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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

[0001] This application claims priority to U.S. provisional patent application 60/611,127 filed 9/17/2004. The contents of the prior application are hereby incorporated in their entirety.

BACKGROUND OF THE INVENTION

[0002] 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 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 adhesion, and function downstream of integrins and growth factor receptors to regulate cytoskeletal changes important for cell adhesion and motility.

[0003] 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* 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 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.

[0004] 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.

[0005] 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

[0006] 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).

[0007] 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 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 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.

[0008] 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 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).

[0009] 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 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.

DETAILED DESCRIPTION OF THE INVENTION

[0010] 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. Methods for using RNAi to silence genes in *C. elegans* are known in the art (Fire A, et al., 1998 Nature 391:806-811; Fire, A. Trends Genet. 15, 358-363 (1999); WO9932619). Genes causing altered phenotypes in the worms were identified as modifiers of the RAC pathway, 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.

[0011] 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 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

[0012] 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.

[0013] The term "MRAC polypeptide" refers to a full-length MRAC protein or a functionally active fragment or derivative thereof. A "functionally active" MRAC

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 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 structural domains of an MRAC, such as a kinase domain or 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.

[0014] 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 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-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) 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 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 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, 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.

[0015] 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.

[0016] 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."

[0017] 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).

[0018] 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.

[0019] 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

[0020] 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 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 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 the invention, as described further below.

[0021] 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 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.

[0022] 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 or functional properties of the MRAC protein in *in vitro* assay systems (e.g. immunoassays).

[0023] 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).

[0024] 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.

[0025] 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

[0026] 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.

[0027] 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 Sanford *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).

[0028] 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) *Scand J Immunol* 40:257-264; Declerck PJ *et al.*, (1995) *J Biol Chem* 270:8397-400).

[0029] 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.

[0030] 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).

[0031] 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.

[0032] 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

[0033] 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.

[0034] 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.

[0035] 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 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.

Small molecule modulators

[0036] 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 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,

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).

[0037] Small molecule modulators identified from screening assays, as described below, 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 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

[0038] 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, 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).

[0039] 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 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 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).

[0040] 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 (1999) *Using antibodies: a laboratory manual*. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press). MRAC antibodies are further discussed below.

[0041] 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.

Antibodies

[0042] 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.

[0043] 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, monoclonal (mAbs), humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab').sub.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 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. Nati.*

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 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 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 such as a laboratory rabbit or mouse is immunized according to conventional protocols.

[0044] 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.

[0045] 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).

[0046] 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).

[0047] 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*).

[0048] 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).

[0049] 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

- [0050] 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.
- [0051] 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.
- [0052] 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

[0053] 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.

[0054] 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.

[0055] 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).

[0056] 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., 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; Novina CD and Sharp P. 2004 Nature 430:161-164; Soutschek J et al 2004 Nature 432:173-178; Hsieh AC et al. (2004) NAR 32(3):893-901).

[0057] Nucleic acid modulators are commonly used as research reagents, diagnostics, and therapeutics. For example, antisense oligonucleotides, which are able to inhibit gene 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 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 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

[0058] 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 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.

[0059] 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

[0060] The type of modulator tested generally determines the type of primary assay.

Primary assays for small molecule modulators

[0061] 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.

[0062] 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.

[0063] 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.

- [0064] 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).
- [0065] A variety of suitable assay systems may be used to identify candidate MRAC and RAC pathway modulators (*e.g.* U.S. Pat. No. 6,165,992 and U.S. Pat. No. 6720162 (kinase assays); 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.
- [0066] Protein kinases, key signal transduction proteins that may be either membrane-associated or intracellular, catalyze the transfer of gamma phosphate from adenosine triphosphate (ATP) to a serine, threonine or tyrosine residue in a protein substrate. Radioassays, which monitor the transfer from [γ -³²P or -³³P]ATP, are frequently used to assay kinase activity. For instance, a scintillation assay for p56 (lck) kinase activity monitors the transfer of the gamma phosphate from [γ -³³P] ATP to a biotinylated peptide substrate. The substrate is captured on a streptavidin coated bead that transmits the signal (Beveridge M et al., J Biomol Screen (2000) 5:205-212). This assay uses the scintillation proximity assay (SPA), in which only radio-ligand bound to receptors tethered to the surface of an SPA bead are detected by the scintillant immobilized within it, allowing binding to be measured without separation of bound from free ligand. Other assays for protein kinase activity may use antibodies that specifically recognize phosphorylated substrates. For instance, the kinase receptor activation (KIRA) assay measures receptor tyrosine kinase activity by ligand stimulating the intact receptor in cultured cells, then capturing solubilized receptor with specific antibodies and

quantifying phosphorylation via phosphotyrosine ELISA (Sadick MD, Dev Biol Stand (1999) 97:121-133). Another example of antibody based assays for protein kinase activity is TRF (time-resolved fluorometry). This method utilizes europium chelate-labeled anti-phosphotyrosine antibodies to detect phosphate transfer to a polymeric substrate coated onto microtiter plate wells. The amount of phosphorylation is then detected using time-resolved, dissociation-enhanced fluorescence (Braunwalder AF, et al., Anal Biochem 1996 Jul 1;238(2):159-64).

[0067] 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 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).

[0068] 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 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 a GTP hydrolysis assay using labeled GTP (e.g., Jones S et al., Molec Biol Cell (1998) 9:2819-2837).

[0069] 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 compounds that interact with different peptide and anion transporters both use fluorescently labeled substrates; the assay for peptide transport additionally uses

multiscreen filtration plates (Blevitt JM et al., J Biomol Screen 1999, 4:87-91; Cihlar T and Ho ES, Anal Biochem 2000, 283:49-55).

[0070] Transcription factors control gene transcription. Electrophoretic mobility shift assay (EMSA) or gel shift assay is one of the most powerful methods for studying protein-DNA interactions. High throughput gel shift assays for transcription factors may involve fluorescence (Cyano dye Cy5) labeled oligodeoxynucleotide duplexes as specific probes and an automatic DNA sequencer for analysis (Ruscher K, et al., (2000) J Biotechnol 78:163-70). Alternatively high throughput methods involve colorimetric assays (Renard P, et al. (2001) Nucleic Acids Res 29(4):E21), or homogeneous fluorescence assays for the detection and quantification of sequence-specific DNA-binding proteins (Heyduk T, and Heyduk E (2001) Nat Biotechnol 20:171-6.)

[0071] High throughput assays based on photometric analysis of the activity of decarboxylase enzymes have been described (Breuer M et al (2002) Anal Bioanal Chem 374:1069-73).

[0072] **Apoptosis assays.** Apoptosis or programmed cell death is a suicide program is activated within the cell, leading to fragmentation of DNA, shrinkage of the cytoplasm, membrane changes and cell death. Apoptosis is mediated by proteolytic enzymes of the caspase family. Many of the altering parameters of a cell are measurable during apoptosis. 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. The Phospho-histone H2B assay is another apoptosis assay, based on phosphorylation of histone H2B as a result of apoptosis. Fluorescent dyes that are associated with phosphohistone H2B may be used to measure the increase of phosphohistone H2B as a result of apoptosis. Apoptosis assays that simultaneously measure multiple parameters associated with apoptosis have also been developed. In such assays, various cellular parameters that can be associated with antibodies or fluorescent dyes, and that mark various stages of apoptosis are labeled, and the results are measured using instruments such as Cellomics™ ArrayScan® HCS System. The measurable parameters and their markers include anti-active caspase-3 antibody which marks intermediate stage apoptosis, anti-PARP-p85 antibody (cleaved PARP) which marks late stage apoptosis, Hoechst labels which label the nucleus and are used to measure nuclear swelling as a measure of early apoptosis and nuclear condensation as a measure of late apoptosis, TOTO-3 fluorescent dye which labels DNA of dead cells with high cell membrane permeability, and anti-alpha-tubulin or F-actin labels, which assess cytoskeletal changes in cells and correlate well with TOTO-3 label..

[0073] 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.

[0074] 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.

[0075] 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).

- [0076] Cell proliferation may also be assayed by colony formation in soft agar, or clonogenic survival assay (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.
- [0077] 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.
- [0078] 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.
- [0079] 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.
- [0080] **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.

[0081] 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 tumor 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.

[0082] 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.

[0083] 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.

[0084] 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 using immunofluorescence techniques in situ on the microchip is measured (Falsey JR et al., Bioconjug Chem. 2001 May-Jun;12(3):346-53).

Primary assays for antibody modulators

[0085] 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, and fluorescent assays.

[0086] In some cases, screening assays described for small molecule modulators may also be used to test antibody modulators.

Primary assays for nucleic acid modulators

[0087] 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 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., 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 detection, are available (Harlow E and Lane D, 1988 and 1999, *supra*).

[0088] 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

[0089] 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.

[0090] 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

[0091] 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

[0092] 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.

[0093] 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.

[0094] 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 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 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 may be utilized for biomarker identification or further

analyses. For immunohistochemistry staining, xenograft tumors are fixed in 4% paraformaldehyde, 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.

[0095] 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 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.

[0096] 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" 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 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 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

[0097] Specific MRAC-modulating agents are useful in a variety of diagnostic and 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), 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.

[0098] 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.

[0099] 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).

[0100] 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.

[0101] 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 antibodies, the immobilization of antibodies, and the like, and instructions for using such kits in diagnosis or therapy are also provided.

[0102] 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 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.

EXAMPLES

[0103] The following experimental section and examples are offered by way of illustration and not by way of limitation.

I. C. elegans RAC screen

[0104] 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 (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 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

[0105] 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

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.

[0106] 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 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	Modif ier Name	Modifier GI_aa
CYFIP1	cytoplasmic FMR1 interacting protein 1 cytoplasmic FMRP interacting protein 1 selective hybridizing clone (mouse) P140SRA-1 KIAA0068 SHYC CYFIP1	NM_014608	1	24307969	16	cytoplasmic FMR1 interacting protein 1	protein binding; actin binding	1253	gex-2	16266926
CYFIP2	cytoplasmic FMR1 interacting protein 2 p53 inducible protein PRO1331 PIR121 CYFIP2	NM_014376 NM_030778	2	24307955	17	cytoplasmic FMR1 interacting protein 2	protein binding; protein binding; actin binding	1253	gex-2	16266926

FMNL1	formin-like FMNL1 FMNL FHOD4 KW-13 C17orf1 MGC1894 C17orf1B MGC21878 leukocyte formin CLL-associated antigen KW-13 formin-like 1	NM_005892	3	33356148	18	formin-like 1	signal transducer	1100	3D239	26251572
FMNL2	formin-like 2 formin homology 2 domain containing 2 formin homology 2 domain containing 1 KIAA1902 FHOD2 FMNL2	NM_052905	4	38524618	19	formin-like 2	profilin binding; protein binding; signal transducer; receptor signaling protein	1093	3D239	26251572
FMNL3	formin-like 3 WW domain binding protein 3 DKFZp762B245 MGC45819 FHOD3 WB P3 FMNL3	NM_175736 NM_198900	5	40217839	20	formin-like 3	protein binding; signal transducer	940	3D239	26251572
FNTA	farnesyltransferase alpha farnesyltransferase, CAAX box, alpha PGGT1A FPTA FNTA	NM_002027	6	4503771	21	farnesyltransferase, CAAX box, alpha	protein farnesyltransferase; protein farnesyltransferase; protein geranylgeranyltransferase	379	4A992	2736325

LOC28326	na similar to Protein farnesyltransferase/geranylgeranyltransferase type I alpha subunit (CAAX farnesyltransferase alpha subunit) (Ras proteins prenyltransferase alpha) (FTase-alpha) (Type I protein geranylgeranyltransferase alpha subunit) (GGTase-I-... LOC28326	XM_208554	7	37541294	22	similar to Protein farnesyltransferase/geranylgeranyltransferase type I alpha subunit (CAAX farnesyltransferase alpha subunit) (Ras proteins prenyltransferase alpha) (FTase-alpha) (Type I protein geranylgeranyltransferase alpha subunit) (GGTase-I-...	na	289	4A992	2736325
C21orf106	chromosome 21 open reading frame 106 disco-interacting protein 2 (Drosophila) homolog DIP2 C21orf106	NM_015151 NM_206889 NM_206890 NM_206891	8	45827692	23	chromosome 21 open reading frame 106	AMP binding	1571	1F517	17506939
KIAA0934	KIAA0934	NM_014974 XM_034536	9	44888818	24	KIAA0934	AMP binding	1556	1F517	17506939
KIAA1463	FLJ34278 KIAA1463 KIAA1463 protein	34327975	10	34327976	25	KIAA1463 protein	AMP binding	1166	1F517	17506939
HEM1	hematopoietic protein 1 membrane-associated protein	NM_005337	11	34485727	26	hematopoietic protein 1	na	1127	gex-3	3876377

	protein hem-1 HEM1									
NCKAP1	NCK-associated protein 1 KIAA0587 MGC8981 NAP125 NAP1 NCKAP1	NM_013436 NM_205842	12	7305303	27	NCK-associated protein 1	na	1128	gex-3	3876377
FRK	PTK5 protein tyrosine kinase 5 PTK5 nuclear tyrosine protein kinase RAK tyrosine-protein kinase FRK FRK fyn-related kinase RAK GTK	NM_002031	13	4503787	28	fyn-related kinase	protein tyrosine kinase; protein tyrosine kinase; non-membrane spanning protein tyrosine kinase; non-membrane spanning protein tyrosine kinase	505	src-1	25150323
TSG101	tumor susceptibility gene 101 TSG101 TSG101	NM_006292	14	5454140	29	tumor susceptibility gene 101	DNA binding; transcription co-repressor; transcription co-repressor	390	4E276	17538634

UMPS	orotate phosphorib osyltransfer ase uridine monophosp hate synthetase (orotate phosphorib osyl transferase and orotidine- 5'- decarboxyl ase) orotate phosphorib osyltransfer ase phosphorib osyltransfer ase orotidin e 5'- phosphate decarboxyl ase UMP synthase O MPdecase OPRtase O PRT UMPS	NM_000373	15	4507835	30	uridine monophos phate synthetase (orotate phosphori bosyl transferase and orotidine- 5'- decarboxy lase)	orotidine- 5'- phosphate decarboxy lase; orotidine- 5'- phosphate decarboxy lase; orotate phosphori bosyltrans ferase; orotate phosphori bosyltrans ferase	480	3L44 6	3874822
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III. High-Throughput In Vitro Fluorescence Polarization Assay

[0107] 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.

