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(54) Title: DIAGNOSIS OF PANCREATIC CANCER BY USING PANCREATIC TARGETS

Summary of CD49b Distribution in Tumors

Cancer Type	Number of Samples Analyzed	% Samples with Positive Staining			
		<50% Tumor Cells with 0/1+ Intensity	>50% Tumor Cells with 0/1+ Intensity	<50% Tumor Cells with 2+/3+ Intensity	>50% Tumor Cells with 2+/3+ Intensity
Pancreatic	10	0	0	0	100
Lung	10	30	0	0	70
Ovarian	10	40	10	40	10
Prostate	10	60	0	30	10
Colon	10	0	0	10	90
Breast	10	30	0	30	40

(57) Abstract: Methods and compositions for diagnosing, detecting a pancreatic disease associated with differential expression of PCATs (e.g., CD49b, CD51, CD71 and ECadherin) in comparison to healthy cells.

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DIAGNOSIS OF PANCREATIC CANCER BY USING PANCREATIC TARGETS**FIELD OF THE INVENTION**

[0001] This invention relates to the fields of molecular biology and oncology. Specifically, the invention provides a molecular marker and a therapeutic agent for use in the diagnosis and treatment of cancers.

BACKGROUND OF THE INVENTION

[0002] Cancer currently constitutes the second most common cause of death in the United States. Carcinomas of the pancreas are the eighth most prevalent form of cancer and fourth among the most common causes of cancer deaths in this country.

[0003] The prognosis for pancreatic carcinoma is, at present, very poor, it displays the lowest five-year survival rate among all cancers. Such prognosis results primarily from delayed diagnosis, due in part to the fact that the early symptoms are shared with other more common abdominal ailments. Despite the advances in diagnostic imaging methods like ultrasonography (US), endoscopic ultrasonography (EUS), dualphase spiral computer tomography (CT), magnetic resonance imaging (MRT), endoscopic retrograde cholangiopancreatography (ERCP) and transcutaneous or EUS-guided fine-needle aspiration (FNA), distinguishing pancreatic carcinoma from benign pancreatic diseases, especially chronic pancreatitis, is difficult because of the similarities in radiological and imaging features and the lack of specific clinical symptoms for pancreatic carcinoma.

[0004] Substantial efforts have been directed to developing tools useful for early diagnosis of pancreatic carcinomas. Nonetheless, a definitive diagnosis is often dependent on exploratory surgery which is inevitably performed after the disease has advanced past the point when early treatment may be effected.

[0005] One promising method for early diagnosis of various forms of cancer is the identification of specific biochemical moieties, termed targets, expressed differentially in the cancerous cells. The targets may be either cell surface proteins or cytosolic proteins. Antibodies or other biomolecules or small molecules which will specifically recognize

and bind to the targets in the cancerous cells potentially provide powerful tools for the diagnosis and treatment of the particular malignancy.

SUMMARY OF THE INVENTION

[0006] A diseased, e.g. malignant, cell often differs from a normal cell by a differential expression of one or more proteins. These differentially expressed proteins, and suitable fragments thereof, are useful as markers for the diagnosis and treatment of the disease.

[0007] Surprisingly, the present inventors discovered that CD49b, CD71, CD51 and E-Cadherin are differentially expressed in pancreatic tumor cells in comparison to normal pancreatic cells. Accordingly, the present invention provides methods and compositions for diagnosing pancreatic diseases, especially malignant pancreatic tumors, using CD49b, CD71, CD51 and E-Cadherin as a target. Pancreatic cancer differentiated protein or nucleic acid targets comprises CD49b (SEQ ID NO: 1 encoded by SEQ ID NO: 10; SEQ ID NO: 2 encoded by SEQ ID NO: 11; SEQ ID NO: 3 encoded by SEQ ID NO: 12), CD71 (SEQ ID NO: 4 encoded by SEQ ID NOS: 13 and 14; SEQ ID NO: 5 encoded by SEQ ID NO: 15), CD51 (SEQ ID NO: 6 encoded by SEQ ID NOS: 16 and 17), or E-Cadherin (SEQ ID NO: 7 encoded by SEQ ID NO: 18, SEQ ID NO: 8 encoded by SEQ ID NO: 19, SEQ ID NO: 9 encoded by SEQ ID NO: 20).

[0008] In the context of the present invention, the differentially expressed PCAT proteins CD49b, CD71, CD51 or E-Cadherin proteins (SEQ ID NOS: 1-9) and suitable fragments thereof, and nucleic acids encoding said protein (SEQ ID NOS: 10-20, which encode SEQ ID NOS: 1-9 as set forth above) and suitable fragments thereof, are respectfully referred to herein as pancreatic cancer associated target (PCAT) proteins, PCAT peptides or PCAT nucleic acids, and collectively as PCATs.

[0009] Specific uses of these PCATs are also provided based on its site of localization and protein characterization (e.g. receptor or enzyme). Some of the PCATs of the present invention serve as targets for one or more classes of therapeutic agents, while others may be suitable for antibody therapeutics. PCATs of the present invention

provide a target for diagnosing a pancreatic cancer or tumor, or predisposition to a pancreatic cancer or tumor mediated by the peptide. Accordingly, the invention provides methods for detecting the presence, or levels of, a PCAT of the present invention in a biological sample such as tissues, cells and biological fluids isolated from a subject.

[0010] The diagnosis method may detect PCAT nucleic acids, proteins, peptides and fragments thereof that are differentially expressed in pancreatic diseases in a test sample, preferably in a biological sample.

[0011] The further embodiment includes but is not limited to, monitoring the disease prognosis (recurrence), diagnosing disease stage, preventing the disease and treating the disease.

[0012] Accordingly, the present invention provides a method for diagnosing or detecting a pancreatic cancer or tumor in a subject comprising: determining the level of a PCAT in a test sample from said subject, wherein a differential level of said PCAT in said sample relative to the level in a control sample from a healthy subject, or the level established for a healthy subject, is indicative of the pancreatic cancer or tumor. The test sample includes but is not limited to a biological sample such as tissue, blood, serum or biological fluid.

[0013] The diagnostic method of the present invention may be suitable for monitoring the disease progression or the treatment progress.

[0014] The diagnostic method of the present invention may be suitable for other epithelial-cell related cancers, such as lung, colon, prostate, ovarian, breast, bladder renal, hepatocellular, pharyngeal, and gastric cancers. In one embodiment, the diagnosis method of the present invention utilizes an array, which is immobilized with two or more PCATs.

[0015] The present invention further provide a composition comprising a plurality of nucleic acids for use in detecting the altered expression of genes in a pancreatic diseased state, wherein said plurality of nucleic acids comprises two or more nucleic acid sequence selected from group consisting of SEQ ID NOS: 10-20 or the complete complements

thereof.. The said nucleic acid sequences are immobilized on a substrate and are hybridizable elements on a microarray.

[0016] The present invention further provide a method for diagnosing or monitoring the treatment of a pancreatic disease in a sample, said method comprising: a) obtaining nucleic acids from a sample; b) contacting the nucleic acids of the sample with an array comprising the plurality of two or more nucleic acids selected from a group consisting of SEQ ID NOS 10-20 under conditions to form one or more hybridization complexes; c) detecting said hybridization complexes; and d) comparing the levels of the hybridization complexes detected in step (c) the level of hybridization complexes detected in a control sample, wherein the altered level of hybridization complexes detected in step (c) compared with the level of hybridization complexes of a control sample correlates with the presence of pancreatic disease.

[0017] The present invention further provides a composition comprising a plurality of two or more proteins for use in detecting the altered expression of genes in a pancreatic diseased state, wherein said plurality of protein are selected from a group consisting of SEQ ID NOS: 1-9, wherein said proteins are immobilized on a substrate.

[0018] The present invention provides a method for diagnosing or monitoring the treatment of a pancreatic disease in a sample, said method comprising: a) obtaining proteins from a sample; b) contacting the proteins of the sample with an array comprising the plurality of two or more antibodies against proteins selected from a group consisting of SEQ ID NOS 1-9; c) detecting said immunocomplex; and d) comparing the levels of the immunocomplexes detected in step (c) the level of hybridization complexes detected in a control sample, wherein the altered level of immunocomplexes detected in step (c) compared with the level of immunocomplexes of a control sample correlates with the presence of pancreatic disease.

DESCRIPTION OF FIGURES

[0019] **Figure 1** Immunohistochemistry studies on various cancer types using anti-CD49b antibody.

[0020] **Figure 2.** Overexpression of peptides correspond to the PCAT proteins in pancreatic cell lines. The protein sequence identification number, the pancreatic cancer cell lines, the expression information, the ratio compare to the control sample are disclosed. The expression is based on measuring the level of the peptides. Numerical representation of overexpression is indicated by more than two. Overexpressed singleton indicates that the peptide peak in diseased sample was detected and there was no peak detected in control samples. .

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS:

1. PCAT Proteins and Peptides

[0021] The present invention provides isolated PCAT peptide and protein molecules consisting of, consisting essentially of, or comprising the amino acid sequences of SEQ ID NOs: 1-9, respectively encoded by the nucleic acid molecules having the nucleotide sequences of SEQ ID NOs: 10-20., as well as all obvious variants of these peptides that are within the art to make and use. Some of these variants are described in detail below.

[0022] A PCAT peptide or protein can be attached to heterologous sequences to form chimeric or fusion proteins. Such chimeric and fusion proteins comprise a peptide operatively linked to a heterologous protein having an amino acid sequence not substantially homologous to the peptide. "Operatively linked" indicates that the peptide and the heterologous protein are fused in-frame. The heterologous protein can be fused to the N-terminus or C-terminus of the peptide.

[0023] In some uses, the fusion protein does not affect the activity of the peptide or protein per se. For example, the fusion protein can include, but is not limited to, fusion proteins, for example beta-galactosidase fusions, yeast two-hybrid GAL fusions, poly-His fusions, MYC-tagged, HI-tagged and Ig fusions. Such fusion proteins, particularly poly-His fusions, can facilitate the purification of recombinant PCAT proteins or peptides. In certain host cells (e.g., mammalian host cells), expression and/or secretion of a protein can be increased by using a heterologous signal sequence.

[0024] A chimeric or fusion PCAT protein or peptide can be produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different protein sequences are ligated together in-frame in accordance with conventional techniques. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene fragments which can subsequently be annealed and re-amplified to generate a chimeric gene sequence (see Ausubel et al., Current Protocols in Molecular Biology, 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety (e.g., a GST protein). A PCAT-encoding nucleic acid can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the PCAT protein or peptide.

[0025] Variants of the PCAT proteins can readily be identified/made using molecular techniques and the sequence information disclosed herein. Further, such variants can readily be distinguished from other peptides based on sequence and/or structural homology to the PCAT peptides of the present invention. The degree of homology/identity present will be based primarily on whether the peptide is a functional variant or non-functional variant, the amount of divergence present in the paralog family and the evolutionary distance between the orthologs.

[0026] To determine the percent identity of two amino acid sequences or two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in one or both of a first and a second amino acid or nucleic acid sequence for optimal alignment and non-homologous sequences can be disregarded for comparison purposes). In a preferred embodiment, at least 30%, 40%, 50%, 60%, 70%, 80%, or 90% or more of the length of a reference sequence is aligned for comparison purposes. The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position (as used herein amino acid or nucleic acid "identity" is equivalent to amino acid or nucleic acid

"homology"). The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences.

[0027] The comparison of sequences and determination of percent identity and similarity between two sequences can be accomplished using a mathematical algorithm. (Computational Molecular Biology, Lesk, A.M., ed., Oxford University Press, New York, 1988; Biocomputing: Informatics and Genome Projects, Smith, D.W., ed., Academic Press, New York, 1993; Computer Analysis of Sequence Data, Part 1, Griffin, A.M., and Griffin, H.G., eds., Humana Press, New Jersey, 1994; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991). In a preferred embodiment, the percent identity between two amino acid sequences is determined using the Needleman and Wunsch (J. Mol. Biol. (48):444-453 (1970)) algorithm which has been incorporated into the GAP program in the GCG software package, using either a Blossum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. In yet another preferred embodiment, the percent identity between two nucleotide sequences is determined using the GAP program in the GCG software package (Devereux, J., et al., Nucleic Acids Res. 12(1):387 (1984)), using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. In another embodiment, the percent identity between two amino acid or nucleotide sequences is determined using the algorithm of E. Myers and W. Miller (CABIOS, 4:11-17 (1989)) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4.

[0028] The nucleic acids and protein sequences of the present invention can further be used as a "query sequence" to perform a search against sequence databases to, for example, identify other family members or related sequences. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul, et al. (J. Mol. Biol. 215:403-10 (1990)). BLAST nucleotide searches can be performed with the

NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to the nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to the proteins of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al. (Nucleic Acids Res. 25(17):3389-3402 (1997)). When utilizing BLAST and gapped BLAST programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used.

[0029] Allelic variants of a PCAT peptide can readily be identified as being a human protein having a high degree (significant) of sequence homology/identity to at least a portion of the PCAT peptide as well as being encoded by the same genetic locus as the PCAT peptide provided herein. Genetic locus can readily be determined based on the genomic information provided in sequence listing, such as the genomic sequence mapped to the reference human. As used herein, two proteins (or a region of the proteins) have significant homology when the amino acid sequences are typically at least about 70-80%, 80-90%, and more typically at least about 90-95% or more homologous. A significantly homologous amino acid sequence, according to the present invention, will be encoded by a nucleic acid sequence that will hybridize to a PCAT peptide encoding nucleic acid molecule under stringent conditions as more fully described below.

[0030] Paralogs of a PCAT peptide can readily be identified as having some degree of significant sequence homology/identity to at least a portion of the PCAT peptide, as being encoded by a gene from humans, and as having similar activity or function. Two proteins will typically be considered paralogs when the amino acid sequences are typically at least about 60% or greater, and more typically at least about 70% or greater homology through a given region or domain. Such paralogs will be encoded by a nucleic acid sequence that will hybridize to a PCAT peptide encoding nucleic acid molecule under moderate to stringent conditions as more fully described below.

[0031] Orthologs of a PCAT peptide can readily be identified as having some degree of significant sequence homology/identity to at least a portion of the PCAT peptide as

well as being encoded by a gene from another organism. Preferred orthologs will be isolated from mammals, preferably primates, for the development of human therapeutic targets and agents. Such orthologs will be encoded by a nucleic acid sequence that will hybridize to a PCAT peptide encoding nucleic acid molecule under moderate to stringent conditions, as more fully described below, depending on the degree of relatedness of the two organisms yielding the proteins.

[0032] Non-naturally occurring variants of the PCAT peptides of the present invention can readily be generated using recombinant techniques. Such variants include, but are not limited to deletions, additions and substitutions in the amino acid sequence of the PCAT peptide. For example, one class of substitutions is conserved amino acid substitution. Such substitutions are those that substitute a given amino acid in a PCAT peptide by another amino acid of like characteristics. Typically seen as conservative substitutions are the replacements, one for another, among the aliphatic amino acids Ala, Val, Leu, and Ile; interchange of the hydroxyl residues Ser and Thr; exchange of the acidic residues Asp and Glu; substitution between the amide residues Asn and Gln; exchange of the basic residues Lys and Arg; and replacements among the aromatic residues Phe and Tyr. Guidance concerning which amino acid changes are likely to be phenotypically silent are found in Bowie et al., Science 247:1306-1310 (1990).

[0033] Variant PCAT peptides can be fully functional or can lack function in one or more activities, e.g. ability to bind substrate, ability to phosphorylate substrate, ability to mediate signaling, etc. Fully functional variants typically contain only conservative variation or variation in non-critical residues or in non-critical regions.

[0034] Non-functional variants typically contain one or more non-conservative amino acid substitutions, deletions, insertions, inversions, or truncation or a substitution, insertion, inversion, or deletion in a critical residue or critical region.

[0035] Amino acids that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham et al., Science 244:1081-1085 (1989)). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant

molecules are then tested for biological activity such as PCAT activity or in vitro proliferative activity. Sites that are critical for binding partner/substrate binding can also be determined by structural analysis such as X-ray crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith et al., J. Mol. Biol. 224:899-904 (1992); de Vos et al. Science 255:306-312 (1992)).

[0036] The present invention further provides fragments of the PCATs, in addition to proteins and peptides that comprise and consist of such fragments. As used herein, a fragment comprises at least 8, 10, 12, 14, 16, 18, 20 or more contiguous amino acid residues from a PCAT. Such fragments can be chosen based on the ability to retain one or more of the biological activities of the PCAT or could be chosen for the ability to perform a function, e.g. bind a substrate or act as an immunogen. Particularly important fragments are biologically active fragments, peptides that are, for example, about 8 or more amino acids in length. Such fragments will typically comprise a domain or motif of the PCAT, e.g., active site, a transmembrane domain or a substrate-binding domain. Further, possible fragments include, but are not limited to, domain or motif containing fragments, soluble peptide fragments, and fragments containing immunogenic structures. Predicted domains and functional sites are readily identifiable by computer programs well known and readily available to those of skill in the art (e.g., PROSITE analysis).

[0037] Polypeptides often contain amino acids other than the 20 amino acids commonly referred to as the 20 naturally occurring amino acids. Further, many amino acids, including the terminal amino acids, may be modified by natural processes, such as processing and other post-translational modifications, or by chemical modification techniques well known in the art. Common modifications that occur naturally in PCATs are described in basic texts, detailed monographs, and the research literature, and they are well known to those of skill in the art.

[0038] Known modifications include, but are not limited to, acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol,

cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent crosslinks, formation of cystine, formation of pyroglutamate, formylation, gamma carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination.

[0039] Such modifications are well known to those of skill in the art and have been described in great detail in the scientific literature. Several particularly common modifications, glycosylation, lipid attachment, sulfation, gamma-carboxylation of glutamic acid residues, hydroxylation and ADP-ribosylation, for instance, are described in most basic texts, such as *Proteins - Structure and Molecular Properties*, 2nd Ed., T.E. Creighton, W. H. Freeman and Company, New York (1993). Many detailed reviews are available on this subject, such as by Wold, F., *Posttranslational Covalent Modification of Proteins*, B.C. Johnson, Ed., Academic Press, New York 1-12 (1983); Seifter et al. (*Meth. Enzymol.* 182: 626-646 (1990)) and Rattan et al. (*Ann. N.Y. Acad. Sci.* 663:48-62 (1992)).

[0040] Accordingly, the PCATs of the present invention also encompass derivatives or analogs in which a substituted amino acid residue is not one encoded by the genetic code, in which a substituent group is included, in which the mature PCAT is fused with another compound, such as a compound to increase the half-life of the PCAT (for example, polyethylene glycol), or in which the additional amino acids are fused to the mature PCAT, such as a leader or secretory sequence or a sequence for purification of the mature PCAT or a pro-protein sequence.

2. Antibodies against PCAT Proteins or Fragments Thereof

[0041] Antibodies that selectively bind to one of the PCAT proteins or peptides of the present invention can be made using standard procedures known to those of ordinary skills in the art. The term "antibody" is used in the broadest sense, and specifically covers monoclonal antibodies (including full length monoclonal antibodies), polyclonal antibodies, multispecific antibodies (e.g., bispecific antibodies), humanized antibody and

antibody fragments (e.g., Fab, F(ab')₂ and Fv) so long as they exhibit the desired biological activity. Antibodies (Abs) and immunoglobulins (Igs) are glycoproteins having the same structural characteristics. While antibodies exhibit binding specificity to a specific antigen, immunoglobulins include both antibodies and other antibody-like molecules that lack antigen specificity.

[0042] As used herein, antibodies are usually heterotetrameric glycoproteins of about 150,000 daltons, composed of two identical light (L) chains and two identical heavy (H) chains. Each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies between the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intrachain disulfide bridges. Each heavy chain has at one end a variable domain (VH) followed by a number of constant domains. Each light chain has a variable domain at one end (VL) and a constant domain at its other end. The constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light chain variable domain is aligned with the variable domain of the heavy chain. Particular amino acid residues are believed to form an interface between the light and heavy chain variable domains. Chothia et al., *J. Mol. Biol.* 186, 651-63 (1985); Novotny and Haber, *Proc. Natl. Acad. Sci. USA* 82 4592-4596 (1985).

[0043] An "isolated" antibody is one, which has been identified and separated and/or recovered from a component of the environment in which it is produced. Contaminant components of its production environment are materials that would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the antibody will be purified as measurable by at least three different methods: 1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight; 2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator; or 3) to homogeneity by SDS-PAGE under reducing or non-reducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody in situ within recombinant cells since at least one component of the antibody's natural environment will

not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

[0044] An “antigenic region” or “antigenic determinant” or an “epitope” includes any protein determinant capable of specific binding to an antibody. This is the site on an antigen to which each distinct antibody molecule binds. Epitopic determinants usually consist of active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three-dimensional structural characteristics, as well as charge characteristics.

[0045] “Antibody specificity,” is an antibody, which has a stronger binding affinity for an antigen from a first subject species than it has for a homologue of that antigen from a second subject species. Normally, the antibody “bind specifically” to a human antigen (i.e., has a binding affinity (Kd) value of no more than about 1×10^{-7} M, preferably no more than about 1×10^{-8} M and most preferably no more than about 1×10^{-9} M) but has a binding affinity for a homologue of the antigen from a second subject species which is at least about 50 fold, or at least about 500 fold, or at least about 1000 fold, weaker than its binding affinity for the human antigen. The antibody can be of any of the various types of antibodies as defined above, but preferably is a humanized or human antibody (Queen et al., US Patent Nos. 5,530,101, 5,585,089; 5,693,762; and 6,180,370).

