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(21) International Application Number: PCT/US99/17777 (22) International Filing Date: 6 August 1999 (06.08.99) (30) Priority Data: 60/160,065 7 August 1998 (07.08.98) US 60/098,703 1 September 1998 (01.09.98) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications US 09/130,884 (CIP) Filed on 7 August 1998 (07.08.98) US 60/160,065 (CIP) Filed on 7 August 1998 (07.08.98) US 60/098,703 (CIP) Filed on 1 September 1998 (01.09.98) (71) Applicant (for all designated States except US): INCYTE PHARMACEUTICALS, INC. [US/US]; 3174 Porter Drive, Palo Alto, CA 94304 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): HILLMAN, Jennifer, L. [US/US]; 230 Monroe Drive #12, Mountain View, CA 94040 (US). YUE, Henry [US/US]; 826 Lois Avenue,		Sunnyvale, CA 94087 (US). LAL, Preeti [IN/US]; 2382 Lass Drive, Santa Clara, CA 95054 (US). TANG, Y., Tom [CN/US]; 4230 Ranwick Court, San Jose, CA 95118 (US). GORGONE, Gina, A. [US/US]; 1253 Pinecrest Drive, Boulder Cree, CA 95006 (US). GUEGLER, Karl, J. [CH/US]; 1048 Oakland Avenue, Menlo Park, CA 94025 (US). CORLEY, Neil, C. [US/US]; 1240 Dale Avenue #30, Mountain View, CA 94040 (US). BAUGHN, Mariah, R. [US/US]; 14244 Santiago Road, San Leandro, CA 94577 (US). (74) Agents: BILLINGS, Lucy, J. et al.; Incyte Pharmaceuticals, Inc., 3174 Porter Drive, Palo Alto, CA 94304 (US). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published Without international search report and to be republished upon receipt of that report.	
(54) Title: HUMAN RECEPTOR-ASSOCIATED PROTEINS			
(57) Abstract			
The invention provides human receptor-associated proteins (HRAP) and polynucleotides which identify and encode HRAP. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating or preventing disorders associated with expression of HRAP.			

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HUMAN RECEPTOR-ASSOCIATED PROTEINS

TECHNICAL FIELD

5 This invention relates to nucleic acid and amino acid sequences of human receptor-associated proteins and to the use of these sequences in the diagnosis, treatment, and prevention of cell proliferative, autoimmune/inflammatory, reproductive, cardiovascular, and gastrointestinal disorders.

10 BACKGROUND OF THE INVENTION

 The term receptor describes proteins that specifically recognize other molecules. The category is broad and includes proteins with a variety of functions. The bulk of the proteins termed receptors are cell surface proteins which, when they bind extracellular ligands, produce cellular responses in the areas of growth, differentiation, endocytosis, and immune response.

15 Other receptors facilitate the specific transport of proteins out of the endoplasmic reticulum and localize enzymes to a particular compartment of the cell. The term may also be applied to proteins which act as receptors for ligands (with known or unknown chemical composition) which interact with other cellular components. For example, the steroid hormone receptors bind to and regulate transcription of genomic DNA.

20 Regulation of cell proliferation, differentiation, and migration is important for the formation and function of tissues. Secreted regulatory proteins such as growth factors coordinately control these cellular processes and act as mediators in cell-cell signaling pathways. Growth factors are secreted from the cell, and bind to specific cell-surface receptors on target cells. The bound receptors trigger intracellular signal transduction pathways which activate
25 various downstream effectors. Such processes regulate many cell functions including cell proliferation, differentiation, gene transcription, cell motility, and oncogenic transformation.

 Cell surface receptors are typically integral membrane proteins of the plasma membrane. These receptors recognize hormones including the catecholamines, such as epinephrine, norepinephrine, and histamine; peptide hormones such as glucagon, insulin, gastrin, secretin,
30 cholecystokinin, adrenocorticotrophic hormone, follicle stimulating hormone, luteinizing hormone, thyroid stimulating hormone, parathyroid hormone, and vasopressin; growth and differentiation factors such as epidermal growth factor, fibroblast growth factor, transforming growth factor, insulin-like growth factor, platelet-derived growth factor, nerve growth factor, colony-stimulating factors, and erythropoietin; cytokines such as chemokines, interleukins, interferons, and tumor

necrosis factor; small peptide factors such as bombesin, oxytocin, endothelin, angiotensin II, vasoactive intestinal peptide, and bradykinin; neurotransmitters such as neuropeptide Y, neurotensin, neuromedin N, melanocortins, somatostatin, galanin, tachykinins; opioids such as enkephalins, endorphins and dynorphins; and circulatory system-borne signaling molecules such as angiotensin, complement, calcitonin, endothelins, and formyl-methionyl peptides. Cell surface receptors on immune system cells recognize antigens, antibodies, and major histocompatibility complex (MHC)-bound peptide. Other cell surface receptors bind ligands to be internalized by the cell. This receptor-mediated endocytosis functions in the uptake of low density lipoproteins (LDL), transferrin, glucose- or mannose-terminal glycoproteins, galactose-terminal glycoproteins, immunoglobulins, phosphovitellogenins, fibrin, proteinase-inhibitor complexes, plasminogen activators, and thrombospondin (Lodish, H. et al. (1995) Molecular Cell Biology, Scientific American Books, New York, NY, p. 723; Mikhailenko, I. et al. (1997) J. Biol. Chem. 272:6784-6791).

Tumor necrosis factor (TNF) is a pleiotropic cytokine that mediates immune regulation and inflammatory responses. The cellular responses triggered by TNF are initiated through its interaction with two distinct cell surface receptors, TNF-R1 and TNF-R2 (Tartaglia, L.A. and Goeddel, D.V. (1992) Immunol. Today 13:151-153). Both TNF receptors are part of the TNF receptor (TNFR) superfamily, whose members include the Fas antigen, the p75 subunit of the NGF receptor, the TRAIL receptor, TRUNND, SaIF19R, CD27, CD30, and CD40. Members of the TNFR superfamily share the TNFR/NGFR family cysteine-rich region signature, which consists of cysteine-rich pseudo-repeats in the extracellular domains (ExPASy PROSITE document PDOC00561; Pan, G. et al. (1998) FEBS Lett 424:41-45; Bairoch, A. et al. (1997) Nucl. Acids. Res. 25:217-221; and Smith, C.A. et al. (1994) Cell 76:959-962).

Many growth factor receptors, including epidermal growth factor, platelet-derived growth factor, and fibroblast growth factor, contain intrinsic protein kinase activities. When the polypeptide growth factor binds to the receptor, it triggers the autophosphorylation of a tyrosine residue on the receptor. It is believed that these phosphorylated sites are recognition sites for the binding of other cytoplasmic signaling proteins in the signaling pathway that eventually links the initial receptor activation at the cell surface to the activation of a specific intracellular target molecule. These signaling proteins contain a common domain referred to as a SRC homology 2 (SH2) domain. SH2 domains are found in a variety of signaling molecules and oncogenic proteins such as phospholipase C- γ , Ras GTPase activating protein, and pp60^{c-SRC} (Lowenstein, E.J. et al. (1992) Cell 70:431-42).

G protein coupled receptors (GPCR) are integral membrane proteins containing seven

transmembrane regions, an extracellular N-terminus that binds ligand, and a cytoplasmic C-terminus that interacts with G proteins (Strosberg, A.D. (1991) Eur. J. Biochem. 196:1-10). The seven hydrophobic transmembrane domains form a bundle of antiparallel alpha helices which account for structural and functional features of the receptor. In most cases, the bundle of helices forms a binding pocket; however, when the binding site must accommodate bulky molecules, the extracellular N-terminal segment or one or more of the three extracellular loops participate in ligand binding which induces a conformational change in intracellular portions of the receptor. The activated receptor interacts with an intracellular heterotrimeric G-protein complex which triggers further intracellular signaling activities. These activities include interactions with guanine nucleotide binding (G) proteins and the production of second messengers such as cyclic AMP (cAMP), phospholipase C, inositol triphosphate, or interactions with ion channel proteins (Baldwin, J.M. (1994) Curr. Opin. Cell Biol. 6:180-190).

The amino-terminus of the GPCR is extracellular, of variable length, and often glycosylated; the carboxy-terminus is cytoplasmic and generally phosphorylated. Extracellular loops of the GPCR alternate with intracellular loops and link the transmembrane domains. The most conserved domains of GPCRs are the transmembrane domains and the first two cytoplasmic loops. GPCRs range in size from under 400 to over 1000 amino acids (Coughlin, S.R. (1994) Curr. Opin. Cell Biol. 6:191-197).

GPCRs respond to a diverse array of ligands including lipid analogs, amino acids and their derivatives, peptides, cytokines, and specialized stimuli such as light, taste, and odor. GPCRs function in physiological processes including vision (the rhodopsins), smell (the olfactory receptors), neurotransmission (muscarinic acetylcholine, dopamine, and adrenergic receptors), and hormonal response (luteinizing hormone and thyroid-stimulating hormone receptors).

GPCR mutations, which may cause loss of function or constitutive activation, have been associated with numerous human diseases (Coughlin, *supra*). For instance, retinitis pigmentosa may arise from mutations in the rhodopsin gene. Parma, J. et al. (1993, Nature 365:649-651) report that somatic activating mutations in the thyrotropin receptor cause hyperfunctioning thyroid adenomas and suggest that certain G-protein-coupled receptors susceptible to constitutive activation may behave as proto-oncogenes.

The frizzled cell surface receptor, originally identified in Drosophila melanogaster, is important for proper bristle and hair polarity on the wing, leg, thorax, abdomen, and eye of the developing insect (Wang, Y. et al. (1996) J. Biol. Chem. 271:4468-4476). The frizzled gene encodes a 587 amino acid protein which contains an N-terminal signal sequence and seven putative transmembrane regions. The cysteine-rich N-terminus is probably extracellular and the

C-terminus is probably cytosolic. Multiple frizzled gene homologs have been found in rat, mouse, and human. The frizzled receptors are not homologous to other seven-transmembrane-region receptors and their ligands are still unknown.

T cells play a dual role in the immune system as effectors and regulators, coupling antigen
5 recognition with the transmission of signals that induce cell death in infected cells and stimulate proliferation of other immune cells. Although a population of T cells can recognize a wide range of different antigens, an individual T cell can only recognize a single antigen and only when it is presented to the T cell receptor (TCR) as a peptide complexed with a major histocompatibility molecule (MHC) on the surface of an antigen presenting cell. The TCR on most T cells consists
10 of immunoglobulin-like integral membrane glycoproteins containing two polypeptide subunits, α and β , of similar molecular weight. The TCR β subunit has an extracellular domain containing both variable and constant regions, a transmembrane domain that traverses the membrane once, and a short intracellular domain (Saito, H. et al. (1984) *Nature* 309:757-762). The genes for the TCR subunits are constructed through somatic rearrangement of different gene segments.
15 Interaction of antigen in the proper MHC context with the TCR initiates signaling cascades that induce the proliferation, maturation, and function of cellular components of the immune system (Weiss, A. (1991) *Annu. Rev. Genet.* 25: 487-510). Rearrangements in TCR genes and alterations in TCR expression have been noted in lymphomas, leukemias, autoimmune disorders, and immunodeficiency disorders (Aisenberg, A.C. et al. (1985) *N. Engl. J. Med.* 313:529-533; Weiss,
20 supra).

The immunoglobulin E (IgE) receptor is another receptor important in regulating the immune response. The IgE receptor is responsible for initiating the allergic response which begins with the binding of an allergen to receptor-bound IgE. This binding leads to cell activation and the release of mediators such as histamine that are responsible for the manifestations of allergy
25 (Kuester, H. et al. (1992) *J. Biol. Chem.* 267:12782-12787). The high affinity IgE receptor (FceRI) is a tetrameric hetero-oligomer composed of an α chain, a β chain, and two disulfide-linked γ chains. The β chain contains four transmembrane segments and long cytoplasmic domains thought to play an important role in intracellular signaling.

Visual excitation and the phototransmission of light signals is another form of signaling
30 cascade in which receptors play an important role. The process begins in retinal rod cells with the absorption of light by the photoreceptor rhodopsin, a seven-transmembrane containing protein composed of a 40-kDa protein, opsin, and a chromophore, 11-cis-retinal. The photoisomerization of the retinal chromophore initiates a biochemical cascade that leads to a reduction in cyclic-GMP and closure of cyclic-GMP regulated, Ca^{2+} -specific channels in the plasma membrane of the rod.

The resultant membrane hyperpolarization generates a nerve signal. Recovery of the dark state of the rod involves another receptor, recoverin. Recoverin is a Ca^{2+} -binding protein that detects the lowering of cytosolic Ca^{2+} and subsequently binds to and activates guanylate cyclase. Activation of guanylate cyclase leads to increased cyclic-GMP levels and the reopening of Ca^{2+} -specific

5 channels (Stryer, L. (1991) J. Biol. Chem. 266:10711-10714).

Abnormal receptor activity is associated with a variety of diseases and disorders.

Abnormal hormonal secretion is linked to disorders including diabetes insipidus, hyper- and hypoglycemia, Grave's disease and goiter, and Cushing's and Addison's diseases. Cancer cells secrete excessive amounts of hormones or other biologically active peptides. Disorders related to

10 excessive secretion of biologically active peptides by tumor cells include fasting hypoglycemia due to increased insulin secretion from insulinoma-islet cell tumors; hypertension due to increased epinephrine and norepinephrine secreted from pheochromocytomas of the adrenal medulla and sympathetic paraganglia; and carcinoid syndrome, which includes abdominal cramps, diarrhea, and valvular heart disease, caused by excessive amounts of vasoactive substances secreted from

15 intestinal tumors. Tumors may exhibit ectopic synthesis and secretion of biologically active peptides, including ACTH and vasopressin in lung and pancreatic cancers; parathyroid hormone in lung and bladder cancers; calcitonin in lung and breast cancers; and thyroid-stimulating hormone in medullary thyroid carcinoma.

Inflammation is a molecular, cellular, and tissue program during which foreign substances

20 and pathogens are destroyed, and injured tissue is repaired through a variety of biochemical, biophysical, and cellular mechanisms. The principal cellular mediators of inflammation are leukocytes, particularly granulocytes and the monocytes/macrophages. Macrophages recognize, internalize, and destroy a variety of foreign (non-self) and endogenous substances and pathogens, including bacteria, parasites, and viruses. The exact recognition mechanism for non-self

25 pathogens is unknown, but it has been proposed that receptors with broad binding specificity are used to discriminate between self and non-self antigens. Macrophages are also thought to play an important role in the immune response by presenting foreign antigens to lymphocytes.

The discovery of new human receptor-associated proteins and the polynucleotides encoding them satisfies a need in the art by providing new compositions which are useful in the

30 diagnosis, prevention, and treatment of cell proliferative, autoimmune/inflammatory, reproductive, cardiovascular, and gastrointestinal disorders.

SUMMARY OF THE INVENTION

35 The invention features substantially purified polypeptides, human receptor-associated

proteins, referred to collectively as "HRAP". In one aspect, the invention provides a substantially purified polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-16, and fragments thereof.

The invention further provides a substantially purified variant having at least 90% amino acid identity to at least one of the amino acid sequences selected from the group consisting of SEQ ID NO:1-16, and fragments thereof. The invention also provides an isolated and purified polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-16, and fragments thereof. The invention also includes an isolated and purified polynucleotide variant having at least 70% polynucleotide sequence identity to the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-16, and fragments thereof.

Additionally, the invention provides an isolated and purified polynucleotide which hybridizes under stringent conditions to the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-16, and fragments thereof. The invention also provides an isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide encoding the polypeptide comprising the amino acid sequence selected from the group consisting of SEQ ID NO:1-16, and fragments thereof.

The invention also provides an isolated and purified polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:17-32, and fragments thereof. The invention further provides an isolated and purified polynucleotide variant having at least 90% polynucleotide sequence identity to the polynucleotide sequence selected from the group consisting of SEQ ID NO:17-32, and fragments thereof. The invention also provides an isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:17-32, and fragments thereof.

The invention also provides a method for detecting a polynucleotide in a sample containing nucleic acids, the method comprising the steps of (a) hybridizing the complement of the polynucleotide sequence to at least one of the polynucleotides of the sample, thereby forming a hybridization complex; and (b) detecting the hybridization complex, wherein the presence of the hybridization complex correlates with the presence of a polynucleotide in the sample. In one aspect, the method further comprises amplifying the polynucleotide prior to hybridization.

The invention further provides an expression vector containing at least a fragment of the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-16, and fragments thereof. In another aspect, the expression

vector is contained within a host cell.

The invention also provides a method for producing a polypeptide, the method comprising the steps of: (a) culturing the host cell containing an expression vector containing at least a fragment of a polynucleotide under conditions suitable for the expression of the polypeptide; and
5 (b) recovering the polypeptide from the host cell culture.

The invention also provides a pharmaceutical composition comprising a substantially purified polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NO:1-16, and fragments thereof, in conjunction with a suitable pharmaceutical carrier.

The invention further includes a purified antibody which binds to a polypeptide selected
10 from the group consisting of SEQ ID NO:1-16, and fragments thereof. The invention also provides a purified agonist and a purified antagonist to the polypeptide.

The invention also provides a method for treating or preventing a disorder associated with decreased expression or activity of HRAP, the method comprising administering to a subject in need of such treatment an effective amount of a pharmaceutical composition comprising a
15 substantially purified polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NO:1-16, and fragments thereof, in conjunction with a suitable pharmaceutical carrier.

The invention also provides a method for treating or preventing a disorder associated with increased expression or activity of HRAP, the method comprising administering to a subject in
20 need of such treatment an effective amount of an antagonist of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-16, and fragments thereof.

BRIEF DESCRIPTION OF THE TABLES

Table 1 shows nucleotide and polypeptide sequence identification numbers (SEQ ID NO),
25 clone identification numbers (clone ID), cDNA libraries, and cDNA fragments used to assemble full-length sequences encoding HRAP.

Table 2 shows features of each polypeptide sequence including potential motifs, homologous sequences, and methods and algorithms used for identification of HRAP.

Table 3 shows the tissue-specific expression patterns of each nucleic acid sequence as
30 determined by northern analysis, diseases or disorders associated with these tissues, selected fragments of the nucleotide sequences encoding HRAP which are useful as hybridization probes, and the vector into which each cDNA was cloned.

Table 4 describes the tissues used to construct the cDNA libraries from which Incyte cDNA clones encoding HRAP were isolated.

35 Table 5 shows the programs, their descriptions, references, and threshold parameters used

to analyze HRAP.

DESCRIPTION OF THE INVENTION

Before the present proteins, nucleotide sequences, and methods are described, it is
5 understood that this invention is not limited to the particular machines, materials and methods
described, as these may vary. It is also to be understood that the terminology used herein is for the
purpose of describing particular embodiments only, and is not intended to limit the scope of the
present invention which will be limited only by the appended claims.

It must be noted that as used herein and in the appended claims, the singular forms “a,”
10 “an,” and “the” include plural reference unless the context clearly dictates otherwise. Thus, for
example, a reference to “a host cell” includes a plurality of such host cells, and a reference to “an
antibody” is a reference to one or more antibodies and equivalents thereof known to those skilled
in the art, and so forth.

Unless defined otherwise, all technical and scientific terms used herein have the same
15 meanings as commonly understood by one of ordinary skill in the art to which this invention
belongs. Although any machines, materials, and methods similar or equivalent to those described
herein can be used to practice or test the present invention, the preferred machines, materials and
methods are now described. All publications mentioned herein are cited for the purpose of
describing and disclosing the cell lines, protocols, reagents and vectors which are reported in the
20 publications and which might be used in connection with the invention. Nothing herein is to be
construed as an admission that the invention is not entitled to antedate such disclosure by virtue of
prior invention.

DEFINITIONS

“HRAP” refers to the amino acid sequences of substantially purified HRAP obtained from
25 any species, particularly a mammalian species, including bovine, ovine, porcine, murine, equine,
and preferably the human species, from any source, whether natural, synthetic, semi-synthetic, or
recombinant.

The term “agonist” refers to a molecule which, when bound to HRAP, increases or
prolongs the duration of the effect of HRAP. Agonists may include proteins, nucleic acids,
30 carbohydrates, or any other molecules which bind to and modulate the effect of HRAP.

An “allelic variant” is an alternative form of the gene encoding HRAP. Allelic variants
may result from at least one mutation in the nucleic acid sequence and may result in altered
mRNAs or in polypeptides whose structure or function may or may not be altered. Any given
natural or recombinant gene may have none, one, or many allelic forms. Common mutational

changes which give rise to allelic variants are generally ascribed to natural deletions, additions, or substitutions of nucleotides. Each of these types of changes may occur alone, or in combination with the others, one or more times in a given sequence.

"Altered" nucleic acid sequences encoding HRAP include those sequences with deletions, 5 insertions, or substitutions of different nucleotides, resulting in a polynucleotide the same as HRAP or a polypeptide with at least one functional characteristic of HRAP. Included within this definition are polymorphisms which may or may not be readily detectable using a particular oligonucleotide probe of the polynucleotide encoding HRAP, and improper or unexpected hybridization to allelic variants, with a locus other than the normal chromosomal locus for the 10 polynucleotide sequence encoding HRAP. The encoded protein may also be "altered," and may contain deletions, insertions, or substitutions of amino acid residues which produce a silent change and result in a functionally equivalent HRAP. Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues, as long as the biological or immunological activity of HRAP is 15 retained. For example, negatively charged amino acids may include aspartic acid and glutamic acid, positively charged amino acids may include lysine and arginine, and amino acids with uncharged polar head groups having similar hydrophilicity values may include leucine, isoleucine, and valine; glycine and alanine; asparagine and glutamine; serine and threonine; and phenylalanine and tyrosine.