[0108] 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

[0109] 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.

[0110] 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. Kinase assay

[0111] A purified or partially purified MRAC is diluted in a suitable reaction buffer, e.g., 50 mM Hepes, pH 7.5, containing magnesium chloride or manganese chloride (1-20 mM) and a peptide or polypeptide substrate, such as myelin basic protein or casein (1-10 μ g/ml). The final concentration of the kinase is 1-20 nM. The enzyme reaction is conducted in microtiter plates to facilitate optimization of reaction conditions by increasing assay throughput. A 96-well microtiter plate is employed using a final volume 30-100 μ l. The reaction is initiated by the addition of ^{33}P -gamma-ATP (0.5 μ Ci/ml) and

incubated for 0.5 to 3 hours at room temperature. Negative controls are provided by the addition of EDTA, which chelates the divalent cation (Mg^{2+} or Mn^{2+}) required for enzymatic activity. Following the incubation, the enzyme reaction is quenched using EDTA. Samples of the reaction are transferred to a 96-well glass fiber filter plate (MultiScreen, Millipore). The filters are subsequently washed with phosphate-buffered saline, dilute phosphoric acid (0.5%) or other suitable medium to remove excess radiolabeled ATP. Scintillation cocktail is added to the filter plate and the incorporated radioactivity is quantitated by scintillation counting (Wallac/Perkin Elmer). Activity is defined by the amount of radioactivity detected following subtraction of the negative control reaction value (EDTA quench).

VII. Expression analysis

- [0112] 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, Ardaïs, Genome Collaborative, and Ambion.
- [0113] TaqMan® analysis is used to assess expression levels of the disclosed genes in various samples.
- [0114] RNA is extracted from each tissue sample using Qiagen (Valencia, CA) RNeasy kits, following manufacturer's protocols, to a final concentration of 50ng/μl. 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).
- [0115] 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.
- [0116] TaqMan® reactions are carried out following manufacturer's protocols, in 25 μl total volume for 96-well plates and 10 μl 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).

[0117] 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 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., $\text{Tumor} - \text{average}(\text{all normal samples}) > 2 \times \text{STDEV}(\text{all normal samples})$).

[0118] A modulator identified by an assay described herein can be further validated for 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 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 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
 - (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 express the MRAC polypeptide.
3. The method of Claim 2 wherein the cultured cells additionally have defective RAC function.
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.
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.
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.
9. The method of claim 8 wherein the nucleic acid modulator is an antisense oligomer.
10. The method of Claim 8 wherein the nucleic acid modulator is a PMO.
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.
12. The method of Claim 11 wherein the model system is a mouse model with defective RAC function.
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.
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.
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,

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.

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.

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.

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.

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;
determining whether step (c) indicates a likelihood of disease.

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

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<213> Homo sapiens

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Asn	Asp	Pro	Ala	Leu	Arg	Gly	Glu	Lys	Asp	Pro	Lys	Ser	Gly	Phe	Asp
			530												540
Ile	Lys	Val	Pro	Arg	Arg	Ala	Val	Gly	Pro	Ser	Ser	Thr	Gln	Leu	Tyr
															560
Met	Val	Arg	Thr	Met	Leu	Glu	Ser	Leu	Ile	Ala	Asp	Lys	Ser	Gly	Ser
															575
Lys	Lys	Thr	Leu	Arg	Ser	Ser	Leu	Glu	Gly	Pro	Thr	Ile	Leu	Asp	Ile
			580												590
Glu	Lys	Phe	His	Arg	Glu	Ser	Phe	Phe	Tyr	Thr	His	Leu	Ile	Asn	Phe
			595												605
Ser	Glu	Thr	Leu	Gln	Gln	Cys	Cys	Asp	Leu	Ser	Gln	Leu	Trp	Phe	Arg
			610												620
Glu	Phe	Phe	Leu	Glu	Leu	Thr	Met	Gly	Arg	Arg	Ile	Gln	Phe	Pro	Ile
															640
Glu	Met	Ser	Met	Pro	Trp	Ile	Leu	Thr	Asp	His	Ile	Leu	Glu	Thr	Lys
															655
Glu	Ala	Ser	Met	Met	Glu	Tyr	Val	Leu	Tyr	Ser	Leu	Asp	Leu	Tyr	Asn
			660												670
Asp	Ser	Ala	His	Tyr	Ala	Leu	Thr	Arg	Phe	Asn	Lys	Gln	Phe	Leu	Tyr
			675												685
Asp	Glu	Ile	Glu	Ala	Glu	Val	Asn	Leu	Cys	Phe	Asp	Gln	Phe	Val	Tyr
			690												700
Lys	Leu	Ala	Asp	Gln	Ile	Phe	Ala	Tyr	Tyr	Lys	Val	Met	Ala	Gly	Ser
															720
Leu	Leu	Leu	Asp	Lys	Arg	Leu	Arg	Ser	Glu	Cys	Lys	Asn	Gln	Gly	Ala
															735
Thr	Ile	His	Leu	Pro	Pro	Ser	Asn	Arg	Tyr	Glu	Thr	Leu	Leu	Lys	Gln
			740												750
Arg	His	Val	Gln	Leu	Leu	Gly	Arg	Ser	Ile	Asp	Leu	Asn	Arg	Leu	Ile
			755												765
Thr	Gln	Arg	Val	Ser	Ala	Ala	Met	Tyr	Lys	Ser	Leu	Glu	Leu	Ala	Ile
															780
Gly	Arg	Phe	Glu	Ser	Glu	Asp	Leu	Thr	Ser	Ile	Val	Glu	Leu	Asp	Gly

785	790	795	800
Leu Leu Glu Ile Asn Arg Met Thr His Lys Leu Leu Ser Arg Tyr Leu	805	810	815
Thr Leu Asp Gly Phe Asp Ala Met Phe Arg Glu Ala Asn His Asn Val	820	825	830
Ser Ala Pro Tyr Gly Arg Ile Thr Leu His Val Phe Trp Glu Leu Asn	835	840	845
Tyr Asp Phe Leu Pro Asn Tyr Cys Tyr Asn Gly Ser Thr Asn Arg Phe	850	855	860
Val Arg Thr Val Leu Pro Phe Ser Gln Glu Phe Gln Arg Asp Lys Gln	865	870	875
Pro Asn Ala Gln Pro Gln Tyr Leu His Gly Ser Lys Ala Leu Asn Leu	885	890	895
Ala Tyr Ser Ser Ile Tyr Gly Ser Tyr Arg Asn Phe Val Gly Pro Pro	900	905	910
His Phe Gln Val Ile Cys Arg Leu Leu Gly Tyr Gln Gly Ile Ala Val	915	920	925
Val Met Glu Glu Leu Leu Lys Val Val Lys Ser Leu Leu Gln Gly Thr	930	935	940
Ile Leu Gln Tyr Val Lys Thr Leu Met Glu Val Met Pro Lys Ile Cys	945	950	955
Arg Leu Pro Arg His Glu Tyr Gly Ser Pro Gly Ile Leu Glu Phe Phe	965	970	975
His His Gln Leu Lys Asp Ile Val Glu Tyr Ala Glu Leu Lys Thr Val	980	985	990
Cys Phe Gln Asn Leu Arg Glu Val Gly Asn Ala Ile Leu Phe Cys Leu	995	1000	1005
Leu Ile Glu Gln Ser Leu Ser Leu Glu Glu Val Cys Asp Leu Leu	1010	1015	1020
His Ala Ala Pro Phe Gln Asn Ile Leu Pro Arg Val His Val Lys	1025	1030	1035
Glu Gly Glu Arg Leu Asp Ala Lys Met Lys Arg Leu Glu Ser Lys	1040	1045	1050
Tyr Ala Pro Leu His Leu Val Pro Leu Ile Glu Arg Leu Gly Thr	1055	1060	1065
Pro Gln Gln Ile Ala Ile Ala Arg Glu Gly Asp Leu Leu Thr Lys	1070	1075	1080
Glu Arg Leu Cys Cys Gly Leu Ser Met Phe Glu Val Ile Leu Thr			

1085	1090	1095
Arg Ile Arg Ser Phe Leu Asp	Asp Pro Ile Trp Arg Gly Pro Leu	
1100	1105	1110
Pro Ser Asn Gly Val Met His	Val Asp Glu Cys Val Glu Phe His	
1115	1120	1125
Arg Leu Trp Ser Ala Met Gln	Phe Val Tyr Cys Ile Pro Val Gly	
1130	1135	1140
Thr His Glu Phe Thr Val Glu	Gln Cys Phe Gly Asp Gly Leu His	
1145	1150	1155
Trp Ala Gly Cys Met Ile Ile	Val Leu Leu Gly Gln Gln Arg Arg	
1160	1165	1170
Phe Ala Val Leu Asp Phe Cys	Tyr His Leu Leu Lys Val Gln Lys	
1175	1180	1185
His Asp Gly Lys Asp Glu Ile	Ile Lys Asn Val Pro Leu Lys Lys	
1190	1195	1200
Met Val Glu Arg Ile Arg Lys	Phe Gln Ile Leu Asn Asp Glu Ile	
1205	1210	1215
Ile Thr Ile Leu Asp Lys Tyr	Leu Lys Ser Gly Asp Gly Glu Gly	
1220	1225	1230
Thr Pro Val Glu His Val Arg	Cys Phe Gln Pro Pro Ile His Gln	
1235	1240	1245
Ser Leu Ala Ser Ser		
1250		
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Leu Glu Glu Leu Pro Leu Pro Asp Gln Gln Pro Cys Ile Glu Pro Pro		
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Pro Ser Ser Ile Met Tyr Gln Ala Asn Phe Asp Thr Asn Phe Glu Asp		
35	40	45
Arg Asn Ala Phe Val Thr Gly Ile Ala Arg Tyr Ile Glu Gln Ala Thr		
50	55	60
Val His Ser Ser Met Asn Glu Met Leu Glu Glu Gly His Glu Tyr Ala		
65	70	75 80
Val Met Leu Tyr Thr Trp Arg Ser Cys Ser Arg Ala Ile Pro Gln Val		
85	90	95