[0046] The present invention provides an “antibody variant,” which refers to an amino acid sequence variant of an antibody wherein one or more of the amino acid residues have been modified. Such variant necessarily have less than 100% sequence identity or similarity with the amino acid sequence having at least 75% amino acid sequence identity or similarity with the amino acid sequence of either the heavy or light chain variable domain of the antibody, more preferably at least 80%, more preferably at least 85%, more preferably at least 90%, and most preferably at least 95%. Since the method of the invention applies equally to both polypeptides, antibodies and fragments thereof, these terms are sometimes employed interchangeably.

[0047] The term “antibody fragment” refers to a portion of a full-length antibody, generally the antigen binding or variable region. Examples of antibody fragments include

Fab, Fab', F(ab')₂ and Fv fragments. Papain digestion of antibodies produces two identical antigen binding fragments, called the Fab fragment, each with a single antigen binding site, and a residual "Fc" fragment, so-called for its ability to crystallize readily. Pepsin treatment yields an F(ab')₂ fragment that has two antigen binding fragments which are capable of crosslinking antigen, and a residual other fragment (which is termed pFc'). Additional fragments can include diabodies, linear antibodies, single-chain antibody molecules, and multispecific antibodies formed from antibody fragments. As used herein, "functional fragment" with respect to antibodies, refers to Fv, F(ab) and F(ab')₂ fragments.

[0048] An "Fv" fragment is the minimum antibody fragment that contains a complete antigen recognition and binding site. This region consists of a dimer of one heavy and one light chain variable domain in a tight, non-covalent association (V_H-V_L dimer). It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the V_H-V_L dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

[0049] The Fab fragment [also designated as F(ab)] also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab' fragments differ from Fab fragments by the addition of a few residues at the carboxyl terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains have a free thiol group. F(ab') fragments are produced by cleavage of the disulfide bond at the hinge cysteines of the F(ab')₂ pepsin digestion product. Additional chemical couplings of antibody fragments are known to those of ordinary skill in the art.

[0050] The present invention further provides monoclonal antibodies, polyclonal antibodies. In general, to generate antibodies, an isolated peptide is used as an immunogen

and is administered to a mammalian organism, such as a rat, rabbit or mouse. The full-length protein, an antigenic peptide fragment or a fusion protein of the PCAT protein can be used. Particularly important fragments are those covering functional domains. Many methods are known for generating and/or identifying antibodies to a given target peptide. Several such methods are described by Harlow, *Antibodies*, Cold Spring Harbor Press, (1989).

[0051] The term “monoclonal antibody” as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody preparations which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they are synthesized by the hybridoma culture, uncontaminated by other immunoglobulins. The modifier “monoclonal” antibody indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by the hybridoma method first described by Kohler and Milstein, *Nature* 256, 495 (1975), or may be made by recombinant methods, e.g., as described in U.S. Pat. No. 4,816,567. The monoclonal antibodies for use with the present invention may also be isolated from phage antibody libraries using the techniques described in Clackson et al., *Nature* 352: 624-628 (1991), as well as in Marks et al., *J. Mol. Biol.* 222: 581-597 (1991). For detailed procedures for making a monoclonal antibody, see the Example below.

[0052] Polyclonal antibodies may be prepared by any known method or modifications of these methods including obtaining antibodies from patients. For example, a complex of an immunogen such as PCAT protein, peptides or fragments thereof and a carrier protein is prepared and an animal is immunized by the complex

according to the same manner as that described with respect to the above monoclonal antibody preparation and the description in the Example. A serum or plasma containing the antibody against the protein is recovered from the immunized animal and the antibody is separated and purified. The gamma globulin fraction or the IgG antibodies can be obtained, for example, by use of saturated ammonium sulfate or DEAE SEPHADEX, or other techniques known to those skilled in the art.

[0053] The antibody titer in the antiserum can be measured according to the same manner as that described above with respect to the supernatant of the hybridoma culture. Separation and purification of the antibody can be carried out according to the same separation and purification method of antibody as that described with respect to the above monoclonal antibody and in the Example.

[0054] The protein used herein as the immunogen is not limited to any particular type of immunogen. In one aspect, antibodies are preferably prepared from regions or discrete fragments of the PCAT proteins. Antibodies can be prepared from any region of the peptide as described herein. In particular, they are selected from a group consisting of SEQ ID NOS: 1-9 and fragments thereof. An antigenic fragment will typically comprise at least 8 contiguous amino acid residues. The antigenic peptide can comprise, however, at least 10, 12, 14, 16 or more amino acid residues. Such fragments can be selected on a physical property, such as fragments correspond to regions that are located on the surface of the protein, e.g., hydrophilic regions or can be selected based on sequence uniqueness.

[0055] Antibodies may also be produced by inducing production in the lymphocyte population or by screening antibody libraries or panels of highly specific binding reagents as disclosed in Orlandi et al. (1989; Proc Natl Acad Sci 86:3833-3837) or Winter et al. (1991; Nature 349:293-299). A protein may be used in screening assays of phagemid or B-lymphocyte immunoglobulin libraries to identify antibodies having a desired specificity. Numerous protocols for competitive binding or immunoassays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Smith G. P., 1991, Curr. Opin. Biotechnol. 2: 668-673.

[0056] The antibodies of the present invention can also be generated using various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles, which carry the polynucleotide sequences encoding them. In a particular, such phage can be utilized to display antigen-binding domains expressed from a repertoire or combinatorial antibody library (e.g., human or murine). Phage expressing an antigen binding domain that binds the antigen of interest can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid surface or bead. Phage used in these methods are typically filamentous phage including fd and M13 binding domains expressed from phage with Fab, Fv or disulfide stabilized Fv antibody domains recombinantly fused to either the phage gene III or gene VIII protein. Examples of phage display methods that can be used to make the antibodies of the present invention include those disclosed in Brinkman et al., J. Immunol. Methods 182:41-50 (1995); Ames et al., J. Immunol. Methods 184:177-186 (1995); Kettleborough et al., Eur. J. Immunol. 24:952-958 (1994); Persic et al., Gene 187 9-18 (1997); Burton et al., Advances in Immunology 57:191-280 (1994); PCT application No. PCT/GB91/01134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; and U.S. Pat. Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

[0057] Antibody can be also made recombinantly. When using recombinant techniques, the antibody variant can be produced intracellularly, in the periplasmic space, or directly secreted into the medium. If the antibody variant is produced intracellularly, as a first step, the particulate debris, either host cells or lysed fragments, is removed, for example, by centrifugation or ultrafiltration. Carter et al., Bio/Technology 10: 163-167 (1992) describe a procedure for isolating antibodies which are secreted to the periplasmic space of *E. coli*. Briefly, cell paste is thawed in the presence of sodium acetate (pH 3.5), EDTA, and phenylmethylsulfonylfluoride (PMSF) over about 30 minutes. Cell debris can be removed by centrifugation. Where the antibody variant is secreted into the medium, supernatants from such expression systems are generally first concentrated using a commercially available protein concentration filter, for example, an Amicon or Millipore

PELLICON ultrafiltration unit. A protease inhibitor such as PMSF may be included in any of the foregoing steps to inhibit proteolysis and antibiotics may be included to prevent the growth of adventitious contaminants.

[0058] The antibodies or antigen binding fragments may also be produced by genetic engineering. The technology for expression of both heavy and light chain genes in *E. coli* is the subject the following PCT patent applications; publication number WO 901443, WO901443, and WO 9014424 and in Huse et al., 1989 Science 246:1275-1281. The general recombinant methods are well known in the art.

[0059] The antibody composition prepared from the cells can be purified using, for example, hydroxylapatite chromatography, gel electrophoresis, dialysis, and affinity chromatography, with affinity chromatography being the preferred purification technique. The suitability of protein A as an affinity ligand depends on the species and isotype of any immunoglobulin Fc domain that is present in the antibody. Protein A can be used to purify antibodies that are based on human $\delta 1$, $\delta 2$ or $\delta 4$ heavy chains (Lindmark et al., J. Immunol Meth. 62: 1-13 (1983)). Protein G is recommended for all mouse isotypes and for human $\delta 3$ (Guss et al., EMBO J. 5: 1567-1575 (1986)). The matrix to which the affinity ligand is attached is most often agarose, but other matrices are available. Mechanically stable matrices such as controlled pore glass or poly(styrenedivinyl)benzene allow for faster flow rates and shorter processing times than can be achieved with agarose. Where the antibody comprises a CH3 domain, the Bakerbond ABXTM resin (J.T. Baker, Phillipsburg, N.J.) is useful for purification. Other techniques for protein purification such as fractionation on an ion-exchange column, ethanol precipitation, Reverse Phase HPLC, chromatography on silica, chromatography on heparin SEPHAROSE chromatography on an anion or cation exchange resin (such as a polyaspartic acid column), chromatofocusing, SDS-PAGE, and ammonium sulfate precipitation are also available depending on the antibody to be recovered.

[0060] Following any preliminary purification step(s), the mixture comprising the antibody of interest and contaminants may be subjected to low pH hydrophobic

interaction chromatography using an elution buffer at a pH between about 2.5-4.5, preferably performed at low salt concentrations (e.g., from about 0-0.25M salt).

3. PCAT Nucleic Acid Molecules

[0061] Isolated PCAT nucleic acid molecules of the present invention consist of, consist essentially of, or comprise a nucleotide sequence that encodes one of the PCAT peptides of the present invention, an allelic variant thereof, or an ortholog or paralog thereof, particularly SEQ ID NOS: 10-20. As used herein, an “isolated” nucleic acid molecule is one that is separated from other nucleic acid present in the natural source of the nucleic acid. Preferably, an “isolated” nucleic acid is free of sequences which naturally flank the nucleic acid (i.e., sequences located at the 5' and 3' ends of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. However, there can be some flanking nucleotide sequences, for example up to about 5KB, 4KB, 3KB, 2KB, or 1KB or less, particularly contiguous peptide encoding sequences and peptide encoding sequences within the same gene but separated by introns in the genomic sequence. The important point is that the nucleic acid is isolated from remote and unimportant flanking sequences such that it can be subjected to the specific manipulations described herein such as recombinant expression, preparation of probes and primers, and other uses specific to the nucleic acid sequences.

[0062] Moreover, an “isolated” nucleic acid molecule, such as a transcript/cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or chemical precursors or other chemicals when chemically synthesized. However, the nucleic acid molecule can be fused to other coding or regulatory sequences and still be considered isolated.

[0063] For example, recombinant DNA molecules contained in a vector are considered isolated. Further examples of isolated DNA molecules include recombinant DNA molecules maintained in heterologous host cells or purified (partially or substantially) DNA molecules in solution. Isolated RNA molecules include in vivo or in vitro RNA transcripts of the isolated DNA molecules of the present invention. Isolated

nucleic acid molecules according to the present invention further include such molecules produced synthetically.

[0064] The isolated nucleic acid molecules can encode the mature protein plus additional amino or carboxyl-terminal amino acids, or amino acids interior to the mature peptide (when the mature form has more than one peptide chain, for instance). Such sequences may play a role in processing of a protein from precursor to a mature form, facilitate protein trafficking, prolong or shorten protein half-life or facilitate manipulation of a protein for assay or production, among other things. As generally is the case in situ, the additional amino acids may be processed away from the mature protein by cellular enzymes.

[0065] As mentioned above, the isolated nucleic acid molecules include, but are not limited to, the sequence encoding the PCAT peptide alone, the sequence encoding the mature peptide and additional coding sequences, such as a leader or secretory sequence (e.g., a pre-pro or pro-protein sequence), the sequence encoding the mature peptide, with or without the additional coding sequences, plus additional non-coding sequences, for example introns and non-coding 5' and 3' sequences such as transcribed but non-translated sequences that play a role in transcription, mRNA processing (including splicing and polyadenylation signals), ribosome binding and stability of mRNA. In addition, the nucleic acid molecule may be fused to a marker sequence encoding, for example, a peptide that facilitates purification.

[0066] Isolated nucleic acid molecules can be in the form of RNA, such as mRNA, or in the form DNA, including cDNA and genomic DNA obtained by cloning or produced by chemical synthetic techniques or by a combination thereof. The nucleic acid, especially DNA, can be double-stranded or single-stranded. Single-stranded nucleic acid can be the coding strand (sense strand) or the non-coding strand (anti-sense strand).

[0067] The invention further provides nucleic acid molecules that encode fragments of the proteins of the present invention as well as nucleic acid molecules that encode obvious variants of the PCAT proteins of the present invention that are described above. Such nucleic acid molecules may be naturally occurring, such as allelic variants (same

locus), paralogs (different locus), and orthologs (different organism), or may be constructed by recombinant DNA methods or by chemical synthesis. Such non-naturally occurring variants may be made by mutagenesis techniques, including those applied to nucleic acid molecules, cells, or organisms. Accordingly, as discussed above, the variants can contain nucleotide substitutions, deletions, inversions and insertions. Variation can occur in either or both the coding and non-coding regions. The variations can produce both conservative and non-conservative amino acid substitutions.

[0068] A fragment comprises a contiguous nucleotide sequence greater than 12 or more nucleotides. Further, a fragment could at least 30, 40, 50, 100, 250 or 500 nucleotides in length. The length of the fragment will be based on its intended use. For example, the fragment can encode epitope bearing regions of the peptide, or can be useful as DNA probes and primers. Such fragments can be isolated using the known nucleotide sequence to synthesize an oligonucleotide probe. A labeled probe can then be used to screen a cDNA library, genomic DNA library, or mRNA to isolate nucleic acid corresponding to the coding region. Further, primers can be used in PCR reactions to clone specific regions of the gene.

[0069] A probe/primer typically comprises substantially a purified oligonucleotide or oligonucleotide pair. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12, 20, 25, 40, 50 or more consecutive nucleotides.

[0070] Orthologs, homologs, and allelic variants can be identified using methods well known in the art. As described in the Peptide Section, these variants comprise a nucleotide sequence encoding a peptide that is typically 60-70%, 70-80%, 80-90%, and more typically at least about 90-95% or more homologous to the nucleotide sequence. Such nucleic acid molecules can readily be identified as being able to hybridize under moderate to stringent conditions, to the nucleotide sequence shown in the Figure sheets or a fragment of the sequence. Allelic variants can readily be determined by genetic locus of the encoding gene.

[0071] As used herein, the term “hybridizes under stringent conditions” is intended to describe conditions for hybridization and washing under which nucleotide sequences encoding a peptide at least 60-70% homologous to each other typically remain hybridized to each other. The conditions can be such that sequences at least about 60%, at least about 70%, or at least about 80% or more homologous to each other typically remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found in Current Protocols in Molecular Biology, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. One example of stringent hybridization conditions is hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2 X SSC, 0.1% SDS at 50-65°C. Examples of moderate to low stringency hybridization conditions are well known in the art.

4. Vectors and Host Cells

[0072] The invention also provides vectors containing the nucleic acid molecules described herein. The term “vector” refers to a vehicle, preferably a nucleic acid molecule, which can transport the nucleic acid molecules. When the vector is a nucleic acid molecule, the nucleic acid molecules are covalently linked to the vector nucleic acid. With this aspect of the invention, the vector includes a plasmid, single or double stranded phage, a single or double stranded RNA or DNA viral vector, or artificial chromosome, such as a BAC, PAC, YAC, OR MAC.

[0073] A vector can be maintained in the host cell as an extrachromosomal element where it replicates and produces additional copies of the nucleic acid molecules. Alternatively, the vector may integrate into the host cell genome and produce additional copies of the nucleic acid molecules when the host cell replicates.

[0074] The invention provides vectors for the maintenance (cloning vectors) or vectors for expression (expression vectors) of the nucleic acid molecules. The vectors can function in prokaryotic or eukaryotic cells or in both (shuttle vectors).

[0075] Expression vectors contain cis-acting regulatory regions that are operably linked in the vector to the nucleic acid molecules such that transcription of the nucleic

acid molecules is allowed in a host cell. The nucleic acid molecules can be introduced into the host cell with a separate nucleic acid molecule capable of affecting transcription. Thus, the second nucleic acid molecule may provide a trans-acting factor interacting with the cis-regulatory control region to allow transcription of the nucleic acid molecules from the vector. Alternatively, a trans-acting factor may be supplied by the host cell. Finally, a trans-acting factor can be produced from the vector itself. It is understood, however, that in some embodiments, transcription and/or translation of the nucleic acid molecules can occur in a cell-free system.

[0076] The regulatory sequences to which the nucleic acid molecules described herein can be operably linked include promoters for directing mRNA transcription. These include, but are not limited to, the left promoter from bacteriophage, the lac, TRP, and TAC promoters from *E. coli*, the early and late promoters from SV40, the CMV immediate early promoter, the adenovirus early and late promoters, and retrovirus long-terminal repeats.

[0077] In addition to control regions that promote transcription, expression vectors may also include regions that modulate transcription, such as repressor binding sites and enhancers. Examples include the SV40 enhancer, the cytomegalovirus immediate early enhancer, polyoma enhancer, adenovirus enhancers, and retrovirus LTR enhancers.

[0078] In addition to containing sites for transcription initiation and control, expression vectors can also contain sequences necessary for transcription termination and, in the transcribed region a ribosome binding site for translation. Other regulatory control elements for expression include initiation and termination codons as well as polyadenylation signals. The person of ordinary skill in the art would be aware of the numerous regulatory sequences that are useful in expression vectors. Such regulatory sequences are described, for example, in Sambrook et al., *Molecular Cloning: A Laboratory Manual*. 3rd. ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, (2001).

[0079] A variety of expression vectors can be used to express a nucleic acid molecule. Such vectors include chromosomal, episomal, and virus-derived vectors, for

example vectors derived from bacterial plasmids, from bacteriophage, from yeast episomes, from yeast chromosomal elements, including yeast artificial chromosomes, from viruses such as baculoviruses, papovaviruses such as SV40, Vaccinia viruses, adenoviruses, poxviruses, pseudorabies viruses, and retroviruses. Vectors may also be derived from combinations of these sources such as those derived from plasmid and bacteriophage genetic elements, e.g. cosmids and phagemids. Appropriate cloning and expression vectors for prokaryotic and eukaryotic hosts are described in Sambrook et al., *Molecular Cloning: A Laboratory Manual*. 3rd. ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, (2001).

[0080] The regulatory sequence may provide constitutive expression in one or more host cells (i.e. tissue specific) or may provide for inducible expression in one or more cell types such as by temperature, nutrient additive, or exogenous factor such as a hormone or other ligand. A variety of vectors providing for constitutive and inducible expression in prokaryotic and eukaryotic hosts are well known to those of ordinary skill in the art.

[0081] The nucleic acid molecules can be inserted into the vector nucleic acid by well-known methodologies. Generally, the DNA sequence that will ultimately be expressed is joined to an expression vector by cleaving the DNA sequence and the expression vector with one or more restriction enzymes and then ligating the fragments together. Procedures for restriction enzyme digestion and ligation are well known to those of ordinary skill in the art.

[0082] The vector containing the appropriate nucleic acid molecule can be introduced into an appropriate host cell for propagation or expression using well-known techniques. Bacterial cells include, but are not limited to, *E. coli*, *Streptomyces*, and *Salmonella typhimurium*. Eukaryotic cells include, but are not limited to, yeast, insect cells such as *Drosophila*, animal cells such as COS and CHO cells, and plant cells.

[0083] As described herein, it may be desirable to express the peptide as a fusion protein. Accordingly, the invention provides fusion vectors that allow for the production of the peptides. Fusion vectors can increase the expression of a recombinant protein; increase the solubility of the recombinant protein, and aid in the purification of the

protein by acting for example as a ligand for affinity purification. A proteolytic cleavage site may be introduced at the junction of the fusion moiety so that the desired peptide can ultimately be separated from the fusion moiety. Proteolytic enzymes include, but are not limited to, factor Xa, thrombin, and enteroenzyme. Typical fusion expression vectors include pGEX (Smith et al., Gene 67:31-40 (1988)), pMAL (New England Biolabs, Beverly, MA) and pRIT5 (Pharmacia, Piscataway, NJ) which fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein. Examples of suitable inducible non-fusion *E. coli* expression vectors include pTrc (Amann et al., Gene 69:301-315 (1988)) and pET 11d (Studier et al., Gene Expression Technology: Methods in Enzymology 185:60-89 (1990)).

[0084] Recombinant protein expression can be maximized in host bacteria by providing a genetic background wherein the host cell has an impaired capacity to proteolytically cleave the recombinant protein. (Gottesman, S., Gene Expression Technology: Methods in Enzymology 185, Academic Press, San Diego, California (1990) 119-128). Alternatively, the sequence of the nucleic acid molecule of interest can be altered to provide preferential codon usage for a specific host cell, for example *E. coli*. (Wada et al., Nucleic Acids Res. 20:2111-2118 (1992)).

[0085] The nucleic acid molecules can also be expressed by expression vectors suitable for a yeast host. Examples of vectors for expression in yeast e.g., *S. cerevisiae* include pYepSec1 (Baldari, et al., EMBO J. 6:229-234 (1987)), pMFa (Kurjan et al., Cell 30:933-943(1982)), pJRY88 (Schultz et al., Gene 54:113-123 (1987)), and pYES2 (Invitrogen Corporation, San Diego, CA).

[0086] The nucleic acid molecules can also be expressed in insect cells using, for example, baculovirus expression vectors. Baculovirus vectors available for expression of proteins in cultured insect cells (e.g., Sf 9 cells) include the pAc series (Smith et al., Mol. Cell Biol. 3:2156-2165 (1983)) and the pVL series (Lucklow et al., Virology 170:31-39 (1989)).

