Leu
 130 135 140

Ile Val Phe Glu Asn Glu Ser Tyr Val Leu Glu Pro Met Lys Ser Ala
 145 150 155 160

Thr Asn Arg Tyr Lys Leu Phe Pro Ala Lys Lys Leu Lys Ser Val Arg
 165 170 175

Gly Ser Cys Gly Ser His His Asn Thr Pro Asn Leu Ala Ala Lys Asn
 180 185 190

Val Phe Pro Pro Pro Ser Gln Thr Trp Ala Arg Arg His Lys Arg Glu
 195 200 205

Thr Leu Lys Ala Thr Lys Tyr Val Glu Leu Val Ile Val Ala Asp Asn
 210 215 220

Arg Glu Phe Gln Arg Gln Gly Lys Asp Leu Glu Lys Val Lys Gln Arg
 225 230 235 240

97/124

Leu Ile Glu Ile Ala Asn His Val Asp Lys Phe Tyr Arg Pro Leu Asn
 245 250 255

Ile Arg Ile Val Leu Val Gly Val Glu Val Trp Asn Asp Met Asp Lys
 260 265 270

Cys Ser Val Ser Gln Asp Pro Phe Thr Ser Leu His Glu Phe Leu Asp
 275 280 285

Trp Arg Lys Met Lys Leu Leu Pro Arg Lys Ser His Asp Asn Ala Gln
 290 295 300

Leu Val Ser Gly Val Tyr Phe Gln Gly Thr Thr Ile Gly Met Ala Pro
 305 310 315 320

Ile Met Ser Met Cys Thr Ala Asp Gln Ser Gly Gly Ile Val Met Asp
 325 330 335

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

Gly His Asn Phe Gly Met Asn His Asp Thr Leu Asp Arg Gly Cys Ser
 355 360 365

Cys Gln Met Ala Val Glu Lys Gly Gly Cys Ile Met Asn Ala Ser Thr
 370 375 380

Gly Tyr Pro Phe Pro Met Val Phe Ser Ser Cys Ser Arg Lys Asp Leu
 385 390 395 400

Glu Thr Ser Leu Glu Lys Gly Met Gly Val Cys Leu Phe Asn Leu Pro
 405 410 415

Glu Val Arg Glu Ser Phe Gly Gly Gln Lys Cys Gly Asn Arg Phe Val
 420 425 430

Glu Glu Gly Glu Glu Cys Asp Cys Gly Glu Pro Glu Glu Cys Met Asn
 435 440 445

Arg Cys Cys Asn Ala Thr Thr Cys Thr Leu Lys Pro Asp Ala Val Cys
 450 455 460

Ala His Gly Leu Cys Cys Glu Asp Cys Gln Leu Lys Pro Ala Gly Thr
 465 470 475 480

98/124

Ala Cys Arg Asp Ser Ser Asn Ser Cys Asp Leu Pro Glu Phe Cys Thr
485 490 495

Gly Ala Ser Pro His Cys Pro Ala Asn Val Tyr Leu His Asp Gly His
500 505 510

Ser Cys Gln Asp Val Asp Gly Tyr Cys Tyr Asn Gly Ile Cys Gln Thr
515 520 525

His Glu Gln Gln Cys Val Thr Leu Trp Gly Pro Gly Ala Lys Pro Ala
530 535 540

Pro Gly Ile Cys Phe Glu Arg Val Asn Ser Ala Gly Asp Pro Tyr Gly
545 550 555 560

Asn Cys Gly Lys Val Ser Lys Ser Ser Phe Ala Lys Cys Glu Met Arg
565 570 575

Asp Ala Lys Cys Gly Lys Ile Gln Cys Gln Gly Gly Ala Ser Arg Pro
580 585 590

Val Ile Gly Thr Asn Ala Val Ser Ile Glu Thr Asn Ile Pro Leu Gln
595 600 605

Gln Gly Gly Arg Ile Leu Cys Arg Gly Thr His Val Tyr Leu Gly Asp
610 615 620

Asp Met Pro Asp Pro Gly Leu Val Leu Ala Gly Thr Lys Cys Ala Asp
625 630 635 640

Gly Lys Ile Cys Leu Asn Arg Gln Cys Gln Asn Ile Ser Val Phe Gly
645 650 655

Val His Glu Cys Ala Met Gln Cys His Gly Arg Gly Val Cys Asn Asn
660 665 670

Arg Lys Asn Cys His Cys Glu Ala His Trp Ala Pro Pro Phe Cys Asp
675 680 685

Lys Phe Gly Phe Gly Gly Ser Thr Asp Ser Gly Pro Ile Arg Gln Ala
690 695 700

99/124

