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(54) Title: MRACS AS MODIFIERS OF THE RAC PATHWAY AND METHODS OF USE

(57) Abstract: Human MRAC genes are identified as modulators of the RAC pathway, and thus are therapeutic targets for disorders associated with defective RAC function. Methods for identifying modulators of RAC, comprising screening for agents that modulate the activity of MRAC are provided.

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MRACS AS MODIFIERS OF THE RAC PATHWAY AND METHODS OF USE

REFERENCE TO RELATED APPLICATIONS

- 5 This application claims priority to U.S. provisional patent application 60/495,193 filed 8/14/2003. The contents of the prior application are hereby incorporated in their entirety.

BACKGROUND OF THE INVENTION

- 10 Cell movement is an important part of normal developmental and physiological processes (e.g. epiboly, gastrulation and wound healing), and is also important in pathologies such as tumor progression and metastasis, angiogenesis, inflammation and atherosclerosis. The process of cell movement involves alterations of cell-cell and cell-matrix interactions in response to signals, as well as rearrangement of the actin and
- 15 microtubule cytoskeletons. The small GTPases of the Rho/Rac family interact with a variety of molecules to regulate the processes of cell motility, cell-cell adhesion and cell-matrix adhesion. Cdc42 and Rac are implicated in the formation of filopodia and lamellipodia required for initiating cell movement, and Rho regulates stress fiber and focal adhesion formation. Rho/Rac proteins are effectors of cadherin/catenin-mediated cell-cell
- 20 adhesion, and function downstream of integrins and growth factor receptors to regulate cytoskeletal changes important for cell adhesion and motility.

- There are five members of the Rho/Rac family in the *C. elegans* genome. *rho-1* encodes a protein most similar to human RhoA and RhoC, *cdc-42* encodes an ortholog of human Cdc42, and *ced-10*, *mig-2* and *rac-2* encode Rac-related proteins. *ced-10*, *mig-2*
- 25 and *rac-2* have partially redundant functions in the control of a number of cell and axonal migrations in the worm, as inactivation of two or all three of these genes causes enhanced migration defects when compared to the single mutants. Furthermore, *ced-10; mig-2* double mutants have gross morphological and movement defects not seen in either single mutant, possibly as a secondary effect of defects in cell migration or movements during
- 30 morphogenesis. These defects include a completely penetrant uncoordinated phenotype, as well as variably penetrant slow-growth, vulval, withered tail, and sterility defects, none of which are seen in either single mutant.

 The ability to manipulate the genomes of model organisms such as *C. elegans* provides a powerful means to analyze biochemical processes that, due to significant

evolutionary conservation, have direct relevance to more complex vertebrate organisms. Due to a high level of gene and pathway conservation, the strong similarity of cellular processes, and the functional conservation of genes between these model organisms and mammals, identification of the involvement of novel genes in particular pathways and their functions in such model organisms can directly contribute to the understanding of the correlative pathways and methods of modulating them in mammals (see, for example, Dulubova I, et al, J Neurochem 2001 Apr;77(1):229-38; Cai T, et al., Diabetologia 2001 Jan;44(1):81-8; Pasquinelli AE, et al., Nature. 2000 Nov 2;408(6808):37-8; Ivanov IP, et al., EMBO J 2000 Apr 17;19(8):1907-17; Vajo Z et al., Mamm Genome 1999 Oct;10(10):1000-4). For example, a genetic screen can be carried out in an invertebrate model organism having underexpression (e.g. knockout) or overexpression of a gene (referred to as a "genetic entry point") that yields a visible phenotype. Additional genes are mutated in a random or targeted manner. When a gene mutation changes the original phenotype caused by the mutation in the genetic entry point, the gene is identified as a "modifier" involved in the same or overlapping pathway as the genetic entry point. When the genetic entry point is an ortholog of a human gene implicated in a disease pathway, such as RAC, modifier genes can be identified that may be attractive candidate targets for novel therapeutics.

All references cited herein, including patents, patent applications, publications, and sequence information in referenced Genbank identifier numbers, are incorporated herein in their entireties.

SUMMARY OF THE INVENTION

We have discovered genes that modify the RAC pathway in *C. elegans*, and identified their human orthologs, hereinafter referred to as Modifier of RAC (MRAC). The invention provides methods for utilizing these RAC modifier genes and polypeptides to identify MRAC-modulating agents that are candidate therapeutic agents that can be used in the treatment of disorders associated with defective or impaired RAC function and/or MRAC function. Preferred MRAC-modulating agents specifically bind to MRAC polypeptides and restore RAC function. Other preferred MRAC-modulating agents are nucleic acid modulators such as antisense oligomers and RNAi that repress MRAC gene expression or product activity by, for example, binding to and inhibiting the respective nucleic acid (i.e. DNA or mRNA).

MRAC modulating agents may be evaluated by any convenient *in vitro* or *in vivo* assay for molecular interaction with an MRAC polypeptide or nucleic acid. In one embodiment, candidate MRAC modulating agents are tested with an assay system comprising an MRAC polypeptide or nucleic acid. Agents that produce a change in the activity of the assay system relative to controls are identified as candidate RAC
5 modulating agents. The assay system may be cell-based or cell-free. MRAC-modulating agents include MRAC related proteins (e.g. dominant negative mutants, and biotherapeutics); MRAC -specific antibodies; MRAC -specific antisense oligomers and other nucleic acid modulators; and chemical agents that specifically bind to or interact
10 with MRAC or compete with MRAC binding partner (e.g. by binding to an MRAC binding partner). In one specific embodiment, a small molecule modulator is identified using a binding assay. In specific embodiments, the screening assay system is selected from an apoptosis assay, a cell proliferation assay, an angiogenesis assay, and a hypoxic induction assay.

15 In another embodiment, candidate RAC pathway modulating agents are further tested using a second assay system that detects changes in the RAC pathway, such as angiogenic, apoptotic, or cell proliferation changes produced by the originally identified candidate agent or an agent derived from the original agent. The second assay system may use cultured cells or non-human animals. In specific embodiments, the secondary assay
20 system uses non-human animals, including animals predetermined to have a disease or disorder implicating the RAC pathway, such as an angiogenic, apoptotic, or cell proliferation disorder (e.g. cancer).

The invention further provides methods for modulating the MRAC function and/or the RAC pathway in a mammalian cell by contacting the mammalian cell with an agent
25 that specifically binds an MRAC polypeptide or nucleic acid. The agent may be a small molecule modulator, a nucleic acid modulator, or an antibody and may be administered to a mammalian animal predetermined to have a pathology associated with the RAC pathway.

30 DETAILED DESCRIPTION OF THE INVENTION

A genetic screen was designed to identify modifiers of the Rac signaling pathway that also affect cell migrations in *C. elegans*, where various specific genes were silenced by RNA inhibition (RNAi) in a *ced-10; mig-2* double mutant background. Modifiers were identified followed by identification of their orthologs. Accordingly, vertebrate orthologs

of these modifiers, and preferably the human orthologs, MRAC genes (i.e., nucleic acids and polypeptides) are attractive drug targets for the treatment of pathologies associated with a defective RAC signaling pathway, such as cancer. Table 1 (Example II) lists the modifiers and their orthologs.

5 In vitro and in vivo methods of assessing MRAC function are provided herein. Modulation of the MRAC or their respective binding partners is useful for understanding the association of the RAC pathway and its members in normal and disease conditions and for developing diagnostics and therapeutic modalities for RAC related pathologies. MRAC-modulating agents that act by inhibiting or enhancing MRAC expression, directly
10 or indirectly, for example, by affecting an MRAC function such as enzymatic (e.g., catalytic) or binding activity, can be identified using methods provided herein. MRAC modulating agents are useful in diagnosis, therapy and pharmaceutical development.

Nucleic acids and polypeptides of the invention

15 Sequences related to MRAC nucleic acids and polypeptides that can be used in the invention are disclosed in Genbank (referenced by Genbank identifier (GI) or RefSeq number), shown in Table 1 and in the appended sequence listing.

The term "MRAC polypeptide" refers to a full-length MRAC protein or a functionally active fragment or derivative thereof. A "functionally active" MRAC
20 fragment or derivative exhibits one or more functional activities associated with a full-length, wild-type MRAC protein, such as antigenic or immunogenic activity, enzymatic activity, ability to bind natural cellular substrates, etc. The functional activity of MRAC proteins, derivatives and fragments can be assayed by various methods known to one skilled in the art (Current Protocols in Protein Science (1998) Coligan *et al.*, eds., John
25 Wiley & Sons, Inc., Somerset, New Jersey) and as further discussed below. In one embodiment, a functionally active MRAC polypeptide is an MRAC derivative capable of rescuing defective endogenous MRAC activity, such as in cell based or animal assays; the rescuing derivative may be from the same or a different species. For purposes herein, functionally active fragments also include those fragments that comprise one or more
30 structural domains of an MRAC, such as a binding domain. Protein domains can be identified using the PFAM program (Bateman A., et al., Nucleic Acids Res, 1999, 27:260-2). Methods for obtaining MRAC polypeptides are also further described below. In some embodiments, preferred fragments are functionally active, domain-containing fragments comprising at least 25 contiguous amino acids, preferably at least 50, more preferably 75,

and most preferably at least 100 contiguous amino acids of an MRAC. In further preferred embodiments, the fragment comprises the entire functionally active domain.

The term "MRAC nucleic acid" refers to a DNA or RNA molecule that encodes an MRAC polypeptide. Preferably, the MRAC polypeptide or nucleic acid or fragment
5 thereof is from a human, but can also be an ortholog, or derivative thereof with at least 70% sequence identity, preferably at least 80%, more preferably 85%, still more preferably 90%, and most preferably at least 95% sequence identity with human MRAC. Methods of identifying orthologs are known in the art. Normally, orthologs in different species retain the same function, due to presence of one or more protein motifs and/or 3-
10 dimensional structures. Orthologs are generally identified by sequence homology analysis, such as BLAST analysis, usually using protein bait sequences. Sequences are assigned as a potential ortholog if the best hit sequence from the forward BLAST result retrieves the original query sequence in the reverse BLAST (Huynen MA and Bork P, Proc Natl Acad Sci (1998) 95:5849-5856; Huynen MA *et al.*, Genome Research (2000)
15 10:1204-1210). Programs for multiple sequence alignment, such as CLUSTAL (Thompson JD *et al.*, 1994, Nucleic Acids Res 22:4673-4680) may be used to highlight conserved regions and/or residues of orthologous proteins and to generate phylogenetic trees. In a phylogenetic tree representing multiple homologous sequences from diverse species (e.g., retrieved through BLAST analysis), orthologous sequences from two species
20 generally appear closest on the tree with respect to all other sequences from these two species. Structural threading or other analysis of protein folding (e.g., using software by ProCeryon, Biosciences, Salzburg, Austria) may also identify potential orthologs. In evolution, when a gene duplication event follows speciation, a single gene in one species, such as *C. elegans*, may correspond to multiple genes (paralogs) in another, such as
25 human. As used herein, the term "orthologs" encompasses paralogs. As used herein, "percent (%) sequence identity" with respect to a subject sequence, or a specified portion of a subject sequence, is defined as the percentage of nucleotides or amino acids in the candidate derivative sequence identical with the nucleotides or amino acids in the subject sequence (or specified portion thereof), after aligning the sequences and introducing gaps,
30 if necessary to achieve the maximum percent sequence identity, as generated by the program WU-BLAST-2.0a19 (Altschul *et al.*, J. Mol. Biol. (1997) 215:403-410) with all the search parameters set to default values. The HSP S and HSP S2 parameters are dynamic values and are established by the program itself depending upon the composition of the particular sequence and composition of the particular database against which the

sequence of interest is being searched. A % identity value is determined by the number of matching identical nucleotides or amino acids divided by the sequence length for which the percent identity is being reported. "Percent (%) amino acid sequence similarity" is determined by doing the same calculation as for determining % amino acid sequence identity, but including conservative amino acid substitutions in addition to identical amino acids in the computation.

A conservative amino acid substitution is one in which an amino acid is substituted for another amino acid having similar properties such that the folding or activity of the protein is not significantly affected. Aromatic amino acids that can be substituted for each other are phenylalanine, tryptophan, and tyrosine; interchangeable hydrophobic amino acids are leucine, isoleucine, methionine, and valine; interchangeable polar amino acids are glutamine and asparagine; interchangeable basic amino acids are arginine, lysine and histidine; interchangeable acidic amino acids are aspartic acid and glutamic acid; and interchangeable small amino acids are alanine, serine, threonine, cysteine and glycine.

Alternatively, an alignment for nucleic acid sequences is provided by the local homology algorithm of Smith and Waterman (Smith and Waterman, 1981, *Advances in Applied Mathematics* 2:482-489; database: European Bioinformatics Institute; Smith and Waterman, 1981, *J. of Molec.Biol.*, 147:195-197; Nicholas et al., 1998, "A Tutorial on Searching Sequence Databases and Sequence Scoring Methods" (www.psc.edu) and references cited therein.; W.R. Pearson, 1991, *Genomics* 11:635-650). This algorithm can be applied to amino acid sequences by using the scoring matrix developed by Dayhoff (Dayhoff: *Atlas of Protein Sequences and Structure*, M. O. Dayhoff ed., 5 suppl. 3:353-358, National Biomedical Research Foundation, Washington, D.C., USA), and normalized by Gribskov (Gribskov 1986 *Nucl. Acids Res.* 14(6):6745-6763). The Smith-Waterman algorithm may be employed where default parameters are used for scoring (for example, gap open penalty of 12, gap extension penalty of two). From the data generated, the "Match" value reflects "sequence identity."

Derivative nucleic acid molecules of the subject nucleic acid molecules include sequences that hybridize to the nucleic acid sequence of an MRAC. The stringency of hybridization can be controlled by temperature, ionic strength, pH, and the presence of denaturing agents such as formamide during hybridization and washing. Conditions routinely used are set out in readily available procedure texts (*e.g.*, *Current Protocol in Molecular Biology*, Vol. 1, Chap. 2.10, John Wiley & Sons, Publishers (1994); Sambrook *et al.*, *Molecular Cloning*, Cold Spring Harbor (1989)). In some embodiments, a nucleic

acid molecule of the invention is capable of hybridizing to a nucleic acid molecule containing the nucleotide sequence of an MRAC under high stringency hybridization conditions that are: prehybridization of filters containing nucleic acid for 8 hours to overnight at 65° C in a solution comprising 6X single strength citrate (SSC) (1X SSC is 0.15 M NaCl, 0.015 M Na citrate; pH 7.0), 5X Denhardt's solution, 0.05% sodium pyrophosphate and 100 µg/ml herring sperm DNA; hybridization for 18-20 hours at 65° C in a solution containing 6X SSC, 1X Denhardt's solution, 100 µg/ml yeast tRNA and 0.05% sodium pyrophosphate; and washing of filters at 65° C for 1h in a solution containing 0.1X SSC and 0.1% SDS (sodium dodecyl sulfate).

10 In other embodiments, moderately stringent hybridization conditions are used that are: pretreatment of filters containing nucleic acid for 6 h at 40° C in a solution containing 35% formamide, 5X SSC, 50 mM Tris-HCl (pH7.5), 5mM EDTA, 0.1% PVP, 0.1% Ficoll, 1% BSA, and 500 µg/ml denatured salmon sperm DNA; hybridization for 18-20h at 40° C in a solution containing 35% formamide, 5X SSC, 50 mM Tris-HCl (pH7.5), 5mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 µg/ml salmon sperm DNA, and 10% (wt/vol) dextran sulfate; followed by washing twice for 1 hour at 55° C in a solution containing 2X SSC and 0.1% SDS.

Alternatively, low stringency conditions can be used that are: incubation for 8 hours to overnight at 37° C in a solution comprising 20% formamide, 5 x SSC, 50 mM sodium phosphate (pH 7.6), 5X Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured sheared salmon sperm DNA; hybridization in the same buffer for 18 to 20 hours; and washing of filters in 1 x SSC at about 37° C for 1 hour.

Isolation, Production, Expression, and Mis-expression of MRAC Nucleic Acids and Polypeptides

MRAC nucleic acids and polypeptides are useful for identifying and testing agents that modulate MRAC function and for other applications related to the involvement of MRAC in the RAC pathway. MRAC nucleic acids and derivatives and orthologs thereof may be obtained using any available method. For instance, techniques for isolating cDNA or genomic DNA sequences of interest by screening DNA libraries or by using polymerase chain reaction (PCR) are well known in the art. In general, the particular use for the protein will dictate the particulars of expression, production, and purification methods. For instance, production of proteins for use in screening for modulating agents may require methods that preserve specific biological activities of these proteins, whereas

production of proteins for antibody generation may require structural integrity of particular epitopes. Expression of proteins to be purified for screening or antibody production may require the addition of specific tags (*e.g.*, generation of fusion proteins). Overexpression of an MRAC protein for assays used to assess MRAC function, such as involvement in

5 cell cycle regulation or hypoxic response, may require expression in eukaryotic cell lines capable of these cellular activities. Techniques for the expression, production, and purification of proteins are well known in the art; any suitable means therefore may be used (*e.g.*, Higgins SJ and Hames BD (eds.) *Protein Expression: A Practical Approach*, Oxford University Press Inc., New York 1999; Stanbury PF et al., *Principles of*

10 *Fermentation Technology*, 2nd edition, Elsevier Science, New York, 1995; Doonan S (ed.) *Protein Purification Protocols*, Humana Press, New Jersey, 1996; Coligan JE et al, *Current Protocols in Protein Science* (eds.), 1999, John Wiley & Sons, New York). In particular embodiments, recombinant MRAC is expressed in a cell line known to have defective RAC function. The recombinant cells are used in cell-based screening assay systems of

15 the invention, as described further below.

The nucleotide sequence encoding an MRAC polypeptide can be inserted into any appropriate expression vector. The necessary transcriptional and translational signals, including promoter/enhancer element, can derive from the native MRAC gene and/or its flanking regions or can be heterologous. A variety of host-vector expression systems may

20 be utilized, such as mammalian cell systems infected with virus (*e.g.* vaccinia virus, adenovirus, *etc.*); insect cell systems infected with virus (*e.g.* baculovirus); microorganisms such as yeast containing yeast vectors, or bacteria transformed with bacteriophage, plasmid, or cosmid DNA. An isolated host cell strain that modulates the expression of, modifies, and/or specifically processes the gene product may be used.

25 To detect expression of the MRAC gene product, the expression vector can comprise a promoter operably linked to an MRAC gene nucleic acid, one or more origins of replication, and, one or more selectable markers (*e.g.* thymidine kinase activity, resistance to antibiotics, *etc.*). Alternatively, recombinant expression vectors can be identified by assaying for the expression of the MRAC gene product based on the physical

30 or functional properties of the MRAC protein in *in vitro* assay systems (*e.g.* immunoassays).

The MRAC protein, fragment, or derivative may be optionally expressed as a fusion, or chimeric protein product (*i.e.* it is joined via a peptide bond to a heterologous protein sequence of a different protein), for example to facilitate purification or detection.

A chimeric product can be made by ligating the appropriate nucleic acid sequences encoding the desired amino acid sequences to each other using standard methods and expressing the chimeric product. A chimeric product may also be made by protein synthetic techniques, *e.g.* by use of a peptide synthesizer (Hunkapiller *et al.*, Nature (1984) 310:105-111).

Once a recombinant cell that expresses the MRAC gene sequence is identified, the gene product can be isolated and purified using standard methods (*e.g.* ion exchange, affinity, and gel exclusion chromatography; centrifugation; differential solubility; electrophoresis). Alternatively, native MRAC proteins can be purified from natural sources, by standard methods (*e.g.* immunoaffinity purification). Once a protein is obtained, it may be quantified and its activity measured by appropriate methods, such as immunoassay, bioassay, or other measurements of physical properties, such as crystallography.

The methods of this invention may also use cells that have been engineered for altered expression (mis-expression) of MRAC or other genes associated with the RAC pathway. As used herein, mis-expression encompasses ectopic expression, over-expression, under-expression, and non-expression (*e.g.* by gene knock-out or blocking expression that would otherwise normally occur).

Genetically modified animals

Animal models that have been genetically modified to alter MRAC expression may be used in *in vivo* assays to test for activity of a candidate RAC modulating agent, or to further assess the role of MRAC in a RAC pathway process such as apoptosis or cell proliferation. Preferably, the altered MRAC expression results in a detectable phenotype, such as decreased or increased levels of cell proliferation, angiogenesis, or apoptosis compared to control animals having normal MRAC expression. The genetically modified animal may additionally have altered RAC expression (*e.g.* RAC knockout). Preferred genetically modified animals are mammals such as primates, rodents (preferably mice or rats), among others. Preferred non-mammalian species include zebrafish, *C. elegans*, and *Drosophila*. Preferred genetically modified animals are transgenic animals having a heterologous nucleic acid sequence present as an extrachromosomal element in a portion of its cells, *i.e.* mosaic animals (see, for example, techniques described by Jakobovits, 1994, Curr. Biol. 4:761-763.) or stably integrated into its germ line DNA (*i.e.*, in the genomic sequence of most or all of its cells). Heterologous nucleic acid is introduced into

the germ line of such transgenic animals by genetic manipulation of, for example, embryos or embryonic stem cells of the host animal.

Methods of making transgenic animals are well-known in the art (for transgenic mice see Brinster *et al.*, Proc. Nat. Acad. Sci. USA 82: 4438-4442 (1985), U.S. Pat. Nos. 4,736,866 and 4,870,009, both by Leder *et al.*, U.S. Pat. No. 4,873,191 by Wagner *et al.*, and Hogan, B., Manipulating the Mouse Embryo, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., (1986); for particle bombardment see U.S. Pat. No., 4,945,050, by Sandford *et al.*; for transgenic *Drosophila* see Rubin and Spradling, Science (1982) 218:348-53 and U.S. Pat. No. 4,670,388; for transgenic insects see Berghammer A.J. *et al.*, A Universal Marker for Transgenic Insects (1999) Nature 402:370-371; for transgenic Zebrafish see Lin S., Transgenic Zebrafish, Methods Mol Biol. (2000);136:375-3830); for microinjection procedures for fish, amphibian eggs and birds see Houdebine and Chourrout, Experientia (1991) 47:897-905; for transgenic rats see Hammer *et al.*, Cell (1990) 63:1099-1112; and for culturing of embryonic stem (ES) cells and the subsequent production of transgenic animals by the introduction of DNA into ES cells using methods such as electroporation, calcium phosphate/DNA precipitation and direct injection see, e.g., Teratocarcinomas and Embryonic Stem Cells, A Practical Approach, E. J. Robertson, ed., IRL Press (1987)). Clones of the nonhuman transgenic animals can be produced according to available methods (see Wilmut, I. *et al.* (1997) Nature 385:810-813; and PCT International Publication Nos. WO 97/07668 and WO 97/07669).

In one embodiment, the transgenic animal is a "knock-out" animal having a heterozygous or homozygous alteration in the sequence of an endogenous MRAC gene that results in a decrease of MRAC function, preferably such that MRAC expression is undetectable or insignificant. Knock-out animals are typically generated by homologous recombination with a vector comprising a transgene having at least a portion of the gene to be knocked out. Typically a deletion, addition or substitution has been introduced into the transgene to functionally disrupt it. The transgene can be a human gene (e.g., from a human genomic clone) but more preferably is an ortholog of the human gene derived from the transgenic host species. For example, a mouse MRAC gene is used to construct a homologous recombination vector suitable for altering an endogenous MRAC gene in the mouse genome. Detailed methodologies for homologous recombination in mice are available (see Capecchi, Science (1989) 244:1288-1292; Joyner *et al.*, Nature (1989) 338:153-156). Procedures for the production of non-rodent transgenic mammals and other animals are also available (Houdebine and Chourrout, *supra*; Pursel *et al.*, Science (1989)

244:1281-1288; Simms *et al.*, Bio/Technology (1988) 6:179-183). In a preferred embodiment, knock-out animals, such as mice harboring a knockout of a specific gene, may be used to produce antibodies against the human counterpart of the gene that has been knocked out (Claesson MH *et al.*, (1994) Scan J Immunol 40:257-264; Declerck PJ *et al.*, (1995) J Biol Chem. 270:8397-400).

In another embodiment, the transgenic animal is a "knock-in" animal having an alteration in its genome that results in altered expression (e.g., increased (including ectopic) or decreased expression) of the MRAC gene, e.g., by introduction of additional copies of MRAC, or by operatively inserting a regulatory sequence that provides for altered expression of an endogenous copy of the MRAC gene. Such regulatory sequences include inducible, tissue-specific, and constitutive promoters and enhancer elements. The knock-in can be homozygous or heterozygous.

Transgenic nonhuman animals can also be produced that contain selected systems allowing for regulated expression of the transgene. One example of such a system that may be produced is the cre/loxP recombinase system of bacteriophage P1 (Lakso *et al.*, PNAS (1992) 89:6232-6236; U.S. Pat. No. 4,959,317). If a cre/loxP recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the Cre recombinase and a selected protein are required. Such animals can be provided through the construction of "double" transgenic animals, e.g., by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase. Another example of a recombinase system is the FLP recombinase system of *Saccharomyces cerevisiae* (O'Gorman *et al.* (1991) Science 251:1351-1355; U.S. Pat. No. 5,654,182). In a preferred embodiment, both Cre-LoxP and Flp-Frt are used in the same system to regulate expression of the transgene, and for sequential deletion of vector sequences in the same cell (Sun X *et al* (2000) Nat Genet 25:83-6).