[0087] In certain embodiments of the invention, the nucleic acid molecules described herein are expressed in mammalian cells using mammalian expression vectors. Examples

of mammalian expression vectors include pCDM8 (Seed, B. Nature 329:840(1987)) and pMT2PC (Kaufman et al., EMBO J. 6:187-195 (1987)).

[0088] The expression vectors listed herein are provided by way of example only of the well-known vectors available to those of ordinary skill in the art that would be useful to express the nucleic acid molecules. The person of ordinary skill in the art would be aware of other vectors suitable for maintenance propagation or expression of the nucleic acid molecules described herein. These are found for example in Sambrook, J., Fritsh, E. F., and Maniatis, T. Molecular Cloning: A Laboratory Manual. 3rd. ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, (2001).

[0089] The invention also encompasses vectors in which the nucleic acid sequences described herein are cloned into the vector in reverse orientation, but operably linked to a regulatory sequence that permits transcription of antisense RNA. Thus, an antisense transcript can be produced to all, or to a portion, of the nucleic acid molecule sequences described herein, including both coding and non-coding regions. Expression of this antisense RNA is subject to each of the parameters described above in relation to expression of the sense RNA (regulatory sequences, constitutive or inducible expression, tissue-specific expression).

[0090] The invention also relates to recombinant host cells containing the vectors described herein. Host cells therefore include prokaryotic cells, lower eukaryotic cells such as yeast, other eukaryotic cells such as insect cells, and higher eukaryotic cells such as mammalian cells.

[0091] The recombinant host cells are prepared by introducing the vector constructs described herein into the cells by techniques readily available to the person of ordinary skill in the art. These include, but are not limited to, calcium phosphate transfection, DEAE-dextran-mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, lipofection, and other techniques such as those found in Sambrook, et al. (Molecular Cloning: A Laboratory Manual. 3rd. ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, (2001)).

[0092] Host cells can contain more than one vector. Thus, different nucleotide sequences can be introduced on different vectors of the same cell. Similarly, the nucleic acid molecules can be introduced either alone or with other nucleic acid molecules that are not related to the nucleic acid molecules such as those providing trans-acting factors for expression vectors. When more than one vector is introduced into a cell, the vectors can be introduced independently, co-introduced or joined to the nucleic acid molecule vector.

[0093] In the case of bacteriophage and viral vectors, these can be introduced into cells as packaged or encapsulated virus by standard procedures for infection and transduction. Viral vectors can be replication-competent or replication-defective. In the case in which viral replication is defective, replication will occur in host cells providing functions that complement the defects.

[0094] Vectors generally include selectable markers that enable the selection of the subpopulation of cells that contain the recombinant vector constructs. The marker can be contained in the same vector that contains the nucleic acid molecules described herein or may be on a separate vector. Markers include tetracycline or ampicillin-resistance genes for prokaryotic host cells and dihydrofolate reductase or neomycin resistance for eukaryotic host cells. However, any marker that provides selection for a phenotypic trait will be effective.

[0095] While the mature proteins can be produced in bacteria, yeast, mammalian cells, and other cells under the control of the appropriate regulatory sequences, cell-free transcription and translation systems can also be used to produce these proteins using RNA derived from the DNA constructs described herein.

[0096] Where secretion of the peptide is desired, which may be difficult to achieve with multi-transmembrane domain containing proteins such as PCATs, appropriate secretion signals are incorporated into the vector. The signal sequence can be endogenous to the peptides or heterologous to these peptides.

[0097] Where the peptide is not secreted into the medium, the protein can be isolated from the host cell by standard disruption procedures, including freeze thaw, sonication, mechanical disruption, use of lysing agents and the like. The peptide can then be recovered and purified by well-known purification methods including ammonium sulfate precipitation, acid extraction, anion or cationic exchange chromatography, phosphocellulose chromatography, hydrophobic-interaction chromatography, affinity chromatography, hydroxylapatite chromatography, lectin chromatography, or high performance liquid chromatography.

[0098] It is also understood that depending upon the host cell in recombinant production of the peptides described herein, the peptides can have various glycosylation patterns, depending upon the cell, or maybe non-glycosylated as when produced in bacteria. In addition, the peptides may include an initial modified methionine in some cases as a result of a host-mediated process.

[0099] The recombinant host cells expressing the peptides described herein have a variety of uses. First, the cells are useful for producing a PCAT protein or peptide that can be further purified to produce desired amounts of PCAT protein or fragments. Thus, host cells containing expression vectors are useful for peptide production.

[00100] Host cells are also useful for conducting cell-based assays involving the PCAT protein or PCAT protein fragments, such as those described above as well as other formats known in the art. Thus, a recombinant host cell expressing a native PCAT protein is useful for assaying compounds that stimulate or inhibit PCAT protein function.

[00101] Host cells are also useful for identifying PCAT protein mutants in which these functions are affected. If the mutants naturally occur and give rise to a pathology, host cells containing the mutations are useful to assay compounds that have a desired effect on the mutant PCAT protein (for example, stimulating or inhibiting function) which may not be indicated by their effect on the native PCAT protein.

5. Detection and Diagnosis in General

[00102] As used herein, a “biological sample” can be collected from tissues, blood, sera, cell lines or biological fluids such as, plasma, interstitial fluid, urine, cerebrospinal fluid, and the like, containing cells. In preferred embodiments, a biological sample comprises cells or tissues suspected of having diseases (e.g., cells obtained from a biopsy).

[00103] As used herein, a “differential level” is defined as the level of PCAT protein or nucleic acids in a test sample either above or below the level in control samples, wherein the level of control samples is obtained either from a control cell line, a normal tissue or body fluids, or combination thereof, from a healthy subject. While the protein is overexpressed, the expression of PCAT is preferably greater than about 20%, or preferably greater than about 30%, and most preferably greater than about 50% or more of pancreatic disease sample, at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in control samples, as determined using a representative assay provided herein. While the protein is underexpressed, the expression of PCAT is preferably less than about 20%, or preferably less than 30%, and most preferably less than about 50% or more of the pancreatic disease sample, at a level that is at least 0.5 fold, and preferably at least 0.2 fold less than the level of the expression in control samples, as determined using a representative assay provided herein.

[00104] As used herein, a “subject” can be a mammalian subject or non mammalian subject, preferably, a mammalian subject. A mammalian subject can be human or non-human, preferably human. A healthy subject is defined as a subject without detectable pancreatic diseases or pancreatic associated diseases by using conventional diagnostic methods.

[00105] As used herein, the “disease(s)” include pancreatic diseases and pancreatic associated disease. Preferably, the disease is a pancreatic cancer.

[00106] The following terms, as used in the present specification and claims, are intended to have the meaning as defined below, unless indicated otherwise.

[00107] “Treat,” “treating” or “treatment” of a disease includes: (1) inhibiting the disease, i.e., arresting or reducing the development of the disease or its clinical symptoms, or (2) relieving the disease, i.e., causing regression of the disease or its clinical symptoms.

[00108] The term “prophylaxis” is used to distinguish from “treatment,” and to encompass both “preventing” and “suppressing,” it is not always possible to distinguish between “preventing” and “suppressing,” as the ultimate inductive event or events may be unknown, latent, or the patient is not ascertained until well after the occurrence of the event or events. Therefore, the term “protection,” as used herein, is meant to include “prophylaxis.”

[00109] A “therapeutically effective amount” means the amount of an agent that, when administered to a subject for treating a disease, is sufficient to effect such treatment for the disease. The “therapeutically effective amount” will vary depending on the agent, the disease and its severity and the age, weight, etc., of the subject to be treated.

[00110] A “pancreatic disease” includes pancreatic cancer, pancreatic tumor (exocrine or endocrine), pancreatic cysts, acute pancreatitis, chronic pancreatitis, diabetes (type I and II) as well as pancreatic trauma. The method of the present invention is preferably used for treating a pancreatic cancer.

[00111] In one embodiment, when decreased expression or activity of the protein is desired, an inhibitor, antagonist, antibody and the like or a pharmaceutical agent containing one or more of these molecules may be delivered. Such delivery may be effected by methods well known in the art and may include delivery by an antibody specifically targeted to the protein.

[00112] In another embodiment, when increased expression or activity of the protein is desired, the protein, an agonist, an enhancer and the like or a pharmaceutical agent containing one or more of these molecules may be delivered. Such delivery may be effected by methods well known in the art.

6. Diagnosis and Monitoring Treatment method using PCAT Nucleic Acids

a. General Aspects

[00113] The nucleic acid molecules of the present invention are useful for probes, primers, chemical intermediates, and in biological assays. The nucleic acid molecules are useful as a hybridization probe for messenger RNA, transcript/cDNA and genomic DNA to detect or isolate full-length cDNA and genomic clones encoding the PCAT protein or peptide of the invention, or variants thereof

[00114] The probe can correspond to any sequence along the entire length of the nucleic acid molecules of SEQ ID NOs: 10-20. Accordingly, it could be derived from 5' noncoding regions, the coding region, and 3' noncoding regions.

[00115] The nucleic acid molecules are also useful as primers for PCR to amplify any given region of a nucleic acid molecule and are useful to synthesize antisense molecules of desired length and sequence.

[00116] The nucleic acid molecules are also useful for constructing recombinant vectors. Such vectors include expression vectors that express a portion of, or all of, the peptide sequences. The nucleic acid molecules are also useful for expressing antigenic portions of the proteins.

[00117] The nucleic acid molecules are also useful for designing ribozymes corresponding to all, or a part, of the mRNA produced from the nucleic acid molecules described herein.

[00118] The nucleic acid molecules are also useful for constructing host cells expressing a part, or all, of the nucleic acid molecules and peptides.

[00119] The nucleic acid molecules are also useful for constructing transgenic animals expressing all, or a part, of the nucleic acid molecules and peptides.

[00120] In vitro techniques for detection of mRNA include Northern hybridizations and in situ hybridizations. In vitro techniques for detecting DNA include Southern hybridizations and in situ hybridization.

b. Diagnosis methods

[00121] The nucleic acid molecules are also useful as hybridization probes for determining the presence, level, form and distribution of nucleic acid expression. The probes can be used to detect the presence of, or to determine levels of, a specific nucleic acid molecule in cells, tissues, and in organisms. Accordingly, probes corresponding to the peptides described herein can be used to assess expression and/or gene copy number in a given cell, tissue, or organism. These uses are relevant for diagnosis of disorders involving an increase or decrease in PCAT protein expression relative to normal results.

[00122] Probes can be used as a part of a diagnostic test kit for identifying cells or tissues that express a PCAT protein differentially, such as by measuring a level of a PCAT-encoding nucleic acid in a sample of cells from a subject e.g., mRNA or genomic DNA, or determining if a PCAT gene has been mutated.

[00123] The invention also encompasses kits for detecting the presence of a PCAT nucleic acid in a biological sample. For example, the kit can comprise reagents such as a labeled or labelable nucleic acid or agent capable of detecting PCAT nucleic acid in a biological sample; means for determining the amount of PCAT nucleic acid in the sample; and means for comparing the amount of PCAT nucleic acid in the sample with a standard. The compound or agent can be packaged in a suitable container. The kit can further comprise instructions for using the kit to detect PCAT protein mRNA or DNA.

c. Methods of Monitoring Treatment

[00124] The nucleic acid molecules are also useful for monitoring the effectiveness of modulating compounds or agents on the expression or activity of the PCAT gene in clinical trials or in a treatment regimen. Thus, the gene expression pattern (e.g., SEQ ID NOS: 10-20 and fragments thereof) can serve as a barometer for the continuing effectiveness of treatment with the compound, particularly with compounds to which a

patient can develop resistance. The gene expression pattern can also serve as a marker indicative of a physiological response of the affected cells to the compound. Accordingly, such monitoring would allow either increased administration of the compound or the administration of alternative compounds to which the patient has not become resistant. Similarly, if the level of nucleic acid expression falls below a desirable level, administration of the compound could be commensurately decreased.

7. Diagnosis using PCAT Proteins

Protein detections

[00125] The present invention provides methods for diagnosing or detecting the differential presence of PCAT protein. Where PCATs are overexpressed in diseased cells, PCAT proteins are detected directly.

[00126] The information obtained is also used to determine prognosis and appropriate course of treatment. For example, it is contemplated that individuals with a specific PCAT expression or stage of pancreatic diseases may respond differently to a given treatment than individuals lacking the PCAT expression. The information obtained from the diagnostic methods of the present invention thus provides for the personalization of diagnosis and treatment.

[00127] In one embodiment, the present invention provides a method for monitoring pancreatic diseases treatment in a subject comprising: determining the level of a PCAT protein or any fragment(s) or peptide(s) thereof in a test sample from said subject, wherein an level of said PCAT protein similar to the level of said protein in a test sample from a healthy subject, or the level established for a healthy subject, is indicative of successful treatment.

[00128] In another embodiment, the present invention provides a method for diagnosing recurrence of pancreatic diseases following successful treatment in a subject comprising: determining the level of a PCAT protein or any fragment(s) or peptide(s) thereof in a test sample from said subject; wherein a changed level of said PCAT protein relative to the level of said protein in a test sample from a healthy subject,

or the level established for a healthy subject, is indicative of recurrence of pancreatic diseases.

[00129] In yet another embodiment, the present invention provides a method for diagnosing or detecting pancreatic diseases in a subject comprising: determining the level of a PCAT protein or any fragment or peptides thereof in a test sample from said subject; wherein a differential level of said PCAT protein relative to the level of said protein in a test sample from a healthy subject, or the level established for a healthy subject, is indicative of pancreatic diseases.

[00130] In one embodiment, the detected targets comprise, consist essentially of or consist of combinations of PCAT (CD49b, CD71, CD51 or E-Cadherin) proteins or nucleic acids encoding such proteins. The combinations of two, three or four proteins (SEQ ID NOS: 1-9) or nucleic acids (SEQ ID NOS: 10-20) encoding such proteins are selected from a group consisting of CD49b, CD71, CD51 and E-Cadherin.

[00131] In one embodiment, the combinations of the protein or nucleic acid targets for detection of a pancreatic diseases comprises targets selected from a group consisting of CD49b (SEQ ID NO: 1 encoded by SEQ ID NO: 10; SEQ ID NO: 2 encoded by SEQ ID NO: 11; SEQ ID NO: 3 encoded by SEQ ID NO: 12), CD71 (SEQ ID NO: 4 encoded by SEQ ID NOS: 13 and 14; SEQ ID NO: 5 encoded by SEQ ID NO: 15), CD51 (SEQ ID NO: 6 encoded by SEQ ID NOS: 16 and 17), and E-Cadherin (SEQ ID NO: 7 encoded by SEQ ID NO: 18, SEQ ID NO: 8 encoded by SEQ ID NO: 19, SEQ ID NO: 9 encoded by SEQ ID NO: 20).

[00132] The combination comprises proteins or nucleic acids encoding such proteins of CD49b and CD71. The combination comprises proteins or nucleic acids encoding such proteins of CD49b and CD51. The combination comprises proteins or nucleic acids encoding such proteins of CD49b and E-Cadherin. The combination comprises proteins or nucleic acids encoding such proteins of CD51 and CD71. The combination comprises proteins or nucleic acids encoding such proteins of E-Cadherin and CD71. The combination comprises proteins or nucleic acids encoding such proteins of CD51 and E-Cadherin.

[00133] The combination comprises proteins or nucleic acids encoding such proteins of CD49b, CD71 and CD51. The combination comprises proteins or nucleic acids encoding such proteins of CD49b, CD71 and E-Cadherin. The combination comprises proteins or nucleic acids encoding such proteins of CD51, CD71 and E-Cadherin. The combination comprises proteins or nucleic acids encoding such proteins of CD49b, CD51, CD71 and E-Cadherin.

[00134] These methods are also useful for diagnosing diseases that show differential protein expression. As describe earlier, normal, control or standard values or level established from a healthy subject for protein expression are established by combining body fluids or tissue, cell extracts taken from a normal healthy mammalian or human subject with specific antibodies to a protein under conditions for complex formation. Standard values for complex formation in normal and diseased tissues are established by various methods, often photometric means. Then complex formation as it is expressed in a subject sample is compared with the standard values. Deviation from the normal standard and toward the diseased standard provides parameters for disease diagnosis or prognosis while deviation away from the diseased and toward the normal standard may be used to evaluate treatment efficacy.

[00135] In yet another embodiment, the present invention provides a detection or diagnostic method of PCATs by using LC/MS. The proteins from cells are prepared by methods known in the art (e.g., R. Aebersold Nature Biotechnology Volume 21 Number 6 June 2003). The differential expression of proteins in disease and healthy samples are quantitated using Mass Spectrometry and ICAT (Isotope Coded Affinity Tag) labeling, which is known in the art. ICAT is an isotope label technique that allows for discrimination between two populations of proteins, such as a healthy and a disease sample. The LC/MS spectra are collected for the labeled samples. The raw scans from the LC/MS instrument are subjected to peak detection and noise reduction software. Filtered peak lists are then used to detect 'features' corresponding to specific peptides from the original sample(s). Features are characterized by their mass/charge, charge, retention time, isotope pattern and intensity.

[00136] The intensity of a peptide present in both healthy and disease samples can be used to calculate the differential expression, or relative abundance, of the peptide. The intensity of a peptide found exclusively in one sample can be used to calculate a theoretical expression ratio for that peptide (singleton). Expression ratios are calculated for each peptide of each replicate of the experiment. Thus overexpression or under expression of a PCAT protein or peptide are similar to the expression pattern in a test subject indicates the likelihood of having pancreatic diseases or diseases associated with pancreas.

[00137] Immunological methods for detecting and measuring complex formation as a measure of protein expression using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), fluorescence-activated cell sorting (FACS) and antibody arrays. Such immunoassays typically involve the measurement of complex formation between the protein and its specific antibody. These assays and their quantitation against purified, labeled standards are well known in the art (Ausubel, supra, unit 10.1-10.6). A two-site, monoclonal-based immunoassay utilizing antibodies reactive to two non-interfering epitopes is preferred, but a competitive binding assay may be employed (Pound (1998) Immunochemical Protocols, Humana Press, Totowa N.J.). More immunological detections are described in the sections below.

[00138] For diagnostic applications, the antibody or its variant typically will be labeled with a detectable moiety. Numerous labels are available which can be generally grouped into the following categories:

(a) Radioisotopes, such as ^{36}S , ^{14}C , ^{125}I , ^3H , and ^{131}I . The antibody variant can be labeled with the radioisotope using the techniques described in Current Protocols in Immunology, vol 1-2, Coligen et al., Ed., Wiley-Interscience, New York, Pubs. (1991) for example and radioactivity can be measured using scintillation counting.

(b) Fluorescent labels such as rare earth chelates (europium chelates) or fluorescein and its derivatives, rhodamine and its derivatives, dansyl, Lissamine, phycoerythrin and Texas Red are available. The fluorescent labels can be conjugated to

the antibody variant using the techniques disclosed in Current Protocols in Immunology, supra, for example. Fluorescence can be quantified using a fluorometer.

(c) Various enzyme-substrate labels are available and U.S. Pat. Nos. 4,275,149 and 4,318,980 provide a review of some of these. The enzyme generally catalyzes a chemical alteration of the chromogenic substrate which can be measured using various techniques. For example, the enzyme may catalyze a color change in a substrate, which can be measured spectrophotometrically. Alternatively, the enzyme may alter the fluorescence or chemiluminescence of the substrate. Techniques for quantifying a change in fluorescence are described above. The chemiluminescent substrate becomes electronically excited by a chemical reaction and may then emit light which can be measured (using a chemiluminometer, for example) or donates energy to a fluorescent acceptor. Examples of enzymatic labels include luciferases (e.g., firefly luciferase and bacterial luciferase; U.S. Pat. No. 4,737,456), luciferin, 2,3-dihydrophthalazinediones, malate dehydrogenase, urease, peroxidase such as horseradish peroxidase (HRPO), alkaline phosphatase, β -galactosidase, glucoamylase, lysozyme, saccharide oxidases (e.g., glucose oxidase, galactose oxidase, and glucose-6-phosphate dehydrogenase), heterocyclic oxidases (such as uricase and xanthine oxidase), lactoperoxidase, microperoxidase, and the like. Techniques for conjugating enzymes to antibodies are described in O'Sullivan et al., Methods for the Preparation of Enzyme-Antibody Conjugates for Use in Enzyme Immunoassay, in Methods in Enzyme. (Ed. J. Langone & H. Van Vunakis), Academic press, New York, 73: 147-166 (1981).

[00139] Sometimes, the label is indirectly conjugated with the antibody. The skilled artisan will be aware of various techniques for achieving this. For example, the antibody can be conjugated with biotin and any of the three broad categories of labels mentioned above can be conjugated with avidin, or vice versa. Biotin binds selectively to avidin and thus, the label can be conjugated with the antibody in this indirect manner. Alternatively, to achieve indirect conjugation of the label with the antibody, the antibody is conjugated with a small hapten (e.g. digoxin) and one of the different types of labels mentioned above is conjugated with an anti-hapten antibody (e.g. anti-digoxin antibody). Thus, indirect conjugation of the label with the antibody can be achieved.

[00140] The biological samples can then be tested directly for the presence of PCAT by assays (e.g., ELISA or radioimmunoassay) and format (e.g., microwells, dipstick) (as described in International Patent Publication WO 93/03367). Alternatively, proteins in the sample can be size separated (e.g., by polyacrylamide gel electrophoresis (PAGE)), in the presence or absence of sodium dodecyl sulfate (SDS), and the presence of PCAT detected by immunoblotting (e.g., Western blotting). Immunoblotting techniques are generally more effective with antibodies generated against a peptide corresponding to an epitope of a protein, and hence, are particularly suited to the present invention.