20 The terms "amino acid" or "amino acid sequence" refer to an oligopeptide, peptide, polypeptide, or protein sequence, or a fragment of any of these, and to naturally occurring or synthetic molecules. In this context, "fragments," "immunogenic fragments," or "antigenic fragments" refer to fragments of HRAP which are preferably at least 5 to about 15 amino acids in length, most preferably at least 14 amino acids, and which retain some biological activity or 25 immunological activity of HRAP. Where "amino acid sequence" is recited to refer to an amino acid sequence of a naturally occurring protein molecule, "amino acid sequence" and like terms are not meant to limit the amino acid sequence to the complete native amino acid sequence associated with the recited protein molecule.

"Amplification" relates to the production of additional copies of a nucleic acid sequence. 30 Amplification is generally carried out using polymerase chain reaction (PCR) technologies well known in the art.

The term "antagonist" refers to a molecule which, when bound to HRAP, decreases the amount or the duration of the effect of the biological or immunological activity of HRAP.

Antagonists may include proteins, nucleic acids, carbohydrates, antibodies, or any other molecules

which decrease the effect of HRAP.

The term "antibody" refers to intact molecules as well as to fragments thereof, such as Fab, F(ab')₂, and Fv fragments, which are capable of binding the epitopic determinant. Antibodies that bind HRAP polypeptides can be prepared using intact polypeptides or using fragments

5 containing small peptides of interest as the immunizing antigen. The polypeptide or oligopeptide used to immunize an animal (e.g., a mouse, a rat, or a rabbit) can be derived from the translation of RNA, or synthesized chemically, and can be conjugated to a carrier protein if desired. Commonly used carriers that are chemically coupled to peptides include bovine serum albumin, thyroglobulin, and keyhole limpet hemocyanin (KLH). The coupled peptide is then used to immunize the animal.

10 The term "antigenic determinant" refers to that fragment of a molecule (i.e., an epitope) that makes contact with a particular antibody. When a protein or a fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies which bind specifically to antigenic determinants (given regions or three-dimensional structures on the protein). An antigenic determinant may compete with the intact antigen (i.e., the immunogen
15 used to elicit the immune response) for binding to an antibody.

The term "antisense" refers to any composition containing a nucleic acid sequence which is complementary to the "sense" strand of a specific nucleic acid sequence. Antisense molecules may be produced by any method including synthesis or transcription. Once introduced into a cell, the complementary nucleotides combine with natural sequences produced by the cell to form
20 duplexes and to block either transcription or translation. The designation "negative" can refer to the antisense strand, and the designation "positive" can refer to the sense strand.

The term "biologically active," refers to a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule. Likewise, "immunologically active" refers to the capability of the natural, recombinant, or synthetic HRAP, or of any oligopeptide
25 thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies.

The terms "complementary" or "complementarity" refer to the natural binding of polynucleotides by base pairing. For example, the sequence "5' A-G-T 3'" bonds to the complementary sequence "3' T-C-A 5'." Complementarity between two single-stranded molecules
30 may be "partial," such that only some of the nucleic acids bind, or it may be "complete," such that total complementarity exists between the single stranded molecules. The degree of complementarity between nucleic acid strands has significant effects on the efficiency and strength of the hybridization between the nucleic acid strands. This is of particular importance in amplification reactions, which depend upon binding between nucleic acids strands, and in the

design and use of peptide nucleic acid (PNA) molecules.

A "composition comprising a given polynucleotide sequence" or a "composition comprising a given amino acid sequence" refer broadly to any composition containing the given polynucleotide or amino acid sequence. The composition may comprise a dry formulation or an aqueous solution. Compositions comprising polynucleotide sequences encoding HRAP or fragments of HRAP may be employed as hybridization probes. The probes may be stored in freeze-dried form and may be associated with a stabilizing agent such as a carbohydrate. In hybridizations, the probe may be deployed in an aqueous solution containing salts (e.g., NaCl), detergents (e.g., sodium dodecyl sulfate; SDS), and other components (e.g., Denhardt's solution, dry milk, salmon sperm DNA, etc.).

"Consensus sequence" refers to a nucleic acid sequence which has been resequenced to resolve uncalled bases, extended using XL-PCR kit (Perkin-Elmer, Norwalk CT) in the 5' and/or the 3' direction, and resequenced, or which has been assembled from the overlapping sequences of more than one Incyte Clone using a computer program for fragment assembly, such as the GELVIEW Fragment Assembly system (GCG, Madison WI). Some sequences have been both extended and assembled to produce the consensus sequence.

The term "correlates with expression of a polynucleotide" indicates that the detection of the presence of nucleic acids, the same or related to a nucleic acid sequence encoding HRAP, by northern analysis is indicative of the presence of nucleic acids encoding HRAP in a sample, and thereby correlates with expression of the transcript from the polynucleotide encoding HRAP.

A "deletion" refers to a change in the amino acid or nucleotide sequence that results in the absence of one or more amino acid residues or nucleotides.

The term "derivative" refers to the chemical modification of a polypeptide sequence, or a polynucleotide sequence. Chemical modifications of a polynucleotide sequence can include, for example, replacement of hydrogen by an alkyl, acyl, or amino group. A derivative polynucleotide encodes a polypeptide which retains at least one biological or immunological function of the natural molecule. A derivative polypeptide is one modified by glycosylation, pegylation, or any similar process that retains at least one biological or immunological function of the polypeptide from which it was derived.

The term "similarity" refers to a degree of complementarity. There may be partial similarity or complete similarity. The word "identity" may substitute for the word "similarity." A partially complementary sequence that at least partially inhibits an identical sequence from hybridizing to a target nucleic acid is referred to as "substantially similar." The inhibition of hybridization of the completely complementary sequence to the target sequence may be examined

using a hybridization assay (Southern or northern blot, solution hybridization, and the like) under conditions of reduced stringency. A substantially similar sequence or hybridization probe will compete for and inhibit the binding of a completely similar (identical) sequence to the target sequence under conditions of reduced stringency. This is not to say that conditions of reduced stringency are such that non-specific binding is permitted, as reduced stringency conditions require that the binding of two sequences to one another be a specific (i.e., a selective) interaction. The absence of non-specific binding may be tested by the use of a second target sequence which lacks even a partial degree of complementarity (e.g., less than about 30% similarity or identity). In the absence of non-specific binding, the substantially similar sequence or probe will not hybridize to the second non-complementary target sequence.

The phrases "percent identity" or "% identity" refer to the percentage of sequence similarity found in a comparison of two or more amino acid or nucleic acid sequences. Percent identity can be determined electronically, e.g., by using the MEGALIGN program (DNASTAR, Madison WI). The MEGALIGN program can create alignments between two or more sequences according to different methods, e.g., the clustal method. (See, e.g., Higgins, D.G. and P.M. Sharp (1988) *Gene* 73:237-244.) The clustal algorithm groups sequences into clusters by examining the distances between all pairs. The clusters are aligned pairwise and then in groups. The percentage similarity between two amino acid sequences, e.g., sequence A and sequence B, is calculated by dividing the length of sequence A, minus the number of gap residues in sequence A, minus the number of gap residues in sequence B, into the sum of the residue matches between sequence A and sequence B, times one hundred. Gaps of low or of no similarity between the two amino acid sequences are not included in determining percentage similarity. Percent identity between nucleic acid sequences can also be counted or calculated by other methods known in the art, e.g., the Jotun Hein method. (See, e.g., Hein, J. (1990) *Methods Enzymol.* 183:626-645.) Identity between sequences can also be determined by other methods known in the art, e.g., by varying hybridization conditions.

"Human artificial chromosomes" (HACs) are linear microchromosomes which may contain DNA sequences of about 6 kb to 10 Mb in size, and which contain all of the elements required for stable mitotic chromosome segregation and maintenance.

The term "humanized antibody" refers to antibody molecules in which the amino acid sequence in the non-antigen binding regions has been altered so that the antibody more closely resembles a human antibody, and still retains its original binding ability.

"Hybridization" refers to any process by which a strand of nucleic acid binds with a complementary strand through base pairing.

The term "hybridization complex" refers to a complex formed between two nucleic acid sequences by virtue of the formation of hydrogen bonds between complementary bases. A hybridization complex may be formed in solution (e.g., C_0t or R_0t analysis) or formed between one nucleic acid sequence present in solution and another nucleic acid sequence immobilized on a solid support (e.g., paper, membranes, filters, chips, pins or glass slides, or any other appropriate substrate to which cells or their nucleic acids have been fixed).

The words "insertion" or "addition" refer to changes in an amino acid or nucleotide sequence resulting in the addition of one or more amino acid residues or nucleotides, respectively, to the sequence found in the naturally occurring molecule.

"Immune response" can refer to conditions associated with inflammation, trauma, immune disorders, or infectious or genetic disease, etc. These conditions can be characterized by expression of various factors, e.g., cytokines, chemokines, and other signaling molecules, which may affect cellular and systemic defense systems.

The term "microarray" refers to an arrangement of distinct polynucleotides on a substrate.

The terms "element" or "array element" in a microarray context, refer to hybridizable polynucleotides arranged on the surface of a substrate.

The term "modulate" refers to a change in the activity of HRAP. For example, modulation may cause an increase or a decrease in protein activity, binding characteristics, or any other biological, functional, or immunological properties of HRAP.

The phrases "nucleic acid" or "nucleic acid sequence," as used herein, refer to a nucleotide, oligonucleotide, polynucleotide, or any fragment thereof. These phrases also refer to DNA or RNA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent the sense or the antisense strand, to peptide nucleic acid (PNA), or to any DNA-like or RNA-like material. In this context, "fragments" refers to those nucleic acid sequences which, comprise a region of unique polynucleotide sequence that specifically identifies SEQ ID NO:17-32, for example, as distinct from any other sequence in the same genome. For example, a fragment of SEQ ID NO:17-32 is useful in hybridization and amplification technologies and in analogous methods that distinguish SEQ ID NO:17-32 from related polynucleotide sequences. A fragment of SEQ ID NO:17-32 is at least about 15-20 nucleotides in length. The precise length of the fragment of SEQ ID NO:17-32 and the region of SEQ ID NO:17-32 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment. In some cases, a fragment, when translated, would produce polypeptides retaining some functional characteristic, e.g., antigenicity, or structural domain characteristic, e.g., ATP-binding site, of the full-length polypeptide.

The terms "operably associated" or "operably linked" refer to functionally related nucleic acid sequences. A promoter is operably associated or operably linked with a coding sequence if the promoter controls the translation of the encoded polypeptide. While operably associated or operably linked nucleic acid sequences can be contiguous and in the same reading frame, certain genetic elements, e.g., repressor genes, are not contiguously linked to the sequence encoding the polypeptide but still bind to operator sequences that control expression of the polypeptide.

The term "oligonucleotide" refers to a nucleic acid sequence of at least about 6 nucleotides to 60 nucleotides, preferably about 15 to 30 nucleotides, and most preferably about 20 to 25 nucleotides, which can be used in PCR amplification or in a hybridization assay or microarray. "Oligonucleotide" is substantially equivalent to the terms "amplimer," "primer," "oligomer," and "probe," as these terms are commonly defined in the art.

"Peptide nucleic acid" (PNA) refers to an antisense molecule or anti-gene agent which comprises an oligonucleotide of at least about 5 nucleotides in length linked to a peptide backbone of amino acid residues ending in lysine. The terminal lysine confers solubility to the composition. PNAs preferentially bind complementary single stranded DNA or RNA and stop transcript elongation, and may be pegylated to extend their lifespan in the cell.

The term "sample" is used in its broadest sense. A sample suspected of containing nucleic acids encoding HRAP, or fragments thereof, or HRAP itself, may comprise a bodily fluid; an extract from a cell, chromosome, organelle, or membrane isolated from a cell; a cell; genomic DNA, RNA, or cDNA, in solution or bound to a substrate; a tissue; a tissue print; etc.

The terms "specific binding" or "specifically binding" refer to that interaction between a protein or peptide and an agonist, an antibody, or an antagonist. The interaction is dependent upon the presence of a particular structure of the protein, e.g., the antigenic determinant or epitope, recognized by the binding molecule. For example, if an antibody is specific for epitope "A," the presence of a polypeptide containing the epitope A, or the presence of free unlabeled A, in a reaction containing free labeled A and the antibody will reduce the amount of labeled A that binds to the antibody.

The term "stringent conditions" refers to conditions which permit hybridization between polynucleotides and the claimed polynucleotides. Stringent conditions can be defined by salt concentration, the concentration of organic solvent, e.g., formamide, temperature, and other conditions well known in the art. In particular, stringency can be increased by reducing the concentration of salt, increasing the concentration of formamide, or raising the hybridization temperature.

The term "substantially purified" refers to nucleic acid or amino acid sequences that are

removed from their natural environment and are isolated or separated, and are at least about 60% free, preferably about 75% free, and most preferably about 90% free from other components with which they are naturally associated.

A “substitution” refers to the replacement of one or more amino acids or nucleotides by
5 different amino acids or nucleotides, respectively.

“Substrate” refers to any suitable rigid or semi-rigid support including membranes, filters, chips, slides, wafers, fibers, magnetic or nonmagnetic beads, gels, tubing, plates, polymers, microparticles and capillaries. The substrate can have a variety of surface forms, such as wells, trenches, pins, channels and pores, to which polynucleotides or polypeptides are bound.

10 “Transformation” describes a process by which exogenous DNA enters and changes a recipient cell. Transformation may occur under natural or artificial conditions according to various methods well known in the art, and may rely on any known method for the insertion of foreign nucleic acid sequences into a prokaryotic or eukaryotic host cell. The method for transformation is selected based on the type of host cell being transformed and may include, but is
15 not limited to, viral infection, electroporation, heat shock, lipofection, and particle bombardment. The term “transformed” cells includes stably transformed cells in which the inserted DNA is capable of replication either as an autonomously replicating plasmid or as part of the host chromosome, as well as transiently transformed cells which express the inserted DNA or RNA for limited periods of time.

20 A “variant” of HRAP polypeptides refers to an amino acid sequence that is altered by one or more amino acid residues. The variant may have “conservative” changes, wherein a substituted amino acid has similar structural or chemical properties (e.g., replacement of leucine with isoleucine). More rarely, a variant may have “nonconservative” changes (e.g., replacement of glycine with tryptophan). Analogous minor variations may also include amino acid deletions or
25 insertions, or both. Guidance in determining which amino acid residues may be substituted, inserted, or deleted without abolishing biological or immunological activity may be found using computer programs well known in the art, for example, LASERGENE software (DNASTAR).

The term “variant,” when used in the context of a polynucleotide sequence, may encompass a polynucleotide sequence related to HRAP. This definition may also include, for
30 example, “allelic” (as defined above), “splice,” “species,” or “polymorphic” variants. A splice variant may have significant identity to a reference molecule, but will generally have a greater or lesser number of polynucleotides due to alternate splicing of exons during mRNA processing. The corresponding polypeptide may possess additional functional domains or an absence of domains. Species variants are polynucleotide sequences that vary from one species to another. The resulting

polypeptides generally will have significant amino acid identity relative to each other. A polymorphic variant is a variation in the polynucleotide sequence of a particular gene between individuals of a given species. Polymorphic variants also may encompass "single nucleotide polymorphisms" (SNPs) in which the polynucleotide sequence varies by one base. The presence
 5 of SNPs may be indicative of, for example, a certain population, a disease state, or a propensity for a disease state.

THE INVENTION

The invention is based on the discovery of new human receptor-associated proteins (HRAP), the polynucleotides encoding HRAP, and the use of these compositions for the diagnosis,
 10 treatment, or prevention of cell proliferative, autoimmune/inflammatory, reproductive, cardiovascular, and gastrointestinal disorders.

Table 1 lists the Incyte Clones used to derive full length nucleotide sequences encoding HRAP. Columns 1 and 2 show the sequence identification numbers (SEQ ID NO) of the amino acid and nucleic acid sequences, respectively. Column 3 shows the Clone ID of the Incyte Clone
 15 in which nucleic acids encoding each HRAP were identified, and column 4, the cDNA libraries from which these clones were isolated. Column 5 shows Incyte clones, their corresponding cDNA libraries, and shotgun sequences useful as fragments in hybridization technologies, and which are part of the consensus nucleotide sequence of each HRAP.

The columns of Table 2 show various properties of the polypeptides of the invention:
 20 column 1 references the SEQ ID NO; column 2 shows the number of amino acid residues in each polypeptide; column 3, potential phosphorylation sites; column 4, potential glycosylation sites; column 5, the amino acid residues comprising signature sequences and motifs; column 6, the identity of each protein; and column 7, analytical methods used to identify each protein through sequence homology and protein motifs.

The columns of Table 3 show the tissue-specificity and disease-association of nucleotide sequences encoding HRAP. The first column of Table 3 lists the polynucleotide sequence identifiers. The second column lists unique fragments of the nucleotide sequences encoding HRAP which are useful as hybridization probes. The third column lists tissue categories which express HRAP as a fraction of total tissue categories expressing HRAP. The fourth column lists the
 25 disease classes associated with those tissues expressing HRAP. The fifth column lists the vectors used to subclone the cDNA library.

The invention also encompasses HRAP variants. A preferred HRAP variant is one which has at least about 80%, more preferably at least about 90%, and most preferably at least about 95% amino acid sequence identity to the HRAP amino acid sequence, and which contains at least one

functional or structural characteristic of HRAP.

The invention also encompasses polynucleotides which encode HRAP. In a particular embodiment, the invention encompasses a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:17-32, which encodes HRAP.

5 The invention also encompasses a variant of a polynucleotide sequence encoding HRAP. In particular, such a variant polynucleotide sequence will have at least about 70%, more preferably at least about 85%, and most preferably at least about 95% polynucleotide sequence identity to the polynucleotide sequence encoding HRAP. A particular aspect of the invention encompasses a variant of a polynucleotide sequence comprising a sequence selected from the group consisting of
10 SEQ ID NO:17-32 which has at least about 70%, more preferably at least about 85%, and most preferably at least about 95% polynucleotide sequence identity to a nucleic acid sequence selected from the group consisting of SEQ ID NO:17-32. Any one of the polynucleotide variants described above can encode an amino acid sequence which contains at least one functional or structural characteristic of HRAP.

15 It will be appreciated by those skilled in the art that as a result of the degeneracy of the genetic code, a multitude of polynucleotide sequences encoding HRAP, some bearing minimal similarity to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention contemplates each and every possible variation of polynucleotide sequence that could be made by selecting combinations based on possible codon choices. These
20 combinations are made in accordance with the standard triplet genetic code as applied to the polynucleotide sequence of naturally occurring HRAP, and all such variations are to be considered as being specifically disclosed.

 Although nucleotide sequences which encode HRAP and its variants are preferably capable of hybridizing to the nucleotide sequence of the naturally occurring HRAP under
25 appropriately selected conditions of stringency, it may be advantageous to produce nucleotide sequences encoding HRAP or its derivatives possessing a substantially different codon usage, e.g., inclusion of non-naturally occurring codons. Codons may be selected to increase the rate at which expression of the peptide occurs in a particular prokaryotic or eukaryotic host in accordance with the frequency with which particular codons are utilized by the host. Other reasons for
30 substantially altering the nucleotide sequence encoding HRAP and its derivatives without altering the encoded amino acid sequences include the production of RNA transcripts having more desirable properties, such as a greater half-life, than transcripts produced from the naturally occurring sequence.

The invention also encompasses production of DNA sequences which encode HRAP and

HRAP derivatives, or fragments thereof, entirely by synthetic chemistry. After production, the synthetic sequence may be inserted into any of the many available expression vectors and cell systems using reagents well known in the art. Moreover, synthetic chemistry may be used to introduce mutations into a sequence encoding HRAP or any fragment thereof.

- 5 Also encompassed by the invention are polynucleotide sequences that are capable of hybridizing to the claimed polynucleotide sequences, and, in particular, to those shown in SEQ ID NO:17-32 and fragments thereof under various conditions of stringency. (See, e.g., Wahl, G.M. and S.L. Berger (1987) *Methods Enzymol.* 152:399-407; Kimmel, A.R. (1987) *Methods Enzymol.* 152:507-511.) For example, stringent salt concentration will ordinarily be less than about 750 mM NaCl and 75 mM trisodium citrate, preferably less than about 500 mM NaCl and 50 mM trisodium citrate, and most preferably less than about 250 mM NaCl and 25 mM trisodium citrate. Low stringency hybridization can be obtained in the absence of organic solvent, e.g., formamide, while high stringency hybridization can be obtained in the presence of at least about 35% formamide, and most preferably at least about 50% formamide. Stringent temperature conditions will
- 10 ordinarily include temperatures of at least about 30°C, more preferably of at least about 37°C, and most preferably of at least about 42°C. Varying additional parameters, such as hybridization time, the concentration of detergent, e.g., sodium dodecyl sulfate (SDS), and the inclusion or exclusion of carrier DNA, are well known to those skilled in the art. Various levels of stringency are accomplished by combining these various conditions as needed. In a preferred embodiment,
- 20 hybridization will occur at 30°C in 750 mM NaCl, 75 mM trisodium citrate, and 1% SDS. In a more preferred embodiment, hybridization will occur at 37°C in 500 mM NaCl, 50 mM trisodium citrate, 1% SDS, 35% formamide, and 100 µg/ml denatured salmon sperm DNA (ssDNA). In a most preferred embodiment, hybridization will occur at 42°C in 250 mM NaCl, 25 mM trisodium citrate, 1% SDS, 50 % formamide, and 200 µg/ml ssDNA. Useful variations on these conditions
- 25 will be readily apparent to those skilled in the art.

