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(54) Titre : PROTEINES DU METABOLISME DE L'ARN

(54) Title: RNA METABOLISM PROTEINS

(57) **Abrégé/Abstract:**

The invention provides human RNA metabolism proteins (RMEP) and polynucleotides which identify and encode RMEP. 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 aberrant expression of RMEP.

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(54) Title: RNA METABOLISM PROTEINS

(57) Abstract: The invention provides human RNA metabolism proteins (RMEP) and polynucleotides which identify and encode RMEP. 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 aberrant expression of RMEP.



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RNA METABOLISM PROTEINS

TECHNICAL FIELD

This invention relates to nucleic acid and amino acid sequences of RNA metabolism proteins
5 and to the use of these sequences in the diagnosis, treatment, and prevention of nervous system,
autoimmune/inflammatory, cell proliferative, and developmental disorders, and in the assessment of the
effects of exogenous compounds on the expression of nucleic acid and amino acid sequences of RNA
metabolism proteins.

10 BACKGROUND OF THE INVENTION

Ribonucleic acid (RNA) is a linear single-stranded polymer of four nucleotides, ATP, CTP,
UTP, and GTP. In most organisms, RNA is transcribed as a copy of deoxyribonucleic acid (DNA),
the genetic material of the organism. In retroviruses RNA rather than DNA serves as the genetic
material. RNA copies of the genetic material encode proteins or serve various structural, catalytic, or
15 regulatory roles in organisms. RNA is classified according to its cellular localization and function.
Messenger RNAs (mRNAs) encode polypeptides. Ribosomal RNAs (rRNAs) are assembled, along
with ribosomal proteins, into ribosomes, which are cytoplasmic particles that translate mRNA into
polypeptides. Transfer RNAs (tRNAs) are cytosolic adaptor molecules that function in mRNA
translation by recognizing both an mRNA codon and the amino acid that matches that codon.
20 Heterogeneous nuclear RNAs (hnRNAs) include mRNA precursors and other nuclear RNAs of
various sizes. Small nuclear RNAs (snRNAs) are a part of the nuclear spliceosome complex that
removes intervening, non-coding sequences (introns) and rejoins exons in pre-mRNAs.

Proteins are associated with RNA during its transcription from DNA, RNA processing, and
translation of mRNA into protein. Proteins are also associated with RNA as it is used for structural,
25 catalytic, and regulatory purposes.

RNA Processing

Various proteins are necessary for processing of transcribed RNAs in the nucleus. Pre-mRNA
processing steps include capping at the 5' end with methylguanosine, polyadenylating the 3' end, and
30 splicing to remove introns. The spliceosomal complex is comprised of five small nuclear
ribonucleoprotein particles (snRNPs) designated U1, U2, U4, U5, and U6. Each snRNP contains a
single species of snRNA and about ten proteins. The RNA components of some snRNPs recognize
and base-pair with intron consensus sequences. The protein components mediate spliceosome
assembly and the splicing reaction.

35 An early step in pre-mRNA cleavage involves the cleavage factor Im (CF Im). The human CF

Im protein aids in the recruitment and assembly of processing factors that make up the 3' end processing complex (Rueggsegger, U. et al (1998) Mol. Cell. 1:243-253). The murine formin binding proteins (FBP's) FBP11 and FBP12 are components of pre-mRNA splicing complexes that facilitate the bridging of 5' and 3' ends of the intron. These proteins function through bridging interactions involving U1 and U2 snRNPs. Autoantibodies to snRNP proteins are found in the blood of patients with systemic lupus erythematosus (Stryer, L. (1995) Biochemistry W.H. Freeman and Company, New York NY, p. 863).

Heterogeneous nuclear ribonucleoproteins (hnRNPs) have been identified that have roles in splicing, exporting of the mature RNAs to the cytoplasm, and mRNA translation (Biamonti, G. et al. (1998) Clin. Exp. Rheumatol. 16:317-326). Some examples of hnRNPs include the yeast proteins Hrp1p, involved in cleavage and polyadenylation at the 3' end of the RNA; Cbp80p, involved in capping the 5' end of the RNA; and Npl3p, a homolog of mammalian hnRNP A1, involved in export of mRNA from the nucleus (Shen, E.C. et al. (1998) Genes Dev. 12:679-691). HnRNPs have been shown to be important targets of the autoimmune response in rheumatic diseases (Biamonti, supra).

Many snRNP and hnRNP proteins are characterized by an RNA recognition motif (RRM). (Reviewed in Birney, E. et al. (1993) Nucleic Acids Res. 21:5803-5816.) The RRM is about 80 amino acids in length and forms four β -strands and two α -helices arranged in an α/β sandwich. The RRM contains a core RNP-1 octapeptide motif along with surrounding conserved sequences. In addition to snRNP proteins, examples of RNA-binding proteins which contain the above motifs include heteronuclear ribonucleoproteins which stabilize nascent RNA and factors which regulate alternative splicing. Alternative splicing factors include developmentally regulated proteins, specific examples of which have been identified in lower eukaryotes such as Drosophila melanogaster and Caenorhabditis elegans. These proteins play key roles in developmental processes such as pattern formation and sex determination, respectively. (See, for example, Hodgkin, J. et al. (1994) Development 120:3681-3689.)

RNA Stability and Degradation

RNA helicases alter and regulate RNA conformation and secondary structure by using energy derived from ATP hydrolysis to destabilize and unwind RNA duplexes. The most well-characterized and ubiquitous family of RNA helicases is the DEAD-box family, so named for the conserved B-type ATP-binding motif which is diagnostic of proteins in this family. Over 40 DEAD-box helicases have been identified in organisms as diverse as bacteria, insects, yeast, amphibians, mammals, and plants. DEAD-box helicases function in diverse processes such as translation initiation, splicing, ribosome assembly, and RNA editing, transport, and stability. Some DEAD-box helicases play tissue- and stage-specific roles in spermatogenesis and embryogenesis. All DEAD-box helicases contain several

conserved sequence motifs spread out over about 420 amino acids. These motifs include an A-type ATP binding motif, the DEAD-box/B-type ATP-binding motif, a serine/arginine/threonine tripeptide of unknown function, and a C-terminal glycine-rich motif with a possible role in substrate binding and unwinding. In addition, alignment of divergent DEAD-box helicase sequences has shown that 37 amino acid residues are identical among these sequences, suggesting that conservation of these residues is important for helicase function. (Reviewed in Linder, P. et al. (1989) Nature 337:121-122.)

Overexpression of the DEAD-box 1 protein (DDX1) may play a role in the progression of neuroblastoma (Nb) and retinoblastoma (Rb) tumors. These observations suggest that DDX1 may promote or enhance tumor progression by altering the normal secondary structure and expression levels of RNA in cancer cells. Other DEAD-box helicases have been implicated either directly or indirectly in ultraviolet light-induced tumors, B-cell lymphoma, and myeloid malignancies. (Reviewed in Godbout, R. et al. (1998) J. Biol. Chem. 273:21161-21168.)

Ribonucleases (RNases) catalyze the hydrolysis of phosphodiester bonds in RNA chains, thus cleaving the RNA. For example, RNase P is a ribonucleoprotein enzyme which cleaves the 5' end of pre-tRNAs as part of their maturation process. RNase H digests the RNA strand of an RNA/DNA hybrid. Such hybrids occur in cells invaded by retroviruses, and RNase H is an important enzyme in the retroviral replication cycle. RNase H domains are often found as a domain associated with reverse transcriptases. RNase activity in serum and cell extracts is elevated in a variety of cancers and infectious diseases (Schein, C.H. (1997) Nat. Biotechnol. 15:529-536). Regulation of RNase activity is being investigated as a means to control tumor angiogenesis, allergic reactions, viral infection and replication, and fungal infections.

Degradation of mRNAs having premature termination or nonsense codons is accomplished through a surveillance mechanism that has been termed nonsense-mediated mRNA decay (NMD). This mechanism helps eliminate flawed mRNAs that might code for nonfunctional or deleterious polypeptides. Various NMD components are linked to both yeast and human RNA metabolism disorders (Hentze, M. and Kulozik, A. (1999) Cell 96:307-310).

TRANSLATION

Ribosomal RNAs (rRNAs) are assembled, along with ribosomal proteins, into ribosomes, which are cytoplasmic particles that translate messenger RNA (mRNA) into polypeptides. The eukaryotic ribosome is composed of a 60S (large) subunit and a 40S (small) subunit, which together form the 80S ribosome. In addition to the 18S, 28S, 5S, and 5.8S rRNAs, ribosomes contain from 50 to over 80 different ribosomal proteins, depending on the organism. Ribosomal proteins are classified according to which subunit they belong (i.e., L, if associated with the large 60S large subunit or S if associated with the small 40S subunit). *E. coli* ribosomes have been the most thoroughly studied and

contain 50 proteins, many of which are conserved in all life forms. The structures of nine ribosomal proteins have been solved to less than 3.0Å resolution (i.e., S5, S6, S17, L1, L6, L9, L12, L14, L30), revealing common motifs, such as β - α - β protein folds in addition to acidic and basic RNA-binding motifs positioned between β -strands. Most ribosomal proteins are believed to contact rRNA directly
5 (reviewed in Liljas, A. and Garber, M. (1995) *Curr. Opin. Struct. Biol.* 5:721-727, see also Woodson, S.A. and Leontis, N.B. (1998) *Curr. Opin. Struct. Biol.* 8:294-300; Ramakrishnan, V. and White, S.W. (1998) *Trends Biochem. Sci.* 23:208-212.)

Ribosomal proteins may undergo post-translational modifications or interact with other ribosome-associated proteins to regulate translation. For example, the highly homologous 40S
10 ribosomal protein S6 kinases (S6K1 and S6K2) play a key role in the regulation of cell growth by controlling the biosynthesis of translational components which make up the protein synthetic apparatus (including the ribosomal proteins). In the case of S6K1, at least eight phosphorylation sites are believed to mediate kinase activation in a hierarchical fashion (Dufner and Thomas (1999) *Exp. Cell. Res.* 253:100-109). Some of the ribosomal proteins, including L1, also function as translational
15 repressors by binding to polycistronic mRNAs encoding ribosomal proteins (reviewed in Liljas, A. supra and Garber, M. supra).

Recent evidence suggests that a number of ribosomal proteins have secondary functions independent of their involvement in protein biosynthesis. These proteins function as regulators of cell proliferation and, in some instances, as inducers of cell death. For example, the expression of human
20 ribosomal protein L13a has been shown to induce apoptosis by arresting cell growth in the G2/M phase of the cell cycle. Inhibition of expression of L13a induces apoptosis in target cells, which suggests that this protein is necessary, in the appropriate amount, for cell survival. Similar results have been obtained in yeast where inactivation of yeast homologues of L13a, rp22 and rp23, results in severe growth retardation and death. A closely related ribosomal protein, L7, arrests cells in G1 and
25 also induces apoptosis. Thus, it appears that a subset of ribosomal proteins may function as cell cycle checkpoints and compose a new family of cell proliferation regulators.

Mapping of individual ribosomal proteins on the surface of intact ribosomes is accomplished using 3D immunocryoelectronmicroscopy, whereby antibodies raised against specific ribosomal proteins are visualized. Progress has been made toward the mapping of L1, L7, and L12 while the
30 structure of the intact ribosome has been solved to only 20-25Å resolution and inconsistencies exist among different crude structures (Frank, J. (1997) *Curr. Opin. Struct. Biol.* 7:266-272).

Three distinct sites have been identified on the ribosome. The aminoacyl-tRNA acceptor site (A site) receives charged tRNAs (with the exception of the initiator-tRNA). The peptidyl-tRNA site (P site) binds the nascent polypeptide as the amino acid from the A site is added to the elongating
35 chain. Deacylated tRNAs bind in the exit site (E site) prior to their release from the ribosome. The

structure of the ribosome is reviewed in Stryer, L. (1995) Biochemistry W.H. Freeman and Company, New York NY pp. 888-9081; Lodish, H. et al. (1995) Molecular Cell Biology Scientific American Books, New York NY pp. 119-138; and Lewin, B (1997) Genes VI Oxford University Press, Inc. New York, NY).

5

tRNA Charging

Correct translation of the genetic code depends upon each amino acid forming a linkage with the appropriate transfer RNA (tRNA). The aminoacyl-tRNA synthetases (aaRSs) are essential proteins found in all living organisms. The aaRSs are responsible for the activation and correct attachment of an amino acid with its cognate tRNA, as the first step in protein biosynthesis. Prokaryotic organisms have at least twenty different types of aaRSs, one for each different amino acid, while eukaryotes usually have two aaRSs, a cytosolic form and a mitochondrial form, for each different amino acid. The 20 aaRS enzymes can be divided into two structural classes. Class I enzymes add amino acids to the 2' hydroxyl at the 3' end of tRNAs while Class II enzymes add amino acids to the 3' hydroxyl at the 3' end of tRNAs. Each class is characterized by a distinctive topology of the catalytic domain. Class I enzymes contain a catalytic domain based on the nucleotide-binding 'Rossmann fold'. In particular, a consensus tetrapeptide motif is highly conserved (Prosite Document PDOC00161, Aminoacyl-transfer RNA synthetases class-I signature). Class II enzymes contain a central catalytic domain, which consists of a seven-stranded antiparallel β -sheet domain, as well as N- and C- terminal regulatory domains.

Class II enzymes are separated into two groups based on the heterodimeric or homodimeric structure of the enzyme; the latter group is further subdivided by the structure of the N- and C-terminal regulatory domains (Hartlein, M. and Cusack, S. (1995) J. Mol. Evol. 40:519-530). The different aaRSs are believed to be the result of divergent evolution, likely following gene duplication events. Notably, amino acids such as Gln, were among the last to appear in nature and evolutionary studies suggest that Gln-RSs appeared first in eukaryotes and were later horizontally transferred to prokaryotes (Lamour, V. et al. (1994) Proc. Natl. Acad. Sci. U.S.A. 91:8670-74 and Siatecka, M. et al. (1998) Eur. J. Biochem. 256:80-7). The importance of Gln-RS and Gln-tRNA^{Gln} are discussed below.

In addition to their function in protein synthesis, specific aminoacyl tRNA synthetases also play roles in cellular fidelity, RNA splicing, RNA trafficking, apoptosis, and transcriptional and translational regulation. For example, human tyrosyl-tRNA synthetase can be proteolytically cleaved into two fragments with distinct cytokine activities. The carboxy-terminal domain exhibits monocyte and leukocyte chemotaxis activity as well as stimulating production of myeloperoxidase, tumor necrosis factor- α , and tissue factor. The N-terminal domain binds to the interleukin-8 type A receptor and functions as an interleukin-8-like cytokine. Human tyrosyl-tRNA synthetase is secreted from

apoptotic tumor cells and may accelerate apoptosis (Wakasugi, K. and Schimmel, P. (1999) Science 284:147-151). Mitochondrial *Neurospora crassa* TyrRS and *S. cerevisiae* LeuRS are essential factors for certain group I intron splicing activities, and human mitochondrial LeuRS can substitute for the yeast LeuRS in a yeast null strain. Certain bacterial aaRSs are involved in regulating their own

5 transcription or translation (Martinis, *supra*). Several aaRSs are able to synthesize diadenosine oligophosphates, a class of signalling molecules with roles in cell proliferation, differentiation, and apoptosis (Kisselev, L.L et al. (1998) FEBS Lett. 427:157-163; Vartanian, A. et al. (1999) FEBS Lett. 456:175-180).

Under optimal conditions, polypeptide synthesis proceeds at a rate of approximately 40 amino acid residues per second. The rate of misincorporation during translation is on the order of 10^{-4} and is primarily the result of aminoacyl-t-RNAs being charged with the incorrect amino acid. Incorrectly charged tRNA are toxic to cells as they result in the incorporation of incorrect amino acid residues into an elongating polypeptide. The rate of translation is presumed to be a compromise between the optimal rate of elongation and the need for translational fidelity. Mathematical calculations predict

15 that 10^{-4} is indeed the maximum acceptable error rate for protein synthesis in a biological system (reviewed in Stryer, L. *supra* and Watson, J. et al. (1987) The Benjamin/Cummings Publishing Co., Inc. Menlo Park, CA). A particularly error prone aminoacyl-tRNA charging event, the charging of tRNA^{Gln} with Gln. A mechanism exist for the correction of this mischarging event which likely has its origins in evolution. Gln was among the last of the 20 naturally occurring amino acids used

20 polypeptide synthesis to appear in nature. Gram positive eubacteria, cyanobacteria, Archeae, and eukaryotic organelles posses a noncanonical pathway for the synthesis of Gln-tRNA^{Gln} based on the transformation of Glu-tRNA^{Gln} (synthesized by Glu-tRNA synthetase, GluRS) using the enzyme Glu-tRNA^{Gln} amidotransferase (Glu-AdT). The reactions involved in the transamidation pathway are as follows (Curnow, A.W. et al. (1997) Nucleic Acids Symposium 36:2-4):

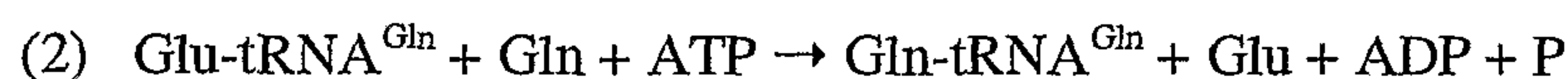
25

GluRS



Glu-AdT

30



A similar enzyme, Asp-tRNA^{Asn} amidotransferase, exists in Archaea, which transforms Asp-tRNA^{Asn} to Asn-tRNA^{Asn}. Formylase, the enzyme that transforms Met-tRNA^{fMet} to fMet-tRNA^{fMet} in eubacteria, is likely to be a related enzyme. A hydrolytic activity has also been identified that destroys

35 mischarged Val-tRNA^{Ile} (Schimmel, P. et al. (1998) FASEB J. 12:1599-1609). I likely scenario for

the evolution of Glu-AdT in primitive life forms is the absence a specific glutaminyl-tRNA synthetase (GlnRS), requiring an alternative pathway for the synthesis of Gln-tRNA^{Gln}. In fact, deletion of the Glu-AdT operon in Gram positive bacteria is lethal (Curnow, A.W. et al. (1997) Proc. Natl. Acad. Sci. U.S.A. 94:11819-11826). The existence of GluRS activity in other organisms has been inferred by the

5 high degree of conservation in translation machinery in nature; however, GluRS has not been identified in all organisms, including Homo sapiens. Such an enzyme would be responsible for ensuring translational fidelity and reducing the synthesis of defective polypeptides.

Autoantibodies against aminoacyl-tRNAs are generated by patients with autoimmune diseases such as rheumatic arthritis, dermatomyositis and polymyositis, and correlate strongly with

10 complicating interstitial lung disease (ILD) (Freist, W. et al. (1999) Biol. Chem. 380:623-646; Freist, W. et al. (1996) Biol. Chem. Hoppe Seyler 377:343-356). These antibodies appear to be generated in response to viral infection, and coxsackie virus has been used to induce experimental viral myositis in animals.

Comparison of aaRS structures between humans and pathogens has been useful in the design

15 of novel antibiotics (Schimmel, supra). Genetically engineered aaRSs have been utilized to allow site-specific incorporation of unnatural amino acids into proteins in vivo (Liu, D.R. et al. (1997) Proc. Natl. Acad. Sci. USA 94:10092-10097).

Translation Initiation

20 Initiation of translation can be divided into three stages. The first stage brings an initiator transfer RNA (Met-tRNA_f) together with the 40S ribosomal subunit to form the 43S preinitiation complex. The second stage binds the 43S preinitiation complex to the mRNA, followed by migration of the complex to the correct AUG initiation codon. The third stage brings the 60S ribosomal subunit to the 40S subunit to generate an 80S ribosome at the initiation codon. Regulation of translation

25 primarily involves the first and second stage in the initiation process (V.M. Pain (1996) Eur. J. Biochem. 236:747-771).

Several initiation factors, many of which contain multiple subunits, are involved in bringing an initiator tRNA and 40S ribosomal subunit together. One eukaryotic initiation factor (EIF) EIF5A is an 18-kD protein containing the unique amino acid residue, hypusine (N epsilon-(4-amino-2-

30 hydroxybutyl)lysine) (Rinaudo, M. et al. (1993) Gene 137:303-307). eIF2, a guanine nucleotide binding protein, recruits the initiator tRNA to the 40S ribosomal subunit. Only when eIF2 is bound to GTP does it associate with the initiator tRNA. eIF2B, a guanine nucleotide exchange protein, is responsible for converting eIF2 from the GDP-bound inactive form to the GTP-bound active form. Two other factors, eIF1A and eIF3 bind and stabilize the 40S subunit by interacting with 18S

35 ribosomal RNA and specific ribosomal structural proteins. eIF3 is also involved in association of the

40S ribosomal subunit with mRNA. The Met-tRNA_f, eIF1A, eIF3, and 40S ribosomal subunit together make up the 43S preinitiation complex (Pain, supra).

Additional factors are required for binding of the 43S preinitiation complex to an mRNA molecule, and the process is regulated at several levels. eIF4F is a complex consisting of three
 5 proteins: eIF4E, eIF4A, and eIF4G. eIF4E recognizes and binds to the mRNA 5'-terminal m⁷GTP cap, eIF4A is a bidirectional RNA-dependent helicase, and eIF4G is a scaffolding polypeptide. eIF4G has three binding domains. The N-terminal third of eIF4G interacts with eIF4E, the central third interacts with eIF4A, and the C-terminal third interacts with eIF3 bound to the 43S preinitiation complex. Thus, eIF4G acts as a bridge between the 40S ribosomal subunit and the mRNA (M.W.
 10 Hentze (1997) Science 275:500-501).

The ability of eIF4F to initiate binding of the 43S preinitiation complex is regulated by structural features of the mRNA. The mRNA molecule has an untranslated region (UTR) between the 5' cap and the AUG start codon. In some mRNAs this region forms secondary structures that impede binding of the 43S preinitiation complex. The helicase activity of eIF4A is thought to function in
 15 removing this secondary structure to facilitate binding of the 43S preinitiation complex (Pain, supra).

Translation Elongation

Elongation is the process whereby additional amino acids are joined to the initiator methionine to form the complete polypeptide chain. The elongation factors EF1 α , EF1 β γ , and EF2
 20 are involved in elongating the polypeptide chain following initiation. EF1 α is a GTP-binding protein. In EF1 α 's GTP-bound form, it brings an aminoacyl-tRNA to the ribosome's A site. The amino acid attached to the newly arrived aminoacyl-tRNA forms a peptide bond with the initiator methionine. The GTP on EF1 α is hydrolyzed to GDP, and EF1 α -GDP dissociates from the ribosome. EF1 β γ binds EF1 α -GDP and induces the dissociation of GDP from EF1 α , allowing EF1 α to bind GTP and a
 25 new cycle to begin.

As subsequent aminoacyl-tRNAs are brought to the ribosome, EF-G, another GTP-binding protein, catalyzes the translocation of tRNAs from the A site to the P site and finally to the E site of the ribosome. This allows the processivity of translation.

30 Translation Termination

The release factor eRF carries out termination of translation. eRF recognizes stop codons in the mRNA, leading to the release of the polypeptide chain from the ribosome.

The discovery of new RNA metabolism proteins and the polynucleotides encoding them satisfies a need in the art by providing new compositions which are useful in the diagnosis, prevention, and
 35 treatment of nervous system, autoimmune/inflammatory, cell proliferative, and developmental disorders,

and in the assessment of the effects of exogenous compounds on the expression of nucleic acid and amino acid sequences of RNA metabolism proteins.

nervous system disorders, autoimmune/inflammatory disorders, and cell proliferative disorders including cancer

5

SUMMARY OF THE INVENTION

The invention features purified polypeptides, RNA metabolism proteins, referred to collectively as "RMEP" and individually as "RMEP-1," "RMEP-2," "RMEP-3," "RMEP-4," "RMEP-5," "RMEP-6," "RMEP-7," "RMEP-8," "RMEP-9," "RMEP-10," "RMEP-11," "RMEP-12," "RMEP-13," "RMEP-14," "RMEP-15," "RMEP-16," "RMEP-17," "RMEP-18," "RMEP-19," "RMEP-20," "RMEP-21," "RMEP-22," "RMEP-23," "RMEP-24," "RMEP-25," "RMEP-26," "RMEP-27," "RMEP-28," "RMEP-29," "RMEP-30," "RMEP-31," "RMEP-32," "RMEP-33," "RMEP-34," "RMEP-35," "RMEP-36," "RMEP-37," "RMEP-38," "RMEP-39," "RMEP-40," "RMEP-41," "RMEP-42," "RMEP-43," "RMEP-44," "RMEP-45," "RMEP-46," and "RMEP-47." In one aspect, the invention provides an isolated polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-47, b) a naturally occurring polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-47, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-47, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-47. In one alternative, the invention provides an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1-47.

The invention further provides an isolated polynucleotide encoding a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-47, b) a naturally occurring polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-47, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-47, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-47. In one alternative, the polynucleotide encodes a polypeptide selected from the group consisting of SEQ ID NO:1-47. In another alternative, the polynucleotide is selected from the group consisting of SEQ ID NO:48-94.

Additionally, the invention provides a recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide encoding a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-47, b) a naturally occurring polypeptide comprising an amino acid sequence at least 90% identical

to an amino acid sequence selected from the group consisting of SEQ ID NO:1-47, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-47, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-47. In one alternative, the invention provides a cell
5 transformed with the recombinant polynucleotide. In another alternative, the invention provides a transgenic organism comprising the recombinant polynucleotide.

The invention also provides a method for producing a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-47, b) a naturally occurring polypeptide comprising an amino acid sequence at least 90%
10 identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-47, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-47, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-47. The method comprises a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a
15 recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide encoding the polypeptide, and b) recovering the polypeptide so expressed.

Additionally, the invention provides an isolated antibody which specifically binds to a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-47, b) a naturally occurring polypeptide comprising
20 an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-47, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-47, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-47.

The invention further provides an isolated polynucleotide selected from the group consisting of
25 a) a polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:48-94, b) a naturally occurring polynucleotide comprising a polynucleotide sequence at least 90% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:48-94, c) a polynucleotide complementary to the polynucleotide of a), d) a polynucleotide complementary to the polynucleotide of b), and e) an RNA equivalent of a)-d). In one alternative, the polynucleotide
30 comprises at least 60 contiguous nucleotides.

Additionally, the invention provides a method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide selected from the group consisting of a) a polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:48-94, b) a naturally occurring polynucleotide comprising a polynucleotide sequence at least 90%

identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:48-94, c) a polynucleotide complementary to the polynucleotide of a), d) a polynucleotide complementary to the polynucleotide of b), and e) an RNA equivalent of a)-d). The method comprises a) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence

5 complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide or fragments thereof, and b) detecting the presence or absence of said hybridization complex, and optionally, if present, the amount thereof. In one alternative, the probe comprises at least 60 contiguous nucleotides.

10 The invention further provides a method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide selected from the group consisting of a) a polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:48-94, b) a naturally occurring polynucleotide comprising a polynucleotide sequence at least 90% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:48-94, c) a
15 polynucleotide complementary to the polynucleotide of a), d) a polynucleotide complementary to the polynucleotide of b), and e) an RNA equivalent of a)-d). The method comprises a) amplifying said target polynucleotide or fragment thereof using polymerase chain reaction amplification, and b) detecting the presence or absence of said amplified target polynucleotide or fragment thereof, and, optionally, if present, the amount thereof.

20 The invention further provides a composition comprising an effective amount of a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-47, b) a naturally occurring polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-47, c) a biologically active fragment of a polypeptide having an amino acid sequence
25 selected from the group consisting of SEQ ID NO:1-47, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-47, and a pharmaceutically acceptable excipient. In one embodiment, the composition comprises an amino acid sequence selected from the group consisting of SEQ ID NO:1-47. The invention additionally provides a method of treating a disease or condition associated with decreased expression of functional RMEP,
30 comprising administering to a patient in need of such treatment the composition.

The invention also provides a method for screening a compound for effectiveness as an agonist of a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-47, b) a naturally occurring polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence selected from the

group consisting of SEQ ID NO:1-47, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-47, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-47. The method comprises a) exposing a sample comprising the polypeptide to a compound, and b) detecting agonist activity in the sample. In one alternative, the invention provides a composition comprising an agonist compound identified by the method and a pharmaceutically acceptable excipient. In another alternative, the invention provides a method of treating a disease or condition associated with decreased expression of functional RMEP, comprising administering to a patient in need of such treatment the composition.

10 Additionally, the invention provides a method for screening a compound for effectiveness as an antagonist of a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-47, b) a naturally occurring polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-47, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-47, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-47. The method comprises a) exposing a sample comprising the polypeptide to a compound, and b) detecting antagonist activity in the sample. In one alternative, the invention provides a composition comprising an antagonist compound identified by the method and a pharmaceutically acceptable excipient. In another alternative, the invention provides a method of treating a disease or condition associated with overexpression of functional RMEP, comprising administering to a patient in need of such treatment the composition.

25 The invention further provides a method of screening for a compound that specifically binds to a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-47, b) a naturally occurring polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-47, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-47, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-47. The method comprises a) combining the polypeptide with at least one test compound under suitable conditions, and b) detecting binding of the polypeptide to the test compound, thereby identifying a compound that specifically binds to the polypeptide.

30 The invention further provides a method of screening for a compound that modulates the activity of a polypeptide selected from the group consisting of a) a polypeptide comprising an amino

acid sequence selected from the group consisting of SEQ ID NO:1-47, b) a naturally occurring polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-47, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-47, and
5 d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-47. The method comprises a) combining the polypeptide with at least one test compound under conditions permissive for the activity of the polypeptide, b) assessing the activity of the polypeptide in the presence of the test compound, and c) comparing the activity of the polypeptide in the presence of the test compound with the activity of the polypeptide in the absence of
10 the test compound, wherein a change in the activity of the polypeptide in the presence of the test compound is indicative of a compound that modulates the activity of the polypeptide.

The invention further provides a method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence selected from the group consisting of SEQ ID NO:48-94, the method comprising a) exposing a sample
15 comprising the target polynucleotide to a compound, and b) detecting altered expression of the target polynucleotide.

The invention further provides a method for assessing toxicity of a test compound, said method comprising a) treating a biological sample containing nucleic acids with the test compound; b) hybridizing the nucleic acids of the treated biological sample with a probe comprising at least 20
20 contiguous nucleotides of a polynucleotide selected from the group consisting of i) a polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:48-94, ii) a naturally occurring polynucleotide comprising a polynucleotide sequence at least 90% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:48-94, iii) a polynucleotide having a sequence complementary to i), iv) a polynucleotide complementary to the
25 polynucleotide of ii), and v) an RNA equivalent of i)-iv). Hybridization occurs under conditions whereby a specific hybridization complex is formed between said probe and a target polynucleotide in the biological sample, said target polynucleotide selected from the group consisting of i) a polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:48-94, ii) a naturally occurring polynucleotide comprising a polynucleotide sequence at least 90%
30 identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:48-94, iii) a polynucleotide complementary to the polynucleotide of i), iv) a polynucleotide complementary to the polynucleotide of ii), and v) an RNA equivalent of i)-iv). Alternatively, the target polynucleotide comprises a fragment of a polynucleotide sequence selected from the group consisting of i)-v) above; c) quantifying the amount of hybridization complex; and d) comparing the amount of hybridization
35 complex in the treated biological sample with the amount of hybridization complex in an untreated

biological sample, wherein a difference in the amount of hybridization complex in the treated biological sample is indicative of toxicity of the test compound.

BRIEF DESCRIPTION OF THE TABLES

5 Table 1 summarizes the nomenclature for the full length polynucleotide and polypeptide sequences of the present invention.

Table 2 shows the GenBank identification number and annotation of the nearest GenBank homolog for polypeptides of the invention. The probability score for the match between each polypeptide and its GenBank homolog is also shown.

10 Table 3 shows structural features of polypeptide sequences of the invention, including predicted motifs and domains, along with the methods, algorithms, and searchable databases used for analysis of the polypeptides.

Table 4 lists the cDNA fragments which were used to assemble polynucleotide sequences of the invention, along with selected fragments of the polynucleotide sequences.

15 Table 5 shows the representative cDNA library for polynucleotides of the invention.

Table 6 provides an appendix which describes the tissues and vectors used for construction of the cDNA libraries shown in Table 5.

Table 7 shows the tools, programs, and algorithms used to analyze the polynucleotides and polypeptides of the invention, along with applicable descriptions, references, and threshold parameters.

20

DESCRIPTION OF THE INVENTION

Before the present proteins, nucleotide sequences, and methods are described, it is 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
25 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," "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
30 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 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 publications and which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is
5 not entitled to antedate such disclosure by virtue of prior invention.

DEFINITIONS

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

10 The term “agonist” refers to a molecule which intensifies or mimics the biological activity of RMEP. Agonists may include proteins, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of RMEP either by directly interacting with RMEP or by acting on components of the biological pathway in which RMEP participates.

An “allelic variant” is an alternative form of the gene encoding RMEP. Allelic variants may
15 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. A gene may have none, one, or many allelic variants of its naturally occurring form. 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
20 a given sequence.

“Altered” nucleic acid sequences encoding RMEP include those sequences with deletions, insertions, or substitutions of different nucleotides, resulting in a polypeptide the same as RMEP or a polypeptide with at least one functional characteristic of RMEP. Included within this definition are polymorphisms which may or may not be readily detectable using a particular oligonucleotide probe of
25 the polynucleotide encoding RMEP, and improper or unexpected hybridization to allelic variants, with a locus other than the normal chromosomal locus for the polynucleotide sequence encoding RMEP. 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 RMEP. Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility,
30 hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues, as long as the biological or immunological activity of RMEP is retained. For example, negatively charged amino acids may include aspartic acid and glutamic acid, and positively charged amino acids may include lysine and arginine. Amino acids with uncharged polar side chains having similar hydrophilicity values may include: asparagine and glutamine; and serine and threonine. Amino acids with uncharged side chains

having similar hydrophilicity values may include: leucine, isoleucine, and valine; glycine and alanine; and phenylalanine and tyrosine.

The terms “amino acid” and “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
5 molecules. Where “amino acid sequence” is recited to refer to a 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. Amplification is generally carried out using polymerase chain reaction (PCR) technologies well known
10 in the art.

The term “antagonist” refers to a molecule which inhibits or attenuates the biological activity of RMEP. Antagonists may include proteins such as antibodies, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of RMEP either by directly interacting with RMEP or by acting on components of the biological pathway in which RMEP
15 participates.

The term “antibody” refers to intact immunoglobulin molecules as well as to fragments thereof, such as Fab, F(ab')₂, and Fv fragments, which are capable of binding an epitopic determinant. Antibodies that bind RMEP polypeptides can be prepared using intact polypeptides or using fragments containing small peptides of interest as the immunizing antigen. The polypeptide or oligopeptide used to
20 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.

The term “antigenic determinant” refers to that region of a molecule (i.e., an epitope) that makes
25 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 (particular regions or three-dimensional structures on the protein). An antigenic determinant may compete with the intact antigen (i.e., the immunogen used to elicit the immune response) for binding to an antibody.

30 The term “antisense” refers to any composition capable of base-pairing with the “sense” (coding) strand of a specific nucleic acid sequence. Antisense compositions may include DNA; RNA; peptide nucleic acid (PNA); oligonucleotides having modified backbone linkages such as phosphorothioates, methylphosphonates, or benzylphosphonates; oligonucleotides having modified sugar groups such as 2'-methoxyethyl sugars or 2'-methoxyethoxy sugars; or oligonucleotides having modified

bases such as 5-methyl cytosine, 2'-deoxyuracil, or 7-deaza-2'-deoxyguanosine. Antisense molecules may be produced by any method including chemical synthesis or transcription. Once introduced into a cell, the complementary antisense molecule base-pairs with a naturally occurring nucleic acid sequence produced by the cell to form duplexes which block either transcription or translation. The designation
5 "negative" or "minus" can refer to the antisense strand, and the designation "positive" or "plus" can refer to the sense strand of a reference DNA molecule.

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

"Complementary" describes the relationship between two single-stranded nucleic acid sequences that anneal by base-pairing. For example, 5'-AGT-3' pairs with its complement,
3'-TCA-5'.

15 A "composition comprising a given polynucleotide sequence" and 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 RMEP or fragments of RMEP may be employed as hybridization probes. The probes may be stored in freeze-dried form and may be associated
20 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 subjected to repeated DNA sequence analysis to resolve uncalled bases, extended using the XL-PCR kit (Applied Biosystems,
25 Foster City CA) in the 5' and/or the 3' direction, and resequenced, or which has been assembled from one or more overlapping cDNA, EST, or genomic DNA fragments using a computer program for fragment assembly, such as the GELVIEW fragment assembly system (GCG, Madison WI) or Phrap (University of Washington, Seattle WA). Some sequences have been both extended and assembled to produce the consensus sequence.

30 "Conservative amino acid substitutions" are those substitutions that are predicted to least interfere with the properties of the original protein, i.e., the structure and especially the function of the protein is conserved and not significantly changed by such substitutions. The table below shows amino acids which may be substituted for an original amino acid in a protein and which are regarded as conservative amino acid substitutions.

	Original Residue	Conservative Substitution
	Ala	Gly, Ser
	Arg	His, Lys
	Asn	Asp, Gln, His
5	Asp	Asn, Glu
	Cys	Ala, Ser
	Gln	Asn, Glu, His
	Glu	Asp, Gln, His
	Gly	Ala
10	His	Asn, Arg, Gln, Glu
	Ile	Leu, Val
	Leu	Ile, Val
	Lys	Arg, Gln, Glu
	Met	Leu, Ile
15	Phe	His, Met, Leu, Trp, Tyr
	Ser	Cys, Thr
	Thr	Ser, Val
	Trp	Phe, Tyr
	Tyr	His, Phe, Trp
20	Val	Ile, Leu, Thr

Conservative amino acid substitutions generally maintain (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a beta sheet or alpha helical conformation, (b) the charge or hydrophobicity of the molecule at the site of the substitution, and/or (c) the bulk of the side chain.

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 a chemically modified polynucleotide or polypeptide. Chemical modifications of a polynucleotide can include, for example, replacement of hydrogen by an alkyl, acyl, hydroxyl, 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.

A "detectable label" refers to a reporter molecule or enzyme that is capable of generating a measurable signal and is covalently or noncovalently joined to a polynucleotide or polypeptide.

"Differential expression" refers to increased or upregulated; or decreased, downregulated, or absent gene or protein expression, determined by comparing at least two different samples. Such comparisons may be carried out between, for example, a treated and an untreated sample, or a diseased and a normal sample.

A "fragment" is a unique portion of RMEP or the polynucleotide encoding RMEP which is identical in sequence to but shorter in length than the parent sequence. A fragment may comprise up

to the entire length of the defined sequence, minus one nucleotide/amino acid residue. For example, a fragment may comprise from 5 to 1000 contiguous nucleotides or amino acid residues. A fragment used as a probe, primer, antigen, therapeutic molecule, or for other purposes, may be at least 5, 10, 15, 16, 20, 25, 30, 40, 50, 60, 75, 100, 150, 250 or at least 500 contiguous nucleotides or amino acid residues in length. Fragments may be preferentially selected from certain regions of a molecule. For example, a polypeptide fragment may comprise a certain length of contiguous amino acids selected from the first 250 or 500 amino acids (or first 25% or 50%) of a polypeptide as shown in a certain defined sequence. Clearly these lengths are exemplary, and any length that is supported by the specification, including the Sequence Listing, tables, and figures, may be encompassed by the present
 10 embodiments.