Asp Asn Gln Gly Leu Thr Ile Gly Ile Leu Val Thr Ile Leu Cys Leu
 705 710 715 720

Leu Ala Ala Gly Phe Val Val Tyr Leu Lys Arg Lys Thr Leu Ile Arg
 725 730 735

Leu Leu Phe Thr Asn Lys Lys Thr Thr Ile Glu Lys Leu Arg Cys Val
 740 745 750

Arg Pro Ser Arg Pro Pro Arg Gly Phe Gln Pro Cys Gln Ala His Leu
 755 760 765

Gly His Leu Gly Lys Gly Leu Met Arg Lys Pro Pro Asp Ser Tyr Pro
 770 775 780

Pro Lys Asp Asn Pro Arg Arg Leu Leu Gln Cys Gln Asn Val Asp Ile
 785 790 795 800

Ser Arg Pro Leu Asn Gly Leu Asn Val Pro Gln Pro Gln Ser Thr Gln
 805 810 815

Arg Val Leu Pro Pro Leu His Arg Ala Pro Arg Ala Pro Ser Val Pro
 820 825 830

Ala Arg Pro Leu Pro Ala Lys Pro Ala Leu Arg Gln Ala Gln Gly Thr
 835 840 845

Cys Lys Pro Asn Pro Pro Gln Lys Pro Leu Pro Ala Asp Pro Leu Ala
 850 855 860

Arg Thr Thr Arg Leu Thr His Ala Leu Ala Arg Thr Pro Gly Gln Trp
 865 870 875 880

Glu Thr Gly Leu Arg Leu Ala Pro Leu Arg Pro Ala Pro Gln Tyr Pro
 885 890 895

His Gln Val Pro Arg Ser Thr His Thr Ala Tyr Ile Lys
 900 905

<210> 381

<211> 76

<212> PRT

<213> Homo sapiens

100/124

<400> 381

Glu Glu Gly Glu Glu Cys Asp Cys Gly Glu Pro Glu Glu Cys Met Asn
 1 5 10 15

Arg Cys Cys Asn Ala Thr Thr Cys Thr Leu Lys Pro Asp Ala Val Cys
 20 25 30

Ala His Gly Leu Cys Cys Glu Asp Cys Gln Leu Lys Pro Ala Gly Thr
 35 40 45

Ala Cys Arg Asp Ser Ser Asn Ser Cys Asp Leu Pro Glu Phe Cys Thr
 50 55 60

Gly Ala Ser Pro His Cys Pro Ala Asn Val Tyr Leu
 65 70 75

<210> 382

<211> 116

<212> PRT

<213> Homo sapiens

<400> 382

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

His Tyr Leu Gln Asp Gly Thr Asp Val Ser Leu Ala Arg Asn Tyr Thr
 20 25 30

Val Ile Leu Gly His Cys Tyr Tyr His Gly His Val Arg Gly Tyr Ser
 35 40 45

Asp Ser Ala Val Ser Leu Ser Thr Cys Ser Gly Leu Arg Gly Leu Ile
 50 55 60

Val Phe Glu Asn Glu Ser Tyr Val Leu Glu Pro Met Lys Ser Ala Thr
 65 70 75 80

Asn Arg Tyr Lys Leu Phe Pro Ala Lys Lys Leu Lys Ser Val Arg Gly
 85 90 95

Ser Cys Gly Ser His His Asn Thr Pro Asn Leu Ala Ala Lys Asn Val
 100 105 110

Phe Pro Pro Pro
 115

101/124

<210> 383

<211> 203

<212> PRT

<213> Homo sapiens

<400> 383

Lys Tyr Val Glu Leu Val Ile Val Ala Asp Asn Arg Glu Phe Gln Arg
 1 5 10 15

Gln Gly Lys Asp Leu Glu Lys Val Lys Gln Arg Leu Ile Glu Ile Ala
 20 25 30

Asn His Val Asp Lys Phe Tyr Arg Pro Leu Asn Ile Arg Ile Val Leu
 35 40 45

Val Gly Val Glu Val Trp Asn Asp Met Asp Lys Cys Ser Val Ser Gln
 50 55 60

Asp Pro Phe Thr Ser Leu His Glu Phe Leu Asp Trp Arg Lys Met Lys
 65 70 75 80

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

Tyr Phe Gln Gly Thr Thr Ile Gly Met Ala Pro Ile Met Ser Met Cys
 100 105 110

Thr Ala Asp Gln Ser Gly Gly Ile Val Met Asp His Ser Asp Asn Pro
 115 120 125

Leu Gly Ala Ala Val Thr Leu Ala His Glu Leu Gly His Asn Phe Gly
 130 135 140