The genetically modified animals can be used in genetic studies to further elucidate the RAC pathway, as animal models of disease and disorders implicating defective RAC function, and for *in vivo* testing of candidate therapeutic agents, such as those identified in screens described below. The candidate therapeutic agents are administered to a genetically modified animal having altered MRAC function and phenotypic changes are compared with appropriate control animals such as genetically modified animals that receive placebo treatment, and/or animals with unaltered MRAC expression that receive candidate therapeutic agent.

In addition to the above-described genetically modified animals having altered MRAC function, animal models having defective RAC function (and otherwise normal MRAC function), can be used in the methods of the present invention. For example, a RAC knockout mouse can be used to assess, *in vivo*, the activity of a candidate RAC modulating agent identified in one of the *in vitro* assays described below. Preferably, the candidate RAC modulating agent when administered to a model system with cells defective in RAC function, produces a detectable phenotypic change in the model system indicating that the RAC function is restored, i.e., the cells exhibit normal cell cycle progression.

Modulating Agents

The invention provides methods to identify agents that interact with and/or modulate the function of MRAC and/or the RAC pathway. Modulating agents identified by the methods are also part of the invention. Such agents are useful in a variety of diagnostic and therapeutic applications associated with the RAC pathway, as well as in further analysis of the MRAC protein and its contribution to the RAC pathway. Accordingly, the invention also provides methods for modulating the RAC pathway comprising the step of specifically modulating MRAC activity by administering an MRAC-interacting or -modulating agent.

As used herein, an "MRAC-modulating agent" is any agent that modulates MRAC function, for example, an agent that interacts with MRAC to inhibit or enhance MRAC activity or otherwise affect normal MRAC function. MRAC function can be affected at any level, including transcription, protein expression, protein localization, and cellular or extra-cellular activity. In a preferred embodiment, the MRAC - modulating agent specifically modulates the function of the MRAC. The phrases "specific modulating agent", "specifically modulates", etc., are used herein to refer to modulating agents that directly bind to the MRAC polypeptide or nucleic acid, and preferably inhibit, enhance, or otherwise alter, the function of the MRAC. These phrases also encompass modulating agents that alter the interaction of the MRAC with a binding partner, substrate, or cofactor (e.g. by binding to a binding partner of an MRAC, or to a protein/binding partner complex, and altering MRAC function). In a further preferred embodiment, the MRAC- modulating agent is a modulator of the RAC pathway (e.g. it restores and/or upregulates RAC function) and thus is also a RAC-modulating agent.

Preferred MRAC-modulating agents include small molecule compounds; MRAC-interacting proteins, including antibodies and other biotherapeutics; and nucleic acid modulators such as antisense and RNA inhibitors. The modulating agents may be formulated in pharmaceutical compositions, for example, as compositions that may
5 comprise other active ingredients, as in combination therapy, and/or suitable carriers or excipients. Techniques for formulation and administration of the compounds may be found in "Remington's Pharmaceutical Sciences" Mack Publishing Co., Easton, PA, 19th edition.

10 **Small molecule modulators**

Small molecules are often preferred to modulate function of proteins with enzymatic function, and/or containing protein interaction domains. Chemical agents, referred to in the art as "small molecule" compounds are typically organic, non-peptide molecules, having a molecular weight up to 10,000, preferably up to 5,000, more
15 preferably up to 1,000, and most preferably up to 500 daltons. This class of modulators includes chemically synthesized molecules, for instance, compounds from combinatorial chemical libraries. Synthetic compounds may be rationally designed or identified based on known or inferred properties of the MRAC protein or may be identified by screening compound libraries. Alternative appropriate modulators of this class are natural products,
20 particularly secondary metabolites from organisms such as plants or fungi, which can also be identified by screening compound libraries for MRAC-modulating activity. Methods for generating and obtaining compounds are well known in the art (Schreiber SL, Science (2000) 151: 1964-1969; Radmann J and Gunther J, Science (2000) 151:1947-1948).

Small molecule modulators identified from screening assays, as described below,
25 can be used as lead compounds from which candidate clinical compounds may be designed, optimized, and synthesized. Such clinical compounds may have utility in treating pathologies associated with the RAC pathway. The activity of candidate small molecule modulating agents may be improved several-fold through iterative secondary functional validation, as further described below, structure determination, and candidate
30 modulator modification and testing. Additionally, candidate clinical compounds are generated with specific regard to clinical and pharmacological properties. For example, the reagents may be derivatized and re-screened using *in vitro* and *in vivo* assays to optimize activity and minimize toxicity for pharmaceutical development.

Protein Modulators

Specific MRAC-interacting proteins are useful in a variety of diagnostic and therapeutic applications related to the RAC pathway and related disorders, as well as in validation assays for other MRAC-modulating agents. In a preferred embodiment,

5 MRAC-interacting proteins affect normal MRAC function, including transcription, protein expression, protein localization, and cellular or extra-cellular activity. In another embodiment, MRAC-interacting proteins are useful in detecting and providing information about the function of MRAC proteins, as is relevant to RAC related disorders, such as cancer (e.g., for diagnostic means).

10 An MRAC-interacting protein may be endogenous, i.e. one that naturally interacts genetically or biochemically with an MRAC, such as a member of the MRAC pathway that modulates MRAC expression, localization, and/or activity. MRAC-modulators include dominant negative forms of MRAC-interacting proteins and of MRAC proteins themselves. Yeast two-hybrid and variant screens offer preferred methods for identifying
15 endogenous MRAC-interacting proteins (Finley, R. L. et al. (1996) in DNA Cloning-Expression Systems: A Practical Approach, eds. Glover D. & Hames B. D (Oxford University Press, Oxford, England), pp. 169-203; Fashema SF et al., Gene (2000) 250:1-14; Drees BL Curr Opin Chem Biol (1999) 3:64-70; Vidal M and Legrain P Nucleic Acids Res (1999) 27:919-29; and U.S. Pat. No. 5,928,868). Mass spectrometry is an alternative
20 preferred method for the elucidation of protein complexes (reviewed in, e.g., Pandley A and Mann M, Nature (2000) 405:837-846; Yates JR 3rd, Trends Genet (2000) 16:5-8).

An MRAC-interacting protein may be an exogenous protein, such as an MRAC-specific antibody or a T-cell antigen receptor (see, e.g., Harlow and Lane (1988) Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory; Harlow and Lane
25 (1999) Using antibodies: a laboratory manual. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press). MRAC antibodies are further discussed below.

In preferred embodiments, an MRAC-interacting protein specifically binds an MRAC protein. In alternative preferred embodiments, an MRAC-modulating agent binds an MRAC substrate, binding partner, or cofactor.

30

Antibodies

In another embodiment, the protein modulator is an MRAC specific antibody agonist or antagonist. The antibodies have therapeutic and diagnostic utilities, and can be used in screening assays to identify MRAC modulators. The antibodies can also be used

in dissecting the portions of the MRAC pathway responsible for various cellular responses and in the general processing and maturation of the MRAC.

Antibodies that specifically bind MRAC polypeptides can be generated using known methods. Preferably the antibody is specific to a mammalian ortholog of MRAC polypeptide, and more preferably, to human MRAC. Antibodies may be polyclonal, 5 monoclonal (mAbs), humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab')₂ fragments, fragments produced by a FAb expression library, anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above. Epitopes of MRAC which are particularly antigenic can be selected, for example, by 10 routine screening of MRAC polypeptides for antigenicity or by applying a theoretical method for selecting antigenic regions of a protein (Hopp and Wood (1981), Proc. Natl. Acad. Sci. U.S.A. 78:3824-28; Hopp and Wood, (1983) Mol. Immunol. 20:483-89; Sutcliffe et al., (1983) Science 219:660-66) to the amino acid sequence of an MRAC. Monoclonal antibodies with affinities of 10^8 M^{-1} preferably 10^9 M^{-1} to 10^{10} M^{-1} , or 15 stronger can be made by standard procedures as described (Harlow and Lane, *supra*; Goding (1986) Monoclonal Antibodies: Principles and Practice (2d ed) Academic Press, New York; and U.S. Pat. Nos. 4,381,292; 4,451,570; and 4,618,577). Antibodies may be generated against crude cell extracts of MRAC or substantially purified fragments thereof. If MRAC fragments are used, they preferably comprise at least 10, and more preferably, at 20 least 20 contiguous amino acids of an MRAC protein. In a particular embodiment, MRAC-specific antigens and/or immunogens are coupled to carrier proteins that stimulate the immune response. For example, the subject polypeptides are covalently coupled to the keyhole limpet hemocyanin (KLH) carrier, and the conjugate is emulsified in Freund's complete adjuvant, which enhances the immune response. An appropriate immune system 25 such as a laboratory rabbit or mouse is immunized according to conventional protocols.

The presence of MRAC-specific antibodies is assayed by an appropriate assay such as a solid phase enzyme-linked immunosorbant assay (ELISA) using immobilized corresponding MRAC polypeptides. Other assays, such as radioimmunoassays or fluorescent assays might also be used.

30 Chimeric antibodies specific to MRAC polypeptides can be made that contain different portions from different animal species. For instance, a human immunoglobulin constant region may be linked to a variable region of a murine mAb, such that the antibody derives its biological activity from the human antibody, and its binding specificity from the murine fragment. Chimeric antibodies are produced by splicing

together genes that encode the appropriate regions from each species (Morrison et al., Proc. Natl. Acad. Sci. (1984) 81:6851-6855; Neuberger et al., Nature (1984) 312:604-608; Takeda et al., Nature (1985) 31:452-454). Humanized antibodies, which are a form of chimeric antibodies, can be generated by grafting complementary-determining regions (CDRs) (Carlos, T. M., J. M. Harlan. 1994. Blood 84:2068-2101) of mouse antibodies into a background of human framework regions and constant regions by recombinant DNA technology (Riechmann LM, et al., 1988 Nature 323: 323-327). Humanized antibodies contain ~10% murine sequences and ~90% human sequences, and thus further reduce or eliminate immunogenicity, while retaining the antibody specificities (Co MS, and Queen C. 1991 Nature 351: 501-501; Morrison SL. 1992 Ann. Rev. Immun. 10:239-265). Humanized antibodies and methods of their production are well-known in the art (U.S. Pat. Nos. 5,530,101, 5,585,089, 5,693,762, and 6,180,370).

MRAC-specific single chain antibodies which are recombinant, single chain polypeptides formed by linking the heavy and light chain fragments of the Fv regions via an amino acid bridge, can be produced by methods known in the art (U.S. Pat. No. 4,946,778; Bird, Science (1988) 242:423-426; Huston et al., Proc. Natl. Acad. Sci. USA (1988) 85:5879-5883; and Ward et al., Nature (1989) 334:544-546).

Other suitable techniques for antibody production involve in vitro exposure of lymphocytes to the antigenic polypeptides or alternatively to selection of libraries of antibodies in phage or similar vectors (Huse et al., Science (1989) 246:1275-1281). As used herein, T-cell antigen receptors are included within the scope of antibody modulators (Harlow and Lane, 1988, *supra*).

The polypeptides and antibodies of the present invention may be used with or without modification. Frequently, antibodies will be labeled by joining, either covalently or non-covalently, a substance that provides for a detectable signal, or that is toxic to cells that express the targeted protein (Menard S, et al., Int J. Biol Markers (1989) 4:131-134). A wide variety of labels and conjugation techniques are known and are reported extensively in both the scientific and patent literature. Suitable labels include radionuclides, enzymes, substrates, cofactors, inhibitors, fluorescent moieties, fluorescent emitting lanthanide metals, chemiluminescent moieties, bioluminescent moieties, magnetic particles, and the like (U.S. Pat. Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; and 4,366,241). Also, recombinant immunoglobulins may be produced (U.S. Pat. No. 4,816,567). Antibodies to cytoplasmic polypeptides may

be delivered and reach their targets by conjugation with membrane-penetrating toxin proteins (U.S. Pat. No. 6,086,900).

When used therapeutically in a patient, the antibodies of the subject invention are typically administered parenterally, when possible at the target site, or intravenously. The therapeutically effective dose and dosage regimen is determined by clinical studies. Typically, the amount of antibody administered is in the range of about 0.1 mg/kg –to about 10 mg/kg of patient weight. For parenteral administration, the antibodies are formulated in a unit dosage injectable form (e.g., solution, suspension, emulsion) in association with a pharmaceutically acceptable vehicle. Such vehicles are inherently nontoxic and non-therapeutic. Examples are water, saline, Ringer's solution, dextrose solution, and 5% human serum albumin. Nonaqueous vehicles such as fixed oils, ethyl oleate, or liposome carriers may also be used. The vehicle may contain minor amounts of additives, such as buffers and preservatives, which enhance isotonicity and chemical stability or otherwise enhance therapeutic potential. The antibodies' concentrations in such vehicles are typically in the range of about 1 mg/ml to about 10 mg/ml. Immunotherapeutic methods are further described in the literature (US Pat. No. 5,859,206; WO0073469).

Specific biotherapeutics

In a preferred embodiment, an MRAC-interacting protein may have biotherapeutic applications. Biotherapeutic agents formulated in pharmaceutically acceptable carriers and dosages may be used to activate or inhibit signal transduction pathways. This modulation may be accomplished by binding a ligand, thus inhibiting the activity of the pathway; or by binding a receptor, either to inhibit activation of, or to activate, the receptor. Alternatively, the biotherapeutic may itself be a ligand capable of activating or inhibiting a receptor. Biotherapeutic agents and methods of producing them are described in detail in U.S. Pat. No. 6,146,628.

When the MRAC is a ligand, it may be used as a biotherapeutic agent to activate or inhibit its natural receptor. Alternatively, antibodies against MRAC, as described in the previous section, may be used as biotherapeutic agents.

When the MRAC is a receptor, its ligand(s), antibodies to the ligand(s) or the MRAC itself may be used as biotherapeutics to modulate the activity of MRAC in the RAC pathway.

Nucleic Acid Modulators

Other preferred MRAC-modulating agents comprise nucleic acid molecules, such as antisense oligomers or double stranded RNA (dsRNA), which generally inhibit MRAC activity. Preferred nucleic acid modulators interfere with the function of the MRAC nucleic acid such as DNA replication, transcription, translocation of the MRAC RNA to the site of protein translation, translation of protein from the MRAC RNA, splicing of the MRAC RNA to yield one or more mRNA species, or catalytic activity which may be engaged in or facilitated by the MRAC RNA.

In one embodiment, the antisense oligomer is an oligonucleotide that is sufficiently complementary to an MRAC mRNA to bind to and prevent translation, preferably by binding to the 5' untranslated region. MRAC-specific antisense oligonucleotides, preferably range from at least 6 to about 200 nucleotides. In some embodiments the oligonucleotide is preferably at least 10, 15, or 20 nucleotides in length. In other embodiments, the oligonucleotide is preferably less than 50, 40, or 30 nucleotides in length. The oligonucleotide can be DNA or RNA or a chimeric mixture or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone. The oligonucleotide may include other appending groups such as peptides, agents that facilitate transport across the cell membrane, hybridization-triggered cleavage agents, and intercalating agents.

In another embodiment, the antisense oligomer is a phosphothioate morpholino oligomer (PMO). PMOs are assembled from four different morpholino subunits, each of which contain one of four genetic bases (A, C, G, or T) linked to a six-membered morpholine ring. Polymers of these subunits are joined by non-ionic phosphodiamidate intersubunit linkages. Details of how to make and use PMOs and other antisense oligomers are well known in the art (e.g. see WO99/18193; Probst JC, Antisense Oligodeoxynucleotide and Ribozyme Design, Methods. (2000) 22(3):271-281; Summerton J, and Weller D. 1997 Antisense Nucleic Acid Drug Dev. :7:187-95; US Pat. No. 5,235,033; and US Pat No. 5,378,841).

Alternative preferred MRAC nucleic acid modulators are double-stranded RNA species mediating RNA interference (RNAi). RNAi is the process of sequence-specific, post-transcriptional gene silencing in animals and plants, initiated by double-stranded RNA (dsRNA) that is homologous in sequence to the silenced gene. Methods relating to the use of RNAi to silence genes in *C. elegans*, *Drosophila*, plants, and humans are known

in the art (Fire A, et al., 1998 Nature 391:806-811; Fire, A. Trends Genet. 15, 358-363 (1999); Sharp, P. A. RNA interference 2001. Genes Dev. 15, 485-490 (2001); Hammond, S. M., et al., Nature Rev. Genet. 2, 110-1119 (2001); Tuschl, T. Chem. Biochem. 2, 239-245 (2001); Hamilton, A. et al., Science 286, 950-952 (1999); Hammond, S. M., et al.,
5 Nature 404, 293-296 (2000); Zamore, P. D., et al., Cell 101, 25-33 (2000); Bernstein, E., et al., Nature 409, 363-366 (2001); Elbashir, S. M., et al., Genes Dev. 15, 188-200 (2001); WO0129058; WO9932619; Elbashir SM, et al., 2001 Nature 411:494-498).

Nucleic acid modulators are commonly used as research reagents, diagnostics, and therapeutics. For example, antisense oligonucleotides, which are able to inhibit gene
10 expression with exquisite specificity, are often used to elucidate the function of particular genes (see, for example, U.S. Pat. No. 6,165,790). Nucleic acid modulators are also used, for example, to distinguish between functions of various members of a biological pathway. For example, antisense oligomers have been employed as therapeutic moieties in the treatment of disease states in animals and man and have been demonstrated in numerous
15 clinical trials to be safe and effective (Milligan JF, *et al*, Current Concepts in Antisense Drug Design, J Med Chem. (1993) 36:1923-1937; Tonkinson JL *et al.*, Antisense Oligodeoxynucleotides as Clinical Therapeutic Agents, Cancer Invest. (1996) 14:54-65). Accordingly, in one aspect of the invention, an MRAC-specific nucleic acid modulator is used in an assay to further elucidate the role of the MRAC in the RAC pathway, and/or its
20 relationship to other members of the pathway. In another aspect of the invention, an MRAC-specific antisense oligomer is used as a therapeutic agent for treatment of RAC-related disease states.

Assay Systems

25 The invention provides assay systems and screening methods for identifying specific modulators of MRAC activity. As used herein, an "assay system" encompasses all the components required for performing and analyzing results of an assay that detects and/or measures a particular event. In general, primary assays are used to identify or confirm a modulator's specific biochemical or molecular effect with respect to the MRAC
30 nucleic acid or protein. In general, secondary assays further assess the activity of an MRAC modulating agent identified by a primary assay and may confirm that the modulating agent affects MRAC in a manner relevant to the RAC pathway. In some cases, MRAC modulators will be directly tested in a secondary assay.

In a preferred embodiment, the screening method comprises contacting a suitable assay system comprising an MRAC polypeptide or nucleic acid with a candidate agent under conditions whereby, but for the presence of the agent, the system provides a reference activity (e.g. binding activity), which is based on the particular molecular event the screening method detects. A statistically significant difference between the agent-biased activity and the reference activity indicates that the candidate agent modulates MRAC activity, and hence the RAC pathway. The MRAC polypeptide or nucleic acid used in the assay may comprise any of the nucleic acids or polypeptides described above.

Primary Assays

The type of modulator tested generally determines the type of primary assay.

Primary assays for small molecule modulators

For small molecule modulators, screening assays are used to identify candidate modulators. Screening assays may be cell-based or may use a cell-free system that recreates or retains the relevant biochemical reaction of the target protein (reviewed in Sittampalam GS *et al.*, Curr Opin Chem Biol (1997) 1:384-91 and accompanying references). As used herein the term "cell-based" refers to assays using live cells, dead cells, or a particular cellular fraction, such as a membrane, endoplasmic reticulum, or mitochondrial fraction. The term "cell free" encompasses assays using substantially purified protein (either endogenous or recombinantly produced), partially purified or crude cellular extracts. Screening assays may detect a variety of molecular events, including protein-DNA interactions, protein-protein interactions (e.g., receptor-ligand binding), transcriptional activity (e.g., using a reporter gene), enzymatic activity (e.g., via a property of the substrate), activity of second messengers, immunogenicity and changes in cellular morphology or other cellular characteristics. Appropriate screening assays may use a wide range of detection methods including fluorescent, radioactive, colorimetric, spectrophotometric, and amperometric methods, to provide a read-out for the particular molecular event detected.

Cell-based screening assays usually require systems for recombinant expression of MRAC and any auxiliary proteins demanded by the particular assay. Appropriate methods for generating recombinant proteins produce sufficient quantities of proteins that retain their relevant biological activities and are of sufficient purity to optimize activity and assure assay reproducibility. Yeast two-hybrid and variant screens, and mass spectrometry

provide preferred methods for determining protein-protein interactions and elucidation of protein complexes. In certain applications, when MRAC-interacting proteins are used in screens to identify small molecule modulators, the binding specificity of the interacting protein to the MRAC protein may be assayed by various known methods such as substrate processing (e.g. ability of the candidate MRAC-specific binding agents to function as negative effectors in MRAC-expressing cells), binding equilibrium constants (usually at least about 10^7 M^{-1} , preferably at least about 10^8 M^{-1} , more preferably at least about 10^9 M^{-1}), and immunogenicity (e.g. ability to elicit MRAC specific antibody in a heterologous host such as a mouse, rat, goat or rabbit). For enzymes and receptors, binding may be assayed by, respectively, substrate and ligand processing.

The screening assay may measure a candidate agent's ability to specifically bind to or modulate activity of an MRAC polypeptide, a fusion protein thereof, or to cells or membranes bearing the polypeptide or fusion protein. The MRAC polypeptide can be full length or a fragment thereof that retains functional MRAC activity. The MRAC polypeptide may be fused to another polypeptide, such as a peptide tag for detection or anchoring, or to another tag. The MRAC polypeptide is preferably human MRAC, or is an ortholog or derivative thereof as described above. In a preferred embodiment, the screening assay detects candidate agent-based modulation of MRAC interaction with a binding target, such as an endogenous or exogenous protein or other substrate that has MRAC-specific binding activity, and can be used to assess normal MRAC gene function.

Suitable assay formats that may be adapted to screen for MRAC modulators are known in the art. Preferred screening assays are high throughput or ultra high throughput and thus provide automated, cost-effective means of screening compound libraries for lead compounds (Fernandes PB, Curr Opin Chem Biol (1998) 2:597-603; Sundberg SA, Curr Opin Biotechnol 2000, 11:47-53). In one preferred embodiment, screening assays uses fluorescence technologies, including fluorescence polarization, time-resolved fluorescence, and fluorescence resonance energy transfer. These systems offer means to monitor protein-protein or DNA-protein interactions in which the intensity of the signal emitted from dye-labeled molecules depends upon their interactions with partner molecules (e.g., Selvin PR, Nat Struct Biol (2000) 7:730-4; Fernandes PB, *supra*; Hertzberg RP and Pope AJ, Curr Opin Chem Biol (2000) 4:445-451).

A variety of suitable assay systems may be used to identify candidate MRAC and RAC pathway modulators (e.g. U.S. Pat. Nos. 5,550,019 and 6,133,437 (apoptosis assays);

and U.S. Pat. Nos. 5,976,782, 6,225,118 and 6,444,434 (angiogenesis assays), among others). Specific preferred assays are described in more detail below.

5 G-protein-coupled receptors (GPCRs) comprise a large family of cell surface receptors that mediate a diverse array of biological functions. They selectively respond to a wide variety of extracellular chemical stimuli to activate specific signaling cascades. Assays may measure reporter gene activity or changes in intracellular calcium ions, or other second messengers (Durocher Y *et al.*, Anal Biochem (2000) 284: 316-326; Miller TR *et al.*, J Biomol Screen (1999) 4:249-258). Such assays may utilize chimeric G α proteins that will couple to many different GPCRs and thus facilitate "universal" screening
10 assays (Coward P *et al.*, Anal Biochem (1999) 270:242-248; Milligan G and Rees S *et al.*, Trends Pharmacol Sci (1999) 20:118-124).

GPCRs exert their effects through heterotrimeric G proteins, which cycle between active GTP- and inactive GDP-bound forms. Receptors catalyze the activation of G proteins by promoting exchange of GDP for GTP, while G proteins catalyze their own
15 deactivation through their intrinsic GTPase activity. GEFs accelerate GDP dissociation and GTP binding, while GAPs stimulate GTP hydrolysis to GDP. The same assays used to monitor GPCR activity may thus be applied to monitor the activity of GEFs or GAPs. Alternatively, GEF activity may be assayed by the release of labeled GDP from the appropriate GTPase or by the uptake of labelled GTP. GAP activity may be monitored via
20 a GTP hydrolysis assay using labeled GTP (*e.g.*, Jones S *et al.*, Molec Biol Cell (1998) 9:2819-2837).

Transporter proteins carry a range of substrates, including nutrients, ions, amino acids, and drugs, across cell membranes. Assays for modulators of transporters may use labeled substrates. For instance, exemplary high throughput screens to identify
25 compounds that interact with different peptide and anion transporters both use fluorescently labeled substrates; the assay for peptide transport additionally uses multiscreeen filtration plates (Blevitt JM *et al.*, J Biomol Screen 1999, 4:87-91; Cihlar T and Ho ES, Anal Biochem 2000, 283:49-55).