A fragment of SEQ ID NO:48-94 comprises a region of unique polynucleotide sequence that specifically identifies SEQ ID NO:48-94, for example, as distinct from any other sequence in the genome from which the fragment was obtained. A fragment of SEQ ID NO:48-94 is useful, for example, in hybridization and amplification technologies and in analogous methods that distinguish
 15 SEQ ID NO:48-94 from related polynucleotide sequences. The precise length of a fragment of SEQ ID NO:48-94 and the region of SEQ ID NO:48-94 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

A fragment of SEQ ID NO:1-47 is encoded by a fragment of SEQ ID NO:48-94. A fragment of SEQ ID NO:1-47 comprises a region of unique amino acid sequence that specifically identifies
 20 SEQ ID NO:1-47. For example, a fragment of SEQ ID NO:1-47 is useful as an immunogenic peptide for the development of antibodies that specifically recognize SEQ ID NO:1-47. The precise length of a fragment of SEQ ID NO:1-47 and the region of SEQ ID NO:1-47 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

25 A "full length" polynucleotide sequence is one containing at least a translation initiation codon (e.g., methionine) followed by an open reading frame and a translation termination codon. A "full length" polynucleotide sequence encodes a "full length" polypeptide sequence.

"Homology" refers to sequence similarity or, interchangeably, sequence identity, between two or more polynucleotide sequences or two or more polypeptide sequences.

30 The terms "percent identity" and "% identity," as applied to polynucleotide sequences, refer to the percentage of residue matches between at least two polynucleotide sequences aligned using a standardized algorithm. Such an algorithm may insert, in a standardized and reproducible way, gaps in the sequences being compared in order to optimize alignment between two sequences, and therefore achieve a more meaningful comparison of the two sequences.

35 Percent identity between polynucleotide sequences may be determined using the default

parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program. This program is part of the LASERGENE software package, a suite of molecular biological analysis programs (DNASTAR, Madison WI). CLUSTAL V is described in Higgins, D.G. and P.M. Sharp (1989) CABIOS 5:151-153 and in Higgins, D.G. et al. (1992) CABIOS 8:189-191.

- 5 For pairwise alignments of polynucleotide sequences, the default parameters are set as follows: Ktuple=2, gap penalty=5, window=4, and "diagonals saved"=4. The "weighted" residue weight table is selected as the default. Percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polynucleotide sequences.

- Alternatively, a suite of commonly used and freely available sequence comparison algorithms is provided by the National Center for Biotechnology Information (NCBI) Basic Local Alignment Search Tool (BLAST) (Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410), which is available from several sources, including the NCBI, Bethesda, MD, and on the Internet at <http://www.ncbi.nlm.nih.gov/BLAST/>. The BLAST software suite includes various sequence analysis programs including "blastn," that is used to align a known polynucleotide sequence with other polynucleotide sequences from a variety of databases. Also available is a tool called "BLAST 2 Sequences" that is used for direct pairwise comparison of two nucleotide sequences. "BLAST 2 Sequences" can be accessed and used interactively at <http://www.ncbi.nlm.nih.gov/gorf/bl2.html>. The "BLAST 2 Sequences" tool can be used for both blastn and blastp (discussed below). BLAST programs are commonly used with gap and other parameters set to default settings. For example, to compare two nucleotide sequences, one may use blastn with the "BLAST 2 Sequences" tool Version 2.0.12 (April-21-2000) set at default parameters. Such default parameters may be, for example:

Matrix: BLOSUM62

Reward for match: 1

Penalty for mismatch: -2

- 25 *Open Gap: 5 and Extension Gap: 2 penalties*

Gap x drop-off: 50

Expect: 10

Word Size: 11

Filter: on

- 30 Percent identity may be measured over the length of an entire defined sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined sequence, for instance, a fragment of at least 20, at least 30, at least 40, at least 50, at least 70, at least 100, or at least 200 contiguous nucleotides. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences

shown herein, in the tables, figures, or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

Nucleic acid sequences that do not show a high degree of identity may nevertheless encode similar amino acid sequences due to the degeneracy of the genetic code. It is understood that changes in
5 a nucleic acid sequence can be made using this degeneracy to produce multiple nucleic acid sequences that all encode substantially the same protein.

The phrases “percent identity” and “% identity,” as applied to polypeptide sequences, refer to the percentage of residue matches between at least two polypeptide sequences aligned using a standardized algorithm. Methods of polypeptide sequence alignment are well-known. Some alignment
10 methods take into account conservative amino acid substitutions. Such conservative substitutions, explained in more detail above, generally preserve the charge and hydrophobicity at the site of substitution, thus preserving the structure (and therefore function) of the polypeptide.

Percent identity between polypeptide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment
15 program (described and referenced above). For pairwise alignments of polypeptide sequences using CLUSTAL V, the default parameters are set as follows: Ktuple=1, gap penalty=3, window=5, and “diagonals saved”=5. The PAM250 matrix is selected as the default residue weight table. As with polynucleotide alignments, the percent identity is reported by CLUSTAL V as the “percent similarity” between aligned polypeptide sequence pairs.

20 Alternatively the NCBI BLAST software suite may be used. For example, for a pairwise comparison of two polypeptide sequences, one may use the “BLAST 2 Sequences” tool Version 2.0.12 (April-21-2000) with blastp set at default parameters. Such default parameters may be, for example:

Matrix: BLOSUM62

Open Gap: 11 and Extension Gap: 1 penalties

25 *Gap x drop-off: 50*

Expect: 10

Word Size: 3

Filter: on

Percent identity may be measured over the length of an entire defined polypeptide sequence, for
30 example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined polypeptide sequence, for instance, a fragment of at least 15, at least 20, at least 30, at least 40, at least 50, at least 70 or at least 150 contiguous residues. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures or Sequence Listing, may be used to

describe a length over which percentage identity may be measured.

“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 chromosome replication, segregation and maintenance.

5 The term “humanized antibody” refers to an antibody molecule 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 the process by which a polynucleotide strand anneals with a complementary strand through base pairing under defined hybridization conditions. Specific
10 hybridization is an indication that two nucleic acid sequences share a high degree of complementarity. Specific hybridization complexes form under permissive annealing conditions and remain hybridized after the “washing” step(s). The washing step(s) is particularly important in determining the stringency of the hybridization process, with more stringent conditions allowing less non-specific binding, i.e., binding between pairs of nucleic acid strands that are not perfectly matched. Permissive conditions for
15 annealing of nucleic acid sequences are routinely determinable by one of ordinary skill in the art and may be consistent among hybridization experiments, whereas wash conditions may be varied among experiments to achieve the desired stringency, and therefore hybridization specificity. Permissive annealing conditions occur, for example, at 68°C in the presence of about 6 x SSC, about 1% (w/v) SDS, and about 100 µg/ml sheared, denatured salmon sperm DNA.

20 Generally, stringency of hybridization is expressed, in part, with reference to the temperature under which the wash step is carried out. Such wash temperatures are typically selected to be about 5°C to 20°C lower than the thermal melting point (T_m) for the specific sequence at a defined ionic strength and pH. The T_m is the temperature (under defined ionic strength and pH) at which 50% of the target sequence hybridizes to a perfectly matched probe. An equation for calculating T_m and conditions for
25 nucleic acid hybridization are well known and can be found in Sambrook, J. et al. (1989) Molecular Cloning: A Laboratory Manual, 2nd ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; specifically see volume 2, chapter 9.

High stringency conditions for hybridization between polynucleotides of the present invention include wash conditions of 68°C in the presence of about 0.2 x SSC and about 0.1% SDS, for 1 hour.
30 Alternatively, temperatures of about 65°C, 60°C, 55°C, or 42°C may be used. SSC concentration may be varied from about 0.1 to 2 x SSC, with SDS being present at about 0.1%. Typically, blocking reagents are used to block non-specific hybridization. Such blocking reagents include, for instance, sheared and denatured salmon sperm DNA at about 100-200 µg/ml. Organic solvent, such as formamide at a concentration of about 35-50% v/v, may also be used under particular circumstances,

such as for RNA:DNA hybridizations. Useful variations on these wash conditions will be readily apparent to those of ordinary skill in the art. Hybridization, particularly under high stringency conditions, may be suggestive of evolutionary similarity between the nucleotides. Such similarity is strongly indicative of a similar role for the nucleotides and their encoded polypeptides.

5 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
10 their nucleic acids have been fixed).

The words "insertion" and "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.

"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
15 various factors, e.g., cytokines, chemokines, and other signaling molecules, which may affect cellular and systemic defense systems.

An "immunogenic fragment" is a polypeptide or oligopeptide fragment of RMEP which is capable of eliciting an immune response when introduced into a living organism, for example, a mammal. The term "immunogenic fragment" also includes any polypeptide or oligopeptide fragment of
20 RMEP which is useful in any of the antibody production methods disclosed herein or known in the art.

The term "microarray" refers to an arrangement of a plurality of polynucleotides, polypeptides, or other chemical compounds on a substrate.

The terms "element" and "array element" refer to a polynucleotide, polypeptide, or other chemical compound having a unique and defined position on a microarray.

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

The phrases "nucleic acid" and "nucleic acid sequence" refer to a nucleotide, oligonucleotide, polynucleotide, or any fragment thereof. These phrases also refer to DNA or RNA of genomic or
30 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.

"Operably linked" refers to the situation in which a first nucleic acid sequence is placed in a functional relationship with a second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence if the promoter affects the transcription or expression of the coding

sequence. Operably linked DNA sequences may be in close proximity or contiguous and, where necessary to join two protein coding regions, in the same reading frame.

“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.

“Post-translational modification” of an RMEP may involve lipidation, glycosylation, phosphorylation, acetylation, racemization, proteolytic cleavage, and other modifications known in the art. These processes may occur synthetically or biochemically. Biochemical modifications will vary by cell type depending on the enzymatic milieu of RMEP.

“Probe” refers to nucleic acid sequences encoding RMEP, their complements, or fragments thereof, which are used to detect identical, allelic or related nucleic acid sequences. Probes are isolated oligonucleotides or polynucleotides attached to a detectable label or reporter molecule. Typical labels include radioactive isotopes, ligands, chemiluminescent agents, and enzymes. “Primers” are short nucleic acids, usually DNA oligonucleotides, which may be annealed to a target polynucleotide by complementary base-pairing. The primer may then be extended along the target DNA strand by a DNA polymerase enzyme. Primer pairs can be used for amplification (and identification) of a nucleic acid sequence, e.g., by the polymerase chain reaction (PCR).

Probes and primers as used in the present invention typically comprise at least 15 contiguous nucleotides of a known sequence. In order to enhance specificity, longer probes and primers may also be employed, such as probes and primers that comprise at least 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, or at least 150 consecutive nucleotides of the disclosed nucleic acid sequences. Probes and primers may be considerably longer than these examples, and it is understood that any length supported by the specification, including the tables, figures, and Sequence Listing, may be used.

Methods for preparing and using probes and primers are described in the references, for example Sambrook, J. et al. (1989) Molecular Cloning: A Laboratory Manual, 2nd ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; Ausubel, F.M. et al. (1987) Current Protocols in Molecular Biology, Greene Publ. Assoc. & Wiley-Intersciences, New York NY; Innis, M. et al. (1990) PCR Protocols, A Guide to Methods and Applications, Academic Press, San Diego CA. PCR primer pairs can be derived from a known sequence, for example, by using computer programs intended for that purpose such as Primer (Version 0.5, 1991, Whitehead Institute for Biomedical Research, Cambridge MA).

Oligonucleotides for use as primers are selected using software known in the art for such

purpose. For example, OLIGO 4.06 software is useful for the selection of PCR primer pairs of up to 100 nucleotides each, and for the analysis of oligonucleotides and larger polynucleotides of up to 5,000 nucleotides from an input polynucleotide sequence of up to 32 kilobases. Similar primer selection programs have incorporated additional features for expanded capabilities. For example, the PrimOU
5 primer selection program (available to the public from the Genome Center at University of Texas South West Medical Center, Dallas TX) is capable of choosing specific primers from megabase sequences and is thus useful for designing primers on a genome-wide scope. The Primer3 primer selection program (available to the public from the Whitehead Institute/MIT Center for Genome Research, Cambridge MA) allows the user to input a “mispriming library,” in which sequences to avoid as primer binding
10 sites are user-specified. Primer3 is useful, in particular, for the selection of oligonucleotides for microarrays. (The source code for the latter two primer selection programs may also be obtained from their respective sources and modified to meet the user’s specific needs.) The PrimeGen program (available to the public from the UK Human Genome Mapping Project Resource Centre, Cambridge UK) designs primers based on multiple sequence alignments, thereby allowing selection of primers that
15 hybridize to either the most conserved or least conserved regions of aligned nucleic acid sequences. Hence, this program is useful for identification of both unique and conserved oligonucleotides and polynucleotide fragments. The oligonucleotides and polynucleotide fragments identified by any of the above selection methods are useful in hybridization technologies, for example, as PCR or sequencing primers, microarray elements, or specific probes to identify fully or partially complementary
20 polynucleotides in a sample of nucleic acids. Methods of oligonucleotide selection are not limited to those described above.

A “recombinant nucleic acid” is a sequence that is not naturally occurring or has a sequence that is made by an artificial combination of two or more otherwise separated segments of sequence. This artificial combination is often accomplished by chemical synthesis or, more commonly, by the
25 artificial manipulation of isolated segments of nucleic acids, e.g., by genetic engineering techniques such as those described in Sambrook, *supra*. The term recombinant includes nucleic acids that have been altered solely by addition, substitution, or deletion of a portion of the nucleic acid. Frequently, a recombinant nucleic acid may include a nucleic acid sequence operably linked to a promoter sequence. Such a recombinant nucleic acid may be part of a vector that is used, for example, to transform a cell.

30 Alternatively, such recombinant nucleic acids may be part of a viral vector, e.g., based on a vaccinia virus, that could be used to vaccinate a mammal wherein the recombinant nucleic acid is expressed, inducing a protective immunological response in the mammal.

A “regulatory element” refers to a nucleic acid sequence usually derived from untranslated regions of a gene and includes enhancers, promoters, introns, and 5' and 3' untranslated regions (UTRs).

Regulatory elements interact with host or viral proteins which control transcription, translation, or RNA stability.

“Reporter molecules” are chemical or biochemical moieties used for labeling a nucleic acid, amino acid, or antibody. Reporter molecules include radionuclides; enzymes; fluorescent,
5 chemiluminescent, or chromogenic agents; substrates; cofactors; inhibitors; magnetic particles; and other moieties known in the art.

An “RNA equivalent,” in reference to a DNA sequence, is composed of the same linear sequence of nucleotides as the reference DNA sequence with the exception that all occurrences of the nitrogenous base thymine are replaced with uracil, and the sugar backbone is composed of ribose instead
10 of deoxyribose.

The term “sample” is used in its broadest sense. A sample suspected of containing RMEP, nucleic acids encoding RMEP, or fragments thereof 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.

15 The terms “specific binding” and “specifically binding” refer to that interaction between a protein or peptide and an agonist, an antibody, an antagonist, a small molecule, or any natural or synthetic binding composition. 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 comprising the epitope
20 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 “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 60% free, preferably at least 75% free, and most preferably at least 90% free from other components with which
25 they are naturally associated.

A “substitution” refers to the replacement of one or more amino acid residues or nucleotides by different amino acid residues 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,
30 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.

A “transcript image” refers to the collective pattern of gene expression by a particular cell type or tissue under given conditions at a given time.

“Transformation” describes a process by which exogenous DNA is introduced into 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 not limited to, bacteriophage or 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.

A "transgenic organism," as used herein, is any organism, including but not limited to animals and plants, in which one or more of the cells of the organism contains heterologous nucleic acid introduced by way of human intervention, such as by transgenic techniques well known in the art. The nucleic acid is introduced into the cell, directly or indirectly by introduction into a precursor of the cell, by way of deliberate genetic manipulation, such as by microinjection or by infection with a recombinant virus. The term genetic manipulation does not include classical cross-breeding, or in vitro fertilization, but rather is directed to the introduction of a recombinant DNA molecule. The transgenic organisms contemplated in accordance with the present invention include bacteria, cyanobacteria, fungi, plants and animals. The isolated DNA of the present invention can be introduced into the host by methods known in the art, for example infection, transfection, transformation or transconjugation. Techniques for transferring the DNA of the present invention into such organisms are widely known and provided in references such as Sambrook et al. (1989), supra.

A "variant" of a particular nucleic acid sequence is defined as a nucleic acid sequence having at least 40% sequence identity to the particular nucleic acid sequence over a certain length of one of the nucleic acid sequences using blastn with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of nucleic acids may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% or greater sequence identity over a certain defined length. A variant may be described as, for example, an "allelic" (as defined above), "splice," "species," or "polymorphic" variant. A splice variant may have significant identity to a reference molecule, but will generally have a greater or lesser number of polynucleotides due to alternative splicing of exons during mRNA processing. The corresponding polypeptide may possess additional functional domains or lack domains that are present in the reference molecule. Species variants are polynucleotide sequences that vary from one species to another. The resulting polypeptides will generally 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 nucleotide base. The presence of SNPs may be indicative of, for example, a certain population, a disease state, or a propensity for a disease state.

A “variant” of a particular polypeptide sequence is defined as a polypeptide sequence having at least 40% sequence identity to the particular polypeptide sequence over a certain length of one of the polypeptide sequences using blastp with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of polypeptides may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% or greater sequence identity over a certain defined length of one of the polypeptides.

THE INVENTION

The invention is based on the discovery of new human RNA metabolism proteins (RMEP), the polynucleotides encoding RMEP, and the use of these compositions for the diagnosis, treatment, or prevention of nervous system, autoimmune/inflammatory, cell proliferative, and developmental disorders.

Table 1 summarizes the nomenclature for the full length polynucleotide and polypeptide sequences of the invention. Each polynucleotide and its corresponding polypeptide are correlated to a single Incyte project identification number (Incyte Project ID). Each polypeptide sequence is denoted by both a polypeptide sequence identification number (Polypeptide SEQ ID NO:) and an Incyte polypeptide sequence number (Incyte Polypeptide ID) as shown. Each polynucleotide sequence is denoted by both a polynucleotide sequence identification number (Polynucleotide SEQ ID NO:) and an Incyte polynucleotide consensus sequence number (Incyte Polynucleotide ID) as shown.

Table 2 shows sequences with homology to the polypeptides of the invention as identified by BLAST analysis against the GenBank protein (genpept) database. Columns 1 and 2 show the polypeptide sequence identification number (Polypeptide SEQ ID NO:) and the corresponding Incyte polypeptide sequence number (Incyte Polypeptide ID) for polypeptides of the invention. Column 3 shows the GenBank identification number (Genbank ID NO:) of the nearest GenBank homolog. Column 4 shows the probability score for the match between each polypeptide and its GenBank homolog. Column 5 shows the annotation of the GenBank homolog along with relevant citations where applicable, all of which are expressly incorporated by reference herein.

Table 3 shows various structural features of the polypeptides of the invention. Columns 1 and 2 show the polypeptide sequence identification number (SEQ ID NO:) and the corresponding Incyte polypeptide sequence number (Incyte Polypeptide ID) for each polypeptide of the invention. Column 3

shows the number of amino acid residues in each polypeptide. Column 4 shows potential phosphorylation sites, and column 5 shows potential glycosylation sites, as determined by the MOTIFS program of the GCG sequence analysis software package (Genetics Computer Group, Madison WI). Column 6 shows amino acid residues comprising signature sequences, domains, and motifs. Column 7 shows analytical methods for protein structure/function analysis and in some cases, searchable databases to which the analytical methods were applied.

Together, Tables 2 and 3 summarize the properties of polypeptides of the invention, and these properties establish that the claimed polypeptides are RNA metabolism proteins. SEQ ID NO:46 is 29% identical to Glu-tRNA^{Gln} amidotransferase, subunit A, of *Neisseria meningitidis* (GenBank ID g7226601) as determined by the Basic Local Alignment Search Tool (BLAST, see Table 2). The BLAST probability score is 1.3e-37, which indicates the probability of obtaining the observed polypeptide sequence alignment by chance. SEQ ID NO:46 also contains amidase signature sequences as determined by searching for statistically significant matches in the hidden Markov model (HMM)-based PFAM database of conserved protein family domains (see Table 3). Data from BLIMPS and PROFILESCAN analyses provide further corroborative evidence that SEQ ID NO:46 contains amidase signature sequences, features of polypeptides involved in transamination reactions. These data provide evidence that SEQ ID NO:46 is related to the Glu-tRNA^{Gln} amidotransferases found in prokaryotes and some cellular organelles but, until the instant invention, not in humans. SEQ ID NO:47 is 97% identical to the 60S acidic ribosomal protein of *Zea mays* (GenBank ID g790508) as determined by the Basic Local Alignment Search Tool (BLAST, see Table 2). The BLAST probability score is 5.4e-51. SEQ ID NO:47 also contains a 60S acidic ribosomal protein domain as determined by searching for statistically significant matches in the hidden Markov model (HMM)-based PFAM database of conserved protein family domains (see Table 3). Data from BLIMPS analyses provide further corroborative evidence that SEQ ID NO:47 is a phosphorylated (hence likely to be acidic) ribosomal protein. SEQ ID NO:1-45 were analyzed and annotated in a similar manner. The algorithms and parameters for the analysis of SEQ ID NO:1-47 are described in Table 7.

As shown in Table 4, the full length polynucleotide sequences of the present invention were assembled using cDNA sequences or coding (exon) sequences derived from genomic DNA, or any combination of these two types of sequences. Columns 1 and 2 list the polynucleotide sequence identification number (Polynucleotide SEQ ID NO:) and the corresponding Incyte polynucleotide consensus sequence number (Incyte Polynucleotide ID) for each polynucleotide of the invention. Column 3 shows the length of each polynucleotide sequence in basepairs. Column 4 lists fragments of the polynucleotide sequences which are useful, for example, in hybridization or amplification technologies that identify SEQ ID NO:48-94 or that distinguish between SEQ ID NO:48-94 and

related polynucleotide sequences. Column 5 shows identification numbers corresponding to cDNA sequences, coding sequences (exons) predicted from genomic DNA, and/or sequence assemblages comprised of both cDNA and genomic DNA. These sequences were used to assemble the full length polynucleotide sequences of the invention. Columns 6 and 7 of Table 4 show the nucleotide start (5') and stop (3') positions of the cDNA sequences in column 5 relative to their respective full length sequences.

The identification numbers in Column 5 of Table 4 may refer specifically, for example, to Incyte cDNAs along with their corresponding cDNA libraries. For example, 642017H1 is the identification number of an Incyte cDNA sequence, and BRSTNOT03 is the cDNA library from which it is derived. Incyte cDNAs for which cDNA libraries are not indicated were derived from pooled cDNA libraries (e.g., 70822015V1). Alternatively, the identification numbers in column 5 may refer to GenBank cDNAs or ESTs (e.g., g1136841) which contributed to the assembly of the full length polynucleotide sequences. Alternatively, the identification numbers in column 5 may refer to coding regions predicted by Genscan analysis of genomic DNA. The Genscan-predicted coding sequences may have been edited prior to assembly. (See Example IV.) Alternatively, the identification numbers in column 5 may refer to assemblages of both cDNA and Genscan-predicted exons brought together by an "exon stitching" algorithm. (See Example V.) Alternatively, the identification numbers in column 5 may refer to assemblages of both cDNA and Genscan-predicted exons brought together by an "exon-stretching" algorithm. (See Example V.) In some cases, Incyte cDNA coverage redundant with the sequence coverage shown in column 5 was obtained to confirm the final consensus polynucleotide sequence, but the relevant Incyte cDNA identification numbers are not shown.

Table 5 shows the representative cDNA libraries for those full length polynucleotide sequences which were assembled using Incyte cDNA sequences. The representative cDNA library is the Incyte cDNA library which is most frequently represented by the Incyte cDNA sequences which were used to assemble and confirm the above polynucleotide sequences. The tissues and vectors which were used to construct the cDNA libraries shown in Table 5 are described in Table 6.

The invention also encompasses RMEP variants. A preferred RMEP variant is one which has at least about 80%, or alternatively at least about 90%, or even at least about 95% amino acid sequence identity to the RMEP amino acid sequence, and which contains at least one functional or structural characteristic of RMEP.

The invention also encompasses polynucleotides which encode RMEP. In a particular embodiment, the invention encompasses a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:48-94, which encodes RMEP. The polynucleotide sequences of SEQ ID NO:48-94, as presented in the Sequence Listing, embrace the equivalent RNA sequences,

wherein occurrences of the nitrogenous base thymine are replaced with uracil, and the sugar backbone is composed of ribose instead of deoxyribose.

The invention also encompasses a variant of a polynucleotide sequence encoding RMEP. In particular, such a variant polynucleotide sequence will have at least about 70%, or alternatively at least
5 about 85%, or even at least about 95% polynucleotide sequence identity to the polynucleotide sequence encoding RMEP. A particular aspect of the invention encompasses a variant of a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:48-94 which has at least about 70%, or alternatively at least about 85%, or even at least about 95% polynucleotide sequence identity to a nucleic acid sequence selected from the group consisting of SEQ ID NO:48-94.
10 Any one of the polynucleotide variants described above can encode an amino acid sequence which contains at least one functional or structural characteristic of RMEP.

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

Although nucleotide sequences which encode RMEP and its variants are generally capable of
20 hybridizing to the nucleotide sequence of the naturally occurring RMEP under appropriately selected conditions of stringency, it may be advantageous to produce nucleotide sequences encoding RMEP 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
25 are utilized by the host. Other reasons for substantially altering the nucleotide sequence encoding RMEP 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 RMEP and
30 RMEP 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 RMEP or any fragment thereof.

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:48-94 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.) Hybridization conditions, including annealing and wash conditions, are described in "Definitions."

5 Methods for DNA sequencing are well known in the art and may be used to practice any 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 (Applied Biosystems), thermostable T7 polymerase (Amersham Pharmacia Biotech, Piscataway NJ), or combinations of polymerases and proofreading exonucleases such as those found in the ELONGASE amplification
10 system (Life Technologies, Gaithersburg MD). Preferably, sequence preparation is automated with machines such as the MICROLAB 2200 liquid transfer system (Hamilton, Reno NV), PTC200 thermal cycler (MJ Research, Watertown MA) and ABI CATALYST 800 thermal cycler (Applied Biosystems). Sequencing is then carried out using either the ABI 373 or 377 DNA sequencing system (Applied Biosystems), the MEGABACE 1000 DNA sequencing system (Molecular Dynamics, Sunnyvale CA),
15 or other systems known in the art. The resulting sequences are analyzed using a variety of 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 RMEP may be extended utilizing a partial nucleotide
20 sequence and employing various PCR-based methods known in the art to detect upstream 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
25 from a circularized template. The template is derived from restriction 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
30 ligations may be used to insert an 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.* 19:3055-3060). 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 using appropriate
15 software (e.g., GENOTYPER and SEQUENCE NAVIGATOR, Applied Biosystems), 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 which
20 encode RMEP may be cloned in recombinant DNA molecules that direct expression of RMEP, 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 RMEP.

 The nucleotide sequences of the present invention can be engineered using methods generally
25 known in the art in order to alter RMEP-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, oligonucleotide-mediated site-directed mutagenesis may be used to introduce mutations that create new restriction sites,
30 alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

 The nucleotides of the present invention may be subjected to DNA shuffling techniques such as MOLECULARBREEDING (Maxygen Inc., Santa Clara CA; described in U.S. Patent Number 5,837,458; Chang, C.-C. et al. (1999) Nat. Biotechnol. 17:793-797; Christians, F.C. et al. (1999) Nat. Biotechnol. 17:259-264; and Cramer, A. et al. (1996) Nat. Biotechnol. 14:315-319) to alter or

improve the biological properties of RMEP, such as its biological or enzymatic activity or its ability to bind to other molecules or compounds. DNA shuffling is a process by which a library of gene variants is produced using PCR-mediated recombination of gene fragments. The library is then subjected to selection or screening procedures that identify those gene variants with the desired
5 properties. These preferred variants may then be pooled and further subjected to recursive rounds of DNA shuffling and selection/screening. Thus, genetic diversity is created through "artificial" breeding and rapid molecular evolution. For example, fragments of a single gene containing random point mutations may be recombined, screened, and then reshuffled until the desired properties are optimized. Alternatively, fragments of a given gene may be recombined with fragments of
10 homologous genes in the same gene family, either from the same or different species, thereby maximizing the genetic diversity of multiple naturally occurring genes in a directed and controllable manner.

In another embodiment, sequences encoding RMEP 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) Nucleic Acids
15 Symp. Ser. 7:215-223; and Horn, T. et al. (1980) Nucleic Acids Symp. Ser. 7:225-232.) Alternatively, RMEP itself or a fragment thereof may be synthesized using chemical methods. For example, peptide synthesis can be performed using various solution-phase or solid-phase techniques. (See, e.g., Creighton, T. (1984) Proteins, Structures and Molecular Properties, WH Freeman, New York NY, pp. 55-60; and Roberge, J.Y. et al. (1995) Science 269:202-204.) Automated synthesis may be achieved using the ABI
20 431A peptide synthesizer (Applied Biosystems). Additionally, the amino acid sequence of RMEP, 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 or a polypeptide having a sequence of a naturally occurring polypeptide.

The peptide may be substantially purified by preparative high performance liquid
25 chromatography. (See, e.g., Chiez, R.M. and F.Z. Regnier (1990) Methods Enzymol. 182:392-421.) The composition of the synthetic peptides may be confirmed by amino acid analysis or by sequencing. (See, e.g., Creighton, supra, pp. 28-53.)

In order to express a biologically active RMEP, the nucleotide sequences encoding RMEP or derivatives thereof may be inserted into an appropriate expression vector, i.e., a vector which contains
30 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 RMEP. Such elements may vary in their strength and specificity. Specific initiation signals may also be used to achieve more efficient translation of sequences encoding RMEP. Such signals

include the ATG initiation codon and adjacent sequences, e.g. the Kozak sequence. In cases where sequences encoding RMEP 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
 5 translational control signals 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.)

10 Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding RMEP 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)
 15 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 RMEP. These include, but are not limited to, microorganisms such as 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);
 20 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. (See, e.g., Sambrook, supra; Ausubel, supra; Van Heeke, G. and S.M. Schuster (1989) *J. Biol. Chem.* 264:5503-5509; 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; Takamatsu, N. (1987) *EMBO J.* 6:307-311; The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY, pp. 191-196; Logan, J. and T. Shenk (1984) *Proc. Natl. Acad. Sci. USA* 81:3655-3659; and Harrington, J.J. et al. (1997) *Nat. Genet.* 15:345-355.) 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. (See, e.g., Di Nicola,
 30 M. et al. (1998) *Cancer Gen. Ther.* 5(6):350-356; Yu, M. et al. (1993) *Proc. Natl. Acad. Sci. USA* 90(13):6340-6344; Buller, R.M. et al. (1985) *Nature* 317(6040):813-815; McGregor, D.P. et al. (1994) *Mol. Immunol.* 31(3):219-226; and Verma, I.M. and N. Somia (1997) *Nature* 389:239-242.) The invention is not limited by the 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 RMEP. For example, routine cloning, subcloning, and propagation of polynucleotide sequences encoding RMEP can be achieved using a multifunctional *E. coli* vector such as PBLUESCRIPT (Stratagene, La Jolla CA) or PSPO1 plasmid (Life Technologies). Ligation of sequences encoding RMEP into the vector's multiple cloning site
 5 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. and S.M. Schuster (1989) J. Biol. Chem. 264:5503-5509.) When large quantities of RMEP are needed, e.g. for the production of antibodies,
 10 vectors which direct high level expression of RMEP may be used. For example, vectors containing the strong, inducible SP6 or T7 bacteriophage promoter may be used.

Yeast expression systems may be used for production of RMEP. A number of vectors containing constitutive or inducible promoters, such as alpha factor, alcohol oxidase, and PGH promoters, may be used in the yeast *Saccharomyces cerevisiae* or *Pichia pastoris*. In addition, such
 15 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*; Bitter, G.A. et al. (1987) Methods Enzymol. 153:516-544; and Scorer, C.A. et al. (1994) Bio/Technology 12:181-184.)

Plant systems may also be used for expression of RMEP. Transcription of sequences encoding
 20 RMEP may be driven by 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
 25 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 RMEP may be ligated into an
 30 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 RMEP in host cells. (See, e.g., Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. USA 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 RMEP in cell lines is preferred. For example, sequences encoding RMEP 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* and *apr* 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* and *pat* confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively. (See, e.g., Wigler, M. et al. (1980) Proc. Natl. Acad. Sci. USA 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. USA 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.)

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 RMEP is inserted within a marker gene sequence, transformed cells containing sequences encoding RMEP can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a sequence encoding RMEP 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 RMEP and that express RMEP may be identified by a variety of procedures known to those of skill in the art. These procedures
5 include, but are not limited to, DNA-DNA or DNA-RNA hybridizations, PCR 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 RMEP using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include
10 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 RMEP 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. Paul MN, Sect. IV; Coligan, J.E. et al.
15 (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 RMEP include oligolabeling,
20 nick translation, end-labeling, or PCR amplification using a labeled nucleotide. Alternatively, the sequences encoding RMEP, 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 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
25 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, fluorescent, chemiluminescent, or chromogenic agents, as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with nucleotide sequences encoding RMEP may be cultured under
30 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 sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides which encode RMEP may be designed to contain signal sequences which direct secretion of RMEP 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 of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a “prepro” or “pro” 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 the American Type Culture Collection (ATCC, Manassas VA) and may be chosen to ensure the correct modification and processing of the foreign protein.

10 In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences encoding RMEP 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 RMEP protein containing a heterologous moiety that can be recognized by a commercially available antibody may facilitate the screening of peptide libraries for inhibitors of RMEP activity. Heterologous protein and peptide
15 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,
20 respectively. FLAG, *c-myc*, and hemagglutinin (HA) enable immunoaffinity purification of fusion proteins using commercially available monoclonal and polyclonal antibodies that specifically recognize these epitope tags. A fusion protein may also be engineered to contain a proteolytic cleavage site located between the RMEP encoding sequence and the heterologous protein sequence, so that RMEP may be cleaved away from the heterologous moiety following purification. Methods for fusion protein
25 expression and purification are discussed in Ausubel (1995, supra, ch. 10). A variety of commercially available kits may also be used to facilitate expression and purification of fusion proteins.

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

RMEP of the present invention or fragments thereof may be used to screen for compounds that specifically bind to RMEP. At least one and up to a plurality of test compounds may be screened for specific binding to RMEP. Examples of test compounds include antibodies, oligonucleotides,

proteins (e.g., receptors), or small molecules.

In one embodiment, the compound thus identified is closely related to the natural ligand of RMEP, e.g., a ligand or fragment thereof, a natural substrate, a structural or functional mimetic, or a natural binding partner. (See, e.g., Coligan, J.E. et al. (1991) Current Protocols in Immunology 1(2): Chapter 5.) Similarly, the compound can be closely related to the natural receptor to which RMEP binds, or to at least a fragment of the receptor, e.g., the ligand binding site. In either case, the compound can be rationally designed using known techniques. In one embodiment, screening for these compounds involves producing appropriate cells which express RMEP, either as a secreted protein or on the cell membrane. Preferred cells include cells from mammals, yeast, Drosophila, or E. coli. Cells expressing RMEP or cell membrane fractions which contain RMEP are then contacted with a test compound and binding, stimulation, or inhibition of activity of either RMEP or the compound is analyzed.

An assay may simply test binding of a test compound to the polypeptide, wherein binding is detected by a fluorophore, radioisotope, enzyme conjugate, or other detectable label. For example, the assay may comprise the steps of combining at least one test compound with RMEP, either in solution or affixed to a solid support, and detecting the binding of RMEP to the compound. Alternatively, the assay may detect or measure binding of a test compound in the presence of a labeled competitor. Additionally, the assay may be carried out using cell-free preparations, chemical libraries, or natural product mixtures, and the test compound(s) may be free in solution or affixed to a solid support.

RMEP of the present invention or fragments thereof may be used to screen for compounds that modulate the activity of RMEP. Such compounds may include agonists, antagonists, or partial or inverse agonists. In one embodiment, an assay is performed under conditions permissive for RMEP activity, wherein RMEP is combined with at least one test compound, and the activity of RMEP in the presence of a test compound is compared with the activity of RMEP in the absence of the test compound. A change in the activity of RMEP in the presence of the test compound is indicative of a compound that modulates the activity of RMEP. Alternatively, a test compound is combined with an in vitro or cell-free system comprising RMEP under conditions suitable for RMEP activity, and the assay is performed. In either of these assays, a test compound which modulates the activity of RMEP may do so indirectly and need not come in direct contact with the test compound. At least one and up to a plurality of test compounds may be screened.

In another embodiment, polynucleotides encoding RMEP or their mammalian homologs may be “knocked out” in an animal model system using homologous recombination in embryonic stem (ES) cells. Such techniques are well known in the art and are useful for the generation of animal models of human disease. (See, e.g., U.S. Patent Number 5,175,383 and U.S. Patent Number 5,767,337.) For example, mouse ES cells, such as the mouse 129/SvJ cell line, are derived from the early mouse embryo

and grown in culture. The ES cells are transformed with a vector containing the gene of interest disrupted by a marker gene, e.g., the neomycin phosphotransferase gene (neo; Capecchi, M.R. (1989) Science 244:1288-1292). The vector integrates into the corresponding region of the host genome by homologous recombination. Alternatively, homologous recombination takes place using the Cre-loxP
 5 system to knockout a gene of interest in a tissue- or developmental stage-specific manner (Marth, J.D. (1996) Clin. Invest. 97:1999-2002; Wagner, K.U. et al. (1997) Nucleic Acids Res. 25:4323-4330).

Transformed ES cells are identified and microinjected into mouse cell blastocysts such as those from the C57BL/6 mouse strain. The blastocysts are surgically transferred to pseudopregnant dams, and the resulting chimeric progeny are genotyped and bred to produce heterozygous or homozygous strains.

10 Transgenic animals thus generated may be tested with potential therapeutic or toxic agents.

Polynucleotides encoding RMEP may also be manipulated in vitro in ES cells derived from human blastocysts. Human ES cells have the potential to differentiate into at least eight separate cell lineages including endoderm, mesoderm, and ectodermal cell types. These cell lineages differentiate into, for example, neural cells, hematopoietic lineages, and cardiomyocytes (Thomson, J.A. et al. (1998)
 15 Science 282:1145-1147).

Polynucleotides encoding RMEP can also be used to create "knockin" humanized animals (pigs) or transgenic animals (mice or rats) to model human disease. With knockin technology, a region of a polynucleotide encoding RMEP is injected into animal ES cells, and the injected sequence integrates into the animal cell genome. Transformed cells are injected into blastulae, and the blastulae are implanted as
 20 described above. Transgenic progeny or inbred lines are studied and treated with potential pharmaceutical agents to obtain information on treatment of a human disease. Alternatively, a mammal inbred to overexpress RMEP, e.g., by secreting RMEP in its milk, may also serve as a convenient source of that protein (Janne, J. et al. (1998) Biotechnol. Annu. Rev. 4:55-74).

THERAPEUTICS

25 Chemical and structural similarity, e.g., in the context of sequences and motifs, exists between regions of RMEP and RNA metabolism proteins. In addition, the expression of RMEP is closely associated with diseased, proliferative, tumorous, and nervous tissues, adrenal tissue, brain tumor tissue, fetal colon tissue, adult colon tissue, prostate epithelial tissue, lymph node cancer tissue, ovarian tissue, pancreatic tissue, and fetal spleen tissue, as well as with diseases of the lung, and
 30 physiological conditions that result in anoxia. Therefore, RMEP appears to play a role in nervous system, autoimmune/inflammatory, cell proliferative, and developmental disorders, as well as neoplasms involving lung-specific tissues. In the treatment of disorders associated with increased RMEP expression or activity, it is desirable to decrease the expression or activity of RMEP. In the treatment of disorders associated with decreased RMEP expression or activity, it is desirable to

increase the expression or activity of RMEP.

