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(54) Title: MP2153S AS MODIFIERS OF THE p21 OR p53 PATHWAY AND METHODS OF USE

(57) Abstract: Human MP2153 genes are identified as modulators of the p21 or p53 pathway, and thus are therapeutic targets for disorders associated with defective p21 or p53 function. Methods for identifying modulators of p21 or p53, comprising screening for agents that modulate the activity of MP2153 are provided.



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MP2153S AS MODIFIERS OF THE p21 or p53 PATHWAY AND METHODS OF USE

REFERENCE TO RELATED APPLICATIONS

5 This application claims priority to U.S. provisional patent applications 60/401,701 filed 8/7/2002, 60/411,017 filed 9/16/2002, and 60/437,107 filed 12/30/2002. The contents of the prior applications are hereby incorporated in their entirety.

BACKGROUND OF THE INVENTION

10 The p53 gene is mutated in over 50 different types of human cancers, including familial and spontaneous cancers, and is believed to be the most commonly mutated gene in human cancer (Zambetti and Levine, FASEB (1993) 7:855-865; Hollstein, *et al.*, Nucleic Acids Res. (1994) 22:3551-3555). Greater than 90% of mutations in the p53 gene are missense mutations that alter a single amino acid that inactivates p53 function.

15 Aberrant forms of human p53 are associated with poor prognosis, more aggressive tumors, metastasis, and short survival rates (Mitsudomi *et al.*, Clin Cancer Res 2000 Oct; 6(10):4055-63; Koshland, Science (1993) 262:1953).

The human p53 protein normally functions as a central integrator of signals including DNA damage, hypoxia, nucleotide deprivation, and oncogene activation (Prives, 20 Cell (1998) 95:5-8). In response to these signals, p53 protein levels are greatly increased with the result that the accumulated p53 activates cell cycle arrest or apoptosis depending on the nature and strength of these signals. Indeed, multiple lines of experimental evidence have pointed to a key role for p53 as a tumor suppressor (Levine, Cell (1997) 88:323-331). For example, homozygous p53 "knockout" mice are developmentally 25 normal but exhibit nearly 100% incidence of neoplasia in the first year of life (Donehower *et al.*, Nature (1992) 356:215-221).

The biochemical mechanisms and pathways through which p53 functions in normal and cancerous cells are not fully understood, but one clearly important aspect of p53 function is its activity as a gene-specific transcriptional activator. Among the genes 30 with known p53-response elements are several with well-characterized roles in either regulation of the cell cycle or apoptosis, including GADD45, p21/Waf1/Cip1, cyclin G, Bax, IGF-BP3, and MDM2 (Levine, Cell (1997) 88:323-331).

The p21/CDKN1/WAF1/CIP1 protein (El-Deiry, W. S.; *et al.* Cell 75: 817-825, 1993; Harper, J. W.; *et al.* Cell 75: 805-816, 1993; Huppi, K. *et al.* Oncogene 9: 3017-3020, 35 1994) is a cell cycle control protein that inhibits cyclin-kinase activity, is tightly regulated

at the transcriptional level by p53, and mediates p53 suppression of tumor cell growth. Along with p53, p21 appears to be essential for maintaining the G2 checkpoint in human cells (Bunz, F.; Dutriaux, A.; et al. Science 282:1497-1501, 1998). Sequences of P21 are well-conserved throughout evolution, and have been identified in species as diverse as
5 human (Genbank Identifier 13643057), *Drosophila melanogaster* (GI# 1684911), *Caenorhabditis elegans* (GI#4966283), and yeast (GI#2656016).

The ability to manipulate the genomes of model organisms such as *Drosophila* provides a powerful means to analyze biochemical processes that, due to significant evolutionary conservation, have direct relevance to more complex vertebrate organisms.
10 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,
15 Mechler BM et al., 1985 EMBO J 4:1551-1557; Gateff E. 1982 Adv. Cancer Res. 37: 33-74; Watson KL., et al., 1994 J Cell Sci. 18: 19-33; Miklos GL, and Rubin GM. 1996 Cell 86:521-529; Wassarman DA, et al., 1995 Curr Opin Gen Dev 5: 44-50; and Booth DR. 1999 Cancer Metastasis Rev. 18: 261-284). For example, a genetic screen can be carried out in an invertebrate model organism having underexpression (e.g. knockout) or
20 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
25 implicated in a disease pathway, such as p21 or p53, modifier genes can be identified that may be attractive candidate targets for novel therapeutics.