[00141] Antibody binding may also be detected by "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitation reactions, immunodiffusion assays, in situ immunoassays (e.g., using colloidal gold, enzyme or radioisotope labels, for example), precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays, etc.), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc.

[00142] In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention. As is well known in the art, the immunogenic peptide should be provided free of the carrier molecule used in any immunization protocol. For example, if the peptide was conjugated to KLH, it may be conjugated to BSA, or used directly, in a screening assay. In some embodiments, an automated detection assay is utilized. Methods for the automation of immunoassays are well known in the art (See e.g., U.S. Pat. Nos. 5,885,530, 4,981,785, 6,159,750, and 5,358,691, each of which is herein incorporated by reference). In some embodiments, the analysis and presentation of results is also automated. For example, in some embodiments, software that generates a prognosis based on the presence or absence of a series of antigens is utilized.

[00143] Competitive binding assays rely on the ability of a labeled standard to compete with the test sample for binding with a limited amount of antibody. The amount of antigen in the test sample is inversely proportional to the amount of standard that becomes bound to the antibodies. To facilitate determining the amount of standard that becomes bound, the antibodies generally are insolubilized before or after the competition. As a result, the standard and test sample that are bound to the antibodies may conveniently be separated from the standard and test sample, which remain unbound.

[00144] Sandwich assays involve the use of two antibodies, each capable of binding to a different immunogenic portion, or epitope, or the protein to be detected. In a sandwich assay, the test sample to be analyzed is bound by a first antibody, which is immobilized on a solid support, and thereafter a second antibody binds to the test sample, thus forming an insoluble three-part complex. See e.g., U.S. Pat. No. 4,376,110. The second antibody may itself be labeled with a detectable moiety (direct sandwich assays) or may be measured using an anti-immunoglobulin antibody that is labeled with a detectable moiety (indirect sandwich assay). For example, one type of sandwich assay is an ELISA assay, in which case the detectable moiety is an enzyme.

[00145] The antibodies may also be used for in vivo diagnostic assays. Generally, the antibody is labeled with a radionucleotide (such as ^{111}In , ^{99}Tc , ^{14}C , ^{131}I , ^3H , ^{32}P or ^{35}S) so that the tumor can be localized using immunoscintigraphy. In one embodiment, antibodies or fragments thereof bind to the extracellular domains of two or more PCAT targets and the affinity value (K_d) is less than $1 \times 10^8 \text{ M}$.

[00146] Antibodies for diagnostic use may be labeled with probes suitable for detection by various imaging methods. Methods for detection of probes include, but are not limited to, fluorescence, light, confocal and electron microscopy; magnetic resonance imaging and spectroscopy; fluoroscopy, computed tomography and positron emission tomography. Suitable probes include, but are not limited to, fluorescein, rhodamine, eosin and other fluorophores, radioisotopes, gold, gadolinium and other lanthanides, paramagnetic iron, fluorine-18 and other positron-emitting radionuclides. Additionally, probes may be bi- or multi-functional and be detectable by more than one of the methods

listed. These antibodies may be directly or indirectly labeled with said probes. Attachment of probes to the antibodies includes covalent attachment of the probe, incorporation of the probe into the antibody, and the covalent attachment of a chelating compound for binding of probe, amongst others well recognized in the art.

[00147] For immunohistochemistry, the disease tissue sample may be fresh or frozen or may be embedded in paraffin and fixed with a preservative such as formalin (see Example). The fixed or embedded section contains the sample are contacted with a labeled primary antibody and secondary antibody, wherein the antibody is used to detect the PCAT protein express *in situ*. The detailed procedure is shown in the Example.

[00148] Antibodies against a PCAT protein or peptide are useful to detect the presence of one of the proteins of the present invention in cells or tissues to determine the pattern of expression of the protein among various tissues in an organism and over the course of normal development.

[00149] Further, such antibodies can be used to detect protein in situ, in vitro, or in a cell lysate or supernatant in order to evaluate the abundance and pattern of expression. Also, such antibodies can be used to assess abnormal tissue distribution or abnormal expression during development or progression of a biological condition. Antibody detection of circulating fragments of the full length protein can be used to identify turnover.

[00150] Further, the antibodies can be used to assess expression in disease states such as in active stages of the disease or in an individual with a predisposition toward disease related to the protein's function. When a disorder is caused by an inappropriate tissue distribution, developmental expression, level of expression of the protein, or expressed/processed form, the antibody can be prepared against the normal protein. Experimental data as provided in Table 1 indicates expression in human pancreatic cell lines. If a disorder is characterized by a specific mutation in the protein, antibodies specific for this mutant protein can be used to assay for the presence of the specific mutant protein.

[00151] The antibodies can also be used to assess normal and aberrant subcellular localization of cells in the various tissues in an organism. Experimental data as provided in Table 1 indicates expression in human pancreatic cell lines. The diagnostic uses can be applied, not only in genetic testing, but also in monitoring a treatment modality. Accordingly, where treatment is ultimately aimed at correcting expression level or the presence of aberrant sequence and aberrant tissue distribution or developmental expression, antibodies directed against the protein or relevant fragments can be used to monitor therapeutic efficacy. More detection and diagnostic methods are described in detail below.

[00152] Additionally, antibodies are useful in pharmacogenomic analysis. Thus, antibodies prepared against polymorphic proteins can be used to identify individuals that require modified treatment modalities. The antibodies are also useful as diagnostic tools, as an immunological marker for aberrant protein analyzed by electrophoretic mobility, isoelectric point, tryptic peptide digest, and other physical assays known to those in the art.

[00153] The antibodies are also useful for tissue typing. Where a specific protein has been correlated with expression in a specific tissue, antibodies that are specific for this protein can be used to identify a tissue type.

[00154] The invention also encompasses kits for using antibodies to detect the presence of a protein in a biological sample. The kit can comprise antibodies such as a labeled or labelable antibody and a compound or agent for detecting protein in a biological sample; means for determining the amount of protein in the sample; means for comparing the amount of protein in the sample with a standard; and instructions for use. Such a kit can be supplied to detect a single protein or epitope or can be configured to detect one of a multitude of epitopes, such as in an antibody detection array. Arrays are described in detail below for nucleic acid arrays and similar methods have been developed for antibody arrays.

8. Array:

[00155] “Array” refers to an ordered arrangement of at least two transcripts, proteins or peptides, or antibodies on a substrate. At least one of the transcripts, proteins, or antibodies represents a control or standard, and the other transcript, protein, or antibody is of diagnostic or therapeutic interest. The arrangement of at least two and up to about 40,000 transcripts, proteins, or antibodies on the substrate assures that the size and signal intensity of each labeled complex, formed between each transcript and at least one nucleic acid, each protein and at least one ligand or antibody, or each antibody and at least one protein to which the antibody specifically binds, is individually distinguishable.

[00156] An “expression profile” is a representation of gene expression in a sample. A nucleic acid expression profile is produced using sequencing, hybridization, or amplification technologies using transcripts from a sample. A protein expression profile, although time delayed, mirrors the nucleic acid expression profile and is produced using gel electrophoresis, mass spectrometry, or an array and labeling moieties or antibodies which specifically bind the protein. The nucleic acids, proteins, or antibodies specifically binding the protein may be used in solution or attached to a substrate, and their detection is based on methods well known in the art.

[00157] A substrate includes but is not limited to, paper, nylon or other type of membrane, filter, chip, glass slide, or any other suitable solid support.

[00158] The present invention also provides an antibody array. Antibody arrays have allowed the development of techniques for high-throughput screening of recombinant antibodies. Such methods use robots to pick and grid bacteria containing antibody genes, and a filter-based ELISA to screen and identify clones that express antibody fragments. Because liquid handling is eliminated and the clones are arrayed from master stocks, the same antibodies can be spotted multiple times and screened against multiple antigens simultaneously. For more information, see de Wildt et al. (2000) Nat. Biotechnol. 18:989-94.

[00159] The array is prepared and used according to the methods described in U.S. Patent No. 5,837,832, Chee et al., PCT application W095/11995 (Chee et al.), Lockhart, D. J. et al. (1996; Nat. Biotech. 14: 1675-1680) and Schena, M. et al. (1996; Proc. Natl. Acad. Sci. 93: 10614-10619), US Patent No. 5,807,522, Brown et al., all of which are incorporated herein in their entirety by reference.

[00160] In one embodiment, the combinations of the protein or nucleic acid targets for detection of a pancreatic diseases comprises targets selected from a group consisting of CD49b (SEQ ID NO: 1 encoded by SEQ ID NO: 10; SEQ ID NO: 2 encoded by SEQ ID NO: 11; SEQ ID NO: 3 encoded by SEQ ID NO: 12), CD71 (SEQ ID NO: 4 encoded by SEQ ID NOS: 13 and 14; SEQ ID NO: 5 encoded by SEQ ID NO: 15), CD51 (SEQ ID NO: 6 encoded by SEQ ID NOS: 16 and 17), and E-Cadherin (SEQ ID NO: 7 encoded by SEQ ID NO: 18, SEQ ID NO: 8 encoded by SEQ ID NO: 19, SEQ ID NO: 9 encoded by SEQ ID NO: 20).

[00161] The combination comprises proteins or nucleic acids encoding such proteins of CD49b and CD71. The combination comprises proteins or nucleic acids encoding such proteins of CD49b and CD51. The combination comprises proteins or nucleic acids encoding such proteins of CD49b and E-Cadherin. The combination comprises proteins or nucleic acids encoding such proteins of CD51 and CD71. The combination comprises proteins or nucleic acids encoding such proteins of E-Cadherin and CD71. The combination comprises proteins or nucleic acids encoding such proteins of CD51 and E-Cadherin.

[00162] The combination comprises proteins or nucleic acids encoding such proteins of CD49b, CD71 and CD51. The combination comprises proteins or nucleic acids encoding such proteins of CD49b, CD71 and E-Cadherin. The combination comprises proteins or nucleic acids encoding such proteins of CD51, CD71 and E-Cadherin. The combination comprises proteins or nucleic acids encoding such proteins of CD49b, CD51, CD71 and E-Cadherin.

[00163] In one embodiment, a nucleic acid array or a microarray, preferably composed of a large number of unique, single-stranded nucleic acid sequences, usually either

synthetic antisense oligonucleotides or fragments of cDNAs, fixed to a solid support. The oligonucleotides are preferably about 6-60 nucleotides in length, more preferably 15-30 nucleotides in length, and most preferably about 20-25 nucleotides in length.

[00164] In order to produce oligonucleotides to a known sequence for an array, the gene(s) of interest (or an ORF identified from the contigs of the present invention) is typically examined using a computer algorithm which starts at the 5' or at the 3' end of the nucleotide sequence. Typical algorithms will then identify oligomers of defined length that are unique to the gene, have a GC content within a range suitable for hybridization, and lack predicted secondary structure that may interfere with hybridization. In certain situations it may be appropriate to use pairs of oligonucleotides on an array. The "pairs" will be identical, except for one nucleotide that preferably is located in the center of the sequence. The second oligonucleotide in the pair (mismatched by one) serves as a control. The number of oligonucleotide pairs may range from two to one million. The oligomers are synthesized at designated areas on a substrate using a light-directed chemical process, wherein the substrate may be paper, nylon or other type of membrane, filter, chip, glass slide or any other suitable solid support as described above.

[00165] In another aspect, an oligonucleotide may be synthesized on the surface of the substrate by using a chemical coupling procedure and an ink jet application apparatus, as described in PCT application W095/251116 (Baldeschweiler et al.) which is incorporated herein in its entirety by reference.

[00166] A gene expression profile comprises the expression of a plurality of transcripts as measured by hybridization with a sample. The transcripts of the invention may be used as elements on an array to produce a gene expression profile. In one embodiment, the array is used to diagnose or monitor the progression of disease. Researchers can assess and catalog the differences in gene expression between healthy and diseased tissues or cells.

[00167] For example, the transcript or probe may be labeled by standard methods and added to a biological sample from a patient under conditions for the formation of

hybridization complexes. After an incubation period, the sample is washed and the amount of label (or signal) associated with hybridization complexes, is quantified and compared with a standard value. If complex formation in the patient sample is significantly altered (higher or lower) in comparison to either a normal or disease standard, then differential expression indicates the presence of a disorder.

[00168] In order to provide standards for establishing differential expression, normal and disease expression profiles are established. This is accomplished by combining a sample taken from normal subjects, either animal or human or nonmammal, with a transcript under conditions for hybridization to occur. Standard hybridization complexes may be quantified by comparing the values obtained using normal subjects with values from an experiment in which a known amount of a purified sequence is used. Standard values obtained in this manner may be compared with values obtained from samples from patients who were diagnosed with a particular condition, disease, or disorder. Deviation from standard values toward those associated with a particular disorder is used to diagnose that disorder.

[00169] By analyzing changes in patterns of gene expression, disease can be diagnosed at earlier stages before the patient is symptomatic. The invention can be used to formulate a prognosis and to design a treatment regimen. The invention can also be used to monitor the efficacy of treatment. For treatments with known side effects, the array is employed to improve the treatment regimen. A dosage is established that causes a change in genetic expression patterns indicative of successful treatment. Expression patterns associated with the onset of undesirable side effects are avoided.

[00170] In another embodiment, animal models which mimic a human disease can be used to characterize expression profiles associated with a particular condition, disease, or disorder; or treatment of the condition, disease, or disorder. Novel treatment regimens may be tested in these animal models using arrays to establish and then follow expression profiles over time. In addition, arrays may be used with cell cultures or tissues removed from animal models to rapidly screen large numbers of candidate drug molecules, looking for ones that produce an expression profile similar to those of known therapeutic

drugs, with the expectation that molecules with the same expression profile will likely have similar therapeutic effects. Thus, the invention provides the means to rapidly determine the molecular mode of action of a drug.

[00171] Such assays may also be used to evaluate the efficacy of a particular therapeutic treatment regimen in animal studies or in clinical trials or to monitor the treatment of an individual patient. Once the presence of a condition is established and a treatment protocol is initiated, diagnostic assays may be repeated on a regular basis to determine if the level of expression in the patient begins to approximate that which is observed in a normal subject. The results obtained from successive assays may be used to show the efficacy of treatment over a period ranging from several days to years.

WORKING EXAMPLES:

1. Pancreatic cell line model system

[00172] Analysis of gene expression in various pancreatic cancer cell lines as well as pancreatic duct epithelial tissue has shown that the cell line Hs766T correlates well with normal tissue. For this reason, this cell line is reported in the literature as being a good surrogate for normal tissue in analyses of differential expression between pancreatic adenocarcinoma (and derived tumor lines) and normal tissue (or surrogate, Hs766T). The model system employed here involves the use of Hs766T as a “normal” reference to which cell surface expression in tumor derived cell lines is compared.

[00173] Differentially expressed PCAT and candidate modulators are validated in various tissues, cancer and normal pancreas and cell lines, to confirm that they are differentially expressed. Details of the pancreatic tumor cell lines that were used for this study, as well as the pancreatic line Hs766T are provided in Table 1 below.

Table 1. Cell Lines and Media

Cell line	ATCC Reference	Base medium	Glutamine	Non-essential amino acids	Sodium Carbonate	Sodium Pyruvate	Hepes	Fetal Bovine Serum
Panc-1	CRL-1469	DMEM	2 mM	1% (w/v)	0.1% (w/v)	1 mM		10% (v/v)
Hs766t	HTB-134	DMEM	2 mM	1% (w/v)	0.1% (w/v)	1 mM		10% (v/v)
SU.86.86	CRL-1837	DMEM	2 mM	1% (w/v)	0.1% (w/v)	1 mM		10% (v/v)
AsPC1	CRL-1682	RPMI	2 mM	1% (w/v)	0.1% (w/v)	1 mM	10 mM	20% (v/v)
HPAF II	CRL-1997	DMEM	2 mM	1% (w/v)	0.1% (w/v)	1 mM		10% (v/v)
HPAC	CRL-2119	DMEM	2 mM	1% (w/v)	0.1% (w/v)	1 mM		10% (v/v)
Mia-Paca-2	CRL-1420	DMEM	2 mM	1% (w/v)	0.1% (w/v)	1 mM		10% (v/v)
Mpanc-96	CRL-2380	RPMI	2 mM	1% (w/v)	0.1% (w/v)	1 mM	10 mM	10% (v/v)
BxPC-3	CRL-1687	RPMI	2 mM	1% (w/v)	0.1% (w/v)	1 mM	10 mM	10% (v/v)
Capan-2	HTB-80	DMEM	2 mM	1% (w/v)	0.1% (w/v)	1 mM		10% (v/v)

2. Pancreatic cancer cell line culture

[00174] Cell lines are grown in a culturing medium that is supplemented as necessary with growth factors and serum (as described in Table 1). Cultures are established from frozen stocks in which the cells are suspended in a freezing medium (cell culture medium with 10% DMSO [v/v]) and flash frozen in liquid nitrogen. Frozen stocks prepared this way are stored in liquid nitrogen vapor. Cell cultures are established by rapidly thawing frozen stocks at 37°C. Thawed stock cultures are slowly transferred to a culture vessel containing a large volume of culture medium that is supplemented. For maintenance of culture, cells are seeded at 1×10^5 cells/per ml in a suitable medium and incubated at 37°C until confluence of cells in the culture vessel exceeds 50% by area. At this time, cells are harvested from the culture vessel using enzymes or EDTA where necessary. The density of harvested, viable cells is estimated by hemocytometry and the culture reseeded as above. A passage of this nature is repeated no more than 25 times at which point the culture is destroyed and reestablished from frozen stocks as described above.

[00175] For analyses of cell surface protein expression in cultured cell lines, cells are grown as described above. At a period 24 h prior to the experiment, the cell line is passaged as described above. This yielded cell densities that are <50% confluent and growing exponentially. Typically, triplicate analyses of differential expression are performed for each line relative to Hs766T for the purpose of identifying statistically significant reproducible differentially expressed proteins.

3. Antibody Development

Polyclonal antibody preparations:

[00176] Polyclonal antibodies against recombinant proteins are raised in rabbits (Green Mountain Antibodies, Burlington, VT). Briefly, two New Zealand rabbits are immunized with 0.1mg of antigen in complete Freund's adjuvant. Subsequent immunizations are carried out using 0.05mg of antigen in incomplete Freund's adjuvant at days 14, 21 and 49. Bleeds are collected and screened for recognition of the antigen by solid phase ELISA and western blot analysis. The IgG fraction is separated by

centrifugation at 20,000Xg for 20 minutes followed by a 50% ammonium sulfate cut. The pelleted protein is resuspended in 5mM Tris and separated by ion exchange chromatography. Fractions are pooled based on IgG content. Antigen-specific antibody is affinity purified using Pierce AMINOLINK resin coupled to the appropriate antigen.

Isolation of Antibody Fragments Directed Against PCATs from A Library of scFvs

[00177] Naturally occurring V-genes isolated from human PBLs are constructed into a library of antibody fragments which contain reactivities against PCAT to which the donor may or may not have been exposed (see e.g., U.S. Pat. No. 5,885,793 incorporated herein by reference in its entirety).

[00178] Rescue of the Library: A library of scFvs is constructed from the RNA of human PBLs as described in PCT publication WO 92/01047. To rescue phage displaying antibody fragments, approximately 10^9 *E. coli* harboring the phagemid are used to inoculate 50 ml of 2x TY containing 1% glucose and 100 µg/ml of ampicillin (2.times.TY-AMP-GLU) and grown to an O.D. of 0.8 with shaking. Five ml of this culture is used to inoculate 50 ml of 2.times.TY-AMP-GLU, 2×10^8 TU of delta gene 3 helper (M13 delta gene III, see PCT publication WO 92/01047) are added and the culture incubated at 37 °C. for 45 minutes without shaking and then at 37 °C. for 45 minutes with shaking. The culture is centrifuged at 4000 r.p.m. for 10 min. and the pellet resuspended in 2 liters of 2 x TY containing 100 µg/ml ampicillin and 50 ug/ml kanamycin and grown overnight. Phage are prepared as described in PCT publication WO 92/01047.

[00179] M13 delta gene III is prepared as follows: M13 delta gene III helper phage does not encode gene III protein, hence the phage(mid) displaying antibody fragments have a greater avidity of binding to antigen. Infectious M13 delta gene III particles are made by growing the helper phage in cells harboring a pUC19 derivative supplying the wild type gene III protein during phage morphogenesis. The culture is incubated for 1 hour at 37 °C without shaking and then for a further hour at 37 °C with shaking. Cells are spun down (IEC-Centra 8,400 r.p.m. for 10 min), resuspended in 300 ml 2 x TY broth containing 100 µg ampicillin/ml and 25 µg kanamycin/ml (2 x TY-AMP-KAN) and grown overnight, shaking at 37 °C. Phage particles are purified and concentrated from the

culture medium by two PEG-precipitations (Sambrook et al., 1990), resuspended in 2 ml PBS and passed through a 0.45 μ m filter (MINISART NML; Sartorius) to give a final concentration of approximately 10¹³ transducing units/ml (ampicillin-resistant clones).