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

Ser Lys Trp Ser Ala His Val Met Glu Val Tyr Ser Trp Lys Leu Val
 405 410 415
 His Pro Thr Asp Lys Phe Cys Asn Lys Asp Cys Pro Gly Thr Ala Glu
 420 425 430
 Glu Tyr Glu Arg Ala Thr Arg Tyr Asn Tyr Thr Ser Glu Glu Lys Phe
 435 440 445
 Ala Phe Val Glu Val Ile Ala Met Ile Lys Gly Leu Gln Val Leu Met
 450 455 460
 Gly Arg Met Glu Ser Val Phe Asn Gln Ala Ile Arg Asn Thr Ile Tyr
 465 470 475 480
 Ala Ala Leu Gln Asp Phe Ala Gln Val Thr Leu Arg Glu Pro Leu Arg
 485 490 495
 Gln Ala Val Arg Lys Lys Lys Asn Val Leu Ile Ser Val Leu Gln Ala
 500 505 510
 Ile Arg Lys Thr Ile Cys Asp Trp Glu Gly Gly Arg Glu Pro Pro Asn
 515 520 525
 Asp Pro Cys Leu Arg Gly Glu Lys Asp Pro Lys Gly Gly Phe Asp Ile
 530 535 540
 Lys Val Pro Arg Arg Ala Val Gly Pro Ser Ser Thr Gln Leu Tyr Met
 545 550 555 560
 Val Arg Thr Met Leu Glu Ser Leu Ile Ala Asp Lys Ser Gly Ser Lys
 565 570 575
 Lys Thr Leu Arg Ser Ser Leu Asp Gly Pro Ile Val Leu Ala Ile Glu
 580 585 590
 Asp Phe His Lys Gln Ser Phe Phe Phe Thr His Leu Leu Asn Ile Ser
 595 600 605
 Glu Ala Leu Gln Gln Cys Cys Asp Leu Ser Gln Leu Trp Phe Arg Glu
 610 615 620
 Phe Phe Leu Glu Leu Thr Met Gly Arg Arg Ile Gln Phe Pro Ile Glu
 625 630 635 640
 Met Ser Met Pro Trp Ile Leu Thr Asp His Ile Leu Glu Thr Lys Glu
 645 650 655
 Pro Ser Met Met Glu Tyr Val Leu Tyr Pro Leu Asp Leu Tyr Asn Asp
 660 665 670
 Ser Ala Tyr Tyr Ala Leu Thr Lys Phe Lys Lys Gln Phe Leu Tyr Asp
 675 680 685
 Glu Ile Glu Ala Glu Val Asn Leu Cys Phe Asp Gln Phe Val Tyr Lys
 690 695 700

Leu Ala Asp Gln Ile Phe Ala Tyr Tyr Lys Ala Met Ala Gly Ser Val
 705 710 715 720
 Leu Leu Asp Lys Arg Phe Arg Ala Glu Cys Lys Asn Tyr Gly Val Ile
 725 730 735
 Ile Pro Tyr Pro Pro Ser Asn Arg Tyr Glu Thr Leu Leu Lys Gln Arg
 740 745 750
 His Val Gln Leu Leu Gly Arg Ser Ile Asp Leu Asn Arg Leu Ile Thr
 755 760 765
 Gln Arg Thr Ser Ala Ala Met Tyr Lys Ser Leu Asp Gln Ala Ile Ser
 770 775 780
 Arg Phe Glu Ser Glu Asp Leu Thr Ser Ile Val Glu Leu Glu Trp Leu
 785 790 795 800
 Leu Glu Ile Asn Arg Leu Thr His Arg Leu Leu Cys Lys His Met Thr
 805 810 815
 Leu Asp Ser Phe Asp Ala Met Phe Arg Glu Ala Asn His Asn Val Ser
 820 825 830
 Ala Pro Tyr Gly Arg Ile Thr Leu His Val Phe Trp Glu Leu Asn Phe
 835 840 845
 Asp Phe Leu Pro Asn Tyr Cys Tyr Asn Gly Ser Thr Asn Arg Phe Val
 850 855 860
 Arg Thr Ala Ile Pro Phe Thr Gln Glu Pro Gln Arg Asp Lys Pro Ala
 865 870 875 880
 Asn Val Gln Pro Tyr Tyr Leu Tyr Gly Ser Lys Pro Leu Asn Ile Ala
 885 890 895
 Tyr Ser His Ile Tyr Ser Ser Tyr Arg Asn Phe Val Gly Pro Pro His
 900 905 910
 Phe Lys Thr Ile Cys Arg Leu Leu Gly Tyr Gln Gly Ile Ala Val Val
 915 920 925
 Met Glu Glu Leu Leu Lys Ile Val Lys Ser Leu Leu Gln Gly Thr Ile
 930 935 940
 Leu Gln Tyr Val Lys Thr Leu Ile Glu Val Met Pro Lys Ile Cys Arg
 945 950 955 960
 Leu Pro Arg His Glu Tyr Gly Ser Pro Gly Ile Leu Glu Phe Phe His
 965 970 975
 His Gln Leu Lys Asp Ile Ile Glu Tyr Ala Glu Leu Lys Thr Asp Val
 980 985 990
 Phe Gln Ser Leu Arg Glu Val Gly Asn Ala Ile Leu Phe Cys Leu Leu
 995 1000 1005

Ile Glu Gln Ala Leu Ser Gln Glu Glu Val Cys Asp Leu Leu His
 1010 1015 1020
 Ala Ala Pro Phe Gln Asn Ile Leu Pro Arg Val Tyr Ile Lys Glu
 1025 1030 1035
 Gly Glu Arg Leu Glu Val Arg Met Lys Arg Leu Glu Ala Lys Tyr
 1040 1045 1050
 Ala Pro Leu His Leu Val Pro Leu Ile Glu Arg Leu Gly Thr Pro
 1055 1060 1065
 Gln Gln Ile Ala Ile Ala Arg Glu Gly Asp Leu Leu Thr Lys Glu
 1070 1075 1080
 Arg Leu Cys Cys Gly Leu Ser Met Phe Glu Val Ile Leu Thr Arg
 1085 1090 1095
 Ile Arg Ser Tyr Leu Gln Asp Pro Ile Trp Arg Gly Pro Pro Pro
 1100 1105 1110
 Thr Asn Gly Val Met His Val Asp Glu Cys Val Glu Phe His Arg
 1115 1120 1125
 Leu Trp Ser Ala Met Gln Phe Val Tyr Cys Ile Pro Val Gly Thr
 1130 1135 1140
 Asn Glu Phe Thr Ala Glu Gln Cys Phe Gly Asp Gly Leu Asn Trp
 1145 1150 1155
 Ala Gly Cys Ser Ile Ile Val Leu Leu Gly Gln Gln Arg Arg Phe
 1160 1165 1170
 Asp Leu Phe Asp Phe Cys Tyr His Leu Leu Lys Val Gln Arg Gln
 1175 1180 1185
 Asp Gly Lys Asp Glu Ile Ile Lys Asn Val Pro Leu Lys Lys Met
 1190 1195 1200
 Ala Asp Arg Ile Arg Lys Tyr Gln Ile Leu Asn Asn Glu Val Phe
 1205 1210 1215
 Ala Ile Leu Asn Lys Tyr Met Lys Ser Val Glu Thr Asp Ser Ser
 1220 1225 1230
 Thr Val Glu His Val Arg Cys Phe Gln Pro Pro Ile His Gln Ser
 1235 1240 1245
 Leu Ala Thr Thr Cys
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Met Gly Asn Ala Ala Gly Ser Ala Glu Gln Pro Ala Gly Pro Ala Ala
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 Pro Pro Pro Lys Gln Pro Ala Pro Pro Lys Gln Pro Met Pro Ala Ala
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 Gly Glu Leu Glu Glu Arg Phe Asn Arg Ala Leu Asn Cys Met Asn Leu
 35 40 45
 Pro Pro Asp Lys Val Gln Leu Leu Ser Gln Tyr Asp Asn Glu Lys Lys
 50 55 60
 Trp Glu Leu Ile Cys Asp Gln Glu Arg Phe Gln Val Lys Asn Pro Pro
 65 70 75 80
 Ala Ala Tyr Ile Gln Lys Leu Lys Ser Tyr Val Asp Thr Gly Gly Val
 85 90 95
 Ser Arg Lys Val Ala Ala Asp Trp Met Ser Asn Leu Gly Phe Lys Arg
 100 105 110
 Arg Val Gln Glu Ser Thr Gln Val Leu Arg Glu Leu Glu Thr Ser Leu
 115 120 125
 Arg Thr Asn His Ile Gly Trp Val Gln Glu Phe Leu Asn Glu Glu Asn
 130 135 140
 Arg Gly Leu Asp Val Leu Leu Glu Tyr Leu Ala Phe Ala Gln Cys Ser
 145 150 155 160
 Val Thr Tyr Asp Met Glu Ser Thr Asp Asn Gly Ala Ser Asn Ser Glu
 165 170 175
 Lys Asn Lys Pro Leu Glu Gln Ser Val Glu Asp Leu Ser Lys Gly Pro
 180 185 190
 Pro Ser Ser Val Pro Lys Ser Arg His Leu Thr Ile Lys Leu Thr Pro
 195 200 205
 Ala His Ser Arg Lys Ala Leu Arg Asn Ser Arg Ile Val Ser Gln Lys
 210 215 220
 Asp Asp Val His Val Cys Ile Met Cys Leu Arg Ala Ile Met Asn Tyr
 225 230 235 240
 Gln Ser Gly Phe Ser Leu Val Met Asn His Pro Ala Cys Val Asn Glu
 245 250 255
 Ile Ala Leu Ser Leu Asn Asn Lys Asn Pro Arg Thr Lys Ala Leu Val
 260 265 270
 Leu Glu Leu Leu Ala Ala Val Cys Leu Val Arg Gly Gly His Asp Ile
 275 280 285
 Ile Leu Ala Ala Phe Asp Asn Phe Lys Glu Val Cys Gly Glu Gln His
 290 295 300

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

Pro Pro Pro Pro Gly Gly Pro Pro Asp Ala Leu Gly Arg Arg Asp Ser
 610 615 620
 Glu Leu Gly Pro Gly Val Lys Ala Lys Lys Pro Ile Gln Thr Lys Phe
 625 630 635 640
 Arg Met Pro Leu Leu Asn Trp Val Ala Leu Lys Pro Ser Gln Ile Thr
 645 650 655
 Gly Thr Val Phe Thr Glu Leu Asn Asp Glu Lys Val Leu Gln Glu Leu
 660 665 670
 Asp Met Ser Asp Phe Glu Glu Gln Phe Lys Thr Lys Ser Gln Gly Pro
 675 680 685
 Ser Leu Asp Leu Ser Ala Leu Lys Ser Lys Ala Ala Gln Lys Ala Pro
 690 695 700
 Ser Lys Ala Thr Leu Ile Glu Ala Asn Arg Ala Lys Asn Leu Ala Ile
 705 710 715 720
 Thr Leu Arg Lys Gly Asn Leu Gly Ala Glu Arg Ile Cys Gln Ala Ile
 725 730 735
 Glu Ala Tyr Asp Leu Gln Ala Leu Gly Leu Asp Phe Leu Glu Leu Leu
 740 745 750
 Met Arg Phe Leu Pro Thr Glu Tyr Glu Arg Ser Leu Ile Thr Arg Phe
 755 760 765
 Glu Arg Glu Gln Arg Pro Met Glu Glu Leu Ser Glu Glu Asp Arg Phe
 770 775 780
 Met Leu Cys Phe Ser Arg Ile Pro Arg Leu Pro Glu Arg Met Thr Thr
 785 790 795 800
 Leu Thr Phe Leu Gly Asn Phe Pro Asp Thr Ala Gln Leu Leu Met Pro
 805 810 815
 Gln Leu Asn Ala Ile Ile Ala Ala Ser Met Ser Ile Lys Ser Ser Asp
 820 825 830
 Lys Leu Arg Gln Ile Leu Glu Ile Val Leu Ala Phe Gly Asn Tyr Met
 835 840 845
 Asn Ser Ser Lys Arg Gly Ala Ala Tyr Gly Phe Arg Leu Gln Ser Leu
 850 855 860
 Asp Ala Leu Leu Glu Met Lys Ser Thr Asp Arg Lys Gln Thr Leu Leu
 865 870 875 880
 His Tyr Leu Val Lys Val Ile Ala Glu Lys Tyr Pro Gln Leu Thr Gly
 885 890 895
 Phe His Ser Asp Leu His Phe Leu Asp Lys Ala Gly Ser Val Ser Leu
 900 905 910

Asp Ser Val Leu Ala Asp Val Arg Ser Leu Gln Arg Gly Leu Glu Leu
 915 920 925
 Thr Gln Arg Glu Phe Val Arg Gln Asp Asp Cys Met Val Leu Lys Glu
 930 935 940
 Phe Leu Arg Ala Asn Ser Pro Thr Met Asp Lys Leu Leu Ala Asp Ser
 945 950 955 960
 Lys Thr Ala Gln Glu Ala Phe Glu Ser Val Val Glu Tyr Phe Gly Glu
 965 970 975
 Asn Pro Lys Thr Thr Ser Pro Gly Leu Phe Phe Ser Leu Phe Ser Arg
 980 985 990
 Phe Ile Lys Ala Tyr Lys Lys Ala Glu Gln Glu Val Glu Gln Trp Lys
 995 1000 1005
 Lys Glu Ala Ala Ala Gln Glu Ala Gly Ala Asp Thr Pro Gly Lys
 1010 1015 1020
 Gly Glu Pro Pro Ala Pro Lys Ser Pro Pro Lys Ala Arg Arg Pro
 1025 1030 1035
 Gln Met Asp Leu Ile Ser Glu Leu Lys Arg Arg Gln Gln Lys Glu
 1040 1045 1050
 Pro Leu Ile Tyr Glu Ser Asp Arg Asp Gly Ala Ile Glu Asp Ile
 1055 1060 1065
 Ile Thr Val Ile Lys Thr Val Pro Phe Thr Ala Arg Thr Gly Lys
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 Arg Thr Ser Arg Leu Leu Cys Glu Ala Ser Leu Gly Glu Glu Met
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 Pro Leu
 1100
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 Met Gly Asn Ala Gly Ser Met Asp Ser Gln Gln Thr Asp Phe Arg Ala
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 His Asn Val Pro Leu Lys Leu Pro Met Pro Glu Pro Gly Glu Leu Glu
 20 25 30
 Glu Arg Phe Ala Ile Val Leu Asn Ala Met Asn Leu Pro Pro Asp Lys
 35 40 45
 Ala Arg Leu Leu Arg Gln Tyr Asp Asn Glu Lys Lys Trp Glu Leu Ile
 50 55 60
 Cys Asp Gln Glu Arg Phe Gln Val Lys Asn Pro Pro His Thr Tyr Ile