Therefore, in one embodiment, RMEP 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 RMEP. Examples of such disorders include, but are not limited to, a nervous system disorder such as epilepsy, ischemic cerebrovascular disease, stroke, cerebral neoplasms, Alzheimer's disease, Pick's disease, Huntington's disease, dementia, Parkinson's disease and other extrapyramidal disorders, amyotrophic lateral sclerosis and other motor neuron disorders, progressive neural muscular atrophy, retinitis pigmentosa, hereditary ataxias, multiple sclerosis and other demyelinating diseases, bacterial and viral meningitis, brain abscess, subdural empyema, epidural abscess, suppurative intracranial thrombophlebitis, myelitis and radiculitis, viral central nervous system disease; prion diseases including kuru, Creutzfeldt-Jakob disease, and Gerstmann-Straussler-Scheinker syndrome; fatal familial insomnia, nutritional and metabolic diseases of the nervous system, neurofibromatosis, tuberous sclerosis, cerebelloretinal hemangioblastomatosis, encephalotrigeminal syndrome, mental retardation and other developmental disorder of the central nervous system, cerebral palsy, a neuroskeletal disorder, an autonomic nervous system disorder, a cranial nerve disorder, a spinal cord disease, muscular dystrophy and other neuromuscular disorder, a peripheral nervous system disorder, dermatomyositis and polymyositis; inherited, metabolic, endocrine, and toxic myopathy; myasthenia gravis, periodic paralysis; a mental disorder including mood, anxiety, and schizophrenic disorders; seasonal affective disorder (SAD); akathisia, amnesia, catatonia, diabetic neuropathy, tardive dyskinesia, dystonias, paranoid psychoses, postherpetic neuralgia, and Tourette's disorder; an autoimmune/inflammatory disorder such as acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, 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 cell proliferative disorder such as actinic keratosis, arteriosclerosis, 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, cancers 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 a developmental disorder such as renal tubular acidosis, anemia, Cushing's syndrome, achondroplastic dwarfism, Duchenne and Becker muscular dystrophy, epilepsy, gonadal dysgenesis, WAGR syndrome (Wilms' tumor, aniridia, genitourinary abnormalities, and mental retardation), Smith-Magenis syndrome, myelodysplastic syndrome, hereditary mucoepithelial dysplasia, hereditary keratodermas, hereditary neuropathies such as Charcot-Marie-Tooth disease and neurofibromatosis, hypothyroidism, hydrocephalus, seizure disorders such as Sydenham's chorea and cerebral palsy, spina bifida, anencephaly, craniorachischisis, congenital glaucoma, cataract, and sensorineural hearing loss.

In another embodiment, a vector capable of expressing RMEP 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 RMEP including, but not limited to, those described above.

In a further embodiment, a composition comprising a substantially purified RMEP 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 RMEP including, but not limited to, those provided above.

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

In a further embodiment, an antagonist of RMEP may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of RMEP. Examples of such disorders include, but are not limited to, those nervous system, autoimmune/inflammatory, cell proliferative, and developmental described above. In one aspect, an antibody which specifically binds RMEP may be used directly as an antagonist or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissues which express RMEP.

In an additional embodiment, a vector expressing the complement of the polynucleotide encoding RMEP may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of RMEP 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 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.

5 An antagonist of RMEP may be produced using methods which are generally known in the art. In particular, purified RMEP may be used to produce antibodies or to screen libraries of pharmaceutical agents to identify those which specifically bind RMEP. Antibodies to RMEP 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
10 by a Fab expression library. Neutralizing antibodies (i.e., those which inhibit dimer formation) are generally 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 RMEP or with any fragment or oligopeptide thereof which has immunogenic properties. Depending on the host species, various adjuvants may be used to increase
15 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.

It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to RMEP
20 have an amino acid sequence consisting of at least about 5 amino acids, and generally will consist 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. Short stretches of RMEP amino acids may be fused with those of another protein, such as KLH, and antibodies to the chimeric molecule may be produced.

25 Monoclonal antibodies to RMEP 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-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. USA 80:2026-2030; and Cole, S.P. et al.
30 (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 antigen specificity and biological activity, can be used. (See, e.g., Morrison, S.L. et al. (1984) Proc. Natl. Acad. Sci. USA 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 RMEP-specific single chain antibodies. Antibodies with related specificity, but of distinct idiotypic composition, may be generated by chain shuffling from random combinatorial immunoglobulin libraries. (See, e.g., Burton, D.R.

5 (1991) Proc. Natl. Acad. Sci. USA 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. USA 86:3833-3837; Winter, G. et al. (1991) Nature 349:293-299.)

10 Antibody fragments which contain specific binding sites for RMEP 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 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.
15 (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 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 RMEP and its specific
20 antibody. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering RMEP epitopes is generally used, but a competitive binding assay may also be employed (Pound, supra).

Various methods such as Scatchard analysis in conjunction with radioimmunoassay techniques may be used to assess the affinity of antibodies for RMEP. Affinity is expressed as an association
25 constant, K_a , which is defined as the molar concentration of RMEP-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 heterogeneous in their affinities for multiple RMEP epitopes, represents the average affinity, or avidity, of the antibodies for RMEP. The K_a determined for a preparation of monoclonal antibodies, which are monospecific for a particular RMEP epitope,
30 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 RMEP-antibody complex must withstand rigorous 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 RMEP, preferably in active form, from the antibody (Catty, D. (1988)

Antibodies, Volume I: A Practical Approach, IRL Press, Washington DC; Liddell, J.E. and A. Cryer (1991) A Practical Guide to Monoclonal Antibodies, John Wiley & Sons, New York NY).

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 generally employed in procedures requiring precipitation of RMEP-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 RMEP, or any fragment or complement thereof, may be used for therapeutic purposes. In one aspect, modifications of gene expression can be achieved by designing complementary sequences or antisense molecules (DNA, RNA, PNA, or modified oligonucleotides) to the coding or regulatory regions of the gene encoding RMEP. Such technology is well known in the art, and antisense oligonucleotides or larger fragments can be designed from various locations along the coding or control regions of sequences encoding RMEP. (See, e.g., Agrawal, S., ed. (1996) Antisense Therapeutics, Humana Press Inc., Totawa NJ.)

In therapeutic use, any gene delivery system suitable for introduction of the antisense sequences into appropriate target cells can be used. Antisense sequences can be delivered intracellularly in the form of an expression plasmid which, upon transcription, produces a sequence complementary to at least a portion of the cellular sequence encoding the target protein. (See, e.g., Slater, J.E. et al. (1998) *J. Allergy Clin. Immunol.* 102(3):469-475; and Scanlon, K.J. et al. (1995) 9(13):1288-1296.) Antisense sequences can also be introduced intracellularly through the use of viral vectors, such as retrovirus and adeno-associated virus vectors. (See, e.g., Miller, A.D. (1990) *Blood* 76:271; Ausubel, supra; Uckert, W. and W. Walther (1994) *Pharmacol. Ther.* 63(3):323-347.) Other gene delivery mechanisms include liposome-derived systems, artificial viral envelopes, and other systems known in the art. (See, e.g., Rossi, J.J. (1995) *Br. Med. Bull.* 51(1):217-225; Boado, R.J. et al. (1998) *J. Pharm. Sci.* 87(11):1308-1315; and Morris, M.C. et al. (1997) *Nucleic Acids Res.* 25(14):2730-2736.)

In another embodiment of the invention, polynucleotides encoding RMEP may be used for somatic or germline gene therapy. Gene therapy may be performed to (i) correct a genetic deficiency (e.g., in the cases of severe combined immunodeficiency (SCID)-X1 disease characterized by X-linked inheritance (Cavazzana-Calvo, M. et al. (2000) *Science* 288:669-672), severe combined immunodeficiency syndrome associated with an inherited adenosine deaminase (ADA) deficiency (Blaese, R.M. et al. (1995) *Science* 270:475-480; Bordignon, C. et al. (1995) *Science* 270:470-475),

cystic fibrosis (Zabner, J. et al. (1993) *Cell* 75:207-216; Crystal, R.G. et al. (1995) *Hum. Gene Therapy* 6:643-666; Crystal, R.G. et al. (1995) *Hum. Gene Therapy* 6:667-703), thalassemias, familial hypercholesterolemia, and hemophilia resulting from Factor VIII or Factor IX deficiencies (Crystal, R.G. (1995) *Science* 270:404-410; Verma, I.M. and N. Somia (1997) *Nature* 389:239-242)), (ii) express a conditionally lethal gene product (e.g., in the case of cancers which result from unregulated cell proliferation), or (iii) express a protein which affords protection against intracellular parasites (e.g., against human retroviruses, such as human immunodeficiency virus (HIV) (Baltimore, D. (1988) *Nature* 335:395-396; Poeschla, E. et al. (1996) *Proc. Natl. Acad. Sci. USA* 93:11395-11399), hepatitis B or C virus (HBV, HCV); fungal parasites, such as Candida albicans and Paracoccidioides brasiliensis; and

10 protozoan parasites such as Plasmodium falciparum and Trypanosoma cruzi). In the case where a genetic deficiency in RMEP expression or regulation causes disease, the expression of RMEP from an appropriate population of transduced cells may alleviate the clinical manifestations caused by the genetic deficiency.

In a further embodiment of the invention, diseases or disorders caused by deficiencies in RMEP

15 are treated by constructing mammalian expression vectors encoding RMEP and introducing these vectors by mechanical means into RMEP-deficient cells. Mechanical transfer technologies for use with cells in vivo or ex vitro include (i) direct DNA microinjection into individual cells, (ii) ballistic gold particle delivery, (iii) liposome-mediated transfection, (iv) receptor-mediated gene transfer, and (v) the use of DNA transposons (Morgan, R.A. and W.F. Anderson (1993) *Annu. Rev. Biochem.* 62:191-217; Ivics, Z. (1997) *Cell* 91:501-510; Boulay, J-L. and H. Récipon (1998) *Curr. Opin. Biotechnol.* 9:445-450).

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Expression vectors that may be effective for the expression of RMEP include, but are not limited to, the PCDNA 3.1, EPITAG, PRCCMV2, PREP, PVAX vectors (Invitrogen, Carlsbad CA), PCMV-SCRIPT, PCMV-TAG, PEGSH/PERV (Stratagene, La Jolla CA), and PTET-OFF, PTET-ON,

25 PTRE2, PTRE2-LUC, PTK-HYG (Clontech, Palo Alto CA). RMEP may be expressed using (i) a constitutively active promoter, (e.g., from cytomegalovirus (CMV), Rous sarcoma virus (RSV), SV40 virus, thymidine kinase (TK), or β -actin genes), (ii) an inducible promoter (e.g., the tetracycline-regulated promoter (Gossen, M. and H. Bujard (1992) *Proc. Natl. Acad. Sci. USA* 89:5547-5551; Gossen, M. et al. (1995) *Science* 268:1766-1769; Rossi, F.M.V. and H.M. Blau (1998) *Curr. Opin. Biotechnol.* 9:451-456), commercially available in the T-REX plasmid (Invitrogen)); the ecdysone-inducible promoter (available in the plasmids PVGRXR and PIND; Invitrogen); the FK506/rapamycin inducible promoter; or the RU486/mifepristone inducible promoter (Rossi, F.M.V. and Blau, H.M. supra)), or (iii) a tissue-specific promoter or the native promoter of the endogenous gene encoding RMEP from a normal individual.

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Commercially available liposome transformation kits (e.g., the PERFECT LIPID TRANSFECTION KIT, available from Invitrogen) allow one with ordinary skill in the art to deliver polynucleotides to target cells in culture and require minimal effort to optimize experimental parameters. In the alternative, transformation is performed using the calcium phosphate method (Graham, F.L. and A.J. Eb (1973) Virology 52:456-467), or by electroporation (Neumann, E. et al. (1982) EMBO J. 1:841-845). The introduction of DNA to primary cells requires modification of these standardized mammalian transfection protocols.

In another embodiment of the invention, diseases or disorders caused by genetic defects with respect to RMEP expression are treated by constructing a retrovirus vector consisting of (i) the polynucleotide encoding RMEP under the control of an independent promoter or the retrovirus long terminal repeat (LTR) promoter, (ii) appropriate RNA packaging signals, and (iii) a Rev-responsive element (RRE) along with additional retrovirus *cis*-acting RNA sequences and coding sequences required for efficient vector propagation. Retrovirus vectors (e.g., PFB and PFBNEO) are commercially available (Stratagene) and are based on published data (Riviere, I. et al. (1995) Proc. Natl. Acad. Sci. USA 92:6733-6737), incorporated by reference herein. The vector is propagated in an appropriate vector producing cell line (VPCL) that expresses an envelope gene with a tropism for receptors on the target cells or a promiscuous envelope protein such as VSVg (Armentano, D. et al. (1987) J. Virol. 61:1647-1650; Bender, M.A. et al. (1987) J. Virol. 61:1639-1646; Adam, M.A. and A.D. Miller (1988) J. Virol. 62:3802-3806; Dull, T. et al. (1998) J. Virol. 72:8463-8471; Zufferey, R. et al. (1998) J. Virol. 72:9873-9880). U.S. Patent Number 5,910,434 to Rigg ("Method for obtaining retrovirus packaging cell lines producing high transducing efficiency retroviral supernatant") discloses a method for obtaining retrovirus packaging cell lines and is hereby incorporated by reference. Propagation of retrovirus vectors, transduction of a population of cells (e.g., CD4⁺ T-cells), and the return of transduced cells to a patient are procedures well known to persons skilled in the art of gene therapy and have been well documented (Ranga, U. et al. (1997) J. Virol. 71:7020-7029; Bauer, G. et al. (1997) Blood 89:2259-2267; Bonyhadi, M.L. (1997) J. Virol. 71:4707-4716; Ranga, U. et al. (1998) Proc. Natl. Acad. Sci. USA 95:1201-1206; Su, L. (1997) Blood 89:2283-2290).

In the alternative, an adenovirus-based gene therapy delivery system is used to deliver polynucleotides encoding RMEP to cells which have one or more genetic abnormalities with respect to the expression of RMEP. The construction and packaging of adenovirus-based vectors are well known to those with ordinary skill in the art. Replication defective adenovirus vectors have proven to be versatile for importing genes encoding immunoregulatory proteins into intact islets in the pancreas (Csete, M.E. et al. (1995) Transplantation 27:263-268). Potentially useful adenoviral vectors are described in U.S. Patent Number 5,707,618 to Armentano ("Adenovirus vectors for gene therapy"),

hereby incorporated by reference. For adenoviral vectors, see also Antinozzi, P.A. et al. (1999) *Annu. Rev. Nutr.* 19:511-544 and Verma, I.M. and N. Somia (1997) *Nature* 18:389:239-242, both incorporated by reference herein.

In another alternative, a herpes-based, gene therapy delivery system is used to deliver
5 polynucleotides encoding RMEP to target cells which have one or more genetic abnormalities with respect to the expression of RMEP. The use of herpes simplex virus (HSV)-based vectors may be especially valuable for introducing RMEP to cells of the central nervous system, for which HSV has a tropism. The construction and packaging of herpes-based vectors are well known to those with ordinary skill in the art. A replication-competent herpes simplex virus (HSV) type 1-based vector has been used
10 to deliver a reporter gene to the eyes of primates (Liu, X. et al. (1999) *Exp. Eye Res.* 169:385-395). The construction of a HSV-1 virus vector has also been disclosed in detail in U.S. Patent Number 5,804,413 to DeLuca ("Herpes simplex virus strains for gene transfer"), which is hereby incorporated by reference. U.S. Patent Number 5,804,413 teaches the use of recombinant HSV d92 which consists of a genome containing at least one exogenous gene to be transferred to a cell under the control of the
15 appropriate promoter for purposes including human gene therapy. Also taught by this patent are the construction and use of recombinant HSV strains deleted for ICP4, ICP27 and ICP22. For HSV vectors, see also Goins, W.F. et al. (1999) *J. Virol.* 73:519-532 and Xu, H. et al. (1994) *Dev. Biol.* 163:152-161, hereby incorporated by reference. The manipulation of cloned herpesvirus sequences, the generation of recombinant virus following the transfection of multiple plasmids containing different
20 segments of the large herpesvirus genomes, the growth and propagation of herpesvirus, and the infection of cells with herpesvirus are techniques well known to those of ordinary skill in the art.

In another alternative, an alphavirus (positive, single-stranded RNA virus) vector is used to deliver polynucleotides encoding RMEP to target cells. The biology of the prototypic alphavirus, Semliki Forest Virus (SFV), has been studied extensively and gene transfer vectors have been based on
25 the SFV genome (Garoff, H. and K.-J. Li (1998) *Curr. Opin. Biotechnol.* 9:464-469). During alphavirus RNA replication, a subgenomic RNA is generated that normally encodes the viral capsid proteins. This subgenomic RNA replicates to higher levels than the full length genomic RNA, resulting in the overproduction of capsid proteins relative to the viral proteins with enzymatic activity (e.g., protease and polymerase). Similarly, inserting the coding sequence for RMEP into the alphavirus
30 genome in place of the capsid-coding region results in the production of a large number of RMEP-coding RNAs and the synthesis of high levels of RMEP in vector transduced cells. While alphavirus infection is typically associated with cell lysis within a few days, the ability to establish a persistent infection in hamster normal kidney cells (BHK-21) with a variant of Sindbis virus (SIN) indicates that the lytic replication of alphaviruses can be altered to suit the needs of the gene therapy application

(Dryga, S.A. et al. (1997) Virology 228:74-83). The wide host range of alphaviruses will allow the introduction of RMEP into a variety of cell types. The specific transduction of a subset of cells in a population may require the sorting of cells prior to transduction. The methods of manipulating infectious cDNA clones of alphaviruses, performing alphavirus cDNA and RNA transfections, and
5 performing alphavirus infections, are well known to those with ordinary skill in the art.

Oligonucleotides derived from the transcription initiation site, e.g., between about positions -10 and +10 from the start site, may also be employed to inhibit gene expression. 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 for the binding of polymerases,
10 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.

15 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 catalyze endonucleolytic cleavage of sequences encoding RMEP.

20 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 be evaluated for secondary structural features which may render the oligonucleotide inoperable. The suitability of
25 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 include techniques for chemically synthesizing oligonucleotides such as solid phase phosphoramidite chemical synthesis.
30 Alternatively, RNA molecules may be generated by in vitro and in vivo transcription of DNA sequences encoding RMEP. 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 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 and can be extended in all of these molecules by the inclusion of nontraditional bases such as inosine, queosine, and
5 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.

An additional embodiment of the invention encompasses a method for screening for a compound which is effective in altering expression of a polynucleotide encoding RMEP. Compounds which may be effective in altering expression of a specific polynucleotide may include, but are not
10 limited to, oligonucleotides, antisense oligonucleotides, triple helix-forming oligonucleotides, transcription factors and other polypeptide transcriptional regulators, and non-macromolecular chemical entities which are capable of interacting with specific polynucleotide sequences. Effective compounds may alter polynucleotide expression by acting as either inhibitors or promoters of polynucleotide expression. Thus, in the treatment of disorders associated with increased RMEP
15 expression or activity, a compound which specifically inhibits expression of the polynucleotide encoding RMEP may be therapeutically useful, and in the treatment of disorders associated with decreased RMEP expression or activity, a compound which specifically promotes expression of the polynucleotide encoding RMEP may be therapeutically useful.

At least one, and up to a plurality, of test compounds may be screened for effectiveness in
20 altering expression of a specific polynucleotide. A test compound may be obtained by any method commonly known in the art, including chemical modification of a compound known to be effective in altering polynucleotide expression; selection from an existing, commercially-available or proprietary library of naturally-occurring or non-natural chemical compounds; rational design of a compound based on chemical and/or structural properties of the target polynucleotide; and selection from a
25 library of chemical compounds created combinatorially or randomly. A sample comprising a polynucleotide encoding RMEP is exposed to at least one test compound thus obtained. The sample may comprise, for example, an intact or permeabilized cell, or an in vitro cell-free or reconstituted biochemical system. Alterations in the expression of a polynucleotide encoding RMEP are assayed by any method commonly known in the art. Typically, the expression of a specific nucleotide is detected
30 by hybridization with a probe having a nucleotide sequence complementary to the sequence of the polynucleotide encoding RMEP. The amount of hybridization may be quantified, thus forming the basis for a comparison of the expression of the polynucleotide both with and without exposure to one or more test compounds. Detection of a change in the expression of a polynucleotide exposed to a test compound indicates that the test compound is effective in altering the expression of the
35 polynucleotide. A screen for a compound effective in altering expression of a specific polynucleotide

can be carried out, for example, using a Schizosaccharomyces pombe gene expression system (Atkins, D. et al. (1999) U.S. Patent No. 5,932,435; Arndt, G.M. et al. (2000) Nucleic Acids Res. 28:E15) or a human cell line such as HeLa cell (Clarke, M.L. et al. (2000) Biochem. Biophys. Res. Commun. 268:8-13). A particular embodiment of the present invention involves screening a combinatorial
5 library of oligonucleotides (such as deoxyribonucleotides, ribonucleotides, peptide nucleic acids, and modified oligonucleotides) for antisense activity against a specific polynucleotide sequence (Bruice, T.W. et al. (1997) U.S. Patent No. 5,686,242; Bruice, T.W. et al. (2000) U.S. Patent No. 6,022,691).

Many methods for introducing vectors into cells or tissues are available and equally suitable for use in vivo, in vitro, and ex vivo. For ex vivo therapy, vectors may be introduced into stem cells taken
10 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) Nat. Biotechnol. 15:462-466.)

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

An additional embodiment of the invention relates to the administration of a composition which generally comprises an active ingredient formulated with a pharmaceutically acceptable excipient. Excipients may include, for example, sugars, starches, celluloses, gums, and proteins. Various
20 formulations are commonly known and are thoroughly discussed in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing, Easton PA). Such compositions may consist of RMEP, antibodies to RMEP, and mimetics, agonists, antagonists, or inhibitors of RMEP.

The 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,
25 intraventricular, pulmonary, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means.

Compositions for pulmonary administration may be prepared in liquid or dry powder form. These compositions are generally aerosolized immediately prior to inhalation by the patient. In the case of small molecules (e.g. traditional low molecular weight organic drugs), aerosol delivery of fast-acting
30 formulations is well-known in the art. In the case of macromolecules (e.g. larger peptides and proteins), recent developments in the field of pulmonary delivery via the alveolar region of the lung have enabled the practical delivery of drugs such as insulin to blood circulation (see, e.g., Patton, J.S. et al., U.S. Patent No. 5,997,848). Pulmonary delivery has the advantage of administration without needle injection, and obviates the need for potentially toxic penetration enhancers.

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

Specialized forms of compositions may be prepared for direct intracellular delivery of macromolecules comprising RMEP or fragments thereof. For example, liposome preparations containing a cell-impermeable macromolecule may promote cell fusion and intracellular delivery of the macromolecule. Alternatively, RMEP or a fragment thereof may be joined to a short cationic N-terminal portion from the HIV Tat-1 protein. Fusion proteins thus generated have been found to transduce into the cells of all tissues, including the brain, in a mouse model system (Schwarze, S.R. et al. (1999) Science 285:1569-1572).

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, monkeys, or pigs. An animal model may also be used to determine the appropriate concentration range and 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 RMEP or fragments thereof, antibodies of RMEP, and agonists, antagonists or inhibitors of RMEP, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be 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 toxic to therapeutic effects is the therapeutic index, which can be expressed as the LD_{50}/ED_{50} ratio. Compositions which exhibit large therapeutic indices are preferred. The data obtained from cell 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 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 compositions may be 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

In another embodiment, antibodies which specifically bind RMEP may be used for the diagnosis of disorders characterized by expression of RMEP, or in assays to monitor patients being treated with RMEP or agonists, antagonists, or inhibitors of RMEP. Antibodies useful for diagnostic purposes may be prepared in the same manner as described above for therapeutics. Diagnostic assays for RMEP include methods which utilize the antibody and a label to detect RMEP 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 RMEP, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of RMEP expression. Normal or standard values for RMEP expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, for example, human subjects, with antibodies to RMEP under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, such as photometric means. Quantities of RMEP 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 RMEP may be used for diagnostic purposes. The polynucleotides which may be used include oligonucleotide sequences, complementary RNA and DNA molecules, and PNAs. The polynucleotides may be used to detect and quantify gene expression in biopsied tissues in which expression of RMEP may be correlated with disease. The diagnostic assay may be used to determine absence, presence, and excess expression of RMEP, and to monitor regulation of RMEP levels during therapeutic intervention.

In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding RMEP or closely related molecules may be used to identify nucleic acid sequences which encode RMEP. 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 will determine whether the probe identifies only naturally occurring sequences encoding RMEP, allelic variants, or related

sequences.

Probes may also be used for the detection of related sequences, and may have at least 50% sequence identity to any of the RMEP encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:48-94 or from
 5 genomic sequences including promoters, enhancers, and introns of the RMEP gene.

Means for producing specific hybridization probes for DNAs encoding RMEP include the cloning of polynucleotide sequences encoding RMEP or RMEP derivatives into vectors for the 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
 10 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.

Polynucleotide sequences encoding RMEP may be used for the diagnosis of disorders associated with expression of RMEP. Examples of such disorders include, but are not limited to, a nervous system
 15 disorder such as epilepsy, ischemic cerebrovascular disease, stroke, cerebral neoplasms, Alzheimer's disease, Pick's disease, Huntington's disease, dementia, Parkinson's disease and other extrapyramidal disorders, amyotrophic lateral sclerosis and other motor neuron disorders, progressive neural muscular atrophy, retinitis pigmentosa, hereditary ataxias, multiple sclerosis and other demyelinating diseases, bacterial and viral meningitis, brain abscess, subdural empyema, epidural abscess, suppurative
 20 intracranial thrombophlebitis, myelitis and radiculitis, viral central nervous system disease; prion diseases including kuru, Creutzfeldt-Jakob disease, and Gerstmann-Straussler-Scheinker syndrome; fatal familial insomnia, nutritional and metabolic diseases of the nervous system, neurofibromatosis, tuberous sclerosis, cerebelloretinal hemangioblastomatosis, encephalotrigeminal syndrome, mental retardation and other developmental disorder of the central nervous system, cerebral palsy, a neuroskeletal disorder, an
 25 autonomic nervous system disorder, a cranial nerve disorder, a spinal cord disease, muscular dystrophy and other neuromuscular disorder, a peripheral nervous system disorder, dermatomyositis and polymyositis; inherited, metabolic, endocrine, and toxic myopathy; myasthenia gravis, periodic paralysis; a mental disorder including mood, anxiety, and schizophrenic disorders; seasonal affective disorder (SAD); akathisia, amnesia, catatonia, diabetic neuropathy, tardive dyskinesia, dystonias,
 30 paranoid psychoses, postherpetic neuralgia, and Tourette's disorder; an autoimmune/inflammatory disorder such as acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's

disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, 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 cell proliferative disorder such as actinic keratosis, arteriosclerosis, 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, cancers 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 a developmental disorder such as renal tubular acidosis, anemia, Cushing's syndrome, achondroplastic dwarfism, Duchenne and Becker muscular dystrophy, epilepsy, gonadal dysgenesis, WAGR syndrome (Wilms' tumor, aniridia, genitourinary abnormalities, and mental retardation), Smith-Magenis syndrome, myelodysplastic syndrome, hereditary mucoepithelial dysplasia, hereditary keratodermas, hereditary neuropathies such as Charcot-Marie-Tooth disease and neurofibromatosis, hypothyroidism, hydrocephalus, seizure disorders such as Sydenham's chorea and cerebral palsy, spina bifida, anencephaly, craniorachischisis, congenital glaucoma, cataract, and sensorineural hearing loss. The polynucleotide sequences encoding RMEP may be used in Southern or northern analysis, dot blot, or other membrane-based technologies; in PCR technologies; in dipstick, pin, and multiformat ELISA-like assays; and in microarrays utilizing fluids or tissues from patients to detect altered RMEP expression. Such qualitative or quantitative methods are well known in the art.

In a particular aspect, the nucleotide sequences encoding RMEP may be useful in assays that detect the presence of associated disorders, particularly those mentioned above. The nucleotide sequences encoding RMEP 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 quantified 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 RMEP 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.

In order to provide a basis for the diagnosis of a disorder associated with expression of RMEP, 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
5 fragment thereof, encoding RMEP, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained from 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
10 presence of a disorder.

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

15 With respect to cancer, the presence of an abnormal amount of transcript (either under- or 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
20 progression of the cancer.

Additional diagnostic uses for oligonucleotides designed from the sequences encoding RMEP 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 RMEP, or a fragment of a polynucleotide complementary to the polynucleotide encoding RMEP, and will be
25 employed under optimized conditions for identification of a specific gene or condition. Oligomers may also be employed under less stringent conditions for detection or quantification of closely related DNA or RNA sequences.

In a particular aspect, oligonucleotide primers derived from the polynucleotide sequences encoding RMEP may be used to detect single nucleotide polymorphisms (SNPs). SNPs are
30 substitutions, insertions and deletions that are a frequent cause of inherited or acquired genetic disease in humans. Methods of SNP detection include, but are not limited to, single-stranded conformation polymorphism (SSCP) and fluorescent SSCP (fSSCP) methods. In SSCP, oligonucleotide primers derived from the polynucleotide sequences encoding RMEP are used to amplify DNA using the polymerase chain reaction (PCR). The DNA may be derived, for example, from diseased or normal

tissue, biopsy samples, bodily fluids, and the like. SNPs in the DNA cause differences in the secondary and tertiary structures of PCR products in single-stranded form, and these differences are detectable using gel electrophoresis in non-denaturing gels. In fSCCP, the oligonucleotide primers are fluorescently labeled, which allows detection of the amplimers in high-throughput equipment such as DNA sequencing machines. Additionally, sequence database analysis methods, termed in silico SNP (isSNP), are capable of identifying polymorphisms by comparing the sequence of individual overlapping DNA fragments which assemble into a common consensus sequence. These computer-based methods filter out sequence variations due to laboratory preparation of DNA and sequencing errors using statistical models and automated analyses of DNA sequence chromatograms. In the alternative, SNPs may be detected and characterized by mass spectrometry using, for example, the high throughput MASSARRAY system (Sequenom, Inc., San Diego CA).

Methods which may also be used to quantify the expression of RMEP include radiolabeling or biotinylating nucleotides, coamplification of a control nucleic acid, and 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. 212:229-236.) The speed of quantitation of multiple samples may be accelerated by running the assay in a high-throughput format where the oligomer or polynucleotide of interest is presented in various dilutions and a spectrophotometric or colorimetric response gives rapid quantitation.

In further embodiments, oligonucleotides or longer fragments derived from any of the polynucleotide sequences described herein may be used as elements on a microarray. The microarray can be used in transcript imaging techniques which monitor the relative expression levels of large numbers of genes simultaneously as described below. The microarray may also be used 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, to monitor progression/regression of disease as a function of gene expression, and to develop and monitor the activities of therapeutic agents in the treatment of disease. In particular, this information may be used to develop a pharmacogenomic profile of a patient in order to select the most appropriate and effective treatment regimen for that patient. For example, therapeutic agents which are highly effective and display the fewest side effects may be selected for a patient based on his/her pharmacogenomic profile.

In another embodiment, RMEP, fragments of RMEP, or antibodies specific for RMEP may be used as elements on a microarray. The microarray may be used to monitor or measure protein-protein interactions, drug-target interactions, and gene expression profiles, as described above.

A particular embodiment relates to the use of the polynucleotides of the present invention to generate a transcript image of a tissue or cell type. A transcript image represents the global pattern of

gene expression by a particular tissue or cell type. Global gene expression patterns are analyzed by quantifying the number of expressed genes and their relative abundance under given conditions and at a given time. (See Seilhamer et al., "Comparative Gene Transcript Analysis," U.S. Patent Number 5,840,484, expressly incorporated by reference herein.) Thus a transcript image may be generated by
5 hybridizing the polynucleotides of the present invention or their complements to the totality of transcripts or reverse transcripts of a particular tissue or cell type. In one embodiment, the hybridization takes place in high-throughput format, wherein the polynucleotides of the present invention or their complements comprise a subset of a plurality of elements on a microarray. The resultant transcript image would provide a profile of gene activity.

10 Transcript images may be generated using transcripts isolated from tissues, cell lines, biopsies, or other biological samples. The transcript image may thus reflect gene expression in vivo, as in the case of a tissue or biopsy sample, or in vitro, as in the case of a cell line.

Transcript images which profile the expression of the polynucleotides of the present invention may also be used in conjunction with in vitro model systems and preclinical evaluation of
15 pharmaceuticals, as well as toxicological testing of industrial and naturally-occurring environmental compounds. All compounds induce characteristic gene expression patterns, frequently termed molecular fingerprints or toxicant signatures, which are indicative of mechanisms of action and toxicity (Nuwaysir, E.F. et al. (1999) Mol. Carcinog. 24:153-159; Steiner, S. and N.L. Anderson (2000) Toxicol. Lett. 112-113:467-471, expressly incorporated by reference herein). If a test compound has a signature similar to
20 that of a compound with known toxicity, it is likely to share those toxic properties. These fingerprints or signatures are most useful and refined when they contain expression information from a large number of genes and gene families. Ideally, a genome-wide measurement of expression provides the highest quality signature. Even genes whose expression is not altered by any tested compounds are important as well, as the levels of expression of these genes are used to normalize the rest of the expression data. The
25 normalization procedure is useful for comparison of expression data after treatment with different compounds. While the assignment of gene function to elements of a toxicant signature aids in interpretation of toxicity mechanisms, knowledge of gene function is not necessary for the statistical matching of signatures which leads to prediction of toxicity. (See, for example, Press Release 00-02 from the National Institute of Environmental Health Sciences, released February 29, 2000, available at
30 <http://www.niehs.nih.gov/oc/news/toxchip.htm>.) Therefore, it is important and desirable in toxicological screening using toxicant signatures to include all expressed gene sequences.

In one embodiment, the toxicity of a test compound is assessed by treating a biological sample containing nucleic acids with the test compound. Nucleic acids that are expressed in the treated biological sample are hybridized with one or more probes specific to the polynucleotides of the

present invention, so that transcript levels corresponding to the polynucleotides of the present invention may be quantified. The transcript levels in the treated biological sample are compared with levels in an untreated biological sample. Differences in the transcript levels between the two samples are indicative of a toxic response caused by the test compound in the treated sample.

5 Another particular embodiment relates to the use of the polypeptide sequences of the present invention to analyze the proteome of a tissue or cell type. The term proteome refers to the global pattern of protein expression in a particular tissue or cell type. Each protein component of a proteome can be subjected individually to further analysis. Proteome expression patterns, or profiles, are analyzed by quantifying the number of expressed proteins and their relative abundance under given conditions and at
10 a given time. A profile of a cell's proteome may thus be generated by separating and analyzing the polypeptides of a particular tissue or cell type. In one embodiment, the separation is achieved using two-dimensional gel electrophoresis, in which proteins from a sample are separated by isoelectric focusing in the first dimension, and then according to molecular weight by sodium dodecyl sulfate slab gel electrophoresis in the second dimension (Steiner and Anderson, supra). The proteins are visualized
15 in the gel as discrete and uniquely positioned spots, typically by staining the gel with an agent such as Coomassie Blue or silver or fluorescent stains. The optical density of each protein spot is generally proportional to the level of the protein in the sample. The optical densities of equivalently positioned protein spots from different samples, for example, from biological samples either treated or untreated with a test compound or therapeutic agent, are compared to identify any changes in protein spot density
20 related to the treatment. The proteins in the spots are partially sequenced using, for example, standard methods employing chemical or enzymatic cleavage followed by mass spectrometry. The identity of the protein in a spot may be determined by comparing its partial sequence, preferably of at least 5 contiguous amino acid residues, to the polypeptide sequences of the present invention. In some cases, further sequence data may be obtained for definitive protein identification.

25 A proteomic profile may also be generated using antibodies specific for RMEP to quantify the levels of RMEP expression. In one embodiment, the antibodies are used as elements on a microarray, and protein expression levels are quantified by exposing the microarray to the sample and detecting the levels of protein bound to each array element (Lueking, A. et al. (1999) *Anal. Biochem.* 270:103-111; Mendoze, L.G. et al. (1999) *Biotechniques* 27:778-788). Detection may be performed by a variety of
30 methods known in the art, for example, by reacting the proteins in the sample with a thiol- or amino-reactive fluorescent compound and detecting the amount of fluorescence bound at each array element.

Toxicant signatures at the proteome level are also useful for toxicological screening, and should be analyzed in parallel with toxicant signatures at the transcript level. There is a poor correlation between transcript and protein abundances for some proteins in some tissues (Anderson, N.L. and J.

Seilhamer (1997) Electrophoresis 18:533-537), so proteome toxicant signatures may be useful in the analysis of compounds which do not significantly affect the transcript image, but which alter the proteomic profile. In addition, the analysis of transcripts in body fluids is difficult, due to rapid degradation of mRNA, so proteomic profiling may be more reliable and informative in such cases.

5 In another embodiment, the toxicity of a test compound is assessed by treating a biological sample containing proteins with the test compound. Proteins that are expressed in the treated biological sample are separated so that the amount of each protein can be quantified. The amount of each protein is compared to the amount of the corresponding protein in an untreated biological sample. A difference in the amount of protein between the two samples is indicative of a toxic response to the test compound
10 in the treated sample. Individual proteins are identified by sequencing the amino acid residues of the individual proteins and comparing these partial sequences to the polypeptides of the present invention.

In another embodiment, the toxicity of a test compound is assessed by treating a biological sample containing proteins with the test compound. Proteins from the biological sample are incubated with antibodies specific to the polypeptides of the present invention. The amount of protein recognized
15 by the antibodies is quantified. The amount of protein in the treated biological sample is compared with the amount in an untreated biological sample. A difference in the amount of protein between the two samples is indicative of a toxic response to the test compound in the treated sample.

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.
20 USA 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. USA 94:2150-2155; and Heller, M.J. et al. (1997) U.S. Patent No. 5,605,662.) Various types of microarrays are well known and thoroughly described in DNA Microarrays: A Practical Approach, M. Schena, ed. (1999) Oxford University Press, London, hereby expressly incorporated by reference.

25 In another embodiment of the invention, nucleic acid sequences encoding RMEP may be used to generate hybridization probes useful in mapping the naturally occurring genomic sequence. Either coding or noncoding sequences may be used, and in some instances, noncoding sequences may be preferable over coding sequences. For example, conservation of a coding sequence among members of a multi-gene family may potentially cause undesired cross hybridization during chromosomal
30 mapping. 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 (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.) Once mapped, the nucleic acid sequences of the invention may be used to develop genetic linkage maps, for example, which correlate the inheritance of a disease state with the inheritance of a particular chromosome region or restriction fragment length polymorphism (RFLP). (See, for example, Lander, E.S. and D. Botstein (1986) Proc. Natl. Acad. Sci. USA 83:7353-7357.)

5 Fluorescent in situ hybridization (FISH) may be correlated with other physical 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) World Wide Web site. Correlation between the location of the gene encoding RMEP on a physical map and a specific disorder, or a predisposition to a specific disorder, may help define the region of DNA
10 associated with that disorder and thus may further positional cloning efforts.