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

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SUMMARY OF THE INVENTION

We have discovered genes that modify the p21 or p53 pathway in *Drosophila*, and identified their human orthologs, hereinafter referred to as modifier of p21 and p53 (MP2153). The invention provides methods for utilizing these p21 or p53 modifier genes

and polypeptides to identify MP2153-modulating agents that are candidate therapeutic agents that can be used in the treatment of disorders associated with defective or impaired p21 or p53 function and/or MP2153 function. Preferred MP2153-modulating agents specifically bind to MP2153 polypeptides and restore p21 or p53 function. Other preferred MP2153-modulating agents are nucleic acid modulators such as antisense oligomers and RNAi that repress MP2153 gene expression or product activity by, for example, binding to and inhibiting the respective nucleic acid (i.e. DNA or mRNA).

MP2153 modulating agents may be evaluated by any convenient *in vitro* or *in vivo* assay for molecular interaction with an MP2153 polypeptide or nucleic acid. In one embodiment, candidate MP2153 modulating agents are tested with an assay system comprising a MP2153 polypeptide or nucleic acid. Agents that produce a change in the activity of the assay system relative to controls are identified as candidate p21 or p53 modulating agents. The assay system may be cell-based or cell-free. MP2153-modulating agents include MP2153 related proteins (e.g. dominant negative mutants, and biotherapeutics); MP2153 -specific antibodies; MP2153 -specific antisense oligomers and other nucleic acid modulators; and chemical agents that specifically bind to or interact with MP2153 or compete with MP2153 binding partner (e.g. by binding to an MP2153 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.

In another embodiment, candidate p21 or p53 pathway modulating agents are further tested using a second assay system that detects changes in the p21 or p53 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 p21 or p53 pathway, such as an angiogenic, apoptotic, or cell proliferation disorder (e.g. cancer).

The invention further provides methods for modulating the MP2153 function and/or the p21 or p53 pathway in a mammalian cell by contacting the mammalian cell with an agent that specifically binds a MP2153 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 the p21 or p53 pathway.

DETAILED DESCRIPTION OF THE INVENTION

5 Genetic screens were designed to identify modifiers of the p21 or p53 pathway in *Drosophila*. For p53, a genetic modifier screen was carried out in which p53 was overexpressed in the wing (Ollmann M, et al., Cell 2000 101: 91-101). For p21, a dominant loss of function screen was carried out in *Drosophila* to identify genes that interact with the cyclin dependent kinase inhibitor, p21 (Bourne HR, et al., Nature (1990) 348(6297):125-132; Marshall CJ, Trends Genet (1991) 7(3):91-95). Expression of the p21
10 gene in the eye causes deterioration of normal eye morphology. Modifiers of the eye phenotype were identified as members of the p21 pathway. In each screen, modifiers were identified, followed by identification of their orthologs. Accordingly, vertebrate orthologs of these modifiers, and preferably the human orthologs, MP2153 genes (i.e., nucleic acids and polypeptides) are attractive drug targets for the treatment of pathologies associated
15 with a defective p21 or p53 signaling pathway, such as cancer. Table 1 (Example III) lists the modifiers and their orthologs.

In vitro and in vivo methods of assessing MP2153 function are provided herein. Modulation of the MP2153 or their respective binding partners is useful for understanding
20 the association of the p21 or p53 pathway and its members in normal and disease conditions and for developing diagnostics and therapeutic modalities for p21 or p53 related pathologies. MP2153-modulating agents that act by inhibiting or enhancing MP2153 expression, directly or indirectly, for example, by affecting an MP2153 function such as enzymatic (e.g., catalytic) or binding activity, can be identified using methods
25 provided herein. MP2153 modulating agents are useful in diagnosis, therapy and pharmaceutical development.

Nucleic acids and polypeptides of the invention

Sequences related to MP2153 nucleic acids and polypeptides that can be used in
30 the invention are disclosed in Genbank (referenced by Genbank identifier (GI) or RefSeq number), and shown in Table 1.