- The washing steps which follow hybridization can also vary in stringency. Wash stringency conditions can be defined by salt concentration and by temperature. As above, wash stringency can be increased by decreasing salt concentration or by increasing temperature. For example, stringent salt concentration for the wash steps will preferably be less than about 30 mM NaCl and 3 mM trisodium citrate, and most preferably less than about 15 mM NaCl and 1.5 mM trisodium citrate. Stringent temperature conditions for the wash steps will ordinarily include
- 30 temperature of at least about 25°C, more preferably of at least about 42°C, and most preferably of at least about 68°C. In a preferred embodiment, wash steps will occur at 25°C in 30 mM NaCl, 3 mM trisodium citrate, and 0.1% SDS. In a more preferred embodiment, wash steps will occur at

42°C in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS. In a most preferred embodiment, wash steps will occur at 68°C in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS.

Additional variations on these conditions will be readily apparent to those skilled in the art.

Methods for DNA sequencing are well known in the art and may be used to practice any
5 of the embodiments of the invention. The methods may employ such enzymes as the Klenow
fragment of DNA polymerase I, SEQUENASE (US Biochemical, Cleveland OH), Taq polymerase
(Perkin-Elmer), thermostable T7 polymerase (Amersham Pharmacia Biotech, Piscataway NJ), or
combinations of polymerases and proofreading exonucleases such as those found in the
ELONGASE amplification system (Life Technologies, Gaithersburg MD). Preferably, sequence
10 preparation is automated with machines such as the Hamilton MICROLAB 2200 (Hamilton, Reno
NV), Peltier Thermal Cycler 200 (PTC200; MJ Research, Watertown MA) and the ABI
CATALYST 800 (Perkin-Elmer). Sequencing is then carried out using either ABI 373 or 377
DNA sequencing systems (Perkin-Elmer) or the MEGABACE 1000 DNA sequencing system
(Molecular Dynamics, Sunnyvale CA). The resulting sequences are analyzed using a variety of
15 algorithms which are well known in the art. (See, e.g., Ausubel, F.M. (1997) Short Protocols in
Molecular Biology, John Wiley & Sons, New York NY, unit 7.7; Meyers, R.A. (1995) Molecular
Biology and Biotechnology, Wiley VCH, New York NY, pp. 856-853.)

The nucleic acid sequences encoding HRAP may be extended utilizing a partial nucleotide
sequence and employing various PCR-based methods known in the art to detect upstream
20 sequences, such as promoters and regulatory elements. For example, one method which may be
employed, restriction-site PCR, uses universal and nested primers to amplify unknown sequence
from genomic DNA within a cloning vector. (See, e.g., Sarkar, G. (1993) *PCR Methods Applic.*
2:318-322.) Another method, inverse PCR, uses primers that extend in divergent directions to
amplify unknown sequence from a circularized template. The template is derived from restriction
25 fragments comprising a known genomic locus and surrounding sequences. (See, e.g., Triglia, T. et
al. (1988) *Nucleic Acids Res.* 16:8186.) A third method, capture PCR, involves PCR
amplification of DNA fragments adjacent to known sequences in human and yeast artificial
chromosome DNA. (See, e.g., Lagerstrom, M. et al. (1991) *PCR Methods Applic.* 1:111-119.) In
this method, multiple restriction enzyme digestions and ligations may be used to insert an
30 engineered double-stranded sequence into a region of unknown sequence before performing PCR.
Other methods which may be used to retrieve unknown sequences are known in the art. (See, e.g.,
Parker, J.D. et al. (1991) *Nucleic Acids Res.* 19:3055-306). Additionally, one may use PCR,
nested primers, and PROMOTERFINDER libraries (Clontech, Palo Alto CA) to walk genomic
DNA. This procedure avoids the need to screen libraries and is useful in finding intron/exon

junctions. For all PCR-based methods, primers may be designed using commercially available software, such as OLIGO 4.06 Primer Analysis software (National Biosciences, Plymouth MN) or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the template at temperatures of about 68°C to 72°C.

5 When screening for full-length cDNAs, it is preferable to use libraries that have been size-selected to include larger cDNAs. In addition, random-primed libraries, which often include sequences containing the 5' regions of genes, are preferable for situations in which an oligo d(T) library does not yield a full-length cDNA. Genomic libraries may be useful for extension of sequence into 5' non-transcribed regulatory regions.

10 Capillary electrophoresis systems which are commercially available may be used to analyze the size or confirm the nucleotide sequence of sequencing or PCR products. In particular, capillary sequencing may employ flowable polymers for electrophoretic separation, four different nucleotide-specific, laser-stimulated fluorescent dyes, and a charge coupled device camera for detection of the emitted wavelengths. Output/light intensity may be converted to electrical signal
15 using appropriate software (e.g., GENOTYPER and SEQUENCE NAVIGATOR, Perkin-Elmer), and the entire process from loading of samples to computer analysis and electronic data display may be computer controlled. Capillary electrophoresis is especially preferable for sequencing small DNA fragments which may be present in limited amounts in a particular sample.

 In another embodiment of the invention, polynucleotide sequences or fragments thereof
20 which encode HRAP may be cloned in recombinant DNA molecules that direct expression of HRAP, or fragments or functional equivalents thereof, in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences which encode substantially the same or a functionally equivalent amino acid sequence may be produced and used to express HRAP.

25 The nucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter HRAP-encoding sequences for a variety of purposes including, but not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. For example,
30 oligonucleotide-mediated site-directed mutagenesis may be used to introduce mutations that create new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

 In another embodiment, sequences encoding HRAP may be synthesized, in whole or in part, using chemical methods well known in the art. (See, e.g., Caruthers, M.H. et al. (1980) Nucl.

Acids Res. Symp. Ser. 215-223, and Horn, T. et al. (1980) Nucl. Acids Res. Symp. Ser. 225-232.) Alternatively, HRAP itself or a fragment thereof may be synthesized using chemical methods. For example, peptide synthesis can be performed using various solid-phase techniques. (See, e.g., Roberge, J.Y. et al. (1995) Science 269:202-204.) Automated synthesis may be achieved using
5 the ABI 431A Peptide Synthesizer (Perkin-Elmer). Additionally, the amino acid sequence of HRAP, or any part thereof, may be altered during direct synthesis and/or combined with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

The peptide may be substantially purified by preparative high performance liquid chromatography. (See, e.g., Chiez, R.M. and F.Z. Regnier (1990) Methods Enzymol. 182:392-
10 421.) The composition of the synthetic peptides may be confirmed by amino acid analysis or by sequencing. (See, e.g., Creighton, T. (1984) Proteins, Structures and Molecular Properties, WH Freeman, New York NY.)

In order to express a biologically active HRAP, the nucleotide sequences encoding HRAP or derivatives thereof may be inserted into an appropriate expression vector, i.e., a vector which
15 contains the necessary elements for transcriptional and translational control of the inserted coding sequence in a suitable host. These elements include regulatory sequences, such as enhancers, constitutive and inducible promoters, and 5' and 3' untranslated regions in the vector and in polynucleotide sequences encoding HRAP. Such elements may vary in their strength and specificity. Specific initiation signals may also be used to achieve more efficient translation of
20 sequences encoding HRAP. Such signals include the ATG initiation codon and adjacent sequences, e.g. the Kozak sequence. In cases where sequences encoding HRAP and its initiation codon and upstream regulatory sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a fragment thereof, is inserted, exogenous translational control signals
25 including an in-frame ATG initiation codon should be provided by the vector. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers appropriate for the particular host cell system used. (See, e.g., Scharf, D. et al. (1994) Results Probl. Cell Differ. 20:125-162.)

30 Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding HRAP and appropriate transcriptional and translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. (See, e.g., Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview NY, ch. 4, 8, and

16-17; Ausubel, F.M. et al. (1995) Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, ch. 9, 13, and 16.)

A variety of expression vector/host systems may be utilized to contain and express sequences encoding HRAP. These include, but are not limited to, microorganisms such as
5 bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with viral expression vectors (e.g., baculovirus); plant cell systems transformed with viral expression vectors (e.g., cauliflower mosaic virus, CaMV, or tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems. The invention is not limited by the
10 host cell employed.

In bacterial systems, a number of cloning and expression vectors may be selected depending upon the use intended for polynucleotide sequences encoding HRAP. For example, routine cloning, subcloning, and propagation of polynucleotide sequences encoding HRAP can be achieved using a multifunctional E. coli vector such as PBLUESCRIPT (Stratagene, La Jolla CA)
15 or PSPORT1 plasmid (Life Technologies). Ligation of sequences encoding HRAP into the vector's multiple cloning site disrupts the *lacZ* gene, allowing a colorimetric screening procedure for identification of transformed bacteria containing recombinant molecules. In addition, these vectors may be useful for in vitro transcription, dideoxy sequencing, single strand rescue with helper phage, and creation of nested deletions in the cloned sequence. (See, e.g., Van Heeke, G.
20 and S.M. Schuster (1989) J. Biol. Chem. 264:5503-5509.) When large quantities of HRAP are needed, e.g. for the production of antibodies, vectors which direct high level expression of HRAP may be used. For example, vectors containing the strong, inducible T5 or T7 bacteriophage promoter may be used.

Yeast expression systems may be used for production of HRAP. A number of vectors
25 containing constitutive or inducible promoters, such as alpha factor, alcohol oxidase, and PGH, may be used in the yeast Saccharomyces cerevisiae or Pichia pastoris. In addition, such vectors direct either the secretion or intracellular retention of expressed proteins and enable integration of foreign sequences into the host genome for stable propagation. (See, e.g., Ausubel, 1995, supra; Grant et al. (1987) Methods Enzymol. 153:516-54; and Scorer, C. A. et al. (1994) Bio/Technology
30 12:181-184.)

Plant systems may also be used for expression of HRAP. Transcription of sequences encoding HRAP may be driven viral promoters, e.g., the 35S and 19S promoters of CaMV used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) EMBO J. 6:307-311). Alternatively, plant promoters such as the small subunit of RUBISCO or

heat shock promoters may be used. (See, e.g., Coruzzi, G. et al. (1984) EMBO J. 3:1671-1680; Broglie, R. et al. (1984) Science 224:838-843; and Winter, J. et al. (1991) Results Probl. Cell Differ. 17:85-105.) These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. (See, e.g., The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY, pp. 191-196.)

In mammalian cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, sequences encoding HRAP may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain infective virus which expresses HRAP in host cells. (See, e.g., Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. 81:3655-3659.) In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells. SV40 or EBV-based vectors may also be used for high-level protein expression.

Human artificial chromosomes (HACs) may also be employed to deliver larger fragments of DNA than can be contained in and expressed from a plasmid. HACs of about 6 kb to 10 Mb are constructed and delivered via conventional delivery methods (liposomes, polycationic amino polymers, or vesicles) for therapeutic purposes. (See, e.g., Harrington, J.J. et al. (1997) Nat Genet. 15:345-355.)

For long term production of recombinant proteins in mammalian systems, stable expression of HRAP in cell lines is preferred. For example, sequences encoding HRAP can be transformed into cell lines using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for about 1 to 2 days in enriched media before being switched to selective media. The purpose of the selectable marker is to confer resistance to a selective agent, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be propagated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase and adenine phosphoribosyltransferase genes, for use in *tk* or *ap^r* cells, respectively. (See, e.g., Wigler, M. et al. (1977) Cell 11:223-232; Lowy, I. et al. (1980) Cell 22:817-823.) Also, antimetabolite, antibiotic, or herbicide resistance can be used as the basis for selection. For example, *dhfr* confers resistance to methotrexate; *neo* confers resistance to the aminoglycosides neomycin and G-418; and *als* or *pat* confer resistance to chlorsulfuron and phosphinotricin acetyltransferase,

respectively. (See, e.g., Wigler, M. et al. (1980) *Proc. Natl. Acad. Sci.* 77:3567-3570; Colbere-Garapin, F. et al. (1981) *J. Mol. Biol.* 150:1-14.) Additional selectable genes have been described, e.g., *trpB* and *hisD*, which alter cellular requirements for metabolites. (See, e.g., Hartman, S.C. and R.C. Mulligan (1988) *Proc. Natl. Acad. Sci.* 85:8047-8051.) Visible markers, e.g., anthocyanins, green fluorescent proteins (GFP; Clontech), β glucuronidase and its substrate β -glucuronide, or luciferase and its substrate luciferin may be used. These markers can be used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system. (See, e.g., Rhodes, C.A. (1995) *Methods Mol. Biol.* 55:121-131.)

10 Although the presence/absence of marker gene expression suggests that the gene of interest is also present, the presence and expression of the gene may need to be confirmed. For example, if the sequence encoding HRAP is inserted within a marker gene sequence, transformed cells containing sequences encoding HRAP can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a sequence encoding HRAP
15 under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

 In general, host cells that contain the nucleic acid sequence encoding HRAP and that express HRAP may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations, PCR
20 amplification, and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein sequences.

 Immunological methods for detecting and measuring the expression of HRAP using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques
25 include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on HRAP is preferred, but a competitive binding assay may be employed. These and other assays are well known in the art. (See, e.g., Hampton, R. et al. (1990) Serological Methods, a Laboratory Manual, APS Press, St
30 Paul MN, Sect. IV; Coligan, J. E. et al. (1997) Current Protocols in Immunology, Greene Pub. Associates and Wiley-Interscience, New York NY; and Pound, J.D. (1998) Immunochemical Protocols, Humana Press, Totowa NJ).

 A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled

hybridization or PCR probes for detecting sequences related to polynucleotides encoding HRAP include oligolabeling, nick translation, end-labeling, or PCR amplification using a labeled nucleotide. Alternatively, the sequences encoding HRAP, or any fragments thereof, may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are
5 commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits, such as those provided by Amersham Pharmacia Biotech, Promega (Madison WI), and US Biochemical. Suitable reporter molecules or labels which may be used for ease of detection include radionuclides, enzymes,
10 fluorescent, chemiluminescent, or chromogenic agents, as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with nucleotide sequences encoding HRAP may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a transformed cell may be secreted or retained intracellularly depending on the
15 sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides which encode HRAP may be designed to contain signal sequences which direct secretion of HRAP through a prokaryotic or eukaryotic cell membrane.

In addition, a host cell strain may be chosen for its ability to modulate expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications
20 of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" form of the protein may also be used to specify protein targeting, folding, and/or activity. Different host cells which have specific cellular machinery and characteristic mechanisms for post-translational activities (e.g., CHO, HeLa, MDCK, HEK293, and WI38), are available from
25 the American Type Culture Collection (ATCC, Manassas, VA) and may be chosen to ensure the correct modification and processing of the foreign protein.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences encoding HRAP may be ligated to a heterologous sequence resulting in translation of a fusion protein in any of the aforementioned host systems. For example, a chimeric HRAP protein
30 containing a heterologous moiety that can be recognized by a commercially available antibody may facilitate the screening of peptide libraries for inhibitors of HRAP activity. Heterologous protein and peptide moieties may also facilitate purification of fusion proteins using commercially available affinity matrices. Such moieties include, but are not limited to, glutathione S-transferase (GST), maltose binding protein (MBP), thioredoxin (Trx), calmodulin binding peptide (CBP), 6-

His, FLAG, *c-myc*, and hemagglutinin (HA). GST, MBP, Trx, CBP, and 6-His enable purification of their cognate fusion proteins on immobilized glutathione, maltose, phenylarsine oxide, calmodulin, and metal-chelate resins, respectively. FLAG, *c-myc*, and hemagglutinin (HA) enable immunoaffinity purification of fusion proteins using commercially available monoclonal and
5 polyclonal antibodies that specifically recognize these epitope tags. A fusion protein may also be engineered to contain a proteolytic cleavage site located between the HRAP encoding sequence and the heterologous protein sequence, so that HRAP may be cleaved away from the heterologous moiety following purification. Methods for fusion protein expression and purification are discussed in Ausubel (1995, supra, ch 10). A variety of commercially available kits may also be
10 used to facilitate expression and purification of fusion proteins.

In a further embodiment of the invention, synthesis of radiolabeled HRAP may be achieved in vitro using the TNT rabbit reticulocyte lysate or wheat germ extract systems (Promega). These systems couple transcription and translation of protein-coding sequences operably associated with the T7, T3, or SP6 promoters. Translation takes place in the presence of
15 a radiolabeled amino acid precursor, preferably ³⁵S-methionine.

Fragments of HRAP may be produced not only by recombinant production, but also by direct peptide synthesis using solid-phase techniques. (See, e.g., Creighton, supra, pp. 55-60.) Protein synthesis may be performed by manual techniques or by automation. Automated synthesis may be achieved, for example, using the ABI 431A Peptide Synthesizer (Perkin-Elmer). Various
20 fragments of HRAP may be synthesized separately and then combined to produce the full length molecule.

THERAPEUTICS

Chemical and structural similarity, e.g., in the context of sequences and motifs, exists between regions of HRAP and human receptor-associated proteins. In addition, the expression of
25 HRAP is closely associated with cell proliferative disorders, such as cancer, and with inflammation and the immune response. HRAP are expressed in libraries from cancerous tissues, hematopoietic tissues, reproductive tissues, cardiovascular tissues, and gastrointestinal tissues (Table 3). Therefore, HRAP appears to play a role in cell proliferative, autoimmune/inflammatory, reproductive, cardiovascular, and gastrointestinal disorders.
30 Therefore, in the treatment of disorders associated with increased expression or activity of HRAP, it is desirable to decrease the expression or activity of HRAP. In the treatment of disorders associated with decreased expression or activity of HRAP, it is desirable to provide the protein or to increase the expression of HRAP.

Therefore, in one embodiment, HRAP or a fragment or derivative thereof may be

administered to a subject to treat or prevent a disorder associated with decreased expression or activity of HRAP. Examples of such disorders include, but are not limited to, a cell proliferative disorder such as actinic keratosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, a cancer of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; and an autoimmune/inflammatory disorder such as actinic keratosis, acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, arteriosclerosis, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, bronchitis, bursitis, cholecystitis, cirrhosis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, paroxysmal nocturnal hemoglobinuria, hepatitis, hypereosinophilia, irritable bowel syndrome, episodic lymphopenia with lymphocytotoxins, mixed connective tissue disease (MCTD), multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, myelofibrosis, osteoarthritis, osteoporosis, pancreatitis, polycythemia vera, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, primary thrombocythemia, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma.

25 In another embodiment, a vector capable of expressing HRAP or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of HRAP including, but not limited to, those described above.

In a further embodiment, a pharmaceutical composition comprising a substantially purified HRAP in conjunction with a suitable pharmaceutical carrier may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of HRAP including, but not limited to, those provided above.

30 In still another embodiment, an agonist which modulates the activity of HRAP may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of HRAP including, but not limited to, those listed above.

In a further embodiment, an antagonist of HRAP may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of HRAP. Examples of such disorders include, but are not limited to, a cell proliferative disorder such as actinic keratosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD),

5 myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, a cancer of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen,

10 testis, thymus, thyroid, and uterus; an autoimmune/inflammatory disorder such as actinic keratosis, acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, arteriosclerosis, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, bronchitis, bursitis, cholecystitis, cirrhosis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis,

15 diabetes mellitus, emphysema, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, paroxysmal nocturnal hemoglobinuria, hepatitis, hypereosinophilia, irritable bowel syndrome, episodic lymphopenia with lymphocytotoxins, mixed connective tissue disease (MCTD), multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, myelofibrosis, osteoarthritis,

20 osteoporosis, pancreatitis, polycythemia vera, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, primary thrombocythemia, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections,

25 and trauma; a reproductive disorder such as a disorder of prolactin production, infertility, including tubal disease, ovulatory defects, and endometriosis, a disruption of the estrous cycle, a disruption of the menstrual cycle, polycystic ovary syndrome, ovarian hyperstimulation syndrome, an endometrial or ovarian tumor, a uterine fibroid, an autoimmune disorder, an ectopic pregnancy, and teratogenesis, cancer of the breast, fibrocystic breast disease, and galactorrhea, a disruption of

30 spermatogenesis, abnormal sperm physiology, cancer of the testis, cancer of the prostate, benign prostatic hyperplasia, prostatitis, Peyronie's disease, carcinoma of the male breast, and gynecomastia; a cardiovascular disorder such as arteriovenous fistula, atherosclerosis, hypertension, vasculitis, Raynaud's disease, aneurysms, arterial dissections, varicose veins, thrombophlebitis and phlebothrombosis, and vascular tumors, congestive heart failure, ischemic

heart disease, angina pectoris, myocardial infarction, hypertensive heart disease, degenerative valvular heart disease, calcific aortic valve stenosis, congenitally bicuspid aortic valve, mitral annular calcification, mitral valve prolapse, rheumatic fever and rheumatic heart disease, infective endocarditis, nonbacterial thrombotic endocarditis, endocarditis of systemic lupus erythematosus, 5 carcinoid heart disease, cardiomyopathy, myocarditis, pericarditis, neoplastic heart disease, and congenital heart disease; and a gastrointestinal disorder such as dysphagia, peptic esophagitis, esophageal spasm, esophageal stricture, esophageal carcinoma, dyspepsia, indigestion, gastritis, gastric carcinoma, anorexia, nausea, emesis, gastroparesis, antral or pyloric edema, abdominal angina, pyrosis, gastroenteritis, intestinal obstruction, an infection of the intestinal tract, peptic 10 ulcer, cholelithiasis, cholecystitis, cholestasis, pancreatitis, pancreatic carcinoma, biliary tract disease, hepatitis, hyperbilirubinemia, cirrhosis, passive congestion of the liver, hepatoma, infectious colitis, ulcerative colitis, ulcerative proctitis, Crohn's disease, Whipple's disease, Mallory-Weiss syndrome, colonic carcinoma, colonic obstruction, irritable bowel syndrome, short bowel syndrome, diarrhea, constipation, gastrointestinal hemorrhage, and acquired 15 immunodeficiency syndrome (AIDS) enteropathy. In one aspect, an antibody which specifically binds HRAP may be used directly as an antagonist or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissue which express HRAP.