30 **Apoptosis assays.** Assays for apoptosis may be performed by terminal deoxynucleotidyl transferase-mediated digoxigenin-11-dUTP nick end labeling (TUNEL) assay. The TUNEL assay is used to measure nuclear DNA fragmentation characteristic of apoptosis (Lazebnik *et al.*, 1994, Nature 371, 346), by following the incorporation of fluorescein-dUTP (Yonehara *et al.*, 1989, J. Exp. Med. 169, 1747). Apoptosis may further

be assayed by acridine orange staining of tissue culture cells (Lucas, R., et al., 1998, Blood 15:4730-41). Other cell-based apoptosis assays include the caspase-3/7 assay and the cell death nucleosome ELISA assay. The caspase 3/7 assay is based on the activation of the caspase cleavage activity as part of a cascade of events that occur during programmed cell death in many apoptotic pathways. In the caspase 3/7 assay (commercially available Apo-ONE™ Homogeneous Caspase-3/7 assay from Promega, cat# 67790), lysis buffer and caspase substrate are mixed and added to cells. The caspase substrate becomes fluorescent when cleaved by active caspase 3/7. The nucleosome ELISA assay is a general cell death assay known to those skilled in the art, and available commercially (Roche, Cat# 1774425). This assay is a quantitative sandwich-enzyme-immunoassay which uses monoclonal antibodies directed against DNA and histones respectively, thus specifically determining amount of mono- and oligonucleosomes in the cytoplasmic fraction of cell lysates. Mono and oligonucleosomes are enriched in the cytoplasm during apoptosis due to the fact that DNA fragmentation occurs several hours before the plasma membrane breaks down, allowing for accumulation in the cytoplasm. Nucleosomes are not present in the cytoplasmic fraction of cells that are not undergoing apoptosis. An apoptosis assay system may comprise a cell that expresses an MRAC, and that optionally has defective RAC function (e.g. RAC is over-expressed or under-expressed relative to wild-type cells). A test agent can be added to the apoptosis assay system and changes in induction of apoptosis relative to controls where no test agent is added, identify candidate RAC modulating agents. In some embodiments of the invention, an apoptosis assay may be used as a secondary assay to test a candidate RAC modulating agents that is initially identified using a cell-free assay system. An apoptosis assay may also be used to test whether MRAC function plays a direct role in apoptosis. For example, an apoptosis assay may be performed on cells that over- or under-express MRAC relative to wild type cells. Differences in apoptotic response compared to wild type cells suggests that the MRAC plays a direct role in the apoptotic response. Apoptosis assays are described further in US Pat. No. 6,133,437.

Cell proliferation and cell cycle assays. Cell proliferation may be assayed via bromodeoxyuridine (BRDU) incorporation. This assay identifies a cell population undergoing DNA synthesis by incorporation of BRDU into newly-synthesized DNA. Newly-synthesized DNA may then be detected using an anti-BRDU antibody (Hoshino *et*

al., 1986, Int. J. Cancer 38, 369; Campana *et al.*, 1988, J. Immunol. Meth. 107, 79), or by other means.

Cell proliferation is also assayed via phospho-histone H3 staining, which identifies a cell population undergoing mitosis by phosphorylation of histone H3. Phosphorylation of histone H3 at serine 10 is detected using an antibody specific to the phosphorylated form of the serine 10 residue of histone H3. (Chadlee, D.N. 1995, J. Biol. Chem 270:20098-105). Cell Proliferation may also be examined using [³H]-thymidine incorporation (Chen, J., 1996, Oncogene 13:1395-403; Jeoung, J., 1995, J. Biol. Chem. 270:18367-73). This assay allows for quantitative characterization of S-phase DNA syntheses. In this assay, cells synthesizing DNA will incorporate [³H]-thymidine into newly synthesized DNA. Incorporation can then be measured by standard techniques such as by counting of radioisotope in a scintillation counter (e.g., Beckman LS 3800 Liquid Scintillation Counter). Another proliferation assay uses the dye Alamar Blue (available from Biosource International), which fluoresces when reduced in living cells and provides an indirect measurement of cell number (Voytik-Harbin SL et al., 1998, In Vitro Cell Dev Biol Anim 34:239-46). Yet another proliferation assay, the MTS assay, is based on in vitro cytotoxicity assessment of industrial chemicals, and uses the soluble tetrazolium salt, MTS. MTS assays are commercially available, for example, the Promega CellTiter 96[®] Aqueous Non-Radioactive Cell Proliferation Assay (Cat.# G5421).

Cell proliferation may also be assayed by colony formation in soft agar (Sambrook et al., Molecular Cloning, Cold Spring Harbor (1989)). For example, cells transformed with MRAC are seeded in soft agar plates, and colonies are measured and counted after two weeks incubation.

Cell proliferation may also be assayed by measuring ATP levels as indicator of metabolically active cells. Such assays are commercially available, for example Cell Titer-Glo[™], which is a luminescent homogeneous assay available from Promega.

Involvement of a gene in the cell cycle may be assayed by flow cytometry (Gray JW et al. (1986) Int J Radiat Biol Relat Stud Phys Chem Med 49:237-55). Cells transfected with an MRAC may be stained with propidium iodide and evaluated in a flow cytometer (available from Becton Dickinson), which indicates accumulation of cells in different stages of the cell cycle.

Accordingly, a cell proliferation or cell cycle assay system may comprise a cell that expresses an MRAC, and that optionally has defective RAC function (e.g. RAC is over-expressed or under-expressed relative to wild-type cells). A test agent can be added

to the assay system and changes in cell proliferation or cell cycle relative to controls where no test agent is added, identify candidate RAC modulating agents. In some embodiments of the invention, the cell proliferation or cell cycle assay may be used as a secondary assay to test a candidate RAC modulating agents that is initially identified using another assay system such as a cell-free assay system. A cell proliferation assay may also be used to test whether MRAC function plays a direct role in cell proliferation or cell cycle. For example, a cell proliferation or cell cycle assay may be performed on cells that over- or under-express MRAC relative to wild type cells. Differences in proliferation or cell cycle compared to wild type cells suggests that the MRAC plays a direct role in cell proliferation or cell cycle.

Angiogenesis. Angiogenesis may be assayed using various human endothelial cell systems, such as umbilical vein, coronary artery, or dermal cells. Suitable assays include Alamar Blue based assays (available from Biosource International) to measure proliferation; migration assays using fluorescent molecules, such as the use of Becton Dickinson Falcon HTS FluoroBlock cell culture inserts to measure migration of cells through membranes in presence or absence of angiogenesis enhancer or suppressors; and tubule formation assays based on the formation of tubular structures by endothelial cells on Matrigel® (Becton Dickinson). Accordingly, an angiogenesis assay system may comprise a cell that expresses an MRAC, and that optionally has defective RAC function (e.g. RAC is over-expressed or under-expressed relative to wild-type cells). A test agent can be added to the angiogenesis assay system and changes in angiogenesis relative to controls where no test agent is added, identify candidate RAC modulating agents. In some embodiments of the invention, the angiogenesis assay may be used as a secondary assay to test a candidate RAC modulating agents that is initially identified using another assay system. An angiogenesis assay may also be used to test whether MRAC function plays a direct role in cell proliferation. For example, an angiogenesis assay may be performed on cells that over- or under-express MRAC relative to wild type cells. Differences in angiogenesis compared to wild type cells suggests that the MRAC plays a direct role in angiogenesis. U.S. Pat. Nos. 5,976,782, 6,225,118 and 6,444,434, among others, describe various angiogenesis assays.

Hypoxic induction. The alpha subunit of the transcription factor, hypoxia inducible factor-1 (HIF-1), is upregulated in tumor cells following exposure to hypoxia in

vitro. Under hypoxic conditions, HIF-1 stimulates the expression of genes known to be important in tumour cell survival, such as those encoding glycolytic enzymes and VEGF. Induction of such genes by hypoxic conditions may be assayed by growing cells transfected with MRAC in hypoxic conditions (such as with 0.1% O₂, 5% CO₂, and balance N₂, generated in a Napco 7001 incubator (Precision Scientific)) and normoxic conditions, followed by assessment of gene activity or expression by Taqman®. For example, a hypoxic induction assay system may comprise a cell that expresses an MRAC, and that optionally has defective RAC function (e.g. RAC is over-expressed or under-expressed relative to wild-type cells). A test agent can be added to the hypoxic induction assay system and changes in hypoxic response relative to controls where no test agent is added, identify candidate RAC modulating agents. In some embodiments of the invention, the hypoxic induction assay may be used as a secondary assay to test a candidate RAC modulating agents that is initially identified using another assay system. A hypoxic induction assay may also be used to test whether MRAC function plays a direct role in the hypoxic response. For example, a hypoxic induction assay may be performed on cells that over- or under-express MRAC relative to wild type cells. Differences in hypoxic response compared to wild type cells suggests that the MRAC plays a direct role in hypoxic induction.

Cell adhesion. Cell adhesion assays measure adhesion of cells to purified adhesion proteins, or adhesion of cells to each other, in presence or absence of candidate modulating agents. Cell-protein adhesion assays measure the ability of agents to modulate the adhesion of cells to purified proteins. For example, recombinant proteins are produced, diluted to 2.5g/mL in PBS, and used to coat the wells of a microtiter plate. The wells used for negative control are not coated. Coated wells are then washed, blocked with 1% BSA, and washed again. Compounds are diluted to 2× final test concentration and added to the blocked, coated wells. Cells are then added to the wells, and the unbound cells are washed off. Retained cells are labeled directly on the plate by adding a membrane-permeable fluorescent dye, such as calcein-AM, and the signal is quantified in a fluorescent microplate reader.

Cell-cell adhesion assays measure the ability of agents to modulate binding of cell adhesion proteins with their native ligands. These assays use cells that naturally or recombinantly express the adhesion protein of choice. In an exemplary assay, cells expressing the cell adhesion protein are plated in wells of a multiwell plate. Cells

expressing the ligand are labeled with a membrane-permeable fluorescent dye, such as BCECF, and allowed to adhere to the monolayers in the presence of candidate agents. Unbound cells are washed off, and bound cells are detected using a fluorescence plate reader.

5 High-throughput cell adhesion assays have also been described. In one such assay, small molecule ligands and peptides are bound to the surface of microscope slides using a microarray spotter, intact cells are then contacted with the slides, and unbound cells are washed off. In this assay, not only the binding specificity of the peptides and modulators against cell lines are determined, but also the functional cell signaling of attached cells
10 using immunofluorescence techniques in situ on the microchip is measured (Falsey JR et al., Bioconjug Chem. 2001 May-Jun;12(3):346-53).

Tubulogenesis. Tubulogenesis assays monitor the ability of cultured cells, generally endothelial cells, to form tubular structures on a matrix substrate, which
15 generally simulates the environment of the extracellular matrix. Exemplary substrates include MatrigelTM (Becton Dickinson), an extract of basement membrane proteins containing laminin, collagen IV, and heparin sulfate proteoglycan, which is liquid at 4° C and forms a solid gel at 37° C. Other suitable matrices comprise extracellular components such as collagen, fibronectin, and/or fibrin. Cells are stimulated with a pro-angiogenic
20 stimulant, and their ability to form tubules is detected by imaging. Tubules can generally be detected after an overnight incubation with stimuli, but longer or shorter time frames may also be used. Tube formation assays are well known in the art (e.g., Jones MK et al., 1999, Nature Medicine 5:1418-1423). These assays have traditionally involved stimulation with serum or with the growth factors FGF or VEGF. Serum represents an
25 undefined source of growth factors. In a preferred embodiment, the assay is performed with cells cultured in serum free medium, in order to control which process or pathway a candidate agent modulates. Moreover, we have found that different target genes respond differently to stimulation with different pro-angiogenic agents, including inflammatory angiogenic factors such as TNF-alpha. Thus, in a further preferred embodiment, a
30 tubulogenesis assay system comprises testing an MRAC's response to a variety of factors, such as FGF, VEGF, phorbol myristate acetate (PMA), TNF-alpha, ephrin, etc.

Cell Migration. An invasion/migration assay (also called a migration assay) tests the ability of cells to overcome a physical barrier and to migrate towards pro-angiogenic

signals. Migration assays are known in the art (e.g., Paik JH et al., 2001, J Biol Chem 276:11830-11837). In a typical experimental set-up, cultured endothelial cells are seeded onto a matrix-coated porous lamina, with pore sizes generally smaller than typical cell size. The matrix generally simulates the environment of the extracellular matrix, as described above. The lamina is typically a membrane, such as the transwell polycarbonate membrane (Corning Costar Corporation, Cambridge, MA), and is generally part of an upper chamber that is in fluid contact with a lower chamber containing pro-angiogenic stimuli. Migration is generally assayed after an overnight incubation with stimuli, but longer or shorter time frames may also be used. Migration is assessed as the number of cells that crossed the lamina, and may be detected by staining cells with hemotoxylin solution (VWR Scientific, South San Francisco, CA), or by any other method for determining cell number. In another exemplary set up, cells are fluorescently labeled and migration is detected using fluorescent readings, for instance using the Falcon HTS FluoroBlok (Becton Dickinson). While some migration is observed in the absence of stimulus, migration is greatly increased in response to pro-angiogenic factors. As described above, a preferred assay system for migration/invasion assays comprises testing an MRAC's response to a variety of pro-angiogenic factors, including tumor angiogenic and inflammatory angiogenic agents, and culturing the cells in serum free medium.

Sprouting assay. A sprouting assay is a three-dimensional *in vitro* angiogenesis assay that uses a cell-number defined spheroid aggregation of endothelial cells ("spheroid"), embedded in a collagen gel-based matrix. The spheroid can serve as a starting point for the sprouting of capillary-like structures by invasion into the extracellular matrix (termed "cell sprouting") and the subsequent formation of complex anastomosing networks (Korff and Augustin, 1999, J Cell Sci 112:3249-58). In an exemplary experimental set-up, spheroids are prepared by pipetting 400 human umbilical vein endothelial cells into individual wells of a nonadhesive 96-well plates to allow overnight spheroidal aggregation (Korff and Augustin: J Cell Biol 143: 1341-52, 1998). Spheroids are harvested and seeded in 900 μ l of methocel-collagen solution and pipetted into individual wells of a 24 well plate to allow collagen gel polymerization. Test agents are added after 30 min by pipetting 100 μ l of 10-fold concentrated working dilution of the test substances on top of the gel. Plates are incubated at 37°C for 24h. Dishes are fixed at the end of the experimental incubation period by addition of paraformaldehyde. Sprouting

intensity of endothelial cells can be quantitated by an automated image analysis system to determine the cumulative sprout length per spheroid.

Primary assays for antibody modulators

5 For antibody modulators, appropriate primary assays test is a binding assay that tests the antibody's affinity to and specificity for the MRAC protein. Methods for testing antibody affinity and specificity are well known in the art (Harlow and Lane, 1988, 1999, *supra*). The enzyme-linked immunosorbant assay (ELISA) is a preferred method for detecting MRAC-specific antibodies; others include FACS assays, radioimmunoassays, 10 and fluorescent assays.

In some cases, screening assays described for small molecule modulators may also be used to test antibody modulators.

Primary assays for nucleic acid modulators

15 For nucleic acid modulators, primary assays may test the ability of the nucleic acid modulator to inhibit or enhance MRAC gene expression, preferably mRNA expression. In general, expression analysis comprises comparing MRAC expression in like populations of cells (*e.g.*, two pools of cells that endogenously or recombinantly express MRAC) in the presence and absence of the nucleic acid modulator. Methods for analyzing mRNA 20 and protein expression are well known in the art. For instance, Northern blotting, slot blotting, ribonuclease protection, quantitative RT-PCR (*e.g.*, using the TaqMan®, PE Applied Biosystems), or microarray analysis may be used to confirm that MRAC mRNA expression is reduced in cells treated with the nucleic acid modulator (*e.g.*, Current Protocols in Molecular Biology (1994) Ausubel FM *et al.*, eds., John Wiley & Sons, Inc., 25 chapter 4; Freeman WM *et al.*, Biotechniques (1999) 26:112-125; Kallioniemi OP, Ann Med 2001, 33:142-147; Blohm DH and Guiseppi-Elie, A Curr Opin Biotechnol 2001, 12:41-47). Protein expression may also be monitored. Proteins are most commonly detected with specific antibodies or antisera directed against either the MRAC protein or specific peptides. A variety of means including Western blotting, ELISA, or in situ 30 detection, are available (Harlow E and Lane D, 1988 and 1999, *supra*).

In some cases, screening assays described for small molecule modulators, particularly in assay systems that involve MRAC mRNA expression, may also be used to test nucleic acid modulators.

Secondary Assays

Secondary assays may be used to further assess the activity of MRAC-modulating agent identified by any of the above methods to confirm that the modulating agent affects MRAC in a manner relevant to the RAC pathway. As used herein, MRAC-modulating agents encompass candidate clinical compounds or other agents derived from previously identified modulating agent. Secondary assays can also be used to test the activity of a modulating agent on a particular genetic or biochemical pathway or to test the specificity of the modulating agent's interaction with MRAC.

Secondary assays generally compare like populations of cells or animals (*e.g.*, two pools of cells or animals that endogenously or recombinantly express MRAC) in the presence and absence of the candidate modulator. In general, such assays test whether treatment of cells or animals with a candidate MRAC-modulating agent results in changes in the RAC pathway in comparison to untreated (or mock- or placebo-treated) cells or animals. Certain assays use "sensitized genetic backgrounds", which, as used herein, describe cells or animals engineered for altered expression of genes in the RAC or interacting pathways.

Cell-based assays

Cell based assays may detect endogenous RAC pathway activity or may rely on recombinant expression of RAC pathway components. Any of the aforementioned assays may be used in this cell-based format. Candidate modulators are typically added to the cell media but may also be injected into cells or delivered by any other efficacious means.

Animal Assays

A variety of non-human animal models of normal or defective RAC pathway may be used to test candidate MRAC modulators. Models for defective RAC pathway typically use genetically modified animals that have been engineered to mis-express (*e.g.*, over-express or lack expression in) genes involved in the RAC pathway. Assays generally require systemic delivery of the candidate modulators, such as by oral administration, injection, etc.

In a preferred embodiment, RAC pathway activity is assessed by monitoring neovascularization and angiogenesis. Animal models with defective and normal RAC are used to test the candidate modulator's affect on MRAC in Matrigel® assays. Matrigel® is an extract of basement membrane proteins, and is composed primarily of laminin, collagen

IV, and heparin sulfate proteoglycan. It is provided as a sterile liquid at 4° C, but rapidly forms a solid gel at 37° C. Liquid Matrigel® is mixed with various angiogenic agents, such as bFGF and VEGF, or with human tumor cells which over-express the MRAC. The mixture is then injected subcutaneously(SC) into female athymic nude mice (Taconic, Germantown, NY) to support an intense vascular response. Mice with Matrigel® pellets may be dosed via oral (PO), intraperitoneal (IP), or intravenous (IV) routes with the candidate modulator. Mice are euthanized 5 - 12 days post-injection, and the Matrigel® pellet is harvested for hemoglobin analysis (Sigma plasma hemoglobin kit). Hemoglobin content of the gel is found to correlate the degree of neovascularization in the gel.

10 In another preferred embodiment, the effect of the candidate modulator on MRAC is assessed via tumorigenicity assays. Tumor xenograft assays are known in the art (see, e.g., Ogawa K et al., 2000, *Oncogene* 19:6043-6052). Xenografts are typically implanted SC into female athymic mice, 6-7 week old, as single cell suspensions either from a pre-existing tumor or from *in vitro* culture. The tumors which express the MRAC

15 endogenously are injected in the flank, 1×10^5 to 1×10^7 cells per mouse in a volume of 100 μ L using a 27gauge needle. Mice are then ear tagged and tumors are measured twice weekly. Candidate modulator treatment is initiated on the day the mean tumor weight reaches 100 mg. Candidate modulator is delivered IV, SC, IP, or PO by bolus administration. Depending upon the pharmacokinetics of each unique candidate

20 modulator, dosing can be performed multiple times per day. The tumor weight is assessed by measuring perpendicular diameters with a caliper and calculated by multiplying the measurements of diameters in two dimensions. At the end of the experiment, the excised tumors maybe utilized for biomarker identification or further analyses. For immunohistochemistry staining, xenograft tumors are fixed in 4% paraformaldehyde,

25 0.1M phosphate, pH 7.2, for 6 hours at 4°C, immersed in 30% sucrose in PBS, and rapidly frozen in isopentane cooled with liquid nitrogen.

In another preferred embodiment, tumorigenicity is monitored using a hollow fiber assay, which is described in U.S. Pat No. US 5,698,413. Briefly, the method comprises implanting into a laboratory animal a biocompatible, semi-permeable encapsulation device

30 containing target cells, treating the laboratory animal with a candidate modulating agent, and evaluating the target cells for reaction to the candidate modulator. Implanted cells are generally human cells from a pre-existing tumor or a tumor cell line. After an appropriate period of time, generally around six days, the implanted samples are harvested for evaluation of the candidate modulator. Tumorigenicity and modulator efficacy may be

evaluated by assaying the quantity of viable cells present in the macrocapsule, which can be determined by tests known in the art, for example, MTT dye conversion assay, neutral red dye uptake, trypan blue staining, viable cell counts, the number of colonies formed in soft agar, the capacity of the cells to recover and replicate in vitro, etc.

5 In another preferred embodiment, a tumorigenicity assay use a transgenic animal, usually a mouse, carrying a dominant oncogene or tumor suppressor gene knockout under the control of tissue specific regulatory sequences; these assays are generally referred to as transgenic tumor assays. In a preferred application, tumor development in the transgenic model is well characterized or is controlled. In an exemplary model, the "RIP1-Tag2"
10 transgene, comprising the SV40 large T-antigen oncogene under control of the insulin gene regulatory regions is expressed in pancreatic beta cells and results in islet cell carcinomas (Hanahan D, 1985, Nature 315:115-122; Parangi S et al, 1996, Proc Natl Acad Sci USA 93: 2002-2007; Bergers G et al, 1999, Science 284:808-812). An "angiogenic switch," occurs at approximately five weeks, as normally quiescent capillaries in a subset
15 of hyperproliferative islets become angiogenic. The RIP1-TAG2 mice die by age 14 weeks. Candidate modulators may be administered at a variety of stages, including just prior to the angiogenic switch (e.g., for a model of tumor prevention), during the growth of small tumors (e.g., for a model of intervention), or during the growth of large and/or invasive tumors (e.g., for a model of regression). Tumorigenicity and modulator efficacy
20 can be evaluating life-span extension and/or tumor characteristics, including number of tumors, tumor size, tumor morphology, vessel density, apoptotic index, etc.

Diagnostic and therapeutic uses

Specific MRAC-modulating agents are useful in a variety of diagnostic and
25 therapeutic applications where disease or disease prognosis is related to defects in the RAC pathway, such as angiogenic, apoptotic, or cell proliferation disorders. Accordingly, the invention also provides methods for modulating the RAC pathway in a cell, preferably a cell pre-determined to have defective or impaired RAC function (e.g. due to overexpression, underexpression, or misexpression of RAC, or due to gene mutations),
30 comprising the step of administering an agent to the cell that specifically modulates MRAC activity. Preferably, the modulating agent produces a detectable phenotypic change in the cell indicating that the RAC function is restored. The phrase "function is restored", and equivalents, as used herein, means that the desired phenotype is achieved, or is brought closer to normal compared to untreated cells. For example, with restored

RAC function, cell proliferation and/or progression through cell cycle may normalize, or be brought closer to normal relative to untreated cells. The invention also provides methods for treating disorders or disease associated with impaired RAC function by administering a therapeutically effective amount of an MRAC -modulating agent that modulates the RAC pathway. The invention further provides methods for modulating MRAC function in a cell, preferably a cell pre-determined to have defective or impaired MRAC function, by administering an MRAC -modulating agent. Additionally, the invention provides a method for treating disorders or disease associated with impaired MRAC function by administering a therapeutically effective amount of an MRAC -modulating agent.

The discovery that MRAC is implicated in RAC pathway provides for a variety of methods that can be employed for the diagnostic and prognostic evaluation of diseases and disorders involving defects in the RAC pathway and for the identification of subjects having a predisposition to such diseases and disorders.

Various expression analysis methods can be used to diagnose whether MRAC expression occurs in a particular sample, including Northern blotting, slot blotting, ribonuclease protection, quantitative RT-PCR, and microarray analysis. (*e.g.*, Current Protocols in Molecular Biology (1994) Ausubel FM *et al.*, eds., John Wiley & Sons, Inc., chapter 4; Freeman WM *et al.*, Biotechniques (1999) 26:112-125; Kallioniemi OP, Ann Med 2001, 33:142-147; Blohm and Guiseppi-Elie, Curr Opin Biotechnol 2001, 12:41-47). Tissues having a disease or disorder implicating defective RAC signaling that express an MRAC, are identified as amenable to treatment with an MRAC modulating agent. In a preferred application, the RAC defective tissue overexpresses an MRAC relative to normal tissue. For example, a Northern blot analysis of mRNA from tumor and normal cell lines, or from tumor and matching normal tissue samples from the same patient, using full or partial MRAC cDNA sequences as probes, can determine whether particular tumors express or overexpress MRAC. Alternatively, the TaqMan® is used for quantitative RT-PCR analysis of MRAC expression in cell lines, normal tissues and tumor samples (PE Applied Biosystems).