35

370					375					380					
Ala	Glu	Thr	Lys	Asn	Ala	Ala	Leu	Glu	Arg	Val	Glu	Glu	Leu	Glu	Glu
385					390					395					400
Asn	Ile	Ser	His	Leu	Ser	Glu	Lys	Leu	Gln	Asp	Thr	Glu	Asn	Glu	Ala
				405					410					415	
Met	Ser	Lys	Ile	Val	Glu	Leu	Glu	Lys	Gln	Leu	Met	Gln	Arg	Asn	Lys
			420				425						430		
Glu	Leu	Asp	Val	Val	Arg	Glu	Ile	Tyr	Lys	Asp	Ala	Asn	Thr	Gln	Val
		435					440					445			
His	Thr	Leu	Arg	Lys	Met	Val	Lys	Glu	Lys	Glu	Glu	Ala	Ile	Gln	Arg
	450					455					460				
Gln	Ser	Thr	Leu	Glu	Lys	Lys	Ile	His	Glu	Leu	Glu	Lys	Gln	Gly	Thr
465				470						475					480
Ile	Lys	Ile	Gln	Lys	Lys	Gly	Asp	Gly	Asp	Ile	Ala	Ile	Leu	Pro	Val
			485					490						495	
Val	Ala	Ser	Gly	Thr	Leu	Ser	Met	Gly	Ser	Glu	Val	Val	Ala	Gly	Asn
			500					505					510		
Ser	Val	Gly	Pro	Thr	Met	Gly	Ala	Ala	Ser	Ser	Gly	Pro	Leu	Pro	Pro
		515					520					525			
Pro	Pro	Pro	Pro	Leu	Pro	Pro	Ser	Ser	Asp	Thr	Pro	Glu	Thr	Val	Gln
	530					535					540				
Asn	Gly	Pro	Val	Thr	Pro	Pro	Met	Pro	Pro	Pro	Pro	Pro	Pro	Pro	Pro
545				550					555						560
Pro	Pro	Pro	Pro	Pro	Pro	Pro	Pro	Pro	Pro	Pro	Pro	Pro	Pro	Pro	Pro
				565					570					575	
Gly	Pro	Ala	Ser	Glu	Thr	Val	Pro	Ala	Pro	Pro	Leu	Ala	Pro	Pro	Leu
			580				585						590		
Pro	Ser	Ala	Pro	Pro	Leu	Pro	Gly	Thr	Ser	Ser	Pro	Thr	Val	Val	Phe
		595					600					605			
Asn	Ser	Gly	Leu	Ala	Ala	Val	Lys	Ile	Lys	Lys	Pro	Ile	Lys	Thr	Lys
	610					615					620				
Phe	Arg	Met	Pro	Val	Phe	Asn	Trp	Val	Ala	Leu	Lys	Pro	Asn	Gln	Ile
625				630					635						640
Asn	Gly	Thr	Val	Phe	Asn	Glu	Ile	Asp	Asp	Glu	Arg	Ile	Leu	Glu	Asp
			645					650					655		
Leu	Asn	Val	Asp	Glu	Phe	Glu	Glu	Ile	Phe	Lys	Thr	Lys	Ala	Gln	Gly
			660				665						670		
Pro	Ala	Ile	Asp	Leu	Ser	Ser	Ser	Lys	Gln	Lys	Ile	Pro	Gln	Lys	Gly

675					680					685					
Ser	Asn	Lys	Val	Thr	Leu	Leu	Glu	Ala	Asn	Arg	Ala	Lys	Asn	Leu	Ala
690					695					700					
Ile	Thr	Leu	Arg	Lys	Ala	Gly	Lys	Thr	Ala	Asp	Glu	Ile	Cys	Lys	Ala
705					710					715					720
Ile	His	Val	Phe	Asp	Leu	Lys	Thr	Leu	Pro	Val	Asp	Phe	Val	Glu	Cys
				725					730					735	
Leu	Met	Arg	Phe	Leu	Pro	Thr	Glu	Asn	Glu	Val	Lys	Val	Leu	Arg	Leu
			740					745					750		
Tyr	Glu	Arg	Glu	Arg	Lys	Pro	Leu	Glu	Asn	Leu	Ser	Asp	Glu	Asp	Arg
		755					760					765			
Phe	Met	Met	Gln	Phe	Ser	Lys	Ile	Glu	Arg	Leu	Met	Gln	Lys	Met	Thr
	770					775					780				
Ile	Met	Ala	Phe	Ile	Gly	Asn	Phe	Ala	Glu	Ser	Ile	Gln	Met	Leu	Thr
785					790					795					800
Pro	Gln	Leu	His	Ala	Ile	Ile	Ala	Ala	Ser	Val	Ser	Ile	Lys	Ser	Ser
				805					810					815	
Gln	Lys	Leu	Lys	Lys	Ile	Leu	Glu	Ile	Ile	Leu	Ala	Leu	Gly	Asn	Tyr
			820					825					830		
Met	Asn	Ser	Ser	Lys	Arg	Gly	Ala	Val	Tyr	Gly	Phe	Lys	Leu	Gln	Ser
		835				840						845			
Leu	Asp	Leu	Leu	Leu	Asp	Thr	Lys	Ser	Thr	Asp	Arg	Lys	Gln	Thr	Leu
	850					855					860				
Leu	His	Tyr	Ile	Ser	Asn	Val	Val	Lys	Glu	Lys	Tyr	His	Gln	Val	Ser
865					870					875					880
Leu	Phe	Tyr	Asn	Glu	Leu	His	Tyr	Val	Glu	Lys	Ala	Ala	Ala	Val	Ser
				885					890					895	
Leu	Glu	Asn	Val	Leu	Leu	Asp	Val	Lys	Glu	Leu	Gln	Arg	Gly	Met	Asp
		900						905					910		
Leu	Thr	Lys	Arg	Glu	Tyr	Thr	Met	His	Asp	His	Asn	Thr	Leu	Leu	Lys
		915					920					925			
Glu	Phe	Ile	Leu	Asn	Asn	Glu	Gly	Lys	Leu	Lys	Lys	Leu	Gln	Asp	Asp
	930					935					940				
Ala	Lys	Ile	Ala	Gln	Asp	Ala	Phe	Asp	Asp	Val	Val	Lys	Tyr	Phe	Gly
945					950					955					960
Glu	Asn	Pro	Lys	Thr	Thr	Pro	Pro	Ser	Val	Phe	Phe	Pro	Val	Phe	Val
				965					970					975	
Arg	Phe	Val	Lys	Ala	Tyr	Lys	Gln	Ala	Glu	Glu	Glu	Asn	Glu	Leu	Arg

980 985 990
 Lys Lys Gln Glu Gln Ala Leu Met Glu Lys Leu Leu Glu Gln Glu Ala
 995 1000 1005
 Leu Met Glu Gln Gln Asp Pro Lys Ser Pro Ser His Lys Ser Lys
 1010 1015 1020
 Arg Gln Gln Gln Glu Leu Ile Ala Glu Leu Arg Arg Arg Gln Val
 1025 1030 1035
 Lys Asp Asn Arg His Val Tyr Glu Gly Lys Asp Gly Ala Ile Glu
 1040 1045 1050
 Asp Ile Ile Thr Asp Leu Arg Asn Gln Pro Tyr Arg Arg Ala Asp
 1055 1060 1065
 Ala Val Arg Arg Ser Val Arg Arg Arg Phe Asp Asp Gln Asn Leu
 1070 1075 1080
 Arg Ser Val Asn Gly Ala Glu Ile Thr Met
 1085 1090
 <210> 20
 <211> 940
 <212> PRT
 <213> Homo sapiens
 <400> 20
 Met Gly Asn Leu Glu Ser Ala Glu Gly Val Pro Gly Glu Pro Pro Ser
 1 5 10 15
 Val Pro Leu Leu Leu Pro Pro Gly Lys Met Pro Met Pro Glu Pro Cys
 20 25 30
 Glu Leu Glu Glu Arg Phe Ala Leu Val Leu Ser Ser Met Asn Leu Pro
 35 40 45
 Pro Asp Lys Ala Arg Leu Leu Arg Gln Tyr Asp Asn Glu Lys Lys Trp
 50 55 60
 Asp Leu Ile Cys Asp Gln Glu Arg Phe Gln Val Lys Asn Pro Pro His
 65 70 75 80
 Thr Tyr Ile Gln Lys Leu Gln Ser Phe Leu Asp Pro Ser Val Thr Arg
 85 90 95
 Lys Lys Phe Arg Arg Arg Val Gln Glu Ser Thr Lys Val Leu Arg Glu
 100 105 110
 Leu Glu Ile Ser Leu Arg Thr Asn His Ile Gly Trp Val Arg Glu Phe
 115 120 125
 Leu Asn Asp Glu Asn Lys Gly Leu Asp Val Leu Val Asp Tyr Leu Ser
 130 135 140
 Phe Ala Gln Cys Ser Val Met Phe Asp Phe Glu Gly Leu Glu Ser Gly
 145 150 155 160

Asp Asp Gly Ala Phe Asp Lys Leu Arg Ser Trp Ser Arg Ser Ile Glu
 165 170 175
 Asp Leu Gln Pro Pro Ser Ala Leu Ser Ala Pro Phe Thr Asn Ser Leu
 180 185 190
 Ala Arg Ser Ala Arg Gln Ser Val Leu Arg Tyr Ser Thr Leu Pro Gly
 195 200 205
 Arg Arg Ala Leu Lys Asn Ser Arg Leu Val Ser Gln Lys Asp Asp Val
 210 215 220
 His Val Cys Ile Leu Cys Leu Arg Ala Ile Met Asn Tyr Gln Tyr Gly
 225 230 235 240
 Phe Asn Leu Val Met Ser His Pro His Ala Val Asn Glu Ile Ala Leu
 245 250 255
 Ser Leu Asn Asn Lys Asn Pro Arg Thr Lys Ala Leu Val Leu Glu Leu
 260 265 270
 Leu Ala Ala Val Cys Leu Val Arg Gly Gly His Glu Ile Ile Leu Ala
 275 280 285
 Ala Phe Asp Asn Phe Lys Glu Val Cys Lys Glu Leu His Arg Phe Glu
 290 295 300
 Lys Leu Met Glu Tyr Phe Arg Asn Glu Asp Ser Asn Ile Asp Phe Met
 305 310 315 320
 Val Ala Cys Met Gln Phe Ile Asn Ile Val Val His Ser Val Glu Asp
 325 330 335
 Met Asn Phe Arg Val His Leu Gln Tyr Glu Phe Thr Lys Leu Gly Leu
 340 345 350
 Glu Glu Phe Leu Gln Lys Ser Arg His Thr Glu Ser Glu Lys Leu Gln
 355 360 365
 Val Gln Ile Gln Ala Tyr Leu Asp Asn Val Phe Asp Val Gly Gly Leu
 370 375 380
 Leu Glu Asp Ala Glu Thr Lys Asn Val Ala Leu Glu Lys Val Glu Glu
 385 390 395 400
 Leu Glu Glu His Val Ser His Leu Thr Glu Lys Leu Leu Asp Leu Glu
 405 410 415
 Asn Glu Asn Met Met Arg Val Ala Glu Leu Glu Lys Gln Leu Leu Gln
 420 425 430
 Arg Glu Lys Glu Leu Glu Ser Ile Lys Glu Thr Tyr Glu Asn Thr Ser
 435 440 445
 His Gln Val His Thr Leu Arg Arg Leu Ile Lys Glu Lys Glu Glu Ala
 450 455 460