Met Asn His Asp Thr Leu Asp Arg Gly Cys Ser Cys Gln Met Ala Val
 145 150 155 160

Glu Lys Gly Gly Cys Ile Met Asn Ala Ser Thr Gly Tyr Pro Phe Pro
 165 170 175

Met Val Phe Ser Ser Cys Ser Arg Lys Asp Leu Glu Thr Ser Leu Glu
 180 185 190

Lys Gly Met Gly Val Cys Leu Phe Asn Leu Pro
 195 200

102/124

<210> 384

<211> 3534

<212> DNA

<213> Homo sapiens

<400> 384

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cttttttaaa aatgaaaggc tagaagagct cagcggcggc gcgggccgtg cgcgagggtc      180
ccggagctga ctgccgagg caggaaatcc ctccggtcgc gacgcccggc cccgctcggc      240
gcccgcgtgg gatggtgcag cgctcgccgc cgggcccag agctgctgca ctgaaggccg      300
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gacttggaga ccagcctgga gaaaggaatg ggggtgtgcc tgtttaacct gccggaagtc     1560
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103/124

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gtttccatag	aaacaaacat	ccccctgcag	caaggaggcc	ggattctgtg	ccgggggacc	2160
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gacatcagca	gacctctcaa	cggcctgaat	gtccctcagc	cccagtcaac	tcagcgagt	2760
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gctgtgctgt	gctatggtgc	tctgtctact	tgacaggtta	cttgtaaatt	attaatttat	3240
gcagaatgtt	gattacagt	cagtgcgctg	tagtaggcat	ttttaccatc	actgagtttt	3300

104/124

ccatggcagg aaggcttggt gtgcttttag tatttttagtg aacttgaaat atcctgcttg 3360
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<210> 385

<211> 2208

<212> DNA

<213> Homo sapiens

<400> 385

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105/124

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<210> 386

<211> 2214

<212> DNA

<213> Homo sapiens

<400> 386

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107/124

<210> 387

<211> 735

<212> PRT

<213> Homo sapiens

<400> 387

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Leu Trp Asn Gln Gly Arg Ala Asp Glu Val Val Ser Ala Ser Val Arg
 35 40 45

Ser Gly Asp Leu Trp Ile Pro Val Lys Ser Phe Asp Ser Lys Asn His
 50 55 60

Pro Glu Val Leu Asn Ile Arg Leu Gln Arg Glu Ser Lys Glu Leu Ile
 65 70 75 80

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

Thr His Tyr Leu Gln Asp Gly Thr Asp Val Ser Leu Ala Arg Asn Tyr
 100 105 110

Thr Gly His Cys Tyr Tyr His Gly His Val Arg Gly Tyr Ser Asp Ser
 115 120 125

Ala Val Ser Leu Ser Thr Cys Ser Gly Leu Arg Gly Leu Ile Val Phe
 130 135 140

Glu Asn Glu Ser Tyr Val Leu Glu Pro Met Lys Ser Ala Thr Asn Arg
 145 150 155 160

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

Gly Ser His His Asn Thr Pro Asn Leu Ala Ala Lys Asn Val Phe Pro
 180 185 190

Pro Pro Ser Gln Thr Trp Ala Arg Arg His Lys Arg Glu Thr Leu Lys
 195 200 205

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Ala Thr Lys Tyr Val Glu Leu Val Ile Val Ala Asp Asn Arg Glu Phe
 210 215 220