In an additional embodiment, a vector expressing the complement of the polynucleotide encoding HRAP may be administered to a subject to treat or prevent a disorder associated with 20 increased expression or activity of HRAP including, but not limited to, those described above.

In other embodiments, any of the proteins, antagonists, antibodies, agonists, complementary sequences, or vectors of the invention may be administered in combination with other appropriate therapeutic agents. Selection of the appropriate agents for use in combination therapy may be made by one of ordinary skill in the art, according to conventional pharmaceutical 25 principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

An antagonist of HRAP may be produced using methods which are generally known in 30 the art. In particular, purified HRAP may be used to produce antibodies or to screen libraries of pharmaceutical agents to identify those which specifically bind HRAP. Antibodies to HRAP may also be generated using methods that are well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies, Fab fragments, and fragments produced by a Fab expression library. Neutralizing antibodies (i.e., those which

inhibit dimer formation) are especially preferred for therapeutic use.

For the production of antibodies, various hosts including goats, rabbits, rats, mice, humans, and others may be immunized by injection with HRAP or with any fragment or oligopeptide thereof which has immunogenic properties. Depending on the host species, various
5 adjuvants may be used to increase immunological response. Such adjuvants include, but are not limited to, Freund's, mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, KLH, and dinitrophenol. Among adjuvants used in humans, BCG (bacilli Calmette-Guerin) and Corynebacterium parvum are especially preferable.

10 It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to HRAP have an amino acid sequence consisting of at least about 5 amino acids, and, more preferably, of at least about 10 amino acids. It is also preferable that these oligopeptides, peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein and contain the entire amino acid sequence of a small, naturally occurring molecule. Short stretches of
15 HRAP amino acids may be fused with those of another protein, such as KLH, and antibodies to the chimeric molecule may be produced.

Monoclonal antibodies to HRAP may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-
20 hybridoma technique. (See, e.g., Kohler, G. et al. (1975) Nature 256:495-497; Kozbor, D. et al. (1985) J. Immunol. Methods 81:31-42; Cote, R.J. et al. (1983) Proc. Natl. Acad. Sci. 80:2026-2030; and Cole, S.P. et al. (1984) Mol. Cell Biol. 62:109-120.)

In addition, techniques developed for the production of "chimeric antibodies," such as the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate
25 antigen specificity and biological activity, can be used. (See, e.g., Morrison, S.L. et al. (1984) Proc. Natl. Acad. Sci. 81:6851-6855; Neuberger, M.S. et al. (1984) Nature 312:604-608; and Takeda, S. et al. (1985) Nature 314:452-454.) Alternatively, techniques described for the production of single chain antibodies may be adapted, using methods known in the art, to produce HRAP-specific single chain antibodies. Antibodies with related specificity, but of distinct
30 idiotypic composition, may be generated by chain shuffling from random combinatorial immunoglobulin libraries. (See, e.g., Burton D.R. (1991) Proc. Natl. Acad. Sci. 88:10134-10137.)

Antibodies may also be produced by inducing in vivo production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly specific binding reagents as disclosed in the literature. (See, e.g., Orlandi, R. et al. (1989) Proc. Natl. Acad. Sci. 86:

3833-3837; Winter, G. et al. (1991) Nature 349:293-299.)

Antibody fragments which contain specific binding sites for HRAP may also be generated. For example, such fragments include, but are not limited to, F(ab')₂ fragments produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing the disulfide
5 bridges of the F(ab')₂ fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity. (See, e.g., Huse, W.D. et al. (1989) Science 246:1275-1281.)

Various immunoassays may be used for screening to identify antibodies having the desired specificity. Numerous protocols for competitive binding or immunoradiometric assays
10 using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such immunoassays typically involve the measurement of complex formation between HRAP and its specific antibody. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering HRAP epitopes is preferred, but a competitive binding assay may also be employed (Pound, supra).

15 Various methods such as Scatchard analysis in conjunction with radioimmunoassay techniques may be used to assess the affinity of antibodies for HRAP. Affinity is expressed as an association constant, K_a , which is defined as the molar concentration of HRAP-antibody complex divided by the molar concentrations of free antigen and free antibody under equilibrium conditions. The K_a determined for a preparation of polyclonal antibodies, which are
20 heterogeneous in their affinities for multiple HRAP epitopes, represents the average affinity, or avidity, of the antibodies for HRAP. The K_a determined for a preparation of monoclonal antibodies, which are monospecific for a particular HRAP epitope, represents a true measure of affinity. High-affinity antibody preparations with K_a ranging from about 10^9 to 10^{12} L/mole are preferred for use in immunoassays in which the HRAP-antibody complex must withstand rigorous
25 manipulations. Low-affinity antibody preparations with K_a ranging from about 10^6 to 10^7 L/mole are preferred for use in immunopurification and similar procedures which ultimately require dissociation of HRAP, preferably in active form, from the antibody (Catty, D. (1988) Antibodies, Volume I: A Practical Approach, IRL Press, Washington, DC; Liddell, J. E. and Cryer, A. (1991) A Practical Guide to Monoclonal Antibodies, John Wiley & Sons, New York NY).

30 The titer and avidity of polyclonal antibody preparations may be further evaluated to determine the quality and suitability of such preparations for certain downstream applications. For example, a polyclonal antibody preparation containing at least 1-2 mg specific antibody/ml, preferably 5-10 mg specific antibody/ml, is preferred for use in procedures requiring precipitation of HRAP-antibody complexes. Procedures for evaluating antibody specificity, titer, and avidity,

and guidelines for antibody quality and usage in various applications, are generally available. (See, e.g., Catty, supra, and Coligan et al. supra.)

In another embodiment of the invention, the polynucleotides encoding HRAP, or any fragment or complement thereof, may be used for therapeutic purposes. In one aspect, the
5 complement of the polynucleotide encoding HRAP may be used in situations in which it would be desirable to block the transcription of the mRNA. In particular, cells may be transformed with sequences complementary to polynucleotides encoding HRAP. Thus, complementary molecules or fragments may be used to modulate HRAP activity, or to achieve regulation of gene function. Such technology is now well known in the art, and sense or antisense oligonucleotides or larger
10 fragments can be designed from various locations along the coding or control regions of sequences encoding HRAP.

Expression vectors derived from retroviruses, adenoviruses, or herpes or vaccinia viruses, or from various bacterial plasmids, may be used for delivery of nucleotide sequences to the targeted organ, tissue, or cell population. Methods which are well known to those skilled in the art
15 can be used to construct vectors to express nucleic acid sequences complementary to the polynucleotides encoding HRAP. (See, e.g., Sambrook, supra; Ausubel, 1995, supra.)

Genes encoding HRAP can be turned off by transforming a cell or tissue with expression vectors which express high levels of a polynucleotide, or fragment thereof, encoding HRAP. Such constructs may be used to introduce untranslatable sense or antisense sequences into a cell. Even
20 in the absence of integration into the DNA, such vectors may continue to transcribe RNA molecules until they are disabled by endogenous nucleases. Transient expression may last for a month or more with a non-replicating vector, and may last even longer if appropriate replication elements are part of the vector system.

As mentioned above, modifications of gene expression can be obtained by designing
25 complementary sequences or antisense molecules (DNA, RNA, or PNA) to the control, 5', or regulatory regions of the gene encoding HRAP. Oligonucleotides derived from the transcription initiation site, e.g., between about positions -10 and +10 from the start site, are preferred. Similarly, inhibition can be achieved using triple helix base-pairing methodology. Triple helix pairing is useful because it causes inhibition of the ability of the double helix to open sufficiently
30 for the binding of polymerases, transcription factors, or regulatory molecules. Recent therapeutic advances using triplex DNA have been described in the literature. (See, e.g., Gee, J.E. et al. (1994) in Huber, B.E. and B.I. Carr, Molecular and Immunologic Approaches, Futura Publishing, Mt. Kisco NY, pp. 163-177.) A complementary sequence or antisense molecule may also be designed to block translation of mRNA by preventing the transcript from binding to ribosomes.

Ribozymes, enzymatic RNA molecules, may also be used to catalyze the specific cleavage of RNA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme molecule to complementary target RNA, followed by endonucleolytic cleavage. For example, engineered hammerhead motif ribozyme molecules may specifically and efficiently
5 catalyze endonucleolytic cleavage of sequences encoding HRAP.

Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites, including the following sequences: GUA, GUU, and GUC. Once identified, short RNA sequences of between 15 and 20 ribonucleotides, corresponding to the region of the target gene containing the cleavage site, may
10 be evaluated for secondary structural features which may render the oligonucleotide inoperable. The suitability of candidate targets may also be evaluated by testing accessibility to hybridization with complementary oligonucleotides using ribonuclease protection assays.

Complementary ribonucleic acid molecules and ribozymes of the invention may be prepared by any method known in the art for the synthesis of nucleic acid molecules. These
15 include techniques for chemically synthesizing oligonucleotides such as solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by in vitro and in vivo transcription of DNA sequences encoding HRAP. Such DNA sequences may be incorporated into a wide variety of vectors with suitable RNA polymerase promoters such as T7 or SP6. Alternatively, these cDNA constructs that synthesize complementary RNA, constitutively or
20 inducibly, can be introduced into cell lines, cells, or tissues.

RNA molecules may be modified to increase intracellular stability and half-life. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends of the molecule, or the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages within the backbone of the molecule. This concept is inherent in the production of PNAs
25 and can be extended in all of these molecules by the inclusion of nontraditional bases such as inosine, queosine, and wybutosine, as well as acetyl-, methyl-, thio-, and similarly modified forms of adenine, cytidine, guanine, thymine, and uridine which are not as easily recognized by endogenous endonucleases.

Many methods for introducing vectors into cells or tissues are available and equally
30 suitable for use in vivo, in vitro, and ex vivo. For ex vivo therapy, vectors may be introduced into stem cells taken from the patient and clonally propagated for autologous transplant back into that same patient. Delivery by transfection, by liposome injections, or by polycationic amino polymers may be achieved using methods which are well known in the art. (See, e.g., Goldman, C.K. et al. (1997) Nature Biotechnology 15:462-466.)

Any of the therapeutic methods described above may be applied to any subject in need of such therapy, including, for example, mammals such as dogs, cats, cows, horses, rabbits, monkeys, and most preferably, humans.

An additional embodiment of the invention relates to the administration of a
5 pharmaceutical or sterile composition, in conjunction with a pharmaceutically acceptable carrier, for any of the therapeutic effects discussed above. Such pharmaceutical compositions may consist of HRAP, antibodies to HRAP, and mimetics, agonists, antagonists, or inhibitors of HRAP. The compositions may be administered alone or in combination with at least one other agent, such as a stabilizing compound, which may be administered in any sterile, biocompatible pharmaceutical
10 carrier including, but not limited to, saline, buffered saline, dextrose, and water. The compositions may be administered to a patient alone, or in combination with other agents, drugs, or hormones.

The pharmaceutical compositions utilized in this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal,
15 enteral, topical, sublingual, or rectal means.

In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically-acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Further details on techniques for formulation and administration may be found
20 in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing, Easton PA).

Pharmaceutical compositions for oral administration can be formulated using pharmaceutically acceptable carriers well known in the art in dosages suitable for oral administration. Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for ingestion by
25 the patient.

Pharmaceutical preparations for oral use can be obtained through combining active compounds with solid excipient and processing the resultant mixture of granules (optionally, after grinding) to obtain tablets or dragee cores. Suitable auxiliaries can be added, if desired. Suitable excipients include carbohydrate or protein fillers, such as sugars, including lactose, sucrose,
30 mannitol, and sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose, such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; gums, including arabic and tragacanth; and proteins, such as gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, and alginic acid or a salt thereof, such as sodium alginate.

Dragee cores may be used in conjunction with suitable coatings, such as concentrated sugar solutions, which may also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for
5 product identification or to characterize the quantity of active compound, i.e., dosage.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating, such as glycerol or sorbitol. Push-fit capsules can contain active ingredients mixed with fillers or binders, such as lactose or starches, lubricants, such as talc or magnesium stearate, and, optionally, stabilizers. In soft
10 capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid, or liquid polyethylene glycol with or without stabilizers.

Pharmaceutical formulations suitable for parenteral administration may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiologically buffered saline. Aqueous injection suspensions may contain
15 substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils, such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate, triglycerides, or liposomes. Non-lipid polycationic amino polymers may also be used for delivery. Optionally, the
20 suspension may also contain suitable stabilizers or agents to increase the solubility of the compounds and allow for the preparation of highly concentrated solutions.

For topical or nasal administration, penetrants appropriate to the particular barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

The pharmaceutical compositions of the present invention may be manufactured in a
25 manner that is known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes.

The pharmaceutical composition may be provided as a salt and can be formed with many acids, including but not limited to, hydrochloric, sulfuric, acetic, lactic, tartaric, malic, and succinic acid. Salts tend to be more soluble in aqueous or other protonic solvents than are the
30 corresponding free base forms. In other cases, the preferred preparation may be a lyophilized powder which may contain any or all of the following: 1 mM to 50 mM histidine, 0.1% to 2% sucrose, and 2% to 7% mannitol, at a pH range of 4.5 to 5.5, that is combined with buffer prior to use.

After pharmaceutical compositions have been prepared, they can be placed in an

appropriate container and labeled for treatment of an indicated condition. For administration of HRAP, such labeling would include amount, frequency, and method of administration.

Pharmaceutical compositions suitable for use in the invention include compositions wherein the active ingredients are contained in an effective amount to achieve the intended
5 purpose. The determination of an effective dose is well within the capability of those skilled in the art.

For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays, e.g., of neoplastic cells or in animal models such as mice, rats, rabbits, dogs, or pigs. An animal model may also be used to determine the appropriate concentration range and
10 route of administration. Such information can then be used to determine useful doses and routes for administration in humans.

A therapeutically effective dose refers to that amount of active ingredient, for example HRAP or fragments thereof, antibodies of HRAP, and agonists, antagonists or inhibitors of HRAP, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be
15 determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such as by calculating the ED_{50} (the dose therapeutically effective in 50% of the population) or LD_{50} (the dose lethal to 50% of the population) statistics. The dose ratio of therapeutic to toxic effects is the therapeutic index, and it can be expressed as the ED_{50}/LD_{50} ratio. Pharmaceutical compositions which exhibit large therapeutic indices are preferred. The data obtained from cell
20 culture assays and animal studies are used to formulate a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that includes the ED_{50} with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, the sensitivity of the patient, and the route of administration.

The exact dosage will be determined by the practitioner, in light of factors related to the
25 subject requiring treatment. Dosage and administration are adjusted to provide sufficient levels of the active moiety or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, the general health of the subject, the age, weight, and gender of the subject, time and frequency of administration, drug combination(s), reaction sensitivities, and response to therapy. Long-acting pharmaceutical compositions may be
30 administered every 3 to 4 days, every week, or biweekly depending on the half-life and clearance rate of the particular formulation.

Normal dosage amounts may vary from about 0.1 μg to 100,000 μg , up to a total dose of about 1 gram, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art.

Those skilled in the art will employ different formulations for nucleotides than for proteins or their inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells, conditions, locations, etc.

DIAGNOSTICS

- 5 In another embodiment, antibodies which specifically bind HRAP may be used for the diagnosis of disorders characterized by expression of HRAP, or in assays to monitor patients being treated with HRAP or agonists, antagonists, or inhibitors of HRAP. Antibodies useful for diagnostic purposes may be prepared in the same manner as described above for therapeutics. Diagnostic assays for HRAP include methods which utilize the antibody and a label to detect
- 10 HRAP in human body fluids or in extracts of cells or tissues. The antibodies may be used with or without modification, and may be labeled by covalent or non-covalent attachment of a reporter molecule. A wide variety of reporter molecules, several of which are described above, are known in the art and may be used.

- A variety of protocols for measuring HRAP, including ELISAs, RIAs, and FACS, are
- 15 known in the art and provide a basis for diagnosing altered or abnormal levels of HRAP expression. Normal or standard values for HRAP expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, preferably human, with antibody to HRAP under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, preferably by photometric means. Quantities of
- 20 HRAP expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.

- In another embodiment of the invention, the polynucleotides encoding HRAP may be used for diagnostic purposes. The polynucleotides which may be used include oligonucleotide
- 25 sequences, complementary RNA and DNA molecules, and PNAs. The polynucleotides may be used to detect and quantitate gene expression in biopsied tissues in which expression of HRAP may be correlated with disease. The diagnostic assay may be used to determine absence, presence, and excess expression of HRAP, and to monitor regulation of HRAP levels during therapeutic intervention.

- 30 In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding HRAP or closely related molecules may be used to identify nucleic acid sequences which encode HRAP. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a conserved motif, and the stringency of the hybridization or

amplification (maximal, high, intermediate, or low), will determine whether the probe identifies only naturally occurring sequences encoding HRAP, allelic variants, or related sequences.

Probes may also be used for the detection of related sequences, and should preferably have at least 50% sequence identity to any of the HRAP encoding sequences. The hybridization
5 probes of the subject invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:17-32 or from genomic sequences including promoters, enhancers, and introns of the HRAP gene.

Means for producing specific hybridization probes for DNAs encoding HRAP include the cloning of polynucleotide sequences encoding HRAP or HRAP derivatives into vectors for the
10 production of mRNA probes. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by means of the addition of the appropriate RNA polymerases and the appropriate labeled nucleotides. Hybridization probes may be labeled by a variety of reporter groups, for example, by radionuclides such as ^{32}P or ^{35}S , or by enzymatic labels, such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems, and the like.

15 Polynucleotide sequences encoding HRAP may be used for the diagnosis of disorders associated with expression of HRAP. Examples of such disorders include, but are not limited to, a cell proliferative disorder such as actinic keratosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma,
20 leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, a cancer of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; an autoimmune/inflammatory disorder such as actinic keratosis, acquired immunodeficiency
25 syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, arteriosclerosis, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, bronchitis, bursitis, cholecystitis, cirrhosis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's
30 syndrome, gout, Graves' disease, Hashimoto's thyroiditis, paroxysmal nocturnal hemoglobinuria, hepatitis, hypereosinophilia, irritable bowel syndrome, episodic lymphopenia with lymphocytotoxins, mixed connective tissue disease (MCTD), multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, myelofibrosis, osteoarthritis, osteoporosis, pancreatitis, polycythemia vera, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis,

scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, primary thrombocythemia, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma; a reproductive disorder such as
5 a disorder of prolactin production, infertility, including tubal disease, ovulatory defects, and endometriosis, a disruption of the estrous cycle, a disruption of the menstrual cycle, polycystic ovary syndrome, ovarian hyperstimulation syndrome, an endometrial or ovarian tumor, a uterine fibroid, an autoimmune disorder, an ectopic pregnancy, and teratogenesis, cancer of the breast, fibrocystic breast disease, and galactorrhea, a disruption of spermatogenesis, abnormal sperm
10 physiology, cancer of the testis, cancer of the prostate, benign prostatic hyperplasia, prostatitis, Peyronie's disease, carcinoma of the male breast, and gynecomastia; a cardiovascular disorder such as arteriovenous fistula, atherosclerosis, hypertension, vasculitis, Raynaud's disease, aneurysms, arterial dissections, varicose veins, thrombophlebitis and phlebothrombosis, and vascular tumors, congestive heart failure, ischemic heart disease, angina pectoris, myocardial
15 infarction, hypertensive heart disease, degenerative valvular heart disease, calcific aortic valve stenosis, congenitally bicuspid aortic valve, mitral annular calcification, mitral valve prolapse, rheumatic fever and rheumatic heart disease, infective endocarditis, nonbacterial thrombotic endocarditis, endocarditis of systemic lupus erythematosus, carcinoid heart disease, cardiomyopathy, myocarditis, pericarditis, neoplastic heart disease, and congenital heart disease;
20 and a gastrointestinal disorder such as dysphagia, peptic esophagitis, esophageal spasm, esophageal stricture, esophageal carcinoma, dyspepsia, indigestion, gastritis, gastric carcinoma, anorexia, nausea, emesis, gastroparesis, antral or pyloric edema, abdominal angina, pyrosis, gastroenteritis, intestinal obstruction, an infection of the intestinal tract, peptic ulcer, cholelithiasis, cholecystitis, cholestasis, pancreatitis, pancreatic carcinoma, biliary tract disease, hepatitis,
25 hyperbilirubinemia, cirrhosis, passive congestion of the liver, hepatoma, infectious colitis, ulcerative colitis, ulcerative proctitis, Crohn's disease, Whipple's disease, Mallory-Weiss syndrome, colonic carcinoma, colonic obstruction, irritable bowel syndrome, short bowel syndrome, diarrhea, constipation, gastrointestinal hemorrhage, and acquired immunodeficiency syndrome (AIDS) enteropathy. The polynucleotide sequences encoding HRAP may be used in
30 Southern or northern analysis, dot blot, or other membrane-based technologies; in PCR technologies; in dipstick, pin, and ELISA assays; and in microarrays utilizing fluids or tissues from patients to detect altered HRAP expression. Such qualitative or quantitative methods are well known in the art.