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 exact chromosomal locus is not known. This information is
15 valuable to investigators searching for disease genes using positional cloning or other gene discovery techniques. Once the gene or genes responsible for a disease or syndrome have 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 instant invention may
20 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, RMEP, 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
25 solid support, borne on a cell surface, or located intracellularly. The formation of binding complexes between RMEP 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
30 synthesized on a solid substrate. The test compounds are reacted with RMEP, or fragments thereof, and washed. Bound RMEP is then detected by methods well known in the art. Purified RMEP 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 RMEP specifically compete with a test compound for binding RMEP. In this manner, antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with RMEP.

In additional embodiments, the nucleotide sequences which encode RMEP 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 embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

The disclosures of all patents, applications, and publications mentioned above and below, including U.S. Ser. No. 60/201,875, U.S. Ser. No. 60/200,184, U.S. Ser. No. 60/202,090, U.S. Ser. No. 60/210,232, and U.S. Ser. No. 60/220,553, are hereby expressly incorporated by reference.

15

EXAMPLES

I. Construction of cDNA Libraries

Incyte cDNAs were derived from cDNA libraries described in the LIFESEQ GOLD database (Incyte Genomics, Palo Alto CA) and shown in Table 4, column 5. 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 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 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, Chatsworth 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).

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 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

5 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), PSPORT1 plasmid (Life Technologies), PCDNA2.1 plasmid (Invitrogen, Carlsbad CA), PBK-CMV plasmid (Stratagene), or pINCY (Incyte Genomics, Palo Alto CA), or derivatives thereof. Recombinant plasmids were transformed into competent *E. coli* cells
10 including XL1-Blue, XL1-BlueMRF, or SOLR from Stratagene or DH5 α , DH10B, or ElectroMAX DH10B from Life Technologies.

II. Isolation of cDNA Clones

Plasmids obtained as described in Example I were recovered from host cells by in vivo excision using the UNIZAP vector system (Stratagene) or by cell lysis. Plasmids were purified using at least one
15 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 R.E.A.L. PREP 96 plasmid purification kit from QIAGEN. Following precipitation, plasmids were resuspended in 0.1 ml of distilled water and stored, with or without lyophilization, at 4°C.

20 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 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
25 (Labsystems Oy, Helsinki, Finland).

III. Sequencing and Analysis

Incyte cDNA recovered in plasmids as described in Example II were sequenced as follows. Sequencing reactions were processed using standard methods or high-throughput instrumentation such as the ABI CATALYST 800 (Applied Biosystems) thermal cycler or the PTC-200 thermal cycler (MJ
30 Research) in conjunction with the HYDRA microdispenser (Robbins Scientific) or the MICROLAB 2200 (Hamilton) liquid transfer system. cDNA sequencing reactions were prepared using reagents provided by Amersham Pharmacia Biotech or supplied in ABI sequencing kits such as the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Applied Biosystems). Electrophoretic separation of cDNA sequencing reactions and detection of labeled polynucleotides were

carried out using the MEGABACE 1000 DNA sequencing system (Molecular Dynamics); the ABI PRISM 373 or 377 sequencing system (Applied Biosystems) in conjunction with standard ABI protocols and base calling software; or other sequence analysis systems known in the art. Reading frames within the cDNA sequences were identified using standard methods (reviewed in Ausubel, 1997, supra, unit 7.7). Some of the cDNA sequences were selected for extension using the techniques disclosed in Example VIII.

The polynucleotide sequences derived from Incyte cDNAs were validated by removing vector, linker, and poly(A) sequences and by masking ambiguous bases, using algorithms and programs based on BLAST, dynamic programming, and dinucleotide nearest neighbor analysis. The Incyte cDNA sequences or translations thereof were then queried against a selection of public databases such as the GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases, and BLOCKS, PRINTS, DOMO, PRODOM, and hidden Markov model (HMM)-based protein family databases such as PFAM. (HMM is a probabilistic approach which analyzes consensus primary structures of gene families. See, for example, Eddy, S.R. (1996) Curr. Opin. Struct. Biol. 6:361-365.) The queries were performed using programs based on BLAST, FASTA, BLIMPS, and HMMER. The Incyte cDNA sequences were assembled to produce full length polynucleotide sequences. Alternatively, GenBank cDNAs, GenBank ESTs, stitched sequences, stretched sequences, or Genscan-predicted coding sequences (see Examples IV and V) were used to extend Incyte cDNA assemblages to full length. Assembly was performed using programs based on Phred, Phrap, and Consed, and cDNA assemblages 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 polypeptide sequences. Alternatively, a polypeptide of the invention may begin at any of the methionine residues of the full length translated polypeptide. Full length polypeptide sequences were subsequently analyzed by querying against databases such as the GenBank protein databases (genpept), SwissProt, BLOCKS, PRINTS, DOMO, PRODOM, Prosite, and hidden Markov model (HMM)-based protein family databases such as PFAM. Full length polynucleotide sequences are also analyzed using MACDNASIS PRO software (Hitachi Software Engineering, South San Francisco CA) and LASERGENE software (DNASTAR). Polynucleotide and polypeptide sequence alignments are generated using default parameters specified by the CLUSTAL algorithm as incorporated into the MEGALIGN multisequence alignment program (DNASTAR), which also calculates the percent identity between aligned sequences.

Table 7 summarizes the tools, programs, and algorithms used for the analysis and assembly of Incyte cDNA and full length sequences and provides applicable descriptions, references, and threshold parameters. The first column of Table 7 shows the tools, programs, and algorithms used, the second column provides brief descriptions thereof, the third column presents appropriate references, all of

which are incorporated by reference herein in their entirety, 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 score or the lower the probability value, the greater the identity between two sequences).

5 The programs described above for the assembly and analysis of full length polynucleotide and polypeptide sequences were also used to identify polynucleotide sequence fragments from SEQ ID NO:48-94. Fragments from about 20 to about 4000 nucleotides which are useful in hybridization and amplification technologies are described in Table 4, column 4.

IV. Identification and Editing of Coding Sequences from Genomic DNA

10 Putative RNA metabolism proteins were initially identified by running the Genscan gene identification program against public genomic sequence databases (e.g., gbpri and gbhtg). Genscan is a general-purpose gene identification program which analyzes genomic DNA sequences from a variety of organisms (See Burge, C. and S. Karlin (1997) J. Mol. Biol. 268:78-94, and Burge, C. and S. Karlin (1998) Curr. Opin. Struct. Biol. 8:346-354). The program concatenates predicted exons to form an
15 assembled cDNA sequence extending from a methionine to a stop codon. The output of Genscan is a FASTA database of polynucleotide and polypeptide sequences. The maximum range of sequence for Genscan to analyze at once was set to 30 kb. To determine which of these Genscan predicted cDNA sequences encode RNA metabolism proteins, the encoded polypeptides were analyzed by querying against PFAM models for RNA metabolism proteins. Potential RNA metabolism proteins were also
20 identified by homology to Incyte cDNA sequences that had been annotated as RNA metabolism proteins. These selected Genscan-predicted sequences were then compared by BLAST analysis to the genpept and gbpri public databases. Where necessary, the Genscan-predicted sequences were then edited by comparison to the top BLAST hit from genpept to correct errors in the sequence predicted by Genscan, such as extra or omitted exons. BLAST analysis was also used to find any Incyte cDNA or public
25 cDNA coverage of the Genscan-predicted sequences, thus providing evidence for transcription. When Incyte cDNA coverage was available, this information was used to correct or confirm the Genscan predicted sequence. Full length polynucleotide sequences were obtained by assembling Genscan-predicted coding sequences with Incyte cDNA sequences and/or public cDNA sequences using the assembly process described in Example III. Alternatively, full length polynucleotide sequences were
30 derived entirely from edited or unedited Genscan-predicted coding sequences.

V. Assembly of Genomic Sequence Data with cDNA Sequence Data

"Stitched" Sequences

Partial cDNA sequences were extended with exons predicted by the Genscan gene identification program described in Example IV. Partial cDNAs assembled as described in Example III were mapped

to genomic DNA and parsed into clusters containing related cDNAs and Genscan exon predictions from one or more genomic sequences. Each cluster was analyzed using an algorithm based on graph theory and dynamic programming to integrate cDNA and genomic information, generating possible splice variants that were subsequently confirmed, edited, or extended to create a full length sequence.

5 Sequence intervals in which the entire length of the interval was present on more than one sequence in the cluster were identified, and intervals thus identified were considered to be equivalent by transitivity. For example, if an interval was present on a cDNA and two genomic sequences, then all three intervals were considered to be equivalent. This process allows unrelated but consecutive genomic sequences to be brought together, bridged by cDNA sequence. Intervals thus identified were then “stitched” together
10 by the stitching algorithm in the order that they appear along their parent sequences to generate the longest possible sequence, as well as sequence variants. Linkages between intervals which proceed along one type of parent sequence (cDNA to cDNA or genomic sequence to genomic sequence) were given preference over linkages which change parent type (cDNA to genomic sequence). The resultant stitched sequences were translated and compared by BLAST analysis to the genpept and gbpr public
15 databases. Incorrect exons predicted by Genscan were corrected by comparison to the top BLAST hit from genpept. Sequences were further extended with additional cDNA sequences, or by inspection of genomic DNA, when necessary.

“Stretched” Sequences

Partial DNA sequences were extended to full length with an algorithm based on BLAST
20 analysis. First, partial cDNAs assembled as described in Example III were queried against public databases such as the GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases using the BLAST program. The nearest GenBank protein homolog was then compared by BLAST analysis to either Incyte cDNA sequences or GenScan exon predicted sequences described in Example IV. A chimeric protein was generated by using the resultant high-scoring segment pairs (HSPs) to map the
25 translated sequences onto the GenBank protein homolog. Insertions or deletions may occur in the chimeric protein with respect to the original GenBank protein homolog. The GenBank protein homolog, the chimeric protein, or both were used as probes to search for homologous genomic sequences from the public human genome databases. Partial DNA sequences were therefore “stretched” or extended by the addition of homologous genomic sequences. The resultant stretched sequences were examined to
30 determine whether it contained a complete gene.

VI. Chromosomal Mapping of RMEP Encoding Polynucleotides

The sequences which were used to assemble SEQ ID NO:48-94 were compared with sequences from the Incyte LIFESEQ database and public domain databases using BLAST and other implementations of the Smith-Waterman algorithm. Sequences from these databases that matched

SEQ ID NO:48-94 were assembled into clusters of contiguous and overlapping sequences using assembly algorithms such as Phrap (Table 7). Radiation hybrid and genetic mapping data available from public resources such as the Stanford Human Genome Center (SHGC), Whitehead Institute for Genome Research (WIGR), and Généthon were used to determine if any of the clustered sequences
 5 had been previously mapped. Inclusion of a mapped sequence in a cluster resulted in the assignment of all sequences of that cluster, including its particular SEQ ID NO:, to that map location.

Map locations are represented by ranges, or intervals, of human chromosomes. The map position of an interval, in centiMorgans, is measured relative to the terminus of the chromosome's p-arm. (The centiMorgan (cM) is a unit of measurement based on recombination frequencies between
 10 chromosomal markers. On average, 1 cM is roughly equivalent to 1 megabase (Mb) of DNA in humans, although this can vary widely due to hot and cold spots of recombination.) The cM distances are based on genetic markers mapped by Généthon which provide boundaries for radiation hybrid markers whose sequences were included in each of the clusters. Human genome maps and other resources available to the public, such as the NCBI "GeneMap'99" World Wide Web site
 15 (<http://www.ncbi.nlm.nih.gov/genemap/>), can be employed to determine if previously identified disease genes map within or in proximity to the intervals indicated above.

In this manner, SEQ ID NO:53 was mapped to chromosome 1 within the interval from 159.6 to 164.1 centiMorgans. SEQ ID NO:61 was mapped to chromosome 8 within the interval from 30.70 to 60.00 centiMorgans. SEQ ID NO:69 was mapped to chromosome 10 within the interval from
 20 158.30 centiMorgans to the q terminus. SEQ ID NO:70 was mapped to chromosome 1 within the interval from 63.90 to 74.80 centiMorgans. SEQ ID NO:71 was mapped to chromosome 1 within the interval from 159.60 to 164.10 centiMorgans. SEQ ID NO:73 was mapped to chromosome 11 within the interval from 34.30 to 37.00 centiMorgans. SEQ ID NO:75 was mapped to chromosome 2 within the interval from 107.10 to 118.00 centiMorgans. SEQ ID NO:76 was mapped to chromosome 7
 25 within the interval from 7.80 to 10.60 centiMorgans. SEQ ID NO:79 was mapped to chromosome 22 within the interval from 22.20 to 40.20 centiMorgans. SEQ ID NO:81 was mapped to chromosome 4 within the interval from the p terminus to 6.70 centiMorgans. SEQ ID NO: 84 was mapped to chromosome 5 within the interval from 156.0 to 157.6 centiMorgans. SEQ ID NO: 88 was mapped to chromosome 11 within the interval from 117.9 to 123.5 centiMorgans. SEQ ID NO:91 was mapped to
 30 chromosome 5 within the interval from 152.3 to 155.5 centiMorgans.

VII. Analysis of Polynucleotide Expression

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)
 35 *supra*, ch. 4 and 16.)

Analogous computer techniques applying BLAST were used to search for identical or related molecules in cDNA databases such as GenBank or LIFESEQ (Incyte Genomics). 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
 5 of the search is the product score, which is defined as:

$$\frac{\text{BLAST Score} \times \text{Percent Identity}}{5 \times \text{minimum} \{ \text{length}(\text{Seq. 1}), \text{length}(\text{Seq. 2}) \}}$$

10 The product score takes into account both the degree of similarity between two sequences and the length of the sequence match. The product score is a normalized value between 0 and 100, and is calculated as follows: the BLAST score is multiplied by the percent nucleotide identity and the product is divided by (5 times the length of the shorter of the two sequences). The BLAST score is calculated by assigning a score of +5 for every base that matches in a high-scoring segment pair (HSP), and -4 for every
 15 mismatch. Two sequences may share more than one HSP (separated by gaps). If there is more than one HSP, then the pair with the highest BLAST score is used to calculate the product score. The product score represents a balance between fractional overlap and quality in a BLAST alignment. For example, a product score of 100 is produced only for 100% identity over the entire length of the shorter of the two sequences being compared. A product score of 70 is produced either by 100% identity and 70%
 20 overlap at one end, or by 88% identity and 100% overlap at the other. A product score of 50 is produced either by 100% identity and 50% overlap at one end, or 79% identity and 100% overlap.

Alternatively, polynucleotide sequences encoding RMEP are analyzed with respect to the tissue sources from which they were derived. For example, some full length sequences are assembled, at least in part, with overlapping Incyte cDNA sequences (see Example III). Each cDNA sequence is derived
 25 from a cDNA library constructed from a human tissue. Each human tissue is classified into one of the following organ/tissue categories: cardiovascular system; connective tissue; digestive system; embryonic structures; endocrine system; exocrine glands; genitalia, female; genitalia, male; germ cells; hemic and immune system; liver; musculoskeletal system; nervous system; pancreas; respiratory system; sense organs; skin; stomatognathic system; unclassified/mixed; or urinary tract. The number of libraries
 30 in each category is counted and divided by the total number of libraries across all categories. Similarly, each human tissue is classified into one of the following disease/condition categories: cancer, cell line, developmental, inflammation, neurological, trauma, cardiovascular, pooled, and other, and the number of libraries in each category is counted and divided by the total number of libraries across all categories. The resulting percentages reflect the tissue- and disease-specific expression of cDNA encoding RMEP.

cDNA sequences and cDNA library/tissue information are found in the LIFESEQ GOLD database (Incyte Genomics, Palo Alto CA).

VIII. Extension of RMEP Encoding Polynucleotides

Full length polynucleotide sequences were also produced by extension of an appropriate
5 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 was
synthesized 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
10 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
15 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 2-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,
20 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
25 quantitation reagent (0.25% (v/v) PICOGREEN; Molecular Probes, Eugene OR) dissolved in 1X TE
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
30 on a 1 % agarose 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, and 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% dimethylsulfoxide (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 (Applied Biosystems).

In like manner, full length polynucleotide sequences are verified using the above procedure or are used to obtain 5' regulatory sequences using the above procedure along with oligonucleotides designed for such extension, and an appropriate genomic library.

IX. Labeling and Use of Individual Hybridization Probes

Hybridization probes derived from SEQ ID NO:48-94 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 μ Ci 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 conditions of up to, for example, 0.1 x saline sodium citrate and 0.5% sodium dodecyl sulfate.

Hybridization patterns are visualized using autoradiography or an alternative imaging means and compared.

X. Microarrays

The linkage or synthesis of array elements upon a microarray can be achieved utilizing photolithography, piezoelectric printing (ink-jet printing, See, e.g., Baldeschweiler, supra), mechanical microspotting technologies, and derivatives thereof. The substrate in each of the aforementioned technologies should be uniform and solid with a non-porous surface (Schena (1999), supra). Suggested substrates include silicon, silica, glass slides, glass chips, and silicon wafers. Alternatively, a procedure 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 using available methods and machines well known to those of ordinary skill in the art and may contain any appropriate number of elements. (See, e.g., Schena, M. et al. (1995) *Science* 270:467-470; Shalon, D. et al. (1996) *Genome Res.* 6:639-645; Marshall, A. and J. Hodgson (1998) *Nat. Biotechnol.* 16:27-31.)

Full length cDNAs, Expressed Sequence Tags (ESTs), or fragments or oligomers thereof may comprise the elements of the microarray. Fragments or oligomers suitable for hybridization can be selected using software well known in the art such as LASERGENE software (DNASTAR). The array elements are hybridized with polynucleotides in a biological sample. The polynucleotides in the biological sample are conjugated to a fluorescent label or other molecular tag for ease of detection. After hybridization, nonhybridized nucleotides from the biological sample are removed, and a fluorescence scanner is used to detect hybridization at each array element. Alternatively, laser desorption and mass spectrometry may be used for detection of hybridization. The degree of complementarity and the relative abundance of each polynucleotide which hybridizes to an element on the microarray may be assessed. In one embodiment, microarray preparation and usage is described in detail below.

Tissue or Cell Sample Preparation

Total RNA is isolated from tissue samples using the guanidinium thiocyanate method and poly(A)⁺ RNA is purified using the oligo-(dT) cellulose method. Each poly(A)⁺ RNA sample is reverse transcribed using MMLV reverse-transcriptase, 0.05 pg/μl oligo-(dT) primer (21mer), 1X first strand buffer, 0.03 units/μl RNase inhibitor, 500 μM dATP, 500 μM dGTP, 500 μM dTTP, 40 μM dCTP, 40 μM dCTP-Cy3 (BDS) or dCTP-Cy5 (Amersham Pharmacia Biotech). The reverse transcription reaction is performed in a 25 ml volume containing 200 ng poly(A)⁺ RNA with GEMBRIGHT kits (Incyte). Specific control poly(A)⁺ RNAs are synthesized by in vitro transcription from non-coding yeast genomic DNA. After incubation at 37° C for 2 hr, each reaction sample (one

with Cy3 and another with Cy5 labeling) is treated with 2.5 ml of 0.5M sodium hydroxide and incubated for 20 minutes at 85° C to stop the reaction and degrade the RNA. Samples are purified using two successive CHROMA SPIN 30 gel filtration spin columns (CLONTECH Laboratories, Inc. (CLONTECH), Palo Alto CA) and after combining, both reaction samples are ethanol precipitated
5 using 1 ml of glycogen (1 mg/ml), 60 ml sodium acetate, and 300 ml of 100% ethanol. The sample is then dried to completion using a SpeedVAC (Savant Instruments Inc., Holbrook NY) and resuspended in 14 µl 5X SSC/0.2% SDS.

Microarray Preparation

Sequences of the present invention are used to generate array elements. Each array element is
10 amplified from bacterial cells containing vectors with cloned cDNA inserts. PCR amplification uses primers complementary to the vector sequences flanking the cDNA insert. Array elements are amplified in thirty cycles of PCR from an initial quantity of 1-2 ng to a final quantity greater than 5 µg. Amplified array elements are then purified using SEPHACRYL-400 (Amersham Pharmacia Biotech).

15 Purified array elements are immobilized on polymer-coated glass slides. Glass microscope slides (Corning) are cleaned by ultrasound in 0.1% SDS and acetone, with extensive distilled water washes between and after treatments. Glass slides are etched in 4% hydrofluoric acid (VWR Scientific Products Corporation (VWR), West Chester PA), washed extensively in distilled water, and coated with 0.05% aminopropyl silane (Sigma) in 95% ethanol. Coated slides are cured in a 110°C
20 oven.

Array elements are applied to the coated glass substrate using a procedure described in US Patent No. 5,807,522, incorporated herein by reference. 1 µl of the array element DNA, at an average concentration of 100 ng/µl, is loaded into the open capillary printing element by a high-speed robotic apparatus. The apparatus then deposits about 5 nl of array element sample per slide.

25 Microarrays are UV-crosslinked using a STRATALINKER UV-crosslinker (Stratagene). Microarrays are washed at room temperature once in 0.2% SDS and three times in distilled water. Non-specific binding sites are blocked by incubation of microarrays in 0.2% casein in phosphate buffered saline (PBS) (Tropix, Inc., Bedford MA) for 30 minutes at 60° C followed by washes in 0.2% SDS and distilled water as before.

Hybridization

Hybridization reactions contain 9 µl of sample mixture consisting of 0.2 µg each of Cy3 and Cy5 labeled cDNA synthesis products in 5X SSC, 0.2% SDS hybridization buffer. The sample mixture is heated to 65° C for 5 minutes and is aliquoted onto the microarray surface and covered with an 1.8 cm² coverslip. The arrays are transferred to a waterproof chamber having a cavity just slightly
35 larger than a microscope slide. The chamber is kept at 100% humidity internally by the addition of

140 μ l of 5X SSC in a corner of the chamber. The chamber containing the arrays is incubated for about 6.5 hours at 60° C. The arrays are washed for 10 min at 45° C in a first wash buffer (1X SSC, 0.1% SDS), three times for 10 minutes each at 45° C in a second wash buffer (0.1X SSC), and dried.

Detection

5 Reporter-labeled hybridization complexes are detected with a microscope equipped with an Innova 70 mixed gas 10 W laser (Coherent, Inc., Santa Clara CA) capable of generating spectral lines at 488 nm for excitation of Cy3 and at 632 nm for excitation of Cy5. The excitation laser light is focused on the array using a 20X microscope objective (Nikon, Inc., Melville NY). The slide containing the array is placed on a computer-controlled X-Y stage on the microscope and raster-
10 scanned past the objective. The 1.8 cm x 1.8 cm array used in the present example is scanned with a resolution of 20 micrometers.

In two separate scans, a mixed gas multiline laser excites the two fluorophores sequentially. Emitted light is split, based on wavelength, into two photomultiplier tube detectors (PMT R1477, Hamamatsu Photonics Systems, Bridgewater NJ) corresponding to the two fluorophores. Appropriate
15 filters positioned between the array and the photomultiplier tubes are used to filter the signals. The emission maxima of the fluorophores used are 565 nm for Cy3 and 650 nm for Cy5. Each array is typically scanned twice, one scan per fluorophore using the appropriate filters at the laser source, although the apparatus is capable of recording the spectra from both fluorophores simultaneously.

The sensitivity of the scans is typically calibrated using the signal intensity generated by a
20 cDNA control species added to the sample mixture at a known concentration. A specific location on the array contains a complementary DNA sequence, allowing the intensity of the signal at that location to be correlated with a weight ratio of hybridizing species of 1:100,000. When two samples from different sources (e.g., representing test and control cells), each labeled with a different fluorophore, are hybridized to a single array for the purpose of identifying genes that are differentially expressed,
25 the calibration is done by labeling samples of the calibrating cDNA with the two fluorophores and adding identical amounts of each to the hybridization mixture.

The output of the photomultiplier tube is digitized using a 12-bit RTI-835H analog-to-digital (A/D) conversion board (Analog Devices, Inc., Norwood MA) installed in an IBM-compatible PC computer. The digitized data are displayed as an image where the signal intensity is mapped using a
30 linear 20-color transformation to a pseudocolor scale ranging from blue (low signal) to red (high signal). The data is also analyzed quantitatively. Where two different fluorophores are excited and measured simultaneously, the data are first corrected for optical crosstalk (due to overlapping emission spectra) between the fluorophores using each fluorophore's emission spectrum.

A grid is superimposed over the fluorescence signal image such that the signal from each spot
35 is centered in each element of the grid. The fluorescence signal within each element is then integrated

to obtain a numerical value corresponding to the average intensity of the signal. The software used for signal analysis is the GEMTOOLS gene expression analysis program (Incyte).

XI. Complementary Polynucleotides

Sequences complementary to the RMEP-encoding sequences, or any parts thereof, are used to
5 detect, decrease, or inhibit expression of naturally occurring RMEP. 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 RMEP. To inhibit transcription, a complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent
10 promoter binding to the coding sequence. To inhibit translation, a complementary oligonucleotide is designed to prevent ribosomal binding to the RMEP-encoding transcript.

XII. Expression of RMEP

Expression and purification of RMEP is achieved using bacterial or virus-based expression systems. For expression of RMEP in bacteria, cDNA is subcloned into an appropriate vector containing
15 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 RMEP upon induction with isopropyl beta-D-thiogalactopyranoside (IPTG). Expression of
20 RMEP 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 RMEP 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
25 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, RMEP is synthesized as a fusion protein with, e.g., glutathione S-
30 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 RMEP 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 RMEP obtained by these methods can be used directly in the assays shown in Examples XVI and XVII where applicable.

XIII. Functional Assays

RMEP function is assessed by expressing the sequences encoding RMEP 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, for example, an endothelial or hematopoietic cell line, 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 the apoptotic state of the cells and other cellular properties. 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 RMEP on gene expression can be assessed using highly purified populations of cells transfected with sequences encoding RMEP and either CD64 or CD64-GFP. 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 RMEP and other genes of interest can be analyzed by northern analysis or microarray techniques.

XIV. Production of RMEP Specific Antibodies

RMEP 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.

Alternatively, the RMEP 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.)

Typically, oligopeptides of about 15 residues in length are synthesized using an ABI 431A peptide synthesizer (Applied Biosystems) 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 antipeptide and anti-RMEP activity by, for example, binding the peptide or RMEP to a substrate, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radio-iodinated goat anti-rabbit IgG.

XV. Purification of Naturally Occurring RMEP Using Specific Antibodies

Naturally occurring or recombinant RMEP is substantially purified by immunoaffinity chromatography using antibodies specific for RMEP. An immunoaffinity column is constructed by covalently coupling anti-RMEP 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 RMEP are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of RMEP (e.g., high ionic strength buffers in the presence of detergent). The column is eluted under conditions that disrupt antibody/RMEP 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 RMEP is collected.

XVI. Identification of Molecules Which Interact with RMEP

RMEP, or biologically active fragments thereof, are labeled with ^{125}I Bolton-Hunter reagent. (See, e.g., Bolton A.E. and W.M. Hunter (1973) *Biochem. J.* 133:529-539.) Candidate molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled RMEP, washed, and any wells with labeled RMEP complex are assayed. Data obtained using different concentrations of

RMEP are used to calculate values for the number, affinity, and association of RMEP with the candidate molecules.

Alternatively, molecules interacting with RMEP are analyzed using the yeast two-hybrid system as described in Fields, S. and O. Song (1989) *Nature* 340:245-246, or using commercially
5 available kits based on the two-hybrid system, such as the MATCHMAKER system (Clontech).

RMEP may also be used in the PATHCALLING process (CuraGen Corp., New Haven CT) which employs the yeast two-hybrid system in a high-throughput manner to determine all interactions between the proteins encoded by two large libraries of genes (Nandabalan, K. et al. (2000) U.S. Patent No. 6,057,101).

10 XVII. Demonstration of RMEP Activity

RMEP activity is demonstrated by a polyacrylamide gel mobility-shift assay. In preparation for this assay, RMEP is expressed by transforming a mammalian cell line such as COS7, HeLa or CHO with a eukaryotic expression vector containing RMEP cDNA. The cells are incubated for 48-72 hours after transformation under conditions appropriate for the cell line to allow expression and
15 accumulation of RMEP. Extracts containing solubilized proteins can be prepared from cells expressing RMEP by methods well known in the art. Portions of the extract containing RMEP are added to [³²P]-labeled RNA. Radioactive RNA can be synthesized in vitro by techniques well known in the art. The mixtures are incubated at 25 °C in the presence of RNase inhibitors under buffered conditions for 5-10 minutes. After incubation, the samples are analyzed by polyacrylamide gel
20 electrophoresis followed by autoradiography. The presence of a band on the autoradiogram indicates the formation of a complex between RMEP and the radioactive transcript. A band of similar mobility will not be present in samples prepared using control extracts prepared from untransformed cells.

In the alternative, ribosomal protein function of RMEP is assessed by expressing the sequences encoding ribosomal proteins at physiologically elevated levels in mammalian cell culture
25 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 Corporation), both of which contain the cytomegalovirus promoter (P_{CMV}). Between 5-10 µg of recombinant vector are transfected into a human cell line, preferably of endothelial or hematopoietic origin, using either liposome formulations or
30 electroporation. 1-2 µg of an additional plasmid containing sequences encoding a marker protein are cotransfected.

Transient 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
35 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 the apoptotic state of the cells and other cellular properties.

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 MG (1994) Flow Cytometry, Oxford University Press, New York NY.

The influence of ribosomal proteins on gene expression can be assessed using highly purified populations of cells transfected with sequences encoding a ribosomal protein and either CD64 or CD64-GFP. 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, Inc., 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 a ribosomal protein and other genes of interest can be analyzed by northern analysis or microarray techniques.

In the alternative, RMEP activity is measured as the aminoacylation of a substrate tRNA in the presence of [^{14}C]cysteine. RMEP is incubated with tRNA^{cys} and [^{14}C]cysteine (or appropriate tRNA and amino acid substrates) in a buffered solution. [^{14}C]-labeled product is separated from free [^{14}C]-amino acid by chromatography, and the incorporated [^{14}C] is quantified by scintillation counter. The amount of [^{14}C] detected is proportional to the activity of RMEP in this assay.

In the alternative, RMEP activity is measured by incubating a sample containing RMEP in a solution containing 1 mM ATP, 5 mM Hepes-KOH (pH 7.0), 2.5 mM KCl, 1.5 mM magnesium chloride, and 0.5 mM DTT along with misacylated [^{14}C]-Glu-tRNA^{Gln} (e.g., 1 μM) and a similar concentration of unlabeled L-glutamine. Following the quenching of the reaction with 3 M sodium acetate (pH 5.0), the mixture is extracted with an equal volume of water-saturated phenol, and the aqueous and organic phases are separated by centrifugation at $15,000 \times g$ at room temperature for 1 min. The aqueous phase is removed and precipitated with 3 volumes of ethanol at -70°C for 15 min. The precipitated aminoacyl-tRNAs are recovered by centrifugation at $15,000 \times g$ at 4°C for 15 min. The pellet is resuspended in 25 mM KOH, deacylated at 65°C for 10 min., neutralized with 0.1 M HCl (to final pH 6-7), and dried under vacuum. The dried pellet is resuspended in water and spotted onto a cellulose TLC plate. The plate is developed in either isopropanol/formic acid/water or

ammonia/water/chloroform/methanol, The image is subjected to densitometric analysis and the relative amounts of Glu and Gln are calculated based on the Rf values and relative intensities of the spots. RMEP activity is calculated based on the amount of Gln resulting from the transformation of Glu while acylated as Glu-tRNA^{Gln} (adapted from Curnow, A.W. et al. (1997) Proc. Natl. Acad. Sci. 5 94:11819-26).

Various modifications and variations of the described methods and systems of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with certain embodiments, it should be 10 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 intended to be within the scope of the following claims.

Table 1

Incyte Project ID	Polypeptide SEQ ID NO:	Incyte Polypeptide ID	Polynucleotide SEQ ID NO:	Incyte Polynucleotide ID
1622129	1	1622129CD1	48	1622129CB1
1820078	2	1820078CD1	49	1820078CB1
1527017	3	1527017CD1	50	1527017CB1
1647264	4	1647264CD1	51	1647264CB1
1721989	5	1721989CD1	52	1721989CB1
1730581	6	1730581CD1	53	1730581CB1
1740714	7	1740714CD1	54	1740714CB1
1850596	8	1850596CD1	55	1850596CB1
1856109	9	1856109CD1	56	1856109CB1
1921719	10	1921719CD1	57	1921719CB1
2099829	11	2099829CD1	58	2099829CB1
2416915	12	2416915CD1	59	2416915CB1
2472784	13	2472784CD1	60	2472784CB1
2598981	14	2598981CD1	61	2598981CB1
2738075	15	2738075CD1	62	2738075CB1
2279049	16	2279049CD1	63	2279049CB1
2660904	17	2660904CD1	64	2660904CB1
3179424	18	3179424CD1	65	3179424CB1
2885096	19	2885096CD1	66	2885096CB1
2901076	20	2901076CD1	67	2901076CB1
3074572	21	3074572CD1	68	3074572CB1
1437895	22	1437895CD1	69	1437895CB1
1454656	23	1454656CD1	70	1454656CB1
121130	24	121130CD1	71	121130CB1
1257715	25	1257715CD1	72	1257715CB1
1342022	26	1342022CD1	73	1342022CB1
194704	27	194704CD1	74	194704CB1
607270	28	607270CD1	75	607270CB1
758546	29	758546CD1	76	758546CB1
866043	30	866043CD1	77	866043CB1
927065	31	927065CD1	78	927065CB1
938071	32	938071CD1	79	938071CB1

Table 1 (cont.)

Incyte Project ID	Polypeptide SEQ ID NO:	Incyte Polypeptide ID	Polynucleotide SEQ ID NO:	Incyte Polynucleotide ID
3295984	33	3295984CD1	80	3295984CB1
4545237	34	4545237CD1	81	4545237CB1
4942964	35	4942964CD1	82	4942964CB1
5702144	36	5702144CD1	83	5702144CB1
5862945	37	5862945CD1	84	5862945CB1
6319547	38	6319547CD1	85	6319547CB1
000124	39	000124CD1	86	000124CB1
1659474	40	1659474CD1	87	1659474CB1
2267892	41	2267892CD1	88	2267892CB1
2670307	42	2670307CD1	89	2670307CB1
4524210	43	4524210CD1	90	4524210CB1
5584860	44	5584860CD1	91	5584860CB1
5807892	45	5807892CD1	92	5807892CB1
3210044	46	3210044CD1	93	3210044CB1
4942454	47	4942454CD1	94	4942454CB1

Table 2

Polypeptide SEQ ID NO:	Incyte Polypeptide ID	GenBank ID NO:	Probability Score	GenBank Homolog
1	1622129CD1	g8927590	1.00E-136	[fl1][Homo sapiens] (AF281133) exosome component Rrp41
3	1527017CD1	g4689132	8.20E-87	30S ribosomal protein S7 homolog [Homo sapiens]
4	1647264CD1	g6651037	2.80E-38	similar to RNA binding protein [Mus musculus domesticus]
5	1721989CD1	g868267	9.80E-20	Weak similarity to ribosomal protein L14 (SP:RL14_CHLTR, P28533) [Caenorhabditis elegans]. Wilson, R. et al. (1994) 2.2 Mb of contiguous nucleotide sequence from chromosome III of C. elegans, Nature 368:32-38.
6	1730581CD1	g3721940	7.70E-91	NO27 [Xenopus laevis]
7	1740714CD1	g2570925	6.00E-139	Survival of motor neuron protein interacting protein 1; SIP1; SMN protein interacting protein 1 [Homo sapiens]. Fischer, U. et al. (1997) The SMN-SIP1 complex has an essential role in spliceosomal snRNP biogenesis, Cell 90:1023-1029.
8	1850596CD1	g619302	2.80E-129	RNA-binding protein=Merc {alternatively spliced}, murine teratocarcinoma cell line, PCC4. Duhl, D.M. et al. (1994) Pleiotropic effects of the mouse lethal yellow (Ay) mutation explained by deletion of a maternally expressed gene and the simultaneous production of agouti fusion RNAs, Development 120:1695-1708.
9	1856109CD1	g2688625	4.70E-05	Ribonuclease III (rnc) [Borrelia burgdorferi]. Fraser, C.M. et al. (1997) Genomic sequence of a Lyme disease spirochete, Borrelia burgdorferi, Nature 390:580-586.
10	1921719CD1	g1842111	1.00E-10	decoy [Arabidopsis thaliana]
11	2099829CD1	g6015629	6.20E-89	muscle protein 684 [Mus musculus]
12	2416915CD1	g8347090	1.00E-131	[fl1][Mus musculus] putative zinc finger protein FLIZ1

Table 2 (cont.)

Polypeptide SEQ ID NO:	Incyte Polypeptide ID	GenBank ID NO:	Probability Score	GenBank Homolog
13	2472784CD1	g2098575	8.60E-163	F25451_2 [Homo sapiens]
14	2598981CD1	g4220489	2.80E-141	putative cleavage and polyadenylation specificity factor [Arabidopsis thaliana] (Lin, X. et al. (1999) Nature 402: 761-768)
15	2738075CD1	g5531845	1.00E-12	[Homo sapiens] RNA-binding protein
18	3179424CD1	g7106069	8.00E-08	[fl][Schizosaccharomyces pombe] putative mitochondrial ribosomal protein; L34 family
19	2885096CD1	g5102832	3.50E-79	bK150C2.3 (PUTATIVE novel protein similar to APOBEC1 (Apolipoprotein B mRNA editing protein) and Phorbolin) [Homo sapiens]
20	2901076CD1	g7158880	0	[fl][Rattus norvegicus] serine-arginine-rich splicing regulatory protein SRRP86
21	3074572CD1	g1381029	0	RNA polymerase I associated factor (PAF53) [Mus musculus] (Hanada, K. et al. (1996) EMBO J. 15: 2217-2226)
22	1437895CD1	g2696613	6.60E-140	ATP-dependent RNA helicase #46 [Homo sapiens]
23	1454656CD1	g4981903	5.30E-09	ribosomal protein S15 [Thermotoga maritima]
24	121130CD1	g3721940	8.50E-92	NO27 [Xenopus laevis]
25	1257715CD1	g1870014	1.60E-26	pth [Mycobacterium tuberculosis]
26	1342022CD1	g304525	1.60E-76	ribosomal protein S14 [Cricketulus griseus]
27	194704CD1	g1699023	1.90E-46	putative arginine-aspartate-rich RNA binding protein [Arabidopsis thaliana]
28	607270CD1	g4138828	1.60E-18	[Candida albicans] ribosomal protein S9 small subunit precursor
29	758546CD1	g2440181	4.00E-46	putative 40s ribosomal protein [Schizosaccharomyces pombe]
30	866043CD1	g3283220	8.60E-33	splicing factor hPRP17 [Homo sapiens]
31	927065CD1	g4100563	2.60E-58	ribonuclease P protein subunit p14 [Homo sapiens]
32	938071CD1	g12654241	1.00E-102	[Homo sapiens] (BC000940) Similar to splicing factor, arginine/serine-rich 4 (SRP75)

Table 2 (cont.)