Gln Arg Gln Gly Lys Asp Leu Glu Lys Val Lys Gln Arg Leu Ile Glu
 225 230 235 240

Ile Ala Asn His Val Asp Lys Phe Tyr Arg Pro Leu Asn Ile Arg Ile
 245 250 255

Val Leu Val Gly Val Glu Val Trp Asn Asp Met Asp Lys Cys Ser Val
 260 265 270

Ser Gln Asp Pro Phe Thr Ser Leu His Glu Phe Leu Asp Trp Arg Lys
 275 280 285

Met Lys Leu Leu Pro Arg Lys Ser His Asp Asn Ala Gln Leu Val Ser
 290 295 300

Gly Val Tyr Phe Gln Gly Thr Thr Ile Gly Met Ala Pro Ile Met Ser
 305 310 315 320

Met Cys Thr Ala Asp Gln Ser Gly Gly Ile Val Met Asp His Ser Asp
 325 330 335

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

Phe Gly Met Asn His Asp Thr Leu Asp Arg Gly Cys Ser Cys Gln Met
 355 360 365

Ala Val Glu Lys Gly Gly Cys Ile Met Asn Ala Ser Thr Gly Tyr Pro
 370 375 380

Phe Pro Met Val Phe Ser Ser Cys Ser Arg Lys Asp Leu Glu Thr Ser
 385 390 395 400

Leu Glu Lys Gly Met Gly Val Cys Leu Phe Asn Leu Pro Glu Val Arg
 405 410 415

Glu Ser Phe Gly Gly Gln Lys Cys Gly Asn Arg Phe Val Glu Glu Gly
 420 425 430

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Glu Glu Cys Asp Cys Gly Glu Pro Glu Glu Cys Met Asn Arg Cys Cys
 435 440 445

Asn Ala Thr Thr Cys Thr Leu Lys Pro Asp Ala Val Cys Ala His Gly
 450 455 460

Leu Cys Cys Glu Asp Cys Gln Leu Lys Pro Ala Gly Thr Ala Cys Arg
 465 470 475 480

Asp Ser Ser Asn Ser Cys Asp Leu Pro Glu Phe Cys Thr Gly Ala Ser
 485 490 495

Pro His Cys Pro Ala Asn Val Tyr Leu His Asp Gly His Ser Cys Gln
 500 505 510

Asp Val Asp Gly Tyr Cys Tyr Asn Gly Ile Cys Gln Thr His Glu Gln
 515 520 525

Gln Cys Val Thr Leu Trp Gly Pro Gly Ala Lys Pro Ala Pro Gly Ile
 530 535 540

Cys Phe Glu Arg Val Asn Ser Ala Gly Asp Pro Tyr Gly Asn Cys Gly
 545 550 555 560

Lys Val Ser Lys Ser Ser Phe Ala Lys Cys Glu Met Arg Asp Ala Lys
 565 570 575

Cys Gly Lys Ile Gln Cys Gln Gly Gly Ala Ser Arg Pro Val Ile Gly
 580 585 590

Thr Asn Ala Val Ser Ile Glu Thr Asn Ile Pro Leu Gln Gln Gly Gly
 595 600 605

Arg Ile Leu Cys Arg Gly Thr His Val Tyr Leu Gly Asp Asp Met Pro
 610 615 620

Asp Pro Gly Leu Val Leu Ala Gly Thr Lys Cys Ala Asp Gly Lys Ile
 625 630 635 640

Cys Leu Asn Arg Gln Cys Gln Asn Ile Ser Val Phe Gly Val His Glu
 645 650 655

Cys Ala Met Gln Cys His Gly Arg Gly Val Cys Asn Asn Arg Lys Asn
 660 665 670

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Cys His Cys Glu Ala His Trp Ala Pro Pro Phe Cys Asp Lys Phe Gly
675 680 685

Phe Gly Gly Ser Thr Asp Ser Gly Pro Ile Arg Gln Ala Glu Ala Arg
690 695 700

Gln Glu Ala Ala Glu Ser Asn Arg Glu Arg Gly Gln Gly Gln Glu Pro
705 710 715 720

Val Gly Ser Gln Glu His Ala Ser Thr Ala Ser Leu Thr Leu Ile
725 730 735

<210> 388

<211> 737

<212> PRT

<213> Homo sapiens

<400> 388

Met Ala Ala Arg Pro Leu Pro Val Ser Pro Ala Arg Ala Leu Leu Leu
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Ala Leu Ala Gly Ala Leu Leu Ala Pro Cys Glu Ala Arg Gly Val Ser
20 25 30

Leu Trp Asn Gln Gly Arg Ala Asp Glu Val Val Ser Ala Ser Val Arg
35 40 45

Ser Gly Asp Leu Trp Ile Pro Val Lys Ser Phe Asp Ser Lys Asn His
50 55 60

Pro Glu Val Leu Asn Ile Arg Leu Gln Arg Glu Ser Lys Glu Leu Ile
65 70 75 80

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

Thr His Tyr Leu Gln Asp Gly Thr Asp Val Ser Leu Ala Arg Asn Tyr
100 105 110

Thr Gly His Cys Tyr Tyr His Gly His Val Arg Gly Tyr Ser Asp Ser
115 120 125

Ala Val Ser Leu Ser Thr Cys Ser Gly Leu Arg Gly Leu Ile Val Phe
130 135 140

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Glu Asn Glu Ser Tyr Val Leu Glu Pro Met Lys Ser Ala Thr Asn Arg
 145 150 155 160