The term "MP2153 polypeptide" refers to a full-length MP2153 protein or a functionally active fragment or derivative thereof. A "functionally active" MP2153 fragment or derivative exhibits one or more functional activities associated with a full-

length, wild-type MP2153 protein, such as antigenic or immunogenic activity, enzymatic activity, ability to bind natural cellular substrates, etc. The functional activity of MP2153 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 MP2153 polypeptide is a MP2153 derivative capable of rescuing defective endogenous MP2153 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 MP2153, 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 MP2153 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 MP2153. In further preferred embodiments, the fragment comprises the entire functionally active domain.

The term "MP2153 nucleic acid" refers to a DNA or RNA molecule that encodes a MP2153 polypeptide. Preferably, the MP2153 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 MP2153. 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 *Drosophila*, 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.

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

Alternatively, an alignment for nucleic acid sequences is provided by the local homology algorithm of Smith and Waterman (Smith and Waterman, 1981, Advances in Applied Mathematics 2:482-489; database: European Bioinformatics Institute; Smith and Waterman, 1981, J. of Molec.Biol., 147:195-197; Nicholas et al., 1998, "A Tutorial on Searching Sequence Databases and Sequence Scoring Methods" (www.psc.edu) and

references cited therein.; W.R. Pearson, 1991, Genomics 11:635-650). This algorithm can be applied to amino acid sequences by using the scoring matrix developed by Dayhoff (Dayhoff: Atlas of Protein Sequences and Structure, M. O. Dayhoff ed., 5 suppl. 3:353-358, National Biomedical Research Foundation, Washington, D.C., USA), and normalized
5 by Gribskov (Gribskov 1986 Nucl. Acids Res. 14(6):6745-6763). The Smith-Waterman algorithm may be employed where default parameters are used for scoring (for example, gap open penalty of 12, gap extension penalty of two). From the data generated, the "Match" value reflects "sequence identity."

Derivative nucleic acid molecules of the subject nucleic acid molecules include
10 sequences that hybridize to the nucleic acid sequence of an MP2153. 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
15 *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 MP2153 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
20 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).

25 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),
30 5mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 µg/ml salmon sperm DNA, and 10% (wt/vol) dextran sulfate; followed by washing twice for 1 hour at 55° C in a solution containing 2X SSC and 0.1% SDS.

Alternatively, low stringency conditions can be used that are: incubation for 8 hours to overnight at 37° C in a solution comprising 20% formamide, 5 x SSC, 50 mM

sodium phosphate (pH 7.6), 5X Denhardt's solution, 10% dextran sulfate, and 20 μ g/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.

5 **Isolation, Production, Expression, and Mis-expression of MP2153 Nucleic Acids and Polypeptides**

MP2153 nucleic acids and polypeptides, are useful for identifying and testing agents that modulate MP2153 function and for other applications related to the involvement of MP2153 in the p21 or p53 pathway. MP2153 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 MP2153 protein for assays used to assess MP2153 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 MP2153 is expressed in a cell line known to have defective p21 or p53 function (*e.g.* SAOS-2 osteoblasts, H1299 lung cancer cells, C33A and HT3 cervical cancer cells, HT-29 and DLD-1 colon cancer cells, among others, for p53 and HCT116 colon cancer cells for p21, available from American Type Culture Collection (ATCC), Manassas, VA). The recombinant cells are used in cell-based screening assay systems of the invention, as described further below.

The nucleotide sequence encoding an MP2153 polypeptide can be inserted into any appropriate expression vector. The necessary transcriptional and translational signals, including promoter/enhancer element, can derive from the native MP2153 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.

To detect expression of the MP2153 gene product, the expression vector can comprise a promoter operably linked to an MP2153 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 MP2153 gene product based on the physical or functional properties of the MP2153 protein in *in vitro* assay systems (*e.g.* immunoassays).

The MP2153 protein, fragment, or derivative may be optionally expressed as a fusion, or chimeric protein product (*i.e.* it is joined via a peptide bond to a heterologous protein sequence of a different protein), for example to facilitate purification or detection.

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

Once a recombinant cell that expresses the MP2153 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 MP2153 proteins can be purified from natural sources, by standard methods (*e.g.* immunoaffinity purification). Once a protein is obtained, it may be quantified and its activity measured by appropriate methods, such as immunoassay, bioassay, or other measurements of physical properties, such as crystallography.