In a particular aspect, the nucleotide sequences encoding HRAP may be useful in assays

that detect the presence of associated disorders, particularly those mentioned above. The nucleotide sequences encoding HRAP may be labeled by standard methods and added to a fluid or tissue sample from a patient under conditions suitable for the formation of hybridization complexes. After a suitable incubation period, the sample is washed and the signal is quantitated
5 and compared with a standard value. If the amount of signal in the patient sample is significantly altered in comparison to a control sample then the presence of altered levels of nucleotide sequences encoding HRAP in the sample indicates the presence of the associated disorder. Such assays may also be used to evaluate the efficacy of a particular therapeutic treatment regimen in animal studies, in clinical trials, or to monitor the treatment of an individual patient.

10 In order to provide a basis for the diagnosis of a disorder associated with expression of HRAP, a normal or standard profile for expression is established. This may be accomplished by combining body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding HRAP, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained from
15 normal subjects with values from an experiment in which a known amount of a substantially purified polynucleotide is used. Standard values obtained in this manner may be compared with values obtained from samples from patients who are symptomatic for a disorder. Deviation from standard values is used to establish the presence of a disorder.

Once the presence of a disorder is established and a treatment protocol is initiated,
20 hybridization 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 the 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 months.

With respect to cancer, the presence of an abnormal amount of transcript (either under- or
25 overexpressed) in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

30 Additional diagnostic uses for oligonucleotides designed from the sequences encoding HRAP may involve the use of PCR. These oligomers may be chemically synthesized, generated enzymatically, or produced in vitro. Oligomers will preferably contain a fragment of a polynucleotide encoding HRAP, or a fragment of a polynucleotide complementary to the polynucleotide encoding HRAP, and will be employed under optimized conditions for

identification of a specific gene or condition. Oligomers may also be employed under less stringent conditions for detection or quantitation of closely related DNA or RNA sequences.

Methods which may also be used to quantitate the expression of HRAP include radiolabeling or biotinylating nucleotides, coamplification of a control nucleic acid, and
5 interpolating results from standard curves. (See, e.g., Melby, P.C. et al. (1993) J. Immunol. Methods 159:235-244; Duplaa, C. et al. (1993) Anal. Biochem. 229-236.) The speed of quantitation of multiple samples may be accelerated by running the assay in an ELISA format where the oligomer of interest is presented in various dilutions and a spectrophotometric or colorimetric response gives rapid quantitation.

10 In further embodiments, oligonucleotides or longer fragments derived from any of the polynucleotide sequences described herein may be used as targets in a microarray. The microarray can be used to monitor the expression level of large numbers of genes simultaneously and to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, and
15 to develop and monitor the activities of therapeutic agents.

Microarrays may be prepared, used, and analyzed using methods known in the art. (See, e.g., Brennan, T.M. et al. (1995) U.S. Patent No. 5,474,796; Schena, M. et al. (1996) Proc. Natl. Acad. Sci. 93:10614-10619; Baldeschweiler et al. (1995) PCT application WO95/251116; Shalon, D. et al. (1995) PCT application WO95/35505; Heller, R.A. et al. (1997) Proc. Natl. Acad. Sci.
20 94:2150-2155; and Heller, M.J. et al. (1997) U.S. Patent No. 5,605,662.)

In another embodiment of the invention, nucleic acid sequences encoding HRAP may be used to generate hybridization probes useful in mapping the naturally occurring genomic sequence. The sequences may be mapped to a particular chromosome, to a specific region of a chromosome, or to artificial chromosome constructions, e.g., human artificial chromosomes
25 (HACs), yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), bacterial P1 constructions, or single chromosome cDNA libraries. (See, e.g., Harrington, J.J. et al. (1997) Nat Genet. 15:345-355; Price, C.M. (1993) Blood Rev. 7:127-134; and Trask, B.J. (1991) Trends Genet. 7:149-154.)

Fluorescent in situ hybridization (FISH) may be correlated with other physical
30 chromosome mapping techniques and genetic map data. (See, e.g., Heinz-Ulrich, et al. (1995) in Meyers, supra, pp. 965-968.) Examples of genetic map data can be found in various scientific journals or at the Online Mendelian Inheritance in Man (OMIM) site. Correlation between the location of the gene encoding HRAP on a physical chromosomal map and a specific disorder, or a predisposition to a specific disorder, may help define the region of DNA associated with that

disorder. The nucleotide sequences of the invention may be used to detect differences in gene sequences among normal, carrier, and affected individuals.

In situ hybridization of chromosomal preparations and physical mapping techniques, such as linkage analysis using established chromosomal markers, may be used for extending genetic maps. Often the placement of a gene on the chromosome of another mammalian species, such as mouse, may reveal associated markers even if the number or arm of a particular human chromosome is not known. New sequences can be assigned to chromosomal arms by physical mapping. This provides valuable information to investigators searching for disease genes using positional cloning or other gene discovery techniques. Once the disease or syndrome has been crudely localized by genetic linkage to a particular genomic region, e.g., ataxia-telangiectasia to 11q22-23, any sequences mapping to that area may represent associated or regulatory genes for further investigation. (See, e.g., Gatti, R.A. et al. (1988) Nature 336:577-580.) The nucleotide sequence of the subject invention may also be used to detect differences in the chromosomal location due to translocation, inversion, etc., among normal, carrier, or affected individuals.

In another embodiment of the invention, HRAP, its catalytic or immunogenic fragments, or oligopeptides thereof can be used for screening libraries of compounds in any of a variety of drug screening techniques. The fragment employed in such screening may be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The formation of binding complexes between HRAP and the agent being tested may be measured.

Another technique for drug screening provides for high throughput screening of compounds having suitable binding affinity to the protein of interest. (See, e.g., Geysen, et al. (1984) PCT application WO84/03564.) In this method, large numbers of different small test compounds are synthesized on a solid substrate. The test compounds are reacted with HRAP, or fragments thereof, and washed. Bound HRAP is then detected by methods well known in the art. Purified HRAP can also be coated directly onto plates for use in the aforementioned drug screening techniques. Alternatively, non-neutralizing antibodies can be used to capture the peptide and immobilize it on a solid support.

In another embodiment, one may use competitive drug screening assays in which neutralizing antibodies capable of binding HRAP specifically compete with a test compound for binding HRAP. In this manner, antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with HRAP.

In additional embodiments, the nucleotide sequences which encode HRAP may be used in any molecular biology techniques that have yet to be developed, provided the new techniques rely on properties of nucleotide sequences that are currently known, including, but not limited to, such

properties as the triplet genetic code and specific base pair interactions.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of
5 the remainder of the disclosure in any way whatsoever.

The disclosures of all patents, applications, and publications mentioned above and below, in particular U.S. Ser. No. [Atty. Docket No. PF-0571 P] filed August 7, 1998, and U.S. Ser. No. 60/098,703, filed September 1, 1998, are hereby expressly incorporated by reference.

10

EXAMPLES

I. Construction of cDNA Libraries

RNA was purchased from Clontech or isolated from tissues described in Table 4. Some tissues were homogenized and lysed in guanidinium isothiocyanate, while others were homogenized and lysed in phenol or in a suitable mixture of denaturants, such as TRIZOL (Life
15 Technologies), a monophasic solution of phenol and guanidine isothiocyanate. The resulting lysates were centrifuged over CsCl cushions or extracted with chloroform. RNA was precipitated from the lysates with either isopropanol or sodium acetate and ethanol, or by other routine methods.

Phenol extraction and precipitation of RNA were repeated as necessary to increase RNA
20 purity. In some cases, RNA was treated with DNase. For most libraries, poly(A⁺) RNA was isolated using oligo d(T)-coupled paramagnetic particles (Promega), OLIGOTEX latex particles (QIAGEN, Valencia CA), or an OLIGOTEX mRNA purification kit (QIAGEN). Alternatively, RNA was isolated directly from tissue lysates using other RNA isolation kits, e.g., the POLY(A)PURE mRNA purification kit (Ambion, Austin TX).

25 In some cases, Stratagene was provided with RNA and constructed the corresponding cDNA libraries. Otherwise, cDNA was synthesized and cDNA libraries were constructed with the UNIZAP vector system (Stratagene) or SUPERScript plasmid system (Life Technologies), using the recommended procedures or similar methods known in the art. (See, e.g., Ausubel, 1997, supra, units 5.1-6.6). Reverse transcription was initiated using oligo d(T) or random
30 primers. Synthetic oligonucleotide adapters were ligated to double stranded cDNA, and the cDNA was digested with the appropriate restriction enzyme or enzymes. For most libraries, the cDNA was size-selected (300-1000 bp) using SEPHACRYL S1000, SEPHAROSE CL2B, or SEPHAROSE CL4B column chromatography (Amersham Pharmacia Biotech) or preparative agarose gel electrophoresis. cDNAs were ligated into compatible restriction enzyme sites of the

polylinker of a suitable plasmid, e.g., PBLUESCRIPT plasmid (Stratagene), PSPO1 plasmid (Life Technologies), or pINCY (Incyte Pharmaceuticals, Palo Alto CA). Recombinant plasmids were transformed into competent *E. coli* cells including XL1-Blue, XL1-BlueMRF, or SOLR from Stratagene or DH5 α , DH10B, or ElectroMAX DH10B from Life Technologies.

5 **II. Isolation of cDNA Clones**

Plasmids were recovered from host cells by in vivo excision, using the UNIZAP vector system (Stratagene) or cell lysis. Plasmids were purified using at least one of the following: a Magic or WIZARD Minipreps DNA purification system (Promega); an AGTC Miniprep purification kit (Edge Biosystems, Gaithersburg MD); and QIAWELL 8 Plasmid, QIAWELL 8 Plus Plasmid, QIAWELL 8 Ultra Plasmid purification systems or the REAL Prep 96 plasmid kit from QIAGEN. Following precipitation, plasmids were resuspended in 0.1 ml of distilled water and stored, with or without lyophilization, at 4°C.

Alternatively, plasmid DNA was amplified from host cell lysates using direct link PCR in a high-throughput format (Rao, V.B. (1994) Anal. Biochem. 216:1-14). Host cell lysis and
15 thermal cycling steps were carried out in a single reaction mixture. Samples were processed and stored in 384-well plates, and the concentration of amplified plasmid DNA was quantified fluorometrically using PICOGREEN dye (Molecular Probes, Eugene OR) and a Fluoroskan II fluorescence scanner (Labsystems Oy, Helsinki, Finland).

III. Sequencing and Analysis

20 The cDNAs were prepared for sequencing using the ABI CATALYST 800 (Perkin-Elmer) or the HYDRA microdispenser (Robbins Scientific) or MICROLAB 2200 (Hamilton) systems in combination with the PTC-200 thermal cyclers (MJ Research). The cDNAs were sequenced using the ABI PRISM 373 or 377 sequencing systems (Perkin-Elmer) and standard ABI protocols, base calling software, and kits. In one alternative, cDNAs were sequenced using the MEGABACE
25 1000 DNA sequencing system (Molecular Dynamics). In another alternative, the cDNAs were amplified and sequenced using the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Perkin-Elmer). In yet another alternative, cDNAs were sequenced using solutions and dyes from Amersham Pharmacia Biotech. Reading frames for the ESTs were determined using standard methods (reviewed in Ausubel, 1997, supra, unit 7.7). Some of the cDNA
30 sequences were selected for extension using the techniques disclosed in Example V.

The polynucleotide sequences derived from cDNA, extension, and shotgun sequencing were assembled and analyzed using a combination of software programs which utilize algorithms well known to those skilled in the art. Table 5 summarizes the software programs, descriptions, references, and threshold parameters used. The first column of Table 5 shows the tools, programs,

and algorithms used, the second column provides a brief description thereof, the third column presents the references which are incorporated by reference herein, and the fourth column presents, where applicable, the scores, probability values, and other parameters used to evaluate the strength of a match between two sequences (the higher the probability the greater the homology). Sequences were analyzed using MACDNASIS PRO software (Hitachi Software Engineering, S. San Francisco CA) and LASERGENE software (DNASTAR).

The polynucleotide sequences were validated by removing vector, linker, and polyA sequences and by masking ambiguous bases, using algorithms and programs based on BLAST, dynamic programming, and dinucleotide nearest neighbor analysis. The sequences were then queried against a selection of public databases such as GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases, and BLOCKS to acquire annotation, using programs based on BLAST, FASTA, and BLIMPS. The sequences were assembled into full length polynucleotide sequences using programs based on Phred, Phrap, and Consed, and were screened for open reading frames using programs based on GeneMark, BLAST, and FASTA. The full length polynucleotide sequences were translated to derive the corresponding full length amino acid sequences, and these full length sequences were subsequently analyzed by querying against databases such as the GenBank databases (described above), SwissProt, BLOCKS, PRINTS, PFAM, and Prosite.

IV. Northern Analysis

Northern analysis is a laboratory technique used to detect the presence of a transcript of a gene and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, *supra*, ch. 7; Ausubel, 1995, *supra*, ch. 4 and 16.)

Analogous computer techniques applying BLAST were used to search for identical or related molecules in nucleotide databases such as GenBank or LIFESEQ database (Incyte Pharmaceuticals). This analysis is much faster than multiple membrane-based hybridizations. In addition, the sensitivity of the computer search can be modified to determine whether any particular match is categorized as exact or similar. The basis of the search is the product score, which is defined as:

$$\frac{\% \text{ sequence identity} \times \% \text{ maximum BLAST score}}{100}$$

The product score takes into account both the degree of similarity between two sequences and the length of the sequence match. For example, with a product score of 40, the match will be exact within a 1% to 2% error, and, with a product score of 70, the match will be exact. Similar

molecules are usually identified by selecting those which show product scores between 15 and 40, although lower scores may identify related molecules.

The results of northern analyses are reported a percentage distribution of libraries in which the transcript encoding HRAP occurred. Analysis involved the categorization of cDNA libraries
 5 by organ/tissue and disease. The organ/tissue categories included cardiovascular, dermatologic, developmental, endocrine, gastrointestinal, hematopoietic/immune, musculoskeletal, nervous, reproductive, and urologic. The disease categories included cancer, inflammation/trauma, fetal, neurological, and pooled. For each category, the number of libraries expressing the sequence of interest was counted and divided by the total number of libraries across all categories. Percentage
 10 values of tissue-specific and disease expression are reported in Table 3.

V. Extension of HRAP Encoding Polynucleotides

The full length nucleic acid sequences of SEQ ID NO:17-22 were produced by extension of the component fragments described in Table 1, Column 5, using oligonucleotide primers based on those fragments. One primer was synthesized to initiate extension of an antisense
 15 polynucleotide, and the other was synthesized to initiate extension of a sense polynucleotide. Primers were used to facilitate the extension of the known sequence "outward" generating amplicons containing new unknown nucleotide sequence for the region of interest. The initial primers were designed from the cDNA using OLIGO 4.06 software (National Biosciences), or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of
 20 about 50% or more, and to anneal to the target sequence at temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would result in hairpin structures and primer-primer dimerizations was avoided.

Selected human cDNA libraries (Life Technologies) were used to extend the sequence. If more than one extension is necessary or desired, additional sets of primers are designed to further
 25 extend the known region.

High fidelity amplification was obtained by following the instructions for the XL-PCR kit (Perkin-Elmer Corp.) and thoroughly mixing the enzyme and reaction mix. PCR was performed using the PTC-200 thermal cycler (MJ Research), beginning with 40 pmol of each primer and the recommended concentrations of all other components of the kit, with the following parameters:

30	Step 1	94° C for 1 min (initial denaturation)
	Step 2	65° C for 1 min
	Step 3	68° C for 6 min
	Step 4	94° C for 15 sec
	Step 5	65° C for 1 min
35	Step 6	68° C for 7 min
	Step 7	Repeat steps 4 through 6 for an additional 15 cycles
	Step 8	94° C for 15 sec

- Step 9 65° C for 1 min
 Step 10 68° C for 7:15 min
 Step 11 Repeat steps 8 through 10 for an additional 12 cycles
 Step 12 72° C for 8 min
 5 Step 13 4° C (and holding)

A 5 μ l to 10 μ l aliquot of the reaction mixture was analyzed by electrophoresis on a low concentration (about 0.6% to 0.8%) agarose mini-gel to determine which reactions were successful in extending the sequence. Bands thought to contain the largest products were excised from the
 10 gel, purified using QIAQUICK purification kit (QIAGEN Inc.), and trimmed of overhangs using Klenow enzyme to facilitate religation and cloning.

After ethanol precipitation, the products were redissolved in 13 μ l of ligation buffer, 1 μ l T4-DNA ligase (15 units) and 1 μ l T4 polynucleotide kinase were added, and the mixture was incubated at room temperature for 2 to 3 hours, or overnight at 16° C. Competent *E. coli* cells (in
 15 40 μ l of appropriate media) were transformed with 3 μ l of ligation mixture and cultured in 80 μ l of SOC medium. (See, e.g., Sambrook, *supra*, Appendix A, p. 2.) After incubation for one hour at 37° C, the *E. coli* mixture was plated on Luria Bertani (LB) agar (See, e.g., Sambrook, *supra*, Appendix A, p. 1) containing carbenicillin (2x carb). The following day, several colonies were randomly picked from each plate and cultured in 150 μ l of liquid LB/2x carb medium placed in an
 20 individual well of an appropriate commercially-available sterile 96-well microtiter plate. The following day, 5 μ l of each overnight culture was transferred into a non-sterile 96-well plate and, after dilution 1:10 with water, 5 μ l from each sample was transferred into a PCR array.

For PCR amplification, 18 μ l of concentrated PCR reaction mix (3.3x) containing 4 units of rTth DNA polymerase, a vector primer, and one or both of the gene specific primers used for
 25 the extension reaction were added to each well. Amplification was performed using the following conditions:

- Step 1 94° C for 60 sec
 Step 2 94° C for 20 sec
 Step 3 55° C for 30 sec
 30 Step 4 72° C for 90 sec
 Step 5 Repeat steps 2 through 4 for an additional 29 cycles
 Step 6 72° C for 180 sec
 Step 7 4° C (and holding)

35 Aliquots of the PCR reactions were run on agarose gels together with molecular weight markers. The sizes of the PCR products were compared to the original partial cDNAs, and appropriate clones were selected, ligated into plasmid, and sequenced.

In like manner, the nucleotide sequences of SEQ ID NO:17-22 is used to obtain 5' regulatory sequences using the procedure above, oligonucleotides designed for 5' extension, and

an appropriate genomic library.

The full length nucleic acid sequences of SEQ ID NO:23-32 were produced by extension of an appropriate fragment of the full length molecule using oligonucleotide primers designed from this fragment. One primer was synthesized to initiate 5' extension of the known fragment, and the other primer, to initiate 3' extension of the known fragment. The initial primers were designed using OLIGO 4.06 software (National Biosciences), or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the target sequence at temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would result in hairpin structures and primer-primer dimerizations was avoided.

Selected human cDNA libraries were used to extend the sequence. If more than one extension was necessary or desired, additional or nested sets of primers were designed.

High fidelity amplification was obtained by PCR using methods well known in the art. PCR was performed in 96-well plates using the PTC-200 thermal cycler (MJ Research, Inc.). The reaction mix contained DNA template, 200 nmol of each primer, reaction buffer containing Mg^{2+} , $(NH_4)_2SO_4$, and β -mercaptoethanol, Taq DNA polymerase (Amersham Pharmacia Biotech), ELONGASE enzyme (Life Technologies), and Pfu DNA polymerase (Stratagene), with the following parameters for primer pair PCI A and PCI B: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C. In the alternative, the parameters for primer pair T7 and SK+ were as follows: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 57°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C.

The concentration of DNA in each well was determined by dispensing 100 μ l PICOGREEN quantitation reagent (0.25% (v/v) PICOGREEN; Molecular Probes, Eugene OR) dissolved in 1XTE and 0.5 μ l of undiluted PCR product into each well of an opaque fluorimeter plate (Corning Costar, Acton MA), allowing the DNA to bind to the reagent. The plate was scanned in a Fluoroskan II (Labsystems Oy, Helsinki, Finland) to measure the fluorescence of the sample and to quantify the concentration of DNA. A 5 μ l to 10 μ l aliquot of the reaction mixture was analyzed by electrophoresis on a 1 % agarose mini-gel to determine which reactions were successful in extending the sequence.

The extended nucleotides were desalted and concentrated, transferred to 384-well plates, digested with CviJI cholera virus endonuclease (Molecular Biology Research, Madison WI), and sonicated or sheared prior to religation into pUC 18 vector (Amersham Pharmacia Biotech). For shotgun sequencing, the digested nucleotides were separated on low concentration (0.6 to 0.8%) agarose gels, fragments were excised, and agar digested with Agar ACE (Promega). Extended

clones were religated using T4 ligase (New England Biolabs, Beverly MA) into pUC 18 vector (Amersham Pharmacia Biotech), treated with Pfu DNA polymerase (Stratagene) to fill-in restriction site overhangs, and transfected into competent *E. coli* cells. Transformed cells were selected on antibiotic-containing media, individual colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x carb liquid media.