Phe Gln Arg Arg Cys His Leu Glu Pro Asn Val Arg Gly Leu Glu Ser
 465 470 475 480
 Val Asp Ser Glu Ala Leu Ala Arg Val Gly Pro Ala Glu Leu Ser Glu
 485 490 495
 Gly Met Pro Pro Ser Asp Leu Asp Leu Leu Ala Pro Ala Pro Pro Pro
 500 505 510
 Glu Glu Val Leu Pro Leu Pro Pro Pro Ala Pro Pro Leu Pro Pro
 515 520 525
 Pro Pro Pro Pro Leu Pro Asp Lys Cys Pro Pro Ala Pro Pro Leu Pro
 530 535 540
 Gly Ala Ala Pro Ser Val Val Leu Thr Val Gly Leu Ser Ala Ile Arg
 545 550 555 560
 Ile Lys Lys Pro Ile Lys Thr Lys Phe Arg Leu Pro Val Phe Asn Trp
 565 570 575
 Thr Ala Leu Lys Pro Asn Gln Ile Ser Gly Thr Val Phe Ser Glu Leu
 580 585 590
 Asp Asp Glu Lys Ile Leu Glu Asp Leu Asp Leu Asp Lys Phe Glu Glu
 595 600 605
 Leu Phe Lys Thr Lys Ala Gln Gly Pro Ala Leu Asp Leu Ile Cys Ser
 610 615 620
 Lys Asn Lys Thr Ala Gln Lys Ala Ala Ser Lys Val Thr Leu Leu Glu
 625 630 635 640
 Ala Asn Arg Ala Lys Asn Leu Ala Ile Thr Leu Arg Lys Ala Gly Arg
 645 650 655
 Ser Ala Glu Glu Ile Cys Arg Ala Ile His Thr Phe Asp Leu Gln Thr
 660 665 670
 Leu Pro Val Asp Phe Val Glu Cys Leu Met Arg Phe Leu Pro Thr Glu
 675 680 685
 Ala Glu Val Lys Leu Leu Arg Gln Tyr Glu Arg Glu Arg Gln Pro Leu
 690 695 700
 Glu Glu Leu Ala Ala Glu Asp Arg Phe Met Leu Leu Phe Ser Lys Val
 705 710 715 720
 Glu Arg Leu Thr Gln Arg Met Ala Gly Met Ala Phe Leu Gly Asn Phe
 725 730 735
 Gln Asp Asn Leu Gln Met Leu Thr Pro Gln Leu Asn Ala Ile Ile Ala
 740 745 750
 Ala Ser Ala Ser Val Lys Ser Ser Gln Lys Leu Lys Gln Met Leu Glu
 755 760 765

Ile Ile Leu Ala Leu Gly Asn Tyr Met Asn Ser Ser Lys Arg Gly Ala
770 775 780

Val Tyr Gly Phe Lys Leu Gln Ser Leu Asp Leu Leu Leu Asp Thr Lys
785 790 795 800

Ser Thr Asp Arg Lys Met Thr Leu Leu His Phe Ile Ala Leu Thr Val
805 810 815

Lys Glu Lys Tyr Pro Asp Leu Ala Asn Phe Trp His Glu Leu His Phe
820 825 830

Val Glu Lys Ala Ala Ala Val Ser Leu Glu Asn Val Leu Leu Asp Val
835 840 845

Lys Glu Leu Gly Arg Gly Met Glu Leu Ile Arg Arg Glu Cys Ser Ile
850 855 860

His Asp Asn Ser Val Leu Arg Asn Phe Leu Ser Thr Asn Glu Gly Lys
865 870 875 880

Leu Asp Lys Leu Gln Arg Asp Ala Lys Thr Ala Glu Glu Ala Tyr Asn
885 890 895

Ala Val Val Arg Tyr Phe Gly Glu Ser Pro Lys Thr Thr Pro Pro Ser
900 905 910

Val Phe Phe Pro Val Phe Val Arg Phe Ile Arg Ser Tyr Lys Lys Gln
915 920 925

Asn Lys Arg Met Lys Pro Ala Arg Ser Arg Arg Arg
930 935 940

<210> 21

<211> 379

<212> PRT

<213> Homo sapiens

<400> 21

Met Ala Ala Thr Glu Gly Val Gly Glu Ala Ala Gln Gly Gly Glu Pro
1 5 10 15

Gly Gln Pro Ala Gln Pro Pro Pro Gln Pro His Pro Pro Pro Pro Gln
20 25 30

Gln Gln His Lys Glu Glu Met Ala Ala Glu Ala Gly Glu Ala Val Ala
35 40 45

Ser Pro Met Asp Asp Gly Phe Val Ser Leu Asp Ser Pro Ser Tyr Val
50 55 60

Leu Tyr Arg Asp Arg Ala Glu Trp Ala Asp Ile Asp Pro Val Pro Gln
65 70 75 80

Asn Asp Gly Pro Asn Pro Val Val Gln Ile Ile Tyr Ser Asp Lys Phe
85 90 95

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

<210> 22
 <211> 289
 <212> PRT

<213> Homo sapiens

<400> 22

Met Ala Ala Thr Glu Gly Val Gly Glu Ala Ala Gln Gly Gly Glu Pro
 1 5 10 15

Arg Gln Leu Glu Gln Pro Pro Pro Gln Pro His Pro Pro Leu Pro Gln
 20 25 30

Glu Gln His Glu Glu Glu Met Ala Ala Glu Ala Gly Glu Ala Val Ala
 35 40 45

Ser Pro Met Asp Asp Gly Phe Leu Ser Leu Asp Ser Pro Ser Tyr Val
 50 55 60

Pro Tyr Arg His Phe Arg Arg Val Leu Leu Lys Ser Leu Gln Lys Asp
 65 70 75 80

Leu His Glu Glu Met Asn Tyr Ile Thr Glu Ile Ile Glu Gly Gln Pro
 85 90 95

Lys Asn Tyr Leu Val Cys His Asn Arg Arg Val Ile Val Glu Trp Leu
 100 105 110

Arg Asp Pro Ser Gln Glu Pro Glu Phe Ile Asp Asn Ile Leu Asn Gln
 115 120 125

Asp Ala Lys Asn Tyr His Ala Trp Gln His Arg Gln Trp Val Ile Gln
 130 135 140

Glu Phe Lys Leu Trp Asp Asn Glu Leu Gln Tyr Val Asp Gln Leu Leu
 145 150 155 160

Lys Glu Asp Val Arg Asn Asn Ser Val Trp Asn Arg Arg Tyr Phe Val
 165 170 175

Ile Ser Asn Thr Thr Gly Tyr Asn Asp Cys Ala Val Leu Glu Arg Glu
 180 185 190

Val Gln Tyr Thr Leu Glu Met Ile Gln Leu Val Pro His Asn Ser Ser
 195 200 205

Trp Asn Tyr Leu Lys Gly Ile Leu Gln Asp Arg Gly Leu Ser Lys Tyr
 210 215 220

Pro Asn Leu Leu Asn Gln Leu Leu Asp Leu Gln Pro Ser His Ser Ser
 225 230 235 240

Pro Tyr Leu Ile Ala Phe Leu Val Gly Ile Tyr Glu Asp Met Leu Glu
 245 250 255

Asn Gln Cys Val Asn Lys Glu Asp Ile Leu Asn Asn Ala Leu Gly Leu
 260 265 270

Cys Glu Ile Leu Ala Lys Glu Lys Asp Met Ile Arg Lys Glu Tyr Trp
 275 280 285

Arg

<210> 23
 <211> 1571
 <212> PRT
 <213> Homo sapiens
 <400> 23
 Met Ala Asp Arg Gly Cys Pro Leu Glu Ala Ala Pro Leu Pro Ala Glu
 1 5 10 15
 Val Arg Glu Ser Leu Ala Glu Leu Glu Leu Glu Leu Ser Glu Gly Asp
 20 25 30
 Ile Thr Gln Lys Gly Tyr Glu Lys Lys Arg Ala Lys Leu Leu Ala Arg
 35 40 45
 Tyr Ile Pro Leu Ile Gln Gly Ile Asp Pro Ser Leu Gln Ala Glu Asn
 50 55 60
 Arg Ile Pro Gly Pro Ser Gln Thr Thr Ala Ala Ala Pro Lys Gln Gln
 65 70 75 80
 Lys Ser Arg Pro Thr Ala Ser Arg Asp Glu Arg Phe Arg Ser Asp Val
 85 90 95
 His Thr Glu Ala Val Gln Ala Ala Leu Ala Lys Tyr Lys Glu Arg Lys
 100 105 110
 Met Pro Met Pro Ser Lys Arg Arg Ser Val Leu Val His Ser Ser Val
 115 120 125
 Glu Thr Tyr Thr Pro Pro Asp Thr Ser Ser Ala Ser Glu Asp Glu Gly
 130 135 140
 Ser Leu Arg Arg Pro Gly Arg Leu Thr Ser Thr Pro Leu Gln Ser His
 145 150 155 160
 Ser Ser Val Glu Pro Trp Leu Asp Arg Val Ile Gln Gly Ser Ser Thr
 165 170 175
 Ser Ser Ser Ala Ser Ser Thr Ser Ser His Pro Gly Gly Arg Pro Thr
 180 185 190
 Thr Ala Pro Ser Ala Ala Ala Thr Pro Gly Ala Ala Ala Thr Thr Ala
 195 200 205
 Leu Ala Gly Leu Glu Ala His Thr His Ile Asp Leu His Ser Ala Pro
 210 215 220
 Pro Asp Val Thr Thr Gly Leu Val Glu His Ser Tyr Phe Glu Arg Pro
 225 230 235 240
 Gln Val Ala Ser Val Arg Ser Val Pro Arg Gly Cys Ser Gly Ser Met
 245 250 255
 Leu Glu Thr Ala Asp Gly Val Pro Val Asn Ser Arg Val Ser Ser Lys
 260 265 270

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

Val Val Ser Val Pro Tyr Ala Leu Met Lys Ala Asn Pro Leu Ser Trp
 580 585 590
 Ile Gln Lys Val Cys Phe Tyr Lys Ala Arg Ala Ala Leu Val Lys Ser
 595 600 605
 Arg Asp Met His Trp Ser Leu Leu Ala Gln Arg Gly Gln Arg Asp Val
 610 615 620
 Ser Leu Ser Ser Leu Arg Met Leu Ile Val Ala Asp Gly Ala Asn Pro
 625 630 635 640
 Trp Ser Ile Ser Ser Cys Asp Ala Phe Leu Asn Val Phe Gln Ser Arg
 645 650 655
 Gly Leu Arg Pro Glu Val Ile Cys Pro Cys Ala Ser Ser Pro Glu Ala
 660 665 670
 Leu Thr Val Ala Ile Arg Arg Pro Pro Asp Leu Gly Gly Pro Pro Pro
 675 680 685
 Arg Lys Ala Val Leu Ser Met Asn Gly Leu Ser Tyr Gly Val Ile Arg
 690 695 700
 Val Asp Thr Glu Glu Lys Leu Ser Val Leu Thr Val Gln Asp Val Gly
 705 710 715 720
 Gln Val Met Pro Gly Ala Asn Val Cys Val Val Lys Leu Glu Gly Thr
 725 730 735
 Pro Tyr Leu Cys Lys Thr Asp Glu Val Gly Glu Ile Cys Val Ser Ser
 740 745 750
 Ser Ala Thr Gly Thr Ala Tyr Tyr Gly Leu Leu Gly Ile Thr Lys Asn
 755 760 765
 Val Phe Glu Ala Val Pro Val Thr Thr Gly Gly Ala Pro Ile Phe Asp
 770 775 780
 Arg Pro Phe Thr Arg Thr Gly Leu Leu Gly Phe Ile Gly Pro Asp Asn
 785 790 795 800
 Leu Val Phe Ile Val Gly Lys Leu Asp Gly Leu Met Val Thr Gly Val
 805 810 815
 Arg Arg His Asn Ala Asp Asp Val Val Ala Thr Ala Leu Ala Val Glu
 820 825 830
 Pro Met Lys Phe Val Tyr Arg Gly Arg Ile Ala Val Phe Ser Val Thr
 835 840 845
 Val Leu His Asp Asp Arg Ile Val Leu Val Ala Glu Gln Arg Pro Asp
 850 855 860
 Ala Ser Glu Glu Asp Ser Phe Gln Trp Met Ser Arg Val Leu Gln Ala
 865 870 875 880