Polypeptide SEQ ID NO:	Incyte Polypeptide ID	GenBank ID NO:	Probability Score	GenBank Homolog
33	3295984CD1	g673454	0	Spermatid perinuclear RNA binding protein [Mus musculus] Schumacher, J.M. et al. (1995) J. Cell Biol. 129:1023-1032
34	4545237CD1	g6899218	1.60E-16	ribosomal protein S5 [Ureaplasma urealyticum]
35	4942964CD1	g10803047	1.00E-68	[fl][Zea mays] 40S ribosomal protein S24
36	5702144CD1	g3328106	1.10E-82	Translational release factor 1 [Homo sapiens] Zhang, Y. and Spremulli, L.L. (1998) Biochim. Biophys. Acta 1443:245-250
37	5862945CD1	g1001933	1.30E-08	ribosomal protein L22 [Thermus thermophilus]
38	6319547CD1	g8573021	1.00E-07	[5' incom][Leishmania major] PolyA Binding Protein 1
39	000124CD1	g3860586	1.10E-43	POLY(A) POLYMERASE (pcnB) [Rickettsia prowazekii]
40	1659474CD1	g2950473	6.70E-13	DNA-dependent rna polymerase polypeptide [Schizosaccharomyces]
41	2267892CD1	g3646126	5.70E-205	ATP-dependent RNA helicase [Homo sapiens]
42	2670307CD1	g3152934	6.20E-176	[Mus musculus] Jun coactivator Jab1 Aravind, L. and Ponting, C.P. (1998) Protein Sci. 7:1250-1254
43	4524210CD1	g3258435	1.80E-38	389aa long hypothetical nucleolar protein [Pyrococcus]
44	5584860CD1	g3879784	1.50E-116	Similar to RNA recognition motif(aka RRM, RBD) [C. elegans]
45	5807892CD1	g1573164	5.70E-15	ribosomal protein S16 (rps16) [Haemophilus influenzae]
46	3210044CD1	g7226601	1.30E-37	Glu-tRNA(Gln) amidotransferase, subunit A [Neisseria meningitidis]. Tettelin, H. et al. (2000) Science 287:1809-1815.
47	4942454CD1	g790508	5.40E-51	60S acidic ribosomal protein [Zea mays]. Goddemeier, M.L. et al. (1996) Plant. Mol. Biol. 30:655-658.

Table 3

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
1	1622129CD1	245	S82, S119, S174, T226		Amino acid tRNA ligase motif (Aa_Trna_Ligase_Ii_lgcg_motif): Y12-D36 3' exoribonuclease family (RNase_PH): R13-A220 Ribonuclease PH proteins:BL01277C:P117-L147 NUCLEOTIDYLTRANSFERASE TRANSFERASE POLYRIBONUCLEOTIDE PROTEIN PHOSPHORYLASE POLYNUCLEOTIDE RIBONUCLEASE PH PNPASE RNABINDING: PD002075: R13-L228 NUCLEOTIDYLTRANSFERASE; POLYRIBONUCLEOTIDE; PHOSPHORYLASE; POLYNUCLEOTIDE DOMAIN: DM03520 P50849 1-615: L6-R222	MOTIFS HMMER-PFAM BLIMPS-BLOCKS BLAST-PRODOM
2	1820078CD1	118	T20	N77	RIBONUCLEOPROTEIN HETEROGENEOUS NUCLEAR U SCAFFOLD ATTACHMENT FACTOR A HNRNP PROTEIN (ROU(1)): PD024707: P34-Y100 (p = 1.3e-05)	BLAST-DOMO BLAST-PRODOM
3	1527017CD1	179	S4, S5, S9, S10, S21, S67, S143		Signal cleavage: M1-A54 Ribosomal protein S7p/S5: S4-W178 Ribosomal protein S7 protein; BL00052A: I74-A120, BL00052B: K145-R171 Ribosomal protein S10 protein: BL00361A: V107-K122 Ribosomal protein: ribosomal s7.prf: M1-H83 RIBOSOMAL PROTEIN S7 30S rRNA-BINDING CHLOROPLAST 40S/MITOCHONDRION S5: PD000817: S5-W178 RIBOSOMAL PROTEIN S7: DM00334 P29765 26-155: F31-R177	SPSCAN HMMER-PFAM BLIMPS-BLOCKS BLIMPS-BLOCKS PROFILESAN BLAST-PRODOM BLAST-DOMO

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
4	1647264CD1	101	S60, T26, T47	N19	Transmembrane domain (transmem_domain): L27-Y45, S64-V86 RNA binding protein homolog (R07E5.12): PD068568: P15-D101 Signal cleavage (signal_cleavage): M1-S19	HMMER
5	1721989CD1	145	T97, S126, Y134		Ribosomal protein L14: A31-V145 Ribosomal protein L14: BL00049C:P94-K129 SIMILARITY TO RIBOSOMAL PROTEIN L14 RIBOSOMAL PROTEIN: PD080736: I32-V145	BLAST-PRODOM HMMER-PFAM BLIMPS-BLOCKS
6	1730581CD1	249	T14, S18, S49, S75, S133, T243		NO27 PROTEIN (predicted nucleolar protein): PD173812: M1-L113 NUCLEOLIN: DM02740 S32644 630-703:R141-G205 RNA-BINDING RGG-BOX DOMAIN: DM04007 S49193 21-239:G103-R202	BLAST-PRODOM BLAST-DOMO BLAST-DOMO
7	1740714CD1	265	S19, T48, S81, T112, S138, S178, S227, S235	N83, N132	PROTEIN SURVIVAL OF MOTOR NEURON INTERACTING: PD039299: M25-D262	BLAST-PRODOM
8	1850596CD1	306	S2, T11, S36, S177, S199, S206, S252, T262, T275, T286, S288, T298,	N9, N261	Rnp_1 motif: K55-Y62 RNA recognition motif. (a.k.a. RRM and RBD): rrm: V23-I87 RIBONUCLEOPROTEIN NUCLEAR PROTEIN RNABINDING HNRNP HETEROGENEOUS C1 NUCLEOPROTEIN C PHOSPHORYLATION: PD015984: N88-D220 RNA; EUKARYOTIC; C2; RIBONUCLEOPROTEIN DOMAIN: DM08081 A47318 6-293: Q6-A304 Eukaryotic RNA-binding domain: BL00030B: K55-N64	MOTIFS HMMER-PFAM BLAST-PRODOM BLAST-DOMO BLIMPS-BLOCKS

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
9	1856109CD1	332	S61, S121, T161, T179, S206, T224, S251, T322,	N82, N249, N315	Signal peptide (signal_peptide): M1-G30 Double-stranded RNA binding motif (dsrm): P237-L304 (score = 0.1) HYPOTHETICAL 49.1 KD PROTEIN F02A9.4 IN CHROMOSOME III: PD140911: D67-R311 PROTEIN RNABINDING RNA REPEAT DEAMINASE HYDROLASE ADENOSINE DOUBLESTRANDED III NUCLEAR: PD001171:P237-L304 (p = 0.0090)	HMMER HMMER-PFAM BLAST-PRODOM BLAST-PRODOM
10	1921719CD1	279	S28, S85, T138, T183, T194, T214, T256		Signal cleavage (signal_cleavage): M1-G42 DECOY 60S RIBOSOMAL PROTEIN L30 MITOCHONDRIAL PRECURSOR YML30 MITOCHONDRION TRANSIT: PD037326:R136-P209 (p = 1.6e-08)	SPSCAN BLAST-PRODOM
11	2099829CD1	239	S4, S11, T15 T36, Y39, S80, S93, T105, T108, T120, Y124, S171, T203, S212, S225, S229, S233, S235,	N106	Ribosomal protein L10 (Ribosomal_L10): K18-T117 PROTEIN RIBOSOMAL SIMILAR 60S ACIDIC PO UFD4CAP1 INTERGENIC REGION: PD037726: M1-G213 RAT ACIDIC RIBOSOMAL PROTEIN: DM00904 P29764 1-318:V10-S212	HMMER-PFAM BLAST-PRODOM BLAST-DOMO
12	2416915CD1	291	T18 T20 T32 T37 S77 T113 S165 T235 S59 S112 T285 S289 Y76		SUPPRESSOR OF SABLE RNA-BINDING NUCLEAR HOMOLOG PD032978:K221-K288	BLAST_PRODOM

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
13	2472784CD1	451	S29 S131 S337 S338 S343 S399 S290 T389		Eukaryotic putative RNA-binding region RNP-1 Signature K393-F400 ATP/GTP-binding site motif A (P-loop) G22-S29 RNA recognition motif. (RRM, RBD, or RNP domain) I354-L425 Eukaryotic RNA-binding BL00030A:I354-F372 BL00030B:K393-D402 F25451_2 PD057917:L144-R206 PD056050:G305-R353 RIBONUCLEOPROTEIN REPEAT DM00012 Q10355 25-106:W347-S428 DM00012 P32588 154-238:D350-L425 DM00012 P31483 87-172:A349-K424 DM00012 Q05966 1-83:D351-S428 POLYADENYLATION CLEAVAGE SPECIFICITY RNA BINDING PD005421:Y179-L370 Eukaryotic putative RNA-binding region RNP-1 Signature K51-F58 signal_cleavage: M1-A64 RNA recognition motif. (RRM, RBD, or RNP domain) rrm:V12-A83 Eukaryotic RNA-binding region RNP-1 proteins BL00030A:V12-F30 BL00030B:K51-D60	MOTIFS MOTIFS HMMER_PFAM BLAST_BLIMPS BLAST_PRODOM BLAST_DOMO BLAST_PRODOM MOTIFS SPSCAN HMMER_PFAM BLIMPS_BLOCKS
14	2598981CD1	600	T209 T254 T520 T577 S213 T272 T512 Y50 Y175			
15	2738075CD1	217	T207 T47 S198 T22 S155 S193 T194 S210	N66		

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
15					Eukaryotic putative RNA-binding region RNP-1 signature rnp_1.prf:N23-I85	PROFILES SCAN
					RIBONUCLEOPROTEIN REPEAT DM00012 S20940 151-238:V12-A86 DM00012 Q04836 234-321:V12-A86 DM00012 P19339 205-288:S10-N73 DM00012 P38159 3-84:P7-A86	BLIMPS_DOMO
16	2279049CD1	319	S275 T20 S234 T264 S80 T119 T268	N153	Aminoacyl-transfer RNA synthetases class-II Signatures H255-E278	MOTIFS
17	2660904CD1	108			Ribosomal protein S15 signature G30-G101	PROFILES SCAN
18	3179424CD1	92	S71 T12		signal_cleavage: M1-S15 Ribosomal protein L34 N51-H92 Ribosomal protein L34 BL00784:G50-R87	SPSCAN HMMER_PFAM BLIMPS_BLOCKS
19	2885096CD1	268	T78 T162 S241 Y91 T198 S222	N109 N193	Cytidine and deoxycytidylate deaminases zinc-binding region signature H144-V182 signal_cleavage: M1-S21 Cytidine and deoxycytidylate deaminases zinc-binding region BL00903:Y169-C178 APOLIPOPROTEIN B MRNA EDITING PROTEIN DM04741 P51908 1-228:K129-V239 DM04741 P41238 1-235:H144-V239 DM04741 A53853 1-236:H144-V239	MOTIFS SPSCAN BLIMPS_BLOCKS BLAST_DOMO

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
20	2901076CD1	624	S329 S351 S359 S367 T380 S502 S519 S520 S558 S61 S297 S319 S324 S487 S493 S505 S508 T511 T514 S524 S543 S553 S573 S618 T159 S175 T194 S557 T619	N25 N254 N339 N485 N570 N616	RNA recognition motif. (RRM, RBD, or RNP domain) rrm:V184-I253 rrm:I21-V93 ARGININE RICH SPLICEOSOME SPLICING FACTOR PD037489:V20-G139 TYPE B REPEAT REPEAT DM05511 S26650 1-1203:P264-R539 DM05511 P18583 113-1296:P264-R539	HMMER_PFAM BLAST_PRODOR BLAST_DOMO
21	3074572CD1	419	S8 S20 T64 T130 T144 T153 S331 S364 S380 S409 S296 S385 T419 T42 S137 T174 S221 S230 T239 S265 S390	N93 N161 N237	RNA POLYMERASE I DNA DIRECTED TRANSFERASE TRANSCRIPTION NUCLEAR PROTEIN PD025048:Q21-R415	BLAST_PRODOR
22	1437895CD1	743	S11 S25 S70 S341 S383 S561 S671 T732 S13 S49 T325 S351 S397 T642 T658 Y247 Y293 Y602	N10 N154 N425 N473 N560 N577	DEAH-box subfamily ATP-dependent helicase proteins: BL00690A:G85-Q94 BL00690B:T116-E133 BL00690C:I182-S191 DEAD and DEAH box families ATP-dependent helicases signatures (deah_atp_helicase.prf): D163-P209 ATP-dependent RNA helicase: PD001259:F401-H544 DEAH-box subfamily ATP-dependent helicases: DM00649 P53131 84-705:L55-Y677 Atp_Gtp_A: G85-S92	BLIMPS-BLOCKS PROFILESCAN BLAST-PRODOR BLAST-DOMO MOTIFS

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
23	1454656CD1	284	S57 S160 T232 T244 T279 S88 S165 T200		Ribosomal protein S15 (Ribosomal_S15): S151-E215	HMMER-PFAM
					Ribosomal protein S15 signature (ribosomal_s15.prf): P146-E215	PROFILESAN
24	121130CD1	248	T14 S49 S74 S132 S18 T242		NO27 protein (PD173812): M1-L112 Nucleolin: DM02740 S32644 630-703:R140-G204	BLAST-PRODOM BLAST-DOMO
25	1257715CD1	214	S137 T112 S181		Peptidyl-tRNA hydrolase (Pept_tRNA_hydro): W31-Q208 Peptidyl-tRNA hydrolase: BL01195B:L88-G99 BL01195C:V116-N154 BL01195D:M156-G164	HMMER-PFAM BLIMPS-BLOCKS
					Peptidyl-tRNA hydrolase (PD005324): M32-I199	BLAST-PRODOM
					Peptidyl-tRNA hydrolase: DM02080 P44682 1-193:M32-I199	BLAST-DOMO
26	1342022CD1	184	T2 S16 S19 S81 S172 T173 S69	N71 N136	Ribosomal protein S11 (Ribosomal_S11): G62-R180 Ribosomal protein S11: BL00054A:G62-S102 BL00054B:K139-R180 Ribosomal_S11: G144-L184	HMMER-PFAM BLIMPS-BLOCKS PROFILESAN
					Ribosomal protein S11 (PD001010): G62-R180	BLAST-PRODOM
					E. coli ribosomal protein S11: DM00861 P19950 16-148:G51-L184	BLAST-DOMO
					Ribosomal_S11: D164-D171	MOTIFS
27	194704CD1	371	S270 S280 S291 S317 T17 S120 S152 S257 T283 S321 S339 S342 S360 T52 T111 T231 S332 Y173		Aspartate-arginine-rich mRNA binding protein (PD017473): F30-K230 RNP-1: DM03434 P08621 359-483:R204-K323	BLAST-PRODOM BLAST-DOMO

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
28	607270CD1	396	S13 T63 S64 T153 S252 T278 S290 T392 T68 T100 S214 S270 T357 Y218 Y262		signal_peptide: M1-A25 Ribosomal protein S9/S16 (Ribosomal_S9): G274-R396 Ribosomal protein S9: BL00360A:K275-Q301 BL00360B:F317-L352 BL00360C:L370-R396 Ribosomal protein S9 signature (ribosomal_s9.prf): I306-R396 Ribosomal protein S9 (PD001627): G274-R396 Ribosomal protein S9: DM00779 P38120 149-277:D263-R396 Ribosomal_S9: G334-L352 S4 domain (S4): R109-D156 Ribosomal protein S4: DM00205 P32899 101-174:V101-Y173 WD domain, G-beta repeat: WD40:G20-D58 WD40:E60-D100 WD40:M199-S239 WD40:A243-H282	HMMER HMMER-PFAM BLIMPS-BLOCKS PROFILESAN BLAST-PRODOM BLAST-DOMO MOTIFS HMMER-PFAM BLAST-DOMO HMMER-PFAM
29	758546CD1	184	S153 T159 S163 Y48			
30	866043CD1	282	T10 S67 T76 T103 S109 S136 S153 S200 S239 T5 T57 S131			
31	927065CD1	125	T65 Y21			MOTIFS

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
32	938071CD1	365	S23 S24 S132 T172 S186 S187 S201 S202 S210 S254 S261 S116 S132 T161 S176 T177 S178 S213 S215 S217 S219 S223 S224 S257 S265 S269 T282 T300 S301 S325 S350 S24 S27 S33 S36 S71 S110 S125 S149 S193 S202 S246 Y324	N69		MOTIFS
33	3295984CD1	672	Y137 Y297 S24 S36 T56 T58 T120 S182 S343 T345 T427 T455 S465 S470 S474 S490 S496 S3 T52 T120 T159 S182 S201 S333 T345 S435 T438 S510	N72 N180 N472 N476 N482 N485 N486 N489	L381-L402 Leucine Zipper Double-stranded RNA binding protein: G554-A567 Double-stranded RNA binding motif: L388-M451, G511-L574 RNA-binding Protein L448-M464, G411-V424, N558-A567 ZINC FINGER RNA BINDING SPERMATID PROTEIN R80-D329 SPERMATID PERINUCLEAR RNA BINDING PROTEIN F575-G648, P330-L392, G452-N513 TRANSCRIPTION; RNA; SPERMATID; PERINUCLEAR M1-P369 DOUBLE-STRANDED RNA BINDING DOMAIN N370-I461, T494-K584	MOTIFS BLIMPS_PFAM HMMER_PFAM BLIMPS_PRODOR BLAST_PRODOR BLAST_PRODOR BLAST_DOMO BLAST_DOMO

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
34	4545237CD1	430	S240 T94 S161 T214 T232 S354 T118 T232 T262 S295 S386		signal peptide M1-G20 Ribosomal protein S5 I222-G352 Ribosomal protein S5 pro T220-A271 I303-S339 Ribosomal protein S5 signature I222-R284 RIBOSOMAL PROTEIN S5 I222-N341 RIBOSOMAL PROTEIN S5 R226-G367	HMMER HMMER_PFAM BLIMPS_BLOCKS PROFILES SCAN BLAST_PROD OM BLAST_DOMO
35	4942964CD1	137	T11 T14 T19 S109 Y95 S41 T104	N39	Ribosomal_S24e F70-N84 F28-K111 Ribosomal protein S24e Ribosomal protein S24e signature E47-A103 Ribosomal protein S24e V10-E54, I61-K105 Arginine repressor N20-G71 Protein_S24E V10-K146 RIBOSOMAL 40S S24 S24E V29-K111	MOTIFS HMMER_PFAM PROFILES SCAN BLIMPS_BLOCKS BLIMPS_PFAM BLAST_DOMO BLAST_PROD OM

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
36	5702144CD1	380	Y169 S247 T45 T342 S362 S371 T208 T243 S321 S377	N255 N340	Leucine_Zipper L57-L78 L64-L85 L71-L92 Rf_Prok_I R245-V261 signal peptide M1-G20 Prokaryotic-type class I peptide chain release factor RF-1 G138-R338 Prokaryotic-type class I peptide chain release factors signature E123-R161, I184-Q226, D238-K284, G316-R338 PROKARYOTIC-TYPE CLASS I PEPTIDE CHAIN RELEASE FACTORS L224-S377 PEPTIDE CHAIN RELEASE FACTOR G138-R338	MOTIFS MOTIFS HMMER HMMER_PFAM BLIMPS_BLOCKS BLAST_DOMO BLAST_PRODOM
37	5862945CD1	206	S42 S141 Y83		Signal peptide M1-T35 Ribosomal protein L22 H69-K105, V128-L172 Ribosomal protein L22 signature R131-E192	SPSCAN BLIMPS_BLOCKS PROFILES SCAN
38	6319547CD1	190	S96 T140 S188 T178 T179 S20 T78 S128	N12 N136	Rnp_1 R69-F76 Eukaryotic putative RNA-binding region RNP-1 signature L45-K97 RNA recognition motif L27-V101 Eukaryotic RNA-binding L27-L45 R69-T78	MOTIFS PROFILES SCAN HMMER_PFAM BLIMPS_BLOCKS

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
39	000124CD1	434	S18 S47 T165 S274 T307 S389 S400 T29 T112 T124 S289 T359 Y368	N272 N152 N199 N217	Poly A polymerase family T110-E276 RNA BINDING PROCESSING POLYNUCLEOTIDE G63-G248 RNA BINDING POLYMERASE L51-G248	HMIMER_PFAM BLAST_PRODUM BLAST_DOMO
40	1659474CD1	339	S60 T244 S329 T69 T254 T315 Y238			MOTIFS
41	2267892CD1	599	T18 T79 S86 S129 S213 S282 S283 S320 S344 T397 S457 T503 T569 S589 S22 T92 T585 S77 S99 S110 S381 S492 T517		Atp_Gtp_A A209-T216 Helicase conserved C-terminal domain Y496-T503 DEAD/DEAH box helicase Q178-E389 Helicases conserved C-terminal domain K426-G507 DEAD-box subfamily ATP-dependent helicases G184-P222, M225-I250, V312-L335, V465-G510 DEAD-BOX SUBFAMILY ATP-DEPENDENT HELICASES N179-I542 RNA BINDING NUCLEAR DNA FACTOR I422-G507, D182-S258 Mov34/MPN/PAD1 family H50-A314 SUBUNIT 26S MOV34 S12 PAD1 HOMOLOG F52-R282 PAD1 related protein I57-S254	MOTIFS BLIMPS_PFAM HMIMER_PFAM HMIMER_PFAM BLIMPS_BLOCKS BLAST_DOMO BLAST_PRODUM HMIMER_PFAM BLAST_PRODUM BLAST_DOMO
42	2670307CD1	334	S24 S148 S231 T257 T310 S270 S307	N332		

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
43	4524210CD1	448	S159 T285 S319 T355 T413 S417 Y182 T33 S159 S265		Nol1_Nop2_Sun F296-G307 NOL1/NOP2/sun family Y194-K369 NOL1/NOP2/sun family I217-I231, G239-G262, F296-G309, K342-L367 NUCLEOLAR SUN P120 PROLIFERATING CELL ANTIGEN R176-E379 NOL1/NOP2/FMU FAMILY L197-V363	MOTIFS HMMER_PFAM BLIMPS_BLOCKS BLAST_PRODUM BLAST_DOMO HMMER_PFAM BLIMPS_BLOCKS BLAST_PRODUM HMMER_PFAM BLIMPS_BLOCKS BLAST_PRODUM BLAST-DOMO BLIMPS-BLOCKS PROFILES SCAN HMMER HMMER-PFAM SPSCAN
44	5584860CD1	420	S218 S86 S102 S126 S142 T187 T242 T244 S102 Y181	N294	RNA recognition motif L234-V300 RNA-binding motif L234-F252 RNA BINDING PROTEIN L223-E314 Ribosomal protein S16 G24-S84 Ribosomal protein S16 H16-L51, L68-A94 RIBOSOMAL S16 NUCLEASE G25-A81	BLAST_PRODUM HMMER_PFAM BLIMPS_BLOCKS BLAST_PRODUM BLAST-DOMO BLIMPS-BLOCKS PROFILES SCAN HMMER HMMER-PFAM SPSCAN
45	5807892CD1	137	T18 T27 S122 S60 T105 T125 T130		AMIDASES: DM00646 A53101 91-465:V94-G338 Amidase proteins: BL00571: N219-S270 Amidase signature (amidases.prf): G235-G278 Transmembrane domain (transmem_domain): I33-P58 Amidase: D93-P313, R443-L537 Signal cleavage: M1-G56	BLAST_PRODUM BLAST-DOMO BLIMPS-BLOCKS PROFILES SCAN HMMER HMMER-PFAM SPSCAN
46	3210044CD1	556	T30, T64, T153, 210, S231, S254, S344, T353, S389, S458	N165, N199		

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
47	4942454CD1	111	S19, S47, S101, S108		RAT ACIDIC RIBOSOMAL PROTEIN P1: DM00632 S54179 1-112: M1-D111 Ribosomal protein P2 Signature: PR00456E: A75-A89; PR00456F: K98-L109 RIBOSOMAL PROTEIN, ACIDIC 60S PHOSPHORYLATION P2, P1, L12 MULTIGENE FAMILY: PD001928: M1-D111 60S acidic ribosomal protein (60s_ribosomal): M1-D111	BLAST-DOMO BLIMPS-PRINTS BLAST-PRODOR HMMER-PFAM

Table 4

Polynucleotide SEQ ID NO:	Incyte Polynucleotide ID	Sequence Length	Selected Fragments	Sequence Fragments	5' Position	3' Position
48	1622129CB1	882	1-59	642017H1 (BRSTNOT03) 483782F1 (HNT2RAT01)	1 176	270 882
49	1820078CB1	1220	1-41, 833-1220	71164239V1 70024116D1 1293767T6 (PGANNOT03) 6571082H1 (MCLDTXN05)	647 564 403 1	1220 1220 1203 490
50	1527017CB1	2020	1-209, 1415-2020	1541283H1 (SINTTUT01) 1824377H1 (GBLATUT01) 1659084T6 (URETTUT01) 1527017T1 (UCMCL5T01) SBMA03026F1 1438348F1 (PANCNOT08) 2735749H2 (OVARNOT09) 1647264H1 (PROSTUT09) g1136841	1266 1 1279 744 324 226 286 149 1	1473 265 2020 1407 858 769 508 384 637
51	1647264CB1	637	1-40	1721989F6 (BLADNOT06) 079812F1 (SYNORAB01) 1525770T1 (UCMCL5T01) 1457506F6 (COLNFET02) 915914R1 (BRSTNOT04) 1730581F6 (BRSTTUT08) 2693987T6 (LUNGNOT23) 102784H1 (ADRENOR01)	1 146 1109 486 306 1546 953 1	419 717 1566 1012 884 2061 1565 406
52	1721989CB1	717	1-21	1740714CT1 (HIPONON01) 3074962H1 (BONEUNT01)	1 1	1307 277
53	1730581CB1	2061	1-24, 1219-1514	820443R1 (KERANOT02) 2018418H1 (THP1NOT01) 1989582H1 (CORPNOT02) 1855681H1 (HNT3AZT01) 3563740H1 (SKINNNOT05) 3147502H1 (PENCNOT05)	493 813 986 1 141 282	1131 1160 1357 270 470 643
54	1740714CB1	1307	1-43, 1111-1142			
55	1850596CB1	1357				

Table 4 (cont.)

Polynucleotide SEQ ID NO:	Incyte Polynucleotide ID	Sequence Length	Selected Fragments	Sequence Fragments	5' Position	3' Position
56	1856109CB1	1749	1-29, 1201-1749	6708693H1 (HEAADIR01)	1411	1738
				1518037F1 (BLADTUT04)	460	979
				2367008F6 (ADREN07)	1547	1749
				875652T1 (LUNGAST01)	1073	1718
				1981031R6 (LUNGUT03)	563	1109
57	1921719CB1	991	1-79	1806093F6 (SINTNOT13)	1	525
				1921719T6 (BRSTTUT01)	335	973
				902176H1 (BRSTTUT03)	697	991
				1522552F1 (BLADTUT04)	1	429
				g1155846	718	1065
58	2099829CB1	1188	1024-1188	1868148T6 (SKINBIT01)	402	972
				1984185T6 (LUNGAST01)	248	889
				3135711H1 (SMCCNOT01)	1	274
				313888H1 (LUNGNOT02)	690	1006
				1569836F6 (UTRSNOT05)	37	519
59	2416915CB1	1454	1-22	3177069T6 (UTRSTUT04)	830	1454
				2172869H1 (ENDCNOT03)	761	1026
				3873555H1 (HEARNOT06)	446	741
				3584701H1 (293TF4T01)	1	315
				1926194R6 (BRSTNOT02)	1161	1588
60	2472784CB1	1588	1-242, 288-726	2701446H1 (OVARUT01)	775	1135
				908518R2 (COLNNOT09)	1	616
				2834469H1 (TLYMNOT03)	1	274
				599142R6 (BRSTNOT02)	1229	1588
				2023191F6 (CONNNOT01)	1038	1588
61	2598981CB1	2111	557-1153, 1-22	2470222F6 (THP1NOT03)	546	1113
				1727193H1 (PROSNOT14)	387	634
				1593669X16C1 (BRAINOT14)	289	954
				SBZA06347V1	936	1527
				SBZA04028V1	1236	2111

Table 4 (cont.)

Polynucleotide SEQ ID NO:	Incyte Polynucleotide ID	Sequence Length	Selected Fragments	Sequence Fragments	5' Position	3' Position
61				1593669X11C1 (BRAINT14)	52	711
				SBZA02427V1	1159	1621
				2450029H1 (ENDANOT01)	1	227
62	2738075CB1	1155	1-36, 597-623	222536F1 (PANCNOT01)	15	622
				2055577R6 (BEPINOT01)	801	1155
				222536R1 (PANCNOT01)	55	1155
63	2279049CB1	1673		1597077F6 (BRAINT14)	445	1005
				438020T6 (THYRNOT01)	938	1650
				1798393F6 (COLNNOT27)	1208	1673
64	2660904CB1	584	1-229, 519-584	2458985F6 (ENDANOT01)	1	458
				3050984H1 (LUNGNOT25)	409	687
				71284614V1	387	584
65	3179424CB1	978	1-189	70937372V1	1	514
				3204102F6 (PENCNOT03)	1	632
				586088F1 (PROSNOT02)	307	978
66	2885096CB1	1055	1-278	1702519X13C1 (BLADTUT05)	127	778
				3887887H1 (UTRSNOT05)	813	1055
				1876565F6 (LEUKNOT03)	552	1043
67	2901076CB1	2220	1189-1491, 634-662	2885096F6 (SINJNOT02)	1	454
				5635858H1 (UTRSTMR01)	1333	1585
				3524308H1 (ESOGTUN01)	333	644
				1285251F6 (COLNNOT16)	552	1152
				3254924X309D1 (OVRTUN01)	39	491
				1260590R1 (SYNORAT05)	892	1508
				5117929H1 (SMCBUNT01)	1	278
				1285251T1 (COLNNOT16)	792	1218
				1852576F6 (LUNGFEET03)	1730	2220

Table 4 (cont.)

Polynucleotide SEQ ID NO:	Incyte Polynucleotide ID	Sequence Length	Selected Fragments	Sequence Fragments	5' Position	3' Position
67				2921502H1 (SININOT04)	1457	1740
				4936943H1 (OVARNON03)	1665	1904
68	3074572CB1	1890	1-24, 1837-1890	1558589F1 (SPLNNOT04)	1011	1432
				SAEA01339F1	1325	1890
				157743R6 (THP1PLB02)	221	725
				SAEA01587F1	769	1343
				3173159H1 (UTRSTUT04)	1	278
				SAEA01593R1	286	843
69	1437895CB1	2893	845-1749, 1-43, 2872-2893	2630813H1 (COLNTUT15)	2042	2283
				4919358H1 (TESTNOT11)	1384	1615
				3205068H1 (PENCNOT03)	1623	1888
				3877384F6 (HEARNOT06)	305	799
				1493166R6 (PROSNON01)	2324	2884
				4840634H1 (OSTENOT01)	903	1171
				3550295H1 (BRONDIT01)	1	244
				6453094H1 (COLNDIC01)	192	757
				1400075F1 (BRAITUT08)	1046	1606
				g1377484	2337	2893
				1437895T1 (PANCNOT08)	2244	2863
				786771F1 (PROSNOT05)	2707	2892
				1582477H1 (DUODNOT01)	1599	1793
				g1102494	2314	2892
				1437895F1 (PANCNOT08)	1731	2278
				3628841F6 (COLNNOT38)	722	1098
70	1454656CB1	885	1-47	782659R1 (MYOMNOT01)	523	885
				938801R1 (CERVNOT01)	505	876
				876916T1 (LUNGAST01)	280	867
				4843096H1 (OSTENOT01)	23	314
				g1617769	1	414

Table 4 (cont.)

Polynucleotide SEQ ID NO:	Incyte Polynucleotide ID	Sequence Length	Selected Fragments	Sequence Fragments	5' Position	3' Position
71	121130CB1	1269	1-42	1457506F6 (COLNFET02)	530	1055
				915914R1 (BRSTNOT04)	352	929
				3730083H1 (SMCCNON03)	974	1269
				5217827H1 (BRSTNOT35)	258	521
				5376327H1 (BRAXNOT01)	14	254
				g1716816	1	395
72	1257715CB1	1066	835-1066, 1-22	102784H1 (ADRENOR01)	63	452
				g3048792	746	1066
				1680736H1 (STOMFET01)	1	221
				1901049F6 (BLADTUT06)	320	825
73	1342022CB1	639	1-98	1731204F6 (BRSTTUT08)	17	669
				1908142T6 (CONNTUT01)	1	614
				2257149R6 (OVARTUT01)	100	639
				834691H1 (PROSNOT07)	1181	1420
74	194704CB1	1420	822-852, 1051-1420	1701714F6 (BLADTUT05)	32	698
				1822010F6 (GBLATUT01)	361	983
				2584972H1 (BRAITUT22)	1156	1420
				1395146H1 (THYRNOT03)	1	255
				2060393R6 (OVARNOT03)	807	1420
				607270H1 (BRSTTUT01)	1	265
75	607270CB1	1457	1-103, 680-892	607270X11 (BRSTTUT01)	104	745
				1558989F6 (SPLNNOT04)	448	973
				449792F1 (TLYMNOT02)	780	1457
				1488271H1 (UCMCL5T01)	429	691
76	758546CB1	1184	1-53	489544F1 (HNT2AGT01)	506	1184
				489544R1 (HNT2AGT01)	58	664
				2657989H1 (LUNGTUT09)	1	229
				5278386H1 (MUSLNOT01)	693	891
77	866043CB1	1638	1-561	004388T6 (HMC1NOT01)	990	1615
				5039960H1 (COLHTTUT01)	704	952
				866043R6 (BRAITUT03)	1266	1638

Table 4 (cont.)

Polynucleotide SEQ ID NO:	Incyte Polynucleotide ID	Sequence Length	Selected Fragments	Sequence Fragments	5' Position	3' Position
77				2295207R6 (BRSTNOT05)	171	638
				3398785H1 (UTRSNOT16)	1	226
				5421565H1 (PROSTMT07)	468	715
				004388R6 (HMC1NOT01)	838	1355
78	927065CB1	701		SXAF04722V1	254	701
				SXAE03477V1	13	411
				g1545603	1	614
79	938071CB1	1829	1070-1829, 513-561, 828-910, 689-768	2570862T6 (HIPOAZT01)	852	1407
				2344188T6 (TESTTUT02)	168	744
				2061053R6 (OVARNOT03)	1077	1413
				2962659T6 (ADRENOT09)	296	882
				2371642H1 (ADRENOT07)	1210	1425
				g1141976	1335	1829
				3148824H1 (ADRENON04)	1	274
80	3295984CB1	2541	1-242, 2385-2541	SCGA02064V1	287	1013
				SCGA02183V1	1784	2326
				261729R6 (HNT2AGT01)	1055	1668
				SCGA00610V1	1221	1778
				SCGA10196V1	1588	2118
				4526287F6 (LYMBTXT01)	1	532
				3813241H1 (TONSNOT03)	2255	2541
				SCGA05805V1	591	1162
81	4545237CB1	1647	525-567	1561512F6 (SPLNNOT04)	219	830
				1639525F6 (UTRSNOT06)	1226	1647
				1649445F6 (PROSTUT09)	874	1378
				2013721X28C1 (TESTNOT03)	560	1154
				5882142H1 (LIVRNON08)	559	832
82	4942964CB1	735	704-735	567202H1 (MMLR3DT01)	1	252
				4942964T6 (BRAIFEN05)	1	735

Table 4 (cont.)

Polynucleotide SEQ ID NO:	Incyte Polynucleotide ID	Sequence Length	Selected Fragments	Sequence Fragments	5' Position	3' Position
83	5702144CB1	2614	1-93, 1719-1901	1481581F6 (CORPNOT02)	724	1378
				2287840X12F1 (BRAINON01)	464	906
				1962628R6 (BRSTNOT04)	2107	2614
				2160148F6 (ENDCNOT02)	1866	2324
				2287840X14F1 (BRAINON01)	370	861
				1329248F1 (PANCNOT07)	1529	2094
				968129X11F1 (BRSTNOT05)	1093	1612
84	5862945CB1	736	1-34	1635830F6 (UTRSNOT06)	1	454
				280637F1 (LIVRNOT02)	106	736
				2244058F6 (PANCNOT02)	1	510
85	6319547CB1	1046	1-33	2383076F6 (ISLTNOT01)	574	1046
				3014264H1 (MUSCNOT07)	509	809
				5571304F6 (TLYMNOT08)	142	782
				591563H1 (BRAVUNT02)	1	241
				000124T6 (U937NOT01)	1742	2266
86	000124CB1	2266	1-32, 2085-2266	789548R6 (PROSTUT03)	1100	1600
				3519565R6 (LUNGNON03)	1196	1782
				902790R6 (BRSTTUT03)	629	1123
				3039556F6 (BRSTNOT16)	1	611
				SBZA03954V1	482	1008
87	1659474CB1	1041	927-954, 677-709, 833-857	1865044F6 (PROSNOT19)	615	1041
				SAYA00579F1	352	833
				4005010F6 (ENDCNOT04)	1	533
88	2267892CB1	2722	2347-2722	2290718X14F1 (BRAINON01)	726	1230
				3139431F6 (SMCCNOT02)	529	1043
				1970333F6 (UCMCL5T01)	888	1350

Table 4 (cont.)

Polynucleotide SEQ ID NO:	Incyte Polynucleotide ID	Sequence Length	Selected Fragments	Sequence Fragments	5' Position	3' Position
88				3815067H1 (TONSNOT03)	1574	1844
				082326R1 (HUVESB01)	1828	2448
				082326F1 (HUVESB01)	2007	2710
				2287150X13F1 (BRAINON01)	1	546
89	2670307CB1	1287	1-382	256073F1 (HNT2RAT01)	2581	2722
				3925865H1 (KIDNNOT19)	1219	1479
				1420665F1 (KIDNNOT09)	1276	1828
				008243F1 (HMC1NOT01)	315	1287
				1295856F1 (PGANNOT03)	969	1287
				1304866F1 (PLACNOT02)	732	1287
				1353856F1 (LATRTUT02)	1	485
90	4524210CB1	2226	509-1516	SCIA00216V1	430	1034
				SCIA00181V1	1251	1780
				2256793X309B2 (OVRTUT01)	1645	2225
				SCIA03684V1	1161	1705
				2256793X318D4 (OVRTUT01)	1	517
				2058779H1 (OVARNOT03)	1999	2226
				SCIA02060V1	665	1237
91	5584860CB1	2362	1-49, 1066-2362	1965766R6 (BRSTNOT04)	1954	2362
				1850306T6 (LJNGFET03)	1698	2340
				842676R1 (PROSTUT05)	712	1279
				71054273V1 (SG0000314)	1	614
				2105411R6 (BRAITUT03)	1293	1767
				SAEB02217F1	1191	1752
				377688R6 (NEUTFMT01)	541	1153
92	5807892CB1	731	1-68	3745266F6 (THYMNOT08)	1	495
				958760R1 (KIDNNOT05)	416	731

Table 4 (cont.)

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				7705613J1 (UTRETUE01)	1	541
				70821405V1	1195	1807
				70818955V1	511	1069
				6016193H1 (HNT2UNN03)	1127	1739
94	4942454CB1	660	1-23	70821946V1 (SG0000294)	1653	2088
				4942454T6 (BRAIFEN03)	3	660
				4942454F6 (BRAIFEN03)	1	589

Table 5

Polynucleotide SEQ ID NO:	Incyte Project ID	Representative Library
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49	1820078CB1	LUNGNOT20
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51	1647264CB1	LUNGNOT27
52	1721989CB1	ISLTNOT01
53	1730581CB1	LUNGTUT03
54	1740714CB1	TIYMNOT02
56	1856109CB1	BLADTUT04
57	1921719CB1	BRSTTUT01
58	2099829CB1	ENDANOT01
59	2416915CB1	BLADTUT05
60	2472784CB1	BRSTNOT02
61	2598981CB1	LIVRNON08
62	2738075CB1	BRAITUT02
63	2279049CB1	BRAINOT14
64	2660904CB1	LUNGTUT09
65	3179424CB1	KIDNNOT09
66	2885096CB1	BLADTUT04
67	2901076CB1	ENDCNON02
68	3074572CB1	SINTFET03
69	1437895CB1	PANCNOT08
70	1454656CB1	ADRENOT03
71	121130CB1	SPLNFET01
72	1257715CB1	MENITUT03
73	1342022CB1	COLNFET02
74	194704CB1	OVARNOT03
76	758546CB1	COLNNOT11
77	866043CB1	BRAITUT03
78	927065CB1	LNODNOT03
79	938071CB1	EP1PNON05
80	3295984CB1	THP1NOT03

Table 5 (cont.)