Various other diagnostic methods may be performed, for example, utilizing reagents such as the MRAC oligonucleotides, and antibodies directed against an MRAC, as described above for: (1) the detection of the presence of MRAC gene mutations, or the detection of either over- or under-expression of MRAC mRNA relative to the non-disorder state; (2) the detection of either an over- or an under-abundance of MRAC gene product

relative to the non-disorder state; and (3) the detection of perturbations or abnormalities in the signal transduction pathway mediated by MRAC.

Kits for detecting expression of MRAC in various samples, comprising at least one antibody specific to MRAC, all reagents and/or devices suitable for the detection of
5 antibodies, the immobilization of antibodies, and the like, and instructions for using such kits in diagnosis or therapy are also provided.

Thus, in a specific embodiment, the invention is drawn to a method for diagnosing a disease or disorder in a patient that is associated with alterations in MRAC expression, the method comprising: a) obtaining a biological sample from the patient; b) contacting
10 the sample with a probe for MRAC expression; c) comparing results from step (b) with a control; and d) determining whether step (c) indicates a likelihood of the disease or disorder. Preferably, the disease is cancer. The probe may be either DNA or protein, including an antibody.

15 EXAMPLES

The following experimental section and examples are offered by way of illustration and not by way of limitation.

I. C. elegans RAC enhancer screen

20 A genetic screen was designed to identify modifiers of the Rac signaling pathway that also affect cell migrations in *C. elegans*. The basis of this screen is the observation that *ced-10* and *mig-2* single mutants resemble wildtype worms in morphology and movement, whereas double mutants have strong morphological and movement defects. In the primary screen, the function of individual genes is inactivated by RNA interference
25 (RNAi) in wildtype, *ced-10* and *mig-2* worms at the L4 stage. The progeny of the RNA treated animals are then examined for morphological and movement defects resembling those of the *ced-10*; *mig-2* double mutant. All genes that give such a phenotype in a *ced-10* or *mig-2* mutant background but not in a wildtype background are then tested in a direct cell migration assay. In the cell migration assay, a subset of mechanosensory
30 neurons known as AVM and ALM are scored for their final positions in the animal using a GFP marker expressed in these cells. This migration assay is done in both wildtype and a *ced-10* or *mig-2* mutant background. Since the AVM and ALM cells normally migrate and reach their final position during the first larval stage, scoring of position is done in later larval or adult stages. Those genes that cause short or misguided migrations of these

neurons when inactivated in a wildtype or rac mutant background are potentially relevant for treatment of diseases that involve cell migrations.

II. Analysis of Table 1

5 BLAST analysis (Altschul et al., *supra*) was employed to identify orthologs of *C. elegans* modifiers. The columns "MRAC symbol", and "MRAC name aliases " provide a symbol and the known name abbreviations for the Targets, where available, from Genbank. "MRAC RefSeq_NA or GI_NA", "MRAC GI_AA", "MRAC NAME", and "MRAC Description" provide the reference DNA sequences for the MRACs as available
10 from National Center for Biology Information (NCBI), MRAC protein Genbank identifier number (GI#), MRAC name, and MRAC description, all available from Genbank, respectively. The length of each amino acid is in the "MRAC Protein Length" column.

Names and Protein sequences of *C. elegans* modifiers of RAC from screen (Example I), are represented in the "Modifier Name" and "Modifier GI_AA" column by
15 GI#, respectively.

Table 1

MRAC Symbol	MRAC Name Aliases	MRAC RefSeq_NA or GI_NA	NA SE Q ID NO	MRAC GI_aa	AA SE Q ID NO	MRAC name	MRAC Description	MRA C Protein length	Modifi er Name	Modifi er GI_aa
ITGA3	ITGA3 VL3A CD49C CD49c GAPB3 integrin, alpha 3 (antigen CD49C, alpha 3 subunit of VLA-3 receptor)	NM_002204 NM_005501	1	4504747	17	integrin, alpha 3 (antigen CD49C, alpha 3 subunit of VLA-3 receptor)	small GTPase mediated signal transduction; phagocytosis; integrin-mediated signaling pathway; integrin-mediated signaling pathway; integrin-mediated signaling pathway; protein complex assembly; cell motility; cell-matrix adhesion; cell proliferation	1051	ina-1	17553940

ITGA6	ITGA6 CD49f integrin, alpha 6	NM_000210	2	4557675	18	integrin, alpha 6	wound healing; small GTPase mediated signal transduction; epidermal differentiation; integrin-mediated signaling pathway; integrin-mediated signaling pathway; regulation of cell adhesion; cell-matrix adhesion; response to wounding; progesterone biosynthesis; cell migration; cell-substrate junction assembly; anti-apoptosis; T-cell differentiation; delayed hypersensitivity response; signal transduction; luteinization	1073	ina-1	17553940
ITGA7	ITGA7 integrin, alpha 7	NM_002206	3	4504753	19	integrin, alpha 7	muscle development; homophilic cell adhesion; cell-matrix adhesion	1137	ina-1	17553940
LAMA3	LAMA3 E170 LAMNA epiligrin BM600 150kD subunit nicein 150kD subunit kalinin 165kD subunit laminin alpha-3 chain laminin-5, alpha3 chain epiligrin 170 kda subunit epiligrin alpha 3 subunit laminin, alpha 3	NM_000227	4	4557711	20	laminin, alpha 3	regulation of cell shape; cell adhesion; epidermal differentiation; integrin-mediated signaling pathway; cell-matrix adhesion; response to wounding; cell migration	1713	epi-1	17539624

LAMA5	LAMA5 KIAA1907 laminin alpha-5 chain laminin, alpha 5	NM_005560	5	21264602	21	laminin, alpha 5	wound healing; cell adhesion; cell-matrix adhesion; leukocyte cell adhesion; substrate-bound cell migration	3695	epi-1	17539624
MCF2	MCF2 DBL Oncogene MCF2 (oncogene DBL) MCF.2 cell line derived transforming sequence	NM_005369	6	19923310	22	MCF.2 cell line derived transforming sequence	activation of JUN kinase; Rho protein signal transduction; actin cytoskeleton organization and biogenesis; actin filament-based process; cell proliferation	925	XD417	25151218
MCF2L	MCF2L DBS OST ARHGEF14 FLJ12122 KIAA0362 DBL's big sister guanine nucleotide exchange factor DBS MCF2 transforming sequence-like protein MCF.2 cell line derived transforming sequence-like	NM_024979	7	27777655	23	MCF.2 cell line derived transforming sequence-like	negative regulation of cell proliferation	984	XD417	25151218
KIAA0861	KIAA0861 Rho family guanine-nucleotide exchange factor	NM_015078	8	27903823	24	Rho family guanine-nucleotide exchange factor	small GTPase mediated signal transduction; negative regulation of cell proliferation; axon guidance; cell growth and/or maintenance; signal transduction	1031	XD417	25151218
LOC126147	LOC126147 hypothetical protein BC018697	NM_145807	9	24308065	25	hypothetical protein BC018697	cell adhesion; axon guidance; cell motility; morphogenesis; neurogenesis; cell migration; cell growth	489	unc-6	17570167
NTN1	NTN1 NTN1L netrin 1, mouse, homolog of netrin 1	NM_004822	10	4758840	26	netrin 1	axon guidance; cell motility; neurogenesis; cell-cell	604	unc-6	17570167

							signaling			
NTN2L	NTN2L netrin 2 (chicken)-like Netrin-2, chicken, homolog of, like netrin 2-like (chicken)	NM_006181	11	5453810	27	netrin 2-like (chicken)	axon guidance; chemotaxis	580	unc-6	17570167
NTN4	NTN4 PRO3091 beta-netrin netrin 4	NM_021229	12	11139301	28	netrin 4	cell adhesion; axon guidance; cell growth and/or maintenance; morphogenesis; neurogenesis	628	unc-6	17570167
SDC1	SDC1 SDC CD138 SYND1 syndecan 1	NM_002997	13	29568086	29	syndecan 1	cell adhesion	310	sdn-1	25150517
SDC2	SDC2 HSPG HSPG1 SYND2 fibroglycan heparan sulfate proteoglycan core protein syndecan 2 (heparan sulfate proteoglycan 1, cell surface-associated, fibroglycan)	NM_002998	14	27804307	30	syndecan 2 (heparan sulfate proteoglycan 1, cell surface-associated, fibroglycan)	cell adhesion; cell adhesion; FGF receptor signaling pathway; cell migration; cell differentiation; positive regulation of cell proliferation; positive regulation of cell proliferation; development; MAPKKK cascade; activation of MAPK	201	sdn-1	25150517
SDC3	SDC3 SDCN SYND3 KIAA0468 syndecan 3 (N-syndecan)	NM_014654	15	7662138	31	syndecan 3 (N-syndecan)	regulation of cell shape; cytoskeleton organization and biogenesis; hemopoiesis; angiogenesis; cell surface receptor linked signal transduction; cell communication; feeding behavior; cell growth and/or maintenance; formation of a cell surface projection	384	sdn-1	25150517

SDC4	SDC4 SYND4 RYUDOCAN syndecan 4 (amphiglycan, ryudocan)	NM_002999	16	450686 1	32	syndeca n 4 (amphig lycan, ryudoca n)	cell adhesion; cell adhesion; cell growth and/or maintenance; response to wounding; regulation of proteolysis and peptidolysis; cell proliferation; negative regulation of blood coagulation; cell growth; development; inflammatory response	198	sdn-1	251505 17
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III. High-Throughput In Vitro Fluorescence Polarization Assay

Fluorescently-labeled MRAC peptide/substrate are added to each well of a 96-well microtiter plate, along with a test agent in a test buffer (10 mM HEPES, 10 mM NaCl, 6 mM magnesium chloride, pH 7.6). Changes in fluorescence polarization, determined by using a Fluorolite FPM-2 Fluorescence Polarization Microtiter System (Dynatech Laboratories, Inc), relative to control values indicates the test compound is a candidate modifier of MRAC activity.

IV. High-Throughput In Vitro Binding Assay.

³³P-labeled MRAC peptide is added in an assay buffer (100 mM KCl, 20 mM HEPES pH 7.6, 1 mM MgCl₂, 1% glycerol, 0.5% NP-40, 50 mM beta-mercaptoethanol, 1 mg/ml BSA, cocktail of protease inhibitors) along with a test agent to the wells of a Neutralite-avidin coated assay plate and incubated at 25°C for 1 hour. Biotinylated substrate is then added to each well and incubated for 1 hour. Reactions are stopped by washing with PBS, and counted in a scintillation counter. Test agents that cause a difference in activity relative to control without test agent are identified as candidate RAC modulating agents.

V. Immunoprecipitations and Immunoblotting

For coprecipitation of transfected proteins, 3×10^6 appropriate recombinant cells containing the MRAC proteins are plated on 10-cm dishes and transfected on the following day with expression constructs. The total amount of DNA is kept constant in

each transfection by adding empty vector. After 24 h, cells are collected, washed once with phosphate-buffered saline and lysed for 20 min on ice in 1 ml of lysis buffer containing 50 mM Hepes, pH 7.9, 250 mM NaCl, 20 mM -glycerophosphate, 1 mM sodium orthovanadate, 5 mM p-nitrophenyl phosphate, 2 mM dithiothreitol, protease inhibitors (complete, Roche Molecular Biochemicals), and 1% Nonidet P-40. Cellular debris is removed by centrifugation twice at $15,000 \times g$ for 15 min. The cell lysate is incubated with 25 μ l of M2 beads (Sigma) for 2 h at 4 °C with gentle rocking.

After extensive washing with lysis buffer, proteins bound to the beads are solubilized by boiling in SDS sample buffer, fractionated by SDS-polyacrylamide gel electrophoresis, transferred to polyvinylidene difluoride membrane and blotted with the indicated antibodies. The reactive bands are visualized with horseradish peroxidase coupled to the appropriate secondary antibodies and the enhanced chemiluminescence (ECL) Western blotting detection system (Amersham Pharmacia Biotech).

VI. Expression analysis

All cell lines used in the following experiments are NCI (National Cancer Institute) lines, and are available from ATCC (American Type Culture Collection, Manassas, VA 20110-2209). Normal and tumor tissues are obtained from Impath, UC Davis, Clontech, Stratagene, Ardais, Genome Collaborative, and Ambion.

TaqMan® analysis is used to assess expression levels of the disclosed genes in various samples.

RNA is extracted from each tissue sample using Qiagen (Valencia, CA) RNeasy kits, following manufacturer's protocols, to a final concentration of 50ng/ μ l. Single stranded cDNA is then synthesized by reverse transcribing the RNA samples using random hexamers and 500ng of total RNA per reaction, following protocol 4304965 of Applied Biosystems (Foster City, CA).

Primers for expression analysis using TaqMan® assay (Applied Biosystems, Foster City, CA) are prepared according to the TaqMan® protocols, and the following criteria: a) primer pairs are designed to span introns to eliminate genomic contamination, and b) each primer pair produced only one product. Expression analysis is performed using a 7900HT instrument.

TaqMan® reactions are carried out following manufacturer's protocols, in 25 μ l total volume for 96-well plates and 10 μ l total volume for 384-well plates, using 300nM primer and 250 nM probe, and approximately 25ng of cDNA. The standard curve for

result analysis is prepared using a universal pool of human cDNA samples, which is a mixture of cDNAs from a wide variety of tissues so that the chance that a target will be present in appreciable amounts is good. The raw data are normalized using 18S rRNA (universally expressed in all tissues and cells).

5 For each expression analysis, tumor tissue samples are compared with matched normal tissues from the same patient. A gene is considered overexpressed in a tumor when the level of expression of the gene is 2 fold or higher in the tumor compared with its matched normal sample. In cases where normal tissue is not available, a universal pool of cDNA samples is used instead. In these cases, a gene is considered overexpressed in a
10 tumor sample when the difference of expression levels between a tumor sample and the average of all normal samples from the same tissue type is greater than 2 times the standard deviation of all normal samples (i.e., $\text{Tumor} - \text{average}(\text{all normal samples}) > 2 \times \text{STDEV}(\text{all normal samples})$).

 A modulator identified by an assay described herein can be further validated for
15 therapeutic effect by administration to a tumor in which the gene is overexpressed. A decrease in tumor growth confirms therapeutic utility of the modulator. Prior to treating a patient with the modulator, the likelihood that the patient will respond to treatment can be diagnosed by obtaining a tumor sample from the patient, and assaying for expression of the gene targeted by the modulator. The expression data for the gene(s) can also be used
20 as a diagnostic marker for disease progression. The assay can be performed by expression analysis as described above, by antibody directed to the gene target, or by any other available detection method.

WHAT IS CLAIMED IS:

1. A method of identifying a candidate RAC pathway modulating agent, said
5 method comprising the steps of:
 - (a) providing an assay system comprising an MRAC polypeptide or nucleic acid;
 - (b) contacting the assay system with a test agent under conditions whereby, but for the presence of the test agent, the system provides a reference activity; and
10 (c) detecting a test agent-biased activity of the assay system, wherein a difference between the test agent-biased activity and the reference activity identifies the test agent as a candidate RAC pathway modulating agent.
2. The method of Claim 1 wherein the assay system comprises cultured cells that
15 express the MRAC polypeptide.
3. The method of Claim 2 wherein the cultured cells additionally have defective RAC function.
- 20 4. The method of Claim 1 wherein the assay system includes a screening assay comprising an MRAC polypeptide, and the candidate test agent is a small molecule modulator.
5. The method of Claim 4 wherein the assay is a binding assay.
25
6. The method of Claim 1 wherein the assay system is selected from the group consisting of an apoptosis assay system, a cell proliferation assay system, an angiogenesis assay system, and a hypoxic induction assay system.
- 30 7. The method of Claim 1 wherein the assay system includes a binding assay comprising an MRAC polypeptide and the candidate test agent is an antibody.

8. The method of Claim 1 wherein the assay system includes an expression assay comprising an MRAC nucleic acid and the candidate test agent is a nucleic acid modulator.

5 9. The method of claim 8 wherein the nucleic acid modulator is an antisense oligomer.

10 10. The method of Claim 8 wherein the nucleic acid modulator is a PMO.

10 11. The method of Claim 1 additionally comprising:

(d) administering the candidate RAC pathway modulating agent identified in (c) to a model system comprising cells defective in RAC function and, detecting a phenotypic change in the model system that indicates that the RAC function is restored.

15 12. The method of Claim 11 wherein the model system is a mouse model with defective RAC function.

20 13. A method for modulating a RAC pathway of a cell comprising contacting a cell defective in RAC function with a candidate modulator that specifically binds to an MRAC polypeptide, whereby RAC function is restored.

25 14. The method of claim 13 wherein the candidate modulator is administered to a vertebrate animal predetermined to have a disease or disorder resulting from a defect in RAC function.

 15. The method of Claim 13 wherein the candidate modulator is selected from the group consisting of an antibody and a small molecule.

30 16. The method of Claim 1, comprising the additional steps of:

(d) providing a secondary assay system comprising cultured cells or a non-human animal expressing MRAC ,

(e) contacting the secondary assay system with the test agent of (b) or an agent derived therefrom under conditions whereby, but for the presence of the test agent or agent derived therefrom, the system provides a reference activity; and

- (f) detecting an agent-biased activity of the second assay system,
wherein a difference between the agent-biased activity and the reference activity of
the second assay system confirms the test agent or agent derived therefrom as a candidate
RAC pathway modulating agent,
5 and wherein the second assay detects an agent-biased change in the RAC pathway.

17. The method of Claim 16 wherein the secondary assay system comprises
cultured cells.

- 10 18. The method of Claim 16 wherein the secondary assay system comprises a non-
human animal.

19. The method of Claim 18 wherein the non-human animal mis-expresses a RAC
pathway gene.

15

20. A method of modulating RAC pathway in a mammalian cell comprising
contacting the cell with an agent that specifically binds an MRAC polypeptide or nucleic
acid.

- 20 21. The method of Claim 20 wherein the agent is administered to a mammalian
animal predetermined to have a pathology associated with the RAC pathway.

22. The method of Claim 20 wherein the agent is a small molecule modulator, a
nucleic acid modulator, or an antibody.

25

23. A method for diagnosing a disease in a patient comprising:
obtaining a biological sample from the patient;
contacting the sample with a probe for MRAC expression;
comparing results from step (b) with a control;
30 determining whether step (c) indicates a likelihood of disease.

24. The method of claim 23 wherein said disease is cancer.

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 Gly Ser Leu Phe Gly Tyr Ser Val Ala Leu His Arg Gln Thr Glu Arg
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 Gln Gln Arg Tyr Leu Leu Leu Ala Gly Ala Pro Arg Glu Leu Ala Val
 65 70 75 80
 Pro Asp Gly Tyr Thr Asn Arg Thr Gly Ala Val Tyr Leu Cys Pro Leu
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 Thr Ala His Lys Asp Asp Cys Glu Arg Met Asn Ile Thr Val Lys Asn
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 Asp Pro Gly His His Ile Ile Glu Asp Met Trp Leu Gly Val Thr Val
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 Ala Ser Gln Gly Pro Ala Gly Arg Val Leu Val Cys Ala His Arg Tyr
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 Thr Gln Val Leu Trp Ser Gly Ser Glu Asp Gln Arg Arg Met Val Gly
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 Lys Cys Tyr Val Arg Gly Asn Asp Leu Glu Leu Asp Ser Ser Asp Asp
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 Glu Thr Gly Met Cys Gln Leu Gly Thr Ser Gly Gly Phe Thr Gln Asn
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 Thr Val Tyr Phe Gly Ala Pro Gly Ala Tyr Asn Trp Lys Gly Asn Ser
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 225 230 235 240

Asp Pro Glu Asp Gln Gly Asn Leu Tyr Ile Gly Tyr Thr Met Gln Val
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Gly Ser Phe Ile Leu His Pro Lys Asn Ile Thr Ile Val Thr Gly Ala
260 265 270

Pro Arg His Arg His Met Gly Ala Val Phe Leu Leu Ser Gln Glu Ala
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Gly Gly Asp Leu Arg Arg Arg Gln Val Leu Glu Gly Ser Gln Val Gly
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Ala Tyr Phe Gly Ser Ala Ile Ala Leu Ala Asp Leu Asn Asn Asp Gly
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Trp Gln Asp Leu Leu Val Gly Ala Pro Tyr Tyr Phe Glu Arg Lys Glu
325 330 335

Glu Val Gly Gly Ala Ile Tyr Val Phe Met Asn Gln Ala Gly Thr Ser
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Phe Pro Ala His Pro Ser Leu Leu Leu His Gly Pro Ser Gly Ser Ala
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Gln Asp Ile Ala Val Gly Ala Pro Phe Glu Gly Leu Gly Lys Val Tyr
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Ile Tyr His Ser Ser Ser Lys Gly Leu Leu Arg Gln Pro Gln Gln Val
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Ile His Gly Glu Lys Leu Gly Leu Pro Gly Leu Ala Thr Phe Gly Tyr
420 425 430

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Thr Leu Leu Val Asp Tyr Thr Leu Gln Thr Ser Leu Ser Met Val Asn
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His Arg Leu Gln Ser Phe Phe Gly Gly Thr Val Met Gly Glu Ser Gly
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Met Lys Thr Val Glu Asp Val Gly Ser Pro Leu Lys Tyr Glu Phe Gln
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Val Gly Pro Met Gly Glu Gly Leu Val Gly Leu Gly Thr Leu Val Leu
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Gly Leu Glu Trp Pro Tyr Glu Val Ser Asn Gly Lys Trp Leu Leu Tyr
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Pro Thr Glu Ile Thr Val His Gly Asn Gly Ser Trp Pro Cys Arg Pro
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Pro Gly Asp Leu Ile Asn Pro Leu Asn Leu Thr Leu Ser Asp Pro Gly
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Asp Arg Pro Ser Ser Pro Gln Arg Arg Arg Arg Gln Leu Asp Pro Gly
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Gly Gly Gln Gly Pro Pro Pro Val Thr Leu Ala Ala Ala Lys Lys Ala
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Lys Ser Glu Thr Val Leu Thr Cys Ala Thr Gly Arg Ala His Cys Val
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Trp Leu Glu Cys Pro Ile Pro Asp Ala Pro Val Val Thr Asn Val Thr
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Val Lys Ala Arg Val Trp Asn Ser Thr Phe Ile Glu Asp Tyr Arg Asp
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Phe Asp Arg Val Arg Val Asn Gly Trp Ala Thr Leu Phe Leu Arg Thr
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Ser Ile Pro Thr Ile Asn Met Glu Asn Lys Thr Thr Trp Phe Ser Val
 965 970 975

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

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Tyr Asp Asp Leu Gly Lys Val Phe Ile Tyr His Gly Ser Ala Asn Gly
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Ile Asn Thr Lys Pro Thr Gln Val Leu Lys Gly Ile Ser Pro Tyr Phe
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Gly Tyr Ser Ile Ala Gly Asn Met Asp Leu Asp Arg Asn Ser Tyr Pro
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Arg Pro Val Ile Asn Ile Gln Lys Thr Ile Thr Val Thr Pro Asn Arg
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Ile Asp Leu Arg Gln Lys Thr Ala Cys Gly Ala Pro Ser Gly Ile Cys
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Leu Gln Val Lys Ser Cys Phe Glu Tyr Thr Ala Asn Pro Ala Gly Tyr
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Asn Pro Ser Ile Ser Ile Val Gly Thr Leu Glu Ala Glu Lys Glu Arg
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Arg Lys Ser Gly Leu Ser Ser Arg Val Gln Phe Arg Asn Gln Gly Ser
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Glu Pro Lys Tyr Thr Gln Glu Leu Thr Leu Lys Arg Gln Lys Gln Lys
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Val Cys Met Glu Glu Thr Leu Trp Leu Gln Asp Asn Ile Arg Asp Lys
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Leu Arg Pro Ile Pro Ile Thr Ala Ser Val Glu Ile Gln Glu Pro Ser
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Ser Arg Arg Arg Val Asn Ser Leu Pro Glu Val Leu Pro Ile Leu Asn
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Ser Asp Glu Pro Lys Thr Ala His Ile Asp Val His Phe Leu Lys Glu
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Cys Glu Pro Gln Lys Glu Ile Asn Ser Leu Asn Leu Thr Glu Ser His
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Arg Lys Phe Ser Leu Phe Ala Glu Arg Lys Tyr Gln Thr Leu Asn Cys
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 965 970 975

Ala Phe Ile Asp Val Thr Ala Ala Ala Glu Asn Ile Arg Leu Pro Asn
 980 985 990

Ala Gly Thr Gln Val Arg Val Thr Val Phe Pro Ser Lys Thr Val Ala
 995 1000 1005

Gln Tyr Ser Gly Val Pro Trp Trp Ile Ile Leu Val Ala Ile Leu
 1010 1015 1020

Ala Gly Ile Leu Met Leu Ala Leu Leu Val Phe Ile Leu Trp Lys
 1025 1030 1035

Cys Gly Phe Phe Lys Arg Asn Lys Lys Asp His Tyr Asp Ala Thr
 1040 1045 1050

Tyr His Lys Ala Glu Ile His Ala Gln Pro Ser Asp Lys Glu Arg
 1055 1060 1065

Leu Thr Ser Asp Ala
 1070

<210> 19

<211> 1137

<212> PRT

<213> Homo sapiens

<400> 19

Met Ala Gly Ala Arg Ser Arg Asp Pro Trp Gly Ala Ser Gly Ile Cys
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Tyr Leu Phe Gly Ser Leu Leu Val Glu Leu Leu Phe Ser Arg Ala Val
 20 25 30