The methods of this invention may also use cells that have been engineered for altered expression (mis-expression) of MP2153 or other genes associated with the p21 or

p53 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).

5 **Genetically modified animals**

Animal models that have been genetically modified to alter MP2153 expression may be used in *in vivo* assays to test for activity of a candidate p21 or p53 modulating agent, or to further assess the role of MP2153 in a p21 or p53 pathway process such as apoptosis or cell proliferation. Preferably, the altered MP2153 expression results in a
10 detectable phenotype, such as decreased or increased levels of cell proliferation, angiogenesis, or apoptosis compared to control animals having normal MP2153 expression. The genetically modified animal may additionally have altered p21 or p53 expression (e.g. p21 or p53 knockout). Preferred genetically modified animals are mammals such as primates, rodents (preferably mice or rats), among others. Preferred
15 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
20 all of its cells). Heterologous nucleic acid is introduced into the germ line of such transgenic animals by genetic manipulation of, for example, embryos or embryonic stem cells of the host animal.

Methods of making transgenic animals are well-known in the art (for transgenic mice see Brinster et al., Proc. Nat. Acad. Sci. USA 82: 4438-4442 (1985), U.S. Pat. Nos.
25 4,736,866 and 4,870,009, both by Leder et al., U.S. Pat. No. 4,873,191 by Wagner et al., and Hogan, B., Manipulating the Mouse Embryo, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., (1986); for particle bombardment see U.S. Pat. No., 4,945,050, by Sandford *et al.*; for transgenic *Drosophila* see Rubin and Spradling, Science (1982) 218:348-53 and U.S. Pat. No. 4,670,388; for transgenic insects see Berghammer A.J. *et al.*, A Universal Marker for Transgenic Insects (1999) Nature 402:370-371; for transgenic Zebrafish see Lin S., Transgenic Zebrafish, Methods Mol Biol. (2000);136:375-3830); for microinjection procedures for fish, amphibian eggs and birds see Houdebine and Chourrout, Experientia (1991) 47:897-905; for transgenic rats see Hammer *et al.*, Cell (1990) 63:1099-1112; and for culturing of embryonic stem (ES) cells and the subsequent

production of transgenic animals by the introduction of DNA into ES cells using methods such as electroporation, calcium phosphate/DNA precipitation and direct injection see, e.g., *Teratocarcinomas and Embryonic Stem Cells, A Practical Approach*, E. J. Robertson, ed., IRL Press (1987)). Clones of the nonhuman transgenic animals can be produced according to available methods (see Wilmut, I. *et al.* (1997) *Nature* 385:810-813; and PCT International Publication Nos. WO 97/07668 and WO 97/07669).

In one embodiment, the transgenic animal is a "knock-out" animal having a heterozygous or homozygous alteration in the sequence of an endogenous MP2153 gene that results in a decrease of MP2153 function, preferably such that MP2153 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 MP2153 gene is used to construct a homologous recombination vector suitable for altering an endogenous MP2153 gene in the mouse genome. Detailed methodologies for homologous recombination in mice are available (see Capecchi, *Science* (1989) 244:1288-1292; Joyner *et al.*, *Nature* (1989) 338:153-156). Procedures for the production of non-rodent transgenic mammals and other animals are also available (Houdebine and Chourrout, *supra*; Pursel *et al.*, *Science* (1989) 244:1281-1288; Simms *et al.*, *Bio/Technology* (1988) 6:179-183). In a preferred embodiment, knock-out animals, such as mice harboring a knockout of a specific gene, may be used to produce antibodies against the human counterpart of the gene that has been knocked out (Claesson MH *et al.*, (1994) *Scan J Immunol* 40:257-264; Declerck PJ *et al.*, (1995) *J Biol Chem.* 270:8397-400).

In another embodiment, the transgenic animal is a "knock-in" animal having an alteration in its genome that results in altered expression (e.g., increased (including ectopic) or decreased expression) of the MP2153 gene, e.g., by introduction of additional copies of MP2153, or by operatively inserting a regulatory sequence that provides for altered expression of an endogenous copy of the MP2153 gene. Such regulatory sequences include inducible, tissue-specific, and constitutive promoters and enhancer elements. The knock-in can be homozygous or heterozygous.