[00180] Panning of the Library: IMMUNOTUBES (Nunc) are coated overnight in PBS with 4 ml of either 100 μ g/ml or 10 μ g/ml of a polypeptide of the present invention. Tubes are blocked with 2% Marvel-PBS for 2 hours at 37 °C and then washed 3 times in PBS. Approximately 10¹³ TU of phage is applied to the tube and incubated for 30 minutes at room temperature tumbling on an over and under turntable and then left to stand for another 1.5 hours. Tubes are washed 10 times with PBS 0.1% Tween-20 and 10 times with PBS. Phage are eluted by adding 1 ml of 100 mM triethylamine and rotating 15 minutes on an under and over turntable after which the solution is immediately neutralized with 0.5 ml of 1.0M Tris-HCl, pH 7.4. Phages are then used to infect 10 ml of mid-log *E. coli* TG1 by incubating eluted phage with bacteria for 30 minutes at 37 °C. The *E. coli* are then plated on TYE plates containing 1% glucose and 100 μ g/ml ampicillin. The resulting bacterial library is then rescued with delta gene 3 helper phage as described above to prepare phage for a subsequent round of selection. This process is then repeated for a total of 4 rounds of affinity purification with tube-washing increased to 20 times with PBS, 0.1% Tween-20 and 20 times with PBS for rounds 3 and 4.

[00181] Characterization of Binders: Eluted phage from the 3rd and 4th rounds of selection are used to infect *E. coli* HB 2151 and soluble scFv is produced (Marks, et al., 1991) from single colonies for assay. ELISAs are performed with microtitre plates coated with either 10 μ g/ml of the polypeptide of the present invention in 50 mM bicarbonate pH 9.6. Clones positive in ELISA are further characterized by PCR fingerprinting (see, e.g., PCT publication WO 92/01047) and then by sequencing.

Monoclonal Antibody Generation

[00182] i) Materials:

[00183] 1) Complete Media No Sera (CMNS) for washing of the myeloma and spleen cells; Hybridoma medium CM - HAT {Cell Mab (BD), 10% FBS (or HS); 5% Origen

HCF (hybridoma cloning factor) containing 4mM L-glutamine and antibiotics} to be used for plating hybridomas after the fusion.

[00184] 2) Hybridoma medium CM - HT (NO AMINOPTERIN) (Cell Mab (BD), 10% FBS 5% Origen HCF containing 4mM L-glutamine and antibiotics) to be used for fusion maintenance are stored in the refrigerator at 4-6 °C. The fusions are fed on days 4, 8, and 12, and subsequent passages. Inactivated and pre-filtered commercial Fetal Bovine serum (FBS) or Horse Serum (HS) are thawed and stored in the refrigerator at 4 °C and must be pretested for myeloma growth from single cells.

[00185] 3) The L-glutamine (200mM, 100X solution), which is stored at -20 °C freezer, is thawed and warmed until completely in solution. The L-glutamine is dispensed into media to supplement growth. L-glutamine is added to 2 mM for myelomas, and 4 mM for hybridoma media. Further the Penicillin, Streptomycin, Amphotericin (antibacterial-antifungal stored at -20 °C) is thawed and added to Cell Mab Media to 1%.

[00186] 4) Myeloma growth media is Cell Mab Media (Cell Mab Media, QUANTUM YIELD from BD is stored in the refrigerator at 4 °C in the dark) which are added L-glutamine to 2 mM and antibiotic/antimycotic solution to 1% and is called CMNS.

[00187] 5) 1 bottle of PEG 1500 in Hepes (Roche, NJ)

[00188] 6) 8-Azaguanine is stored as the dried powder supplied by SIGMA at -700 °C until needed. Reconstitute 1 vial / 500 ml of media and add entire contents to 500 ml media (eg. 2 vials/ liter).

[00189] 7) Myeloma Media is CM which has 10% FBS (or HS) and 8-Aza (1 X) stored in the refrigerator at 4 °C.

[00190] 8) Clonal cell medium D (Stemcell, Vancouver) contains HAT and methyl cellulose for semi-solid direct cloning from the fusion.

[00191] 9) Hybridoma supplements HT [hypoxanthine, thymidine] are to be used in medium for the selection of hybridomas and maintenance of hybridomas through the cloning stages respectively.

[00192] 10) Origen HCF can be obtained directly from Igen and is a cell supernatant produced from a macrophage-like cell-line. It can be thawed and aliquoted to 15 ml tubes at 5 ml per tube and stored frozen at -20 °C. Positive Hybridomas are fed HCF through the first subcloning and are gradually weaned. It is not necessary to continue to supplement unless you have a particularly difficult hybridoma clone. This and other additives have been shown to be more effective in promoting new hybridoma growth than conventional feeder layers.

[00193] ii) Procedure

[00194] To generate monoclonal antibodies, mice are immunized with 5-50 ug of antigen either intra-peritoneal (i.p.) or by intravenous injection in the tail vein (i.v.). Typically, the antigen used is a recombinant protein that is generated as described above. The primary immunization takes place 2 months prior to the harvesting of splenocytes from the mouse and the immunization is typically boosted by i.v. injection of 5-50 ug of antigen every two weeks. At least one week prior to expected fusion date, a fresh vial of myeloma cells is thawed and cultured. Several flasks at different densities are maintained in order that a culture at the optimum density is ensured at the time of fusion. The optimum density is determined to be $3-6 \times 10^5$ cells/ml. Two to five days before the scheduled fusion, a final immunization is administered of ~5ug of antigen in PBS i.p. or i.v.

[00195] Myeloma cells are washed with 30 ml serum free media by centrifugation at $500 \times g$ at 4°C for 5 minutes. Viable cell density is determined in resuspended cells using hemocytometry and vital stains. Cells resuspended in complete growth medium are stored at 37°C during the preparation of splenocytes. Meanwhile, to test aminopterin sensitivity, 1×10^6 myeloma cells are transferred to a 15ml conical tube and centrifuged at 500g at 4°C for 5 minutes. The resulting pellet is resuspended in 15 ml of HAT media and cells plated at 2 drops/well on a 96 well plate.

[00196] To prepare splenocytes from immunized mice, the animals are euthanised and submerged in 70% EtOH. Under sterile conditions, the spleen is surgically removed and placed in 10ml of RPMI medium supplemented with 20% fetal calf serum in a Petri dish.

Cells are extricated from the spleen by infusing the organ with medium >50 times using a 21g syringe.

[00197] Cells are harvested and washed by centrifugation (at 500 x g at 4°C for 5 minutes) with 30 ml of medium. Cells are resuspended in 10 ml of medium and the density of viable cells determined by hemocytometry using vital stains. The splenocytes are mixed with myeloma cells at a ratio of 5:1 (spleen cells: myeloma cells). Both the myeloma and spleen cells are washed 2 more times with 30 ml of RPMI-CMNS. Spin at 800 rpm for 12 minutes.

[00198] Supernatant is removed and cells are resuspended in 5 ml of RPMI-CMNS and are pooled to bring the volume to 30 ml and spun down as before. The cell pellet is broken up by gentle tapping and resuspended in 1 ml of BMB PEG1500 (prewarmed to 37°C) added dropwise with a 1 cc needle over 1 minute.

[00199] RPMI-CMNS is added to the PEG cells to slowly dilute out the PEG. Cells are centrifuged and diluted in 5 ml of Complete media and 95 ml of Clonacell Medium D (HAT) media (with 5 ml of HCF). The cells are plated out at 10 ml per small petri plate.

[00200] Myeloma/HAT control is prepared as follows. Dilute about 1000 P3X63 Ag8.653 myeloma cells into 1 ml of medium D and transfer into a single well of a 24 well plate. Plates are placed in incubator, with two plates inside of a large petri plate, with an additional petri plate full of distilled water, for 10-18 days under 5% CO₂ overlay at 37°C. Clones are picked from semisolid agarose into 96 well plates containing 150-200 ul of CM- HT. Supernatants are screened 4 days later in ELISA, and positive clones are moved up to 24 well plates. Heavy growth will require changing of the media at day 8 (+/- 150 ml). One should further decrease the HCF to 0.5% (gradually- 2%, then 1%, then 0.5%) in the cloning plates.

[00201] For further references see Kohler G, and C. Milstein Continuous cultures of fused cells secreting antibody of predefined specificity. 1975. Nature 256: 495-497; Lane, R.D. A short duration polyethylene glycol fusion technique for increasing production of monoclonal antibody-secreting hybridomas. 1985. J. Immunol. Meth. 81:223-228;

Harlow, E. and D. Lane. Antibodies: A Laboratory Manual. Cold Spring Harbor Laboratory Press. 1988; Kubitz, D. The Scripps Research Institute. La Jolla. Personal Communication; Zhong, G., Berry, J.D., and Choukri, S. (1996) Mapping epitopes of Chlamydia trachomatis neutralizing monoclonal antibodies using phage random peptide libraries. J. Indust. Microbiol. Biotech. 19, 71-76; Berry, J.D. , Licea, A., Popkov, M., Cortez, X., Fuller, R., Elia, M., Kerwin, L., and C.F. Barbas III. (2003) Rapid monoclonal antibody generation via dendritic cell targeting in vivo. Hybridoma and Hybridomics 22 (1), 23-31.

4. Expression Validation

mRNA Expression Validation by TAQMAN

[00202] Expression of mRNA is quantitated by RT- PCR using TAQMAN technology. The TAQMAN system couples a 5' fluorogenic nuclease assay with PCR for real time quantitation. A probe is used to monitor the formation of the amplification product.

[00203] Total RNA is isolated from cancer model cell lines using the RNEASY kit (Qiagen) per manufacturer's instructions and included DNase treatment. Normal human tissue RNAs are acquired from commercial vendors (Ambion, Austin, TX; Stratagene, La Jolla, CA, BioChain Institute, Newington, NH) as are RNAs from matched disease/normal tissues.

[00204] Target transcript sequences are identified for the differentially expressed peptides by searching the BlastP database. TAQMAN assays (PCR primer/probe set) specific for those transcripts are identified by searching the CELERA DISCOVERY SYSTEM (CDS) database. The assays are designed to span exon-exon borders and do not amplify genomic DNA.

[00205] The TAQMAN primers and probe sequences are designed by Applied Biosystems (AB) as part of the ASSAYS ON DEMAND product line or by custom design through the AB ASSAYS BY DESIGN service.

[00206] RT-PCR is accomplished using AMPLITAQGOLD and MULTISCRIBE reverse transcriptase in the ONE STEP RT-PCR Master Mix reagent kit (AB) according to the manufacturer's instructions. Probe and primer concentrations are 250 nM and 900 nM, respectively, in a 15 μ l reaction. For each experiment, a master mix of the above components is made and aliquoted into each optical reaction well. Eight nanograms of total RNA is used as the template. Each sample is assayed in triplicate. Quantitative RT-PCR is performed using the ABI PRISM 7900HT SEQUENCE DETECTION SYSTEM (SDS). Cycling parameters follow: 48°C for 30 min. for one cycle; 95 °C for 10 min for one cycle; 95 °C for 15 sec, 60 °C for 1 min. for 40 cycles.

[00207] The SDS software calculates the threshold cycle (C_T) for each reaction, and C_T values are used to quantitate the relative amount of starting template in the reaction. The C_T values for each set of three reactions are averaged for all subsequent calculations

[00208] Data are analyzed for fold difference in expression using an endogenous control for normalization and measuring expressing relative to a normal tissue or normal cell line reference. The choice of endogenous control is determined empirically by testing various candidates against the cell line and tissue RNA panels and selecting the one with the least variation in expression. Relative changes in expression are quantitated using the $2^{-\Delta\Delta C_T}$ Method. (See Livak, *et al.*, 2001, Methods 25: 402-408; User bulletin #2: ABI PRISM 7700 SEQUENCE DETECTION SYSTEM.)

Protein Expression Validation by Western

[00209] Western blot analysis of target proteins is carried out using whole cell extracts prepared from each of the pancreatic cell lines. To make cell extracts, the cells are resuspended in Lysis buffer (125mM Tris, pH 7.5, 150mM NaCl, 2% SDS, 5mM EDTA, 0.5% NP-40) and passed through a 20-gauge needle. Lysates are centrifuged at 5,000Xg for 5 minutes at 4°C. The supernatants are collected and a protease inhibitor cocktail (Sigma) is added. The Pierce BCA assay is used to quantitate total protein. Samples are separated by SDS-PAGE and transferred to either a nitrocellulose or PVDF membrane. The WESTERN BREEZE kit from Invitrogen is used for western blot analysis. Primary antibodies are either purchased from commercially available sources or prepared using

one of the methods described in Section 3. For this application, antibodies are typically diluted 1:500 to 1:10,000 in a diluent buffer. Blots are developed using Pierce NBT.

Tissue Flow Cytometry Analysis check tense.

[00210] Post tissue processing, cells are sorted by flow cytometry known in the art to enrich for epithelial cells. Alternatively, cells isolated from pancreatic tissue are stained directly with EpCAM (for epithelial cells) and the specific antibody to PCAT. Cell numbers and viability are determined by PI exclusion (GUAVA) for cells isolated from both normal and tumor pancreatic tissue. A minimum of 0.5×10^6 cells are used for each analysis. Cells are washed once with Flow Staining Buffer (0.5% BSA, 0.05% NaN₃ in D-PBS).

[00211] To the cells, 20 μ l of an antibody against PCATs are added. An additional 5 μ l of EpCAM antibody conjugated to APC are added when unsorted cells are used in the experiment. Cells are incubated with antibodies for 30 minutes at 4°C. Cells are washed once with Flow Staining Buffer and either analyzed immediately on the LSR flow cytometry apparatus or fixed in 1% formaldehyde and store at 4°C until LSR analysis.

5. Detection and Diagnosis of PCAT by Liquid Chromatography and Mass Spectrometry (LC/MS)

[00212] The differential expression of proteins in disease and healthy samples are quantitated using Mass Spectrometry and ICAT (Isotope Coded Affinity Tag) labeling. ICAT is an isotope label technique that allows for discrimination between two populations of proteins, such as from a healthy and a disease sample that are pooled together for experimental purposes or two acquisitions of the same sample for classification of true sample peptides from LC/MS noise artifacts.

[00213] The proteins from cells are prepared by methods known in the art. The LC/MS spectra are collected for the labeled samples and processed using the following steps:

[00214] The raw scans from the LC/MS instrument are subjected to peak detection and noise reduction using standard software. Filtered peak lists are then used to detect

“features” corresponding to specific peptides from the original sample(s). Features are characterized by their mass/charge, charge, retention time, isotope pattern and intensity.

[00215] Similar experiments are repeated in order to increase the confidence in detection of a peptide. These multiple acquisitions are computationally aggregated into one experiment. Experiments involving healthy and disease samples use the known effects of the ICAT label to classify the peptides as originating from a particular sample or from both samples. The intensity of a peptide present in both healthy and disease samples is used to calculate the differential expression, or relative abundance, of the peptide. The intensity of a peptide found exclusively in one sample is used to calculate a theoretical expression ratio for that peptide (singleton). Expression ratios are calculated for each peptide of each replicate of the experiment (see Figure 2).

[00216] Statistical tests are performed to assess the robustness of the data and statistically significant differentials selected. These tests a) ensure that similar features are detected in all replicates of the experiment; b) assess the distribution of the log ratios of all peptides (a Gaussian is expected); c) calculate the overall pair wise correlations between ICAT LC/MS maps to ensure that the expression ratios for peptides are reproducible across the multiple replicates; and d) aggregate multiple experiments in order to compare the expression ratio of a peptide in multiple diseases or disease samples.

6. Expression Validation by IHC in tissue sections

Tissue sections

[00217] Paraffin embedded, fixed tissue sections are obtained from a panel of normal tissues (Adrenal, Bladder, Lymphocytes, Bone Marrow, Breast, Cerebellum, Cerebral cortex, Colon, Endothelium, Eye, Fallopian tube, Small Intestine, Heart, Kidney (glomerulus, tubule), Liver, Lung, Testes and Thyroid) as well as 30 tumor samples with matched normal adjacent tissues from pancreas, lung, colon, prostate, ovarian and breast. In addition, other tissues are selected for testing such as bladder renal, hepatocellular, pharyngeal and gastric tumor tissues.

[00218] Esophageal replicate sections are also obtained from numerous tumor types (Bladder Cancer, Lung Cancer, Breast Cancer, Melanoma, Colon Cancer, Non-Hodgkins Lymphoma, Endometrial Cancer, Ovarian Cancer, Head and Neck Cancer, Prostate Cancer, Leukemia [ALL and CML] and Rectal Cancer). Sections are stained with hemotoxylin and eosin and histologically examined to ensure adequate representation of cell types in each tissue section.

[00219] An identical set of tissues are obtained from frozen sections and are used in those instances where it is not possible to generate antibodies that are suitable for fixed sections. Frozen tissues do not require an antigen retrieval step.

Hemotoxylin and Eosin staining of paraffin embedded, fixed tissue sections.

[00220] Sections are deparaffinized in 3 changes of xylene or xylene substitute for 2-5 minutes each. Sections are rinsed in 2 changes of absolute alcohol for 1-2 minutes each, in 95% alcohol for 1 minute, followed by 80% alcohol for 1 minute. Slides are washed well in running water and stained in Gill solution 3 hemotoxylin for 3 to 5 minutes. Following a vigorous wash in running water for 1 minute, sections are stained in Scott's solution for 2 minutes. Sections are washed for 1 min in running water then counterstained in Eosin solution for 2-3 minutes depending upon development of desired staining intensity. Following a brief wash in 95% alcohol, sections are dehydrated in three changes of absolute alcohol for 1 minute each and three changes of xylene or xylene substitute for 1-2 minutes each. Slides are coverslipped and stored for analysis.

Optimization of antibody staining

[00221] For each antibody, a positive and negative control sample is generated using data from the ICAT analysis of the pancreatic cancer cell lines. Cell lines are selected that are known to express low levels of a particular target as determined from the ICAT data. This cell line is the reference normal control "Hs766T." Similarly, a pancreatic tumor line known to overexpress the target is selected as positive control.

Antigen retrieval

[00222] Sections are deparaffinized and rehydrated by washing 3 times for 5 minutes in xylene; two times for 5 minutes in 100% ethanol; two times for 5 minutes in 95% ethanol; and once for 5 minutes in 80% ethanol. Sections are then placed in endogenous blocking solution (methanol + 2% hydrogen peroxide) and incubated for 20 minutes at room temperature. Sections are rinsed twice for 5 minutes each in deionized water and twice for 5 minutes in phosphate buffered saline (PBS), pH 7.4. Alternatively, where necessary sections are deparaffinized by High Energy Antigen Retrieval as follows: sections are washed three times for 5 minutes in xylene; two times for 5 minutes in 100% ethanol; two times for 5 minutes in 95% ethanol; and once for 5 minutes in 80% ethanol. Sections are placed in a Coplin jar with dilute antigen retrieval solution (10 mM citrate acid, pH 6). The Coplin jar containing slides is placed in a vessel filled with water and microwaved on high for 2 - 3 minutes (700 watt oven). Following cooling for 2 - 3 minutes, steps 3 and 4 are repeated four times (depending on the tissue), followed by cooling for 20 minutes at room temperature. Sections are then rinsed in deionized water, two times for 5 minutes, placed in modified endogenous oxidation blocking solution (PBS + 2% hydrogen peroxide) and rinsed for 5 minutes in PBS.

Blocking and Staining

[00223] Sections are blocked with PBS/1% bovine serum albumin (PBA) for 1 hour at room temperature followed by incubation in normal serum diluted in PBA (2%) for 30 minutes at room temperature to reduce non-specific binding of antibody. Incubations are performed in a sealed humidity chamber to prevent air-drying of the tissue sections. (The choice of blocking serum is the same as the species of the biotinylated secondary antibody). Excess antibody is gently removed by shaking and sections covered with primary antibody diluted in PBA and incubated either at room temperature for 1 hour or overnight at 4°C. (Care is taken that the sections do not touch during incubation). Sections are rinsed twice for 5 minutes in PBS, shaking gently. Excess PBS is removed by gently shaking. The sections are covered with diluted biotinylated secondary antibody in PBA and incubated for 30 minutes to 1 hour at room temperature in the humidity

chamber. If using a monoclonal primary antibody, addition of 2% rat serum is used to decrease the background on rat tissue sections. Following incubation, sections are rinsed twice for 5 minutes in PBS, shaking gently. Excess PBS is removed and sections incubated for 1 hour at room temperature in VECTASTAIN ABC reagent (Vector Laboratories, Burlingame, CA) according to kit instructions. The lid of the humidity chamber is secured during all incubations to ensure a moist environment. Sections are rinsed twice for 5 minutes in PBS, shaking gently.

Develop and Counterstain

[00224] Sections are incubated for 2 minutes in peroxidase substrate solution that is made up immediately prior to use as follows: 10mg diaminobenzidine (DAB) dissolved in 10ml 50 mM sodium phosphate buffer, pH 7.4; 12.5 microliters 3% CoCl₂/NiCl₂ in deionized water; 1.25 microliters hydrogen peroxide.

[00225] Slides are rinsed well three times for 10 min in deionized water and counterstained with 0.01% Light Green acidified with 0.01% acetic acid for 1-2 minutes depending on intensity of counterstain desired.

[00226] Slides are rinsed three times for 5 minutes with deionized water and dehydrated two times for 2 minutes in 95% ethanol; two times for 2 minutes in 100% ethanol; and two times for 2 minutes in xylene. Stained slides are mounted for visualization by microscopy.

Results

[00227] From Figure 1, pancreatic cancer tissue has 100 % of the samples where greater than 50% of the tumor cells stained with the highest intensity, using anti-CD49b antibody. Similarly, lung cancer tissue has 70% and colon cancer has 90% of the samples where greater than 50% of the tumor cells stained with the highest intensity.