Ile Asp Ser Ile His Gln Val Gly Val Tyr Cys Leu Ala Leu Val Pro
 885 890 895
 Ala Asn Thr Leu Pro Lys Ala Pro Leu Gly Gly Ile His Ile Ser Glu
 900 905 910
 Thr Lys Gln Arg Phe Leu Glu Gly Thr Leu His Pro Cys Asn Val Leu
 915 920 925
 Met Cys Pro His Thr Cys Val Thr Asn Leu Pro Lys Pro Arg Gln Lys
 930 935 940
 Gln Pro Glu Val Gly Pro Ala Ser Met Ile Val Gly Asn Leu Val Ala
 945 950 955 960
 Gly Lys Arg Ile Ala Gln Ala Ser Gly Arg Glu Leu Ala His Leu Glu
 965 970 975
 Asp Ser Asp Gln Ala Arg Lys Phe Leu Phe Leu Ala Asp Val Leu Gln
 980 985 990
 Trp Arg Ala His Thr Thr Pro Asp His Pro Leu Phe Leu Leu Leu Asn
 995 1000 1005
 Ala Lys Gly Thr Val Thr Ser Thr Ala Thr Cys Val Gln Leu His
 1010 1015 1020
 Lys Arg Ala Glu Arg Val Ala Ala Ala Leu Met Glu Lys Gly Arg
 1025 1030 1035
 Leu Ser Val Gly Asp His Val Ala Leu Val Tyr Pro Pro Gly Val
 1040 1045 1050
 Asp Leu Ile Ala Ala Phe Tyr Gly Cys Leu Tyr Cys Gly Cys Val
 1055 1060 1065
 Pro Val Thr Val Arg Pro Pro His Pro Gln Asn Leu Gly Thr Thr
 1070 1075 1080
 Leu Pro Thr Val Lys Met Ile Val Glu Val Ser Lys Ser Ala Cys
 1085 1090 1095
 Val Leu Thr Thr Gln Ala Val Thr Arg Leu Leu Arg Ser Lys Glu
 1100 1105 1110
 Ala Ala Ala Ala Val Asp Ile Arg Thr Trp Pro Thr Ile Leu Asp
 1115 1120 1125
 Thr Asp Asp Ile Pro Lys Lys Lys Ile Ala Ser Val Phe Arg Pro
 1130 1135 1140
 Pro Ser Pro Asp Val Leu Ala Tyr Leu Asp Phe Ser Val Ser Thr
 1145 1150 1155
 Thr Gly Ile Leu Ala Gly Val Lys Met Ser His Ala Ala Thr Ser
 1160 1165 1170

Ala Leu Cys Arg Ser Ile Lys	Leu Gln Cys Glu Leu Tyr Pro Ser
1175	1180 1185
Arg Gln Ile Ala Ile Cys Leu	Asp Pro Tyr Cys Gly Leu Gly Phe
1190	1195 1200
Ala Leu Trp Cys Leu Cys Ser	Val Tyr Ser Gly His Gln Ser Val
1205	1210 1215
Leu Val Pro Pro Leu Glu Leu	Glu Ser Asn Val Ser Leu Trp Leu
1220	1225 1230
Ser Ala Val Ser Gln Tyr Lys	Ala Arg Val Thr Phe Cys Ser Tyr
1235	1240 1245
Ser Val Met Glu Met Cys Thr	Lys Gly Leu Gly Ala Gln Thr Gly
1250	1255 1260
Val Leu Arg Met Lys Gly Val	Asn Leu Ser Cys Val Arg Thr Cys
1265	1270 1275
Met Val Val Ala Glu Glu Arg	Pro Arg Ile Ala Leu Thr Gln Ser
1280	1285 1290
Phe Ser Lys Leu Phe Lys Asp	Leu Gly Leu Pro Ala Arg Ala Val
1295	1300 1305
Ser Thr Thr Phe Gly Cys Arg	Val Asn Val Ala Ile Cys Leu Gln
1310	1315 1320
Gly Thr Ala Gly Pro Asp Pro	Thr Thr Val Tyr Val Asp Met Arg
1325	1330 1335
Ala Leu Arg His Asp Arg Val	Arg Leu Val Glu Arg Gly Ser Pro
1340	1345 1350
His Ser Leu Pro Leu Met Glu	Ser Gly Lys Ile Leu Pro Gly Val
1355	1360 1365
Lys Val Ile Ile Ala His Thr	Glu Thr Lys Gly Pro Leu Gly Asp
1370	1375 1380
Ser His Leu Gly Glu Ile Trp	Val Ser Ser Pro His Asn Ala Thr
1385	1390 1395
Gly Tyr Tyr Thr Val Tyr Gly	Glu Glu Ala Leu His Ala Asp His
1400	1405 1410
Phe Ser Ala Arg Leu Ser Phe	Gly Asp Thr Gln Thr Ile Trp Ala
1415	1420 1425
Arg Thr Gly Tyr Leu Gly Phe	Leu Arg Arg Thr Glu Leu Thr Asp
1430	1435 1440
Ala Ser Gly Gly Arg His Asp	Ala Leu Tyr Val Val Gly Ser Leu
1445	1450 1455

Asp Glu Thr Leu Glu Leu Arg Gly Met Arg Tyr His Pro Ile Asp
 1460 1465 1470
 Ile Glu Thr Ser Val Ile Arg Ala His Arg Ser Ile Ala Glu Cys
 1475 1480 1485
 Ala Val Phe Thr Trp Thr Asn Leu Leu Val Val Val Val Glu Leu
 1490 1495 1500
 Asp Gly Leu Glu Gln Asp Ala Leu Asp Leu Val Ala Leu Val Thr
 1505 1510 1515
 Asn Val Val Leu Glu Glu His Tyr Leu Val Val Gly Val Val Val
 1520 1525 1530
 Ile Val Asp Pro Gly Val Ile Pro Ile Asn Ser Arg Gly Glu Lys
 1535 1540 1545
 Gln Arg Met His Leu Arg Asp Gly Phe Leu Ala Asp Gln Leu Asp
 1550 1555 1560
 Pro Ile Tyr Val Ala Tyr Asn Met
 1565 1570
 <210> 24
 <211> 1556
 <212> PRT
 <213> Homo sapiens
 <400> 24
 Met Ala Asp Arg Ser Leu Glu Gly Met Ala Leu Pro Leu Glu Val Arg
 1 5 10 15
 Ala Arg Leu Ala Glu Leu Glu Leu Glu Leu Ser Glu Gly Asp Ile Thr
 20 25 30
 Gln Lys Gly Tyr Glu Lys Lys Arg Ser Lys Leu Ile Gly Ala Tyr Leu
 35 40 45
 Pro Gln Pro Pro Arg Val Asp Gln Ala Leu Pro Gln Glu Arg Arg Ala
 50 55 60
 Pro Val Thr Pro Ser Ser Ala Ser Arg Tyr His Arg Arg Arg Ser Ser
 65 70 75 80
 Gly Ser Arg Asp Glu Arg Tyr Arg Ser Asp Val His Thr Glu Ala Val
 85 90 95
 Gln Ala Ala Leu Ala Lys His Lys Glu Arg Lys Met Ala Val Pro Met
 100 105 110
 Pro Ser Lys Arg Arg Ser Leu Val Val Gln Thr Ser Met Asp Ala Tyr
 115 120 125
 Thr Pro Pro Asp Thr Ser Ser Gly Ser Glu Asp Glu Gly Ser Val Gln
 130 135 140

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

Leu Pro Lys Ser Pro Thr Gly Glu Ile Pro Gln Phe Lys Gly Trp Pro
 450 455 460
 Lys Leu Leu Trp Phe Val Thr Glu Ser Lys His Leu Ser Lys Pro Pro
 465 470 475 480
 Arg Asp Trp Phe Pro His Ile Lys Asp Ala Asn Asn Asp Thr Ala Tyr
 485 490 495
 Ile Glu Tyr Lys Thr Cys Lys Asp Gly Ser Val Leu Gly Val Thr Val
 500 505 510
 Thr Arg Thr Ala Leu Leu Thr His Cys Gln Ala Leu Thr Gln Ala Cys
 515 520 525
 Gly Tyr Thr Glu Ala Glu Thr Ile Val Asn Val Leu Asp Phe Lys Lys
 530 535 540
 Asp Val Gly Leu Trp His Gly Ile Leu Thr Ser Val Met Asn Met Met
 545 550 555 560
 His Val Ile Ser Ile Pro Tyr Ser Leu Met Lys Val Asn Pro Leu Ser
 565 570 575
 Trp Ile Gln Lys Val Cys Gln Tyr Lys Ala Lys Val Ala Cys Val Lys
 580 585 590
 Ser Arg Asp Met His Trp Ala Leu Val Ala His Arg Asp Gln Arg Asp
 595 600 605
 Ile Asn Leu Ser Ser Leu Arg Met Leu Ile Val Ala Asp Gly Ala Asn
 610 615 620
 Pro Trp Ser Ile Ser Ser Cys Asp Ala Phe Leu Asn Val Phe Gln Ser
 625 630 635 640
 Lys Gly Leu Arg Gln Glu Val Ile Cys Pro Cys Ala Ser Ser Pro Glu
 645 650 655
 Ala Leu Thr Val Ala Ile Arg Arg Pro Thr Asp Asp Ser Asn Gln Pro
 660 665 670
 Pro Gly Arg Gly Val Leu Ser Met His Gly Leu Thr Tyr Gly Val Ile
 675 680 685
 Arg Val Asp Ser Glu Glu Lys Leu Ser Val Leu Thr Val Gln Asp Val
 690 695 700
 Gly Leu Val Met Pro Gly Ala Ile Met Cys Ser Val Lys Pro Asp Gly
 705 710 715 720
 Val Pro Gln Leu Cys Arg Thr Asp Glu Ile Gly Glu Leu Cys Val Cys
 725 730 735
 Ala Val Ala Thr Gly Thr Ser Tyr Tyr Gly Leu Ser Gly Met Thr Lys
 740 745 750

Asn Thr Phe Glu Val Phe Pro Met Thr Ser Ser Gly Ala Pro Ile Ser
 755 760 765
 Glu Tyr Pro Phe Ile Arg Thr Gly Leu Leu Gly Phe Val Gly Pro Gly
 770 775 780
 Gly Leu Val Phe Val Val Gly Lys Met Asp Gly Leu Met Val Val Ser
 785 790 795 800
 Gly Arg Arg His Asn Ala Asp Asp Ile Val Ala Thr Ala Leu Ala Val
 805 810 815
 Glu Pro Met Lys Phe Val Tyr Arg Gly Arg Ile Ala Val Phe Ser Val
 820 825 830
 Thr Val Leu His Asp Glu Arg Ile Val Ile Val Ala Glu Gln Arg Pro
 835 840 845
 Asp Ser Thr Glu Glu Asp Ser Phe Gln Trp Met Ser Arg Val Leu Gln
 850 855 860
 Ala Ile Asp Ser Ile His Gln Val Gly Val Tyr Cys Leu Ala Leu Val
 865 870 875 880
 Pro Ala Asn Thr Leu Pro Lys Thr Pro Leu Gly Gly Ile His Leu Ser
 885 890 895
 Glu Thr Lys Gln Leu Phe Leu Glu Gly Ser Leu His Pro Cys Asn Val
 900 905 910
 Leu Met Cys Pro His Thr Cys Val Thr Asn Leu Pro Lys Pro Arg Gln
 915 920 925
 Lys Gln Pro Glu Ile Gly Pro Ala Ser Val Met Val Gly Asn Leu Val
 930 935 940
 Ser Gly Lys Arg Ile Ala Gln Ala Ser Gly Arg Asp Leu Gly Gln Ile
 945 950 955 960
 Glu Asp Asn Asp Gln Ala Arg Lys Phe Leu Phe Leu Ser Glu Val Leu
 965 970 975
 Gln Trp Arg Ala Gln Thr Thr Pro Asp His Ile Leu Tyr Thr Leu Leu
 980 985 990
 Asn Cys Arg Gly Ala Ile Ala Asn Ser Leu Thr Cys Val Gln Leu His
 995 1000 1005
 Lys Arg Ala Glu Lys Ile Ala Val Met Leu Met Glu Arg Gly His
 1010 1015 1020
 Leu Gln Asp Gly Asp His Val Ala Leu Val Tyr Pro Pro Gly Ile
 1025 1030 1035
 Asp Leu Ile Ala Ala Phe Tyr Gly Cys Leu Tyr Ala Gly Cys Val
 1040 1045 1050