Transgenic nonhuman animals can also be produced that contain selected systems allowing for regulated expression of the transgene. One example of such a system that

may be produced is the cre/loxP recombinase system of bacteriophage P1 (Lakso *et al.*, PNAS (1992) 89:6232-6236; U.S. Pat. No. 4,959,317). If a cre/loxP recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the Cre recombinase and a selected protein are required. Such animals can be
5 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,
10 both Cre-LoxP and Flp-Frt are used in the same system to regulate expression of the transgene, and for sequential deletion of vector sequences in the same cell (Sun X *et al.* (2000) Nat Genet 25:83-6).

The genetically modified animals can be used in genetic studies to further elucidate the p21 or p53 pathway, as animal models of disease and disorders implicating defective
15 p21 or p53 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 MP2153 function and phenotypic changes are compared with appropriate control animals such as genetically modified animals that receive placebo treatment, and/or animals with unaltered MP2153 expression that receive
20 candidate therapeutic agent.

In addition to the above-described genetically modified animals having altered MP2153 function, animal models having defective p21 or p53 function (and otherwise normal MP2153 function), can be used in the methods of the present invention. For example, a p21 or p53 knockout mouse can be used to assess, *in vivo*, the activity of a
25 candidate p21 or p53 modulating agent identified in one of the *in vitro* assays described below. p53 knockout mice are described in the literature (Jacks *et al.*, Nature 2001;410:1111-1116, 1043-1044; Donehower *et al.*, *supra*), and p21 knockout mice are also described in the literature (Umanoff H, *et al.*, Proc Natl Acad Sci U S A 1995 Feb 28;92(5):1709-13). Preferably, the candidate p21 or p53 modulating agent when
30 administered to a model system with cells defective in p21 or p53 function, produces a detectable phenotypic change in the model system indicating that the p21 or p53 function is restored, i.e., the cells exhibit normal cell cycle progression.

Modulating Agents

The invention provides methods to identify agents that interact with and/or modulate the function of MP2153 and/or the p21 or p53 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 p21 or p53 pathway, as well as in further analysis of the MP2153 protein and its contribution to the p21 or p53 pathway. Accordingly, the invention also provides methods for modulating the p21 or p53 pathway comprising the step of specifically modulating MP2153 activity by administering a MP2153-interacting or -modulating agent.

As used herein, an “MP2153-modulating agent” is any agent that modulates MP2153 function, for example, an agent that interacts with MP2153 to inhibit or enhance MP2153 activity or otherwise affect normal MP2153 function. MP2153 function can be affected at any level, including transcription, protein expression, protein localization, and cellular or extra-cellular activity. In a preferred embodiment, the MP2153 - modulating agent specifically modulates the function of the MP2153. The phrases “specific modulating agent”, “specifically modulates”, etc., are used herein to refer to modulating agents that directly bind to the MP2153 polypeptide or nucleic acid, and preferably inhibit, enhance, or otherwise alter, the function of the MP2153. These phrases also encompass modulating agents that alter the interaction of the MP2153 with a binding partner, substrate, or cofactor (e.g. by binding to a binding partner of an MP2153, or to a protein/binding partner complex, and altering MP2153 function). In a further preferred embodiment, the MP2153- modulating agent is a modulator of the p21 or p53 pathway (e.g. it restores and/or upregulates p21 or p53 function) and thus is also a p21 or p53-modulating agent.

Preferred MP2153-modulating agents include small molecule compounds; MP2153-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

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 less than 10,000, preferably less than 5,000, more preferably less than 1,000, and most preferably less than 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 MP2153 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 MP2153-modulating activity. Methods for generating and obtaining compounds are well known in the art (Schreiber SL, Science (2000) 151: 1964-1969; Radmann J and Gunther J, Science (2000) 151:1947-1948).

Small molecule modulators identified from screening assays, as described below, 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 p21 or p53 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

Specific MP2153-interacting proteins are useful in a variety of diagnostic and therapeutic applications related to the p21 or p53 pathway and related disorders, as well as in validation assays for other MP2153-modulating agents. In a preferred embodiment, MP2153-interacting proteins affect normal MP2153 function, including transcription, protein expression, protein localization, and cellular or extra-cellular activity. In another embodiment, MP2153-interacting proteins are useful in detecting and providing

information about the function of MP2153 proteins, as is relevant to p21 or p53 related disorders, such as cancer (e.g., for diagnostic means).