Polynucleotide SEQ ID NO:	Incyte Project ID	Representative Library
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83	5702144CB1	PANCNOT07
84	5862945CB1	KERANOT01
85	6319547CB1	PROSNOT16
86	000124CB1	KIDNNOT05
87	1659474CB1	KERANOT01
88	2267892CB1	UCMCL5T01
89	2670307CB1	BRSTTUT01
90	4524210CB1	OVARTUT01
91	5584860CB1	UTRSNOT05
92	5807892CB1	KIDNTUT01
93	3210044CB1	PITUNOT01
94	4942454CB1	BRAIFEN03

Table 6

Library	Vector	Library Description
ADRENOT03	PSPORT1	Library was constructed using RNA isolated from the adrenal tissue of a 17-year-old Caucasian male, who died from cerebral anoxia.
BLADTUT04	pINCY	Library was constructed using RNA isolated from bladder tumor tissue removed from a 60-year-old Caucasian male during a radical cystectomy, prostatectomy, and vasectomy. Pathology indicated grade 3 transitional cell carcinoma in the left bladder wall. Carcinoma in-situ was identified in the dome and trigone. Patient history included tobacco use. Family history included type I diabetes, malignant neoplasm of the stomach, atherosclerotic coronary artery disease, and acute myocardial infarction.
BLADTUT05	pINCY	Library was constructed using RNA isolated from bladder tumor tissue removed from a 66-year-old Caucasian male during a radical prostatectomy, radical cystectomy, and urinary diversion. Pathology indicated grade 3 transitional cell carcinoma on the anterior wall of the bladder. Patient history included lung neoplasm and tobacco abuse in remission. Family history included malignant breast neoplasm, tuberculosis, cerebrovascular disease, atherosclerotic coronary artery disease, and lung cancer.
BRAIFEN03	pINCY	This normalized fetal brain tissue library was constructed from 3.26 million independent clones from a fetal brain library. Starting RNA was made from brain tissue removed from a Caucasian male fetus, who was stillborn with a hypoplastic left heart at 23 weeks' gestation. The library was normalized in 2 rounds using conditions adapted from Soares et al., PNAS (1994) 91:9228 and Bonaldo et al., Genome Research (1996) 6:791, except that a significantly longer (48 hours/round) reannealing hybridization was used.
BRAIFEN05	pINCY	This normalized fetal brain tissue library was constructed from 3.26 million independent clones from a fetal brain library. Starting RNA was made from brain tissue removed from a Caucasian male fetus, who was stillborn with a hypoplastic left heart at 23 weeks' gestation. The library was normalized in 2 rounds using conditions adapted from Soares et al., PNAS (1994) 91:9228 and Bonaldo et al., Genome Research (1996) 6:791, except that a significantly longer (48 hours/round) reannealing hybridization was used.
BRAINOT14	pINCY	Library was constructed using RNA isolated from brain tissue removed from the left frontal lobe of a 40-year-old Caucasian female during excision of a cerebral meningeal lesion. Pathology for the associated tumor tissue indicated grade 4 gemistocytic astrocytoma.

Table 6 (cont.)

Library	Vector	Library Description
BRAITUT02	PSORT1	Library was constructed using RNA isolated from brain tumor tissue removed from the frontal lobe of a 58-year-old Caucasian male during excision of a cerebral meningeal lesion. Pathology indicated a grade 2 metastatic hypernephroma. Patient history included a grade 2 renal cell carcinoma, insomnia, and chronic airway obstruction. Family history included a malignant neoplasm of the kidney.
BRAITUT03	PSORT1	Library was constructed using RNA isolated from brain tumor tissue removed from the left frontal lobe of a 17-year-old Caucasian female during excision of a cerebral meningeal lesion. Pathology indicated a grade 4 fibrillary giant and small-cell astrocytoma. Family history included benign hypertension and cerebrovascular disease.
BRSTNOT02	PSORT1	Library was constructed using RNA isolated from diseased breast tissue removed from a 55-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated proliferative fibrocystic changes characterized by apocrine metaplasia, sclerosing adenosis, cyst formation, and ductal hyperplasia without atypia. Pathology for the associated tumor tissue indicated an invasive grade 4 mammary adenocarcinoma. Patient history included atrial tachycardia and a benign neoplasm. Family history included cardiovascular and cerebrovascular disease.
BRSTTUT01	PSORT1	Library was constructed using RNA isolated from breast tumor tissue removed from a 55-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated invasive grade 4 mammary adenocarcinoma of mixed lobular and ductal type, extensively involving the left breast. The tumor was identified in the deep dermis near the lactiferous ducts with extracapsular extension. Seven mid and low and five high axillary lymph nodes were positive for tumor. Proliferative fibrocystic changes were characterized by apocrine metaplasia, sclerosing adenosis, cyst formation, and ductal hyperplasia without atypia. Patient history included atrial tachycardia, blood in the stool, and a benign breast neoplasm. Family history included benign hypertension, atherosclerotic coronary artery disease, cerebrovascular disease, and depressive disorder.
COLNFET02	pINCY	Library was constructed using RNA isolated from the colon tissue of a Caucasian female fetus, who died at 20 weeks' gestation.
COLNNOT11	PSORT1	Library was constructed using RNA isolated from colon tissue removed from a 60-year-old Caucasian male during a left hemicolectomy.
ENDANOT01	PBLUESCRIPT	Library was constructed using RNA isolated from aortic endothelial cell tissue from an explanted heart removed from a male during a heart transplant.

Table 6 (cont.)

Library	Vector	Library Description
ENDCNON02	pINCY	This normalized coronary artery endothelial cell tissue library was constructed from 444,000 independent clones from an endothelial tissue library. Starting RNA was made from coronary artery endothelial cell tissue removed from a 3-year-old Caucasian male. This library was normalized in two rounds using conditions adapted from Soares et al., (PNAS (1994) 91:9228-9232) and Bonaldo et al., (Genome Research (1996) 6:791-806), using a significantly longer (48 hours/round) reannealing hybridization period.
EPIPNON05	pINCY	This normalized prostate epithelial cell tissue library was constructed from 2.36 million independent clones from a prostate epithelial cell tissue library. Starting RNA was made from untreated prostatic epithelial cell issue removed from a 17-year-old Hispanic male. The library was normalized in two rounds using conditions adapted from Soares et al., PNAS (1994) 91:9228 and Bonaldo et al., Genome Research (1996) 6:791, except that a significantly longer (48 -hours/round) reannealing hybridization was used.
HNT2RAT01	PBLUESCRIPT	Library was constructed at Stratagene (STR937231), using RNA isolated from the hNT2 cell line (derived from a human teratocarcinoma that exhibited properties characteristic of a committed neuronal precursor). Cells were treated with retinoic acid for 24 hours
ISLTNOT01	pINCY	Library was constructed using RNA isolated from a pooled collection of pancreatic islet cells.
KERANOT01	PBLUESCRIPT	Library was constructed using RNA isolated from neonatal keratinocytes obtained from the leg skin of a spontaneously aborted black male.
KIDNNOT05	PSPORT1	Library was constructed using RNA isolated from the kidney tissue of a 2-day-old Hispanic female, who died from cerebral anoxia. Family history included congenital heart disease.
KIDNNOT09	pINCY	Library was constructed using RNA isolated from the kidney tissue of a Caucasian male fetus, who died at 23 weeks' gestation.
KIDNTUT01	PSPORT1	Library was constructed using RNA isolated from the kidney tumor tissue removed from an 8-month-old female during nephroureterectomy. Pathology indicated Wilms' tumor (nephroblastoma), which involved 90 percent of the renal parenchyma. Prior to surgery, the patient was receiving heparin anticoagulant therapy.

Table 6 (cont.)

Library	Vector	Library Description
LIVRNON08	pINCY	This normalized library was constructed from 5.7 million independent clones from a pooled liver tissue library. Starting RNA was made from pooled liver tissue removed from a 4-year-old Hispanic male who died from anoxia and a 16 week female fetus who died after 16-weeks gestation from anencephaly. Serologies were positive for cytomegalovirus in the 4-year-old. Patient history included asthma in the 4-year-old. Family history included taking daily prenatal vitamins and mitral valve prolapse in the mother of the fetus. The library was normalized in 2 rounds using conditions adapted from Soares et al., PNAS (1994) 91:9228 and Bonaldo et al., Genome Research 6 (1996):791, except that a significantly longer (48 hours/round) reannealing hybridization was used.
LNODNOT03	pINCY	Library was constructed using RNA isolated from lymph node tissue obtained from a 67-year-old Caucasian male during a segmental lung resection and bronchoscopy. On microscopic exam, this tissue was found to be extensively necrotic with 10% viable tumor. Pathology for the associated tumor tissue indicated invasive grade 3-4 squamous cell carcinoma. Patient history included hemangioma. Family history included atherosclerotic coronary artery disease, benign hypertension, congestive heart failure, atherosclerotic coronary artery disease.
LUNGNOT14	pINCY	Library was constructed using RNA isolated from lung tissue removed from the left lower lobe of a 47-year-old Caucasian male during a segmental lung resection. Pathology for the associated tumor tissue indicated a grade 4 adenocarcinoma, and the parenchyma showed calcified granuloma. Patient history included benign hypertension and chronic obstructive pulmonary disease. Family history included type II diabetes and acute myocardial infarction.
LUNGNOT20	pINCY	Library was constructed using RNA isolated from right upper lobe lung tissue removed from a 61-year-old Caucasian male. Pathology indicated pancreatic emphysema with blebs in the right anterior upper lobe and apex, as well as emphysema in the right posterior upper lobe. Patient history included angina pectoris, and gastric ulcer. Family history included a subdural hemorrhage, cancer of an unidentified site, atherosclerotic coronary artery disease, and pneumonia.
LUNGNOT27	pINCY	Library was constructed using RNA isolated from lung tissue removed from a 17-year-old Hispanic female.
LUNGNOT03	PSPORT1	Library was constructed using RNA isolated from lung tumor tissue removed from the left lower lobe of a 69-year-old Caucasian male during segmental lung resection. Pathology indicated residual grade 3 invasive squamous cell carcinoma. Patient history included acute myocardial infarction, prostatic hyperplasia, malignant skin neoplasm, and tobacco use.

Table 6 (cont.)

Library	Vector	Library Description
LUNGTUT09	pINCY	Library was constructed using RNA isolated from lung tumor tissue removed from a 68-year-old Caucasian male during segmental lung resection. Pathology indicated invasive grade 3 squamous cell carcinoma and a metastatic tumor. Patient history included type II diabetes, thyroid disorder, depressive disorder, hyperlipidemia, esophageal ulcer, and tobacco use.
MENITUT03	pINCY	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.
OVARNOT03	PSPORT1	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.
OVARTUT01	PSPORT1	Library was constructed using RNA isolated from ovarian tumor tissue removed from a 43-year-old Caucasian female during removal of the fallopian tubes and ovaries. Pathology indicated grade 2 mucinous cystadenocarcinoma involving the entire left ovary. 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.
PANCNOT07	pINCY	Library was constructed using RNA isolated from the pancreatic tissue of a Caucasian male fetus, who died at 23 weeks' gestation.
PANCNOT08	pINCY	Library was constructed using RNA isolated from pancreatic tissue removed from a 65-year-old Caucasian female during radical subtotal pancreatectomy. Pathology for the associated tumor tissue indicated an invasive grade 2 adenocarcinoma. Patient history included type II diabetes, osteoarthritis, cardiovascular disease, benign neoplasm in the large bowel, and a cataract. Previous surgeries included a total splenectomy, cholecystectomy, and abdominal hysterectomy. Family history included cardiovascular disease, type II diabetes, and stomach cancer.
PITUNOT01	PBLUESCRIPT	Library was constructed using RNA obtained from Clontech (ClON 6584-2, lot 35278). The RNA was isolated from the pituitary glands removed from a pool of 18 male and female Caucasian donors, 16 to 70 years old, who died from trauma.

Table 6 (cont.)

Library	Vector	Library Description
PROSNOT16	pINCY	Library was constructed using RNA isolated from diseased prostate tissue removed from a 68-year-old Caucasian male during a radical prostatectomy. Pathology indicated adenofibromatous hyperplasia. Pathology for the associated tumor tissue indicated an adenocarcinoma (Gleason grade 3+4). The patient presented with elevated prostate specific antigen (PSA). During this hospitalization, the patient was diagnosed with myasthenia gravis. Patient history included osteoarthritis, and type II diabetes. Family history included benign hypertension, acute myocardial infarction, hyperlipidemia, and arteriosclerotic coronary artery disease.
SINTFET03	pINCY	Library was constructed using RNA isolated from small intestine tissue removed from a Caucasian female fetus, who died at 20 weeks' gestation.
SPLNFET01	PBLUESCRIPT	Library was constructed at Stratagene, using RNA isolated from a pool of fetal spleen tissue. Following vector packaging, 2 million primary clones were then amplified to stabilize the library for long-term storage. Amplification may significantly skew sequence abundances.
SPLNNOT04	pINCY	Library was constructed using RNA isolated from the spleen tissue of a 2-year-old Hispanic male, who died from cerebral anoxia. Past medical history and serologies were negative.
THP1NOT03	pINCY	Library was constructed using 1 microgram of polyA RNA isolated from untreated THP-1 cells. THP-1 (ATCC TIB 202) is a human promonocyte line derived from the peripheral blood of a 1-year-old Caucasian male with acute monocytic leukemia (ref: Int. J. Cancer (1980) 26:171).
TYMNOT02	PBLUESCRIPT	Library was constructed using RNA isolated from non-adherent peripheral blood mononuclear cells. The blood was obtained from unrelated male and female donors. Cells from each donor were purified on Ficoll Hypaque, then harvested by centrifugation, lysed in a buffer containing GuSCN, and spun through CsCl to obtain RNA for library construction.
UCMCL5T01	PBLUESCRIPT	Library was constructed using RNA isolated from mononuclear cells obtained from the umbilical cord blood of 12 individuals. The cells were cultured for 12 days with IL-5 before RNA was obtained from the pooled lysates.
UTRSNOT05	pINCY	The library was constructed using RNA isolated from the uterine tissue of a 45-year-old Caucasian female during a total abdominal hysterectomy and total colectomy. Pathology for the associated tumor tissue indicated multiple leiomyomas of the myometrium and a grade 2 colonic adenocarcinoma of the cecum. Patient history included multiple sclerosis and mitral valve disorder. Family history included type I diabetes, cerebrovascular disease, atherosclerotic coronary artery disease, malignant skin neoplasm, hypertension, and malignant neoplasm of the colon.

Table 7

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Program	Description	Reference	Parameter Threshold		
ABI FACTURA	A program that removes vector sequences and masks ambiguous bases in nucleic acid sequences.	Applied Biosystems, Foster City, CA.			
ABI/PARACEL FDF	A Fast Data Finder useful in comparing and annotating amino acid or nucleic acid sequences.	Applied Biosystems, Foster City, CA; Paracel Inc., Pasadena, CA.	Mismatch <50%		
ABI AutoAssembler	A program that assembles nucleic acid sequences.	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.	<i>ESTs</i> : Probability value= 1.0E-8 or less <i>Full Length sequences</i> : 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. USA 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.	<i>ESTs</i> : fasta E value=1.06E-6 <i>Assembled ESTs</i> : fasta Identity= 95% or greater and Match length=200 bases or greater; fastx E value=1.0E-8 or less <i>Full Length sequences</i> : fastx score=100 or greater		
BLIMPS	A BLocks IMProved Searcher that matches a sequence against those in BLOCKS, PRINTS, DOMO, PRODOM, and PFAM databases to search for gene families, sequence homology, and structural fingerprint regions.	Henikoff, S. and J.G. Henikoff (1991) Nucleic Acids Res. 19:6565-6572; Henikoff, J.G. and S. Henikoff (1996) Methods Enzymol. 266:88-105; and Attwood, T.K. et al. (1997) J. Chem. Inf. Comput. Sci. 37:417-424.	Probability value= 1.0E-3 or less		
HMMER	An algorithm for searching a query sequence against hidden Markov model (HMM)-based databases of protein family consensus sequences, such as PFAM.	Krogh, A. et al. (1994) J. Mol. Biol. 235:1501-1531; Sonnhammer, E.L.L. et al. (1988) Nucleic Acids Res. 26:320-322; Durbin, R. et al. (1998) Our World View, in a Nutshell, Cambridge Univ. Press, pp. 1-350.	<i>PFAM hits</i> : Probability value= 1.0E-3 or less <i>Signal peptide hits</i> : Score= 0 or greater		

Table 7 (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, M. et al. (1989) Methods Enzymol. 183:146-159; Bairoch, A. et al. (1997) Nucleic Acids Res. 25:217-221.	Normalized quality score≥GCG-specified “HIGH” value for that particular Prosite motif. Generally, score=1.4-2.1.
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=3.5 or greater
TMAP	A program that uses weight matrices to delineate transmembrane segments on protein sequences and determine orientation.	Persson, B. and P. Argos (1994) J. Mol. Biol. 237:182-192; Persson, B. and P. Argos (1996) Protein Sci. 5:363-371.	
TMHMMER	A program that uses a hidden Markov model (HMM) to delineate transmembrane segments on protein sequences and determine orientation.	Sonnhammer, E.L. et al. (1998) Proc. Sixth Intl. Conf. on Intelligent Systems for Mol. Biol., Glasgow et al., eds., The Am. Assoc. for Artificial Intelligence Press, Menlo Park, CA, pp. 175-182.	
Motifs	A program that searches amino acid sequences for patterns that matched those defined in Prosite.	Bairoch, A. et al. (1997) Nucleic Acids Res. 25:217-221; Wisconsin Package Program Manual, version 9, page M51-59, Genetics Computer Group, Madison, WI.	

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 AZIMZAI, Yalda
 AU-YOUNG, Janice
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 BAUGHN, Mariah R.
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Gln	Gly	Lys	Thr	Ser	Ser	Val	Phe	Glu	Asp	Pro	Val	Ile	Ser	Lys
				20					25					30
Phe	Thr	Asn	Met	Met	Met	Ile	Gly	Gly	Asn	Lys	Val	Leu	Ala	Arg
				35					40					45
Ser	Leu	Met	Ile	Gln	Thr	Leu	Glu	Ala	Val	Lys	Arg	Lys	Gln	Phe
				50					55					60
Glu	Lys	Tyr	His	Ala	Ala	Ser	Ala	Glu	Glu	Gln	Ala	Thr	Ile	Glu
				65					70					75
Arg	Asn	Pro	Tyr	Thr	Ile	Phe	His	Gln	Ala	Leu	Lys	Asn	Cys	Glu
				80					85					90
Pro	Met	Ile	Gly	Leu	Val	Pro	Ile	Leu	Lys	Gly	Gly	Arg	Phe	Tyr
				95					100					105
Gln	Val	Pro	Val	Pro	Leu	Pro	Asp	Arg	Arg	Arg	Arg	Phe	Leu	Ala
				110					115					120
Met	Lys	Trp	Met	Ile	Thr	Glu	Cys	Arg	Asp	Lys	Lys	His	Gln	Arg
				125					130					135
Thr	Leu	Met	Pro	Glu	Lys	Leu	Ser	His	Lys	Leu	Leu	Glu	Ala	Phe
				140					145					150
His	Asn	Gln	Gly	Pro	Val	Ile	Lys	Arg	Lys	His	Asp	Leu	His	Lys
				155					160					165
Met	Ala	Glu	Ala	Asn	Arg	Ala	Leu	Ala	His	Tyr	Arg	Trp	Trp	
				170					175					

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<210> 4
 <211> 101
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 1647264CD1

<400> 4
 Met Glu Arg Pro Asp Lys Ala Ala Leu Asn Ala Leu Gln Pro Pro
 1 5 10 15
 Glu Phe Arg Asn Glu Ser Ser Leu Ala Ser Thr Leu Lys Thr Leu
 20 25 30
 Leu Phe Phe Thr Ala Leu Met Ile Thr Val Pro Ile Gly Leu Tyr
 35 40 45
 Phe Thr Thr Lys Ser Tyr Ile Phe Glu Gly Ala Leu Gly Met Ser
 50 55 60
 Asn Arg Asp Ser Tyr Phe Tyr Ala Ala Ile Val Ala Val Val Ala
 65 70 75
 Val His Val Val Leu Ala Leu Phe Val Tyr Val Ala Trp Asn Glu
 80 85 90
 Gly Ser Arg Gln Trp Arg Glu Gly Lys Gln Asp
 95 100

<210> 5
 <211> 145
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 1721989CD1

<400> 5
 Met Ala Phe Phe Thr Gly Leu Trp Gly Pro Phe Thr Cys Val Ser
 1 5 10 15
 Arg Val Leu Ser His His Cys Phe Ser Thr Thr Gly Ser Leu Ser
 20 25 30
 Ala Ile Gln Lys Met Thr Arg Val Arg Val Val Asp Asn Ser Ala
 35 40 45
 Leu Gly Asn Ser Pro Tyr His Arg Ala Pro Arg Cys Ile His Val
 50 55 60
 Tyr Lys Lys Asn Gly Val Gly Lys Val Gly Asp Gln Ile Leu Leu
 65 70 75
 Ala Ile Lys Gly Gln Lys Lys Lys Ala Leu Ile Val Gly His Cys
 80 85 90
 Met Pro Gly Pro Arg Met Thr Pro Arg Phe Asp Ser Asn Asn Val
 95 100 105
 Val Leu Ile Glu Asp Asn Gly Asn Pro Val Gly Thr Arg Ile Lys
 110 115 120
 Thr Pro Ile Pro Thr Ser Leu Arg Lys Arg Glu Gly Glu Tyr Ser
 125 130 135
 Lys Val Leu Ala Ile Ala Gln Asn Phe Val
 140 145

<210> 6
 <211> 249
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 1730581CD1

<400> 6
 Met Ala Ala Gln Ser Ala Pro Lys Val Val Leu Lys Ser Thr Thr

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

<210> 7
 <211> 265
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 1740714CD1

<400> 7			
Met Arg Arg Ala Glu	Leu Ala Gly Leu Lys	Thr Met Ala Trp Val	
1	5	10	15
Pro Ala Glu Ser Ala	Val Glu Glu Leu Met	Pro Arg Leu Leu Pro	
20	25	30	
Val Glu Pro Cys Asp	Leu Thr Glu Gly Phe	Asp Pro Ser Val Pro	
35	40	45	
Pro Arg Thr Pro Gln	Glu Tyr Leu Arg Arg	Val Gln Ile Glu Ala	
50	55	60	
Ala Gln Cys Pro Asp	Val Val Val Ala Gln	Ile Asp Pro Lys Lys	
65	70	75	
Leu Lys Arg Lys Gln	Ser Val Asn Ile Ser	Leu Ser Gly Cys Gln	
80	85	90	
Pro Ala Pro Glu Gly	Tyr Ser Pro Thr Leu	Gln Trp Gln Gln Gln	
95	100	105	
Gln Val Ala Gln Phe	Ser Thr Val Arg Gln	Asn Val Asn Lys His	
110	115	120	
Arg Ser His Trp Lys	Ser Gln Gln Leu Asp	Ser Asn Val Thr Met	
125	130	135	
Pro Lys Ser Glu Asp	Glu Glu Gly Trp Lys	Lys Phe Cys Leu Gly	
140	145	150	
Glu Lys Leu Cys Ala	Asp Gly Ala Val Gly	Pro Ala Thr Asn Glu	
155	160	165	
Ser Pro Gly Ile Asp	Tyr Val Gln Ala Thr	Val Thr Ser Val Leu	

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Glu Tyr Leu Ser	170	175	180
Asn Trp Phe Gly Glu Arg Asp Phe Thr Pro Glu			
185	190	195	
Leu Gly Arg Trp Leu Tyr Ala Leu Leu Ala Cys Leu Glu Lys Pro			
200	205	210	
Leu Leu Pro Glu Ala His Ser Leu Ile Arg Gln Leu Ala Arg Arg			
215	220	225	
Cys Ser Glu Val Arg Leu Leu Val Asp Ser Lys Asp Asp Glu Arg			
230	235	240	
Val Pro Ala Leu Asn Leu Leu Ile Cys Leu Val Ser Arg Tyr Phe			
245	250	255	
Asp Gln Arg Asp Leu Ala Asp Glu Pro Ser			
260	265		

<210> 8
 <211> 306
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 1850596CD1

<400> 8

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

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<210> 9
 <211> 332
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 1856109CD1

<400> 9
 Met Ala Ser Gly Leu Val Arg Leu Leu Gln Gln Gly His Arg Cys
 1 5 10 15
 Leu Leu Ala Pro Val Ala Pro Lys Leu Val Pro Pro Val Arg Gly
 20 25 30
 Val Lys Lys Gly Phe Arg Ala Ala Phe Arg Phe Gln Lys Glu Leu
 35 40 45
 Glu Arg Gln Arg Leu Leu Arg Cys Pro Pro Pro Pro Val Arg Arg
 50 55 60
 Ser Glu Lys Pro Asn Trp Asp Tyr His Ala Glu Ile Gln Ala Phe
 65 70 75
 Gly His Arg Leu Gln Glu Asn Phe Ser Leu Asp Leu Leu Lys Thr
 80 85 90
 Ala Phe Val Asn Ser Cys Tyr Ile Lys Ser Glu Glu Ala Lys Arg
 95 100 105
 Gln Gln Leu Gly Ile Glu Lys Glu Ala Val Leu Leu Asn Leu Lys
 110 115 120
 Ser Asn Gln Glu Leu Ser Glu Gln Gly Thr Ser Phe Ser Gln Thr
 125 130 135
 Cys Leu Thr Gln Phe Leu Glu Asp Glu Tyr Pro Asp Met Pro Thr
 140 145 150
 Glu Gly Ile Lys Asn Leu Val Asp Phe Leu Thr Gly Glu Glu Val
 155 160 165
 Val Cys His Val Ala Arg Asn Leu Ala Val Glu Gln Leu Thr Leu
 170 175 180
 Ser Glu Glu Phe Pro Val Pro Pro Ala Val Leu Gln Gln Thr Phe
 185 190 195
 Phe Ala Val Ile Gly Ala Leu Leu Gln Ser Ser Gly Pro Glu Arg
 200 205 210
 Thr Ala Leu Phe Ile Arg Asp Phe Leu Ile Thr Gln Met Thr Gly
 215 220 225
 Lys Glu Leu Phe Glu Met Trp Lys Ile Ile Asn Pro Met Gly Leu
 230 235 240
 Leu Val Glu Glu Leu Lys Lys Arg Asn Val Ser Ala Pro Glu Ser
 245 250 255
 Arg Leu Thr Arg Gln Ser Gly Gly Thr Thr Ala Leu Pro Leu Tyr
 260 265 270
 Phe Val Gly Leu Tyr Cys Asp Lys Lys Leu Ile Ala Glu Gly Pro
 275 280 285
 Gly Glu Thr Val Leu Val Ala Glu Glu Glu Ala Ala Arg Val Ala
 290 295 300
 Leu Arg Lys Leu Tyr Gly Phe Thr Glu Asn Arg Arg Pro Trp Asn
 305 310 315
 Tyr Ser Lys Pro Lys Glu Thr Leu Arg Ala Glu Lys Ser Ile Thr
 320 325 330
 Ala Ser

<210> 10
 <211> 279
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 1921719CD1

<400> 10

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

<210> 11

<211> 239

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2099829CD1

<400> 11

Met	Pro	Lys	Ser	Lys	Arg	Asp	Lys	Lys	Val	Ser	Leu	Thr	Lys	Thr
1				5					10					15
Ala	Lys	Lys	Gly	Leu	Glu	Leu	Lys	Gln	Asn	Leu	Ile	Glu	Glu	Leu
				20					25					30
Arg	Lys	Cys	Val	Asp	Thr	Tyr	Lys	Tyr	Leu	Phe	Ile	Phe	Ser	Val
				35					40					45
Ala	Asn	Met	Arg	Asn	Ser	Lys	Leu	Lys	Asp	Ile	Arg	Asn	Ala	Trp
				50					55					60
Lys	His	Ser	Arg	Met	Phe	Phe	Gly	Lys	Asn	Lys	Val	Met	Met	Val
				65					70					75
Ala	Leu	Gly	Arg	Ser	Pro	Ser	Asp	Glu	Tyr	Lys	Asp	Asn	Leu	His
				80					85					90
Gln	Val	Ser	Lys	Arg	Leu	Arg	Gly	Glu	Val	Gly	Leu	Leu	Phe	Thr
				95					100					105
Asn	Arg	Thr	Lys	Glu	Glu	Val	Asn	Glu	Trp	Phe	Thr	Lys	Tyr	Thr
				110					115					120
Glu	Met	Asp	Tyr	Ala	Arg	Ala	Gly	Asn	Lys	Ala	Ala	Phe	Thr	Val
				125					130					135

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Ser	Leu	Asp	Pro	Gly	Pro	Leu	Glu	Gln	Phe	Pro	His	Ser	Met	Glu
				140					145					150
Pro	Gln	Leu	Arg	Gln	Leu	Gly	Leu	Pro	Thr	Ala	Leu	Lys	Arg	Gly
				155					160					165
Val	Val	Thr	Leu	Leu	Ser	Asp	Tyr	Glu	Val	Cys	Lys	Glu	Gly	Asp
				170					175					180
Val	Leu	Thr	Pro	Glu	Gln	Ala	Arg	Val	Leu	Lys	Leu	Phe	Gly	Tyr
				185					190					195
Glu	Met	Ala	Glu	Phe	Lys	Val	Thr	Ile	Lys	Tyr	Met	Trp	Asp	Ser
				200					205					210
Gln	Ser	Gly	Arg	Phe	Gln	Gln	Met	Gly	Asp	Asp	Leu	Pro	Glu	Ser
				215					220					225
Ala	Ser	Glu	Ser	Thr	Glu	Glu	Ser	Asp	Ser	Glu	Asp	Asp	Asp	
				230					235					

<210> 12

<211> 291

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2416915CD1

<400> 12

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

<210> 13

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<211> 451
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 2472784CD1

<400> 13

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

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Asp Val Val Arg Lys Lys Gln Lys Glu Lys Lys Lys Leu Gly Leu
 440 445 450
 Arg

<210> 14
 <211> 600
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 2598981CD1

<400> 14
 Met Pro Glu Ile Arg Val Thr Pro Leu Gly Ala Gly Gln Asp Val
 1 5 10 15
 Gly Arg Ser Cys Ile Leu Val Ser Ile Ala Gly Lys Asn Val Met
 20 25 30
 Leu Asp Cys Gly Met His Met Gly Phe Asn Asp Asp Arg Arg Phe
 35 40 45
 Pro Asp Phe Ser Tyr Ile Thr Gln Asn Gly Arg Leu Thr Asp Phe
 50 55 60
 Leu Asp Cys Val Ile Ile Ser His Phe His Leu Asp His Cys Gly
 65 70 75
 Ala Leu Pro Tyr Phe Ser Glu Met Val Gly Tyr Asp Gly Pro Ile
 80 85 90
 Tyr Met Thr His Pro Thr Gln Ala Ile Cys Pro Ile Leu Leu Glu
 95 100 105
 Asp Tyr Arg Lys Ile Ala Val Asp Lys Lys Gly Glu Ala Asn Phe
 110 115 120
 Phe Thr Ser Gln Met Ile Lys Asp Cys Met Lys Lys Val Val Ala
 125 130 135
 Val His Leu His Gln Thr Val Gln Val Asp Asp Glu Leu Glu Ile
 140 145 150
 Lys Ala Tyr Tyr Ala Gly His Val Leu Gly Ala Ala Met Phe Gln
 155 160 165
 Ile Lys Val Gly Ser Glu Ser Val Val Tyr Thr Gly Asp Tyr Asn
 170 175 180
 Met Thr Pro Asp Arg His Leu Gly Ala Ala Trp Ile Asp Lys Cys
 185 190 195
 Arg Pro Asn Leu Leu Ile Thr Glu Ser Thr Tyr Ala Thr Thr Ile
 200 205 210
 Arg Asp Ser Lys Arg Cys Arg Glu Arg Asp Phe Leu Lys Lys Val
 215 220 225
 His Glu Thr Val Glu Arg Gly Gly Lys Val Leu Ile Pro Val Phe
 230 235 240
 Ala Leu Gly Arg Ala Gln Glu Leu Cys Ile Leu Leu Glu Thr Phe
 245 250 255
 Trp Glu Arg Met Asn Leu Lys Val Pro Ile Tyr Phe Ser Thr Gly
 260 265 270
 Leu Thr Glu Lys Ala Asn His Tyr Tyr Lys Leu Phe Ile Pro Trp
 275 280 285
 Thr Asn Gln Lys Ile Arg Lys Thr Phe Val Gln Arg Asn Met Phe
 290 295 300
 Glu Phe Lys His Ile Lys Ala Phe Asp Arg Ala Phe Ala Asp Asn
 305 310 315
 Pro Gly Pro Met Val Val Phe Ala Thr Pro Gly Met Leu His Ala
 320 325 330
 Gly Gln Ser Leu Gln Ile Phe Arg Lys Trp Ala Gly Asn Glu Lys
 335 340 345
 Asn Met Val Ile Met Pro Gly Tyr Cys Val Gln Gly Thr Val Gly
 350 355 360
 His Lys Ile Leu Ser Gly Gln Arg Lys Leu Glu Met Glu Gly Arg
 365 370 375
 Gln Val Leu Glu Val Lys Met Gln Val Glu Tyr Met Ser Phe Ser
 380 385 390

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Ala	His	Ala	Asp	Ala	Lys	Gly	Ile	Met	Gln	Leu	Val	Gly	Gln	Ala	
				395					400					405	
Glu	Pro	Glu	Ser	Val	Leu	Leu	Val	His	Gly	Glu	Ala	Lys	Lys	Met	
				410					415					420	
Glu	Phe	Leu	Lys	Gln	Lys	Ile	Glu	Gln	Glu	Leu	Arg	Val	Asn	Cys	
				425					430					435	
Tyr	Met	Pro	Ala	Asn	Gly	Glu	Thr	Val	Thr	Leu	Pro	Thr	Ser	Pro	
				440					445					450	
Ser	Ile	Pro	Val	Gly	Ile	Ser	Leu	Gly	Leu	Leu	Lys	Arg	Glu	Met	
				455					460					465	
Ala	Gln	Gly	Leu	Leu	Pro	Glu	Ala	Lys	Lys	Pro	Arg	Leu	Leu	His	
				470					475					480	
Gly	Thr	Leu	Ile	Met	Lys	Asp	Ser	Asn	Phe	Arg	Leu	Val	Ser	Ser	
				485					490					495	
Glu	Gln	Ala	Leu	Lys	Glu	Leu	Gly	Leu	Ala	Glu	His	Gln	Leu	Arg	
				500					505					510	
Phe	Thr	Cys	Arg	Val	His	Leu	His	Asp	Thr	Arg	Lys	Glu	Gln	Glu	
				515					520					525	
Thr	Ala	Leu	Arg	Val	Tyr	Ser	His	Leu	Lys	Ser	Val	Leu	Lys	Asp	
				530					535					540	
His	Cys	Val	Gln	His	Leu	Pro	Asp	Gly	Ser	Val	Thr	Val	Glu	Ser	
				545					550					555	
Val	Leu	Leu	Gln	Ala	Ala	Ala	Pro	Ser	Glu	Asp	Pro	Gly	Thr	Lys	
				560					565					570	
Val	Leu	Leu	Val	Ser	Trp	Thr	Tyr	Gln	Asp	Glu	Glu	Leu	Gly	Ser	
				575					580					585	
Phe	Leu	Thr	Ser	Leu	Leu	Lys	Lys	Gly	Leu	Pro	Gln	Ala	Pro	Ser	
				590					595					600	

<210> 15

<211> 217

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2738075CD1

<400> 15

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

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	200	205	210
Asp Glu Glu Glu	Leu Ser Asp		
	215		

<210> 16
 <211> 319
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 2279049CD1

<400> 16
 Met Lys Ile Glu Leu Ser Met Gln Pro Trp Asn Pro Gly Tyr Ser
 1 5 10 15
 Ser Glu Gly Ala Thr Ala Gln Glu Thr Tyr Thr Cys Pro Lys Met
 20 25 30
 Ile Glu Met Glu Gln Ala Glu Ala Gln Leu Ala Glu Leu Asp Leu
 35 40 45
 Leu Ala Ser Met Phe Pro Gly Glu Asn Glu Leu Ile Val Asn Asp
 50 55 60
 Gln Leu Ala Val Ala Glu Leu Lys Asp Cys Ile Glu Lys Lys Thr
 65 70 75
 Met Glu Gly Arg Ser Ser Lys Val Tyr Phe Thr Ile Asn Met Asn
 80 85 90
 Leu Asp Val Ser Asp Glu Lys Met Ala Met Phe Ser Leu Ala Cys
 95 100 105
 Ile Leu Pro Phe Lys Tyr Pro Ala Val Leu Pro Glu Ile Thr Val
 110 115 120
 Arg Ser Val Leu Leu Ser Arg Ser Gln Gln Thr Gln Leu Asn Thr
 125 130 135
 Asp Leu Thr Ala Phe Leu Gln Lys His Cys His Gly Asp Val Cys
 140 145 150
 Ile Leu Asn Ala Thr Glu Trp Val Arg Glu His Ala Ser Gly Tyr
 155 160 165
 Val Ser Arg Asp Thr Ser Ser Ser Pro Thr Thr Gly Ser Thr Val
 170 175 180
 Gln Ser Val Asp Leu Ile Phe Thr Arg Leu Trp Ile Tyr Ser His
 185 190 195
 His Ile Tyr Asn Lys Cys Lys Arg Lys Asn Ile Leu Glu Trp Ala
 200 205 210
 Lys Glu Leu Ser Leu Ser Gly Phe Ser Met Pro Gly Lys Pro Gly
 215 220 225
 Val Val Cys Val Glu Gly Pro Gln Ser Ala Cys Glu Glu Phe Trp
 230 235 240
 Ser Arg Leu Arg Lys Leu Asn Trp Lys Arg Ile Leu Ile Arg His
 245 250 255
 Arg Glu Asp Ile Pro Phe Asp Gly Thr Asn Asp Glu Thr Glu Arg
 260 265 270
 Gln Arg Lys Phe Ser Ile Phe Glu Glu Lys Val Phe Ser Val Asn
 275 280 285
 Gly Ala Arg Gly Asn His Met Asp Phe Gly Gln Leu Tyr Gln Phe
 290 295 300
 Leu Asn Thr Lys Gly Cys Gly Asp Val Phe Gln Met Phe Phe Gly
 305 310 315
 Val Glu Gly Gln

<210> 17
 <211> 108
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 2660904CD1