7. IHC Staining of Frozen Tissue Sections

[00228] Fresh tissues are embedded carefully in OCT in a plastic mold, without trapping air bubbles surrounding the tissue. Tissues are frozen by setting the mold on top of liquid nitrogen until 70-80% of the block turns white at which point the mold is placed on dry ice. The frozen blocks are stored at -80°C. Blocks are sectioned with a cryostat with care taken to avoid warming to greater than -10°C. Initially, the block is equilibrated in the cryostat for about 5 minutes and 6-10mm sections are cut sequentially. Sections are allowed to dry for at least 30 minutes at room temperature. Following drying, tissues are stored at 4°C for short term and -80°C for long term storage.

[00229] Sections are fixed by immersing in acetone jar for 1-2 minutes at room temperature, followed by drying at room temperature. Primary antibody is added (diluted in 0.05 M Tris-saline [0.05 M Tris, 0.15 M NaCl, pH 7.4], 2.5% serum) directly to the sections by covering the section dropwise to cover the tissue entirely. Binding is carried out by incubation a chamber for 1 hour at room temperature. Without letting the sections dry out, the secondary antibody (diluted in Tris-saline/2.5% serum) is added in a similar manner to the primary and incubated as before (at least 45 minutes). Following incubation, the sections are washed gently in Tris-saline for 3-5 minutes and then in Tris-saline/2.5% serum for another 3-5 minutes. If a biotinylated primary antibody is used, in place of the secondary antibody incubation, slides are covered with 100 ul of diluted alkaline phosphatase conjugated streptavidin, incubated for 30 minutes at room temperature and washed as above. Sections are incubated with alkaline phosphatase substrate (1mg/ml Fast Violet; 0.2 mg/ml Naphthol AS-MX phosphate in Tris-Saline pH 8.5) for 10-20 minutes until the desired positive staining is achieved at which point the reaction is stopped by washing twice with Tris-saline. Slides are counter-stained with Mayer's hematoxylin for 30 seconds and washed with tap water for 2-5 minutes. Sections are mounted with Mount coverslips and mounting media.

[00230] All publications and patents mentioned in the above specification are herein incorporated by reference. Various modifications and variations of the described method and system of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the

invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the above-described modes for carrying out the invention, which are obvious to those skilled in the field of molecular biology or related fields, are intended to be within the scope of the following claims.

CLAIMS

1. A method for diagnosing or detecting pancreatic cancer in a subject comprising: determining the level of two or more PCAT proteins, or any fragment(s) thereof, in a test sample from said subject, wherein said PCAT proteins comprise sequences selected from a group consisting of SEQ ID NOS: 1-9 and a combination thereof; wherein a differential level of said PCAT proteins or fragments in said sample relative to the level of said proteins or fragments in a test sample from a healthy subject, or the level established for a healthy subject, is indicative of pancreatic cancer.
2. The method of claim 1, wherein the level of said PCAT protein(s) is determined by contacting one or more antibodies that specifically bind to the antigenic regions of PCAT protein(s).
3. The method of claim 1, wherein the level of four or more proteins are determined.
4. The method of claim 1, wherein the level of six or more proteins are determined.
5. The method of claim 1, wherein the level of eight or more proteins are determined.
6. A method for monitoring pancreatic cancer treatment in a subject comprising:
determining the level of one or more PCAT proteins or any fragment(s) thereof in a test sample from said subject, wherein said PCAT protein(s) comprises a sequence selected from a group consisting of SEQ ID NOS: 1-9 and a combination thereof, wherein an level of said PCAT protein(s) similar to the level of said protein(s) in a test sample from a healthy subject, or the level established for a healthy subject, is indicative of successful treatment.

7. A method for diagnosing recurrence of pancreatic cancer following successful treatment in a subject comprising:
determining the level of one or more PCAT proteins or any fragment(s) thereof in a test sample from said subject, wherein said PCAT protein(s) comprises a sequence selected from a group consisting of SEQ ID NOS: 1-9 or a combination thereof, wherein a changed level of said PCAT protein(s) relative to the level of said protein(s) in a test sample from a healthy subject, or the level established for a healthy subject, is indicative of recurrence of pancreatic cancer.
8. A method for diagnosing or detecting pancreatic cancer in a subject comprising: determining the level of two or more PCAT nucleic acids, or any fragment(s) thereof, in a test sample from said subject, wherein said PCAT nucleic acids comprise sequences selected from a group consisting of SEQ ID NOS: 10-20 and a combination thereof; wherein a differential level of said PCAT nucleic acids or fragment(s) in said sample relative to the level of said nucleic acids or fragments in a test sample from a healthy subject, or the level established for a healthy subject, is indicative of pancreatic cancer.
9. The method of claim 8, wherein the level of said PCAT nucleic acids is determined by contacting two or more probes that specifically hybridize to said PCAT nucleic acids.
10. The method of claim 8, wherein the level of four or more nucleic acids are determined.
11. The method of claim 8, wherein the level of six or more nucleic acids are determined.
12. The method of claim 8, wherein the level of eight or more nucleic acids are determined.

13. A composition comprising a plurality of nucleic acids for use in detecting the differential expression of PCAT genes in a diseased state, wherein said plurality of nucleic acids comprises SEQ ID NOS: 10-20 or the complete complements thereof.

14. The composition of claim 13, wherein said nucleic acids are immobilized on a substrate.

15. The composition of claim 13, wherein said nucleic acid are hybridizable elements on a microarray.

16. A method for diagnosing or monitoring the treatment of pancreatic cancer in a sample, said method comprising:

- a) obtaining nucleic acids from a sample;
- b) contacting the nucleic acids of the sample with an array comprising the plurality of nucleic acids of SEQ ID NOS 10-20 under conditions to form one or more hybridization complexes;
- c) detecting said hybridization complexes; and
- d) comparing the levels of the hybridization complexes detected in step (c) the level of hybridization complexes detected in a control sample, wherein the altered level of hybridization complexes detected in step (c) compared with the level of hybridization complexes of a control sample correlates with the presence of pancreatic cancer.

17. A composition comprising a plurality of proteins for use in detecting the differential expression of genes in a pancreatic diseased state; wherein said plurality of proteins comprises SEQ ID NOS: 1-9.

18. The composition of claim 17, wherein said proteins are immobilized on a substrate.

19. A method for diagnosing or monitoring the treatment of pancreatic cancer in a sample, said method comprising:

- a) obtaining proteins from a sample;

b) contacting the proteins of the sample with an array comprising the plurality of antibodies against proteins of SEQ ID NOS 1-9;

c) detecting said immunocomplex; and

d) comparing the levels of the immunocomplexes detected in step (c) the level of hybridization complexes detected in a control sample, wherein the differential level of immunocomplexes detected in step (c) compared with the level of immunocomplexes of a control sample correlates with the presence of pancreatic cancer.

Figure 1. Summary of CD49b Distribution in Tumors

Cancer Type	Number of Samples Analyzed	% Samples with Positive Staining			
		<50% Tumor Cells with 0/1+ Intensity	>50% Tumor Cells with 0/1+ Intensity	<50% Tumor Cells with 2+/3+ Intensity	>50% Tumor Cells with 2+/3+ Intensity
Pancreatic	10	0	0	0	100
Lung	10	30	0	0	70
Ovarian	10	40	10	40	10
Prostate	10	60	0	30	10
Colon	10	0	0	10	90
Breast	10	30	0	30	40

Figure 2 Overexpression of peptides correlating to the PCATs in Pancreatic cell lins.

PROTEINS	CELL LINES	EXPRESSION	RATIO
SEQ ID NO:1	HPAF_II	over	singleton
	Capan-2	over	singleton
	Capan-2	over	singleton
SEQ ID NO:2	HPAF_II	over	singleton
	Capan-2	over	singleton
	Capan-2	over	singleton
SEQ ID NO:3	HPAF_II	over	singleton
	Capan-2	over	singleton
	Capan-2	over	singleton
SEQ ID NO:4	AsPc-1	over	2.41
	HPAC	over	4.01
SEQ ID NO:5	AsPc-1	over	2.41
	HPAC	over	4.01
SEQ ID NO:6	Capan-2	over	6.30
	HPAF_II	over	singleton
SEQ ID NO: 7	BxPC-3	over	singleton
	Capan-2	over	singleton
	HPAF_II	over	singleton
	SU.86.86	over	singleton
SEQ ID NO: 8	BxPC-3	over	singleton
	Capan-2	over	singleton
	HPAF_II	over	singleton
	SU.86.86	over	singleton
SEQ ID NO: 9 hCP1878030	BxPC-3	over	singleton
	Capan-2	over	singleton
	HPAF_II	over	singleton
	SU.86.86	over	singleton

1543SEQLISTING.TXT

SEQUENCE LISTING

<110> DOMON, Bruno

<120> METHOD FOR DIAGNOSING PANCREATIC DISEASES

<130> CL001543-pct

<160> 20

<170> FastSEQ for windows Version 4.0

<210> 1

<211> 1179

<212> PRT

<213> Homo sapien

<400> 1

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Met Gly Pro Glu Arg Thr Gly Ala Ala Pro Leu Pro Leu Leu Leu Val
1      5      10      15
Leu Ala Leu Ser Gln Gly Ile Leu Asn Cys Cys Leu Ala Tyr Asn Val
20      25      30
Gly Leu Pro Glu Ala Lys Ile Phe Ser Gly Pro Ser Ser Glu Gln Phe
35      40      45
Gly Tyr Ala Val Gln Gln Phe Ile Asn Pro Lys Gly Asn Trp Leu Leu
50      55      60
Val Gly Ser Pro Trp Ser Gly Phe Pro Glu Asn Arg Met Gly Asp Val
65      70      75
Tyr Lys Cys Pro Val Asp Leu Ser Thr Ala Thr Cys Glu Lys Leu Asn
85      90      95
Leu Gln Thr Ser Thr Ser Ile Pro Asn Val Thr Glu Met Lys Thr Asn
100     105     110
Met Ser Leu Gly Leu Ile Leu Thr Arg Asn Met Gly Thr Gly Gly Phe
115     120     125
Leu Thr Cys Gly Pro Leu Trp Ala Gln Gln Cys Gly Asn Gln Tyr Tyr
130     135     140
Thr Thr Gly Val Cys Ser Asp Ile Ser Pro Asp Phe Gln Leu Ser Ala
145     150     155
Ser Phe Ser Pro Ala Thr Gln Pro Cys Pro Ser Leu Ile Asp Val Val
160     165     170
Val Val Cys Asp Glu Ser Asn Ser Ile Tyr Pro Trp Asp Ala Val Lys
175     180     185
Asn Phe Leu Glu Lys Phe Val Gln Gly Leu Asp Ile Gly Pro Thr Lys
190     195     200
Thr Gln Val Gly Leu Ile Gln Tyr Ala Asn Asn Pro Arg Val Val Phe
205     210     215
Asn Leu Asn Thr Tyr Lys Thr Lys Glu Glu Met Ile Val Ala Thr Ser
220     225     230
Gln Thr Ser Gln Tyr Gly Gly Asp Leu Thr Asn Thr Phe Gly Ala Ile
235     240     245
Gln Tyr Ala Arg Lys Tyr Ala Tyr Ser Ala Ala Ser Gly Gly Arg Arg
250     255     260
Ser Ala Thr Lys Val Met Val Val Val Thr Asp Gly Glu Ser His Asp
265     270     275
Gly Ser Met Leu Lys Ala Val Ile Asp Gln Cys Asn His Asp Asn Ile
280     285     290
Leu Arg Phe Gly Ile Ala Val Leu Gly Tyr Leu Asn Arg Asn Ala Leu
295     300     305
Asp Thr Lys Asn Leu Ile Lys Glu Ile Lys Ala Ile Ala Ser Ile Pro
310     315     320
Thr Glu Arg Tyr Phe Phe Asn Val Ser Asp Glu Ala Ala Leu Leu Glu
325     330     335
Lys Ala Gly Thr Leu Gly Glu Gln Ile Phe Ser Ile Glu Gly Thr Val
340     345     350
Gln Gly Gly Asp Asn Phe Gln Met Glu Met Ser Gln Val Gly Phe Ser
355     360     365
Ala Asp Tyr Ser Ser Gln Asn Asp Ile Leu Met Leu Gly Ala Val Gly
370     375     380
Ala Phe Gly Trp Ser Gly Thr Ile Val Gln Lys Thr Ser His Gly His
385     390     395
Leu Ile Phe Pro Lys Gln Ala Phe Asp Gln Ile Leu Gln Asp Arg Asn
400     405     410
His Ser Ser Tyr Leu Gly Tyr Ser Val Ala Ala Ile Ser Thr Gly Glu
415     420     425
Ser Thr His Phe Val Ala Gly Ala Pro Arg Ala Asn Tyr Thr Gly Gln
430     435     440
Ile Val Leu Tyr Ser Val Asn Glu Asn Gly Asn Ile Thr Val Ile Gln
445     450     455

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Page 1

1543SEQLISTING.TXT

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465      470      475      480
Ala His Arg Gly Asp Gln Ile Gly Ser Tyr Phe Gly Ser Val Leu Cys
Ser Val Asp Val Asp Lys Asp Thr Ile Thr Asp Val Leu Leu Val Gly
Ala Pro Met Tyr Met Ser Asp Leu Lys Lys Glu Glu Gly Arg Val Tyr
Leu Phe Thr Ile Lys Glu Gly Ile Leu Gly Gln His Gln Phe Leu Glu
Gly Pro Glu Gly Ile Glu Asn Thr Arg Phe Gly Ser Ala Ile Ala Ala
Leu Ser Asp Ile Asn Met Asp Gly Phe Asn Asp Val Ile Val Gly Ser
Pro Leu Glu Asn Gln Asn Ser Gly Ala Val Tyr Ile Tyr Asn Gly His
Gln Gly Thr Ile Arg Thr Lys Tyr Ser Gln Lys Ile Leu Gly Ser Asp
Gly Ala Phe Arg Ser His Leu Gln Tyr Phe Gly Arg Ser Leu Asp Gly
Tyr Gly Asp Leu Asn Gly Asp Ser Ile Thr Asp Val Ser Ile Gly Ala
Phe Gly Gln Val Val Gln Leu Trp Ser Gln Ser Ile Ala Asp Val Ala
Ile Glu Ala Ser Phe Thr Pro Glu Lys Ile Thr Leu Val Asn Lys Asn
Ala Gln Ile Ile Leu Lys Leu Cys Phe Ser Ala Lys Phe Arg Pro Thr
Lys Gln Asn Asn Gln Val Ala Ile Val Tyr Asn Ile Thr Leu Asp Ala
Asp Gly Phe Ser Ser Arg Val Thr Ser Arg Gly Leu Phe Lys Glu Asn
Asn Glu Arg Cys Leu Gln Lys Asn Met Val Val Asn Gln Ala Gln Ser
Cys Pro Glu His Ile Ile Tyr Ile Gln Glu Pro Ser Asp Val Val Asn
Ser Leu Asp Leu Arg Val Asp Ile Ser Leu Glu Asn Pro Gly Thr Ser
Pro Ala Leu Glu Ala Tyr Ser Glu Thr Ala Lys Val Phe Ser Ile Pro
Phe His Lys Asp Cys Gly Glu Asp Gly Leu Cys Ile Ser Asp Leu Val
Leu Asp Val Arg Gln Ile Pro Ala Ala Gln Glu Gln Pro Phe Ile Val
Ser Asn Gln Asn Lys Arg Leu Thr Phe Ser Val Thr Leu Lys Asn Lys
Arg Glu Ser Ala Tyr Asn Thr Gly Ile Val Val Asp Phe Ser Glu Asn
Leu Phe Phe Ala Ser Phe Ser Leu Pro Val Asp Gly Thr Glu Val Thr
Cys Gln Val Ala Ala Ser Gln Lys Ser Val Ala Cys Asp Val Gly Tyr
Pro Ala Leu Lys Arg Glu Gln Gln Val Thr Phe Thr Ile Asn Phe Asp
Phe Asn Leu Gln Asn Leu Gln Asn Gln Ala Ser Leu Ser Phe Gln Ala
Leu Ser Glu Ser Gln Glu Glu Asn Lys Ala Asp Asn Leu Val Asn Leu
Lys Ile Pro Leu Leu Tyr Asp Ala Glu Ile His Leu Thr Arg Ser Thr
Asn Ile Asn Phe Tyr Glu Ile Ser Ser Asp Gly Asn Val Pro Ser Ile
Val His Ser Phe Glu Asp Val Gly Pro Lys Phe Ile Phe Ser Leu Lys
Val Gly Ser Val Pro Val Ser Met Ala Thr Val Ile Ile His Ile Pro
Gln Tyr Thr Lys Glu Lys Asn Pro Leu Met Tyr Leu Thr Gly Val Gln
Thr Asp Lys Ala Gly Asp Ile Ser Cys Asn Ala Asp Ile Asn Pro Leu
Lys Ile Gly Gln Thr Ser Ser Val Ser Phe Lys Ser Glu Asn Phe
Arg His Thr Lys Glu Leu Asn Cys Arg Thr Ala Ser Cys Ser Asn Val
Thr Cys Trp Leu Lys Asp Val His Met Lys Gly Glu Tyr Phe Val Asn
Val Thr Thr Arg Ile Trp Asn Gly Thr Phe Ala Ser Ser Thr Phe Gln
Thr Val Gln Leu Thr Ala Ala Ala Glu Ile Asn Thr Tyr Asn Pro Glu
1090      1095      1100

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1543SEQLISTING.TXT

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Ile Tyr Val Ile Glu Asp Asn Thr Val Thr Ile Pro Leu Met Ile Met
1105          1110          1115          1120
Lys Pro Asp Glu Lys Ala Glu Val Pro Thr Gly Val Ile Ile Gly Ser
          1125          1130          1135
Ile Ile Ala Gly Ile Leu Leu Leu Leu Ala Leu Val Ala Ile Leu Trp
          1140          1145          1150
Lys Leu Gly Phe Phe Lys Arg Lys Tyr Glu Lys Met Thr Lys Asn Pro
          1155          1160          1165
Asp Glu Ile Asp Glu Thr Thr Glu Leu Ser Ser
          1170          1175

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<210> 2
 <211> 1181
 <212> PRT
 <213> Homo sapien