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

Gly Ser His His Asn Thr Pro Asn Leu Ala Ala Lys Asn Val Phe Pro
 180 185 190

Pro Pro Ser Gln Thr Trp Ala Arg Arg His Lys Arg Glu Thr Leu Lys
 195 200 205

Ala Thr Lys Tyr Val Glu Leu Val Ile Val Ala Asp Asn Arg Glu Phe
 210 215 220

Gln Arg Gln Gly Lys Asp Leu Glu Lys Val Lys Gln Arg Leu Ile Glu
 225 230 235 240

Ile Ala Asn His Val Asp Lys Phe Tyr Arg Pro Leu Asn Ile Arg Ile
 245 250 255

Val Leu Val Gly Val Glu Val Trp Asn Asp Met Asp Lys Cys Ser Val
 260 265 270

Ser Gln Asp Pro Phe Thr Ser Leu His Glu Phe Leu Asp Trp Arg Lys
 275 280 285

Met Lys Leu Leu Pro Arg Lys Ser His Asp Asn Ala Gln Leu Val Ser
 290 295 300

Gly Val Tyr Phe Gln Gly Thr Thr Ile Gly Met Ala Pro Ile Met Ser
 305 310 315 320

Met Cys Thr Ala Asp Gln Ser Gly Gly Ile Val Met Asp His Ser Asp
 325 330 335

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

Phe Gly Met Asn His Asp Thr Leu Asp Arg Gly Cys Ser Cys Gln Met
 355 360 365

112/124

Ala Val Glu Lys Gly Gly Cys Ile Met Asn Ala Ser Thr Gly Tyr Pro
 370 375 380

Phe Pro Met Val Phe Ser Ser Cys Ser Arg Lys Asp Leu Glu Thr Ser
 385 390 395 400

Leu Glu Lys Gly Met Gly Val Cys Leu Phe Asn Leu Pro Glu Val Arg
 405 410 415

Glu Ser Phe Gly Gly Gln Lys Cys Gly Asn Arg Phe Val Glu Glu Gly
 420 425 430

Glu Glu Cys Asp Cys Gly Glu Pro Glu Glu Cys Met Asn Arg Cys Cys
 435 440 445

Asn Ala Thr Thr Cys Thr Leu Lys Pro Asp Ala Val Cys Ala His Gly
 450 455 460

Leu Cys Cys Glu Asp Cys Gln Leu Lys Pro Ala Gly Thr Ala Cys Arg
 465 470 475 480

Asp Ser Ser Asn Ser Cys Asp Leu Pro Glu Phe Cys Thr Gly Ala Ser
 485 490 495

Pro His Cys Pro Ala Asn Val Tyr Leu His Asp Gly His Ser Cys Gln
 500 505 510

Asp Val Asp Gly Tyr Cys Tyr Asn Gly Ile Cys Gln Thr His Glu Gln
 515 520 525

Gln Cys Val Thr Leu Trp Gly Pro Gly Ala Lys Pro Ala Pro Gly Ile
 530 535 540

Cys Phe Glu Arg Val Asn Ser Ala Gly Asp Pro Tyr Gly Asn Cys Gly
 545 550 555 560

Lys Val Ser Lys Ser Ser Phe Ala Lys Cys Glu Met Arg Asp Ala Lys
 565 570 575

Cys Gly Lys Ile Gln Cys Gln Gly Gly Ala Ser Arg Pro Val Ile Gly
 580 585 590

Thr Asn Ala Val Ser Ile Glu Thr Asn Ile Pro Leu Gln Gln Gly Gly
 595 600 605

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Arg Ile Leu Cys Arg Gly Thr His Val Tyr Leu Gly Asp Asp Met Pro
 610 615 620

Asp Pro Gly Leu Val Leu Ala Gly Thr Lys Cys Ala Asp Gly Lys Ile
 625 630 635 640

Cys Leu Asn Arg Gln Cys Gln Asn Ile Ser Val Phe Gly Val His Glu
 645 650 655

Cys Ala Met Gln Cys His Gly Arg Gly Val Cys Asn Asn Arg Lys Asn
 660 665 670

Cys His Cys Glu Ala His Trp Ala Pro Pro Phe Cys Asp Lys Phe Gly
 675 680 685

Phe Gly Gly Ser Thr Asp Ser Gly Pro Ile Arg Gln Ala Gly Lys Glu
 690 695 700

Ala Arg Gln Glu Ala Ala Glu Ser Asn Arg Glu Arg Gly Gln Gly Gln
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Glu Pro Val Gly Ser Gln Glu His Ala Ser Thr Ala Ser Leu Thr Leu
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Ile