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<400> 17

Met	Ser	His	His	Ala	Glu	Ile	Gln	Arg	Asp	Ile	Leu	Glu	Ser	Cys	
1				5					10					15	
Asn	His	Val	Arg	Lys	Lys	Val	Pro	Val	Thr	Phe	Val	Gly	Ala	Gly	
				20					25					30	
Gly	Gln	Asp	Pro	Glu	Val	Pro	Glu	Glu	Leu	Leu	His	Leu	Leu	Gln	
				35					40					45	
Pro	Gly	Gln	Arg	Val	Pro	Gln	Asp	Val	Gln	His	His	Leu	Leu	Glu	
				50					55					60	
Pro	Arg	Asp	Arg	Trp	Ala	His	Leu	Glu	Val	Leu	Lys	Lys	Val	Asp	
				65					70					75	
Leu	Leu	Leu	Gln	Val	Met	Ala	Ala	Thr	Gly	Tyr	Phe	His	Ala	Ser	
				80					85					90	
Leu	Gln	Arg	Gly	Glu	Ile	Met	Arg	Ser	Pro	Gly	Pro	Val	Ala	Arg	
				95					100					105	

Asn Ser Pro

<210> 18

<211> 92

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 3179424CD1

<400> 18

Met	Ala	Val	Leu	Ala	Gly	Ser	Leu	Leu	Gly	Pro	Thr	Ser	Arg	Ser	
1				5					10					15	
Ala	Ala	Leu	Leu	Gly	Gly	Arg	Trp	Leu	Gln	Pro	Arg	Ala	Trp	Leu	
				20					25					30	
Gly	Phe	Pro	Asp	Ala	Trp	Gly	Leu	Pro	Thr	Pro	Gln	Gln	Ala	Arg	
				35					40					45	
Gly	Lys	Ala	Arg	Gly	Asn	Glu	Tyr	Gln	Pro	Ser	Asn	Ile	Lys	Arg	
				50					55					60	
Lys	Asn	Lys	His	Gly	Trp	Val	Arg	Arg	Leu	Ser	Thr	Pro	Ala	Gly	
				65					70					75	
Val	Gln	Val	Ile	Leu	Arg	Arg	Met	Leu	Lys	Gly	Arg	Lys	Ser	Leu	
				80					85					90	

Ser His

<210> 19

<211> 268

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2885096CD1

<400> 19

Met	Ala	Gly	Gly	Val	Pro	Gly	Gln	Pro	Ala	Gly	Val	Gly	Leu	Ala	
1				5					10					15	
Leu	Ile	Ala	Thr	Asp	Ser	Gln	Glu	Thr	Arg	Pro	Gly	Arg	Ala	Gly	
				20					25					30	
Pro	Gly	Ser	Gly	Glu	Ser	Leu	Ser	Ala	Ser	His	Leu	Phe	Ile	Ser	
				35					40					45	
Asp	Phe	Ala	Tyr	Cys	Trp	Glu	Asn	Phe	Val	Cys	Asn	Glu	Gly	Gln	
				50					55					60	
Pro	Phe	Met	Pro	Trp	Tyr	Lys	Phe	Asp	Asp	Asn	Tyr	Ala	Ser	Leu	
				65					70					75	
His	Arg	Thr	Leu	Lys	Glu	Ile	Leu	Arg	Asn	Pro	Met	Glu	Ala	Met	
				80					85					90	
Tyr	Pro	His	Ile	Phe	Tyr	Phe	His	Phe	Lys	Asn	Leu	Leu	Lys	Ala	
				95					100					105	

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

<210> 20

<211> 624

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2901076CD1

<400> 20

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

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Ser	Asn	Asn	Ala	Ile	Val	Lys	Pro	Pro	Glu	Met	Thr	Pro	Gln	Ala	
				260					265					270	
Ala	Ala	Lys	Glu	Leu	Glu	Glu	Val	Met	Lys	Arg	Val	Arg	Glu	Ala	
				275					280					285	
Gln	Ser	Phe	Ile	Ser	Ala	Ala	Ile	Glu	Pro	Glu	Ser	Gly	Lys	Ser	
				290					295					300	
Asn	Glu	Arg	Lys	Gly	Gly	Arg	Ser	Arg	Ser	His	Thr	Arg	Ser	Lys	
				305					310					315	
Ser	Arg	Ser	Ser	Ser	Lys	Ser	His	Ser	Arg	Arg	Lys	Arg	Ser	Gln	
				320					325					330	
Ser	Lys	His	Arg	Ser	Arg	Ser	His	Asn	Arg	Ser	Arg	Ser	Arg	Gln	
				335					340					345	
Lys	Asp	Arg	Arg	Arg	Ser	Lys	Ser	Pro	His	Lys	Lys	Arg	Ser	Lys	
				350					355					360	
Ser	Arg	Glu	Arg	Arg	Lys	Ser	Arg	Ser	Arg	Ser	His	Ser	Arg	Asp	
				365					370					375	
Lys	Arg	Lys	Asp	Thr	Arg	Glu	Lys	Ile	Lys	Glu	Lys	Glu	Arg	Val	
				380					385					390	
Lys	Glu	Lys	Asp	Arg	Glu	Lys	Glu	Arg	Glu	Arg	Glu	Lys	Glu	Arg	
				395					400					405	
Glu	Lys	Glu	Lys	Glu	Arg	Gly	Lys	Asn	Lys	Asp	Arg	Asp	Lys	Glu	
				410					415					420	
Arg	Glu	Lys	Asp	Arg	Glu	Lys	Asp	Lys	Glu	Lys	Asp	Arg	Glu	Arg	
				425					430					435	
Glu	Arg	Glu	Lys	Glu	His	Glu	Lys	Asp	Arg	Asp	Lys	Glu	Lys	Glu	
				440					445					450	
Lys	Glu	Gln	Asp	Lys	Glu	Lys	Glu	Arg	Glu	Lys	Asp	Arg	Ser	Lys	
				455					460					465	
Glu	Ile	Asp	Glu	Lys	Arg	Lys	Lys	Asp	Lys	Lys	Ser	Arg	Thr	Pro	
				470					475					480	
Pro	Arg	Ser	Tyr	Asn	Ala	Ser	Arg	Arg	Ser	Arg	Ser	Ser	Ser	Arg	
				485					490					495	
Glu	Arg	Arg	Arg	Arg	Arg	Ser	Arg	Ser	Ser	Ser	Arg	Ser	Pro	Arg	
				500					505					510	
Thr	Ser	Lys	Thr	Ile	Lys	Arg	Lys	Ser	Ser	Arg	Ser	Pro	Ser	Pro	
				515					520					525	
Arg	Ser	Arg	Asn	Lys	Lys	Asp	Lys	Lys	Arg	Glu	Lys	Glu	Arg	Asp	
				530					535					540	
His	Ile	Ser	Glu	Arg	Arg	Glu	Arg	Glu	Arg	Ser	Thr	Ser	Met	Arg	
				545					550					555	
Lys	Ser	Ser	Asn	Asp	Arg	Asp	Gly	Lys	Glu	Lys	Leu	Glu	Lys	Asn	
				560					565					570	
Ser	Thr	Ser	Leu	Lys	Glu	Lys	Glu	His	Asn	Lys	Glu	Pro	Asp	Ser	
				575					580					585	
Ser	Val	Ser	Lys	Glu	Val	Asp	Asp	Lys	Asp	Ala	Pro	Arg	Thr	Glu	
				590					595					600	
Glu	Asn	Lys	Ile	Gln	His	Asn	Gly	Asn	Cys	Gln	Leu	Asn	Glu	Glu	
				605					610					615	
Asn	Leu	Ser	Thr	Lys	Thr	Glu	Ala	Val							
				620											

<210> 21

<211> 419

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 3074572CD1

<400> 21

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

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

<210> 22

<211> 743

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1437895CD1

<400> 22

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

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Leu	Pro	Tyr	Ser	Ser	Arg	Tyr	Tyr	Lys	Leu	Leu	Lys	Glu	Arg	Glu
				50					55					60
Asp	Leu	Pro	Ile	Trp	Lys	Glu	Lys	Tyr	Ser	Phe	Met	Glu	Asn	Leu
				65					70					75
Leu	Gln	Asn	Gln	Ile	Val	Ile	Val	Ser	Gly	Asp	Ala	Lys	Cys	Gly
				80					85					90
Lys	Ser	Ala	Gln	Val	Pro	Gln	Trp	Cys	Ala	Glu	Tyr	Cys	Leu	Ser
				95					100					105
Ile	His	Tyr	Gln	His	Gly	Gly	Val	Ile	Cys	Thr	Gln	Val	His	Lys
				110					115					120
Gln	Thr	Val	Val	Gln	Leu	Ala	Leu	Arg	Val	Ala	Asp	Glu	Met	Asp
				125					130					135
Val	Asn	Ile	Gly	His	Glu	Val	Gly	Tyr	Val	Ile	Pro	Phe	Glu	Asn
				140					145					150
Cys	Cys	Thr	Asn	Glu	Thr	Ile	Leu	Arg	Tyr	Cys	Thr	Asp	Asp	Met
				155					160					165
Leu	Gln	Arg	Glu	Met	Met	Ser	Asn	Pro	Phe	Leu	Gly	Ser	Tyr	Gly
				170					175					180
Val	Ile	Ile	Leu	Asp	Asp	Ile	His	Glu	Arg	Ser	Ile	Ala	Thr	Asp
				185					190					195
Val	Leu	Leu	Gly	Leu	Leu	Lys	Asp	Val	Leu	Leu	Ala	Arg	Pro	Glu
				200					205					210
Leu	Lys	Leu	Ile	Ile	Asn	Ser	Ser	Pro	His	Leu	Ile	Ser	Lys	Leu
				215					220					225
Asn	Ser	Tyr	Tyr	Gly	Asn	Val	Pro	Val	Ile	Glu	Val	Lys	Asn	Lys
				230					235					240
His	Pro	Val	Glu	Val	Val	Tyr	Leu	Ser	Glu	Ala	Gln	Lys	Asp	Ser
				245					250					255
Phe	Glu	Ser	Ile	Leu	Arg	Leu	Ile	Phe	Glu	Ile	His	His	Ser	Gly
				260					265					270
Glu	Lys	Gly	Asp	Ile	Val	Val	Phe	Leu	Ala	Cys	Glu	Gln	Asp	Ile
				275					280					285
Glu	Lys	Val	Cys	Glu	Thr	Val	Tyr	Gln	Gly	Ser	Asn	Leu	Asn	Pro
				290					295					300
Asp	Leu	Gly	Glu	Leu	Val	Val	Val	Pro	Leu	Tyr	Pro	Lys	Glu	Lys
				305					310					315
Cys	Ser	Leu	Phe	Lys	Pro	Leu	Asp	Glu	Thr	Glu	Lys	Arg	Cys	Gln
				320					325					330
Val	Tyr	Gln	Arg	Arg	Val	Val	Leu	Thr	Thr	Ser	Ser	Gly	Glu	Phe
				335					340					345
Leu	Ile	Trp	Ser	Asn	Ser	Val	Arg	Phe	Val	Ile	Asp	Val	Gly	Val
				350					355					360
Glu	Arg	Arg	Lys	Val	Tyr	Asn	Pro	Arg	Ile	Arg	Ala	Asn	Ser	Leu
				365					370					375
Val	Met	Gln	Pro	Ile	Ser	Gln	Ser	Gln	Ala	Glu	Ile	Arg	Lys	Gln
				380					385					390
Ile	Leu	Gly	Ser	Ser	Ser	Ser	Gly	Lys	Phe	Phe	Cys	Leu	Tyr	Thr
				395					400					405
Glu	Glu	Phe	Ala	Ser	Lys	Asp	Met	Thr	Pro	Leu	Lys	Pro	Ala	Glu
				410					415					420
Met	Gln	Glu	Ala	Asn	Leu	Thr	Ser	Met	Val	Leu	Phe	Met	Lys	Arg
				425					430					435
Ile	Asp	Ile	Ala	Gly	Leu	Gly	His	Cys	Asp	Phe	Met	Asn	Arg	Pro
				440					445					450
Ala	Pro	Glu	Ser	Leu	Met	Gln	Ala	Leu	Glu	Asp	Leu	Asp	Tyr	Leu
				455					460					465
Ala	Ala	Leu	Asp	Asn	Asp	Gly	Asn	Leu	Ser	Glu	Phe	Gly	Ile	Ile
				470					475					480
Met	Ser	Glu	Phe	Pro	Leu	Asp	Pro	Gln	Leu	Ser	Lys	Ser	Ile	Leu
				485					490					495
Ala	Ser	Cys	Glu	Phe	Asp	Cys	Val	Asp	Glu	Val	Leu	Thr	Ile	Ala
				500					505					510
Ala	Met	Val	Thr	Ala	Pro	Asn	Cys	Phe	Ser	His	Val	Pro	His	Gly
				515					520					525
Ala	Glu	Glu	Ala	Ala	Leu	Thr	Cys	Trp	Lys	Thr	Phe	Leu	His	Pro
				530					535					540
Glu	Gly	Asp	His	Phe	Thr	Leu	Ile	Ser	Ile	Tyr	Lys	Ala	Tyr	Gln

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

<210> 23

<211> 284

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1454656CD1

<400> 23

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

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Ala His Arg Arg	215	Ala Leu Cys Ile Arg Val	225
Phe Gln Glu Thr	230	Arg Arg Arg Ala Leu Lys	240
Ala Ala Ala Ala	245	Lys Arg Arg Asn Pro Asp	255
Ser Pro Ala Lys	260	Leu Lys Asp Ser Gln	270
	275		280

<210> 24
 <211> 248
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 121130CD1

<400> 24

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

<210> 25
 <211> 214
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 1257715CD1

<400> 25

Met Arg Pro Gly Gly	Phe Leu Gly Ala	Gly Gln Arg Leu Ser Arg	
1 5	10	15	

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

<210> 26

<211> 184

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1342022CD1

<400> 26

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

<210> 27

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<211> 371
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 194704CD1

<400> 27

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

<210> 28
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 <213> Homo sapiens

<220>
 <221> misc_feature

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<223> Incyte ID No: 607270CD1

<400> 28

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

<210> 29

<211> 184

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 758546CD1

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<400> 29

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

<210> 30

<211> 282

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 866043CD1

<400> 30

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

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Leu Val Thr Gly	215	Val Leu Met Tyr Ser Phe	225
Arg Thr Ala Ser	230	Gln Gly His Thr Gln Ala	240
Cys Val Gly Thr	245	Leu Pro Ser Val Leu Ala	255
Thr Cys Ser Trp	260	Ile Trp His	270
	275		280

<210> 31
 <211> 125
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 927065CD1

Met Pro Ala Pro Ala	1	Ala Thr Tyr Glu Arg	10	Val Val Tyr Lys Asn	15
Pro Ser Glu Tyr His	20	Tyr Met Lys Val Cys	25	Leu Glu Phe Gln Asp	30
Cys Gly Val Gly Leu	35	Asn Ala Ala Gln Phe	40	Lys Gln Leu Leu Ile	45
Ser Ala Val Lys Asp	50	Leu Phe Gly Glu Val	55	Asp Ala Ala Leu Pro	60
Leu Asp Ile Leu Thr	65	Tyr Glu Glu Lys Thr	70	Leu Ser Ala Ile Leu	75
Arg Ile Cys Ser Ser	80	Gly Leu Val Lys Leu	85	Trp Ser Ser Leu Thr	90
Leu Leu Arg Ile Pro	95	Ile Lys Gly Lys Lys	100	Cys Ala Phe Arg Val	105
Ile Gln Val Ser Pro	110	Phe Leu Leu Ala Leu	115	Ser Gly Asn Ser Arg	120
Glu Leu Val Leu Asp	125				

<210> 32
 <211> 365
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 938071CD1

Met Ala Pro Val Ser	1	Gly Ser Arg Ser Pro	10	Asp Arg Glu Ala Ser	15
Gly Ser Gly Gly Arg	20	Arg Arg Ser Ser Ser	25	Lys Ser Pro Lys Pro	30
Ser Lys Ser Ala Arg	35	Ser Pro Arg Gly Arg	40	Arg Ser Arg Ser His	45
Ser Cys Ser Arg Ser	50	Gly Asp Arg Asn Gly	55	Leu Thr His Gln Leu	60
Gly Gly Leu Ser Gln	65	Gly Ser Arg Asn Gln	70	Ser Tyr Arg Ser Arg	75
Ser Arg Ser Arg Ser	80	Arg Glu Arg Pro Ser	85	Ala Pro Arg Gly Ile	90
Pro Phe Ala Ser Ala	95	Ser Ser Ser Val Tyr	100	Tyr Gly Ser Tyr Ser	105
Arg Pro Tyr Gly Ser	110	Asp Lys Pro Trp Pro	115	Ser Leu Leu Asp Lys	120
Glu Arg Glu Glu Ser	125	Leu Arg Gln Lys Arg	130	Leu Ser Glu Arg Glu	135

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Arg	Ile	Gly	Glu	Leu	Gly	Ala	Pro	Glu	Val	Trp	Gly	Leu	Ser	Pro
				140					145					150
Lys	Asn	Pro	Glu	Pro	Asp	Ser	Asp	Glu	His	Thr	Pro	Val	Glu	Asp
				155					160					165
Glu	Glu	Pro	Lys	Lys	Ser	Thr	Thr	Ser	Ala	Ser	Thr	Ser	Glu	Glu
				170					175					180
Glu	Lys	Lys	Lys	Lys	Ser	Ser	Arg	Ser	Lys	Glu	Arg	Ser	Lys	Lys
				185					190					195
Arg	Arg	Lys	Lys	Lys	Ser	Ser	Lys	Arg	Lys	His	Lys	Lys	Tyr	Ser
				200					205					210
Glu	Asp	Ser	Asp	Ser	Asp	Ser	Asp	Ser	Glu	Thr	Asp	Ser	Ser	Asp
				215					220					225
Glu	Asp	Asn	Lys	Arg	Arg	Ala	Lys	Lys	Ala	Lys	Lys	Lys	Glu	Lys
				230					235					240
Lys	Lys	Lys	His	Arg	Ser	Lys	Lys	Tyr	Lys	Lys	Lys	Arg	Ser	Lys
				245					250					255
Lys	Ser	Arg	Lys	Glu	Ser	Ser	Asp	Ser	Ser	Ser	Lys	Glu	Ser	Gln
				260					265					270
Glu	Glu	Phe	Leu	Glu	Asn	Pro	Trp	Lys	Asp	Arg	Thr	Lys	Ala	Glu
				275					280					285
Glu	Pro	Ser	Asp	Leu	Ile	Gly	Pro	Glu	Ala	Pro	Lys	Thr	Leu	Thr
				290					295					300
Ser	Gln	Asp	Asp	Lys	Pro	Leu	Lys	His	Arg	Arg	Met	Glu	Ala	Val
				305					310					315
Arg	Leu	Arg	Lys	Glu	Asn	Gln	Ile	Tyr	Ser	Ala	Asp	Glu	Lys	Arg
				320					325					330
Ala	Leu	Ala	Ser	Phe	Asn	Gln	Glu	Glu	Arg	Arg	Lys	Arg	Glu	Asn
				335					340					345
Lys	Ile	Leu	Ala	Ser	Phe	Arg	Glu	Met	Val	Tyr	Arg	Lys	Thr	Lys
				350					355					360
Gly	Lys	Asp	Asp	Lys										
				365										

<210> 33

<211> 672

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 3295984CD1

<400> 33

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

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Val	Ser	Met	Lys	Asp	Pro	Pro	Asp	Leu	Leu	Asp	Arg	Gln	Lys	Cys
				185					190					195
Leu	Asn	Ala	Leu	Ala	Ser	Leu	Arg	His	Ala	Lys	Trp	Phe	Gln	Ala
				200					205					210
Arg	Ala	Asn	Gly	Leu	Lys	Ser	Cys	Val	Ile	Val	Leu	Arg	Ile	Leu
				215					220					225
Arg	Asp	Leu	Cys	Asn	Arg	Val	Pro	Thr	Trp	Ala	Pro	Leu	Lys	Gly
				230					235					240
Trp	Pro	Leu	Glu	Leu	Ile	Cys	Glu	Lys	Ser	Ile	Gly	Thr	Cys	Asn
				245					250					255
Arg	Pro	Leu	Gly	Ala	Gly	Glu	Ala	Leu	Arg	Arg	Val	Met	Glu	Cys
				260					265					270
Leu	Ala	Ser	Gly	Ile	Leu	Leu	Pro	Gly	Gly	Pro	Gly	Leu	His	Asp
				275					280					285
Pro	Cys	Glu	Arg	Asp	Pro	Thr	Asp	Ala	Leu	Ser	Tyr	Met	Thr	Ile
				290					295					300
Gln	Gln	Lys	Glu	Asp	Ile	Thr	His	Ser	Ala	Gln	His	Ala	Leu	Arg
				305					310					315
Leu	Ser	Ala	Phe	Gly	Gln	Ile	Tyr	Lys	Val	Leu	Glu	Met	Asp	Pro
				320					325					330
Leu	Pro	Ser	Ser	Lys	Pro	Phe	Gln	Lys	Tyr	Ser	Trp	Ser	Val	Thr
				335					340					345
Asp	Lys	Glu	Gly	Ala	Gly	Ser	Ser	Ala	Leu	Lys	Arg	Pro	Phe	Glu
				350					355					360
Asp	Gly	Leu	Gly	Asp	Asp	Lys	Asp	Pro	Asn	Lys	Lys	Met	Lys	Arg
				365					370					375
Asn	Leu	Arg	Lys	Ile	Leu	Asp	Ser	Lys	Ala	Ile	Asp	Leu	Met	Asn
				380					385					390
Ala	Leu	Met	Arg	Leu	Asn	Gln	Ile	Arg	Pro	Gly	Leu	Gln	Tyr	Lys
				395					400					405
Leu	Leu	Ser	Gln	Ser	Gly	Pro	Val	His	Ala	Pro	Val	Phe	Thr	Met
				410					415					420
Ser	Val	Asp	Val	Asp	Gly	Thr	Thr	Tyr	Glu	Ala	Ser	Gly	Pro	Ser
				425					430					435
Lys	Lys	Thr	Ala	Lys	Leu	His	Val	Ala	Val	Lys	Val	Leu	Gln	Ala
				440					445					450
Met	Gly	Tyr	Pro	Thr	Gly	Phe	Asp	Ala	Asp	Ile	Glu	Cys	Met	Ser
				455					460					465
Ser	Asp	Glu	Lys	Ser	Asp	Asn	Glu	Ser	Lys	Asn	Glu	Thr	Val	Ser
				470					475					480
Ser	Asn	Ser	Ser	Asn	Asn	Thr	Gly	Asn	Ser	Thr	Thr	Glu	Thr	Ser
				485					490					495
Ser	Thr	Leu	Glu	Val	Arg	Thr	Gln	Gly	Pro	Ile	Leu	Thr	Ala	Ser
				500					505					510
Gly	Lys	Asn	Pro	Val	Met	Glu	Leu	Asn	Glu	Lys	Arg	Arg	Gly	Leu
				515					520					525
Lys	Tyr	Glu	Leu	Ile	Ser	Glu	Thr	Gly	Gly	Ser	His	Asp	Lys	Arg
				530					535					540
Phe	Val	Met	Glu	Val	Glu	Val	Asp	Gly	Gln	Lys	Phe	Arg	Gly	Ala
				545					550					555
Gly	Pro	Asn	Lys	Lys	Val	Ala	Lys	Ala	Ser	Ala	Ala	Leu	Ala	Ala
				560					565					570
Leu	Glu	Lys	Leu	Phe	Ser	Gly	Pro	Asn	Ala	Ala	Asn	Asn	Lys	Lys
				575					580					585
Lys	Lys	Ile	Ile	Pro	Gln	Ala	Lys	Gly	Val	Val	Asn	Thr	Ala	Val
				590					595					600
Ser	Ala	Ala	Val	Gln	Ala	Val	Arg	Gly	Arg	Gly	Arg	Gly	Thr	Leu
				605					610					615
Thr	Arg	Gly	Ala	Phe	Val	Gly	Ala	Thr	Ala	Ala	Pro	Gly	Tyr	Ile
				620					625					630
Ala	Pro	Gly	Tyr	Gly	Thr	Pro	Tyr	Gly	Tyr	Ser	Thr	Ala	Ala	Pro
				635					640					645
Ala	Tyr	Gly	Leu	Pro	Lys	Arg	Met	Val	Leu	Leu	Pro	Val	Met	Lys
				650					655					660
Phe	Pro	Thr	Tyr	Pro	Val	Pro	His	Tyr	Ser	Phe	Phe			
				665					670					

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<210> 34
 <211> 430
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 4545237CD1

<400> 34
 Met Ala Thr Ala Val Arg Ala Val Gly Cys Leu Pro Val Leu Cys
 1 5 10 15
 Ser Gly Thr Ala Gly His Leu Leu Gly Arg Gln Cys Ser Leu Asn
 20 25 30
 Thr Leu Pro Ala Ala Ser Ile Leu Ala Trp Lys Ser Val Leu Gly
 35 40 45
 Asn Gly His Leu Ser Ser Leu Gly Thr Arg Asp Thr His Pro Tyr
 50 55 60
 Ala Ser Leu Ser Arg Ala Leu Gln Thr Gln Cys Cys Ile Ser Ser
 65 70 75
 Pro Ser His Leu Met Ser Gln Gln Tyr Arg Pro Tyr Ser Phe Phe
 80 85 90
 Thr Lys Leu Thr Ala Asp Glu Leu Trp Lys Gly Ala Leu Ala Glu
 95 100 105
 Thr Gly Ala Gly Ala Lys Lys Gly Arg Gly Lys Arg Thr Lys Lys
 110 115 120
 Lys Lys Arg Lys Asp Leu Asn Arg Gly Gln Ile Ile Gly Glu Gly
 125 130 135
 Arg Tyr Gly Phe Leu Trp Pro Gly Leu Asn Val Pro Leu Met Lys
 140 145 150
 Asn Gly Ala Val Gln Thr Ile Ala Gln Arg Ser Lys Glu Glu Gln
 155 160 165
 Glu Lys Val Glu Ala Asp Met Ile Gln Gln Arg Glu Glu Trp Asp
 170 175 180
 Arg Lys Lys Lys Met Lys Val Lys Arg Glu Arg Gly Trp Ser Gly
 185 190 195
 Asn Ser Trp Gly Gly Ile Ser Leu Gly Pro Pro Asp Pro Gly Pro
 200 205 210
 Cys Gly Glu Thr Tyr Glu Asp Phe Asp Thr Arg Ile Leu Glu Val
 215 220 225
 Arg Asn Val Phe Thr Met Thr Ala Lys Glu Gly Arg Lys Lys Ser
 230 235 240
 Ile Arg Val Leu Val Ala Val Gly Asn Gly Lys Gly Ala Ala Gly
 245 250 255
 Phe Ser Ile Gly Lys Ala Thr Asp Arg Met Asp Ala Phe Arg Lys
 260 265 270
 Ala Lys Asn Arg Ala Val His His Leu His Tyr Ile Glu Arg Tyr
 275 280 285
 Glu Asp His Thr Ile Phe His Asp Ile Ser Leu Arg Phe Lys Arg
 290 295 300
 Thr His Ile Lys Met Lys Lys Gln Pro Lys Gly Tyr Gly Leu Arg
 305 310 315
 Cys His Arg Ala Ile Ile Thr Ile Cys Arg Leu Ile Gly Ile Lys
 320 325 330
 Asp Met Tyr Ala Lys Val Ser Gly Ser Ile Asn Met Leu Ser Leu
 335 340 345
 Thr Gln Gly Leu Phe Arg Gly Leu Ser Arg Gln Glu Thr His Gln
 350 355 360
 Gln Leu Ala Asp Lys Lys Gly Leu His Val Val Glu Ile Arg Glu
 365 370 375
 Glu Cys Gly Pro Leu Pro Ile Val Val Ala Ser Pro Arg Gly Pro
 380 385 390
 Leu Arg Lys Asp Pro Glu Pro Glu Asp Glu Val Pro Asp Val Lys
 395 400 405
 Leu Asp Trp Glu Asp Val Lys Thr Ala Gln Gly Met Lys Arg Ser
 410 415 420
 Val Trp Ser Asn Leu Lys Arg Ala Ala Thr

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425

430

<210> 35
 <211> 137
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 4942964CD1

<400> 35
 Met Ala Asp Ser Lys Ala Thr Ser Ala Val Thr Leu Arg Thr Arg
 1 5 10 15
 Lys Phe Met Thr Asn Arg Leu Leu Ala Arg Lys Gln Phe Val Leu
 20 25 30
 Glu Val Ile His Pro Gly Arg Ala Asn Val Ser Lys Ala Glu Leu
 35 40 45
 Lys Glu Arg Leu Ala Lys Ala Tyr Glu Val Lys Asp Pro Asn Thr
 50 55 60
 Ile Phe Val Phe Lys Phe Arg Thr His Phe Gly Gly Gly Lys Ser
 65 70 75
 Thr Gly Phe Gly Leu Ile Tyr Asp Asn Leu Glu Ala Ala Lys Lys
 80 85 90
 Phe Glu Pro Lys Tyr Arg Leu Ile Arg Asn Gly Leu Ala Thr Lys
 95 100 105
 Val Glu Lys Ser Arg Lys Gln Met Lys Glu Arg Lys Asn Arg Ala
 110 115 120
 Lys Lys Ile Arg Gly Val Lys Lys Thr Lys Ala Gly Asp Ala Lys
 125 130 135
 Lys Lys

<210> 36
 <211> 380
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 5702144CD1

<400> 36
 Met Arg Ser Arg Val Leu Trp Gly Ala Ala Arg Trp Leu Trp Pro
 1 5 10 15
 Arg Arg Ala Val Gly Pro Ala Arg Arg Pro Leu Ser Ser Gly Ser
 20 25 30
 Pro Pro Leu Glu Glu Leu Phe Thr Arg Gly Gly Pro Leu Arg Thr
 35 40 45
 Phe Leu Glu Arg Gln Ala Gly Ser Glu Ala His Leu Lys Val Arg
 50 55 60
 Arg Pro Glu Leu Leu Ala Val Ile Lys Leu Leu Asn Glu Lys Glu
 65 70 75
 Gln Glu Leu Arg Glu Thr Glu His Leu Leu His Asp Glu Asn Glu
 80 85 90
 Asp Leu Arg Lys Leu Ala Glu Asn Glu Ile Thr Leu Cys Gln Lys
 95 100 105
 Glu Ile Thr Gln Leu Lys His Gln Ile Ile Leu Leu Leu Val Pro
 110 115 120
 Ser Glu Glu Thr Asp Glu Asn Asp Leu Ile Leu Glu Val Thr Ala
 125 130 135
 Gly Val Gly Gly Gln Glu Ala Met Leu Phe Thr Ser Glu Ile Phe
 140 145 150
 Asp Met Tyr Gln Gln Tyr Ala Ala Phe Lys Arg Trp His Phe Glu
 155 160 165
 Thr Leu Glu Tyr Phe Pro Ser Glu Leu Gly Gly Leu Arg His Ala
 170 175 180

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Ser	Ala	Ser	Ile	Gly	Gly	Ser	Glu	Ala	Tyr	Arg	His	Met	Lys	Phe
				185					190					195
Glu	Gly	Gly	Val	His	Arg	Val	Gln	Arg	Val	Pro	Lys	Thr	Glu	Lys
				200					205					210
Gln	Gly	Arg	Ile	His	Thr	Ser	Thr	Met	Thr	Val	Ala	Ile	Leu	Pro
				215					220					225
Gln	Pro	Thr	Glu	Ile	Asn	Leu	Val	Ile	Asn	Pro	Lys	Asp	Leu	Arg
				230					235					240
Ile	Asp	Thr	Lys	Arg	Ala	Ser	Gly	Ala	Gly	Gly	Gln	His	Val	Asn
				245					250					255
Thr	Thr	Asp	Ser	Ala	Val	Arg	Ile	Val	His	Leu	Pro	Thr	Gly	Val
				260					265					270
Val	Ser	Glu	Cys	Gln	Gln	Glu	Arg	Ser	Gln	Leu	Lys	Asn	Lys	Glu
				275					280					285
Leu	Ala	Met	Thr	Lys	Leu	Arg	Ala	Lys	Leu	Tyr	Ser	Met	His	Leu
				290					295					300
Glu	Glu	Glu	Ile	Asn	Lys	Arg	Gln	Asn	Ala	Arg	Lys	Ile	Gln	Ile
				305					310					315
Gly	Ser	Lys	Gly	Arg	Ser	Glu	Lys	Ile	Arg	Thr	Tyr	Asn	Phe	Pro
				320					325					330
Gln	Asn	Arg	Val	Thr	Asp	His	Arg	Ile	Asn	Lys	Thr	Leu	His	Asp
				335					340					345
Leu	Glu	Thr	Phe	Met	Gln	Gly	Asp	Tyr	Leu	Leu	Asp	Glu	Leu	Val
				350					355					360
Gln	Ser	Leu	Lys	Glu	Tyr	Ala	Asp	Tyr	Glu	Ser	Leu	Val	Glu	Ile
				365					370					375
Ile	Ser	Gln	Lys	Val										
				380										

<210> 37

<211> 206

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 5862945CD1

<400> 37

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

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<210> 38
 <211> 190
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 6319547CD1

<400> 38
 Met Glu Ala Glu Thr Lys Thr Leu Pro Leu Glu Asn Ala Ser Ile
 1 5 10 15
 Leu Ser Glu Gly Ser Leu Gln Glu Gly His Arg Leu Trp Ile Gly
 20 25 30
 Asn Leu Asp Pro Lys Ile Thr Glu Tyr His Leu Leu Lys Leu Leu
 35 40 45
 Gln Lys Phe Gly Lys Val Lys Gln Phe Asp Phe Leu Phe His Lys
 50 55 60
 Ser Gly Ala Leu Glu Gly Gln Pro Arg Gly Tyr Cys Phe Val Asn
 65 70 75
 Phe Glu Thr Lys Gln Glu Ala Glu Gln Ala Ile Gln Cys Leu Asn
 80 85 90
 Gly Lys Leu Ala Leu Ser Lys Lys Leu Val Val Arg Trp Ala His
 95 100 105
 Ala Gln Val Lys Arg Tyr Asp His Asn Lys Asn Asp Lys Ile Leu
 110 115 120
 Pro Ile Ser Leu Glu Pro Ser Ser Ser Thr Glu Pro Thr Gln Ser
 125 130 135
 Asn Leu Ser Val Thr Ala Lys Ile Lys Ala Ile Glu Ala Lys Leu
 140 145 150
 Lys Met Met Ala Glu Asn Pro Asp Ala Glu Tyr Pro Ala Ala Pro
 155 160 165
 Val Tyr Ser Tyr Phe Lys Pro Pro Asp Lys Lys Arg Thr Thr Pro
 170 175 180
 Tyr Ser Arg Thr Ala Trp Lys Ser Arg Arg
 185 190

<210> 39
 <211> 434
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 000124CD1

<400> 39
 Met Leu Arg Cys Leu Tyr His Trp His Arg Pro Val Leu Asn Arg
 1 5 10 15
 Arg Trp Ser Arg Leu Cys Leu Leu Lys Gln Tyr Leu Phe Thr Met
 20 25 30
 Lys Leu Gln Ser Pro Glu Phe Gln Ser Leu Phe Thr Glu Gly Leu
 35 40 45
 Lys Ser Leu Thr Glu Leu Phe Val Lys Glu Asn His Glu Leu Arg
 50 55 60
 Ile Ala Gly Gly Ala Val Arg Asp Leu Leu Asn Gly Val Lys Pro
 65 70 75
 Gln Asp Ile Asp Phe Ala Thr Thr Ala Thr Pro Thr Gln Met Lys
 80 85 90
 Glu Met Phe Gln Ser Ala Gly Ile Arg Met Ile Asn Asn Arg Gly
 95 100 105
 Glu Lys His Gly Thr Ile Thr Ala Arg Leu His Glu Glu Asn Phe
 110 115 120
 Glu Ile Thr Thr Leu Arg Ile Asp Val Thr Thr Asp Gly Arg His
 125 130 135
 Ala Glu Val Glu Phe Thr Thr Asp Trp Gln Lys Asp Ala Glu Arg
 140 145 150

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Arg	Asp	Leu	Thr	Ile	Asn	Ser	Met	Phe	Leu	Gly	Phe	Asp	Gly	Thr
				155					160					165
Leu	Phe	Asp	Tyr	Phe	Asn	Gly	Tyr	Glu	Asp	Leu	Lys	Asn	Lys	Lys
				170					175					180
Val	Arg	Phe	Val	Gly	His	Ala	Lys	Gln	Arg	Ile	Gln	Glu	Asp	Tyr
				185					190					195
Leu	Arg	Ile	Leu	Arg	Tyr	Phe	Arg	Phe	Tyr	Gly	Arg	Ile	Val	Asp
				200					205					210
Lys	Pro	Gly	Asp	His	Asp	Pro	Glu	Thr	Leu	Glu	Ala	Ile	Ala	Glu
				215					220					225
Asn	Ala	Lys	Gly	Leu	Ala	Gly	Ile	Ser	Gly	Glu	Arg	Ile	Trp	Val
				230					235					240
Glu	Leu	Lys	Lys	Ile	Leu	Val	Gly	Asn	His	Val	Asn	His	Leu	Ile
				245					250					255
His	Leu	Ile	Tyr	Asp	Leu	Asp	Val	Ala	Pro	Tyr	Ile	Gly	Leu	Pro
				260					265					270
Ala	Asn	Ala	Ser	Leu	Glu	Glu	Phe	Asp	Lys	Val	Ser	Lys	Asn	Val
				275					280					285
Asp	Gly	Phe	Ser	Pro	Lys	Pro	Val	Thr	Leu	Leu	Ala	Ser	Leu	Phe
				290					295					300
Lys	Val	Gln	Asp	Asp	Val	Thr	Lys	Leu	Asp	Leu	Arg	Leu	Lys	Ile
				305					310					315
Ala	Lys	Glu	Glu	Lys	Asn	Leu	Gly	Leu	Phe	Ile	Val	Lys	Asn	Arg
				320					325					330
Lys	Asp	Leu	Ile	Lys	Ala	Thr	Asp	Ser	Ser	Asp	Pro	Leu	Lys	Pro
				335					340					345
Tyr	Gln	Asp	Phe	Ile	Ile	Asp	Ser	Arg	Glu	Pro	Asp	Ala	Thr	Thr
				350					355					360
Arg	Val	Cys	Glu	Leu	Leu	Lys	Tyr	Gln	Gly	Glu	His	Cys	Leu	Leu
				365					370					375
Lys	Glu	Met	Gln	Gln	Trp	Ser	Ile	Pro	Pro	Phe	Pro	Val	Ser	Gly
				380					385					390
His	Asp	Ile	Arg	Lys	Val	Gly	Ile	Ser	Ser	Gly	Lys	Glu	Ile	Gly
				395					400					405
Ala	Leu	Leu	Gln	Gln	Leu	Arg	Glu	Gln	Trp	Lys	Lys	Ser	Gly	Tyr
				410					415					420
Gln	Met	Glu	Lys	Asp	Glu	Leu	Leu	Ser	Tyr	Ile	Lys	Lys	Thr	
				425					430					

<210> 40

<211> 339

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1659474CD1

<400> 40

Met	Ala	Ala	Gly	Cys	Ser	Glu	Ala	Pro	Arg	Pro	Thr	Ala	Ala	Ser
1				5					10					15
Asp	Gly	Ser	Leu	Val	Gly	Gln	Ala	Gly	Val	Leu	Pro	Cys	Leu	Glu
				20					25					30
Leu	Pro	Thr	Tyr	Ala	Ala	Ala	Cys	Ala	Leu	Val	Asn	Ser	Arg	Tyr
				35					40					45
Ser	Cys	Leu	Val	Ala	Gly	Pro	His	Gln	Arg	His	Ile	Ala	Leu	Ser
				50					55					60
Pro	Arg	Tyr	Leu	Asn	Arg	Lys	Arg	Thr	Gly	Ile	Arg	Glu	Gln	Leu
				65					70					75
Asp	Ala	Glu	Leu	Leu	Arg	Tyr	Ser	Glu	Ser	Leu	Leu	Gly	Val	Pro
				80					85					90
Ile	Ala	Tyr	Asp	Asn	Ile	Lys	Val	Val	Gly	Glu	Leu	Gly	Asp	Ile
				95					100					105
Tyr	Asp	Asp	Gln	Gly	His	Ile	His	Leu	Asn	Ile	Glu	Ala	Asp	Phe
				110					115					120
Val	Ile	Phe	Cys	Pro	Glu	Pro	Gly	Gln	Lys	Leu	Met	Gly	Ile	Val
				125					130					135