The cells were lysed, and DNA was amplified by PCR using Taq DNA polymerase (Amersham Pharmacia Biotech) and Pfu DNA polymerase (Stratagene) with the following parameters: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 72°C, 2 min; Step 5: steps 2, 3, and 4 repeated 29 times; Step 6: 72°C, 5 min; Step 7: storage at 4°C. DNA was quantified by PICOGREEN reagent (Molecular Probes) as described above. Samples with low DNA recoveries were reamplified using the same conditions as described above. Samples were diluted with 20% dimethylsulphoxide (1:2, v/v), and sequenced using DYENAMIC energy transfer sequencing primers and the DYENAMIC DIRECT kit (Amersham Pharmacia Biotech) or the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Perkin-Elmer).

In like manner, the nucleotide sequence of SEQ ID NO:23-32 is used to obtain 5' regulatory sequences using the procedure above, oligonucleotides designed for such extension, and an appropriate genomic library.

VI. Labeling and Use of Individual Hybridization Probes

Hybridization probes derived from SEQ ID NO:17-32 are employed to screen cDNAs, genomic DNAs, or mRNAs. Although the labeling of oligonucleotides, consisting of about 20 base pairs, is specifically described, essentially the same procedure is used with larger nucleotide fragments. Oligonucleotides are designed using state-of-the-art software such as OLIGO 4.06 software (National Biosciences) and labeled by combining 50 pmol of each oligomer, 250 µCi of [γ -³²P] adenosine triphosphate (Amersham Pharmacia Biotech), and T4 polynucleotide kinase (DuPont NEN, Boston MA). The labeled oligonucleotides are substantially purified using a SEPHADEX G-25 superfine size exclusion dextran bead column (Amersham Pharmacia Biotech). An aliquot containing 10⁷ counts per minute of the labeled probe is used in a typical membrane-based hybridization analysis of human genomic DNA digested with one of the following endonucleases: Ase I, Bgl II, Eco RI, Pst I, Xba I, or Pvu II (DuPont NEN).

The DNA from each digest is fractionated on a 0.7% agarose gel and transferred to nylon membranes (Nytran Plus, Schleicher & Schuell, Durham NH). Hybridization is carried out for 16 hours at 40°C. To remove nonspecific signals, blots are sequentially washed at room temperature under increasingly stringent conditions up to 0.1 x saline sodium citrate and 0.5% sodium dodecyl sulfate. After XOMAT-AR film (Eastman Kodak, Rochester NY) is exposed to the blots to film

for several hours, hybridization patterns are compared visually.

VII. Microarrays

A chemical coupling procedure and an ink jet device can be used to synthesize array elements on the surface of a substrate. (See, e.g., Baldeschweiler, supra.) An array analogous to a dot or slot blot may also be used to arrange and link elements to the surface of a substrate using thermal, UV, chemical, or mechanical bonding procedures. A typical array may be produced by hand or using available methods and machines and contain any appropriate number of elements. After hybridization, nonhybridized probes are removed and a scanner used to determine the levels and patterns of fluorescence. The degree of complementarity and the relative abundance of each probe which hybridizes to an element on the microarray may be assessed through analysis of the scanned images.

Full-length cDNAs, Expressed Sequence Tags (ESTs), or fragments thereof may comprise the elements of the microarray. Fragments suitable for hybridization can be selected using software well known in the art such as LASERGENE software (DNASTAR). Full-length cDNAs, ESTs, or fragments thereof corresponding to one of the nucleotide sequences of the present invention, or selected at random from a cDNA library relevant to the present invention, are arranged on an appropriate substrate, e.g., a glass slide. The cDNA is fixed to the slide using, e.g., UV cross-linking followed by thermal and chemical treatments and subsequent drying. (See, e.g., Schena, M. et al. (1995) *Science* 270:467-470; Shalon, D. et al. (1996) *Genome Res.* 6:639-645.) Fluorescent probes are prepared and used for hybridization to the elements on the substrate. The substrate is analyzed by procedures described above.

VIII. Complementary Polynucleotides

Sequences complementary to the HRAP-encoding sequences, or any parts thereof, are used to detect, decrease, or inhibit expression of naturally occurring HRAP. Although use of oligonucleotides comprising from about 15 to 30 base pairs is described, essentially the same procedure is used with smaller or with larger sequence fragments. Appropriate oligonucleotides are designed using OLIGO 4.06 software (National Biosciences) and the coding sequence of HRAP. To inhibit transcription, a complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent promoter binding to the coding sequence. To inhibit translation, a complementary oligonucleotide is designed to prevent ribosomal binding to the HRAP-encoding transcript.

IX. Expression of HRAP

Expression and purification of HRAP is achieved using bacterial or virus-based expression systems. For expression of HRAP in bacteria, cDNA is subcloned into an appropriate

vector containing an antibiotic resistance gene and an inducible promoter that directs high levels of cDNA transcription. Examples of such promoters include, but are not limited to, the *trp-lac* (*tac*) hybrid promoter and the T5 or T7 bacteriophage promoter in conjunction with the *lac* operator regulatory element. Recombinant vectors are transformed into suitable bacterial hosts, e.g., BL21(DE3). Antibiotic resistant bacteria express HRAP upon induction with isopropyl beta-D-thiogalactopyranoside (IPTG). Expression of HRAP in eukaryotic cells is achieved by infecting insect or mammalian cell lines with recombinant Autographica californica nuclear polyhedrosis virus (AcMNPV), commonly known as baculovirus. The nonessential polyhedrin gene of baculovirus is replaced with cDNA encoding HRAP by either homologous recombination or bacterial-mediated transposition involving transfer plasmid intermediates. Viral infectivity is maintained and the strong polyhedrin promoter drives high levels of cDNA transcription. Recombinant baculovirus is used to infect Spodoptera frugiperda (Sf9) insect cells in most cases, or human hepatocytes, in some cases. Infection of the latter requires additional genetic modifications to baculovirus. (See Engelhard, E. K. et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945.)

In most expression systems, HRAP is synthesized as a fusion protein with, e.g., glutathione S-transferase (GST) or a peptide epitope tag, such as FLAG or 6-His, permitting rapid, single-step, affinity-based purification of recombinant fusion protein from crude cell lysates. GST, a 26-kilodalton enzyme from Schistosoma japonicum, enables the purification of fusion proteins on immobilized glutathione under conditions that maintain protein activity and antigenicity (Amersham Pharmacia Biotech). Following purification, the GST moiety can be proteolytically cleaved from HRAP at specifically engineered sites. FLAG, an 8-amino acid peptide, enables immunoaffinity purification using commercially available monoclonal and polyclonal anti-FLAG antibodies (Eastman Kodak). 6-His, a stretch of six consecutive histidine residues, enables purification on metal-chelate resins (QIAGEN). Methods for protein expression and purification are discussed in Ausubel (1995, supra, ch 10 and 16). Purified HRAP obtained by these methods can be used directly in the following activity assay.

X. Demonstration of HRAP Activity

Receptor activity of HRAP is determined in a ligand-binding assay using candidate ligand molecules in the presence of ¹²⁵I-labeled HRAP. HRAP is labeled with ¹²⁵I Bolton-Hunter reagent. (See, e.g., Bolton et al. (1973) Biochem. J. 133:529.) Candidate ligand molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled HRAP, washed, and any wells with labeled HRAP complex are assayed. Data obtained using different concentrations of HRAP are used to calculate values for the number, affinity, and association of

HRAP with the ligand molecules.

Alternatively, HRAP activity is determined by measuring the stimulation of DNA synthesis in Swiss mouse 3T3 cells. Plasmids containing polynucleotides encoding HRAP are added to quiescent 3T3 cultured cells using transfection methods well known in the art and the transfected cells are then incubated in the presence of [³H]thymidine, a radioactive DNA precursor. Varying amounts of HRAP ligand are then added to the cultured cells. Incorporation of [³H]thymidine into acid-precipitable DNA is measured over an appropriate time interval using a radioisotope counter, and the amount incorporated is directly proportional to the amount of newly synthesized DNA. A linear dose-response curve over at least a hundred-fold HRAP ligand concentration range is indicative of receptor activity. One unit of activity per milliliter is defined as the concentration of HRAP producing a 50% response level, where 100% represents maximal incorporation of [³H]thymidine into acid-precipitable DNA (McKay, I. and Leigh, I., eds. (1993) Growth Factors: A Practical Approach, Oxford University Press, New York, NY, page 73).

XI. Functional Assays

HRAP function is assessed by expressing the sequences encoding HRAP at physiologically elevated levels in mammalian cell culture systems. cDNA is subcloned into a mammalian expression vector containing a strong promoter that drives high levels of cDNA expression. Vectors of choice include pCMV SPORT (Life Technologies) and pCR3.1 (Invitrogen, Carlsbad CA), both of which contain the cytomegalovirus promoter. 5-10 μ g of recombinant vector are transiently transfected into a human cell line, preferably of endothelial or hematopoietic origin, using either liposome formulations or electroporation. 1-2 μ g of an additional plasmid containing sequences encoding a marker protein are co-transfected. Expression of a marker protein provides a means to distinguish transfected cells from nontransfected cells and is a reliable predictor of cDNA expression from the recombinant vector. Marker proteins of choice include, e.g., Green Fluorescent Protein (GFP; Clontech), CD64, or a CD64-GFP fusion protein. Flow cytometry (FCM), an automated, laser optics-based technique, is used to identify transfected cells expressing GFP or CD64-GFP, and to evaluate properties, for example, their apoptotic state. FCM detects and quantifies the uptake of fluorescent molecules that diagnose events preceding or coincident with cell death. These events include changes in nuclear DNA content as measured by staining of DNA with propidium iodide; changes in cell size and granularity as measured by forward light scatter and 90 degree side light scatter; down-regulation of DNA synthesis as measured by decrease in bromodeoxyuridine uptake; alterations in expression of cell surface and intracellular proteins as measured by reactivity with specific antibodies; and alterations in plasma membrane composition as measured by the binding of

fluorescein-conjugated Annexin V protein to the cell surface. Methods in flow cytometry are discussed in Ormerod, M. G. (1994) Flow Cytometry, Oxford, New York NY.

The influence of HRAP on gene expression can be assessed using highly purified populations of cells transfected with sequences encoding HRAP and either CD64 or CD64-GFP.

- 5 CD64 and CD64-GFP are expressed on the surface of transfected cells and bind to conserved regions of human immunoglobulin G (IgG). Transfected cells are efficiently separated from nontransfected cells using magnetic beads coated with either human IgG or antibody against CD64 (DYNAL, Lake Success NY). mRNA can be purified from the cells using methods well known by those of skill in the art. Expression of mRNA encoding HRAP and other genes of interest can
- 10 be analyzed by northern analysis or microarray techniques.

XII. Production of HRAP Specific Antibodies

HRAP substantially purified using polyacrylamide gel electrophoresis (PAGE; see, e.g., Harrington, M.G. (1990) *Methods Enzymol.* 182:488-495), or other purification techniques, is used to immunize rabbits and to produce antibodies using standard protocols.

- 15 Alternatively, the HRAP amino acid sequence is analyzed using LASERGENE software (DNASTAR) to determine regions of high immunogenicity, and a corresponding oligopeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art. (See, e.g., Ausubel, 1995, supra, ch. 11.)

- 20 Typically, oligopeptides 15 residues in length are synthesized using an ABI 431A Peptide Synthesizer (Perkin-Elmer) using fmoc-chemistry and coupled to KLH (Sigma-Aldrich, St. Louis MO) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) to increase immunogenicity. (See, e.g., Ausubel, 1995, supra.) Rabbits are immunized with the oligopeptide-KLH complex in complete Freund's adjuvant. Resulting antisera are tested for
- 25 antipeptide activity by, for example, binding the peptide to plastic, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radio-iodinated goat anti-rabbit IgG.

XIII. Purification of Naturally Occurring HRAP Using Specific Antibodies

- Naturally occurring or recombinant HRAP is substantially purified by immunoaffinity chromatography using antibodies specific for HRAP. An immunoaffinity column is constructed
- 30 by covalently coupling anti-HRAP antibody to an activated chromatographic resin, such as CNBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is blocked and washed according to the manufacturer's instructions.

Media containing HRAP are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of HRAP (e.g., high ionic strength

buffers in the presence of detergent). The column is eluted under conditions that disrupt antibody/HRAP binding (e.g., a buffer of pH 2 to pH 3, or a high concentration of a chaotrope, such as urea or thiocyanate ion), and HRAP is collected.

- Various modifications and variations of the described methods and systems of the
- 5 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 described modes for carrying out the invention which are obvious to those skilled in molecular biology or related fields are
- 10 intended to be within the scope of the following claims.

Table 1

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
1	17	1877651	LEUKNOT03	1451415T6 (PENITUT01), 1877651H1 (LEUKNOT03), 1909038F6 (CONNTUT01), 1909038T6 (CONNTUT01), SBKA03242F1
2	18	2906971	THYMNOT05	960673T1.com (BRSTTUT03), 1270284F6 (BRAINOT09), 1346244F6 (PROSNOT11), 1520075F1 (BLADTUT04), 1928920R6 (BRSTNOT02), 2906971H1 (THYMNOT05)
3	19	2907954	THYMNOT05	2907954F6 (THYMNOT05), 2907954H1 (THYMNOT05), 2937706T6 (THYMFET02), SBJA01787F1, SANA03635F1
4	20	3083742	OVARTUN01	1309538F1 (COLNFET02), 1311438H1 (COLNFET02), 1338635H1 (COLNTUT03), 1389250H1 (EOSINOT01), 1696122H1 (COLNNOT23), 3083742H1 (OVARTUN01)
5	21	3407686	PROSTUS08	743840R1 (BRAITUT01), 828337H1 (PROSNOT06), 916098R1 (BRSTNOT04), 2201671F6 (SPLNFET02), 3205026F6 (PENCNOT03), 3407686F6 (PROSTUS08), 3407686H1 (PROSTUS08)
6	22	3472455	LUNGNOT27	2474766H1 (SMCANOT01), 3459307F6 (293TF1T01), 3472455F6 (LUNGNOT27), 3472455H1 (LUNGNOT27)
7	23	786873	PROSNOT05	786873H1 (PROSNOT05), 786873R1 (PROSNOT05), 1381246F1 (BRAITUT08), 1480352F1 (CORPNOT02), 2121218F6 (BRSTNOT07), 2759368H1 (THP1AZS08), 4864701H1 (PROSTUT09)
8	24	1220371	NEUTGMT01	474976H1 (MMLR2DT01), 522893R6 (MMLR2DT01), 1220371H1 (NEUTGMT01), 1220371R6 (NEUTGMT01), 2925805H1 (SININOT04)
9	25	1258785	MENITUT03	571567R6 (OVARNON01), 1258785H1 (MENITUT03), 1345270F6 (PROSNOT11), 2653626H1 (THYMNOT04), SAYA00466F1, SBAA02409F1, SBAA00792F1
10	26	1361202	LUNGNOT12	1361202H1 (LUNGNOT12), 1736792H1 (COLNNOT22), 1848713F6 (LUNGFET03), 2344578F6 (TESTTUT02), 2908730H1 (THYMNOT05)

Table 1 cont.

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
11	27	2132846	OVARNOT03	1268283F6 (BRAINOT09), 1287786F6 (BRAINOT11), 1416687H1 (BRAINOT12), 1800269F6 (COLNNOT27), 2132846H1 (OVARNOT03), 2132846R6 (OVARNOT03), 2180358H1 (SININOT01), 2839252F6 (DRGLNOT01), 3245166F6 (BRAINOT19)
12	28	2539294	BONRTUT01	000688F1 (U937NOT01), 1266918F1 (BRAINOT09), 1309032F1 (COLNFET02), 1648603F6 (PROSTUT09), 2539294H1 (BONRTUT01), 2888478H1 (LUNGFET04), 4161042H1 (BRSTNOT32)
13	29	2589371	LUNGNOT22	293369R6 (LIVERNOT04), 1240395H1 (LUNGTUT02), 2589371F6 (LUNGNOT22), 2589371H1 (LUNGNOT22), 2852891F6 (BRSTTUT13)
14	30	2656082	THYMNOT04	1603501F6 (LUNGNOT15), 1879528T6 (LEUKNOT03), 1909038F6 (CONNTUT01), 2656082F6 (THYMNOT04), 2656082H1 (THYMNOT04)
15	31	2762182	BRAINOS12	943491R6 (ADRENOT03), 943491T6 (ADRENOT03), 1857150F6 (PROSNOT18), 2466534H1 (THYRNOT08), 2762182H1 (BRAINOS12), 2839252F6 (DRGLNOT01)
16	32	3140659	SMCCNOT02	3140659H1 (SMCCNOT02), 3117812F6 (LUNGTUT13), 264721H1 (HNT2AGT01), 1555673T1 (BLADTUT04), 1987832R6 (LUNGAST01), 3522161H1 (ESOGTUN01), 2506012H1 (CONUTUT01), 2237543H1 (PANCTTUT02), 1728672F6 (PROSNOT14), 1478128F1 and 1478128T1 (CORENOT02)

Table 2

Protein SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Identification	Analytical Methods
1	345	S32 T164 S183 T190 S270 S243 S343	N236		T-cell receptor beta (GI 1100182)	BLAST PFAM BLOCKS
2	487	S3 S183 T149 S235			P2Y Purinoceptor	PRINTS
3	312	S26 S37 T95 S114 T131 S150 T157 S210 S237 S310 Y109	N203		T-cell receptor beta (GI 1100182)	BLAST PFAM BLOCKS
4	309	S79 T98 S129 S165 S191 T212 T238 T253 T261	N2	G protein-coupled receptor: M102-V118	G protein-coupled receptor (GI 1753101)	BLAST PFAM BLOCKS PRINTS PROFILES CAN
5	367	T45 T61 T68 S154	N36 N41 N51 N66 N84 N104 N107 N166		Cystinosin (GI 3036840)	BLAST
6	386	S13 S77 S87 T126 T133 S145 T157 T173 T189 S231 S263 S281 S291 S310 T345 T352 T361 S369	N127 N182 N277	ATP/GTP binding site motif: A185-T192 TNFR/NGFR cysteine- rich region: C99-C180	TRAIL receptor 2 (GI 2529563)	BLAST PFAM

Table 2 cont.

Protein SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Identification	Analytical Methods
7	346	S57 S288 T84 S161	N4	Y223-G243 G135-V153	putative seven pass transmembrane protein	BLAST HMM MOTIFS
8	241	S198 S85 T91 T109 S124 S222 S236 T48 S193	N111 N226	Ig-like domain: H44-I120	DORA protein	BLAST MOTIFS PFAM
9	450	T146 T55 S167 T218 S239 T284 S416 S6 T136 S234 T245 T314 T436 S446 S447 Y125 Y343 Y389 Y415	N312	A230-T237	seven transmembrane domain protein	BLAST MOTIFS
10	269	S19 S31 S43 S72 T154 T176 S221 S18 S78 S89 T125 S146 T173 S194 T263	N41 N82 N161 N195 N206 N242	Signal peptide: M1-S19 Ig-like domain: G35-V111	T-cell receptor alpha	BLAST PFAM MOTIFS HMM
11	190	T23 T96 T117 T165 S173 S184 T17 T92		F22-G41 V68-L89 R102-M121 T92-D111 G114-V132	Recoverin	BLAST MOTIFS BLOCKS PRINTS PFAM
12	450	T199 T282 S2 S24 S114 T141 T331 T429 S108 T121 S277 Y172	N106 N340		thyroid receptor interacting protein	BLAST MOTIFS

Table 2 cont.

Protein SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Identification	Analytical Methods
13	240	S235 S151 T192 T15 S105 S109		T46-A69 V179-L198	IgE receptor beta subunit	BLAST MOTIFS HMM
14	316	S314 S69 T135 S154 S241 T26 T35 S39 S57 T161 S214	N76 N89 N207	Signal peptide: M1-G22 Ig-like domain: T35-S112 T161-V235 Transmembrane: Y286-M306	T-cell receptor beta	BLAST MOTIFS SigPept PFAM HMM
15	172	T3 T5 T78 T99 T147 S155 S166 T74		I4-G23, L120-F135 V50-L71, L146-S166 T74-D93 G96-V114	Recoverin	BLAST MOTIFS BLOCKS PRINTS PFAM
16	364	T11 S87 S156 T218 T225 T255 T256 S294 S313 S342 T343 T143 S210 T265	N253	I231-T243 I37-F55 Y185-V204	Opsin receptor	PRINTS MOTIFS HMM

Table 3

Nucleotide SEQ ID NO:	Selected Fragments of Nucleic Acid Sequence	Tissue Expression (Fraction of Total)	Disease Class (Fraction of Total)	Vector
17		Hematopoietic/Immune (0.333) Gastrointestinal (0.217) Reproductive (0.130)	Inflammation (0.449) Cancer (0.333) Trauma (0.130)	pINCY
18		Reproductive (0.241) Gastrointestinal (0.177) Nervous (0.139)	Cancer (0.481) Inflammation (0.228) Fetal (0.215)	pINCY
19		Hematopoietic/Immune (0.314) Gastrointestinal (0.229) Reproductive (0.129)	Inflammation (0.429) Cancer (0.357) Trauma (0.129)	pINCY
20		Hematopoietic/Immune (0.333) Reproductive (0.333) Gastrointestinal (0.222)	Cancer (0.333) Inflammation (0.333) Fetal (0.111)	PSPORT1
21		Reproductive (0.421) Nervous (0.158) Cardiovascular (0.105)	Cancer (0.474) Inflammation (0.263) Fetal (0.105)	PT7T3
22		Musculoskeletal (0.500) Cardiovascular (0.250) Urologic (0.250)	Fetal (0.500) Cancer (0.250) Inflammation (0.250)	pINCY
23	1105-1149	Reproductive (0.324) Nervous (0.297) Hematopoietic/Immune (0.135)	Cell proliferation (0.676) Inflammation (0.216)	PSPORT1
24	341-385	Hematopoietic/Immune (0.444) Gastrointestinal (0.222) Reproductive (0.111)	Inflammation (0.611) Cell proliferation (0.278)	PSPORT

Table 3 cont.