Ala Phe Asn Leu Asp Val Met Gly Ala Leu Arg Lys Glu Gly Glu Pro
 35 40 45

Gly Ser Leu Phe Gly Phe Ser Val Ala Leu His Arg Gln Leu Gln Pro
 50 55 60

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

Pro Gly Gln Gln Ala Asn Arg Thr Gly Gly Leu Phe Ala Cys Pro Leu
 85 90 95

Ser Leu Glu Glu Thr Asp Cys Tyr Arg Val Asp Ile Asp Gln Gly Ala
 100 105 110

Asp Met Gln Lys Glu Ser Lys Glu Asn Gln Trp Leu Gly Val Ser Val
 115 120 125

Arg Ser Gln Gly Pro Gly Gly Lys Ile Val Thr Cys Ala His Arg Tyr
 130 135 140

Glu Ala Arg Gln Arg Val Asp Gln Ile Leu Glu Thr Arg Asp Met Ile
 145 150 155 160

Gly Arg Cys Phe Val Leu Ser Gln Asp Leu Ala Ile Arg Asp Glu Leu
 165 170 175

Asp Gly Gly Glu Trp Lys Phe Cys Glu Gly Arg Pro Gln Gly His Glu
 180 185 190

Gln Phe Gly Phe Cys Gln Gln Gly Thr Ala Ala Ala Phe Ser Pro Asp
 195 200 205

Ser His Tyr Leu Leu Phe Gly Ala Pro Gly Thr Tyr Asn Trp Lys Gly
 210 215 220

Leu Leu Phe Val Thr Asn Ile Asp Ser Ser Asp Pro Asp Gln Leu Val
 225 230 235 240

Tyr Lys Thr Leu Asp Pro Ala Asp Arg Leu Pro Gly Pro Ala Gly Asp
 245 250 255

Leu Ala Leu Asn Ser Tyr Leu Gly Phe Ser Ile Asp Ser Gly Lys Gly
 260 265 270

Leu Val Arg Ala Glu Glu Leu Ser Phe Val Ala Gly Ala Pro Arg Ala
 275 280 285

Asn His Lys Gly Ala Val Val Ile Leu Arg Lys Asp Ser Ala Ser Arg
 290 295 300

Leu Val Pro Glu Val Met Leu Ser Gly Glu Arg Leu Thr Ser Gly Phe
 305 310 315 320

Gly Tyr Ser Leu Ala Val Ala Asp Leu Asn Ser Asp Gly Trp Pro Asp
 325 330 335

Leu Ile Val Gly Ala Pro Tyr Phe Phe Glu Arg Gln Glu Glu Leu Gly
 340 345 350

Gly Ala Val Tyr Val Tyr Leu Asn Gln Gly Gly His Trp Ala Gly Ile
 355 360 365

Ser Pro Leu Arg Leu Cys Gly Ser Pro Asp Ser Met Phe Gly Ile Ser
 370 375 380

Leu Ala Val Leu Gly Asp Leu Asn Gln Asp Gly Phe Pro Asp Ile Ala
 385 390 395 400

Val Gly Ala Pro Phe Asp Gly Asp Gly Lys Val Phe Ile Tyr His Gly
 405 410 415

Ser Ser Leu Gly Val Val Ala Lys Pro Ser Gln Val Leu Glu Gly Glu
 420 425 430

Ala Val Gly Ile Lys Ser Phe Gly Tyr Ser Leu Ser Gly Ser Leu Asp
 435 440 445

Met Asp Gly Asn Gln Tyr Pro Asp Leu Leu Val Gly Ser Leu Ala Asp
 450 455 460

Thr Ala Val Leu Phe Arg Ala Arg Pro Ile Leu His Val Ser His Glu
 465 470 475 480

Val Ser Ile Ala Pro Arg Ser Ile Asp Leu Glu Gln Pro Asn Cys Ala
 485 490 495

Gly Gly His Ser Val Cys Val Asp Leu Arg Val Cys Phe Ser Tyr Ile
 500 505 510

Ala Val Pro Ser Ser Tyr Ser Pro Thr Val Ala Leu Asp Tyr Val Leu
 515 520 525

Asp Ala Asp Thr Asp Arg Arg Leu Arg Gly Gln Val Pro Arg Val Thr
 530 535 540

Phe Leu Ser Arg Asn Leu Glu Glu Pro Lys His Gln Ala Ser Gly Thr
 545 550 555 560

Val Trp Leu Lys His Gln His Asp Arg Val Cys Gly Asp Ala Met Phe
 565 570 575

Gln Leu Gln Glu Asn Val Lys Asp Lys Leu Arg Ala Ile Val Val Thr
 580 585 590

Leu Ser Tyr Ser Leu Gln Thr Pro Arg Leu Arg Arg Gln Ala Pro Gly
 595 600 605

Gln Gly Leu Pro Pro Val Ala Pro Ile Leu Asn Ala His Gln Pro Ser
 610 615 620

Thr Gln Arg Ala Glu Ile His Phe Leu Lys Gln Gly Cys Gly Glu Asp
 625 630 635 640

Lys Ile Cys Gln Ser Asn Leu Gln Leu Val His Ala Arg Phe Cys Thr
 645 650 655

Arg Val Ser Asp Thr Glu Phe Gln Pro Leu Pro Met Asp Val Asp Gly
 660 665 670

Thr Thr Ala Leu Phe Ala Leu Ser Gly Gln Pro Val Ile Gly Leu Glu
 675 680 685

Leu Met Val Thr Asn Leu Pro Ser Asp Pro Ala Gln Pro Gln Ala Asp
 690 695 700

Gly Asp Asp Ala His Glu Ala Gln Leu Leu Val Met Leu Pro Asp Ser
 705 710 715 720

Leu His Tyr Ser Gly Val Arg Ala Leu Asp Pro Ala Glu Lys Pro Leu

52

Gly Arg Leu Trp Asn Ser Thr Phe Leu Glu Glu Tyr Ser Ala Val Lys
 980 985 990

Ser Leu Glu Val Ile Val Arg Ala Asn Ile Thr Val Lys Ser Ser Ile
 995 1000 1005

Lys Asn Leu Met Leu Arg Asp Ala Ser Thr Val Ile Pro Val Met
 1010 1015 1020

Val Tyr Leu Asp Pro Met Ala Val Val Ala Glu Gly Val Pro Trp
 1025 1030 1035

Trp Val Ile Leu Leu Ala Val Leu Ala Gly Leu Leu Val Leu Ala
 1040 1045 1050

Leu Leu Val Leu Leu Leu Trp Lys Met Gly Phe Phe Lys Arg Ala
 1055 1060 1065

Lys His Pro Glu Ala Thr Val Pro Gln Tyr His Ala Val Lys Ile
 1070 1075 1080

Pro Arg Glu Asp Arg Gln Gln Phe Lys Glu Glu Lys Thr Gly Thr
 1085 1090 1095

Ile Leu Arg Asn Asn Trp Gly Ser Pro Arg Arg Glu Gly Pro Asp
 1100 1105 1110

Ala His Pro Ile Leu Ala Ala Asp Gly His Pro Glu Leu Gly Pro
 1115 1120 1125

Asp Gly His Pro Gly Pro Gly Thr Ala
 1130 1135

<210> 20
 <211> 1713
 <212> PRT
 <213> Homo sapiens

<400> 20

Met Gly Trp Leu Trp Ile Phe Gly Ala Ala Leu Gly Gln Cys Leu Gly
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Tyr Ser Ser Gln Gln Gln Arg Val Pro Phe Leu Gln Pro Pro Gly Gln
 20 25 30

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

Ser Pro Gly Tyr Tyr Arg Asp His Lys Gly Leu Tyr Thr Gly Arg Cys
 50 55 60

Val Pro Cys Asn Cys Asn Gly His Ser Asn Gln Cys Gln Asp Gly Ser
 65 70 75 80

Gly Ile Cys Val Asn Cys Gln His Asn Thr Ala Gly Glu His Cys Glu
 85 90 95

Arg Cys Gln Glu Gly Tyr Tyr Gly Asn Ala Val His Gly Ser Cys Arg
 100 105 110

Ala Cys Pro Cys Pro His Thr Asn Ser Phe Ala Thr Gly Cys Val Val
 115 120 125

Asn Gly Gly Asp Val Arg Cys Ser Cys Lys Ala Gly Tyr Thr Gly Thr
 130 135 140

Gln Cys Glu Arg Cys Ala Pro Gly Tyr Phe Gly Asn Pro Gln Lys Phe
 145 150 155 160

Gly Gly Ser Cys Gln Pro Cys Ser Cys Asn Ser Asn Gly Gln Leu Gly
 165 170 175

Ser Cys His Pro Leu Thr Gly Asp Cys Ile Asn Gln Glu Pro Lys Asp
 180 185 190

Ser Ser Pro Ala Glu Glu Cys Asp Asp Cys Asp Ser Cys Val Met Thr
 195 200 205

Leu Leu Asn Asp Leu Ala Thr Met Gly Glu Gln Leu Arg Leu Val Lys
 210 215 220

Ser Gln Leu Gln Gly Leu Ser Ala Ser Ala Gly Leu Leu Glu Gln Met
 225 230 235 240

Arg His Met Glu Thr Gln Ala Lys Asp Leu Arg Asn Gln Leu Leu Asn
 245 250 255

Tyr Arg Ser Ala Ile Ser Asn His Gly Ser Lys Ile Glu Gly Leu Glu
 260 265 270

Arg Glu Leu Thr Asp Leu Asn Gln Glu Phe Glu Thr Leu Gln Glu Lys

275					280					285						
Ala	Gln	Val	Asn	Ser	Arg	Lys	Ala	Gln	Thr	Leu	Asn	Asn	Asn	Val	Asn	
290						295			300							
Arg	Ala	Thr	Gln	Ser	Ala	Lys	Glu	Leu	Asp	Val	Lys	Ile	Lys	Asn	Val	
305				310				315				320				
Ile	Arg	Asn	Val	His	Ile	Leu	Leu	Lys	Gln	Ile	Ser	Gly	Thr	Asp	Gly	
			325						330			335				
Glu	Gly	Asn	Asn	Val	Pro	Ser	Gly	Asp	Phe	Ser	Arg	Glu	Trp	Ala	Glu	
			340			345						350				
Ala	Gln	Arg	Met	Met	Arg	Glu	Leu	Arg	Asn	Arg	Asn	Phe	Gly	Lys	His	
			355			360						365				
Leu	Arg	Glu	Ala	Glu	Ala	Asp	Lys	Arg	Glu	Ser	Gln	Leu	Leu	Leu	Asn	
370						375				380						
Arg	Ile	Arg	Thr	Trp	Gln	Lys	Thr	His	Gln	Gly	Glu	Asn	Asn	Gly	Leu	
385				390						395		400				
Ala	Asn	Ser	Ile	Arg	Asp	Ser	Leu	Asn	Glu	Tyr	Glu	Ala	Lys	Leu	Ser	
			405						410			415				
Asp	Leu	Arg	Ala	Arg	Leu	Gln	Glu	Ala	Ala	Ala	Gln	Ala	Lys	Gln	Ala	
			420			425						430				
Asn	Gly	Leu	Asn	Gln	Glu	Asn	Glu	Arg	Ala	Leu	Gly	Ala	Ile	Gln	Arg	
435						440						445				
Gln	Val	Lys	Glu	Ile	Asn	Ser	Leu	Gln	Ser	Asp	Phe	Thr	Lys	Tyr	Leu	
450						455						460				
Thr	Thr	Ala	Asp	Ser	Ser	Leu	Leu	Gln	Thr	Asn	Ile	Ala	Leu	Gln	Leu	
465				470						475				480		
Met	Glu	Lys	Ser	Gln	Lys	Glu	Tyr	Glu	Lys	Leu	Ala	Ala	Ser	Leu	Asn	
			485						490			495				
Glu	Ala	Arg	Gln	Glu	Leu	Ser	Asp	Lys	Val	Arg	Glu	Leu	Ser	Arg	Ser	
			500			505						510				
Ala	Gly	Lys	Thr	Ser	Leu	Val	Glu	Glu	Ala	Glu	Lys	His	Ala	Arg	Ser	
515						520						525				

Leu Gln Glu Leu Ala Lys Gln Leu Glu Glu Ile Lys Arg Asn Ala Ser
 530 535 540

Gly Asp Glu Leu Val Arg Cys Ala Val Asp Ala Ala Thr Ala Tyr Glu
 545 550 555 560

Asn Ile Leu Asn Ala Ile Lys Ala Ala Glu Asp Ala Ala Asn Arg Ala
 565 570 575

Ala Ser Ala Ser Glu Ser Ala Leu Gln Thr Val Ile Lys Glu Asp Leu
 580 585 590

Pro Arg Lys Ala Lys Thr Leu Ser Ser Asn Ser Asp Lys Leu Leu Asn
 595 600 605

Glu Ala Lys Met Thr Gln Lys Lys Leu Lys Gln Glu Val Ser Pro Ala
 610 615 620

Leu Asn Asn Leu Gln Gln Thr Leu Asn Ile Val Thr Val Gln Lys Glu
 625 630 635 640

Val Ile Asp Thr Asn Leu Thr Thr Leu Arg Asp Gly Leu His Gly Ile
 645 650 655

Gln Arg Gly Asp Ile Asp Ala Met Ile Ser Ser Ala Lys Ser Met Val
 660 665 670

Arg Lys Ala Asn Asp Ile Thr Asp Glu Val Leu Asp Gly Leu Asn Pro
 675 680 685

Ile Gln Thr Asp Val Glu Arg Ile Lys Asp Thr Tyr Gly Arg Thr Gln
 690 695 700

Asn Glu Asp Phe Lys Lys Ala Leu Thr Asp Ala Asp Asn Ser Val Asn
 705 710 715 720

Lys Leu Thr Asn Lys Leu Pro Asp Leu Trp Arg Lys Ile Glu Ser Ile
 725 730 735

Asn Gln Gln Leu Leu Pro Leu Gly Asn Ile Ser Asp Asn Met Asp Arg
 740 745 750

Ile Arg Glu Leu Ile Gln Gln Ala Arg Asp Ala Ala Ser Lys Val Ala
 755 760 765

Val Pro Met Arg Phe Asn Gly Lys Ser Gly Val Glu Val Arg Leu Pro
 770 775 780

Asn Asp Leu Glu Asp Leu Lys Gly Tyr Thr Ser Leu Ser Leu Phe Leu
 785 790 795 800

Gln Arg Pro Asn Ser Arg Glu Asn Gly Gly Thr Glu Asn Met Phe Val
 805 810 815

Met Tyr Leu Gly Asn Lys Asp Ala Ser Arg Asp Tyr Ile Gly Met Ala
 820 825 830

Val Val Asp Gly Gln Leu Thr Cys Val Tyr Asn Leu Gly Asp Arg Glu
 835 840 845

Ala Glu Leu Gln Val Asp Gln Ile Leu Thr Lys Ser Glu Thr Lys Glu
 850 855 860

Ala Val Met Asp Arg Val Lys Phe Gln Arg Ile Tyr Gln Phe Ala Arg
 865 870 875 880

Leu Asn Tyr Thr Lys Gly Ala Thr Ser Ser Lys Pro Glu Thr Pro Gly
 885 890 895

Val Tyr Asp Met Asp Gly Arg Asn Ser Asn Thr Leu Leu Asn Leu Asp
 900 905 910

Pro Glu Asn Val Val Phe Tyr Val Gly Gly Tyr Pro Pro Asp Phe Lys
 915 920 925

Leu Pro Ser Arg Leu Ser Phe Pro Pro Tyr Lys Gly Cys Ile Glu Leu
 930 935 940

Asp Asp Leu Asn Glu Asn Val Leu Ser Leu Tyr Asn Phe Lys Lys Thr
 945 950 955 960

Phe Asn Leu Asn Thr Thr Glu Val Glu Pro Cys Arg Arg Arg Lys Glu
 965 970 975

Glu Ser Asp Lys Asn Tyr Phe Glu Gly Thr Gly Tyr Ala Arg Val Pro
 980 985 990

Thr Gln Pro His Ala Pro Ile Pro Thr Phe Gly Gln Thr Ile Gln Thr
 995 1000 1005

Thr	Val	Asp	Arg	Gly	Leu	Leu	Phe	Phe	Ala	Glu	Asn	Gly	Asp	Arg
1010						1015					1020			
Phe	Ile	Ser	Leu	Asn	Ile	Glu	Asp	Gly	Lys	Leu	Met	Val	Arg	Tyr
1025						1030					1035			
Lys	Leu	Asn	Ser	Glu	Leu	Pro	Lys	Glu	Arg	Gly	Val	Gly	Asp	Ala
1040						1045					1050			
Ile	Asn	Asn	Gly	Arg	Asp	His	Ser	Ile	Gln	Ile	Lys	Ile	Gly	Lys
1055						1060					1065			
Leu	Gln	Lys	Arg	Met	Trp	Ile	Asn	Val	Asp	Val	Gln	Asn	Thr	Ile
1070						1075					1080			
Ile	Asp	Gly	Glu	Val	Phe	Asp	Phe	Ser	Thr	Tyr	Tyr	Leu	Gly	Gly
1085						1090					1095			
Ile	Pro	Ile	Ala	Ile	Arg	Glu	Arg	Phe	Asn	Ile	Ser	Thr	Pro	Ala
1100						1105					1110			
Phe	Arg	Gly	Cys	Met	Lys	Asn	Leu	Lys	Lys	Thr	Ser	Gly	Val	Val
1115						1120					1125			
Arg	Leu	Asn	Asp	Thr	Val	Gly	Val	Thr	Lys	Lys	Cys	Ser	Glu	Asp
1130						1135					1140			
Trp	Lys	Leu	Val	Arg	Ser	Ala	Ser	Phe	Ser	Arg	Gly	Gly	Gln	Leu
1145						1150					1155			
Ser	Phe	Thr	Asp	Leu	Gly	Leu	Pro	Pro	Thr	Asp	His	Leu	Gln	Ala
1160						1165					1170			
Ser	Phe	Gly	Phe	Gln	Thr	Phe	Gln	Pro	Ser	Gly	Ile	Leu	Leu	Asp
1175						1180					1185			
His	Gln	Thr	Trp	Thr	Arg	Asn	Leu	Gln	Val	Thr	Leu	Glu	Asp	Gly
1190						1195					1200			
Tyr	Ile	Glu	Leu	Ser	Thr	Ser	Asp	Ser	Gly	Gly	Pro	Ile	Phe	Lys
1205						1210					1215			
Ser	Pro	Gln	Thr	Tyr	Met	Asp	Gly	Leu	Leu	His	Tyr	Val	Ser	Val
1220						1225					1230			
Ile	Ser	Asp	Asn	Ser	Gly	Leu	Arg	Leu	Leu	Ile	Asp	Asp	Gln	Leu

1235		1240		1245
Leu Arg Asn Ser Lys Arg	Leu Lys His Ile Ser	Ser Ser Arg Gln		
1250	1255	1260		
Ser Leu Arg Leu Gly Gly	Ser Asn Phe Glu Gly	Cys Ile Ser Asn		
1265	1270	1275		
Val Phe Val Gln Arg Leu	Ser Leu Ser Pro Glu	Val Leu Asp Leu		
1280	1285	1290		
Thr Ser Asn Ser Leu Lys	Arg Asp Val Ser Leu	Gly Gly Cys Ser		
1295	1300	1305		
Leu Asn Lys Pro Pro Phe	Leu Met Leu Leu Lys	Gly Ser Thr Arg		
1310	1315	1320		
Phe Asn Lys Thr Lys Thr	Phe Arg Ile Asn Gln	Leu Leu Gln Asp		
1325	1330	1335		
Thr Pro Val Ala Ser Pro	Arg Ser Val Lys Val	Trp Gln Asp Ala		
1340	1345	1350		
Cys Ser Pro Leu Pro Lys	Thr Gln Ala Asn His	Gly Ala Leu Gln		
1355	1360	1365		
Phe Gly Asp Ile Pro Thr	Ser His Leu Leu Phe	Lys Leu Pro Gln		
1370	1375	1380		
Glu Leu Leu Lys Pro Arg	Ser Gln Phe Ala Val	Asp Met Gln Thr		
1385	1390	1395		
Thr Ser Ser Arg Gly Leu	Val Phe His Thr Gly	Thr Lys Asn Ser		
1400	1405	1410		
Phe Met Ala Leu Tyr Leu	Ser Lys Gly Arg Leu	Val Phe Ala Leu		
1415	1420	1425		
Gly Thr Asp Gly Lys Lys	Leu Arg Ile Lys Ser	Lys Glu Lys Cys		
1430	1435	1440		
Asn Asp Gly Lys Trp His	Thr Val Val Phe Gly	His Asp Gly Glu		
1445	1450	1455		
Lys Gly Arg Leu Val Val	Asp Gly Leu Arg Ala	Arg Glu Gly Ser		
1460	1465	1470		

Leu	Pro	Gly	Asn	Ser	Thr	Ile	Ser	Ile	Arg	Ala	Pro	Val	Tyr	Leu
1475						1480					1485			
Gly	Ser	Pro	Pro	Ser	Gly	Lys	Pro	Lys	Ser	Leu	Pro	Thr	Asn	Ser
1490						1495					1500			
Phe	Val	Gly	Cys	Leu	Lys	Asn	Phe	Gln	Leu	Asp	Ser	Lys	Pro	Leu
1505						1510					1515			
Tyr	Thr	Pro	Ser	Ser	Ser	Phe	Gly	Val	Ser	Ser	Cys	Leu	Gly	Gly
1520						1525					1530			
Pro	Leu	Glu	Lys	Gly	Ile	Tyr	Phe	Ser	Glu	Glu	Gly	Gly	His	Val
1535						1540					1545			
Val	Leu	Ala	His	Ser	Val	Leu	Leu	Gly	Pro	Glu	Phe	Lys	Leu	Val
1550						1555					1560			
Phe	Ser	Ile	Arg	Pro	Arg	Ser	Leu	Thr	Gly	Ile	Leu	Ile	His	Ile
1565						1570					1575			
Gly	Ser	Gln	Pro	Gly	Lys	His	Leu	Cys	Val	Tyr	Leu	Glu	Ala	Gly
1580						1585					1590			
Lys	Val	Thr	Ala	Ser	Met	Asp	Ser	Gly	Ala	Gly	Gly	Thr	Ser	Thr
1595						1600					1605			
Ser	Val	Thr	Pro	Lys	Gln	Ser	Leu	Cys	Asp	Gly	Gln	Trp	His	Ser
1610						1615					1620			
Val	Ala	Val	Thr	Ile	Lys	Gln	His	Ile	Leu	His	Leu	Glu	Leu	Asp
1625						1630					1635			
Thr	Asp	Ser	Ser	Tyr	Thr	Ala	Gly	Gln	Ile	Pro	Phe	Pro	Pro	Ala
1640						1645					1650			
Ser	Thr	Gln	Glu	Pro	Leu	His	Leu	Gly	Gly	Ala	Pro	Ala	Asn	Leu
1655						1660					1665			
Thr	Thr	Leu	Arg	Ile	Pro	Val	Trp	Lys	Ser	Phe	Phe	Gly	Cys	Leu
1670						1675					1680			
Arg	Asn	Ile	His	Val	Asn	His	Ile	Pro	Val	Pro	Val	Thr	Glu	Ala
1685						1690					1695			