<400> 2

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Met Gly Pro Glu Arg Thr Gly Ala Ala Pro Leu Pro Leu Leu Leu Val
1          5          10          15
Leu Ala Leu Ser Gln Gly Ile Leu Asn Cys Cys Leu Ala Tyr Asn Val
          20          25          30
Gly Leu Pro Glu Ala Lys Ile Phe Ser Gly Pro Ser Ser Glu Gln Phe
          35          40          45
Gly Tyr Ala Val Gln Gln Phe Ile Asn Pro Lys Gly Asn Trp Leu Leu
          50          55          60
Val Gly Ser Pro Trp Ser Gly Phe Pro Glu Asn Arg Met Gly Asp Val
65          70          75          80
Tyr Lys Cys Pro Val Asp Leu Ser Thr Ala Thr Cys Glu Lys Leu Asn
          85          90          95
Leu Gln Thr Ser Thr Ser Ile Pro Asn Val Thr Glu Met Lys Thr Asn
          100          105          110
Met Ser Leu Gly Leu Ile Leu Thr Arg Asn Met Gly Thr Gly Gly Phe
          115          120          125
Leu Thr Cys Gly Pro Leu Trp Ala Gln Gln Cys Gly Asn Gln Tyr Tyr
130          135          140
Thr Thr Gly Val Cys Ser Asp Ile Ser Pro Asp Phe Gln Leu Ser Ala
145          150          155          160
Ser Phe Ser Pro Ala Thr Gln Pro Cys Pro Ser Leu Ile Asp Val Val
          165          170          175
Val Val Cys Asp Glu Ser Asn Ser Ile Tyr Pro Trp Asp Ala Val Lys
          180          185          190
Asn Phe Leu Glu Lys Phe Val Gln Gly Leu Asp Ile Gly Pro Thr Lys
          195          200          205
Thr Gln Val Gly Leu Ile Gln Tyr Ala Asn Asn Pro Arg Val Val Phe
210          215          220
Asn Leu Asn Thr Tyr Lys Thr Lys Glu Glu Met Ile Val Ala Thr Ser
225          230          235          240
Gln Thr Ser Gln Tyr Gly Gly Asp Leu Thr Asn Thr Phe Gly Ala Ile
          245          250          255
Gln Tyr Ala Arg Lys Tyr Ala Tyr Ser Ala Ala Ser Gly Gly Arg Arg
          260          265          270
Ser Ala Thr Lys Val Met Val Val Val Thr Asp Gly Glu Ser His Asp
          275          280          285
Gly Ser Met Leu Lys Ala Val Ile Asp Gln Cys Asn His Asp Asn Ile
          290          295          300
Leu Arg Phe Gly Ile Ala Val Leu Gly Tyr Leu Asn Arg Asn Ala Leu
305          310          315          320
Asp Thr Lys Asn Leu Ile Lys Glu Ile Lys Ala Ile Ala Ser Ile Pro
          325          330          335
Thr Glu Arg Tyr Phe Phe Asn Val Ser Asp Glu Ala Ala Leu Leu Glu
          340          345          350
Lys Ala Gly Thr Leu Gly Gln Gln Ile Phe Ser Ile Glu Gly Thr Val
          355          360          365
Gln Gly Gly Asp Asn Phe Gln Met Glu Met Ser Gln Val Gly Phe Ser
          370          375          380
Ala Asp Tyr Ser Ser Gln Asn Asp Ile Leu Met Leu Gly Ala Val Gly
385          390          395          400
Ala Phe Gly Trp Ser Gly Thr Ile Val Gln Lys Thr Ser His Gly His
          405          410          415
Leu Ile Phe Pro Lys Gln Ala Phe Asp Gln Ile Leu Gln Asp Arg Asn
          420          425          430
His Ser Ser Tyr Leu Gly Tyr Ser Val Ala Ala Ile Ser Thr Gly Glu
          435          440          445
Ser Thr His Phe Val Ala Gly Ala Pro Arg Ala Asn Tyr Thr Gly Gln
          450          455          460
Ile Val Leu Tyr Ser Val Asn Glu Asn Gly Asn Ile Thr Val Ile Gln
465          470          475          480
Ala His Arg Gly Asp Gln Ile Gly Ser Tyr Phe Gly Ser Val Leu Cys

```

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1543SEQLISTING.TXT

Ser Val Asp Val 485 Asp Lys Asp Thr Ile 490 Thr Asp Val Leu Leu 495 Gly
 Ala Pro Met Tyr Met Ser Asp Leu 505 Lys Lys Glu Glu Gly Arg Val Tyr
 Leu Phe Thr Ile Lys Glu Gly Ile Leu Gly Gln His Gln Phe Leu Glu
 Gly 530 Pro Glu Gly Ile Glu 535 Asn Thr Arg Phe Gly Ser Ala Ile Ala Ala
 545 Leu Ser Asp Ile Asn Met Asp Gly Phe Asn Asp Val Ile Val Gly Ser
 Pro Leu Glu Asn 565 Gln Asn Ser Gly Ala Val Tyr Ile Tyr Asn Gly His
 Gln Gly Thr Ile Arg Thr Lys Tyr 585 Ser Gln Lys Ile Leu Gly Ser Asp
 Gly Ala 595 Phe Arg Ser His Leu 600 Gln Tyr Phe Gly Arg Ser Leu Asp Gly
 Tyr Gly Asp Leu Asn Gly Asp Ser Ile Thr Asp Val Ser Ile Gly Ala
 625 Phe Gly Gln Val Val Gln Leu Trp Ser Gln Ser Ile Ala Asp Val Ala
 Ile Glu Ala Ser 645 Phe Thr Pro Glu Lys Ile Thr Leu Val Asn Lys Asn
 Ala Gln Ile 660 Leu Lys Leu Cys Phe Ser Ala Lys Phe Arg Pro Thr
 Lys Gln Asn Asn Gln Val Ala 680 Ile Val Tyr Asn Ile Thr Leu Asp Ala
 Asp Gly Phe Ser Ser Arg Val Thr Ser Arg Gly Leu Phe Lys Glu Asn
 705 Asn Glu Arg Cys Leu 710 Gln Lys Asn Met Val Val Asn Gln Ala Gln Ser
 Cys Pro Glu His 725 Ile Ile Tyr Ile Gln Glu Pro Ser Asp Val Val Asn
 Ser Leu Asp 740 Leu Arg Val Asp Ile Ser Leu Glu Asn Pro Gly Thr Ser
 Pro Ala Leu Glu Ala Tyr Ser 760 Glu Thr Ala Lys Val Phe Ser Ile Pro
 Phe His Lys Asp Cys Gly 775 Asp Gly Leu Cys Ile Ser Asp Leu Val
 785 Leu Asp Val Arg Gln Ile Pro Ala Ala Gln Glu Gln Pro Phe Ile Val
 Ser Asn Gln Asn Lys Arg Leu Thr Phe Ser Val Thr Leu Lys Asn Lys
 Arg Glu Ser 820 Ala Tyr Asn Thr Gly Ile Val Val Asp Phe Ser Glu Asn
 Leu Phe Phe Ala Ser Phe Ser 840 Leu Pro Val Asp Gly Thr Glu Val Thr
 Cys Gln Val Ala Ala Ser 855 Gln Lys Ser Val Ala Cys Asp Val Gly Tyr
 865 Pro Ala Leu Lys Arg Glu Gln Gln Val Thr Phe Thr Ile Asn Phe Asp
 Phe Asn Leu Gln Asn Leu Gln Asn Gln Ala Ser Leu Ser Phe Gln Ala
 Leu Ser Glu Ser Gln Glu Glu Asn Lys Ala Asp Asn Leu Val Asn Leu
 Lys Ile Pro Leu Leu Tyr Asp 920 Ala Glu Ile His Leu Thr Arg Ser Thr
 930 Asn Ile Asn Phe Tyr Glu Ile Ser Ser Asp Gly Asn Val Pro Ser Ile
 945 Val His Ser Phe Glu Asp Val Gly Pro Lys Phe Ile Phe Ser Leu Lys
 Val Thr Thr Gly Ser Val Pro Val Ser Met Ala Thr Val Ile Ile His
 Ile Pro Gln Tyr Thr Lys Glu Lys Asn Pro Leu Met Tyr Leu Thr Gly
 Val Gln Thr Asp Lys Ala Gly Asp Ile Ser Cys Asn Ala Asp Ile Asn
 1010 Pro Leu Lys Ile Gly Gln Thr Ser Ser Ser Val Ser Phe Lys Ser Glu
 1025 Asn Phe Arg His Thr Lys Glu Leu Asn Cys Arg Thr Ala Ser Cys Ser
 Asn Val Thr Cys Trp Leu Lys Asp Val 1050 His Met Lys Gly Glu Tyr Phe
 Val Asn Val Thr Thr Arg Ile Trp Asn Gly Thr Phe Ala Ser Ser Thr
 1075 Phe Gln Thr Val Gln Leu Thr Ala Ala Ala Glu Ile Asn Thr Tyr Asn
 1090 Pro Glu Ile Tyr Val Ile Glu Asp Asn Thr Val Thr Ile Pro Leu Met
 1105 1110 1115 1120

1543SEQLISTING.TXT
 Ile Met Lys Pro Asp Glu Lys Ala Glu Val Pro Thr Gly Val Ile Ile
 1125 1130 1135
 Gly Ser Ile Ile Ala Gly Ile Leu Leu Leu Ala Leu Val Ala Ile
 1140 1145 1150
 Leu Trp Lys Leu Gly Phe Phe Lys Arg Lys Tyr Glu Lys Met Thr Lys
 1155 1160 1165
 Asn Pro Asp Glu Ile Asp Glu Thr Thr Glu Leu Ser Ser
 1170 1175 1180

<210> 3
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 <212> PRT
 <213> Homo sapiens

<400> 3
 Met Gly Pro Glu Arg Thr Gly Ala Ala Pro Leu Pro Leu Leu Leu Val
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 20 25 30
 Gly Leu Pro Glu Ala Lys Ile Phe Ser Gly Pro Ser Ser Glu Gln Phe
 35 40 45
 Gly Tyr Ala Val Gln Gln Phe Ile Asn Pro Lys Gly Asn Trp Leu Leu
 50 55 60
 Val Gly Ser Pro Trp Ser Gly Phe Pro Glu Asn Arg Met Gly Asp Val
 65 70 75 80
 Tyr Lys Cys Pro Val Asp Leu Ser Thr Ala Thr Cys Glu Lys Leu Asn
 85 90 95
 Leu Gln Thr Ser Thr Ser Ile Pro Asn Val Thr Glu Met Lys Thr Asn
 100 105 110
 Met Ser Leu Gly Leu Ile Leu Thr Arg Asn Met Gly Thr Gly Gly Phe
 115 120 125
 Leu Thr Cys Gly Pro Leu Trp Ala Gln Gln Cys Gly Asn Gln Tyr Tyr
 130 135 140
 Thr Thr Gly Val Cys Ser Asp Ile Ser Pro Asp Phe Gln Leu Ser Ala
 145 150 155 160
 Ser Phe Ser Pro Ala Thr Gln Pro Cys Pro Ser Leu Ile Asp Val Val
 165 170 175
 Val Val Cys Asp Glu Ser Asn Ser Ile Tyr Pro Trp Asp Ala Val Lys
 180 185 190
 Asn Phe Leu Glu Lys Phe Val Gln Gly Leu Asp Ile Gly Pro Thr Lys
 195 200 205
 Thr Gln Val Gly Leu Ile Gln Tyr Ala Asn Asn Pro Arg Val Val Phe
 210 215 220
 Asn Leu Asn Thr Tyr Lys Thr Lys Glu Glu Met Ile Val Ala Thr Ser
 225 230 235 240
 Gln Thr Ser Gln Tyr Gly Gly Asp Leu Thr Asn Thr Phe Gly Ala Ile
 245 250 255
 Gln Tyr Ala Arg Lys Tyr Ala Tyr Ser Ala Ala Ser Gly Gly Arg Arg
 260 265 270
 Ser Ala Thr Lys Val Met Val Val Thr Asp Gly Glu Ser His Asp
 275 280 285
 Gly Ser Met Leu Lys Ala Val Ile Asp Gln Cys Asn His Asp Asn Ile
 290 295 300
 Leu Arg Phe Gly Ile Ala Val Leu Gly Tyr Leu Asn Arg Asn Ala Leu
 305 310 315 320
 Asp Thr Lys Asn Leu Ile Lys Glu Ile Lys Ala Ile Ala Ser Ile Pro
 325 330 335
 Thr Glu Arg Tyr Phe Phe Asn Val Ser Asp Glu Ala Ala Leu Leu Glu
 340 345 350
 Lys Ala Gly Thr Leu Gly Glu Gln Ile Phe Ser Ile Glu Gly Thr Val
 355 360 365
 Gln Gly Gly Asp Asn Phe Gln Met Glu Met Ser Gln Val Gly Phe Ser
 370 375 380
 Ala Asp Tyr Ser Ser Gln Asn Asp Ile Leu Met Leu Gly Ala Val Gly
 385 390 395 400
 Ala Phe Gly Trp Ser Gly Thr Ile Val Gln Lys Thr Ser His Gly His
 405 410 415
 Leu Ile Phe Pro Lys Gln Ala Phe Asp Gln Ile Leu Gln Asp Arg Asn
 420 425 430
 His Ser Ser Tyr Leu Gly Tyr Ser Val Ala Ala Ile Ser Thr Gly Glu
 435 440 445
 Ser Thr His Phe Val Ala Gly Ala Pro Arg Ala Asn Tyr Thr Gly Gln
 450 455 460
 Ile Val Leu Tyr Ser Val Asn Glu Asn Gly Asn Ile Thr Val Ile Gln
 465 470 475 480
 Ala His Arg Gly Asp Gln Ile Gly Ser Tyr Phe Gly Ser Val Leu Cys
 485 490 495
 Ser Val Asp Val Asp Lys Asp Thr Ile Thr Asp Val Leu Leu Val Gly

1543SEQLISTING.TXT

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500          505          510
Ala Pro Met Tyr Met Ser Asp Leu Lys Lys Glu Glu Gly Arg Val Tyr
515
Leu Phe Thr Ile Lys Lys Gly Ile Leu Gly Gln His Gln Phe Leu Glu
530
Gly Pro Glu Gly Ile Glu Asn Thr Arg Phe Gly Ser Ala Ile Ala Ala
545
Leu Ser Asp Ile Asn Met Asp Gly Phe Asn Asp Val Ile Val Gly Ser
560
Pro Leu Glu Asn Gln Asn Ser Gly Ala Val Tyr Ile Tyr Asn Gly His
580
Gln Gly Thr Ile Arg Thr Lys Tyr Ser Gln Lys Ile Leu Gly Ser Asp
595
Gly Ala Phe Arg Ser His Leu Gln Tyr Phe Gly Arg Ser Leu Asp Gly
610
Tyr Gly Asp Leu Asn Gly Asp Ser Ile Thr Asp Val Ser Ile Gly Ala
625
Phe Gly Gln Val Val Gln Leu Trp Ser Gln Ser Ile Ala Asp Val Ala
645
Ile Glu Ala Ser Phe Thr Pro Glu Lys Ile Thr Leu Val Asn Lys Asn
660
Ala Gln Ile Ile Leu Lys Leu Cys Phe Ser Ala Lys Phe Arg Pro Thr
675
Lys Gln Asn Asn Gln Val Ala Ile Val Tyr Asn Ile Thr Leu Asp Ala
690
Asp Gly Phe Ser Ser Arg Val Thr Ser Arg Gly Leu Phe Lys Glu Asn
705
Asn Glu Arg Cys Leu Gln Lys Asn Met Val Val Asn Gln Ala Gln Ser
720
Cys Pro Glu His Ile Tyr Ile Gln Glu Pro Ser Asp Val Val Asn
735
Ser Leu Asp Leu Arg Val Asp Ile Ser Leu Glu Asn Pro Gly Thr Ser
750
Pro Ala Leu Glu Ala Tyr Ser Glu Thr Ala Lys Val Phe Ser Ile Pro
770
Phe His Lys Asp Cys Gly Glu Asp Gly Leu Cys Ile Ser Asp Leu Val
785
Leu Asp Val Arg Gln Ile Pro Ala Ala Gln Glu Gln Pro Phe Ile Val
800
Ser Asn Gln Asn Lys Arg Leu Thr Phe Ser Val Thr Leu Lys Asn Lys
815
Arg Glu Ser Ala Tyr Asn Thr Gly Ile Val Val Asp Phe Ser Glu Asn
830
Leu Phe Phe Ala Ser Phe Ser Leu Pro Val Asp Gly Thr Glu Val Thr
845
Cys Gln Val Ala Ala Ser Gln Lys Ser Val Ala Cys Asp Val Gly Tyr
860
Pro Ala Leu Lys Arg Glu Gln Gln Val Thr Phe Thr Ile Asn Phe Asp
875
Phe Asn Leu Gln Asn Leu Gln Asn Gln Ala Ser Leu Ser Phe Gln Ala
890
Leu Ser Glu Ser Gln Glu Glu Asn Lys Ala Asp Asn Leu Val Asn Leu
905
Lys Ile Pro Leu Leu Tyr Asp Ala Glu Ile His Leu Thr Arg Ser Thr
920
Asn Ile Asn Phe Tyr Glu Ile Ser Ser Asp Gly Asn Val Pro Ser Ile
935
Val His Ser Phe Glu Asp Val Gly Pro Lys Phe Ile Phe Ser Leu Lys
950
Val Thr Thr Gly Ser Val Pro Val Ser Met Ala Thr Val Ile Ile His
965
Ile Pro Gln Tyr Thr Lys Glu Lys Asn Pro Leu Met Tyr Leu Thr Gly
980
Val Gln Thr Asp Lys Ala Gly Asp Ile Ser Cys Asn Ala Asp Ile Asn
1000
Pro Leu Lys Ile Gly Gln Thr Ser Ser Ser Val Ser Phe Lys Ser Glu
1015
Asn Phe Arg His Thr Lys Glu Leu Asn Cys Arg Thr Ala Ser Cys Ser
1030
Asn Val Thr Cys Trp Leu Lys Asp Val His Met Lys Gly Glu Tyr Phe
1045
Val Asn Val Thr Thr Arg Ile Trp Asn Gly Thr Phe Ala Ser Ser Thr
1060
Phe Gln Thr Val Gln Leu Thr Ala Ala Ala Glu Ile Asn Thr Tyr Asn
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Pro Glu Ile Tyr Val Ile Glu Asp Asn Thr Val Thr Ile Pro Leu Met
1090
Ile Met Lys Pro Asp Glu Lys Ala Glu Val Pro Thr Gly Val Ile Ile
1105
1110
1115
1120
1125
1130
1135

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1543SEQLISTING.TXT
 Gly Ser Ile Ile Ala Gly Ile Leu Leu Leu Ala Leu Val Ala Ile
 1140 1145 1150
 Leu Trp Lys Leu Gly Phe Phe Lys Arg Lys Tyr Glu Lys Met Thr Lys
 1155 1160 1165
 Asn Pro Asp Glu Ile Asp Glu Thr Thr Glu Leu Ser Ser
 1170 1175 1180

<210> 4
 <211> 760
 <212> PRT
 <213> Homo sapiens

<400> 4
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 20 25 30
 Asn Ser His Val Glu Met Lys Leu Ala Val Asp Glu Glu Glu Asn Ala
 35 40 45
 Asp Asn Asn Thr Lys Ala Asn Val Thr Lys Pro Lys Arg Cys Ser Gly
 50 55 60
 Ser Ile Cys Tyr Gly Thr Ile Ala Val Ile Val Phe Phe Leu Ile Gly
 65 70 75 80
 Phe Met Ile Gly Tyr Leu Gly Tyr Cys Lys Gly Val Glu Pro Lys Thr
 85 90 95
 Glu Cys Glu Arg Leu Ala Gly Thr Glu Ser Pro Val Arg Glu Glu Pro
 100 105 110
 Gly Glu Asp Phe Pro Ala Ala Arg Arg Leu Tyr Trp Asp Asp Leu Lys
 115 120 125
 Arg Lys Leu Ser Glu Lys Leu Asp Ser Thr Asp Phe Thr Gly Thr Ile
 130 135 140
 Lys Leu Leu Asn Glu Asn Ser Tyr Val Pro Arg Glu Ala Gly Ser Gln
 145 150 155 160
 Lys Asp Glu Asn Leu Ala Leu Tyr Val Glu Asn Gln Phe Arg Glu Phe
 165 170 175
 Lys Leu Ser Lys Val Trp Arg Asp Gln His Phe Val Lys Ile Gln Val
 180 185 190
 Lys Asp Ser Ala Gln Asn Ser Val Ile Ile Val Asp Lys Asn Gly Arg
 195 200 205
 Leu Val Tyr Leu Val Glu Asn Pro Gly Gly Tyr Val Ala Tyr Ser Lys
 210 215 220
 Ala Ala Thr Val Thr Gly Lys Leu Val His Ala Asn Phe Gly Thr Lys
 225 230 235 240
 Lys Asp Phe Glu Asp Leu Tyr Thr Pro Val Asn Gly Ser Ile Val Ile
 245 250 255
 Val Arg Ala Gly Lys Ile Thr Phe Ala Glu Lys Val Ala Asn Ala Glu
 260 265 270
 Ser Leu Asn Ala Ile Gly Val Leu Ile Tyr Met Asp Gln Thr Lys Phe
 275 280 285
 Pro Ile Val Asn Ala Glu Leu Ser Phe Phe Gly His Ala His Leu Gly
 290 295 300
 Thr Gly Asp Pro Tyr Thr Pro Gly Phe Pro Ser Phe Asn His Thr Gln
 305 310 315 320
 Phe Pro Pro Ser Arg Ser Ser Gly Leu Pro Asn Ile Pro Val Gln Thr
 325 330 335
 Ile Ser Arg Ala Ala Ala Glu Lys Leu Phe Gly Asn Met Glu Gly Asp
 340 345 350
 Cys Pro Ser Asp Trp Lys Thr Asp Ser Thr Cys Arg Met Val Thr Ser
 355 360 365
 Glu Ser Lys Asn Val Lys Leu Thr Val Ser Asn Val Leu Lys Glu Ile
 370 375 380
 Lys Ile Leu Asn Ile Phe Gly Val Ile Lys Gly Phe Val Glu Pro Asp
 385 390 395 400
 His Tyr Val Val Val Gly Ala Gln Arg Asp Ala Trp Gly Pro Gly Ala
 405 410 415
 Ala Lys Ser Gly Val Gly Thr Ala Leu Leu Lys Leu Ala Gln Met
 420 425 430
 Phe Ser Asp Met Val Leu Lys Asp Gly Phe Gln Pro Ser Arg Ser Ile
 435 440 445
 Ile Phe Ala Ser Trp Ser Ala Gly Asp Phe Gly Ser Val Gly Ala Thr
 450 455 460
 Glu Trp Leu Glu Gly Tyr Leu Ser Ser Leu His Leu Lys Ala Phe Thr
 465 470 475 480
 Tyr Ile Asn Leu Asp Lys Ala Val Leu Gly Thr Ser Asn Phe Lys Val
 485 490 495
 Ser Ala Ser Pro Leu Leu Tyr Thr Leu Ile Glu Lys Thr Met Gln Asn
 500 505 510
 Val Lys His Pro Val Thr Gly Gln Phe Leu Tyr Gln Asp Ser Asn Trp

1543SEQLISTING.TXT

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515      520      525
Ala Ser Lys Val Glu Lys Leu Thr Leu Asp Asn Ala Ala Phe Pro Phe
530      535      540
Leu Ala Tyr Ser Gly Ile Pro Ala Val Ser Phe Cys Phe Cys Glu Asp
545      550      555      560
Thr Asp Tyr Pro Tyr Leu Gly Thr Thr Met Asp Thr Tyr Lys Glu Leu
565      570      575
Ile Glu Arg Ile Pro Glu Leu Asn Lys Val Ala Arg Ala Ala Ala Glu
580      585      590
Val Ala Gly Gln Phe Val Ile Lys Leu Thr His Asp Val Glu Leu Asn
595      600      605
Leu Asp Tyr Glu Arg Tyr Asn Ser Gln Leu Leu Ser Phe Val Arg Asp
610      615      620
Leu Asn Gln Tyr Arg Ala Asp Ile Lys Glu Met Gly Leu Ser Leu Gln
625      630      635      640