Pro	Ile	Thr	Val	Arg	Pro	Pro	His	Pro	Gln	Asn	Ile	Ala	Thr	Thr
1055						1060					1065			
Leu	Pro	Thr	Val	Lys	Met	Ile	Val	Glu	Val	Ser	Arg	Ser	Ala	Cys
1070						1075					1080			
Leu	Met	Thr	Thr	Gln	Leu	Ile	Cys	Lys	Leu	Leu	Arg	Ser	Arg	Glu
1085						1090					1095			
Ala	Ala	Ala	Ala	Val	Asp	Val	Arg	Thr	Trp	Pro	Leu	Ile	Leu	Asp
1100						1105					1110			
Thr	Asp	Asp	Leu	Pro	Lys	Lys	Arg	Pro	Ala	Gln	Ile	Cys	Lys	Pro
1115						1120					1125			
Cys	Asn	Pro	Asp	Thr	Leu	Ala	Tyr	Leu	Asp	Phe	Ser	Val	Ser	Thr
1130						1135					1140			
Thr	Gly	Met	Leu	Ala	Gly	Val	Lys	Met	Ser	His	Ala	Ala	Thr	Ser
1145						1150					1155			
Ala	Phe	Cys	Arg	Ser	Ile	Lys	Leu	Gln	Cys	Glu	Leu	Tyr	Pro	Ser
1160						1165					1170			
Arg	Glu	Val	Ala	Ile	Cys	Leu	Asp	Pro	Tyr	Cys	Gly	Leu	Gly	Phe
1175						1180					1185			
Val	Leu	Trp	Cys	Leu	Cys	Ser	Val	Tyr	Ser	Gly	His	Gln	Ser	Ile
1190						1195					1200			
Leu	Ile	Pro	Pro	Ser	Glu	Leu	Glu	Thr	Asn	Pro	Ala	Leu	Trp	Leu
1205						1210					1215			
Leu	Ala	Val	Ser	Gln	Tyr	Lys	Val	Arg	Asp	Thr	Phe	Cys	Ser	Tyr
1220						1225					1230			
Ser	Val	Met	Glu	Leu	Cys	Thr	Lys	Gly	Leu	Gly	Ser	Gln	Thr	Glu
1235						1240					1245			
Ser	Leu	Lys	Ala	Arg	Gly	Leu	Asp	Leu	Ser	Arg	Val	Arg	Thr	Cys
1250						1255					1260			
Val	Val	Val	Ala	Glu	Glu	Arg	Pro	Arg	Ile	Ala	Leu	Thr	Gln	Ser
1265						1270					1275			
Phe	Ser	Lys	Leu	Phe	Lys	Asp	Leu	Gly	Leu	His	Pro	Arg	Ala	Val
1280						1285					1290			
Ser	Thr	Ser	Phe	Gly	Cys	Arg	Val	Asn	Leu	Ala	Ile	Cys	Leu	Gln
1295						1300					1305			
Gly	Thr	Ser	Gly	Pro	Asp	Pro	Thr	Thr	Val	Tyr	Val	Asp	Met	Arg
1310						1315					1320			
Ala	Leu	Arg	His	Asp	Arg	Val	Arg	Leu	Val	Glu	Arg	Gly	Ser	Pro
1325						1330					1335			

His Ser Leu Pro Leu Met Glu Ser Gly Lys Ile Leu Pro Gly Val
 1340 1345 1350
 Arg Ile Ile Ile Ala Asn Pro Glu Thr Lys Gly Pro Leu Gly Asp
 1355 1360 1365
 Ser His Leu Gly Glu Ile Trp Val His Ser Ala His Asn Ala Ser
 1370 1375 1380
 Gly Tyr Phe Thr Ile Tyr Gly Asp Glu Ser Leu Gln Ser Asp His
 1385 1390 1395
 Phe Asn Ser Arg Leu Ser Phe Gly Asp Thr Gln Thr Ile Trp Ala
 1400 1405 1410
 Arg Thr Gly Tyr Leu Gly Phe Leu Arg Arg Thr Glu Leu Thr Asp
 1415 1420 1425
 Ala Asn Gly Glu Arg His Asp Ala Leu Tyr Val Val Gly Ala Leu
 1430 1435 1440
 Asp Glu Ala Met Glu Leu Arg Gly Met Arg Tyr His Pro Ile Asp
 1445 1450 1455
 Ile Glu Thr Ser Val Ile Arg Ala His Lys Ser Val Thr Glu Cys
 1460 1465 1470
 Ala Val Phe Thr Trp Thr Asn Leu Leu Val Val Val Val Glu Leu
 1475 1480 1485
 Asp Gly Ser Glu Gln Glu Ala Leu Asp Leu Val Pro Leu Val Thr
 1490 1495 1500
 Asn Val Val Leu Glu Glu His Tyr Leu Ile Val Gly Val Val Val
 1505 1510 1515
 Val Val Asp Ile Gly Val Ile Pro Ile Asn Ser Arg Gly Glu Lys
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 Pro Ile Tyr Val Ala Tyr Asn Met
 1550 1555
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 Gly Gln Gln Ile Gly Phe Leu Leu Gly Ser Cys Gly Ile Ala Leu Ala

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

340							345							350													
Tyr	Phe	Gly	Leu	Ala	Gly	Val	Thr	Lys	Asn	Thr	Phe	Glu	Val	Ile	Pro												
		355					360					365															
Val	Asn	Ser	Ala	Gly	Ser	Pro	Val	Gly	Asp	Val	Pro	Phe	Ile	Arg	Ser												
	370					375					380																
Gly	Leu	Leu	Gly	Phe	Val	Gly	Pro	Gly	Ser	Leu	Val	Phe	Val	Val	Gly												
385					390					395				400													
Lys	Met	Asp	Gly	Leu	Leu	Met	Val	Ser	Gly	Arg	Arg	His	Asn	Ala	Asp												
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Asp	Ile	Val	Ala	Thr	Gly	Leu	Ala	Val	Glu	Ser	Ile	Lys	Thr	Val	Tyr												
			420					425					430														
Arg	Gly	Arg	Ile	Ala	Val	Phe	Ser	Val	Ser	Val	Phe	Tyr	Asp	Glu	Arg												
		435					440					445															
Ile	Val	Val	Val	Ala	Glu	Gln	Arg	Pro	Asp	Ala	Ser	Glu	Glu	Asp	Ser												
	450					455					460																
Phe	Gln	Trp	Met	Ser	Arg	Val	Leu	Gln	Ala	Ile	Asp	Ser	Ile	His	Gln												
465					470					475				480													
Val	Gly	Val	Tyr	Cys	Leu	Ala	Leu	Val	Pro	Ala	Asn	Thr	Leu	Pro	Lys												
				485					490					495													
Thr	Pro	Leu	Gly	Gly	Ile	His	Ile	Ser	Gln	Thr	Lys	Gln	Leu	Phe	Leu												
			500					505					510														
Glu	Gly	Ser	Leu	His	Pro	Cys	Asn	Ile	Leu	Met	Cys	Pro	His	Thr	Cys												
		515					520					525															
Val	Thr	Asn	Leu	Pro	Lys	Pro	Arg	Gln	Lys	Gln	Pro	Gly	Val	Gly	Pro												
	530					535					540																
Ala	Ser	Val	Met	Val	Gly	Asn	Leu	Val	Ala	Gly	Lys	Arg	Ile	Ala	Gln												
545					550					555				560													
Ala	Ala	Gly	Arg	Asp	Leu	Gly	Gln	Ile	Glu	Glu	Asn	Asp	Leu	Val	Arg												
				565					570					575													
Lys	His	Gln	Phe	Leu	Ala	Glu																					

57

58

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

Thr Val Leu Ala Asp Glu Pro Gly Leu Leu Gly Pro Lys Ala Leu Phe
 355 360 365
 Ala Phe Met Ala Leu Ser Phe Ile Arg Asp Glu Val Thr Trp Leu Val
 370 375 380
 Arg His Thr Glu Asn Val Thr Lys Thr Lys Thr Pro Glu Asp Tyr Ala
 385 390 395 400
 Asp Ser Ser Ile Ala Glu Leu Leu Phe Leu Leu Glu Gly Ile Arg Ser
 405 410 415
 Leu Val Arg Arg His Ile Lys Val Ile Gln Gln Tyr His Leu Gln Tyr
 420 425 430
 Leu Ala Arg Phe Asp Ala Leu Val Leu Ser Asp Ile Ile Gln Asn Leu
 435 440 445
 Ser Val Cys Pro Glu Glu Glu Ser Ile Ile Met Ser Ser Phe Val Ser
 450 455 460
 Ile Leu Ser Ser Leu Asn Leu Lys Gln Val Asp Asn Gly Glu Lys Phe
 465 470 475 480
 Glu Phe Ser Gly Leu Arg Leu Asp Trp Phe Arg Leu Gln Ala Tyr Thr
 485 490 495
 Ser Val Ala Lys Ala Pro Leu His Leu His Glu Asn Pro Asp Leu Ala
 500 505 510
 Lys Val Met Asn Leu Ile Val Phe His Ser Arg Met Leu Asp Ser Val
 515 520 525
 Glu Lys Leu Leu Val Glu Thr Ser Asp Leu Ser Thr Phe Cys Phe His
 530 535 540
 Leu Arg Ile Phe Glu Lys Met Phe Ala Met Thr Leu Glu Glu Ser Ala
 545 550 555 560
 Met Leu Arg Tyr Ala Ile Ala Phe Pro Leu Ile Cys Ala His Phe Val
 565 570 575
 His Cys Thr His Glu Met Cys Pro Glu Glu Tyr Pro His Leu Lys Asn
 580 585 590
 His Gly Leu His His Cys Asn Ser Phe Leu Glu Glu Leu Ala Lys Gln
 595 600 605
 Thr Ser Asn Cys Val Leu Glu Ile Cys Ala Glu Gln Arg Asn Leu Ser
 610 615 620
 Glu Gln Leu Leu Pro Lys His Cys Ala Thr Thr Ile Ser Lys Ala Lys
 625 630 635 640
 Asn Lys Lys Thr Arg Lys Gln Arg Gln Thr Pro Arg Lys Gly Glu Pro
 645 650 655

Glu Arg Asp Lys Pro Gly Ala Glu Ser His Arg Lys Asn Arg Ser Ile
 660 665 670
 Val Thr Asn Met Asp Lys Leu His Leu Asn Leu Thr Glu Leu Ala Leu
 675 680 685
 Thr Met Asn His Val Tyr Ser Phe Ser Val Phe Glu His Thr Ile Phe
 690 695 700
 Pro Ser Glu Tyr Leu Ser Ser His Leu Glu Ala Arg Leu Asn Arg Ala
 705 710 715 720
 Ile Val Trp Leu Ala Gly Tyr Asn Ala Thr Thr Gln Glu Ile Val Arg
 725 730 735
 Pro Ser Glu Leu Leu Ala Gly Val Lys Ala Tyr Ile Gly Phe Ile Gln
 740 745 750
 Ser Leu Ala Gln Phe Leu Gly Ala Asp Ala Ser Arg Val Ile Arg Asn
 755 760 765
 Ala Leu Leu Gln Gln Thr Gln Pro Leu Asp Ser Cys Gly Glu Gln Thr
 770 775 780
 Ile Thr Thr Leu Tyr Thr Asn Trp Tyr Leu Glu Ser Leu Leu Arg Gln
 785 790 795 800
 Ala Ser Ser Gly Thr Ile Ile Leu Ser Pro Ala Met Gln Ala Phe Val
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 Ser Leu Pro Arg Glu Gly Glu Gln Asn Phe Ser Ala Glu Glu Phe Ser
 820 825 830
 Asp Ile Ser Glu Met Arg Ala Leu Ala Glu Leu Leu Gly Pro Tyr Gly
 835 840 845
 Met Lys Phe Leu Ser Glu Asn Leu Met Trp His Val Thr Ser Gln Ile
 850 855 860
 Val Glu Leu Lys Lys Leu Val Val Glu Asn Met Asp Ile Leu Val Gln
 865 870 875 880
 Ile Arg Ser Asn Phe Ser Lys Pro Asp Leu Met Ala Ser Leu Leu Pro
 885 890 895
 Gln Leu Thr Gly Ala Glu Asn Val Leu Lys Arg Met Thr Ile Ile Gly
 900 905 910
 Val Ile Leu Ser Phe Arg Ala Met Ala Gln Glu Gly Leu Arg Glu Val
 915 920 925
 Phe Ser Ser His Cys Pro Phe Leu Met Gly Pro Ile Glu Cys Leu Lys
 930 935 940
 Glu Phe Val Thr Pro Asp Thr Asp Ile Lys Val Thr Leu Ser Ile Phe
 945 950 955 960

Glu Leu Ala Ser Ala Ala Gly Val Gly Cys Asp Ile Asp Pro Ala Leu
 965 970 975
 Val Ala Ala Ile Ala Asn Leu Lys Ala Asp Thr Ser Ser Pro Glu Glu
 980 985 990
 Glu Tyr Lys Val Ala Cys Leu Leu Leu Ile Phe Leu Ala Val Ser Leu
 995 1000 1005
 Pro Leu Leu Ala Thr Asp Pro Ser Ser Phe Tyr Ser Ile Glu Lys
 1010 1015 1020
 Asp Gly Tyr Asn Asn Asn Ile His Cys Leu Thr Lys Ala Ile Ile
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 Gln Val Ser Ala Ala Leu Phe Thr Leu Tyr Asn Lys Asn Ile Glu
 1040 1045 1050
 Thr His Leu Lys Glu Phe Leu Val Val Ala Ser Val Ser Leu Leu
 1055 1060 1065
 Gln Leu Gly Gln Glu Thr Asp Lys Leu Lys Thr Arg Asn Arg Glu
 1070 1075 1080
 Ser Ile Ser Leu Leu Met Arg Leu Val Val Glu Glu Ser Ser Phe
 1085 1090 1095
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 35 40 45
 Ile Asp Lys Asn Leu Glu Ser Ala Val Lys Phe Ile Val Arg Lys Phe
 50 55 60
 Pro Ala Val Glu Thr Arg Asn Asn Asn Gln Gln Leu Ala Gln Leu Gln
 65 70 75 80
 Lys Glu Lys Ser Glu Ile Leu Lys Asn Leu Ala Leu Tyr Tyr Phe Thr
 85 90 95