Leu Glu Val Gln Gly Pro Val Ser Leu Asn Gly Cys Pro Asp Gln
 1700 1705 1710

<210> 21
 <211> 3695
 <212> PRT
 <213> Homo sapiens

<400> 21

Met Ala Lys Arg Leu Cys Ala Gly Ser Ala Leu Cys Val Arg Gly Pro
 1 5 10 15

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

Ala Arg Ala Arg Glu Glu Ala Gly Gly Gly Phe Ser Leu His Pro Pro
 35 40 45

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

Gly Glu Glu Ala Pro Ala Arg Gly Ser Pro Arg Pro Thr Glu Asp Leu
 65 70 75 80

Tyr Cys Lys Leu Val Gly Gly Pro Val Ala Gly Gly Asp Pro Asn Gln
 85 90 95

Thr Ile Arg Gly Gln Tyr Cys Asp Ile Cys Thr Ala Ala Asn Ser Asn
 100 105 110

Lys Ala His Pro Ala Ser Asn Ala Ile Asp Gly Thr Glu Arg Trp Trp
 115 120 125

Gln Ser Pro Pro Leu Ser Arg Gly Leu Glu Tyr Asn Glu Val Asn Val
 130 135 140

Thr Leu Asp Leu Gly Gln Val Phe His Val Ala Tyr Val Leu Ile Lys
 145 150 155 160

Phe Ala Asn Ser Pro Arg Pro Asp Leu Trp Val Leu Glu Arg Ser Met
 165 170 175

Asp Phe Gly Arg Thr Tyr Gln Pro Trp Gln Phe Phe Ala Ser Ser Lys
 180 185 190

Arg Asp Cys Leu Glu Arg Phe Gly Pro Gln Thr Leu Glu Arg Ile Thr

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

Cys Arg Pro Asn Phe Ser Gly Glu Arg Cys Asp Val Cys Ala Glu Gly
 450 455 460

Phe Thr Gly Phe Pro Ser Cys Tyr Pro Thr Pro Ser Ser Ser Asn Asp
 465 470 475 480

Thr Arg Glu Gln Val Leu Pro Ala Gly Gln Ile Val Asn Cys Asp Cys
 485 490 495

Ser Ala Ala Gly Thr Gln Gly Asn Ala Cys Arg Lys Asp Pro Arg Val
 500 505 510

Gly Arg Cys Leu Cys Lys Pro Asn Phe Gln Gly Thr His Cys Glu Leu
 515 520 525

Cys Ala Pro Gly Phe Tyr Gly Pro Gly Cys Gln Pro Cys Gln Cys Ser
 530 535 540

Ser Pro Gly Val Ala Asp Asp Arg Cys Asp Pro Asp Thr Gly Gln Cys
 545 550 555 560

Arg Cys Arg Val Gly Phe Glu Gly Ala Thr Cys Asp Arg Cys Ala Pro
 565 570 575

Gly Tyr Phe His Phe Pro Leu Cys Gln Leu Cys Gly Cys Ser Pro Ala
 580 585 590

Gly Thr Leu Pro Glu Gly Cys Asp Glu Ala Gly Arg Cys Leu Cys Gln
 595 600 605

Pro Glu Phe Ala Gly Pro His Cys Asp Arg Cys Arg Pro Gly Tyr His
 610 615 620

Gly Phe Pro Asn Cys Gln Ala Cys Thr Cys Asp Pro Arg Gly Ala Leu
 625 630 635 640

Asp Gln Leu Cys Gly Ala Gly Gly Leu Cys Arg Cys Arg Pro Gly Tyr
 645 650 655

Thr Gly Thr Ala Cys Gln Glu Cys Ser Pro Gly Phe His Gly Phe Pro
 660 665 670

Ser Cys Val Pro Cys His Cys Ser Ala Glu Gly Ser Leu His Ala Ala
 675 680 685

Cys Asp Pro Arg Ser Gly Gln Cys Ser Cys Arg Pro Arg Val Thr Gly
 690 695 700
 Leu Arg Cys Asp Thr Cys Val Pro Gly Ala Tyr Asn Phe Pro Tyr Cys
 705 710 715 720
 Glu Ala Gly Ser Cys His Pro Ala Gly Leu Ala Pro Val Asp Pro Ala
 725 730 735
 Leu Pro Glu Ala Gln Val Pro Cys Met Cys Arg Ala His Val Glu Gly
 740 745 750
 Pro Ser Cys Asp Arg Cys Lys Pro Gly Phe Trp Gly Leu Ser Pro Ser
 755 760 765
 Asn Pro Glu Gly Cys Thr Arg Cys Ser Cys Asp Leu Arg Gly Thr Leu
 770 775 780
 Gly Gly Val Ala Glu Cys Gln Pro Gly Thr Gly Gln Cys Phe Cys Lys
 785 790 795 800
 Pro His Val Cys Gly Gln Ala Cys Ala Ser Cys Lys Asp Gly Phe Phe
 805 810 815
 Gly Leu Asp Gln Ala Asp Tyr Phe Gly Cys Arg Ser Cys Arg Cys Asp
 820 825 830
 Ile Gly Gly Ala Leu Gly Gln Ser Cys Glu Pro Arg Thr Gly Val Cys
 835 840 845
 Arg Cys Arg Pro Asn Thr Gln Gly Pro Thr Cys Ser Glu Pro Ala Arg
 850 855 860
 Asp His Tyr Leu Pro Asp Leu His His Leu Arg Leu Glu Leu Glu Glu
 865 870 875 880
 Ala Ala Thr Pro Glu Gly His Ala Val Arg Phe Gly Phe Asn Pro Leu
 885 890 895
 Glu Phe Glu Asn Phe Ser Trp Arg Gly Tyr Ala Gln Met Ala Pro Val
 900 905 910
 Gln Pro Arg Ile Val Ala Arg Leu Asn Leu Thr Ser Pro Asp Leu Phe
 915 920 925

Trp Leu Val Phe Arg Tyr Val Asn Arg Gly Ala Met Ser Val Ser Gly
 930 935 940

Arg Val Ser Val Arg Glu Glu Gly Arg Ser Ala Thr Cys Ala Asn Cys
 945 950 955 960

Thr Ala Gln Ser Gln Pro Val Ala Phe Pro Pro Ser Thr Glu Pro Ala
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Phe Ile Thr Val Pro Gln Arg Gly Phe Gly Glu Pro Phe Val Leu Asn
 980 985 990

Pro Gly Thr Trp Ala Leu Arg Val Glu Ala Glu Gly Val Leu Leu Asp
 995 1000 1005

Tyr Val Val Leu Leu Pro Ser Ala Tyr Tyr Glu Ala Ala Leu Leu
 1010 1015 1020

Gln Leu Arg Val Thr Glu Ala Cys Thr Tyr Arg Pro Ser Ala Gln
 1025 1030 1035

Gln Ser Gly Asp Asn Cys Leu Leu Tyr Thr His Leu Pro Leu Asp
 1040 1045 1050

Gly Phe Pro Ser Ala Ala Gly Leu Glu Ala Leu Cys Arg Gln Asp
 1055 1060 1065

Asn Ser Leu Pro Arg Pro Cys Pro Thr Glu Gln Leu Ser Pro Ser
 1070 1075 1080

His Pro Pro Leu Ile Thr Cys Thr Gly Ser Asp Val Asp Val Gln
 1085 1090 1095

Leu Gln Val Ala Val Pro Gln Pro Gly Arg Tyr Ala Leu Val Val
 1100 1105 1110

Glu Tyr Ala Asn Glu Asp Ala Arg Gln Glu Val Gly Val Ala Val
 1115 1120 1125

His Thr Pro Gln Arg Ala Pro Gln Gln Gly Leu Leu Ser Leu His
 1130 1135 1140

Pro Cys Leu Tyr Ser Thr Leu Cys Arg Gly Thr Ala Arg Asp Thr
 1145 1150 1155

Gln Asp His Leu Ala Val Phe His Leu Asp Ser Glu Ala Ser Val

1160		1165		1170
Arg Leu Thr Ala Glu Gln Ala	Arg Phe Phe Leu His Gly Val Thr			
1175		1180		1185
Leu Val Pro Ile Glu Glu Phe	Ser Pro Glu Phe Val Glu Pro Arg			
1190		1195		1200
Val Ser Cys Ile Ser Ser His	Gly Ala Phe Gly Pro Asn Ser Ala			
1205		1210		1215
Ala Cys Leu Pro Ser Arg Phe	Pro Lys Pro Pro Gln Pro Ile Ile			
1220		1225		1230
Leu Arg Asp Cys Gln Val Ile	Pro Leu Pro Pro Gly Leu Pro Leu			
1235		1240		1245
Thr His Ala Gln Asp Leu Thr	Pro Ala Met Ser Pro Ala Gly Pro			
1250		1255		1260
Arg Pro Arg Pro Pro Thr Ala	Val Asp Pro Asp Ala Glu Pro Thr			
1265		1270		1275
Leu Leu Arg Glu Pro Gln Ala	Thr Val Val Phe Thr Thr His Val			
1280		1285		1290
Pro Thr Leu Gly Arg Tyr Ala	Phe Leu Leu His Gly Tyr Gln Pro			
1295		1300		1305
Ala His Pro Thr Phe Pro Val	Glu Val Leu Ile Asn Ala Gly Arg			
1310		1315		1320
Val Trp Gln Gly His Ala Asn	Ala Ser Phe Cys Pro His Gly Tyr			
1325		1330		1335
Gly Cys Arg Thr Leu Val Val	Cys Glu Gly Gln Ala Leu Leu Asp			
1340		1345		1350
Val Thr His Ser Glu Leu Thr	Val Thr Val Arg Val Pro Lys Gly			
1355		1360		1365
Arg Trp Leu Trp Leu Asp Tyr	Val Leu Val Val Pro Glu Asn Val			
1370		1375		1380
Tyr Ser Phe Gly Tyr Leu Arg	Glu Glu Pro Leu Asp Lys Ser Tyr			
1385		1390		1395

Asp	Phe	Ile	Ser	His	Cys	Ala	Ala	Gln	Gly	Tyr	His	Ile	Ser	Pro
1400						1405					1410			
Ser	Ser	Ser	Ser	Leu	Phe	Cys	Arg	Asn	Ala	Ala	Ala	Ser	Leu	Ser
1415						1420					1425			
Leu	Phe	Tyr	Asn	Asn	Gly	Ala	Arg	Pro	Cys	Gly	Cys	His	Glu	Val
1430						1435					1440			
Gly	Ala	Thr	Gly	Pro	Thr	Cys	Glu	Pro	Phe	Gly	Gly	Gln	Cys	Pro
1445						1450					1455			
Cys	His	Ala	His	Val	Ile	Gly	Arg	Asp	Cys	Ser	Arg	Cys	Ala	Thr
1460						1465					1470			
Gly	Tyr	Trp	Gly	Phe	Pro	Asn	Cys	Arg	Pro	Cys	Asp	Cys	Gly	Ala
1475						1480					1485			
Arg	Leu	Cys	Asp	Glu	Leu	Thr	Gly	Gln	Cys	Ile	Cys	Pro	Pro	Arg
1490						1495					1500			
Thr	Ile	Pro	Pro	Asp	Cys	Leu	Leu	Cys	Gln	Pro	Gln	Thr	Phe	Gly
1505						1510					1515			
Cys	His	Pro	Leu	Val	Gly	Cys	Glu	Glu	Cys	Asn	Cys	Ser	Gly	Pro
1520						1525					1530			
Gly	Ile	Gln	Glu	Leu	Thr	Asp	Pro	Thr	Cys	Asp	Thr	Asp	Ser	Gly
1535						1540					1545			
Gln	Cys	Lys	Cys	Arg	Pro	Asn	Val	Thr	Gly	Arg	Arg	Cys	Asp	Thr
1550						1555					1560			
Cys	Ser	Pro	Gly	Phe	His	Gly	Tyr	Pro	Arg	Cys	Arg	Pro	Cys	Asp
1565						1570					1575			
Cys	His	Glu	Ala	Gly	Thr	Ala	Pro	Gly	Val	Cys	Asp	Pro	Leu	Thr
1580						1585					1590			
Gly	Gln	Cys	Tyr	Cys	Lys	Glu	Asn	Val	Gln	Gly	Pro	Lys	Cys	Asp
1595						1600					1605			
Gln	Cys	Ser	Leu	Gly	Thr	Phe	Ser	Leu	Asp	Ala	Ala	Asn	Pro	Lys
1610						1615					1620			

Gly	Cys	Thr	Arg	Cys	Phe	Cys	Phe	Gly	Ala	Thr	Glu	Arg	Cys	Arg
1625						1630					1635			
Ser	Ser	Ser	Tyr	Thr	Arg	Gln	Glu	Phe	Val	Asp	Met	Glu	Gly	Trp
1640						1645					1650			
Val	Leu	Leu	Ser	Thr	Asp	Arg	Gln	Val	Val	Pro	His	Glu	Arg	Gln
1655						1660					1665			
Pro	Gly	Thr	Glu	Met	Leu	Arg	Ala	Asp	Leu	Arg	His	Val	Pro	Glu
1670						1675					1680			
Ala	Val	Pro	Glu	Ala	Phe	Pro	Glu	Leu	Tyr	Trp	Gln	Ala	Pro	Pro
1685						1690					1695			
Ser	Tyr	Leu	Gly	Asp	Arg	Val	Ser	Ser	Tyr	Gly	Gly	Thr	Leu	Arg
1700						1705					1710			
Tyr	Glu	Leu	His	Ser	Glu	Thr	Gln	Arg	Gly	Asp	Val	Phe	Val	Pro
1715						1720					1725			
Met	Glu	Ser	Arg	Pro	Asp	Val	Val	Leu	Gln	Gly	Asn	Gln	Met	Ser
1730						1735					1740			
Ile	Thr	Phe	Leu	Glu	Pro	Ala	Tyr	Pro	Thr	Pro	Gly	His	Val	His
1745						1750					1755			
Arg	Gly	Gln	Leu	Gln	Leu	Val	Glu	Gly	Asn	Phe	Arg	His	Thr	Glu
1760						1765					1770			
Thr	Arg	Asn	Thr	Val	Ser	Arg	Glu	Glu	Leu	Met	Met	Val	Leu	Ala
1775						1780					1785			
Ser	Leu	Glu	Gln	Leu	Gln	Ile	Arg	Ala	Leu	Phe	Ser	Gln	Ile	Ser
1790						1795					1800			
Ser	Ala	Val	Phe	Leu	Arg	Arg	Val	Ala	Leu	Glu	Val	Ala	Ser	Pro
1805						1810					1815			
Ala	Gly	Gln	Gly	Ala	Leu	Ala	Ser	Asn	Val	Glu	Leu	Cys	Leu	Cys
1820						1825					1830			
Pro	Ala	Ser	Tyr	Arg	Gly	Asp	Ser	Cys	Gln	Glu	Cys	Ala	Pro	Gly
1835						1840					1845			

Phe	Tyr	Arg	Asp	Val	Lys	Gly	Leu	Phe	Leu	Gly	Arg	Cys	Val	Pro
1850						1855					1860			
Cys	Gln	Cys	His	Gly	His	Ser	Asp	Arg	Cys	Leu	Pro	Gly	Ser	Gly
1865						1870					1875			
Val	Cys	Val	Asp	Cys	Gln	His	Asn	Thr	Glu	Gly	Ala	His	Cys	Glu
1880						1885					1890			
Arg	Cys	Gln	Ala	Gly	Phe	Val	Ser	Ser	Arg	Asp	Asp	Pro	Ser	Ala
1895						1900					1905			
Pro	Cys	Val	Ser	Cys	Pro	Cys	Pro	Leu	Ser	Val	Pro	Ser	Asn	Asn
1910						1915					1920			
Phe	Ala	Glu	Gly	Cys	Val	Leu	Arg	Gly	Gly	Arg	Thr	Gln	Cys	Leu
1925						1930					1935			
Cys	Lys	Pro	Gly	Tyr	Ala	Gly	Ala	Ser	Cys	Glu	Arg	Cys	Ala	Pro
1940						1945					1950			
Gly	Phe	Phe	Gly	Asn	Pro	Leu	Val	Leu	Gly	Ser	Ser	Cys	Gln	Pro
1955						1960					1965			
Cys	Asp	Cys	Ser	Gly	Asn	Gly	Asp	Pro	Asn	Leu	Leu	Phe	Ser	Asp
1970						1975					1980			
Cys	Asp	Pro	Leu	Thr	Gly	Ala	Cys	Arg	Gly	Cys	Leu	Arg	His	Thr
1985						1990					1995			
Thr	Gly	Pro	Arg	Cys	Glu	Ile	Cys	Ala	Pro	Gly	Phe	Tyr	Gly	Asn
2000						2005					2010			
Ala	Leu	Leu	Pro	Gly	Asn	Cys	Thr	Arg	Cys	Asp	Cys	Thr	Pro	Cys
2015						2020					2025			
Gly	Thr	Glu	Ala	Cys	Asp	Pro	His	Ser	Gly	His	Cys	Leu	Cys	Lys
2030						2035					2040			
Ala	Gly	Val	Thr	Gly	Arg	Arg	Cys	Asp	Arg	Cys	Gln	Glu	Gly	His
2045						2050					2055			
Phe	Gly	Phe	Asp	Gly	Cys	Gly	Gly	Cys	Arg	Pro	Cys	Ala	Cys	Gly
2060						2065					2070			
Pro	Ala	Ala	Glu	Gly	Ser	Glu	Cys	His	Pro	Gln	Ser	Gly	Gln	Cys

2075		2080		2085
His Cys Arg Pro Gly Thr Met Gly Pro Gln Cys Arg Glu Cys Ala				
2090		2095		2100
Pro Gly Tyr Trp Gly Leu Pro Glu Gln Gly Cys Arg Arg Cys Gln				
2105		2110		2115
Cys Pro Gly Gly Arg Cys Asp Pro His Thr Gly Arg Cys Asn Cys				
2120		2125		2130
Pro Pro Gly Leu Ser Gly Glu Arg Cys Asp Thr Cys Ser Gln Gln				
2135		2140		2145
His Gln Val Pro Val Pro Gly Gly Pro Val Gly His Ser Ile His				
2150		2155		2160
Cys Glu Val Cys Asp His Cys Val Val Leu Leu Leu Asp Asp Leu				
2165		2170		2175
Glu Arg Ala Gly Ala Leu Leu Pro Ala Ile His Glu Gln Leu Arg				
2180		2185		2190
Gly Ile Asn Ala Ser Ser Met Ala Trp Ala Arg Leu His Arg Leu				
2195		2200		2205
Asn Ala Ser Ile Ala Asp Leu Gln Ser Gln Leu Arg Ser Pro Leu				
2210		2215		2220
Gly Pro Arg His Glu Thr Ala Gln Gln Leu Glu Val Leu Glu Gln				
2225		2230		2235
Gln Ser Thr Ser Leu Gly Gln Asp Ala Arg Arg Leu Gly Gly Gln				
2240		2245		2250
Ala Val Gly Thr Arg Asp Gln Ala Ser Gln Leu Leu Ala Gly Thr				
2255		2260		2265
Glu Ala Thr Leu Gly His Ala Lys Thr Leu Leu Ala Ala Ile Arg				
2270		2275		2280
Ala Val Asp Arg Thr Leu Ser Glu Leu Met Ser Gln Thr Gly His				
2285		2290		2295
Leu Gly Leu Ala Asn Ala Ser Ala Pro Ser Gly Glu Gln Leu Leu				
2300		2305		2310

Arg Thr	Leu Ala Glu Val	Glu	Arg Leu Leu Trp	Glu	Met Arg Ala
2315		2320		2325	
Arg Asp	Leu Gly Ala Pro	Gln	Ala Ala Ala Glu	Ala	Glu Leu Ala
2330		2335		2340	
Ala Ala	Gln Arg Leu Leu	Ala	Arg Val Gln Glu	Gln	Leu Ser Ser
2345		2350		2355	
Leu Trp	Glu Glu Asn Gln	Ala	Leu Ala Thr Gln	Thr	Arg Asp Arg
2360		2365		2370	
Leu Ala	Gln His Glu Ala	Gly	Leu Met Asp Leu	Arg	Glu Ala Leu
2375		2380		2385	
Asn Arg	Ala Val Asp Ala	Thr	Arg Glu Ala Gln	Glu	Leu Asn Ser
2390		2395		2400	
Arg Asn	Gln Glu Arg Leu	Glu	Glu Ala Leu Gln	Arg	Lys Gln Glu
2405		2410		2415	
Leu Ser	Arg Asp Asn Ala	Thr	Leu Gln Ala Thr	Leu	His Ala Ala
2420		2425		2430	
Arg Asp	Thr Leu Ala Ser	Val	Phe Arg Leu Leu	His	Ser Leu Asp
2435		2440		2445	
Gln Ala	Lys Glu Glu Leu	Glu	Arg Leu Ala Ala	Ser	Leu Asp Gly
2450		2455		2460	
Ala Arg	Thr Pro Leu Leu	Gln	Arg Met Gln Thr	Phe	Ser Pro Ala
2465		2470		2475	
Gly Ser	Lys Leu Arg Leu	Val	Glu Ala Ala Glu	Ala	His Ala Gln
2480		2485		2490	
Gln Leu	Gly Gln Leu Ala	Leu	Asn Leu Ser Ser	Ile	Ile Leu Asp
2495		2500		2505	
Val Asn	Gln Asp Arg Leu	Thr	Gln Arg Ala Ile	Glu	Ala Ser Asn
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Ala Tyr	Ser Arg Ile Leu	Gln	Ala Val Gln Ala	Ala	Glu Asp Ala
2525		2530		2535	

Ala	Gly	Gln	Ala	Leu	Gln	Gln	Ala	Asp	His	Thr	Trp	Ala	Thr	Val
2540						2545					2550			
Val	Arg	Gln	Gly	Leu	Val	Asp	Arg	Ala	Gln	Gln	Leu	Leu	Ala	Asn
2555						2560					2565			
Ser	Thr	Ala	Leu	Glu	Glu	Ala	Met	Leu	Gln	Glu	Gln	Gln	Arg	Leu
2570						2575					2580			
Gly	Leu	Val	Trp	Ala	Ala	Leu	Gln	Gly	Ala	Arg	Thr	Gln	Leu	Arg
2585						2590					2595			
Asp	Val	Arg	Ala	Lys	Lys	Asp	Gln	Leu	Glu	Ala	His	Ile	Gln	Ala
2600						2605					2610			
Ala	Gln	Ala	Met	Leu	Ala	Met	Asp	Thr	Asp	Glu	Thr	Ser	Lys	Lys
2615						2620					2625			
Ile	Ala	His	Ala	Lys	Ala	Val	Ala	Ala	Glu	Ala	Gln	Asp	Thr	Ala
2630						2635					2640			
Thr	Arg	Val	Gln	Ser	Gln	Leu	Gln	Ala	Met	Gln	Glu	Asn	Val	Glu
2645						2650					2655			
Arg	Trp	Gln	Gly	Gln	Tyr	Glu	Gly	Leu	Arg	Gly	Gln	Asp	Leu	Gly
2660						2665					2670			
Gln	Ala	Val	Leu	Asp	Ala	Gly	His	Ser	Val	Ser	Thr	Leu	Glu	Lys
2675						2680					2685			
Thr	Leu	Pro	Gln	Leu	Leu	Ala	Lys	Leu	Ser	Ile	Leu	Glu	Asn	Arg
2690						2695					2700			
Gly	Val	His	Asn	Ala	Ser	Leu	Ala	Leu	Ser	Ala	Ser	Ile	Gly	Arg
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Val	Arg	Glu	Leu	Ile	Ala	Gln	Ala	Arg	Gly	Ala	Ala	Ser	Lys	Val
2720						2725					2730			
Lys	Val	Pro	Met	Lys	Phe	Asn	Gly	Arg	Ser	Gly	Val	Gln	Leu	Arg
2735						2740					2745			
Thr	Pro	Arg	Asp	Leu	Ala	Asp	Leu	Ala	Ala	Tyr	Thr	Ala	Leu	Lys
2750						2755					2760			

Phe	Tyr	Leu	Gln	Gly	Pro	Glu	Pro	Glu	Pro	Gly	Gln	Gly	Thr	Glu
2765						2770					2775			
Asp	Arg	Phe	Val	Met	Tyr	Met	Gly	Ser	Arg	Gln	Ala	Thr	Gly	Asp
2780						2785					2790			
Tyr	Met	Gly	Val	Ser	Leu	Arg	Asp	Lys	Lys	Val	His	Trp	Val	Tyr
2795						2800					2805			
Gln	Leu	Gly	Glu	Ala	Gly	Pro	Ala	Val	Leu	Ser	Ile	Asp	Glu	Asp
2810						2815					2820			
Ile	Gly	Glu	Gln	Phe	Ala	Ala	Val	Ser	Leu	Asp	Arg	Thr	Leu	Gln
2825						2830					2835			
Phe	Gly	His	Met	Ser	Val	Thr	Val	Glu	Arg	Gln	Met	Ile	Gln	Glu
2840						2845					2850			
Thr	Lys	Gly	Asp	Thr	Val	Ala	Pro	Gly	Ala	Glu	Gly	Leu	Leu	Asn
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Leu	Arg	Pro	Asp	Asp	Phe	Val	Phe	Tyr	Val	Gly	Gly	Tyr	Pro	Ser
2870						2875					2880			
Thr	Phe	Thr	Pro	Pro	Pro	Leu	Leu	Arg	Phe	Pro	Gly	Tyr	Arg	Gly
2885						2890					2895			
Cys	Ile	Glu	Met	Asp	Thr	Leu	Asn	Glu	Glu	Val	Val	Ser	Leu	Tyr
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Cys	Ala	Arg	Ser	Lys	Ser	Thr	Gly	Asp	Pro	Trp	Leu	Thr	Asp	Gly
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Ser	Tyr	Leu	Asp	Gly	Thr	Gly	Phe	Ala	Arg	Ile	Ser	Phe	Asp	Ser
2945						2950					2955			
Gln	Ile	Ser	Thr	Thr	Lys	Arg	Phe	Glu	Gln	Glu	Leu	Arg	Leu	Val
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2975						2980					2985			
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Gly Ser Arg Lys Arg Val Leu 3035 3040	Val Arg Val Glu Arg 3045	Ala Thr Val
Tyr Ser Val Glu Gln Asp Asn 3050 3055	Asp Leu Glu Leu Ala 3060	Asp Ala Tyr
Tyr Leu Gly Gly Val Pro Pro 3065 3070	Asp Gln Leu Pro Pro 3075	Ser Leu Arg
Arg Leu Phe Pro Thr Gly Gly 3080 3085	Ser Val Arg Gly Cys 3090	Val Lys Gly
Ile Lys Ala Leu Gly Lys Tyr 3095 3100	Val Asp Leu Lys Arg 3105	Leu Asn Thr
Thr Gly Val Ser Ala Gly Cys 3110 3115	Thr Ala Asp Leu Leu 3120	Val Gly Arg
Ala Met Thr Phe His Gly His 3125 3130	Gly Phe Leu Arg Leu 3135	Ala Leu Ser
Asn Val Ala Pro Leu Thr Gly 3140 3145	Asn Val Tyr Ser Gly 3150	Phe Gly Phe
His Ser Ala Gln Asp Ser Ala 3155 3160	Leu Leu Tyr Tyr Arg 3165	Ala Ser Pro
Asp Gly Leu Cys Gln Val Ser 3170 3175	Leu Gln Gln Gly Arg 3180	Val Ser Leu
Gln Leu Leu Arg Thr Glu Val 3185 3190	Lys Thr Gln Ala Gly 3195	Phe Ala Asp
Gly Ala Pro His Tyr Val Ala 3200 3205	Phe Tyr Ser Asn Ala 3210	Thr Gly Val
Trp Leu Tyr Val Asp Asp Gln 3215 3220	Leu Gln Gln Met Lys 3225	Pro His Arg