Trp Leu Tyr Ser Ala Arg Gly Asp Phe Phe Arg Ala Thr Ser Arg Leu
645      650      655
Thr Thr Asp Phe Gly Asn Ala Glu Lys Thr Asp Arg Phe Val Met Lys
660      665      670
Lys Leu Asn Asp Arg Val Met Arg Val Glu Tyr His Phe Leu Ser Pro
675      680      685
Tyr Val Ser Pro Lys Glu Ser Pro Phe Arg His Val Phe Trp Gly Ser
690      695      700
Gly Ser His Thr Leu Pro Ala Leu Leu Glu Asn Leu Lys Leu Arg Lys
705      710      715      720
Gln Asn Asn Gly Ala Phe Asn Glu Thr Leu Phe Arg Asn Gln Leu Ala
725      730      735      740
Leu Ala Thr Trp Thr Ile Gln Gly Ala Ala Asn Ala Leu Ser Gly Asp
745      750
Val Trp Asp Ile Asp Asn Glu Phe
755      760

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<210> 5
 <211> 804
 <212> PRT
 <213> Homo sapiens

<400> 5

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Met Met Asp Gln Ala Arg Ser Ala Phe Ser Asn Leu Phe Gly Gly Glu
1      5      10      15
Pro Leu Ser Tyr Thr Arg Phe Ser Leu Ala Arg Gln Val Asp Gly Asp
20      25      30
Asn Ser His Val Glu Met Lys Leu Ala Val Asp Glu Glu Glu Asn Ala
35      40      45
Asp Asn Asn Thr Lys Ala Asn Val Thr Lys Pro Lys Arg Cys Ser Gly
50      55      60
Ser Ile Cys Tyr Gly Thr Ile Ala Val Ile Val Phe Phe Leu Ile Gly
65      70      75      80
Phe Met Ile Gly Tyr Leu Gly Tyr Cys Lys Gly Val Glu Pro Lys Thr
85      90      95
Glu Cys Glu Arg Leu Ala Gly Thr Glu Ser Pro Val Arg Glu Glu Pro
100      105      110
Gly Glu Asp Phe Pro Ala Ala Arg Arg Leu Tyr Trp Asp Asp Leu Lys
115      120      125
Arg Lys Leu Ser Glu Lys Leu Asp Ser Thr Asp Phe Thr Gly Thr Ile
130      135      140
Lys Leu Leu Asn Glu Asn Ser Tyr Val Pro Arg Glu Ala Gly Ser Gln
145      150      155      160
Lys Asp Glu Asn Leu Ala Leu Tyr Val Glu Asn Gln Phe Arg Glu Phe
165      170      175
Lys Leu Ser Lys Val Trp Arg Asp Gln His Phe Val Lys Ile Gln Val
180      185      190
Lys Asp Ser Ala Gln Asn Ser Val Ile Ile Val Asp Lys Asn Gly Arg
195      200      205
Leu Val Tyr Leu Val Glu Asn Pro Gly Gly Tyr Val Ala Tyr Ser Lys
210      215      220
Ala Ala Thr Val Thr Gly Lys Leu Val His Ala Asn Phe Gly Thr Lys
225      230      235      240
Lys Asp Phe Glu Asp Leu Tyr Thr Pro Val Asn Gly Ser Ile Val Ile
245      250      255
Val Arg Ala Gly Lys Ile Thr Phe Ala Glu Lys Val Ala Asn Ala Glu
260      265      270
Ser Leu Asn Ala Ile Gly Val Leu Ile Tyr Met Asp Gln Thr Lys Phe
275      280      285
Pro Ile Val Asn Ala Glu Leu Ser Phe Phe Gly His Ala His Leu Gly
290      295      300      305
Thr Gly Asp Pro Tyr Thr Pro Gly Phe Pro Ser Phe Asn His Thr Gln
310      315      320

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Phe Pro Pro Ser Arg Ser Ser Gly Leu Pro Asn Ile Pro Val Gln Thr
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 Ile Ser Arg Ala Ala Ala Glu Lys Leu Phe Gly Asn Met Glu Gly Asp
 340 345 350
 Cys Pro Ser Asp Trp Lys Thr Asp Ser Thr Cys Arg Met Val Thr Ser
 355 360 365
 Glu Ser Lys Asn Val Lys Leu Thr Val Ser Asn Val Leu Lys Glu Ile
 370 375 380
 Lys Ile Leu Asn Ile Phe Gly Val Ile Lys Gly Phe Val Glu Pro Asp
 385 390 395 400
 His Tyr Val Val Val Gly Ala Gln Arg Asp Ala Trp Gly Pro Gly Ala
 405 410 415
 Ala Lys Ser Gly Val Gly Thr Ala Leu Leu Lys Leu Ala Gln Met
 420 425 430
 Phe Ser Asp Met Val Leu Lys Asp Gly Phe Gln Pro Ser Arg Ser Ile
 435 440 445
 Ile Phe Ala Ser Trp Ser Ala Gly Asp Phe Gly Ser Val Gly Ala Thr
 450 455 460
 Glu Trp Leu Glu Gly Tyr Leu Ser Ser Leu His Leu Lys Ala Phe Thr
 465 470 475 480
 Tyr Ile Asn Leu Asp Lys Ala Val Leu Gly Thr Ser Asn Phe Lys Val
 485 490 495
 Ser Ala Ser Pro Leu Leu Tyr Thr Leu Ile Glu Lys Thr Met Gln Asn
 500 505 510
 Met Glu Ser Ser Ser Val Phe Leu Gln His Ser Gly Trp Ser Ala Met
 515 520 525
 Val Arg Ser Trp Leu Thr Ala Ala Ser Thr Ser Trp Val Gln Ala Ile
 530 535 540
 Leu Leu Pro Gln Pro Pro Glu Glu Leu Gly Leu Gln Val Lys His Pro
 545 550 555 560
 Val Thr Gly Gln Phe Leu Tyr Gln Asp Ser Asn Trp Ala Ser Lys Val
 565 570 575
 Glu Lys Leu Thr Leu Asp Asn Ala Ala Phe Pro Phe Leu Ala Tyr Ser
 580 585 590
 Gly Ile Pro Ala Val Ser Phe Cys Phe Cys Glu Asp Thr Asp Tyr Pro
 595 600 605
 Tyr Leu Gly Thr Thr Met Asp Thr Tyr Lys Glu Leu Ile Glu Arg Ile
 610 615 620
 Pro Glu Leu Asn Lys Val Ala Arg Ala Ala Ala Glu Val Ala Gly Gln
 625 630 635 640
 Phe Val Ile Lys Leu Thr His Asp Val Glu Leu Asn Leu Asp Tyr Glu
 645 650 655
 Arg Tyr Asn Ser Gln Leu Leu Ser Phe Val Arg Asp Leu Asn Gln Tyr
 660 665 670
 Arg Ala Asp Ile Lys Glu Met Gly Leu Ser Leu Gln Trp Leu Tyr Ser
 675 680 685
 Ala Arg Gly Asp Phe Phe Arg Ala Thr Ser Arg Leu Thr Thr Asp Phe
 690 695 700
 Gly Asn Ala Glu Lys Thr Asp Arg Phe Val Met Lys Lys Leu Asn Asp
 705 710 715 720
 Arg Val Met Arg Val Glu Tyr His Phe Leu Ser Pro Tyr Val Ser Pro
 725 730 735
 Lys Glu Ser Pro Phe Arg His Val Phe Trp Gly Ser Gly Ser His Thr
 740 745 750
 Leu Pro Ala Leu Leu Glu Asn Leu Lys Leu Arg Lys Gln Asn Asn Gly
 755 760 765
 Ala Phe Asn Glu Thr Leu Phe Arg Asn Gln Leu Ala Leu Ala Thr Trp
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 Asp Asn Glu Phe

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 <213> Homo sapiens

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 35 40 45
 Phe Gly Phe Ala Val Asp Phe Phe Val Pro Ser Ala Ser Ser Arg Met
 50 55 60
 Phe Leu Leu Val Gly Ala Pro Lys Ala Asn Thr Thr Gln Pro Gly Ile
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65	Val	Glu	Gly	Gly	Gln	70	Val	Leu	Lys	Cys	Asp	75	Trp	Ser	Ser	Thr	Arg	80	Arg
					85						90						95		
	Cys	Gln	Pro	Ile	Glu	Phe	Asp	Ala	Thr	Gly	Asn	Arg	Asp	Tyr	Ala	Lys			
	Asp	Asp	Pro	Leu	Glu	Phe	Lys	Ser	His	Gln	Trp	Phe	Gly	Ala	Ser	Val			
	Arg	Ser	Lys	Gln	Asp	Lys	Ile	Leu	Ala	Cys	Ala	Pro	Leu	Tyr	His	Trp			
	Arg	Thr	Glu	Met	Lys	Gln	Glu	Arg	Glu	Pro	Val	Gly	Thr	Cys	Phe	Leu			
	145	Gln	Asp	Gly	Thr	Lys	Thr	Val	Glu	Tyr	Ala	Pro	Cys	Arg	Ser	Gln	Asp		
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	Ile	Asp	Ala	Asp	Gly	Gln	Gly	Phe	Cys	Gln	Gly	Gly	Phe	Ser	Ile	Asp			
	Phe	Thr	Lys	Ala	Asp	Arg	Val	Leu	Leu	Gly	Gly	Pro	Gly	Ser	Phe	Tyr			
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	Trp	Gln	Gly	Gln	Leu	Ile	Ser	Asp	Gln	Val	Ala	Glu	Ile	Val	Ser	Lys			
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	Tyr	Asp	Pro	Asn	Val	Tyr	Ser	Ile	Lys	Tyr	Asn	Asn	Gln	Leu	Ala	Thr			
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	Arg	Thr	Ala	Gln	Ala	Ile	Phe	Asp	Asp	Ser	Tyr	Leu	Gly	Tyr	Ser	Val			
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	Val	Pro	Arg	Ala	Ala	Arg	Thr	Leu	Gly	Met	Val	Tyr	Ile	Tyr	Asp	Gly			
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	Lys	Asn	Met	Ser	Ser	Leu	Tyr	Asn	Phe	Thr	Gly	Glu	Gln	Met	Ala	Ala			
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	Tyr	Phe	Gly	Phe	Ser	Val	Ala	Ala	Thr	Asp	Ile	Asn	Gly	Asp	Asp	Tyr			
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	Ala	Asp	Val	Phe	Ile	Gly	Ala	Pro	Leu	Phe	Met	Asp	Arg	Gly	Ser	Asp			
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	Gly	Lys	Leu	Gln	Glu	Val	Gly	Gln	Val	Ser	Val	Ser	Leu	Gln	Arg	Ala			
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	Ser	Gly	Asp	Phe	Gln	Thr	Thr	Lys	Leu	Asn	Gly	Phe	Glu	Val	Phe	Ala			
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	Pro	Ser	Gln	Ile	Leu	Glu	Gly	Gln	Trp	Ala	Ala	Arg	Ser	Met	Pro	Pro			
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	Ser	Phe	Gly	Tyr	Ser	Met	Lys	Gly	Ala	Thr	Asp	Ile	Asp	Lys	Asn	Gly			
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	Leu	Ile	Val	Ser	Ile	Pro	Leu	Gln	Ala	Asp	Phe	Ile	Gly	Val	Val	Arg			
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Gln Thr Arg Gln Val Val Cys Asp Leu Gly Asn Pro Met Lys Ala Gly
705 Thr Gln Leu Leu Ala 710 Gly Leu Arg Phe Ser Val His Gln Gln Ser Glu
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745
Phe Asp Lys Val Ser Pro Val Val Ser His Lys Val Asp Leu Ala Val
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Leu Ala Ala Val Glu Ile Arg Gly Val Ser Ser Pro Asp His Ile Phe
770
Leu Pro Ile Pro Asn Trp 790 Glu His Lys Glu Asn Pro Glu Thr Glu Glu
785
Asp Val Gly Pro Val 805 Gln His Ile Tyr Glu Leu Arg Asn Asn Gly
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Pro Ser Ser Phe 820 Ser Lys Ala Met Leu His Leu Gln Trp Pro Tyr Lys
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Tyr Asn Asn Asn Thr Leu Leu Tyr Ile Leu His Tyr Asp Ile Asp Gly
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Pro Met Asn Cys Thr Ser Asp 855 Met Glu Ile Asn Pro Leu Arg Ile Lys
865
Ile Ser Ser Leu Gln Thr Thr Glu Lys Asn Asp Thr Val Ala Gly Gln
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Gly Glu Arg Asp His 885 Leu Ile Thr Lys Arg Asp Leu Ala Leu Ser Glu
895
Gly Asp Ile His 900 Thr Leu Gly Cys Gly Val Ala Gln Cys Leu Lys Ile
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Val Cys Gln Val Gly Arg Leu Asp Arg Gly Lys Ser Ala Ile Leu Tyr
915
Val Lys Ser Leu Leu Trp Thr Glu Thr Phe Met Asn Lys Glu Asn Gln
930
Asn His Ser Tyr Ser Leu Lys Ser Ser Ala Ser Phe Asn Val Ile Glu
945
Phe Pro Tyr Lys Asn 950 Leu Pro Ile Glu Asp Ile Thr Asn Ser Thr Leu
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Val Thr Thr Asn Val Thr Trp Gly Ile Gln Pro Ala Pro Met Pro Val
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Pro Val Trp Val Ile Ile Leu Ala Val Leu Ala Gly Leu Leu Leu
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Ala Val Leu Val Phe Val Met Tyr Arg Met Gly Phe Phe Lys Arg Val
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 35 Ala Ala Ile Ala Tyr Thr Ile Leu Ser Gln Asp Pro Glu Leu Pro Asp
 50 Lys Asn Met Phe Thr Ile Asn Arg Asn Thr Gly Val Ile Ser Val Val
 65 Thr Thr Gly Leu Asp Arg Glu Ser Phe Pro Thr Tyr Thr Leu Val Val
 85 Gln Ala Ala Asp Leu Gln Gly Glu Gly Leu Ser Thr Thr Ala Thr Ala
 100 Val Ile Thr Val Thr Asp Thr Asn Asp Asn Pro Pro Ile Phe Asn Pro
 115 Thr Thr Tyr Lys Gly Gln Val Pro Glu Asn Glu Ala Asn Val Val Ile
 130 Thr Thr Leu Lys Val Thr Asp Ala Asp Ala Pro Asn Thr Pro Ala Trp
 145 Glu Ala Val Tyr Thr Ile Leu Asn Asp Asp Gly Gly Gln Phe Val Val
 165 Thr Thr Asn Pro Val Asn Asn Asp Gly Ile Leu Lys Thr Ala Lys Gly
 180 Leu Asp Phe Glu Ala Lys Gln Gln Tyr Ile Leu His Val Ala Val Thr
 195 Asn Val Val Pro Phe Glu Val Ser Leu Thr Thr Ser Thr Ala Thr Val

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

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 <213> Homo sapiens

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 35 Gly Arg Val Leu Gly Arg Val Asn Phe Glu Asp Cys Thr Gly Arg Gln
 50 Arg Thr Ala Tyr Phe Ser Leu Asp Thr Arg Phe Lys Val Gly Thr Asp
 65 Gly Val Ile Thr Val Lys Arg Pro Leu Arg Phe His Asn Pro Gln Ile
 80 His Phe Leu Val Tyr Ala Trp Asp Ser Thr Tyr Arg Lys Phe Ser Thr
 100 Lys Val Thr Leu Asn Thr Val Gly His His His Arg Pro Pro Pro His
 115 Gln Ala Ser Val Ser Gly Ile Gln Ala Glu Leu Leu Thr Phe Pro Asn
 130 135 140

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Gln 155 Ile 155 Lys 180 Ser 180 Asn 155 Lys 155 Asp 155 Lys 185 Glu 155 Gly 155 Val 155 Phe 155 Tyr 190 Ser 155 Ile 155
Thr 155 Gly 195 Gln 155 Gly 155 Ala 155 Asp 155 Thr 155 Pro 155 Val 155 Gly 155 Val 155 Phe 155 Ile 155 Ile 155 Glu 155
Arg 155 Glu 210 Thr 155 Gly 155 Trp 155 Leu 155 Lys 155 Val 155 Thr 155 Glu 155 Pro 155 Leu 155 Asp 155 Arg 155 Glu 155 Arg 155
Ile 225 Ala 155 Thr 155 Tyr 155 Thr 155 Leu 155 Phe 155 Ser 155 His 155 Ala 155 Val 155 Ser 155 Asn 155 Gly 155 Asn 155
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Leu 155 Ser 155 Gln 155 Asp 155 Pro 155 Glu 155 Leu 155 Pro 155 Asp 155 Lys 155 Asn 155 Met 155 Phe 155 Thr 155 Ile 155 Asn 155
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Gln 155 Tyr 155 Ile 155 Leu 155 His 155 Val 155 Ala 155 Val 155 Thr 155 Asn 155 Val 155 Val 155 Pro 155 Phe 155 Glu 155 Val 155
Ser 155 Leu 155 Thr 155 Thr 155 Ser 155 Thr 155 Ala 155 Thr 155 Val 155 Thr 155 Val 155 Asp 155 Val 155 Leu 155 Asp 155 Val 155
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Pro 155 Gln 155 Val 155 Ile 155 Asn 155 Ile 155 Ile 155 Asp 155 Ala 155 Asp 155 Leu 155 Pro 155 Pro 155 Asn 155 Thr 155 Ser 155
Pro 155 Phe 155 Thr 155 Ala 155 Glu 155 Leu 155 Thr 155 His 155 Gly 155 Ala 155 Ser 155 Ala 155 Asn 155 Trp 155 Thr 155 Ile 155
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Gln 155 Asn 155 Lys 155 Asp 155 Gln 155 Val 155 Thr 155 Thr 155 Leu 155 Glu 155 Val 155 Ser 155 Val 155 Cys 155 Asp 155 Cys 155
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Tyr 155 Tyr 155 Tyr 155 Asp 155 Glu 155 Glu 155 Gly 155 Gly 155 Glu 155 Glu 155 Asp 155 Gln 155 Asp 155 Phe 155 Asp 155
Leu 155 Ser 155 Gln 155 Leu 155 His 155 Arg 155 Gly 155 Leu 155 Asp 155 Ala 155 Arg 155 Pro 155 Glu 155 Val 155 Thr 155 Arg 155

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Pro Ala Asn Pro Asp	Glu Ile Gly Asn Phe	Ile Asp Glu Asn Leu Lys
805	810	815
Ala Ala Asp Thr Asp	Pro Thr Ala Pro Tyr	Asp Ser Leu Leu Val
820	825	830
Phe Asp Tyr Glu Gly	Ser Gly Ser Glu Ala	Ala Ser Leu Ser Leu
835	840	845
Asn Ser Ser Glu Ser	Asp Lys Asp Gln Asp	Tyr Asp Tyr Leu Asn Glu
850	855	860
Trp Gly Asn Arg Phe	Lys Lys Leu Ala Asp	Met Tyr Gly Gly Gly Glu
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Asp Asp		

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

<400> 9

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Gly Arg Val Leu Gly Arg Val Asn Phe	Glu Asp Cys Thr Gly Arg Gln
50	60
Arg Thr Ala Tyr Phe Ser Leu Asp Thr	Arg Phe Lys Val Gly Thr Asp
65	75
Gly Val Ile Thr Val Lys Arg Pro Leu	Arg Phe His Asn Pro Gln Ile
85	95
His Phe Leu Val Tyr Ala Trp Asp Ser	Thr Tyr Arg Lys Phe Ser Thr
100	110
Lys Val Thr Leu Asn Thr Val Gly His	His His Arg Pro Pro His
115	125
Gln Ala Ser Val Ser Gly Ile Gln Ala	Glu Leu Leu Thr Phe Pro Asn
130	140
Ser Ser Pro Gly Leu Arg Arg Gln Lys	Arg Asp Trp Val Ile Pro Pro
145	155
Ile Ser Cys Pro Glu Asn Glu Lys Gly	Pro Phe Pro Lys Asn Leu Val
165	175
Gln Ile Lys Ser Asn Lys Asp Lys Glu	Gly Lys Val Phe Tyr Ser Ile
180	190
Thr Gly Gln Gly Ala Asp Thr Pro Pro	Val Gly Val Phe Ile Ile Glu
195	205
Arg Glu Thr Gly Trp Leu Lys Val Thr	Glu Pro Leu Asp Arg Glu Arg
210	220
Ile Ala Thr Tyr Thr Leu Phe Ser His	Ala Val Ser Ser Asn Gly Asn
225	235
Ala Val Glu Asp Pro Met Glu Ile Leu	Ile Thr Val Thr Asp Gln Asn
245	255
Asp Asn Lys Pro Glu Phe Thr Gln Glu	Val Phe Lys Gly Ser Val Met
260	270
Glu Gly Ala Leu Pro Gly Thr Ser Val	Met Glu Val Thr Ala Thr Asp
275	285
Ala Asp Asp Asp Val Asn Thr Tyr Asn	Ala Ala Ile Ala Tyr Thr Ile
290	300
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INTERNATIONAL SEARCH REPORT

International Application No
PC.7/US2004/025268

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/574

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, Sequence Search, WPI Data, PAJ, BIOSIS, EMBASE, INSPEC, FSTA, COMPENDEX

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ANSARI T ET AL: "Decreased E-cadherin expression correlates with lymph node metastasis, high grade and advanced stage in pancreatic cancer" JOURNAL OF PATHOLOGY, vol. 172, no. SUPPL., 1994, page 97A, XP008044674 & 168TH MEETING OF THE PATHOLOGICAL SOCIETY OF GREAT BRITAIN AND IRELAND; LONDON, ENGLAND, UK; JANUARY 5-7, 1994 ISSN: 0022-3417 abstract ----- -/--	1

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

23 March 2005

Date of mailing of the international search report

03 -08- 2005

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International Application No

PC/US2004/025268

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