An MP2153-interacting protein may be endogenous, i.e. one that naturally interacts genetically or biochemically with an MP2153, such as a member of the MP2153 pathway that modulates MP2153 expression, localization, and/or activity. MP2153-modulators include dominant negative forms of MP2153-interacting proteins and of MP2153 proteins themselves. Yeast two-hybrid and variant screens offer preferred methods for identifying endogenous MP2153-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).

An MP2153-interacting protein may be an exogenous protein, such as an MP2153-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). MP2153 antibodies are further discussed below.

In preferred embodiments, an MP2153-interacting protein specifically binds an MP2153 protein. In alternative preferred embodiments, an MP2153-modulating agent binds an MP2153 substrate, binding partner, or cofactor.

Antibodies

In another embodiment, the protein modulator is an MP2153 specific antibody agonist or antagonist. The antibodies have therapeutic and diagnostic utilities, and can be used in screening assays to identify MP2153 modulators. The antibodies can also be used in dissecting the portions of the MP2153 pathway responsible for various cellular responses and in the general processing and maturation of the MP2153.

Antibodies that specifically bind MP2153 polypeptides can be generated using known methods. Preferably the antibody is specific to a mammalian ortholog of MP2153 polypeptide, and more preferably, to human MP2153. Antibodies may be polyclonal, monoclonal (mAbs), humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab')₂ fragments, fragments produced by a FAb expression library, anti-

idiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above. Epitopes of MP2153 which are particularly antigenic can be selected, for example, by routine screening of MP2153 polypeptides for antigenicity or by applying a theoretical method for selecting antigenic regions of a protein (Hopp and Wood (1981), Proc. Natl. Acad. Sci. U.S.A. 78:3824-28; Hopp and Wood, (1983) Mol. Immunol. 20:483-89; Sutcliffe et al., (1983) Science 219:660-66) to the amino acid sequence of an MP2153. 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 MP2153 or substantially purified fragments thereof. If MP2153 fragments are used, they preferably comprise at least 10, and more preferably, at least 20 contiguous amino acids of an MP2153 protein. In a particular embodiment, MP2153-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.

The presence of MP2153-specific antibodies is assayed by an appropriate assay such as a solid phase enzyme-linked immunosorbant assay (ELISA) using immobilized corresponding MP2153 polypeptides. Other assays, such as radioimmunoassays or fluorescent assays might also be used.

Chimeric antibodies specific to MP2153 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).

MP2153-specific single chain antibodies which are recombinant, single chain polypeptides formed by linking the heavy and light chain fragments of the Fv regions via an amino acid bridge, can be produced by methods known in the art (U.S. Pat. No. 4,946,778; Bird, Science (1988) 242:423-426; Huston et al., Proc. Natl. Acad. Sci. USA (1988) 85:5879-5883; and Ward et al., Nature (1989) 334:544-546).

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

The polypeptides and antibodies of the present invention may be used with or without modification. Frequently, antibodies will be labeled by joining, either covalently or non-covalently, a substance that provides for a detectable signal, or that is toxic to cells that express the targeted protein (Menard S, et al., Int J. Biol Markers (1989) 4:131-134). A wide variety of labels and conjugation techniques are known and are reported extensively in both the scientific and patent literature. Suitable labels include radionuclides, enzymes, substrates, cofactors, inhibitors, fluorescent moieties, fluorescent emitting lanthanide metals, chemiluminescent moieties, bioluminescent moieties, magnetic particles, and the like (U.S. Pat. Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; and 4,366,241). Also, recombinant immunoglobulins may be produced (U.S. Pat. No. 4,816,567). Antibodies to cytoplasmic polypeptides may be delivered and reach their targets by conjugation with membrane-penetrating toxin proteins (U.S. Pat. No. 6,086,900).