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Leu	Leu	Leu	Gly	Gly	Leu	Pro	Glu	Ser	Gly	Thr	Ile	Tyr	Asn	Phe
3245						3250					3255			
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3260						3265					3270			
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3275						3280					3285			
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3380						3385					3390			
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Thr	Val	Gly	Phe	Ser	Gly	Cys	Val	Lys	Arg	Leu	Arg	Leu	His	Gly
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3545						3550					3555			
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Glu	Phe	Ser	Thr	Ser	Val	Thr	Arg	Pro	Ser	Val	Leu	Cys	Asp	Gly
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Gln	Trp	His	Arg	Leu	Ala	Val	Met	Lys	Ser	Gly	Asn	Val	Leu	Arg
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Leu	Glu	Val	Asp	Ala	Gln	Ser	Asn	His	Thr	Val	Gly	Pro	Leu	Leu
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Cys	Met	Arg	Arg	Leu	Ala	Val	Asn	Arg	Ser	Pro	Val	Ala	Met	Thr
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Ala Ala
 3695

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 <211> 925
 <212> PRT
 <213> Homo sapiens

<400> 22

Met Ala Glu Ala Asn Pro Arg Arg Gly Lys Met Arg Phe Arg Arg Asn
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Ala Ala Ser Phe Pro Gly Asn Leu His Leu Val Leu Val Leu Arg Pro
 20 25 30

Thr Ser Phe Leu Gln Arg Thr Phe Thr Asp Ile Gly Phe Trp Phe Ser
 35 40 45

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

Ser Asp Leu Leu Thr Tyr Ile Asp Asp Lys Gln Leu Thr Pro Glu Leu
 65 70 75 80

Gly Gly Thr Leu Gln Tyr Cys His Ser Glu Trp Ile Ile Phe Arg Asn
 85 90 95

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

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

Pro Ser Ile Glu Glu Ile Leu Ala Ile Arg Ala Glu Arg Tyr His Leu
 130 135 140

Leu Lys Asn Asp Ile Thr Ala Val Thr Lys Glu Gly Lys Ile Leu Leu
 145 150 155 160

Thr Asn Leu Glu Val Pro Asp Thr Glu Gly Ala Val Ser Ser Arg Leu
 165 170 175

Glu Cys His Arg Gln Ile Ser Gly Asp Trp Gln Thr Ile Asn Lys Leu
 180 185 190

Leu Thr Gln Val His Asp Met Glu Thr Ala Phe Asp Gly Phe Trp Glu
 195 200 205

Lys His Gln Leu Lys Met Glu Gln Tyr Leu Gln Leu Trp Lys Phe Glu
 210 215 220

Gln Asp Phe Gln Gln Leu Val Thr Glu Val Glu Phe Leu Leu Asn Gln
 225 230 235 240

Gln Ala Glu Leu Ala Asp Val Thr Gly Thr Ile Ala Gln Val Lys Gln
 245 250 255

Lys Ile Lys Lys Leu Glu Asn Leu Asp Glu Asn Ser Gln Glu Leu Leu
 260 265 270

Ser Lys Ala Gln Phe Val Ile Leu His Gly His Lys Leu Ala Ala Asn
 275 280 285

His His Tyr Ala Leu Asp Leu Ile Cys Gln Arg Cys Asn Glu Leu Arg
 290 295 300

Tyr Leu Ser Asp Ile Leu Val Asn Glu Ile Lys Ala Lys Arg Ile Gln
 305 310 315 320

Leu Ser Arg Thr Phe Lys Met His Lys Leu Leu Gln Gln Ala Arg Gln
 325 330 335

Cys Cys Asp Glu Gly Glu Cys Leu Leu Ala Asn Gln Glu Ile Asp Lys
 340 345 350

Phe Gln Ser Lys Glu Asp Ala Gln Lys Ala Leu Gln Asp Ile Glu Asn
 355 360 365

Phe Leu Glu Met Ala Leu Pro Phe Ile Asn Tyr Glu Pro Glu Thr Leu
 370 375 380

Gln Tyr Glu Phe Asp Val Ile Leu Ser Pro Glu Leu Lys Val Gln Met
 385 390 395 400

Lys Thr Ile Gln Leu Lys Leu Glu Asn Ile Arg Ser Ile Phe Glu Asn
 405 410 415

Gln Gln Ala Gly Phe Arg Asn Leu Ala Asp Lys His Val Arg Pro Ile
 420 425 430

Gln Phe Val Val Pro Thr Pro Glu Asn Leu Val Thr Ser Gly Thr Pro
 435 440 445

Phe Phe Ser Ser Lys Gln Gly Lys Lys Thr Trp Arg Gln Asn Gln Ser
 450 455 460

Asn Leu Lys Ile Glu Val Val Pro Asp Cys Gln Glu Lys Arg Ser Ser
 465 470 475 480

Gly Pro Ser Ser Ser Leu Asp Asn Gly Asn Ser Leu Asp Val Leu Lys
 485 490 495

Asn His Val Leu Asn Glu Leu Ile Gln Thr Glu Arg Val Tyr Val Arg
 500 505 510

Glu Leu Tyr Thr Val Leu Leu Gly Tyr Arg Ala Glu Met Asp Asn Pro
 515 520 525

Glu Met Phe Asp Leu Met Pro Pro Leu Leu Arg Asn Lys Lys Asp Ile
 530 535 540

Leu Phe Gly Asn Met Ala Glu Ile Tyr Glu Phe His Asn Asp Ile Phe
 545 550 555 560

Leu Ser Ser Leu Glu Asn Cys Ala His Ala Pro Glu Arg Val Gly Pro
 565 570 575

Cys Phe Leu Glu Arg Lys Asp Asp Phe Gln Met Tyr Ala Lys Tyr Cys
 580 585 590

Gln Asn Lys Pro Arg Ser Glu Thr Ile Trp Arg Lys Tyr Ser Glu Cys
 595 600 605

Ala Phe Phe Gln Glu Cys Gln Arg Lys Leu Lys His Arg Leu Arg Leu
 610 615 620

Asp Ser Tyr Leu Leu Lys Pro Val Gln Arg Ile Thr Lys Tyr Gln Leu
 625 630 635 640

Leu Leu Lys Glu Leu Leu Lys Tyr Ser Lys Asp Cys Glu Gly Ser Ala
 645 650 655

Leu Leu Lys Lys Ala Leu Asp Ala Met Leu Asp Leu Leu Lys Ser Val
 660 665 670

Asn Asp Ser Met His Gln Ile Ala Ile Asn Gly Tyr Ile Gly Asn Leu
 675 680 685

Asn Glu Leu Gly Lys Met Ile Met Gln Gly Gly Phe Ser Val Trp Ile
 690 695 700

Gly His Lys Lys Gly Ala Thr Lys Met Lys Asp Leu Ala Arg Phe Lys
 705 710 715 720

Pro Met Gln Arg His Leu Phe Leu Tyr Glu Lys Ala Ile Val Phe Cys
 725 730 735

Lys Arg Arg Val Glu Ser Gly Glu Gly Ser Asp Arg Tyr Pro Ser Tyr
 740 745 750

Ser Phe Lys His Cys Trp Lys Met Asp Glu Val Gly Ile Thr Glu Tyr
 755 760 765

Val Lys Gly Asp Asn Arg Lys Phe Glu Ile Trp Tyr Gly Glu Lys Glu
 770 775 780

Glu Val Tyr Ile Val Gln Ala Ser Asn Val Asp Val Lys Met Thr Trp
 785 790 795 800

Leu Lys Glu Ile Arg Asn Ile Leu Leu Lys Gln Gln Glu Leu Leu Thr
 805 810 815

Val Lys Lys Arg Lys Gln Gln Asp Gln Leu Thr Glu Arg Asp Lys Phe
 820 825 830

Gln Ile Ser Leu Gln Gln Asn Asp Glu Lys Gln Gln Gly Ala Phe Ile
 835 840 845

Ser Thr Glu Glu Thr Glu Leu Glu His Thr Ser Thr Val Val Glu Val
 850 855 860

Cys Glu Ala Ile Ala Ser Val Gln Ala Glu Ala Asn Thr Val Trp Thr
 865 870 875 880

Glu Ala Ser Gln Ser Ala Glu Ile Ser Glu Glu Pro Ala Glu Trp Ser
 885 890 895

Ser Asn Tyr Phe Tyr Pro Thr Tyr Asp Glu Asn Glu Glu Glu Asn Arg
 900 905 910

Pro Leu Met Arg Pro Val Ser Glu Met Ala Leu Leu Tyr

915 920 925

 <210> 23
 <211> 984
 <212> PRT
 <213> Homo sapiens

 <400> 23

 Met Thr Val Arg Arg Leu Ser Leu Leu Cys Arg Asp Leu Trp Ala Leu
 1 5 10 15

 Trp Leu Leu Leu Lys Ala Gly Ala Asp Glu Ile Met His Gln Asp Ile
 20 25 30

 Val Pro Leu Cys Ala Ala Asp Ile Gln Asp Gln Leu Lys Lys Arg Phe
 35 40 45

 Ala Tyr Leu Ser Gly Gly Arg Gly Gln Asp Gly Ser Pro Val Ile Thr
 50 55 60

 Phe Pro Asp Tyr Pro Ala Phe Ser Glu Ile Pro Asp Lys Glu Phe Gln
 65 70 75 80

 Asn Val Met Thr Tyr Leu Thr Ser Ile Pro Ser Leu Gln Asp Ala Gly
 85 90 95

 Ile Gly Phe Ile Leu Val Ile Asp Arg Arg Arg Asp Lys Trp Thr Ser
 100 105 110

 Val Lys Ala Ser Val Leu Arg Ile Ala Ala Ser Phe Pro Ala Asn Leu
 115 120 125

 Gln Leu Val Leu Val Leu Arg Pro Thr Gly Phe Phe Gln Arg Thr Leu
 130 135 140

 Ser Asp Ile Ala Phe Lys Phe Asn Arg Asp Asp Phe Lys Met Lys Val
 145 150 155 160

 Pro Val Ile Met Leu Ser Ser Val Pro Asp Leu His Gly Tyr Ile Asp
 165 170 175

 Lys Ser Gln Leu Thr Glu Asp Leu Gly Gly Thr Leu Asp Tyr Cys His
 180 185 190

 Ser Arg Trp Leu Cys Gln Arg Thr Ala Ile Glu Ser Phe Ala Leu Met
 195 200 205

Val Lys Gln Thr Ala Gln Met Leu Gln Ser Phe Gly Thr Glu Leu Ala
 210 215 220
 Glu Thr Glu Leu Pro Asn Asp Val Gln Ser Thr Ser Ser Val Leu Cys
 225 230 235 240
 Ala His Thr Glu Lys Lys Asp Lys Ala Lys Glu Asp Leu Arg Leu Ala
 245 250 255
 Leu Lys Glu Gly His Ser Val Leu Glu Ser Leu Arg Glu Leu Gln Ala
 260 265 270
 Glu Gly Ser Glu Pro Ser Val Asn Gln Asp Gln Leu Asp Asn Gln Ala
 275 280 285
 Thr Val Gln Arg Leu Leu Ala Gln Leu Asn Glu Thr Glu Ala Ala Phe
 290 295 300
 Asp Glu Phe Trp Ala Lys His Gln Gln Lys Leu Glu Gln Cys Leu Gln
 305 310 315 320
 Leu Arg His Phe Glu Gln Gly Phe Arg Glu Val Lys Ala Ile Leu Asp
 325 330 335
 Ala Ala Ser Gln Lys Ile Ala Thr Phe Thr Asp Ile Gly Asn Ser Leu
 340 345 350
 Ala His Val Glu His Leu Leu Arg Asp Leu Ala Ser Phe Glu Glu Lys
 355 360 365
 Ser Gly Val Ala Val Glu Arg Ala Arg Ala Leu Ser Leu Asp Gly Glu
 370 375 380
 Gln Leu Ile Gly Asn Lys His Tyr Ala Val Asp Ser Ile Arg Pro Lys
 385 390 395 400
 Cys Gln Glu Leu Arg His Leu Cys Asp Gln Phe Ser Ala Glu Ile Ala
 405 410 415
 Arg Arg Arg Gly Leu Leu Ser Lys Ser Leu Glu Leu His Arg Arg Leu
 420 425 430
 Glu Thr Ser Met Lys Trp Cys Asp Glu Gly Ile Tyr Leu Leu Ala Ser
 435 440 445

Gln Pro Val Asp Lys Cys Gln Ser Gln Asp Gly Ala Glu Ala Ala Leu
 450 455 460

Gln Glu Ile Glu Lys Phe Leu Glu Thr Gly Ala Glu Asn Lys Ile Gln
 465 470 475 480

Glu Leu Asn Ala Ile Tyr Lys Glu Tyr Glu Ser Ile Leu Asn Gln Asp
 485 490 495

Leu Met Glu His Val Arg Lys Val Phe Gln Lys Gln Ala Ser Met Glu
 500 505 510

Glu Val Phe His Arg Arg Gln Ala Ser Leu Lys Lys Leu Ala Ala Arg
 515 520 525

Gln Thr Arg Pro Val Gln Pro Val Ala Pro Arg Pro Glu Ala Leu Ala
 530 535 540

Lys Ser Pro Cys Pro Ser Pro Gly Ile Arg Arg Gly Ser Glu Asn Ser
 545 550 555 560

Ser Ser Glu Gly Gly Ala Leu Arg Arg Gly Pro Tyr Arg Arg Ala Lys
 565 570 575

Ser Glu Met Ser Glu Ser Arg Gln Gly Arg Gly Ser Ala Gly Glu Glu
 580 585 590

Glu Glu Ser Leu Ala Ile Leu Arg Arg His Val Met Ser Glu Leu Leu
 595 600 605

Asp Thr Glu Arg Ala Tyr Val Glu Glu Leu Leu Cys Val Leu Glu Gly
 610 615 620

Tyr Ala Ala Glu Met Asp Asn Pro Leu Met Ala His Leu Leu Ser Thr
 625 630 635 640

Gly Leu His Asn Lys Lys Asp Val Leu Phe Gly Asn Met Glu Glu Ile
 645 650 655

Tyr His Phe His Asn Arg Ile Phe Leu Arg Glu Leu Glu Asn Tyr Thr
 660 665 670

Asp Cys Pro Glu Leu Val Gly Arg Cys Phe Leu Glu Arg Met Glu Asp
 675 680 685

Phe Gln Ile Tyr Glu Lys Tyr Cys Gln Asn Lys Pro Arg Ser Glu Ser

690		695		700															
Leu	Trp	Arg	Gln	Cys	Ser	Asp	Cys	Pro	Phe	Phe	Gln	Glu	Cys	Gln	Arg				
705					710					715					720				
Lys	Leu	Asp	His	Lys	Leu	Ser	Leu	Asp	Ser	Tyr	Leu	Leu	Lys	Pro	Val				
				725					730					735					
Gln	Arg	Ile	Thr	Lys	Tyr	Gln	Leu	Leu	Leu	Lys	Glu	Met	Leu	Lys	Tyr				
			740					745					750						
Ser	Arg	Asn	Cys	Glu	Gly	Ala	Glu	Asp	Leu	Gln	Glu	Ala	Leu	Ser	Ser				
		755					760					765							
Ile	Leu	Gly	Ile	Leu	Lys	Ala	Val	Asn	Asp	Ser	Met	His	Leu	Ile	Ala				
770						775				780									
Ile	Thr	Gly	Tyr	Asp	Gly	Asn	Leu	Gly	Asp	Leu	Gly	Lys	Leu	Leu	Met				
785					790					795					800				
Gln	Gly	Ser	Phe	Ser	Val	Trp	Thr	Asp	His	Lys	Arg	Gly	His	Thr	Lys				
				805					810					815					
Val	Lys	Glu	Leu	Ala	Arg	Phe	Lys	Pro	Met	Gln	Arg	His	Leu	Phe	Leu				
			820					825					830						
His	Glu	Lys	Ala	Val	Leu	Phe	Cys	Lys	Lys	Arg	Glu	Glu	Asn	Gly	Glu				
		835					840					845							
Gly	Tyr	Glu	Lys	Ala	Pro	Ser	Tyr	Ser	Tyr	Lys	Gln	Ser	Leu	Asn	Met				
850						855					860								
Ala	Ala	Val	Gly	Ile	Thr	Glu	Asn	Val	Lys	Gly	Asp	Ala	Lys	Lys	Phe				
865					870					875					880				
Glu	Ile	Trp	Tyr	Asn	Ala	Arg	Glu	Glu	Val	Tyr	Ile	Val	Gln	Ala	Pro				
				885					890					895					
Thr	Pro	Glu	Ile	Lys	Ala	Ala	Trp	Val	Asn	Glu	Ile	Arg	Lys	Val	Leu				
			900					905					910						
Thr	Ser	Gln	Leu	Gln	Ala	Cys	Arg	Glu	Ala	Ser	Gln	His	Arg	Ala	Leu				
		915					920					925							
Glu	Gln	Ser	Gln	Ser	Leu	Pro	Leu	Pro	Ala	Pro	Thr	Ser	Thr	Ser	Pro				
930						935					940								

Ser Arg Gly Asn Ser Arg Asn Ile Lys Lys Leu Glu Glu Arg Lys Thr
 945 950 955 960

Asp Pro Leu Ser Leu Glu Gly Tyr Val Ser Ser Ala Pro Leu Thr Lys
 965 970 975

Pro Pro Glu Lys Gly Lys Glu Pro
 980

<210> 24
 <211> 1031
 <212> PRT
 <213> Homo sapiens

<400> 24

Met Thr Tyr Leu Thr Ser Ile Pro Ser Val Glu Ala Ala Ser Ile Gly
 1 5 10 15

Phe Ile Val Val Ile Asp Arg Arg Arg Asp Lys Trp Ser Ser Val Lys
 20 25 30

Ala Ser Leu Thr Arg Ile Ala Val Ala Phe Pro Gly Asn Leu Gln Leu
 35 40 45

Ile Phe Ile Leu Arg Pro Ser Arg Phe Ile Gln Arg Thr Phe Thr Asp
 50 55 60

Ile Gly Ile Lys Tyr Tyr Arg Asn Glu Phe Lys Thr Lys Val Pro Ile
 65 70 75 80

Ile Met Val Asn Ser Val Ser Asp Leu His Gly Tyr Ile Asp Lys Ser
 85 90 95

Gln Leu Thr Arg Glu Leu Gly Gly Thr Leu Glu Tyr Arg His Gly Gln
 100 105 110

Trp Val Asn His Arg Thr Ala Ile Glu Asn Phe Ala Leu Thr Leu Lys
 115 120 125

Thr Thr Ala Gln Met Leu Gln Thr Phe Gly Ser Cys Leu Ala Thr Ala
 130 135 140

Glu Leu Pro Arg Ser Met Leu Ser Thr Glu Asp Leu Leu Met Ser His
 145 150 155 160

Thr Arg Gln Arg Asp Lys Leu Gln Asp Glu Leu Lys Leu Leu Gly Lys
 165 170 175

Gln Gly Thr Thr Leu Leu Ser Cys Ile Gln Glu Pro Ala Thr Lys Cys
 180 185 190

Pro Asn Ser Lys Leu Asn Leu Asn Gln Leu Glu Asn Val Thr Thr Met
 195 200 205

Glu Arg Leu Leu Val Gln Leu Asp Glu Thr Glu Lys Ala Phe Ser His
 210 215 220

Phe Trp Ser Glu His His Leu Lys Leu Asn Gln Cys Leu Gln Leu Gln
 225 230 235 240

His Phe Glu His Asp Phe Cys Lys Ala Lys Leu Ala Leu Asp Asn Leu
 245 250 255

Leu Glu Glu Gln Ala Glu Phe Thr Gly Ile Gly Asp Ser Val Met His
 260 265 270

Val Glu Gln Ile Leu Lys Glu His Lys Lys Leu Glu Glu Lys Ser Gln
 275 280 285

Glu Ser Leu Glu Lys Ala Gln Leu Leu Ala Leu Val Gly Asp Gln Leu
 290 295 300

Ile Gln Ser His His Tyr Ala Ala Asp Ala Ile Arg Pro Arg Cys Val
 305 310 315 320

Glu Leu Arg His Leu Cys Asp Asp Phe Ile Asn Gly Asn Lys Lys Lys
 325 330 335

Trp Asp Ile Leu Gly Lys Ser Leu Glu Phe His Arg Gln Leu Asp Lys
 340 345 350

Val Ser Gln Trp Cys Glu Ala Gly Ile Tyr Leu Leu Ala Ser Gln Ala
 355 360 365

Val Asp Lys Cys Gln Ser Arg Glu Gly Val Asp Ile Ala Leu Asn Asp
 370 375 380

Ile Ala Thr Phe Leu Gly Thr Val Lys Glu Tyr Pro Leu Leu Ser Pro
 385 390 395 400

Lys Glu Phe Tyr Asn Glu Phe Glu Leu Leu Leu Thr Leu Asp Ala Lys

405										410					415				
Ala	Lys	Ala	Gln	Lys	Val	Leu	Gln	Arg	Leu	Asp	Asp	Val	Gln	Glu	Ile				
			420					425					430						
Phe	His	Lys	Arg	Gln	Val	Ser	Leu	Met	Lys	Leu	Ala	Ala	Lys	Gln	Thr				
		435					440					445							
Arg	Pro	Val	Gln	Pro	Val	Ala	Pro	His	Pro	Glu	Ser	Ser	Pro	Lys	Trp				
	450					455					460								
Val	Ser	Ser	Lys	Thr	Ser	Gln	Pro	Ser	Thr	Ser	Val	Pro	Leu	Ala	Arg				
465					470					475					480				
Pro	Leu	Arg	Thr	Ser	Glu	Glu	Pro	Tyr	Thr	Glu	Thr	Glu	Leu	Asn	Ser				
				485					490					495					
Arg	Gly	Lys	Glu	Asp	Asp	Glu	Thr	Lys	Phe	Glu	Val	Lys	Ser	Glu	Glu				
			500					505					510						
Ile	Phe	Glu	Ser	His	His	Glu	Arg	Gly	Asn	Pro	Glu	Leu	Glu	Gln	Gln				
		515					520					525							
Ala	Arg	Leu	Gly	Asp	Leu	Ser	Pro	Arg	Arg	Arg	Ile	Ile	Arg	Asp	Leu				
	530					535					540								
Leu	Glu	Thr	Glu	Glu	Ile	Tyr	Ile	Lys	Glu	Ile	Lys	Ser	Ile	Ile	Asp				
545					550					555					560				
Gly	Tyr	Ile	Thr	Pro	Met	Asp	Phe	Ile	Trp	Leu	Lys	His	Leu	Ile	Pro				
				565					570					575					
Asp	Val	Leu	Gln	Asn	Asn	Lys	Asp	Phe	Leu	Phe	Gly	Asn	Ile	Arg	Glu				
			580					585					590						
Leu	Tyr	Glu	Phe	His	Asn	Arg	Thr	Phe	Leu	Lys	Glu	Leu	Glu	Lys	Cys				
		595					600					605							
Ala	Glu	Asn	Pro	Glu	Leu	Leu	Ala	His	Cys	Phe	Leu	Lys	Arg	Lys	Glu				
	610					615					620								
Asp	Leu	Gln	Ile	Tyr	Phe	Lys	Tyr	His	Lys	Asn	Leu	Pro	Arg	Ala	Arg				
625					630					635					640				
Ala	Ile	Trp	Gln	Glu	Cys	Gln	Asp	Cys	Ala	Tyr	Phe	Gly	Val	Cys	Gln				
			645					650						655					