Nucleotide SEQ ID NO:	Selected Fragments of Nucleic Acid Sequence	Tissue Expression (Fraction of Total)	Disease Class (Fraction of Total)	Vector
25	575-619	Nervous (0.292) Reproductive (0.292) Cardiovascular (0.125)	Cell proliferation (0.792)	pINCY
26	921-956	Hematopoietic/Immune (0.286) Gastrointestinal (0.224) Reproductive (0.184)	Cell proliferation (0.511) Inflammation (0.367)	pINCY
27	15-61	Nervous (0.333) Reproductive (0.167) Cardiovascular (0.111)	Cell proliferation (0.500) Inflammation (0.333)	PSPORT1
28	389-433	Reproductive (0.237) Nervous (0.186) Hematopoietic/Immune (0.124)	Cell proliferation (0.660) Inflammation (0.309)	pINCY
29	125-172	Hematopoietic/Immune (0.306) Gastrointestinal (0.167) Reproductive (0.167)	Cell proliferation (0.583) Inflammation (0.333)	pINCY
30	435-479	Hematopoietic/Immune (0.310) Gastrointestinal (0.225) Reproductive (0.127)	Cell proliferation (0.465) Inflammation (0.437)	pINCY
31	151-194	Nervous (0.357) Endocrine (0.143) Cardiovascular (0.107)	Cell proliferation (0.428) Inflammation (0.393)	PSPORT1
32	659-703	Nervous (0.207) Cardiovascular (0.195) Reproductive (0.171)	Cell proliferation (0.671) Inflammation (0.220)	pINCY

Table 4

Nucleotide SEQ ID NO:	Clone ID	Library	Library Comment
17	1877651	LEUKNOT03	Library was constructed using RNA isolated from white blood cells of a 27-year-old female with blood type A+. The donor tested negative for cytomegalovirus (CMV).
18	2906971	THYMNOT05	Library was constructed using RNA isolated from thymus tissue removed from a 3-year-old Hispanic male during a thymectomy and closure of a patent ductus arteriosus.
19	2907954	THYMNOT05	Library was constructed using RNA isolated from thymus tissue removed from a 3-year-old Hispanic male during a thymectomy and closure of a patent ductus arteriosus.
20	3083742	OVARTUN01	Normalized library was constructed from 5.36 million independent clones obtained from an ovarian tumor library. RNA was isolated from tumor tissue removed from the left ovary of a 58-year-old Caucasian female during a total abdominal hysterectomy, removal of a single ovary, and inguinal hernia repair. Pathology indicated a metastatic grade 3 adenocarcinoma of colonic origin, forming a partially cystic and necrotic tumor mass in the left ovary, and a nodule in the left mesovarium. Patient history included follicular ovarian cyst. The normalization and hybridization conditions were adapted from Soares et al. (PNAS (1994) 91:9928) and Bonaldo et al. (Genome Research (1996) 6:791).

Table 4 cont.

Nucleotide SEQ ID NO:	Clone ID	Library	Library Comment
21	3407686	PROSTUS08	Subtracted prostate tumor library was constructed using 2.36 million clones from a prostate tumor library and was subjected to one round of subtractive hybridization with 448,000 clones from a normal prostate library. The starting library for subtraction was constructed using RNA isolated from a prostate tumor removed from a 59-year-old Caucasian male during a radical prostatectomy with regional lymph node excision. Pathology indicated adenocarcinoma (Gleason grade 3+3) Adenofibromatous hyperplasia was present. The patient presented with elevated prostate-specific antigen (PSA). Patient history included colon diverticuli. Subtractive hybridization conditions were based on the methodologies of Swaroop et al., NAR (1991) 19:1954 and Bonaldo, et al. Genome Research (1996) 6:791.
22	3472455	LUNGNOT27	Library was constructed using RNA isolated from lung tissue removed from a 17-year-old Hispanic female.
23	786873	PROSNOT05	Library was constructed using RNA isolated from diseased prostate tissue removed from a 67-year-old Caucasian male during radical prostatectomy and lymph node biopsy. This library, originally prepared as an unaffected section from the diseased prostate, has been determined to contain some tumor cells. Pathology indicated adenofibromatous hyperplasia was present. Pathology for the associated tumor tissue indicated adenocarcinoma Gleason grade 3+3. Patient history included coronary artery disease, stomach ulcer, and osteoarthritis. Family history included congestive heart failure.
24	1220371	NEUTGMT01	Library was constructed using RNA isolated from peripheral blood granulocytes collected by density gradient centrifugation through Ficoll-Hypaque. The cells were isolated from buffy coat units obtained from 20 unrelated male and female donors. Cells were cultured in 10 nM GM-CSF for 1 hour before washing and harvesting for total RNA preparation.

Table 4 cont.

Nucleotide SEQ ID NO:	Clone ID	Library	Library Comment
25	1258785	MENITUT03	Library was constructed using RNA isolated from brain meningioma tissue removed from a 35-year-old Caucasian female during excision of a cerebral meningeal lesion. Pathology indicated a benign neoplasm in the right cerebellopontine angle of the brain. Patient history included hypothyroidism. Family history included myocardial infarction and breast cancer.
26	1361202	LUNGNOT12	Library was constructed using RNA isolated from lung tissue removed from a 78-year-old Caucasian male during a segmental lung resection and regional lymph node resection. Pathology for the associated tumor tissue indicated an invasive pulmonary grade 3 adenocarcinoma. Patient history included cerebrovascular disease, arteriosclerotic coronary artery disease, thrombophlebitis, chronic obstructive pulmonary disease, and asthma. Family history included intracranial hematoma, cerebrovascular disease, arteriosclerotic coronary artery disease, and type I diabetes.
27	2132846	OVARNOT03	Library was constructed using RNA isolated from ovarian tissue removed from a 43-year-old Caucasian female during removal of the fallopian tubes and ovaries. Pathology for the associated tumor tissue indicated grade 2 mucinous cystadenocarcinoma. Patient history included mitral valve disorder, pneumonia, and viral hepatitis. Family history included atherosclerotic coronary artery disease, pancreatic cancer, stress reaction, cerebrovascular disease, breast cancer, and uterine cancer.
28	2539294	BONRTUT01	Library was constructed using RNA isolated from rib tumor tissue removed from a 16-year-old Caucasian male during a rib osteotomy and a wedge resection of the lung. Pathology indicated a metastatic grade 3 (of 4) osteosarcoma, forming a mass involving the chest wall.

Table 4 cont.

Nucleotide SEQ ID NO:	Clone ID	Library	Library Comment
29	2589371	LUNGNOT22	Library was constructed using RNA isolated from lung tissue removed from a 58-year-old Caucasian female. The tissue sample used to construct this library was found to have tumor contaminant upon microscopic examination. Pathology for the associated tumor tissue indicated a caseating granuloma. Family history included congestive heart failure, breast cancer, secondary bone cancer, acute myocardial infarction, and atherosclerotic coronary artery disease.
30	2656082	THYMNOT04	Library was constructed using RNA isolated from thymus tissue removed from a 3-year-old Caucasian male who died from anoxia.
31	2762182	BRAINOS12	Library was constructed from 4.9 million clones from a brain library by subtraction of abundantly expressed clone pools. RNA was made from brain tissue removed from a 26-year-old Caucasian male during cranioplasty and excision of a cerebral meningeal lesion. Pathology for the associated tumor tissue indicated a grade 4 oligoastrocytoma in the right fronto-parietal part of the brain.
32	3140659	SMCCNOT02	Library was constructed using RNA isolated from smooth muscle cells removed from the coronary artery of a 3-year-old Caucasian male. The cells were treated with TNF alpha and interleukin-1 beta for 20 hours.

Table 5

Program	Description	Reference	Parameter Threshold
ABI FACTURA	A program that removes vector sequences and masks ambiguous bases in nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
ABI/PARACEL FDF	A Fast Data Finder useful in comparing and annotating amino acid or nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA; Paracel Inc., Pasadena, CA.	Mismatch <50%
ABI AutoAssembler	A program that assembles nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
BLAST	A Basic Local Alignment Search Tool useful in sequence similarity search for amino acid and nucleic acid sequences. BLAST includes five functions: blastp, blastn, blastx, tblastn, and tblastx.	Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410; Altschul, S.F. et al. (1997) Nucleic Acids Res. 25: 3389-3402.	ESTs: Probability value= 1.0E-8 or less Full Length sequences: Probability value= 1.0E-10 or less
FASTA	A Pearson and Lipman algorithm that searches for similarity between a query sequence and a group of sequences of the same type. FASTA comprises at least five functions: fasta, tfasta, fastx, tfastx, and ssearch.	Pearson, W.R. and D.J. Lipman (1988) Proc. Natl. Acad. Sci. 85:2444-2448; Pearson, W.R. (1990) Methods Enzymol. 183: 63-98; and Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489.	ESTs: fasta E value=1.06E-6 Assembled ESTs: fasta Identity= 95% or greater and Match length=200 bases or greater; fasta E value=1.0E-8 or less Full Length sequences: fasta score=100 or greater
BLIMPS	A BLocks IMProved Searcher that matches a sequence against those in BLOCKS and PRINTS databases to search for gene families, sequence homology, and structural fingerprint regions.	Henikoff, S. and J.G. Henikoff, Nucl. Acid Res., 19:6565-72, 1991. J.G. Henikoff and S. Henikoff (1996) Methods Enzymol. 266:88-105; and Attwood, T.K. et al. (1997) J. Chem. Inf. Comput. Sci. 37: 417-424.	Score=1000 or greater; Ratio of Score/Strength = 0.75 or larger; and Probability value= 1.0E-3 or less
PFAM	A Hidden Markov Models-based application useful for protein family search.	Krogh, A. et al. (1994) J. Mol. Biol., 235:1501-1531; Sonnhammer, E.L.L. et al. (1988) Nucleic Acids Res. 26:320-322.	Score=10-50 bits, depending on individual protein families

Table 5 cont.

Program	Description	Reference	Parameter Threshold
ProfileScan	An algorithm that searches for structural and sequence motifs in protein sequences that match sequence patterns defined in Prosite.	Gribskov, M. et al. (1988) CABIOS 4:61-66; Gribskov, et al. (1989) Methods Enzymol. 183:146-159; Bairoch, A. et al. (1997) Nucleic Acids Res. 25: 217-221.	Score= 4.0 or greater
Phred	A base-calling algorithm that examines automated sequencer traces with high sensitivity and probability.	Ewing, B. et al. (1998) Genome Res. 8:175-185; Ewing, B. and P. Green (1998) Genome Res. 8:186-194.	
Phrap	A Phils Revised Assembly Program including SWAT and CrossMatch, programs based on efficient implementation of the Smith-Waterman algorithm, useful in searching sequence homology and assembling DNA sequences.	Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489; Smith, T.F. and M. S. Waterman (1981) J. Mol. Biol. 147:195-197; and Green, P., University of Washington, Seattle, WA.	Score= 120 or greater; Match length= 56 or greater
Consed	A graphical tool for viewing and editing Phrap assemblies	Gordon, D. et al. (1998) Genome Res. 8:195-202.	
SPScan	A weight matrix analysis program that scans protein sequences for the presence of secretory signal peptides.	Nielson, H. et al. (1997) Protein Engineering 10:1-6; Claverie, J.M. and S. Audic (1997) CABIOS 12: 431-439.	Score=5 or greater
Motifs	A program that searches amino acid sequences for patterns that matched those defined in Prosite.	Bairoch et al. <u>supra</u> ; Wisconsin Package Program Manual, version 9, page M51-59, Genetics Computer Group, Madison, WI.	

What is claimed is:

1. A substantially purified polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, and fragments thereof.
2. A substantially purified variant having at least 90% amino acid sequence identity to the amino acid sequence of claim 1.
3. An isolated and purified polynucleotide encoding the polypeptide of claim 1.
4. An isolated and purified polynucleotide variant having at least 70% polynucleotide sequence identity to the polynucleotide of claim 3.
5. An isolated and purified polynucleotide which hybridizes under stringent conditions to the polynucleotide of claim 3.
6. An isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide of claim 3.
7. A method for detecting a polynucleotide, the method comprising the steps of:
 - (a) hybridizing the polynucleotide of claim 6 to at least one nucleic acid in a sample, thereby forming a hybridization complex; and
 - (b) detecting the hybridization complex, wherein the presence of the hybridization complex correlates with the presence of the polynucleotide in the sample.
8. The method of claim 7 further comprising amplifying the polynucleotide prior to hybridization.
9. An isolated and purified polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:17-32 and fragments thereof.
10. An isolated and purified polynucleotide variant having at least 90% polynucleotide sequence identity to the polynucleotide of claim 9.
11. An isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide of claim 9.
12. An expression vector comprising at least a fragment of the polynucleotide of claim 3.
13. A host cell comprising the expression vector of claim 12.
14. A method for producing a polypeptide, the method comprising the steps of:
 - a) culturing the host cell of claim 13 under conditions suitable for the expression of the polypeptide; and

b) recovering the polypeptide from the host cell culture.

15. A pharmaceutical composition comprising the polypeptide of claim 1 in conjunction with a suitable pharmaceutical carrier.

16. A purified antibody which specifically binds to the polypeptide of claim 1.

5 17. A purified agonist of the polypeptide of claim 1.

18. A purified antagonist of the polypeptide of claim 1.

19. A method for treating or preventing a disorder associated with decreased expression or activity of HRAP, the method comprising administering to a subject in need of such treatment an effective amount of the pharmaceutical composition of claim 15.

10 20. A method for treating or preventing a disorder associated with increased expression or activity of HRAP, the method comprising administering to a subject in need of such treatment an effective amount of the antagonist of claim 18.

SEQUENCE LISTING

<110> INCYTE PHARMACEUTICALS, INC.

HILLMAN, Jennifer L.

YUE, Henry

LAL, Preeti

TANG, Y. Tom

GORGONE, Gina A.

GUEGLER, Karl J.

CORLEY, Neil C.

BAUGHN, Mariah R.

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Tyr	Met	Asn	Phe	Tyr	Tyr	Lys	Ser	Thr	Glu	Gly	Trp	Ser	Ile	Gly	290	295	300	
Asn	Val	Leu	Leu	Asp	Phe	Thr	Gly	Gly	Ser	Phe	Ser	Leu	Leu	Gln	305	310	315	
Met	Phe	Leu	Gln	Ser	Tyr	Asn	Asn	Asp	Gln	Trp	Thr	Leu	Ile	Phe	320	325	330	
Gly	Asp	Pro	Thr	Lys	Phe	Gly	Leu	Gly	Val	Phe	Ser	Ile	Val	Phe	335	340	345	
Asp	Val	Val	Phe	Phe	Ile	Gln	His	Phe	Cys	Leu	Tyr	Arg	Lys	Arg	350	355	360	
Pro	Gly	Tyr	Asp	Gln	Leu	Asn									365			

<210> 6
 <211> 386
 <212> PRT
 <213> Homo sapiens

 <220>
 <221> misc_feature
 <223> Incyte Clone No: 3472455

<400> 6
 Met Gly Leu Trp Gly Gln Ser Val Pro Thr Ala Ser Ser Ala Arg
 1 5 10 15
 Ala Gly Arg Tyr Pro Gly Ala Arg Thr Ala Ser Gly Thr Arg Pro
 20 25 30
 Trp Leu Leu Asp Pro Lys Ile Leu Lys Phe Val Val Phe Ile Val
 35 40 45
 Ala Val Leu Leu Pro Val Arg Val Asp Ser Ala Thr Ile Pro Arg
 50 55 60
 Gln Asp Glu Val Pro Gln Gln Thr Val Ala Pro Gln Gln Gln Arg
 65 70 75
 Arg Ser Leu Lys Glu Glu Glu Cys Pro Ala Gly Ser His Arg Ser
 80 85 90
 Glu Tyr Thr Gly Ala Cys Asn Pro Cys Thr Glu Gly Val Asp Tyr
 95 100 105
 Thr Ile Ala Ser Asn Asn Leu Pro Ser Cys Leu Leu Cys Thr Val
 110 115 120
 Cys Lys Ser Gly Gln Thr Asn Lys Ser Ser Cys Thr Thr Thr Arg
 125 130 135
 Asp Thr Val Cys Gln Cys Glu Lys Gly Ser Phe Gln Asp Lys Asn
 140 145 150
 Ser Pro Glu Met Cys Arg Thr Cys Arg Thr Gly Cys Pro Arg Gly
 155 160 165
 Met Val Lys Val Ser Asn Cys Thr Pro Arg Ser Asp Ile Lys Cys
 170 175 180
 Lys Asn Glu Ser Ala Ala Ser Ser Thr Gly Lys Thr Pro Ala Ala
 185 190 195
 Glu Glu Thr Val Thr Thr Ile Leu Gly Met Leu Ala Ser Pro Tyr
 200 205 210
 His Tyr Leu Ile Ile Ile Val Val Leu Val Ile Ile Leu Ala Val
 215 220 225
 Val Val Val Gly Phe Ser Cys Arg Lys Lys Phe Ile Ser Tyr Leu
 230 235 240
 Lys Gly Ile Cys Ser Gly Gly Gly Gly Gly Pro Glu Arg Val His
 245 250 255
 Arg Val Leu Phe Arg Arg Arg Ser Cys Pro Ser Arg Val Pro Gly
 260 265 270
 Ala Glu Asp Asn Ala Arg Asn Glu Thr Leu Ser Asn Arg Tyr Leu
 275 280 285
 Gln Pro Thr Gln Val Ser Glu Gln Glu Ile Gln Gly Gln Glu Leu
 290 295 300
 Ala Glu Leu Thr Gly Val Thr Val Glu Ser Pro Glu Glu Pro Gln
 305 310 315
 Arg Leu Leu Glu Gln Ala Glu Ala Glu Gly Cys Gln Arg Arg Arg
 320 325 330
 Leu Leu Val Pro Val Asn Asp Ala Asp Ser Ala Asp Ile Ser Thr
 335 340 345
 Leu Leu Asp Ala Ser Ala Thr Leu Glu Glu Gly His Ala Lys Glu

				350					355					360
Thr	Ile	Gln	Asp	Gln	Leu	Val	Gly	Ser	Glu	Lys	Leu	Phe	Tyr	Glu
				365					370					375
Glu	Asp	Glu	Ala	Gly	Ser	Ala	Thr	Ser	Cys	Leu				
				380					385					

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<210> 7
<211> 346
<212> PRT
<213> Homo sapiens
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<220>
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<223> Incyte Clone No: 786873
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<400> 7															
Met	Glu	Ser	Asn	Leu	Ser	Gly	Leu	Val	Pro	Ala	Ala	Gly	Leu	Val	
1				5					10					15	
Pro	Ala	Leu	Pro	Pro	Ala	Val	Thr	Leu	Gly	Leu	Thr	Ala	Ala	Tyr	
				20					25					30	
Thr	Thr	Leu	Tyr	Ala	Leu	Leu	Phe	Phe	Ser	Val	Tyr	Ala	Gln	Leu	
				35					40					45	
Trp	Leu	Val	Leu	Leu	Tyr	Gly	His	Lys	Arg	Leu	Ser	Tyr	Gln	Thr	
				50					55					60	
Val	Phe	Leu	Ala	Leu	Cys	Leu	Leu	Trp	Ala	Ala	Leu	Arg	Thr	Thr	
				65					70					75	
Leu	Phe	Ser	Phe	Tyr	Phe	Arg	Asp	Thr	Pro	Arg	Ala	Asn	Arg	Leu	
				80					85					90	
Gly	Pro	Leu	Pro	Phe	Trp	Leu	Leu	Tyr	Cys	Cys	Pro	Val	Cys	Leu	
				95					100					105	
Gln	Phe	Phe	Thr	Leu	Thr	Leu	Met	Asn	Leu	Tyr	Phe	Ala	Gln	Val	
				110					115					120	
Val	Phe	Lys	Ala	Lys	Val	Lys	Arg	Arg	Pro	Glu	Met	Ser	Arg	Gly	
				125					130					135	
Leu	Leu	Ala	Val	Arg	Gly	Ala	Phe	Val	Gly	Ala	Ser	Leu	Leu	Phe	
				140					145					150	
Leu	Leu	Val	Asn	Val	Leu	Cys	Ala	Val	Leu	Ser	His	Arg	Arg	Arg	
				155					160					165	
Ala	Gln	Pro	Trp	Ala	Leu	Leu	Leu	Val	Arg	Val	Leu	Val	Ser	Asp	
				170					175					180	
Ser	Leu	Phe	Val	Ile	Cys	Ala	Leu	Ser	Leu	Ala	Ala	Cys	Leu	Cys	
				185					190					195	
Leu	Val	Ala	Arg	Arg	Ala	Pro	Ser	Thr	Ser	Ile	Tyr	Leu	Glu	Ala	
				200					205					210	
Lys	Ala	Asp	Leu	Val	Asn	Asp	Leu	Gly	Asn	Lys	Gly	Tyr	Leu	Val	
				215					220					225	
Phe	Gly	Leu	Ile	Leu	Phe	Val	Trp	Glu	Leu	Leu	Pro	Thr	Thr	Leu	
				230					235					240	
Leu	Val	Gly	Phe	Phe	Arg	Val	His	Arg	Pro	Pro	Gln	Asp	Leu	Ser	
				245					250					255	
Thr	Ser	His	Ile	Leu	Asn	Gly	Gln	Val	Phe	Ala	Ser	Arg	Ser	Tyr	
				260					265					270	
Phe	Phe	Asp	Arg	Ala	Gly	His	Cys	Glu	Asp	Glu	Gly	Cys	Ser	Trp	
				275					280					285	