When used therapeutically in a patient, the antibodies of the subject invention are typically administered parenterally, when possible at the target site, or intravenously. The therapeutically effective dose and dosage regimen is determined by clinical studies. Typically, the amount of antibody administered is in the range of about 0.1 mg/kg –to about 10 mg/kg of patient weight. For parenteral administration, the antibodies are

formulated in a unit dosage injectable form (e.g., solution, suspension, emulsion) in association with a pharmaceutically acceptable vehicle. Such vehicles are inherently nontoxic and non-therapeutic. Examples are water, saline, Ringer's solution, dextrose solution, and 5% human serum albumin. Nonaqueous vehicles such as fixed oils, ethyl oleate, or liposome carriers may also be used. The vehicle may contain minor amounts of additives, such as buffers and preservatives, which enhance isotonicity and chemical stability or otherwise enhance therapeutic potential. The antibodies' concentrations in such vehicles are typically in the range of about 1 mg/ml to about 10 mg/ml. Immunotherapeutic methods are further described in the literature (US Pat. No. 5,859,206; WO0073469).

Nucleic Acid Modulators

Other preferred MP2153-modulating agents comprise nucleic acid molecules, such as antisense oligomers or double stranded RNA (dsRNA), which generally inhibit MP2153 activity. Preferred nucleic acid modulators interfere with the function of the MP2153 nucleic acid such as DNA replication, transcription, translocation of the MP2153 RNA to the site of protein translation, translation of protein from the MP2153 RNA, splicing of the MP2153 RNA to yield one or more mRNA species, or catalytic activity which may be engaged in or facilitated by the MP2153 RNA.

In one embodiment, the antisense oligomer is an oligonucleotide that is sufficiently complementary to an MP2153 mRNA to bind to and prevent translation, preferably by binding to the 5' untranslated region. MP2153-specific antisense oligonucleotides, preferably range from at least 6 to about 200 nucleotides. In some embodiments the oligonucleotide is preferably at least 10, 15, or 20 nucleotides in length. In other embodiments, the oligonucleotide is preferably less than 50, 40, or 30 nucleotides in length. The oligonucleotide can be DNA or RNA or a chimeric mixture or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone. The oligonucleotide may include other appending groups such as peptides, agents that facilitate transport across the cell membrane, hybridization-triggered cleavage agents, and intercalating agents.

In another embodiment, the antisense oligomer is a phosphothioate morpholino oligomer (PMO). PMOs are assembled from four different morpholino subunits, each of which contain one of four genetic bases (A, C, G, or T) linked to a six-membered

morpholine ring. Polymers of these subunits are joined by non-ionic phosphodiarnidate intersubunit linkages. Details of how to make and use PMOs and other antisense oligomers are well known in the art (e.g. see WO99/18193; Probst JC, Antisense Oligodeoxynucleotide and Ribozyme Design, Methods. (2000) 22(3):271-281; Summerton J, and Weller D. 1997 Antisense Nucleic Acid Drug Dev. :7:187-95; US Pat. No. 5,235,033; and US Pat No. 5,378,841).

Alternative preferred MP2153 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).

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 MP2153-specific nucleic acid modulator is used in an assay to further elucidate the role of the MP2153 in the p21 or p53 pathway, and/or its relationship to other members of the pathway. In another aspect of the invention, an MP2153-specific antisense oligomer is used as a therapeutic agent for treatment of p21 or p53-related disease states.

Assay Systems

The invention provides assay systems and screening methods for identifying specific modulators of MP2153 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 MP2153 nucleic acid or protein. In general, secondary assays further assess the activity of a MP2153 modulating agent identified by a primary assay and may confirm that the modulating agent affects MP2153 in a manner relevant to the p21 or p53 pathway. In some cases, MP2153 modulators will be directly tested in a secondary assay.

In a preferred embodiment, the screening method comprises contacting a suitable assay system comprising an MP2153 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 MP2153 activity, and hence the p21 or p53 pathway. The MP2153 polypeptide or nucleic acid used in the assay may comprise any of the nucleic acids or polypeptides described above.