<210> 389

<211> 3018

<212> DNA

<213> Homo sapiens

<400> 389

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gccggcgacg atggcagcgc gcccgctgcc cgtgtccccc gcccgcgccc tctgtctcgc      360
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114/124

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115/124

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 agcagggttt tagttttt 3018

<210> 390

<211> 3066

<212> DNA

<213> Homo sapiens

<400> 390

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cagaggggtg tgcaacaaca ggaagaactg ccaactgcgag gccactggg cacctccctt 2400

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```

ctgtgacaag tttggctttg gaggaagcac agacagcggc cccatccggc aagcagggaa 2460
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cagtgtcccc tttcccagc gacacctcag ccttggcagc cctgatgact ggtctctggc 3000
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gttttt 3066

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<210> 391

<211> 528

<212> DNA

<213> Homo sapiens

<400> 391

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cgaggggtga gcttatggaa ccaaggaaga gctgatgaag ttgtcagtgc ctctgttcgg 60
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aatattcgac tacaacggga aagcaaagaa ctgatcataa atctggaaag aaatgaaggt 180
ctcattgccg gcagtttcac ggaaaccac tatctgcaag acggtactga tgtctccctc 240
gctcgaaatt acacgggtca ctgttactac catggacatg tacggggata ttctgattca 300
gcagtcagtc tcagcacgtg ttctggcttc aggggactta ttgtgtttga aaatgaaagc 360
tatgtcttag aaccaatgaa aagtgaacc aacagataca aactcttccc agcgaagaag 420
ctgaaaagcg tccggggatc atgtggatca catcacaaca caccaaacct cgctgcaaag 480
aatgtgtttc caccaccctc tcagacatgg gcaagaaggc ataaaaga 528

```

<210> 392

<211> 537

<212> DNA

<213> Homo sapiens

<400> 392

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cgaggggtga gcttatggaa cgaaggaaga gctgatgaag ttgtcagtgc ctctgttcgg 60

```

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```

agtggggacc tctggatccc agtgaagagc ttcgactcca agaatcatcc agaagtgctg      120
aatattcgac tacaacggga aagcaaagaa ctgatacataa atctggaaag aaatgaaggt      180
ctcattgcca gcagtttcac ggaaaccac tatctgcaag acggtactga tgtctccctc      240
gctcgaaatt acacggtaat tctgggtcac tgttactacc atggacatgt acggggatat      300
tctgattcag cagtcagtct cagcacgtgt tctgggtctca ggggacttat tgtgtttgaa      360
aatgaaagct atgtcttaga accaatgaaa agtgcaacca acagatacaa actcttccca      420
gcgaagaagc tgaaaagcgt ccggggatca tgtggatcac atcacaacac accaaacctc      480
gctgcaaaga atgtgtttcc accaccctct cagacatggg caagaaggca taaaaga      537

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<210> 393

<211> 420

<212> DNA

<213> Homo sapiens

<400> 393

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tcatgtcagg atgtggacgg ctactgctac aatggcatct gccagactca cgagcagcag      60
tgtgtcacgc tctggggacc aggtgctaaa cctgcccctg ggatctgctt tgagagagtc      120
aattctgcag gtgataccta tggcaactgt ggcaaagtct cgaagagttc ctttgccaaa      180
tgcgagatga gagatgctaa atgtggaaaa atccagtgtc aaggagggtgc cagccggcca      240
gtcattggta ccaatgccgt ttccatagaa acaaacatcc ccctgcagca aggaggccgg      300
attctgtgcc gggggaccca cgtgtacttg ggcgatgaca tgccggaccc agggcttgtg      360
cttgcaggca caaagtgtgc agatggaaaa atctgcctga atcgtcaatg tcaaatatt      420

```

<210> 394

<211> 176

<212> PRT

<213> Homo sapiens

<400> 394

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Arg Gly Val Ser Leu Trp Asn Gln Gly Arg Ala Asp Glu Val Val Ser
1           5           10          15

```

```

Ala Ser Val Arg Ser Gly Asp Leu Trp Ile Pro Val Lys Ser Phe Asp
          20          25          30

```

```

Ser Lys Asn His Pro Glu Val Leu Asn Ile Arg Leu Gln Arg Glu Ser
          35          40          45

```

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Lys Glu Leu Ile Ile Asn Leu Glu Arg Asn Glu Gly Leu Ile Ala Ser
 50 55 60