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

Ile Asp Lys His Ile Ala Glu Leu Ile Phe Tyr Met Glu Glu Leu Arg
 405 410 415
 Ala His Val Arg Lys Tyr Gly Pro Val Met Gln Arg Tyr Tyr Val Gln
 420 425 430
 Tyr Leu Ser Gly Phe Asp Ala Val Val Leu Asn Glu Leu Val Gln Asn
 435 440 445
 Leu Ser Val Cys Pro Glu Asp Glu Ser Ile Ile Met Ser Ser Phe Val
 450 455 460
 Asn Thr Met Thr Ser Leu Ser Val Lys Gln Val Glu Asp Gly Glu Val
 465 470 475 480
 Phe Asp Phe Arg Gly Met Arg Leu Asp Trp Phe Arg Leu Gln Ala Tyr
 485 490 495
 Thr Ser Val Ser Lys Ala Ser Leu Gly Leu Ala Asp His Arg Glu Leu
 500 505 510
 Gly Lys Met Met Asn Thr Ile Ile Phe His Thr Lys Met Val Asp Ser
 515 520 525
 Leu Val Glu Met Leu Val Glu Thr Ser Asp Leu Ser Ile Phe Cys Phe
 530 535 540
 Tyr Ser Arg Ala Phe Glu Lys Met Phe Gln Gln Cys Leu Glu Leu Pro
 545 550 555 560
 Ser Gln Ser Arg Tyr Ser Ile Ala Phe Pro Leu Leu Cys Thr His Phe
 565 570 575
 Met Ser Cys Thr His Glu Leu Cys Pro Glu Glu Arg His His Ile Gly
 580 585 590
 Asp Arg Ser Leu Ser Leu Cys Asn Met Phe Leu Asp Glu Met Ala Lys
 595 600 605
 Gln Ala Arg Asn Leu Ile Thr Asp Ile Cys Thr Glu Gln Cys Thr Leu
 610 615 620
 Ser Asp Gln Leu Leu Pro Lys His Cys Ala Lys Thr Ile Ser Gln Ala
 625 630 635 640
 Val Asn Lys Lys Ser Lys Lys Gln Thr Gly Lys Lys Gly Glu Pro Glu
 645 650 655
 Arg Glu Lys Pro Gly Val Glu Ser Met Arg Lys Asn Arg Leu Val Val
 660 665 670
 Thr Asn Leu Asp Lys Leu His Thr Ala Leu Ser Glu Leu Cys Phe Ser
 675 680 685
 Ile Asn Tyr Val Pro Asn Met Val Val Trp Glu His Thr Phe Thr Pro
 690 695 700

Arg Glu Tyr Leu Thr Ser His Leu Glu Ile Arg Phe Thr Lys Ser Ile
 705 710 715 720
 Val Gly Met Thr Met Tyr Asn Gln Ala Thr Gln Glu Ile Ala Lys Pro
 725 730 735
 Ser Glu Leu Leu Thr Ser Val Arg Ala Tyr Met Thr Val Leu Gln Ser
 740 745 750
 Ile Glu Asn Tyr Val Gln Ile Asp Ile Thr Arg Val Phe Asn Asn Val
 755 760 765
 Leu Leu Gln Gln Thr Gln His Leu Asp Ser His Gly Glu Pro Thr Ile
 770 775 780
 Thr Ser Leu Tyr Thr Asn Trp Tyr Leu Glu Thr Leu Leu Arg Gln Val
 785 790 795 800
 Ser Asn Gly His Ile Ala Tyr Phe Pro Ala Met Lys Ala Phe Val Asn
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 Leu Pro Thr Glu Asn Glu Leu Thr Phe Asn Ala Glu Glu Tyr Ser Asp
 820 825 830
 Ile Ser Glu Met Arg Ser Leu Ser Glu Leu Leu Gly Pro Tyr Gly Met
 835 840 845
 Lys Phe Leu Ser Glu Ser Leu Met Trp His Ile Ser Ser Gln Val Ala
 850 855 860
 Glu Leu Lys Lys Leu Val Val Glu Asn Val Asp Val Leu Thr Gln Met
 865 870 875 880
 Arg Thr Ser Phe Asp Lys Pro Asp Gln Met Ala Ala Leu Phe Lys Arg
 885 890 895
 Leu Ser Ser Val Asp Ser Val Leu Lys Arg Met Thr Ile Ile Gly Val
 900 905 910
 Ile Leu Ser Phe Arg Ser Leu Ala Gln Glu Ala Leu Arg Asp Val Leu
 915 920 925
 Ser Tyr His Ile Pro Phe Leu Val Ser Ser Ile Glu Asp Phe Lys Asp
 930 935 940
 His Ile Pro Arg Glu Thr Asp Met Lys Val Ala Met Asn Val Tyr Glu
 945 950 955 960
 Leu Ser Ser Ala Ala Gly Leu Pro Cys Glu Ile Asp Pro Ala Leu Val
 965 970 975
 Val Ala Leu Ser Ser Gln Lys Ser Glu Asn Ile Ser Pro Glu Glu Glu
 980 985 990
 Tyr Lys Ile Ala Cys Leu Leu Met Val Phe Val Ala Val Ser Leu Pro
 995 1000 1005

Thr Leu Ala Ser Asn Val Met Ser Gln Tyr Ser Pro Ala Ile Glu
 1010 1015 1020
 Gly His Cys Asn Asn Ile His Cys Leu Ala Lys Ala Ile Asn Gln
 1025 1030 1035
 Ile Ala Ala Ala Leu Phe Thr Ile His Lys Gly Ser Ile Glu Asp
 1040 1045 1050
 Arg Leu Lys Glu Phe Leu Ala Leu Ala Ser Ser Ser Leu Leu Lys
 1055 1060 1065
 Ile Gly Gln Glu Thr Asp Lys Thr Thr Thr Arg Asn Arg Glu Ser
 1070 1075 1080
 Val Tyr Leu Leu Leu Asp Met Ile Val Gln Glu Ser Pro Phe Leu
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 35 40 45
 Ala Leu Phe Asp Tyr Gln Ala Arg Thr Ala Glu Asp Leu Ser Phe Arg
 50 55 60
 Ala Gly Asp Lys Leu Gln Val Leu Asp Thr Leu His Glu Gly Trp Trp
 65 70 75 80
 Phe Ala Arg His Leu Glu Lys Arg Arg Asp Gly Ser Ser Gln Gln Leu
 85 90 95
 Gln Gly Tyr Ile Pro Ser Asn Tyr Val Ala Glu Asp Arg Ser Leu Gln
 100 105 110
 Ala Glu Pro Trp Phe Phe Gly Ala Ile Gly Arg Ser Asp Ala Glu Lys
 115 120 125
 Gln Leu Leu Tyr Ser Glu Asn Lys Thr Gly Ser Phe Leu Ile Arg Glu
 130 135 140
 Ser Glu Ser Gln Lys Gly Glu Phe Ser Leu Ser Val Leu Asp Gly Ala

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

450 455 460
 Ile Met Leu Glu Cys Trp Asn Ala Glu Pro Lys Glu Arg Pro Thr Phe
 465 470 475 480
 Glu Thr Leu Arg Trp Lys Leu Glu Asp Tyr Phe Glu Thr Asp Ser Ser
 485 490 495
 Tyr Ser Asp Ala Asn Asn Phe Ile Arg
 500 505
 <210> 29
 <211> 390
 <212> PRT
 <213> Homo sapiens
 <400> 29
 Met Ala Val Ser Glu Ser Gln Leu Lys Lys Met Val Ser Lys Tyr Lys
 1 5 10 15
 Tyr Arg Asp Leu Thr Val Arg Glu Thr Val Asn Val Ile Thr Leu Tyr
 20 25 30
 Lys Asp Leu Lys Pro Val Leu Asp Ser Tyr Val Phe Asn Asp Gly Ser
 35 40 45
 Ser Arg Glu Leu Met Asn Leu Thr Gly Thr Ile Pro Val Pro Tyr Arg
 50 55 60
 Gly Asn Thr Tyr Asn Ile Pro Ile Cys Leu Trp Leu Leu Asp Thr Tyr
 65 70 75 80
 Pro Tyr Asn Pro Pro Ile Cys Phe Val Lys Pro Thr Ser Ser Met Thr
 85 90 95
 Ile Lys Thr Gly Lys His Val Asp Ala Asn Gly Lys Ile Tyr Leu Pro
 100 105 110
 Tyr Leu His Glu Trp Lys His Pro Gln Ser Asp Leu Leu Gly Leu Ile
 115 120 125
 Gln Val Met Ile Val Val Phe Gly Asp Glu Pro Pro Val Phe Ser Arg
 130 135 140
 Pro Ile Ser Ala Ser Tyr Pro Pro Tyr Gln Ala Thr Gly Pro Pro Asn
 145 150 155 160
 Thr Ser Tyr Met Pro Gly Met Pro Gly Gly Ile Ser Pro Tyr Pro Ser
 165 170 175
 Gly Tyr Pro Pro Asn Pro Ser Gly Tyr Pro Gly Cys Pro Tyr Pro Pro
 180 185 190
 Gly Gly Pro Tyr Pro Ala Thr Thr Ser Ser Gln Tyr Pro Ser Gln Pro
 195 200 205
 Pro Val Thr Thr Val Gly Pro Ser Arg Asp Gly Thr Ile Ser Glu Asp
 210 215 220

Thr Ile Arg Ala Ser Leu Ile Ser Ala Val Ser Asp Lys Leu Arg Trp
 225 230 235 240
 Arg Met Lys Glu Glu Met Asp Arg Ala Gln Ala Glu Leu Asn Ala Leu
 245 250 255
 Lys Arg Thr Glu Glu Asp Leu Lys Lys Gly His Gln Lys Leu Glu Glu
 260 265 270
 Met Val Thr Arg Leu Asp Gln Glu Val Ala Glu Val Asp Lys Asn Ile
 275 280 285
 Glu Leu Leu Lys Lys Lys Asp Glu Glu Leu Ser Ser Ala Leu Glu Lys
 290 295 300
 Met Glu Asn Gln Ser Glu Asn Asn Asp Ile Asp Glu Val Ile Ile Pro
 305 310 315 320
 Thr Ala Pro Leu Tyr Lys Gln Ile Leu Asn Leu Tyr Ala Glu Glu Asn
 325 330 335
 Ala Ile Glu Asp Thr Ile Phe Tyr Leu Gly Glu Ala Leu Arg Arg Gly
 340 345 350
 Val Ile Asp Leu Asp Val Phe Leu Lys His Val Arg Leu Leu Ser Arg
 355 360 365
 Lys Gln Phe Gln Leu Arg Ala Leu Met Gln Lys Ala Arg Lys Thr Ala
 370 375 380
 Gly Leu Ser Asp Leu Tyr
 385 390

<210> 30

<211> 480

<212> PRT

<213> Homo sapiens

<400> 30

Met Ala Val Ala Arg Ala Ala Leu Gly Pro Leu Val Thr Gly Leu Tyr
 1 5 10 15

Asp Val Gln Ala Phe Lys Phe Gly Asp Phe Val Leu Lys Ser Gly Leu
 20 25 30

Ser Ser Pro Ile Tyr Ile Asp Leu Arg Gly Ile Val Ser Arg Pro Arg
 35 40 45

Leu Leu Ser Gln Val Ala Asp Ile Leu Phe Gln Thr Ala Gln Asn Ala
 50 55 60

Gly Ile Ser Phe Asp Thr Val Cys Gly Val Pro Tyr Thr Ala Leu Pro
 65 70 75 80

Leu Ala Thr Val Ile Cys Ser Thr Asn Gln Ile Pro Met Leu Ile Arg
 85 90 95

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

Ile Ser Gly Ser Arg Val Ser Met Lys Pro Glu Phe Leu His Leu Thr
405 410 415

Pro Gly Val Gln Leu Glu Ala Gly Gly Asp Asn Leu Gly Gln Gln Tyr
420 425 430

Asn Ser Pro Gln Glu Val Ile Gly Lys Arg Gly Ser Asp Ile Ile Ile
435 440 445

Val Gly Arg Gly Ile Ile Ser Ala Ala Asp Arg Leu Glu Ala Ala Glu
450 455 460

Met Tyr Arg Lys Ala Ala Trp Glu Ala Tyr Leu Ser Arg Leu Gly Val
465 470 475 480