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Asn	Lys	Val	Ser	Ser	Ser	His	Ile	Gly	Cys	Leu	Val	His	Gly	Cys	
				140					145					150	
Phe	Asn	Ala	Ser	Ile	Pro	Lys	Pro	Glu	Gln	Leu	Ser	Ala	Glu	Gln	
				155					160					165	
Trp	Gln	Thr	Met	Glu	Ile	Asn	Met	Gly	Asp	Glu	Leu	Glu	Phe	Glu	
				170					175					180	
Val	Phe	Arg	Leu	Asp	Ser	Asp	Ala	Ala	Gly	Val	Phe	Cys	Ile	Arg	
				185					190					195	
Gly	Lys	Leu	Asn	Ile	Thr	Ser	Leu	Gln	Phe	Lys	Arg	Ser	Glu	Val	
				200					205					210	
Ser	Glu	Glu	Val	Thr	Glu	Asn	Gly	Thr	Glu	Glu	Ala	Ala	Lys	Lys	
				215					220					225	
Pro	Lys	Lys	Lys	Lys	Lys	Lys	Lys	Asp	Pro	Glu	Thr	Tyr	Glu	Val	
				230					235					240	
Asp	Ser	Gly	Thr	Thr	Lys	Leu	Ala	Asp	Asp	Ala	Asp	Asp	Thr	Pro	
				245					250					255	
Met	Glu	Glu	Ser	Ala	Leu	Gln	Asn	Thr	Asn	Asn	Ala	Asn	Gly	Ile	
				260					265					270	
Trp	Glu	Glu	Glu	Pro	Lys	Lys	Lys	Lys	Lys	Lys	Lys	Lys	Lys	His	Gln
				275					280					285	
Glu	Val	Gln	Asp	Gln	Asp	Pro	Val	Phe	Gln	Gly	Ser	Asp	Ser	Ser	
				290					295					300	
Gly	Tyr	Gln	Ser	Asp	His	Lys	Lys	Lys	Lys	Lys	Glu	Lys	Lys	Thr	
				305					310					315	
Asn	Ser	Glu	Glu	Ala	Glu	Phe	Thr	Pro	Pro	Leu	Lys	Cys	Ser	Pro	
				320					325					330	
Lys	Arg	Lys	Gly	Lys	Ser	Asn	Phe	Leu							
				335											

<210> 41

<211> 599

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2267892CD1

<400> 41

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

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Thr	Gly	Ser	Gly	Lys	Thr	Leu	Ala	Phe	Ser	Ile	Pro	Ile	Leu	Met
				215					220					225
Gln	Leu	Lys	Gln	Pro	Ala	Asn	Lys	Gly	Phe	Arg	Ala	Leu	Ile	Ile
				230					235					240
Ser	Pro	Thr	Arg	Glu	Leu	Ala	Ser	Gln	Ile	His	Arg	Glu	Leu	Ile
				245					250					255
Lys	Ile	Ser	Glu	Gly	Thr	Gly	Phe	Arg	Ile	His	Met	Ile	His	Lys
				260					265					270
Ala	Ala	Val	Ala	Ala	Lys	Lys	Phe	Gly	Pro	Lys	Ser	Ser	Lys	Lys
				275					280					285
Phe	Asp	Ile	Leu	Val	Thr	Thr	Pro	Asn	Arg	Leu	Ile	Tyr	Leu	Leu
				290					295					300
Lys	Gln	Asp	Pro	Pro	Gly	Ile	Asp	Leu	Ala	Ser	Val	Glu	Trp	Leu
				305					310					315
Val	Val	Asp	Glu	Ser	Asp	Lys	Leu	Phe	Glu	Asp	Gly	Lys	Thr	Gly
				320					325					330
Phe	Arg	Asp	Gln	Leu	Ala	Ser	Ile	Phe	Leu	Ala	Cys	Thr	Ser	His
				335					340					345
Lys	Val	Arg	Arg	Ala	Met	Phe	Ser	Ala	Thr	Phe	Ala	Tyr	Asp	Val
				350					355					360
Glu	Gln	Trp	Cys	Lys	Leu	Asn	Leu	Asp	Asn	Val	Ile	Ser	Val	Ser
				365					370					375
Ile	Gly	Ala	Arg	Asn	Ser	Ala	Val	Glu	Thr	Val	Glu	Gln	Glu	Leu
				380					385					390
Leu	Phe	Val	Gly	Ser	Glu	Thr	Gly	Lys	Leu	Leu	Ala	Met	Arg	Glu
				395					400					405
Leu	Val	Lys	Lys	Gly	Phe	Asn	Pro	Pro	Val	Leu	Val	Phe	Val	Gln
				410					415					420
Ser	Ile	Glu	Arg	Ala	Lys	Glu	Leu	Phe	His	Glu	Leu	Ile	Tyr	Glu
				425					430					435
Gly	Ile	Asn	Val	Asp	Val	Ile	His	Ala	Glu	Arg	Thr	Gln	Gln	Gln
				440					445					450
Arg	Asp	Asn	Thr	Val	His	Ser	Phe	Arg	Ala	Gly	Lys	Ile	Trp	Val
				455					460					465
Leu	Ile	Cys	Thr	Ala	Leu	Leu	Ala	Arg	Gly	Ile	Asp	Phe	Lys	Gly
				470					475					480
Val	Asn	Leu	Val	Ile	Asn	Tyr	Asp	Phe	Pro	Thr	Ser	Ser	Val	Glu
				485					490					495
Tyr	Ile	His	Arg	Ile	Gly	Arg	Thr	Gly	Arg	Ala	Gly	Asn	Lys	Gly
				500					505					510
Lys	Ala	Ile	Thr	Phe	Phe	Thr	Glu	Asp	Asp	Lys	Pro	Leu	Leu	Arg
				515					520					525
Ser	Val	Ala	Asn	Val	Ile	Gln	Gln	Ala	Gly	Cys	Pro	Val	Pro	Glu
				530					535					540
Tyr	Ile	Lys	Gly	Phe	Gln	Lys	Leu	Leu	Ser	Lys	Gln	Lys	Lys	Lys
				545					550					555
Met	Ile	Lys	Lys	Pro	Leu	Glu	Arg	Glu	Ser	Ile	Ser	Thr	Thr	Pro
				560					565					570
Lys	Cys	Phe	Leu	Glu	Lys	Ala	Lys	Asp	Lys	Gln	Lys	Lys	Val	Thr
				575					580					585
Gly	Gln	Asn	Ser	Lys	Lys	Lys	Val	Ala	Leu	Glu	Asp	Lys	Ser	
				590					595					

<210> 42

<211> 334

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2670307CD1

<400> 42

Met	Ala	Ala	Ser	Gly	Ser	Gly	Met	Ala	Gln	Lys	Thr	Trp	Glu	Leu
1				5					10					15
Ala	Asn	Asn	Met	Gln	Glu	Ala	Gln	Ser	Ile	Asp	Glu	Ile	Tyr	Lys
				20					25					30

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

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<210> 43
 <211> 448
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 4524210CD1

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<400> 43
Met Asn Lys Glu Ile Val Thr Ala Leu Gly Lys Gln Glu Ala Glu
  1          5          10          15
Arg Lys Phe Glu Thr Leu Leu Lys His Leu Ser His Pro Pro Ser
  20          25          30
Phe Thr Thr Val Arg Val Asn Thr His Leu Ala Ser Val Gln His
  35          40          45
Val Lys Asn Leu Leu Leu Asp Glu Leu Gln Lys Gln Phe Asn Gly
  50          55          60
Leu Ser Val Pro Ile Leu Gln His Pro Asp Leu Gln Asp Val Leu
  65          70          75
Leu Ile Pro Val Ile Gly Pro Arg Lys Asn Ile Lys Lys Gln Gln
  80          85          90
Cys Glu Ala Ile Val Gly Ala Gln Cys Gly Asn Ala Val Leu Arg
  95          100         105

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Gly	Ala	His	Val	Tyr	Ala	Pro	Gly	Ile	Val	Ser	Ala	Ser	Gln	Phe
				110					115					120
Met	Lys	Ala	Gly	Asp	Val	Ile	Ser	Val	Tyr	Ser	Asp	Ile	Lys	Gly
				125					130					135
Lys	Cys	Lys	Lys	Gly	Ala	Lys	Glu	Phe	Asp	Gly	Thr	Lys	Val	Phe
				140					145					150
Leu	Gly	Asn	Gly	Ile	Ser	Glu	Leu	Ser	Arg	Lys	Glu	Ile	Phe	Ser
				155					160					165
Gly	Leu	Pro	Glu	Leu	Lys	Gly	Met	Gly	Ile	Arg	Met	Thr	Glu	Pro
				170					175					180
Val	Tyr	Leu	Ser	Pro	Ser	Phe	Asp	Ser	Val	Leu	Pro	Arg	Tyr	Leu
				185					190					195
Phe	Leu	Gln	Asn	Leu	Pro	Ser	Ala	Leu	Val	Ser	His	Val	Leu	Asn
				200					205					210
Pro	Gln	Pro	Gly	Glu	Lys	Ile	Leu	Asp	Leu	Cys	Ala	Ala	Pro	Gly
				215					220					225
Gly	Lys	Thr	Thr	His	Ile	Ala	Ala	Leu	Met	His	Asp	Gln	Gly	Glu
				230					235					240
Val	Ile	Ala	Leu	Asp	Lys	Ile	Phe	Asn	Lys	Val	Glu	Lys	Ile	Lys
				245					250					255
Gln	Asn	Ala	Leu	Leu	Leu	Gly	Leu	Asn	Ser	Ile	Arg	Ala	Phe	Cys
				260					265					270
Phe	Asp	Gly	Thr	Lys	Ala	Val	Lys	Leu	Asp	Met	Val	Glu	Asp	Thr
				275					280					285
Glu	Gly	Glu	Pro	Pro	Phe	Leu	Pro	Glu	Ser	Phe	Asp	Arg	Ile	Leu
				290					295					300
Leu	Asp	Ala	Pro	Cys	Ser	Gly	Met	Gly	Gln	Arg	Pro	Asn	Met	Ala
				305					310					315
Cys	Thr	Trp	Ser	Val	Lys	Glu	Val	Ala	Ser	Tyr	Gln	Pro	Leu	Gln
				320					325					330
Arg	Lys	Leu	Phe	Thr	Ala	Ala	Val	Gln	Leu	Leu	Lys	Pro	Glu	Gly
				335					340					345
Val	Leu	Val	Tyr	Ser	Thr	Cys	Thr	Ile	Thr	Leu	Ala	Glu	Asn	Glu
				350					355					360
Glu	Gln	Val	Ala	Trp	Ala	Leu	Thr	Lys	Phe	Pro	Cys	Leu	Gln	Leu
				365					370					375
Gln	Pro	Gln	Glu	Pro	Gln	Ile	Gly	Gly	Glu	Gly	Met	Arg	Gly	Ala
				380					385					390
Gly	Leu	Ser	Cys	Glu	Gln	Leu	Lys	Gln	Leu	Gln	Arg	Phe	Asp	Pro
				395					400					405
Ser	Ala	Val	Pro	Leu	Pro	Asp	Thr	Asp	Met	Asp	Ser	Leu	Arg	Glu
				410					415					420
Ala	Arg	Arg	Glu	Asp	Met	Leu	Arg	Leu	Ala	Asn	Lys	Asp	Ser	Ile
				425					430					435
Gly	Phe	Phe	Ile	Ala	Lys	Phe	Val	Lys	Cys	Lys	Ser	Thr		
				440					445					

<210> 44

<211> 420

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 5584860CD1

<400> 44

Met	Ala	Thr	Ser	Leu	Gly	Ser	Asn	Thr	Tyr	Asn	Arg	Gln	Asn	Trp
1				5					10					15
Glu	Asp	Ala	Asp	Phe	Pro	Ile	Leu	Cys	Gln	Thr	Cys	Leu	Gly	Glu
				20					25					30
Asn	Pro	Tyr	Ile	Arg	Met	Thr	Lys	Glu	Lys	Tyr	Gly	Lys	Glu	Cys
				35					40					45
Lys	Ile	Cys	Ala	Arg	Pro	Phe	Thr	Val	Phe	Arg	Trp	Cys	Pro	Gly
				50					55					60
Val	Arg	Met	Arg	Phe	Lys	Lys	Thr	Glu	Val	Cys	Gln	Thr	Cys	Ser
				65					70					75

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Lys	Leu	Lys	Asn	Val	Cys	Gln	Thr	Cys	Leu	Leu	Asp	Leu	Glu	Tyr
				80					85					90
Gly	Leu	Pro	Ile	Gln	Val	Arg	Asp	Ala	Gly	Leu	Ser	Phe	Lys	Asp
				95					100					105
Asp	Met	Pro	Lys	Ser	Asp	Val	Asn	Lys	Glu	Tyr	Tyr	Thr	Gln	Asn
				110					115					120
Met	Glu	Arg	Glu	Ile	Ser	Asn	Ser	Asp	Gly	Thr	Arg	Pro	Val	Gly
				125					130					135
Met	Leu	Gly	Lys	Ala	Thr	Ser	Thr	Ser	Asp	Met	Leu	Leu	Lys	Leu
				140					145					150
Ala	Arg	Thr	Thr	Pro	Tyr	Tyr	Lys	Arg	Asn	Arg	Pro	His	Ile	Cys
				155					160					165
Ser	Phe	Trp	Val	Lys	Gly	Glu	Cys	Lys	Arg	Gly	Glu	Glu	Cys	Pro
				170					175					180
Tyr	Arg	His	Glu	Lys	Pro	Thr	Asp	Pro	Asp	Asp	Pro	Leu	Ala	Asp
				185					190					195
Gln	Asn	Ile	Lys	Asp	Arg	Tyr	Tyr	Gly	Ile	Asn	Asp	Pro	Val	Ala
				200					205					210
Asp	Lys	Leu	Leu	Lys	Arg	Ala	Ser	Thr	Met	Pro	Arg	Leu	Asp	Pro
				215					220					225
Pro	Glu	Asp	Lys	Thr	Ile	Thr	Thr	Leu	Tyr	Val	Gly	Gly	Leu	Gly
				230					235					240
Asp	Thr	Ile	Thr	Glu	Thr	Asp	Leu	Arg	Asn	His	Phe	Tyr	Gln	Phe
				245					250					255
Gly	Glu	Ile	Arg	Thr	Ile	Thr	Val	Val	Gln	Arg	Gln	Gln	Cys	Ala
				260					265					270
Phe	Ile	Gln	Phe	Ala	Thr	Arg	Gln	Ala	Ala	Glu	Val	Ala	Ala	Glu
				275					280					285
Lys	Ser	Phe	Asn	Lys	Leu	Ile	Val	Asn	Gly	Arg	Arg	Leu	Asn	Val
				290					295					300
Lys	Trp	Gly	Arg	Ser	Gln	Ala	Ala	Arg	Gly	Lys	Glu	Lys	Glu	Lys
				305					310					315
Asp	Gly	Thr	Thr	Asp	Ser	Gly	Ile	Lys	Leu	Glu	Pro	Val	Pro	Gly
				320					325					330
Leu	Pro	Gly	Ala	Leu	Pro	Pro	Pro	Pro	Ala	Ala	Glu	Glu	Glu	Ala
				335					340					345
Ser	Ala	Asn	Tyr	Phe	Asn	Leu	Pro	Pro	Ser	Gly	Pro	Pro	Ala	Val
				350					355					360
Val	Asn	Ile	Ala	Leu	Pro	Pro	Pro	Pro	Gly	Ile	Ala	Pro	Pro	Pro
				365					370					375
Pro	Pro	Gly	Phe	Gly	Pro	His	Met	Phe	His	Pro	Met	Gly	Pro	Pro
				380					385					390
Pro	Pro	Phe	Met	Arg	Ala	Pro	Gly	Pro	Ile	His	Tyr	Pro	Ser	Gln
				395					400					405
Asp	Pro	Gln	Arg	Met	Gly	Ala	His	Ala	Gly	Lys	His	Ser	Ser	Pro
				410					415					420

<210> 45

<211> 137

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 5807892CD1

<400> 45

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

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Trp	Ile	Gly	Cys	65	Gly	Ala	His	Leu	Ser	70	Lys	Pro	Met	Glu	Lys	75	Leu
				80						85						90	
Leu	Gly	Leu	Ala	95	Gly	Phe	Phe	Pro	Leu	100	His	Pro	Met	Met	Ile	105	Thr
Asn	Ala	Glu	Arg	110	Leu	Arg	Arg	Lys	Arg	115	Ala	Arg	Glu	Val	Leu	120	Leu
Ala	Ser	Gln	Lys	125	Thr	Asp	Ala	Glu	Ala	130	Thr	Asp	Thr	Glu	Ala	135	Thr
Glu	Thr																

<210> 46

<211> 556

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 3210044CD1

<400> 46

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

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Val	Asp	Gln	Asp	Leu	Ile	Met	Thr	Gln	Lys	Lys	Val	Val	Val	His
				335					340					345
Leu	Glu	Thr	Ile	Leu	Gly	Ala	Ser	Val	Gln	His	Val	Lys	Leu	Lys
				350					355					360
Lys	Met	Lys	Tyr	Ser	Phe	Gln	Leu	Trp	Ile	Ala	Met	Met	Ser	Ala
				365					370					375
Lys	Gly	His	Asp	Gly	Lys	Glu	Pro	Val	Lys	Phe	Val	Asp	Leu	Leu
				380					385					390
Gly	Asp	His	Gly	Lys	His	Val	Ser	Pro	Leu	Trp	Glu	Leu	Ile	Lys
				395					400					405
Trp	Cys	Leu	Gly	Leu	Ser	Val	Tyr	Thr	Ile	Pro	Ser	Ile	Gly	Leu
				410					415					420
Ala	Leu	Leu	Glu	Glu	Lys	Leu	Arg	Tyr	Ser	Asn	Glu	Lys	Tyr	Gln
				425					430					435
Lys	Phe	Lys	Ala	Val	Glu	Glu	Ser	Leu	Arg	Lys	Glu	Leu	Val	Asp
				440					445					450
Met	Leu	Gly	Asp	Asp	Gly	Val	Phe	Leu	Tyr	Pro	Ser	His	Pro	Thr
				455					460					465
Val	Ala	Pro	Lys	His	His	Val	Pro	Leu	Thr	Arg	Pro	Phe	Asn	Phe
				470					475					480
Ala	Tyr	Thr	Gly	Val	Phe	Ser	Ala	Leu	Gly	Leu	Pro	Val	Thr	Gln
				485					490					495
Cys	Pro	Leu	Gly	Leu	Asn	Ala	Lys	Gly	Leu	Pro	Leu	Gly	Ile	Gln
				500					505					510
Val	Val	Ala	Gly	Pro	Phe	Asn	Asp	His	Leu	Thr	Leu	Ala	Val	Ala
				515					520					525
Gln	Tyr	Leu	Glu	Lys	Thr	Phe	Gly	Gly	Trp	Val	Cys	Pro	Gly	Lys
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				545					550					555

Phe

<210> 47
 <211> 111
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 4942454CD1

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 20 25 30
 Gly Cys Glu Val Asp Asn Glu Lys Met Glu Leu Leu Leu Ser Gln
 35 40 45
 Leu Ser Gly Lys Asp Ile Thr Glu Leu Ile Ala Ala Gly Arg Glu
 50 55 60
 Lys Phe Ala Ser Val Pro Cys Gly Gly Gly Gly Val Ala Val Ala
 65 70 75
 Ala Ala Ala Pro Ala Ala Gly Gly Ala Pro Ala Ala Glu Ala Lys
 80 85 90
 Lys Glu Glu Lys Val Glu Glu Lys Glu Glu Ser Asp Asp Asp Met
 95 100 105
 Gly Phe Ser Leu Phe Asp
 110

<210> 48
 <211> 882
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 1622129CB1

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<400> 48

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accgggtgga cgggcggcgc gccggggagc tgcgcaagat ccaggcgcgg atgggcgtgt 180
tcgcgcaggc tgacggctcg gcctacattg agcagggcaa caccaaggca ctggctgttg 240
tctacggccc gcacgagatc cggggctccc gggctcgagc cctgccggac agggccctag 300
tgaactgtca atatatgttca gcgaccttca gcacagggtga gcgcaagcga cggccacatg 360
gggaccgtaa gtcctgtgag atgggcctgc agctccgcca gactttcgaa gcagccatcc 420
tcacacagct gcacccacgc tcccagattg atatctatgt gcaggtgcta caggcagatg 480
gtgggaccta tgcagcttgt gtgaatgcag ccacgctggc agtgctggat gccgggatac 540
ccatgagaga ctttgtgtgt gcgtgctcag ctggcttcgt ggacggcaca gccctggcgg 600
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cctcaggaca gattgcgctg cttgagatgg atgcccggct gcacgaggac cacctggagc 720
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<210> 49

<211> 1220

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1820078CB1

<400> 49

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cctctcctgg gcttctcagt gtctcgccgg cgggggttcgg cctgagctgg attgacatag 180
cccttggcgg atttaaacaa cctaaacatt aagcagtaca gctgcctcaa acctttggga 240
ttttcagaat gactgacact gccgaagctg ttccaaagtt tgaagagatg tttgctagta 300
gattcacaga aaatgacaag gagtatcagg aatacctgaa acgccctcct gagtctcctc 360
caattgttga ggaatggaat agcagagctg gtgggaacca aagaaacaga ggcaatcggg 420
tgcaagacaa cagacagttc agaggcaggg acaacagatg ggggtggcca agtgacaatc 480
gatccaatca gtggcatgga cgatcctggg gtaacaacta cccgcaacac agacaagaac 540
cttactatcc ccagcaatat ggacattatg gttacaacca gcggcctcct tacggttact 600
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cttttttttt tttttgcatt tggttaagtga ctatgggtact ttgtgattcc ttaatctata 1140
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<210> 50

<211> 2020

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1527017CB1

<220>

<221> unsure

<222> 1905, 1909, 1936, 1942, 1959, 1967, 1972, 1979, 1989, 1999, 2002

<223> a, t, c, g, or other

<400> 50

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agggtttcct tttggcgctt cccttttgga cccggagtga aaaactctaa cgtccagatc 120
agtggagaga aacgcagatt taggaccctg aggagtcttt ttcacccgtt tcccgtcact 180

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cgctcaggcg cgccgagggc agtccttgtg gggctcctcgt ggccagccaa gatggttgcc 240
cccgcagtga aggttgcccg aggatggtcg ggcctggcgt tgggcgtgcg gcgggctgtc 300
ttgcagcttc caggggctaa ctcagggtgag atggagccgc tatagtcctg aattcaagga 360
tcccttgatt gacaaggaat attatcgcaa gccagtggag gagctaactg aggaggagaa 420
atatgttcgg gagctcaaga agactcagct catcaaagct gctccagcag gggaaaacaa 480
gttctgtgtt tgaagaccca gtcatcagta aattcaccaa catgatgatg ataggaggaa 540
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ttgagaagta ccatgccgct tctgcagagg aacaggcaac catcgaacgc aaccctaca 660
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<210> 51
 <211> 637
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 1647264CB1

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<400> 51
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gcgctgaacg cactgcagcc tcttgagttc agaaatgaaa gctcattagc atctacactg 180
aagacgctcc tgttcttcac agctttaatg atcactgttc ctattggggt atatttcaca 240
actaaatctt acatatttga aggcgcctt gggatgtcca atagggacag ctatttttac 300
gctgctattg ttgcagtggc cgccgtccat gtgggtgctgg ccctctttgt gtatgtggcc 360
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tttatagcat taaattcatt ttttaaaatg ataaatgctg gagggggcca tctgatttga 480
ataaagttga aagaacatgt taaagtcagt cttaaggagt cacgtttgag tatgtaaatt 540
ttgatccttc taatatgttg ggtttgatat tcagttttac tgtatgaatc gattgcaatg 600
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<210> 52
 <211> 717
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 1721989CB1

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tggctttctt tactgggctc tggggccctt tcacctgtgt aagcagagtg ctgagccatc 180

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actgttttcag	caccactggg	agtctgagtg	cgattcagaa	gatgacgcgg	gtacgagtgg	240
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ataagaagaa	tggagtgggc	aaggtgggcg	accagatact	actggccatc	aagggaacaga	360
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ctcagaactt	tgtgtgagtt	gagcccaggc	ctctggttgc	aggactcgtg	aatggagcag	600
ttctgagaac	cacccttttg	ctaagggagc	ttgggagcca	catggctgct	cccttcacac	660
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<210> 53

<211> 2061

<212> DNA

<213> Homo sapiens

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<223> Incyte ID No: 1730581CB1

<400> 53

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catctaacca	accgcccata	tagctaacc	gagccccctc	accgtcaact	cagggttcggc	180
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gaagatagcc	atgctaaaat	gcaattatat	cctcatgttt	atcccaaact	aatcttggac	1920
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<210> 54

<211> 1307

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1740714CB1

<220>

<221> unsure

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<222> 1301

<223> a, t, c, g, or other

<400> 54

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<210> 55

<211> 1357

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1850596CB1

<400> 55

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<210> 56

<211> 1749

<212> DNA

<213> Homo sapiens

<220>

WO 01/83524

PCT/US01/13862

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<223> Incyte ID No: 1856109CB1

<400> 56

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<210> 57

<211> 991

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1921719CB1

<400> 57

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gaagctgatg aaaagaatga ccgaacatcc ctgaacagga agctagacag gaaccttgtc 480
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aacatggaag ccaagttcct aggaaatgca cctgtgggc actacacatt caagttcccc 660
caggcaatgc ggacagagag taacctcgga gccaaagtg tcttcttcaa agcactgcta 720
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<210> 58

<211> 1188

<212> DNA

<213> Homo sapiens

WO 01/83524

PCT/US01/13862

<220>

<221> misc_feature

<223> Incyte ID No: 2099829CB1

<400> 58

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cggaaatgtg tggacaccta caagtacctt ttcattcttct ctgtggccaa catgaggaac 180
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aaggtgatga tgggtggcctt gggtcggagc ccatctgatg aatacaaaga caacctgcac 300
caggtcagca aaagggttgag ggggtgaggtg ggtctcctgt tcaccaaccg cacaaggag 360
gaggtgaatg agtgggttcac gaaatacaca gaaatggact acgcccgcgc tggtaacaaa 420
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<210> 59

<211> 1454

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2416915CB1

<400> 59

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<210> 60

<211> 1588

<212> DNA

<213> Homo sapiens

WO 01/83524

PCT/US01/13862

<220>

<221> misc_feature

<223> Incyte ID No: 2472784CB1

<400> 60

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<210> 61

<211> 2111

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2598981CB1

<400> 61

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<210> 62

<211> 1155

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2738075CB1

<220>

<221> unsure

<222> 1150-1155

<223> a, t, c, g, or other

<400> 62

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<210> 63

<211> 1673

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2279049CB1

<400> 63

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cttcccttta aatacccggc agttctgcct gaaattactg tcagatcagt attattgagt 420
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<210> 64

<211> 584

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2660904CB1

<400> 64

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<210> 65

<211> 978

<212> DNA

<213> Homo sapiens

<220>

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<223> Incyte ID No: 3179424CB1

<400> 65

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<211> 1055

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2885096CB1

<400> 66

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<210> 67

<211> 2220

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

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<400> 67

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<210> 68

<211> 1890

<212> DNA

<213> Homo sapiens

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<223> Incyte ID No: 3074572CB1

<400> 68

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<210> 69

<211> 2893

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

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<211> 885

<212> DNA

<213> Homo sapiens

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<223> Incyte ID No: 1454656CB1

<400> 70

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<400> 71

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<220>
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 <223> Incyte ID No: 1257715CB1

<400> 72

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 <211> 639
 <212> DNA
 <213> Homo sapiens

<220>
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 <223> Incyte ID No: 1342022CB1

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 <223> Incyte ID No: 194704CB1

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<210> 75
 <211> 1457
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature

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<223> Incyte ID No: 607270CB1

<400> 75

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<210> 76

<211> 1184

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 758546CB1

<400> 76

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<210> 77

<211> 1638

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

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<223> Incyte ID No: 866043CB1

<400> 77

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<210> 78

<211> 701

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 927065CB1

<400> 78

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<210> 79

<211> 1829

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 938071CB1

<400> 79

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<210> 80

<211> 2541

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 3295984CB1

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<222> 721

<223> a, t, c, g, or other

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<213> Homo sapiens

<220>

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<220>
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 <223> Incyte ID No: 5862945CB1

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 <213> Homo sapiens

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<210> 86
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 <213> Homo sapiens

<220>
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 <223> Incyte ID No: 000124CB1

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<210> 87

<211> 1041

<212> DNA

<213> Homo sapiens

<220>

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<223> Incyte ID No: 1659474CB1

<400> 87

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1041

<210> 88

<211> 2722

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2267892CB1

<400> 88

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What is claimed is:

1. An isolated polypeptide selected from the group consisting of:
 - a) a polypeptide comprising an amino acid sequence selected from the group consisting of
5 SEQ ID NO:1-47,
 - b) a naturally occurring polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-47,
 - c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-47, and
10 d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-47.
2. An isolated polypeptide of claim 1 selected from the group consisting of SEQ ID NO:1-47.
- 15 3. An isolated polynucleotide encoding a polypeptide of claim 1.
4. An isolated polynucleotide encoding a polypeptide of claim 2.
5. An isolated polynucleotide of claim 4 selected from the group consisting of SEQ ID
20 NO:48-94.
6. A recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim 3.
- 25 7. A cell transformed with a recombinant polynucleotide of claim 6.
8. A transgenic organism comprising a recombinant polynucleotide of claim 6.
9. A method for producing a polypeptide of claim 1, the method comprising:
30 a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide, and said recombinant polynucleotide comprises a promoter sequence operably linked to a polynucleotide encoding the polypeptide of claim 1, and
b) recovering the polypeptide so expressed.
- 35 10. An isolated antibody which specifically binds to a polypeptide of claim 1.

11. An isolated polynucleotide selected from the group consisting of:

a) a polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:48-94,

b) a naturally occurring polynucleotide comprising a polynucleotide sequence at least 90% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:48-94,

c) a polynucleotide complementary to a polynucleotide of a),

d) a polynucleotide complementary to a polynucleotide of b), and

e) an RNA equivalent of a)-d).

12. An isolated polynucleotide comprising at least 60 contiguous nucleotides of a polynucleotide of claim 11.

13. A method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 11, the method comprising:

a) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide or fragments thereof, and

b) detecting the presence or absence of said hybridization complex, and, optionally, if present, the amount thereof.

14. A method of claim 13, wherein the probe comprises at least 60 contiguous nucleotides.

15. A method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 11, the method comprising:

a) amplifying said target polynucleotide or fragment thereof using polymerase chain reaction amplification, and

b) detecting the presence or absence of said amplified target polynucleotide or fragment thereof, and, optionally, if present, the amount thereof.

16. A composition comprising a polypeptide of claim 1 and a pharmaceutically acceptable excipient.

17. A composition of claim 16, wherein the polypeptide has an amino acid sequence selected from the group consisting of SEQ ID NO:1-47.

18. A method for treating a disease or condition associated with decreased expression of functional RMEP, comprising administering to a patient in need of such treatment the composition of claim 16.

5 19. A method for screening a compound for effectiveness as an agonist of a polypeptide of claim 1, the method comprising:

- a) exposing a sample comprising a polypeptide of claim 1 to a compound, and
- b) detecting agonist activity in the sample.

10 20. A composition comprising an agonist compound identified by a method of claim 19 and a pharmaceutically acceptable excipient.

15 21. A method for treating a disease or condition associated with decreased expression of functional RMEP, comprising administering to a patient in need of such treatment a composition of claim 20.

22. A method for screening a compound for effectiveness as an antagonist of a polypeptide of claim 1, the method comprising:

- 20 a) exposing a sample comprising a polypeptide of claim 1 to a compound, and
- b) detecting antagonist activity in the sample.

23. A composition comprising an antagonist compound identified by a method of claim 22 and a pharmaceutically acceptable excipient.

25 24. A method for treating a disease or condition associated with overexpression of functional RMEP, comprising administering to a patient in need of such treatment a composition of claim 23.

25. A method of screening for a compound that specifically binds to the polypeptide of claim 1, said method comprising the steps of:

- 30 a) combining the polypeptide of claim 1 with at least one test compound under suitable conditions, and
- b) detecting binding of the polypeptide of claim 1 to the test compound, thereby identifying a compound that specifically binds to the polypeptide of claim 1.

35 26. A method of screening for a compound that modulates the activity of the polypeptide of

claim 1, said method comprising:

a) combining the polypeptide of claim 1 with at least one test compound under conditions permissive for the activity of the polypeptide of claim 1,

b) assessing the activity of the polypeptide of claim 1 in the presence of the test compound, and

5 c) comparing the activity of the polypeptide of claim 1 in the presence of the test compound with the activity of the polypeptide of claim 1 in the absence of the test compound, wherein a change in the activity of the polypeptide of claim 1 in the presence of the test compound is indicative of a compound that modulates the activity of the polypeptide of claim 1.

10 27. A method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence of claim 5, the method comprising:

a) exposing a sample comprising the target polynucleotide to a compound, under conditions suitable for the expression of the target polynucleotide,

15 b) detecting altered expression of the target polynucleotide, and

c) comparing the expression of the target polynucleotide in the presence of varying amounts of the compound and in the absence of the compound.

28. A method for assessing toxicity of a test compound, said method comprising:

20 a) treating a biological sample containing nucleic acids with the test compound;

b) hybridizing the nucleic acids of the treated biological sample with a probe comprising at least 20 contiguous nucleotides of a polynucleotide of claim 11 under conditions whereby a specific hybridization complex is formed between said probe and a target polynucleotide in the biological sample, said target polynucleotide comprising a polynucleotide sequence of a polynucleotide of claim
25 11 or fragment thereof;

c) quantifying the amount of hybridization complex; and

d) comparing the amount of hybridization complex in the treated biological sample with the amount of hybridization complex in an untreated biological sample, wherein a difference in the amount of hybridization complex in the treated biological sample is indicative of toxicity of the test
30 compound.

29. A diagnostic test for a condition or disease associated with the expression of RMEP in a biological sample comprising the steps of:

a) combining the biological sample with an antibody of claim 10, under conditions suitable

for the antibody to bind the polypeptide and form an antibody:polypeptide complex; and

b) detecting the complex, wherein the presence of the complex correlates with the presence of the polypeptide in the biological sample.

5 30. The antibody of claim 10, wherein the antibody is:

a) a chimeric antibody,

b) a single chain antibody,

c) a Fab fragment,

d) a F(ab')₂ fragment, or

10 e) a humanized antibody.

31. A composition comprising an antibody of claim 10 and an acceptable excipient.

32. A method of diagnosing a condition or disease associated with the expression of RMEP
15 in a subject, comprising administering to said subject an effective amount of the composition of claim 31.

33. A composition of claim 31, wherein the antibody is labeled.

20 34. A method of diagnosing a condition or disease associated with the expression of RMEP in a subject, comprising administering to said subject an effective amount of the composition of claim 33.

35. A method of preparing a polyclonal antibody with the specificity of the antibody of claim
25 10 comprising:

a) immunizing an animal with a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-47, or an immunogenic fragment thereof, under conditions to elicit an antibody response;

b) isolating antibodies from said animal; and

30 c) screening the isolated antibodies with the polypeptide, thereby identifying a polyclonal antibody which binds specifically to a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-47.

36. An antibody produced by a method of claim 35.

37. A composition comprising the antibody of claim 36 and a suitable carrier.

38. A method of making a monoclonal antibody with the specificity of the antibody of claim 10 comprising:

- 5 a) immunizing an animal with a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-47, or an immunogenic fragment thereof, under conditions to elicit an antibody response;
- b) isolating antibody producing cells from the animal;
- c) fusing the antibody producing cells with immortalized cells to form monoclonal antibody-
10 producing hybridoma cells;
- d) culturing the hybridoma cells; and
- e) isolating from the culture monoclonal antibody which binds specifically to a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-47.

15 39. A monoclonal antibody produced by a method of claim 38.

40. A composition comprising the antibody of claim 39 and a suitable carrier.

41. The antibody of claim 10, wherein the antibody is produced by screening a Fab
20 expression library.

42. The antibody of claim 10, wherein the antibody is produced by screening a recombinant immunoglobulin library.

25 43. A method for detecting a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-47 in a sample, comprising the steps of:

- a) incubating the antibody of claim 10 with a sample under conditions to allow specific binding of the antibody and the polypeptide; and
- b) detecting specific binding, wherein specific binding indicates the presence of a polypeptide
30 having an amino acid sequence selected from the group consisting of SEQ ID NO:1-47 in the sample.

44. A method of purifying a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-47 from a sample, the method comprising:

- a) incubating the antibody of claim 10 with a sample under conditions to allow specific

binding of the antibody and the polypeptide; and

b) separating the antibody from the sample and obtaining the purified polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-47.

5 45. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:1.

46. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:2.

47. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:3.

10

48. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:4.

49. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:5.

15

50. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:6.

51. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:7.

52. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:8.

20

53. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:9.

54. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:10.

25

55. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:11.

56. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:12.

57. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:13.

30

58. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:14.

59. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:15.

60. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:16.

61. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:17.

5 62. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:18.

63. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:19.

64. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:20.

10

65. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:21.

66. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:22.

15

67. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:23.

68. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:24.

69. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:25.

20

70. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:26.

71. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:27.

25

72. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:28.

73. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:29.

74. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:30.

30

75. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:31.

76. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:32.

77. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:33.

78. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:34.

5 79. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:35.

80. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:36.

81. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:37.

10

82. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:38.

83. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:39.

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84. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:40.

85. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:41.

86. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:42.

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87. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:43.

88. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:44.

25

89. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:45.

90. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:46.

91. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:47.

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92. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:48.

93. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:49.

94. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:50.

95. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:51.

5 96. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:52.

97. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:53.

98. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:54.

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99. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:55.

100. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID
NO:56.

15

101. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID
NO:57.

102. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID
20 NO:58.

103. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID
NO:59.

25 104. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID
NO:60.

105. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID
NO:61.

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106. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID
NO:62.

107. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID

NO:63.

108. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID
NO:64.

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109. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID
NO:65.

110. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID
10 NO:66.

111. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID
NO:67.

112. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID
15 NO:68.

113. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID
NO:69.

20

114. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID
NO:70.

115. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID
25 NO:71.

116. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID
NO:72.

117. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID
30 NO:73.

118. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID
NO:74.

119. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:75.

120. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:76.

121. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:77.

122. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:78.

123. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:79.

124. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:80.

125. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:81.

126. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:82.

127. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:83.

128. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:84.

129. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:85.

130. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID

NO:86.

131. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID
NO:87.

5

132. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID
NO:88.

133. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID
10 NO:89.

134. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID
NO:90.

15 135. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID
NO:91.

136. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID
NO:92.

20

137. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID
NO:93.

138. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID
25 NO:94.