Ser Phe Thr Glu Thr His Tyr Leu Gln Asp Gly Thr Asp Val Ser Leu
 65 70 75 80

Ala Arg Asn Tyr Thr Gly His Cys Tyr Tyr His Gly His Val Arg Gly
 85 90 95

Tyr Ser Asp Ser Ala Val Ser Leu Ser Thr Cys Ser Gly Leu Arg Gly
 100 105 110

Leu Ile Val Phe Glu Asn Glu Ser Tyr Val Leu Glu Pro Met Lys Ser
 115 120 125

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

Arg Gly Ser Cys Gly Ser His His Asn Thr Pro Asn Leu Ala Ala Lys
 145 150 155 160

Asn Val Phe Pro Pro Pro Ser Gln Thr Trp Ala Arg Arg His Lys Arg
 165 170 175

<210> 395

<211> 179

<212> PRT

<213> Homo sapiens

<400> 395

Arg Gly Val Ser Leu Trp Asn Glu Gly Arg Ala Asp Glu Val Val Ser
 1 5 10 15

Ala Ser Val Arg Ser Gly Asp Leu Trp Ile Pro Val Lys Ser Phe Asp
 20 25 30

Ser Lys Asn His Pro Glu Val Leu Asn Ile Arg Leu Gln Arg Glu Ser
 35 40 45

Lys Glu Leu Ile Ile Asn Leu Glu Arg Asn Glu Gly Leu Ile Ala Ser
 50 55 60

Ser Phe Thr Glu Thr His Tyr Leu Gln Asp Gly Thr Asp Val Ser Leu
 65 70 75 80

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Ala Arg Asn Tyr Thr Val Ile Leu Gly His Cys Tyr Tyr His Gly His
85 90 95

Val Arg Gly Tyr Ser Asp Ser Ala Val Ser Leu Ser Thr Cys Ser Gly
100 105 110

Leu Arg Gly Leu Ile Val Phe Glu Asn Glu Ser Tyr Val Leu Glu Pro
115 120 125

Met Lys Ser Ala Thr Asn Arg Tyr Lys Leu Phe Pro Ala Lys Lys Leu
130 135 140

Lys Ser Val Arg Gly Ser Cys Gly Ser His His Asn Thr Pro Asn Leu
145 150 155 160

Ala Ala Lys Asn Val Phe Pro Pro Pro Ser Gln Thr Trp Ala Arg Arg
165 170 175

His Lys Arg

<210> 396

<211> 140

<212> PRT

<213> Homo sapiens

<400> 396

Ser Cys Gln Asp Val Asp Gly Tyr Cys Tyr Asn Gly Ile Cys Gln Thr
1 5 10 15

His Glu Gln Gln Cys Val Thr Leu Trp Gly Pro Gly Ala Lys Pro Ala
20 25 30

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

Asn Cys Gly Lys Val Ser Lys Ser Ser Phe Ala Lys Cys Glu Met Arg
50 55 60

Asp Ala Lys Cys Gly Lys Ile Gln Cys Gln Gly Gly Ala Ser Arg Pro
65 70 75 80

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

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Gln Gly Gly Arg Ile Leu Cys Arg Gly Thr His Val Tyr Leu Gly Asp
 100 105 110

Asp Met Pro Asp Pro Gly Leu Val Leu Ala Gly Thr Lys Cys Ala Asp
 115 120 125

Gly Lys Ile Cys Leu Asn Arg Gln Cys Gln Asn Ile
 130 135 140

<210> 397

<211> 22

<212> DNA

<213> Homo sapiens

<400> 397

gacaagtttg gctttggagg aa

22

<210> 398

<211> 19

<212> DNA

<213> Homo sapiens

<400> 398

gcgctccctg ttggactct

19

<210> 399

<211> 735

<212> PRT

<213> Homo sapiens

<400> 399

Met Ala Ala Arg Pro Leu Pro Val Ser Pro Ala Arg Ala Leu Leu Leu
 1 5 10 15

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

Leu Trp Asn Gln Gly Arg Ala Asp Glu Val Val Ser Ala Ser Val Arg
 35 40 45

Ser Gly Asp Leu Trp Ile Pro Val Lys Ser Phe Asp Ser Lys Asn His
 50 55 60

Pro Glu Val Leu Asn Ile Arg Leu Gln Arg Glu Ser Lys Glu Leu Ile
 65 70 75 80

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

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Thr His Tyr Leu Gln Asp Gly Thr Asp Val Ser Leu Ala Arg Asn Tyr
 100 105 110