Glu	His	Ser	Arg	Gly	Glu	Ser	Thr	Ser	Met	Ser	Gly	Ser	Leu	Gly
				290					295					300
Ser	Gly	Ser	Trp	Tyr	Gly	Ala	Ile	Gly	Arg	Glu	Pro	Gly	Trp	Tyr
				305					310					315
Gly	Gly	Ser	Gln	Thr	Lys	Thr	Thr	Pro	Leu	Leu	Phe	Ser	Gln	Val
				320					325					330
Pro	Gly	Pro	Gly	Gly	His	His	His	Ser	Leu	Tyr	Ser	Thr	Pro	Gln
				335					340					345

Thr

<210> 8

<211> 241

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone No: 1220371

<400> 8

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

Pro

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<210> 9
<211> 450
<212> PRT
<213> Homo sapiens
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<220>  
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<223> Incyte Clone No: 1258785
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<400> 9															
Met	Gly	Glu	Thr	Met	Ser	Lys	Arg	Leu	Lys	Leu	His	Leu	Gly	Gly	
1				5					10					15	
Glu	Ala	Glu	Met	Glu	Glu	Arg	Ala	Phe	Val	Asn	Pro	Phe	Pro	Asp	
				20					25					30	
Tyr	Glu	Ala	Ala	Ala	Gly	Ala	Leu	Leu	Ala	Ser	Gly	Ala	Ala	Glu	
				35					40					45	
Glu	Thr	Gly	Cys	Val	Arg	Pro	Pro	Ala	Thr	Thr	Asp	Glu	Pro	Gly	
				50					55					60	
Leu	Pro	Phe	His	Gln	Asp	Gly	Lys	Ile	Ile	His	Asn	Phe	Ile	Arg	
				65					70					75	
Arg	Ile	Gln	Thr	Lys	Ile	Lys	Asp	Leu	Leu	Gln	Gln	Met	Glu	Glu	
				80					85					90	
Gly	Leu	Lys	Thr	Ala	Asp	Pro	His	Asp	Cys	Ser	Ala	Tyr	Thr	Gly	
				95					100					105	
Trp	Thr	Gly	Ile	Ala	Leu	Leu	Tyr	Leu	Gln	Leu	Tyr	Arg	Val	Thr	
				110					115					120	
Cys	Asp	Gln	Thr	Tyr	Leu	Leu	Arg	Ser	Leu	Asp	Tyr	Val	Lys	Arg	
				125					130					135	
Thr	Leu	Arg	Asn	Leu	Asn	Gly	Arg	Arg	Val	Thr	Phe	Leu	Cys	Gly	
				140					145					150	
Asp	Ala	Gly	Pro	Leu	Ala	Val	Gly	Ala	Val	Ile	Tyr	His	Lys	Leu	
				155					160					165	
Arg	Ser	Asp	Cys	Glu	Ser	Gln	Glu	Cys	Val	Thr	Lys	Leu	Leu	Gln	
				170					175					180	
Leu	Gln	Arg	Ser	Val	Val	Cys	Gln	Glu	Ser	Asp	Leu	Pro	Asp	Glu	
				185					190					195	
Leu	Leu	Tyr	Gly	Arg	Ala	Gly	Tyr	Leu	Tyr	Ala	Leu	Leu	Tyr	Leu	
				200					205					210	
Asn	Thr	Glu	Ile	Gly	Pro	Gly	Thr	Val	Cys	Glu	Ser	Ala	Ile	Lys	
				215					220					225	
Glu	Val	Val	Asn	Ala	Ile	Ile	Glu	Ser	Gly	Lys	Thr	Leu	Ser	Arg	
				230					235					240	
Glu	Glu	Arg	Lys	Thr	Glu	Arg	Cys	Pro	Leu	Leu	Tyr	Gln	Trp	His	
				245					250					255	
Arg	Lys	Gln	Tyr	Val	Gly	Ala	Ala	His	Gly	Met	Ala	Gly	Ile	Tyr	
				260					265					270	
Tyr	Met	Leu	Met	Gln	Pro	Ala	Ala	Lys	Val	Asp	Gln	Glu	Thr	Leu	
				275					280					285	
Thr	Glu	Met	Val	Lys	Pro	Ser	Ile	Asp	Tyr	Val	Arg	His	Lys	Lys	
				290					295					300	
Phe	Arg	Ser	Gly	Asn	Tyr	Pro	Ser	Ser	Leu	Ser	Asn	Glu	Thr	Asp	
				305					310					315	
Arg	Leu	Val	His	Trp	Cys	His	Gly	Ala	Pro	Gly	Val	Ile	His	Met	
				320					325					330	
Leu	Met	Gln	Ala	Tyr	Lys	Val	Phe	Lys	Glu	Glu	Lys	Tyr			

	335		340		345
Glu Ala Met Glu Cys Ser Asp Val Ile Trp Gln Arg Gly Leu Leu					
	350		355		360
Arg Lys Gly Tyr Gly Ile Cys His Gly Thr Ala Gly Asn Gly Tyr					
	365		370		375
Ser Phe Leu Ser Leu Tyr Arg Leu Thr Gln Asp Lys Lys Tyr Leu					
	380		385		390
Tyr Arg Ala Cys Lys Phe Ala Glu Trp Cys Leu Asp Tyr Gly Ala					
	395		400		405
His Gly Cys Arg Ile Pro Asp Arg Pro Tyr Ser Leu Phe Glu Gly					
	410		415		420
Met Ala Gly Ala Ile His Phe Leu Ser Asp Val Leu Gly Pro Glu					
	425		430		435
Thr Ser Arg Phe Pro Ala Phe Glu Leu Asp Ser Ser Lys Arg Asp					
	440		445		450

<210> 10

<211> 269

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone No: 1361202

<400> 10

Met Glu Thr Leu Leu Gly Leu Leu Ile Leu Trp Leu Gln Leu Gln					
1	5		10		15
Trp Val Ser Ser Lys Gln Glu Val Thr Gln Ile Pro Ala Ala Leu					
	20		25		30
Ser Val Pro Glu Gly Glu Asn Leu Val Leu Asn Cys Ser Phe Thr					
	35		40		45
Asp Ser Ala Ile Tyr Asn Leu Gln Trp Phe Arg Gln Asp Pro Gly					
	50		55		60
Lys Gly Leu Thr Ser Leu Leu Leu Ile Gln Ser Ser Gln Arg Glu					
	65		70		75
Gln Thr Ser Gly Arg Leu Asn Ala Ser Leu Asp Lys Ser Ser Gly					
	80		85		90
Arg Ser Thr Leu Tyr Ile Ala Ala Ser Gln Pro Gly Asp Ser Ala					
	95		100		105
Thr Tyr Leu Cys Ala Val Arg Asp Asn Asp Met Arg Phe Gly Ala					
	110		115		120
Gly Thr Arg Leu Thr Val Lys Pro Asn Ile Gln Asn Pro Asp Pro					
	125		130		135
Ala Val Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val					
	140		145		150
Cys Leu Phe Thr Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser					
	155		160		165
Lys Asp Ser Asp Val Tyr Ile Thr Asp Lys Thr Val Leu Asp Met					
	170		175		180
Arg Ser Met Asp Phe Lys Ser Asn Ser Ala Val Ala Trp Ser Asn					
	185		190		195
Lys Ser Asp Phe Ala Cys Ala Asn Ala Phe Asn Asn Ser Ile Ile					
	200		205		210

Pro	Glu	Asp	Thr	Phe	Phe	Pro	Ser	Pro	Glu	Ser	Ser	Cys	Asp	Val
				215					220					225
Lys	Leu	Val	Glu	Lys	Ser	Phe	Glu	Thr	Asp	Thr	Asn	Leu	Asn	Phe
				230					235					240
Gln	Asn	Leu	Ser	Val	Ile	Gly	Phe	Arg	Ile	Leu	Leu	Leu	Lys	Val
				245					250					255
Ala	Gly	Phe	Asn	Leu	Leu	Met	Thr	Leu	Arg	Leu	Trp	Ser	Ser	
				260					265					

<210> 11
 <211> 190
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte Clone No: 2132846

<400> 11

Met	Gly	Lys	Ser	Asn	Ser	Lys	Leu	Thr	Pro	Glu	Val	Val	Glu	Glu
1				5					10					15
Leu	Thr	Arg	Lys	Thr	Tyr	Phe	Thr	Glu	Lys	Glu	Val	Gln	Gln	Trp
				20					25					30
Tyr	Lys	Gly	Phe	Ile	Lys	Asp	Cys	Pro	Ser	Gly	Gln	Leu	Asp	Ala
				35					40					45
Ala	Gly	Phe	Gln	Lys	Ile	Tyr	Lys	Gln	Phe	Phe	Pro	Phe	Gly	Asp
				50					55					60
Pro	Thr	Lys	Phe	Ala	Thr	Phe	Val	Phe	Asn	Val	Phe	Asp	Glu	Asn
				65					70					75
Lys	Asp	Gly	Arg	Ile	Glu	Phe	Ser	Glu	Phe	Ile	Gln	Ala	Leu	Ser
				80					85					90
Val	Thr	Ser	Arg	Gly	Thr	Leu	Asp	Glu	Lys	Leu	Arg	Trp	Ala	Phe
				95					100					105
Lys	Leu	Tyr	Asp	Leu	Asp	Asn	Asp	Gly	Tyr	Ile	Thr	Arg	Asn	Glu
				110					115					120
Met	Leu	Asp	Ile	Val	Asp	Ala	Ile	Tyr	Gln	Met	Val	Gly	Asn	Thr
				125					130					135
Val	Glu	Leu	Pro	Glu	Glu	Glu	Asn	Thr	Pro	Glu	Lys	Arg	Val	Asp
				140					145					150
Arg	Ile	Phe	Ala	Met	Met	Asp	Lys	Asn	Ala	Asp	Gly	Lys	Leu	Thr
				155					160					165
Leu	Gln	Glu	Phe	Gln	Glu	Gly	Ser	Lys	Ala	Asp	Pro	Ser	Ile	Val
				170					175					180
Gln	Ala	Leu	Ser	Leu	Tyr	Asp	Gly	Leu	Val					
				185					190					

<210> 12
 <211> 450
 <212> PRT
 <213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone No: 2539294

<400> 12

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

Asp	Val	Glu	Ser	Leu	Leu	Val	Gln	Cys	Ile	Leu	Asp	Asn	Thr	Ile	
				395					400					405	
His	Gly	Arg	Ile	Asp	Gln	Val	Asn	Gln	Leu	Leu	Glu	Leu	Asp	His	
				410					415					420	
Gln	Lys	Arg	Gly	Gly	Ala	Arg	Tyr	Thr	Ala	Leu	Asp	Lys	Trp	Thr	
				425					430					435	
Asn	Gln	Leu	Asn	Ser	Leu	Asn	Gln	Ala	Val	Val	Ser	Lys	Leu	Ala	
				440					445					450	

<210> 13

<211> 240

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone No: 2589371

<400> 13

Met	Leu	Leu	Gln	Ser	Gln	Thr	Met	Gly	Val	Ser	His	Ser	Phe	Thr	
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Pro	Lys	Gly	Ile	Thr	Ile	Pro	Gln	Arg	Glu	Lys	Pro	Gly	His	Met	
				20					25					30	
Tyr	Gln	Asn	Glu	Asp	Tyr	Leu	Gln	Asn	Gly	Leu	Pro	Thr	Glu	Thr	
				35					40					45	
Thr	Val	Leu	Gly	Thr	Val	Gln	Ile	Leu	Cys	Cys	Leu	Leu	Ile	Ser	
				50					55					60	
Ser	Leu	Gly	Ala	Ile	Leu	Val	Phe	Ala	Pro	Tyr	Pro	Ser	His	Phe	
				65					70					75	
Asn	Pro	Ala	Ile	Ser	Thr	Thr	Leu	Met	Ser	Gly	Tyr	Pro	Phe	Leu	
				80					85					90	
Gly	Ala	Leu	Cys	Phe	Gly	Ile	Thr	Gly	Ser	Leu	Ser	Ile	Ile	Ser	
				95					100					105	
Gly	Lys	Gln	Ser	Thr	Lys	Pro	Phe	Asp	Leu	Ser	Ser	Leu	Thr	Ser	
				110					115					120	
Asn	Ala	Val	Ser	Ser	Val	Thr	Ala	Gly	Ala	Gly	Leu	Phe	Leu	Leu	
				125					130					135	
Ala	Asp	Ser	Met	Val	Ala	Leu	Arg	Thr	Ala	Ser	Gln	His	Cys	Gly	
				140					145					150	
Ser	Glu	Met	Asp	Tyr	Leu	Ser	Ser	Leu	Pro	Tyr	Ser	Glu	Tyr	Tyr	
				155					160					165	
Tyr	Pro	Ile	Tyr	Glu	Ile	Lys	Asp	Cys	Leu	Leu	Thr	Ser	Val	Ser	
				170					175					180	
Leu	Thr	Gly	Val	Leu	Val	Val	Met	Leu	Ile	Phe	Thr	Val	Leu	Glu	
				185					190					195	
Leu	Leu	Leu	Ala	Ala	Tyr	Ser	Ser	Val	Phe	Trp	Trp	Lys	Gln	Leu	
				200					205					210	
Tyr	Ser	Asn	Asn	Pro	Gly	Ser	Ser	Phe	Ser	Ser	Thr	Gln	Ser	Gln	
				215					220					225	
Asp	His	Ile	Gln	Gln	Val	Lys	Lys	Ser	Ser	Ser	Arg	Ser	Trp	Ile	
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<210> 14
 <211> 316
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte Clone No: 2656082

<400> 14

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

<210> 15
 <211> 172
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte Clone No: 2762182

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 35 40 45
 Phe Ala Thr Phe Val Phe Asn Val Phe Asp Glu Asn Lys Asp Gly
 50 55 60
 Arg Ile Glu Phe Ser Glu Phe Ile Gln Ala Leu Ser Val Thr Ser
 65 70 75
 Arg Gly Thr Leu Asp Glu Lys Leu Arg Trp Ala Phe Lys Leu Tyr
 80 85 90
 Asp Leu Asp Asn Asp Gly Tyr Ile Thr Arg Asn Glu Met Leu Asp
 95 100 105
 Ile Val Asp Ala Ile Tyr Gln Met Val Gly Asn Thr Val Glu Leu
 110 115 120
 Pro Glu Glu Glu Asn Thr Pro Glu Lys Arg Val Asp Arg Ile Phe
 125 130 135
 Ala Met Met Asp Lys Asn Ala Asp Gly Lys Leu Thr Leu Gln Glu
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 Phe Gln Glu Gly Ser Lys Ala Asp Pro Ser Ile Val Gln Ala Leu
 155 160 165
 Ser Leu Tyr Asp Gly Leu Val
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<210> 16
 <211> 364
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte Clone No: 3140659

<400> 16
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 Met Ala Arg Gln Lys Gly Ile Phe Tyr Leu Thr Leu Phe Leu Ile
 35 40 45
 Leu Gly Thr Cys Thr Leu Phe Phe Ala Phe Glu Cys Arg Tyr Leu
 50 55 60
 Ala Val Gln Leu Ser Pro Ala Ile Pro Val Phe Ala Ala Met Leu

				65					70					75
Phe	Leu	Phe	Ser	Met	Ala	Thr	Leu	Leu	Arg	Thr	Ser	Phe	Ser	Asp
				80					85					90
Pro	Gly	Val	Ile	Pro	Arg	Ala	Leu	Pro	Asp	Glu	Ala	Ala	Phe	Ile
				95					100					105
Glu	Met	Glu	Ile	Glu	Ala	Thr	Asn	Gly	Ala	Val	Pro	Gln	Gly	Gln
				110					115					120
Arg	Pro	Pro	Pro	Arg	Ile	Lys	Asn	Phe	Gln	Ile	Asn	Asn	Gln	Ile
				125					130					135
Val	Lys	Leu	Lys	Tyr	Cys	Tyr	Thr	Cys	Lys	Ile	Phe	Arg	Pro	Pro
				140					145					150
Arg	Ala	Ser	His	Cys	Ser	Ile	Cys	Asp	Asn	Cys	Val	Glu	Arg	Phe
				155					160					165
Asp	His	His	Cys	Pro	Trp	Val	Gly	Asn	Cys	Val	Gly	Lys	Arg	Asn
				170					175					180
Tyr	Arg	Tyr	Phe	Tyr	Leu	Phe	Ile	Leu	Ser	Leu	Ser	Leu	Leu	Thr
				185					190					195
Ile	Tyr	Val	Phe	Ala	Phe	Asn	Ile	Val	Tyr	Val	Ala	Leu	Lys	Ser
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Leu	Lys	Ile	Gly	Phe	Leu	Glu	Thr	Leu	Lys	Glu	Thr	Pro	Gly	Thr
				215					220					225
Val	Leu	Glu	Val	Leu	Ile	Cys	Phe	Phe	Thr	Leu	Trp	Ser	Val	Val
				230					235					240
Gly	Leu	Thr	Gly	Phe	His	Thr	Phe	Leu	Val	Ala	Leu	Asn	Gln	Thr
				245					250					255
Thr	Asn	Glu	Asp	Ile	Lys	Gly	Ser	Trp	Thr	Gly	Lys	Asn	Arg	Val
				260					265					270
Gln	Asn	Pro	Tyr	Ser	His	Gly	Asn	Ile	Val	Lys	Asn	Cys	Cys	Glu
				275					280					285
Val	Leu	Cys	Gly	Pro	Leu	Pro	Pro	Ser	Val	Leu	Asp	Arg	Arg	Gly
				290					295					300
Ile	Leu	Pro	Leu	Glu	Glu	Ser	Gly	Ser	Arg	Pro	Pro	Ser	Thr	Gln
				305					310					315
Glu	Thr	Ser	Ser	Ser	Leu	Leu	Pro	Gln	Ser	Pro	Ala	Pro	Thr	Glu
				320					325					330
His	Leu	Asn	Ser	Asn	Glu	Met	Pro	Glu	Asp	Ser	Ser	Thr	Pro	Glu
				335					340					345
Glu	Met	Pro	Pro	Pro	Glu	Pro	Pro	Glu	Pro	Pro	Gln	Glu	Ala	Ala
				350					355					360
Glu	Ala	Glu	Lys											

<210> 17

<211> 1270

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone No: 1877651

<400> 17

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 ccagagtact ctgctgtgcg gtcattctgtc ttctgggggc aggtctctca aatgccggcg 180

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tcatgcagaa cccaagacac ctggtcagga ggaggggaca ggaggcaaga ctgagatgca 240
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aattcatggt ttatctccag aaagaaaata tcatagatga gtcaggaatg ccaaaggaac 360
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gaggagattc ggcagcttat ttctgtgcca gctcaccaca ttcgaagcag gctgagcagt 480
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<210> 18

<211> 2234

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone No: 2906971

<400> 18

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<210> 19

<211> 1552

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone No: 2907954

<400> 19

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tcccagatat aagattatag agaaaaggca gagtgtggct ttttggtgca atcctatatc 180
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<210> 20

<211> 1369

<212> DNA

<213> Homo sapiens

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<221> misc_feature

<223> Incyte Clone No: 3083742

<400> 20

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<210> 21

<211> 2096

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone No: 3407686

<400> 21

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<210> 22

<211> 1431

<212> DNA

<213> Homo sapiens

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<221> misc_feature

<223> Incyte Clone No: 3472455

<400> 22

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<210> 23

<211> 1788

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone No: 786873.

<400> 23

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<210> 24

<211> 1044

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone No: 1220371

<400> 24

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cactcatgag gccgtcacca taaagtgtac ctctctcgca accggatgcc cttctgagca 240
accaacatgc ctgtggtttc gctacgggtg tcaccagcct gagaacctgt gcttggacgg 300
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cctcactgta aacagagtga cttcaaatga cagtgcatt tacatctgtg gaatagcatt 420
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<210> 25

<211> 1605

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone No: 1258785

<400> 25

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<210> 26

<211> 1464

<212> DNA

<213> Homo sapiens

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 <221> misc_feature
 <223> Incyte Clone No: 1361202

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<210> 27
 <211> 960
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte Clone No: 2132846

<400> 27
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<210> 28

<211> 1990

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone No: 2539294

<400> 28

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<210> 29

<211> 1038

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone No: 2589371

<400> 29

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<210> 30

<211> 1260

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone No: 2656082

<400> 30

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<210> 31

<211> 1551

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone No: 2762182

<400> 31

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