Arg Gln Leu Asp His Asn Leu Pro Leu Phe Lys Tyr Leu Lys Gly Pro
 660 665 670

Ser Gln Arg Leu Ile Lys Tyr Gln Met Leu Leu Lys Gly Leu Leu Asp
 675 680 685

Phe Glu Ser Pro Glu Asp Met Glu Ile Asp Pro Gly Glu Leu Gly Gly
 690 695 700

Ser Ala Lys Asp Gly Pro Lys Arg Thr Lys Asp Ser Ala Phe Ser Thr
 705 710 715 720

Glu Leu Gln Gln Ala Leu Ala Val Ile Glu Asp Leu Ile Lys Ser Cys
 725 730 735

Glu Leu Ala Val Asp Leu Ala Ala Val Thr Glu Cys Pro Asp Asp Ile
 740 745 750

Gly Lys Leu Gly Lys Leu Leu Leu His Gly Pro Phe Ser Val Trp Thr
 755 760 765

Ile His Lys Asp Arg Tyr Lys Met Lys Asp Leu Ile Arg Phe Lys Pro
 770 775 780

Ser Gln Arg Gln Ile Tyr Leu Phe Glu Arg Gly Ile Val Phe Cys Lys
 785 790 795 800

Ile Arg Met Glu Pro Gly Asp Gln Gly Leu Ser Pro His Tyr Ser Phe
 805 810 815

Lys Lys Ala Met Lys Leu Met Thr Leu Ser Ile Arg Gln Leu Gly Arg
 820 825 830

Gly Ser His Arg Lys Phe Glu Ile Ala Ser Arg Asn Gly Leu Glu Lys
 835 840 845

Tyr Ile Leu Gln Ala Ala Ser Lys Glu Ile Arg Asp Cys Trp Phe Ser
 850 855 860

Glu Ile Ser Lys Leu Leu Met Glu Gln Gln Asn Asn Ile Lys Asp Gln
 865 870 875 880

Gly Asn Pro Gln Phe Glu Met Ser Thr Ser Lys Gly Ser Gly Ala Gly
 885 890 895

Ser Gly Pro Trp Ile Lys Asn Met Glu Arg Ala Thr Thr Ser Lys Glu
 900 905 910

Asp Pro Ala Ser Ser Thr Gly Gly Ile Lys Gly Cys Ser Ser Arg Glu
 915 920 925

Phe Ser Ser Met Asp Thr Phe Glu Asp Cys Glu Gly Ala Glu Asp Met
 930 935 940

Glu Lys Glu Ser Ser Ala Leu Ser Leu Ala Gly Leu Phe Gln Ser Asp
 945 950 955 960

Asp Ser His Glu Thr Cys Ser Ser Lys Ser Ala Phe Leu Glu Arg Gly
 965 970 975

Glu Ser Ser Gln Gly Glu Lys Glu Glu Arg Asp Glu Glu Glu Thr Ala
 980 985 990

Thr Arg Ser Thr Glu Glu Glu Arg Ala Gly Ala Ser Thr Gly Arg Leu
 995 1000 1005

Ala Pro Ala Gly Ala Thr Ala Gly Phe Gln Ala Arg Ala Leu Arg
 1010 1015 1020

Pro Arg Thr Ser Ala Gln Glu Ser
 1025 1030

<210> 25

<211> 489

<212> PRT

<213> Homo sapiens

<400> 25

Met Pro Val Thr Phe Ala Leu Leu Leu Leu Leu Gly Gln Ala Thr Ala
 1 5 10 15

Asp Pro Cys Tyr Asp Pro Gln Gly Arg Pro Gln Phe Cys Leu Pro Pro
 20 25 30

Val Thr Gln Leu Ala Ala Val Ala Ala Ser Cys Pro Gln Ala Cys Ala
 35 40 45

Leu Ser Pro Gly Asn His Leu Gly Ala Arg Glu Thr Cys Asn Gly Ser
 50 55 60

Leu Thr Leu Ala Leu Gly Gly Pro Phe Leu Leu Thr Ser Val Ser Leu

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

Pro Cys Gln Arg Ile Pro Glu Ala Thr Thr Thr Leu Ala Thr Thr Pro
 325 330 335

Gly Ala Tyr Ser Ser Asp Pro Gln Cys Gln Asn Tyr Cys Asn Met Ser
 340 345 350

Asp Thr Arg Val His Met Ser Leu Arg Arg Tyr Cys Gln Gln Asp His
 355 360 365

Val Leu Arg Ala Gln Val Leu Ala Ser Glu Ala Ala Gly Pro Ala Trp
 370 375 380

Gln Arg Leu Ala Val Arg Val Leu Ala Val Tyr Lys Gln Arg Ala Gln
 385 390 395 400

Pro Val Arg Arg Gly Asp Gln Asp Ala Trp Val Pro Arg Ala Asp Leu
 405 410 415

Thr Cys Gly Cys Leu Arg Leu Gln Pro Gly Thr Asp Tyr Leu Leu Leu
 420 425 430

Gly Ser Ala Val Gly Asp Pro Asp Pro Thr Arg Leu Ile Leu Asp Arg
 435 440 445

His Gly Leu Ala Leu Pro Trp Arg Pro Arg Trp Ala Arg Pro Leu Lys
 450 455 460

Arg Leu Gln Gln Glu Glu Arg Ala Gly Gly Cys Arg Gly Val Arg Ala
 465 470 475 480

Pro Thr Pro Ser Pro Arg Pro Glu His
 485

<210> 26

<211> 604

<212> PRT

<213> Homo sapiens

<400> 26

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

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

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

275	280	285
Gly His Ala Ala Arg Cys Val Arg Asp Arg Thr Asp Ser Leu Val Cys 290 295 300		
Asp Cys Arg His Asn Thr Ala Gly Pro Glu Cys Asp Arg Cys Lys Pro 305 310 315 320		
Phe His Tyr Asp Arg Pro Trp Gln Arg Ala Thr Ala Arg Glu Ala Asn 325 330 335		
Glu Cys Val Ala Cys Asn Cys Asn Leu His Ala Arg Arg Cys Arg Phe 340 345 350		
Asn Met Glu Leu Tyr Lys Leu Ser Gly Arg Lys Ser Gly Gly Val Cys 355 360 365		
Leu Asn Cys Arg His Asn Thr Ala Gly Arg His Cys His Tyr Cys Lys 370 375 380		
Glu Gly Tyr Tyr Arg Asp Met Gly Lys Pro Ile Thr His Arg Lys Ala 385 390 395 400		
Cys Lys Ala Cys Asp Cys His Pro Val Gly Ala Ala Gly Lys Thr Cys 405 410 415		
Asn Gln Thr Thr Gly Gln Cys Pro Cys Lys Asp Gly Val Thr Gly Ile 420 425 430		
Thr Cys Asn Arg Cys Ala Lys Gly Tyr Gln Gln Ser Arg Ser Pro Ile 435 440 445		
Ala Pro Cys Ile Lys Ile Pro Val Ala Pro Pro Thr Thr Ala Ala Ser 450 455 460		
Ser Val Glu Glu Pro Glu Asp Cys Asp Ser Tyr Cys Lys Ala Ser Lys 465 470 475 480		
Gly Lys Leu Lys Ile Asn Met Lys Lys Tyr Cys Lys Lys Asp Tyr Ala 485 490 495		
Val Gln Ile His Ile Leu Lys Ala Asp Lys Ala Gly Asp Trp Trp Lys 500 505 510		
Phe Thr Val Asn Ile Ile Ser Val Tyr Lys Gln Gly Thr Ser Arg Ile 515 520 525		

Arg Arg Gly Asp Gln Ser Leu Trp Ile Arg Ser Arg Asp Ile Ala Cys
 530 535 540

Lys Cys Pro Lys Ile Lys Pro Leu Lys Lys Tyr Leu Leu Leu Gly Asn
 545 550 555 560

Ala Glu Asp Ser Pro Asp Gln Ser Gly Ile Val Ala Asp Lys Ser Ser
 565 570 575

Leu Val Ile Gln Trp Arg Asp Thr Trp Ala Arg Arg Leu Arg Lys Phe
 580 585 590

Gln Gln Arg Glu Lys Lys Gly Lys Cys Lys Lys Ala
 595 600

<210> 27
 <211> 580
 <212> PRT
 <213> Homo sapiens

<400> 27

Met Pro Gly Trp Pro Trp Gly Leu Leu Leu Thr Ala Gly Thr Leu Phe
 1 5 10 15

Ala Ala Leu Ser Pro Gly Pro Pro Ala Pro Ala Asp Pro Cys His Asp
 20 25 30

Glu Gly Gly Ala Pro Arg Gly Cys Val Pro Gly Leu Val Asn Ala Ala
 35 40 45

Leu Gly Arg Glu Val Leu Ala Ser Ser Thr Cys Gly Arg Pro Ala Thr
 50 55 60

Arg Ala Cys Asp Ala Ser Asp Pro Arg Arg Ala His Ser Pro Ala Leu
 65 70 75 80

Leu Thr Ser Pro Gly Gly Thr Ala Ser Pro Leu Cys Trp Arg Ser Glu
 85 90 95

Ser Leu Pro Arg Ala Pro Leu Asn Val Thr Leu Thr Val Pro Leu Gly
 100 105 110

Lys Ala Phe Glu Leu Val Phe Val Ser Leu Arg Phe Cys Ser Ala Pro
 115 120 125

Pro Ala Ser Val Ala Leu Leu Lys Ser Gln Asp His Gly Arg Ser Trp
 130 135 140

Ala Pro Leu Gly Phe Phe Ser Ser His Cys Asp Leu Asp Tyr Gly Arg
 145 150 155 160

Leu Pro Ala Pro Ala Asn Gly Pro Ala Gly Pro Gly Pro Glu Ala Leu
 165 170 175

Cys Phe Pro Ala Pro Leu Ala Gln Pro Asp Gly Ser Gly Leu Leu Ala
 180 185 190

Phe Ser Met Gln Asp Ser Ser Pro Pro Gly Leu Asp Leu Asp Ser Ser
 195 200 205

Pro Val Leu Gln Asp Trp Val Thr Ala Thr Asp Val Arg Val Val Leu
 210 215 220

Thr Arg Pro Ser Thr Ala Gly Asp Pro Arg Asp Met Glu Ala Val Val
 225 230 235 240

Pro Tyr Ser Tyr Ala Ala Thr Asp Leu Gln Val Gly Gly Arg Cys Lys
 245 250 255

Cys Asn Gly His Ala Ser Arg Cys Leu Leu Asp Thr Gln Gly His Leu
 260 265 270

Ile Cys Asp Cys Arg His Gly Thr Glu Gly Pro Asp Cys Gly Arg Cys
 275 280 285

Lys Pro Phe Tyr Cys Asp Arg Pro Trp Gln Arg Ala Thr Ala Arg Glu
 290 295 300

Ser His Ala Cys Leu Ala Cys Ser Cys Asn Gly His Ala Arg Arg Cys
 305 310 315 320

Arg Phe Asn Met Glu Leu Tyr Arg Leu Ser Gly Arg Arg Ser Gly Gly
 325 330 335

Val Cys Leu Asn Cys Arg His Asn Thr Ala Gly Arg His Cys His Tyr
 340 345 350

Cys Arg Glu Gly Phe Tyr Arg Asp Pro Gly Arg Ala Leu Ser Asp Arg
 355 360 365

Arg Ala Cys Arg Ala Cys Asp Cys His Pro Val Gly Ala Ala Gly Lys

370 375 380
 Thr Cys Asn Gln Thr Thr Gly Gln Cys Pro Cys Lys Asp Gly Val Thr
 385 390 395 400
 Gly Leu Thr Cys Asn Arg Cys Ala Pro Gly Phe Gln Gln Ser Arg Ser
 405 410 415
 Pro Val Ala Pro Cys Val Lys Thr Pro Ile Pro Gly Pro Thr Glu Asp
 420 425 430
 Ser Ser Pro Val Gln Pro Gln Asp Cys Asp Ser His Cys Lys Pro Ala
 435 440 445
 Arg Gly Ser Tyr Arg Ile Ser Leu Lys Lys Phe Cys Lys Lys Asp Tyr
 450 455 460
 Ala Val Gln Val Ala Val Gly Ala Arg Gly Glu Ala Arg Gly Ala Trp
 465 470 475 480
 Thr Arg Phe Pro Val Ala Val Leu Ala Val Phe Arg Ser Gly Glu Glu
 485 490 495
 Arg Ala Arg Arg Gly Ser Ser Ala Leu Trp Val Pro Ala Gly Asp Ala
 500 505 510
 Ala Cys Gly Cys Pro Arg Leu Leu Pro Gly Arg Arg Tyr Leu Leu Leu
 515 520 525
 Gly Gly Gly Pro Gly Ala Ala Ala Gly Gly Ala Gly Gly Arg Gly Pro
 530 535 540
 Gly Leu Ile Ala Ala Arg Gly Ser Leu Val Leu Pro Trp Arg Asp Ala
 545 550 555 560
 Trp Thr Arg Arg Leu Arg Arg Leu Gln Arg Arg Glu Arg Arg Gly Arg
 565 570 575
 Cys Ser Ala Ala
 580

<210> 28
 <211> 628
 <212> PRT
 <213> Homo sapiens

<400> 28

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

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

Ala Cys Asn Pro Arg Met Gly Asn Leu Ala Leu Gly Arg Lys Leu Trp
 35 40 45

Ala Asp Thr Thr Cys Gly Gln Asn Ala Thr Glu Leu Tyr Cys Phe Tyr
 50 55 60

Ser Glu Asn Lys Asp Leu Thr Cys Arg Gln Pro Lys Cys Asp Lys Cys
 65 70 75 80

Asn Ala Ala Tyr Pro His Leu Ala His Leu Pro Ser Ala Met Ala Asp
 85 90 95

Ser Ser Phe Arg Phe Pro Arg Thr Trp Trp Gln Ser Ala Glu Asp Val
 100 105 110

His Arg Glu Lys Ile Gln Leu Asp Leu Glu Ala Glu Phe Tyr Phe Thr
 115 120 125

His Leu Ile Val Met Phe Lys Ser Pro Arg Pro Ala Ala Met Val Leu
 130 135 140

Asp Arg Ser Gln Asp Phe Gly Lys Thr Trp Lys Pro Tyr Lys Tyr Phe
 145 150 155 160

Ala Thr Asn Cys Ser Ala Thr Phe Gly Leu Glu Asp Asp Val Val Lys
 165 170 175

Lys Gly Ala Ile Cys Thr Ser Lys Tyr Ser Ser Pro Phe Pro Cys Thr
 180 185 190

Gly Gly Glu Val Ile Phe Lys Ala Leu Ser Pro Pro His Asp Thr Glu
 195 200 205

Asn Pro Tyr Ser Ala Lys Val Gln Glu Gln Leu Lys Ile Thr Asn Leu
 210 215 220

Arg Val Gln Leu Leu Lys Arg Gln Ser Cys Pro Cys Gln Arg Asn Asp
 225 230 235 240

Leu	Asn	Glu	Glu	Pro	Gln	His	Phe	Thr	His	Tyr	Ala	Ile	Tyr	Asp	Phe
				245					250					255	
Ile	Val	Lys	Gly	Ser	Cys	Phe	Cys	Asn	Gly	His	Ala	Asp	Gln	Cys	Ile
			260					265					270		
Pro	Val	His	Gly	Phe	Arg	Pro	Val	Lys	Ala	Pro	Gly	Thr	Phe	His	Met
		275					280					285			
Val	His	Gly	Lys	Cys	Met	Cys	Lys	His	Asn	Thr	Ala	Gly	Ser	His	Cys
	290					295					300				
Gln	His	Cys	Ala	Pro	Leu	Tyr	Asn	Asp	Arg	Pro	Trp	Glu	Ala	Ala	Asp
305					310					315					320
Gly	Lys	Thr	Gly	Ala	Pro	Asn	Glu	Cys	Arg	Ala	Cys	Lys	Cys	Asn	Gly
				325					330					335	
His	Ala	Asp	Thr	Cys	His	Phe	Asp	Val	Asn	Val	Trp	Glu	Ala	Ser	Gly
			340					345					350		
Asn	Arg	Ser	Gly	Gly	Val	Cys	Asp	Asp	Cys	Gln	His	Asn	Thr	Glu	Gly
		355					360					365			
Gln	Tyr	Cys	Gln	Arg	Cys	Lys	Pro	Gly	Phe	Tyr	Arg	Asp	Leu	Arg	Arg
	370					375					380				
Pro	Phe	Ser	Ala	Pro	Asp	Ala	Cys	Lys	Pro	Cys	Ser	Cys	His	Pro	Val
385					390					395					400
Gly	Ser	Ala	Val	Leu	Pro	Ala	Asn	Ser	Val	Thr	Phe	Cys	Asp	Pro	Ser
				405					410					415	
Asn	Gly	Asp	Cys	Pro	Cys	Lys	Pro	Gly	Val	Ala	Gly	Arg	Arg	Cys	Asp
			420					425					430		
Arg	Cys	Met	Val	Gly	Tyr	Trp	Gly	Phe	Gly	Asp	Tyr	Gly	Cys	Arg	Pro
		435					440					445			
Cys	Asp	Cys	Ala	Gly	Ser	Cys	Asp	Pro	Ile	Thr	Gly	Asp	Cys	Ile	Ser
	450					455					460				
Ser	His	Thr	Asp	Ile	Asp	Trp	Cys	His	Glu	Val	Pro	Asp	Phe	Arg	Pro
465					470					475					480
Val	His	Asn	Lys	Ser	Glu	Pro	Ala	Trp	Glu	Trp	Glu	Asp	Ala	Gln	Gly

Ala Gly Ala Leu Gln Asp Ile Thr Leu Ser Gln Gln Thr Pro Ser Thr
50 55 60

Trp Lys Asp Thr Gln Leu Leu Thr Ala Ile Pro Thr Ser Pro Glu Pro
 65 70 75 80

Thr Gly Leu Glu Ala Thr Ala Ala Ser Thr Ser Thr Leu Pro Ala Gly
 85 90 95

Glu Gly Pro Lys Glu Gly Glu Ala Val Val Leu Pro Glu Val Glu Pro
 100 105 110

Gly Leu Thr Ala Arg Glu Gln Glu Ala Thr Pro Arg Pro Arg Glu Thr
 115 120 125

Thr Gln Leu Pro Thr Thr His Gln Ala Ser Thr Thr Thr Ala Thr Thr
 130 135 140

Ala Gln Glu Pro Ala Thr Ser His Pro His Arg Asp Met Gln Pro Gly
 145 150 155 160

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

Thr Pro His Thr Glu Asp Gly Gly Pro Ser Ala Thr Glu Arg Ala Ala
 180 185 190

Glu Asp Gly Ala Ser Ser Gln Leu Pro Ala Ala Glu Gly Ser Gly Glu
 195 200 205

Gln Asp Phe Thr Phe Glu Thr Ser Gly Glu Asn Thr Ala Val Val Ala
 210 215 220

Val Glu Pro Asp Arg Arg Asn Gln Ser Pro Val Asp Gln Gly Ala Thr
 225 230 235 240

Gly Ala Ser Gln Gly Leu Leu Asp Arg Lys Glu Val Leu Gly Gly Val
 245 250 255

Ile Ala Gly Gly Leu Val Gly Leu Ile Phe Ala Val Cys Leu Val Gly
 260 265 270

Phe Met Leu Tyr Arg Met Lys Lys Lys Asp Glu Gly Ser Tyr Ser Leu
 275 280 285

Glu Glu Pro Lys Gln Ala Asn Gly Gly Ala Tyr Gln Lys Pro Thr Lys
 290 295 300

Gln Glu Glu Phe Tyr Ala
305 310

<210> 30
<211> 201
<212> PRT
<213> Homo sapiens

<400> 30

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

Ser Ala Glu Ser Arg Ala Glu Leu Thr Ser Asp Lys Asp Met Tyr Leu
20 25 30

Asp Asn Ser Ser Ile Glu Glu Ala Ser Gly Val Tyr Pro Ile Asp Asp
35 40 45

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

Ser Pro Glu Leu Thr Thr Ser Arg Pro Leu Pro Lys Ile Leu Leu Thr
65 70 75 80

Ser Ala Ala Pro Lys Val Glu Thr Thr Thr Leu Asn Ile Gln Asn Lys
85 90 95

Ile Pro Ala Gln Thr Lys Ser Pro Glu Glu Thr Asp Lys Glu Lys Val
100 105 110

His Leu Ser Asp Ser Glu Arg Lys Met Asp Pro Ala Glu Glu Asp Thr
115 120 125

Asn Val Tyr Thr Glu Lys His Ser Asp Ser Leu Phe Lys Arg Thr Glu
130 135 140

Val Leu Ala Ala Val Thr Ala Gly Gly Val Ile Gly Phe Leu Phe Ala
145 150 155 160

Ile Phe Leu Ile Leu Leu Leu Val Tyr Arg Met Arg Lys Lys Asp Glu
165 170 175

Gly Ser Tyr Asp Leu Gly Glu Arg Lys Pro Ser Ser Ala Ala Tyr Gln
180 185 190

Lys Ala Pro Thr Lys Glu Phe Tyr Ala
195 200

<210> 31
 <211> 384
 <212> PRT
 <213> Homo sapiens

<400> 31

Met Ala Ile Ala Tyr Leu Gly Ser Ser Cys Pro Ser Gln Pro Pro Ser
 1 5 10 15

Ser Leu Ala Leu Ser Leu Ser Pro Thr Pro Ser Asp Phe Glu Gln Glu
 20 25 30

Ser Gly Ile Glu Thr Ala Met Arg Phe Ser Pro Asp Val Ala Leu Ala
 35 40 45

Val Ser Thr Thr Pro Ala Val Leu Pro Thr Thr Asn Ile Gln Pro Val
 50 55 60

Gly Thr Pro Phe Glu Glu Leu Pro Ser Glu Arg Pro Thr Leu Glu Pro
 65 70 75 80

Ala Thr Ser Pro Leu Val Val Thr Glu Val Pro Glu Glu Pro Ser Gln
 85 90 95

Arg Ala Thr Thr Val Ser Thr Thr Met Ala Thr Thr Ala Ala Thr Ser
 100 105 110

Thr Gly Asp Pro Thr Val Ala Thr Val Pro Ala Thr Val Ala Thr Ala
 115 120 125

Thr Pro Ser Thr Pro Ala Ala Pro Pro Phe Thr Ala Thr Thr Ala Val
 130 135 140

Ile Arg Thr Thr Gly Val Arg Arg Leu Leu Pro Leu Pro Leu Thr Thr
 145 150 155 160

Val Ala Thr Ala Arg Ala Thr Thr Pro Glu Ala Pro Ser Pro Pro Thr
 165 170 175

Thr Ala Ala Val Leu Asp Thr Glu Ala Pro Thr Pro Arg Leu Val Ser
 180 185 190

Thr Ala Thr Ser Arg Pro Arg Ala Leu Pro Arg Pro Ala Thr Thr Gln
 195 200 205

Glu Pro Asp Ile Pro Glu Arg Ser Thr Leu Pro Leu Gly Thr Thr Ala
 210 215 220

Pro Gly Pro Thr Glu Val Ala Gln Thr Pro Thr Pro Glu Thr Phe Leu
 225 230 235 240

Thr Thr Ile Arg Asp Glu Pro Glu Val Pro Val Ser Gly Gly Pro Ser
 245 250 255

Gly Asp Phe Glu Leu Pro Glu Glu Glu Thr Thr Gln Pro Asp Thr Ala
 260 265 270

Asn Glu Val Val Ala Val Gly Gly Ala Ala Ala Lys Ala Ser Ser Pro
 275 280 285

Pro Gly Thr Leu Pro Lys Gly Ala Arg Pro Gly Pro Gly Leu Leu Asp
 290 295 300

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

Ile Leu Glu Arg Lys Glu Val Leu Val Ala Val Ile Val Gly Gly Val
 325 330 335

Val Gly Ala Leu Phe Ala Ala Phe Leu Val Thr Leu Leu Ile Tyr Arg
 340 345 350

Met Lys Lys Lys Asp Glu Gly Ser Tyr Thr Leu Glu Glu Pro Lys Gln
 355 360 365

Ala Ser Val Thr Tyr Gln Lys Pro Asp Lys Gln Glu Glu Phe Tyr Ala
 370 375 380

<210> 32

<211> 198

<212> PRT

<213> Homo sapiens

<400> 32

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

Val Ala Glu Ser Ile Arg Glu Thr Glu Val Ile Asp Pro Gln Asp Leu
 20 25 30

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

Val Gly Pro Gly Gln Glu Ser Asp Asp Phe Glu Leu Ser Gly Ser Gly
 50 55 60

Asp Leu Asp Asp Leu Glu Asp Ser Met Ile Gly Pro Glu Val Val His
 65 70 75 80

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

Ser Gln Val Pro Thr Glu Pro Lys Lys Leu Glu Glu Asn Glu Val Ile
 100 105 110

Pro Lys Arg Ile Ser Pro Val Glu Glu Ser Glu Asp Val Ser Asn Lys
 115 120 125

Val Ser Met Ser Ser Thr Val Gln Gly Ser Asn Ile Phe Glu Arg Thr
 130 135 140

Glu Val Leu Ala Ala Leu Ile Val Gly Gly Ile Val Gly Ile Leu Phe
 145 150 155 160

Ala Val Phe Leu Ile Leu Leu Leu Met Tyr Arg Met Lys Lys Lys Asp
 165 170 175

Glu Gly Ser Tyr Asp Leu Gly Lys Lys Pro Ile Tyr Lys Lys Ala Pro
 180 185 190

Thr Asn Glu Phe Tyr Ala
 195

40