Thr Gly His Cys Tyr Tyr His Gly His Val Arg Gly Tyr Ser Asp Ser
 115 120 125

Ala Val Ser Leu Ser Thr Cys Ser Gly Leu Arg Gly Leu Ile Val Phe
 130 135 140

Glu Asn Glu Ser Tyr Val Leu Glu Pro Met Lys Ser Ala Thr Asn Arg
 145 150 155 160

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

Gly Ser His His Asn Thr Pro Asn Leu Ala Ala Lys Asn Val Phe Pro
 180 185 190

Pro Pro Ser Gln Thr Trp Ala Arg Arg His Lys Arg Glu Thr Leu Lys
 195 200 205

Ala Thr Lys Tyr Val Glu Leu Val Ile Val Ala Asp Asn Arg Glu Phe
 210 215 220

Gln Arg Gln Gly Lys Asp Leu Glu Lys Val Lys Gln Arg Leu Ile Glu
 225 230 235 240

Ile Ala Asn His Val Asp Lys Phe Tyr Arg Pro Leu Asn Ile Arg Ile
 245 250 255

Val Leu Val Gly Val Glu Val Trp Asn Asp Met Asp Lys Cys Ser Val
 260 265 270

Ser Gln Asp Pro Phe Thr Ser Leu His Glu Phe Leu Asp Trp Arg Lys
 275 280 285

Met Lys Leu Leu Pro Arg Lys Ser His Asp Asn Ala Gln Leu Val Ser
 290 295 300

Gly Val Tyr Phe Gln Gly Thr Thr Ile Gly Met Ala Pro Ile Met Ser
 305 310 315 320

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Met Cys Thr Ala Asp Gln Ser Gly Gly Ile Val Met Asp His Ser Asp
325 330 335

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

Phe Gly Met Asn His Asp Thr Leu Asp Arg Gly Cys Ser Cys Gln Met
355 360 365

Ala Val Glu Lys Gly Gly Cys Ile Met Asn Ala Ser Thr Gly Tyr Pro
370 375 380

Phe Pro Met Val Phe Ser Ser Cys Ser Arg Lys Asp Leu Glu Thr Ser
385 390 395 400

Leu Glu Lys Gly Met Gly Val Cys Leu Phe Asn Leu Pro Glu Val Arg
405 410 415

Glu Ser Phe Gly Gly Gln Lys Cys Gly Asn Arg Phe Val Glu Glu Gly
420 425 430

Glu Glu Cys Asp Cys Gly Glu Pro Glu Glu Cys Met Asn Arg Cys Cys
435 440 445

Asn Ala Thr Thr Cys Thr Leu Lys Pro Asp Ala Val Cys Ala His Gly
450 455 460

Leu Cys Cys Glu Asp Cys Gln Leu Lys Pro Ala Gly Thr Ala Cys Arg
465 470 475 480

Asp Ser Ser Asn Ser Cys Asp Leu Pro Glu Phe Cys Thr Gly Ala Ser
485 490 495

Pro His Cys Pro Ala Asn Val Tyr Leu His Asp Gly His Ser Cys Gln
500 505 510

Asp Val Asp Gly Tyr Cys Tyr Asn Gly Ile Cys Gln Thr His Glu Gln
515 520 525

Gln Cys Val Thr Leu Trp Gly Pro Gly Ala Lys Pro Ala Pro Gly Ile
530 535 540

Cys Phe Glu Arg Val Asn Ser Ala Gly Asp Pro Tyr Gly Asn Cys Gly
545 550 555 560

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Lys Val Ser Lys Ser Ser Phe Ala Lys Cys Glu Met Arg Asp Ala Lys
565 570 575

Cys Gly Lys Ile Gln Cys Gln Gly Gly Ala Ser Arg Pro Val Ile Gly
580 585 590

Thr Asn Ala Val Ser Ile Glu Thr Asn Ile Pro Leu Gln Gln Gly Gly
595 600 605

Arg Ile Leu Cys Arg Gly Thr His Val Tyr Leu Gly Asp Asp Met Pro
610 615 620

Asp Pro Gly Leu Val Leu Ala Gly Thr Lys Cys Ala Asp Gly Lys Ile
625 630 635 640

Cys Leu Asn Arg Gln Cys Gln Asn Ile Ser Val Phe Gly Val His Glu
645 650 655

Cys Ala Met Gln Cys His Gly Arg Gly Val Cys Asn Asn Arg Lys Asn
660 665 670

Cys His Cys Glu Ala His Trp Ala Pro Pro Phe Cys Asp Lys Phe Gly
675 680 685

Phe Gly Gly Ser Thr Asp Ser Gly Pro Ile Arg Gln Ala Glu Ala Arg
690 695 700

Gln Glu Ala Ala Glu Ser Asn Arg Glu Arg Gly Gln Gly Gln Glu Pro
705 710 715 720

Val Gly Ser Gln Glu His Ala Ser Thr Ala Ser Leu Thr Leu Ile
725 730 735