Primary Assays

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

Primary assays for small molecule modulators

For small molecule modulators, screening assays are used to identify candidate modulators. Screening assays may be cell-based or may use a cell-free system that recreates or retains the relevant biochemical reaction of the target protein (reviewed in Sittampalam GS *et al.*, Curr Opin Chem Biol (1997) 1:384-91 and accompanying references). As used herein the term "cell-based" refers to assays using live cells, dead cells, or a particular cellular fraction, such as a membrane, endoplasmic reticulum, or mitochondrial fraction. The term "cell free" encompasses assays using substantially purified protein (either endogenous or recombinantly produced), partially purified or crude cellular extracts. Screening assays may detect a variety of molecular events, including protein-DNA interactions, protein-protein interactions (*e.g.*, receptor-ligand binding),

transcriptional activity (*e.g.*, using a reporter gene), enzymatic activity (*e.g.*, via a property of the substrate), activity of second messengers, immunogenicity and changes in cellular morphology or other cellular characteristics. Appropriate screening assays may use a wide range of detection methods including fluorescent, radioactive, colorimetric, spectrophotometric, and amperometric methods, to provide a read-out for the particular molecular event detected.

Cell-based screening assays usually require systems for recombinant expression of MP2153 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 MP2153-interacting proteins are used in screens to identify small molecule modulators, the binding specificity of the interacting protein to the MP2153 protein may be assayed by various known methods such as substrate processing (*e.g.* ability of the candidate MP2153-specific binding agents to function as negative effectors in MP2153-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 MP2153 specific antibody in a heterologous host such as a mouse, rat, goat or rabbit). For enzymes and receptors, binding may be assayed by, respectively, substrate and ligand processing.

The screening assay may measure a candidate agent's ability to specifically bind to or modulate activity of a MP2153 polypeptide, a fusion protein thereof, or to cells or membranes bearing the polypeptide or fusion protein. The MP2153 polypeptide can be full length or a fragment thereof that retains functional MP2153 activity. The MP2153 polypeptide may be fused to another polypeptide, such as a peptide tag for detection or anchoring, or to another tag. The MP2153 polypeptide is preferably human MP2153, or is an ortholog or derivative thereof as described above. In a preferred embodiment, the screening assay detects candidate agent-based modulation of MP2153 interaction with a binding target, such as an endogenous or exogenous protein or other substrate that has MP2153-specific binding activity, and can be used to assess normal MP2153 gene function.

Suitable assay formats that may be adapted to screen for MP2153 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
5 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).

10 A variety of suitable assay systems may be used to identify candidate MP2153 and p21 or p53 pathway modulators (*e.g.* U.S. Pat. No. 6,165,992 (kinase assays); U.S. Pat. Nos. 5,550,019 and 6,133,437 (apoptosis assays); U.S. Pat. No. 6,020,135 (p53 modulation), 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.

15 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
20 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).

Kinase assays. In some preferred embodiments the screening assay detects the ability of the test agent to modulate the kinase activity of an MP2153 polypeptide. In
25 further embodiments, a cell-free kinase assay system is used to identify a candidate p21 or p53 modulating agent, and a secondary, cell-based assay, such as an apoptosis or hypoxic induction assay (described below), may be used to further characterize the candidate p21 or p53 modulating agent. Many different assays for kinases have been reported in the literature and are well known to those skilled in the art (*e.g.* U.S. Pat. No. 6,165,992; Zhu
30 et al., Nature Genetics (2000) 26:283-289; and WO0073469). Radioassays, which monitor the transfer of a gamma phosphate are frequently used. For instance, a scintillation assay for p56 (lck) kinase activity monitors the transfer of the gamma phosphate from gamma -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.

5 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
10 (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-
15 resolved, dissociation-enhanced fluorescence (Braunwalder AF, et al., Anal Biochem 1996 Jul 1;238(2):159-64).

Apoptosis assays. Assays for apoptosis may be performed by terminal deoxynucleotidyl transferase-mediated digoxigenin-11-dUTP nick end labeling (TUNEL)
20 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
25 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
30 when cleaved by active caspase 3/7. The nucleosome ELISA assay is a general cell death assay known to those skilled in the art, and available commercially (Roche, Cat# 1774425). This assay is a quantitative sandwich-enzyme-immunoassay which uses monoclonal antibodies directed against DNA and histones respectively, thus specifically determining amount of mono- and oligonucleosomes in the cytoplasmic fraction of cell

lysates. Mono and oligonucleosomes are enriched in the cytoplasm during apoptosis due to the fact that DNA fragmentation occurs several hours before the plasma membrane breaks down, allowing for accumulation in the cytoplasm. Nucleosomes are not present in the cytoplasmic fraction of cells that are not undergoing apoptosis. An apoptosis assay system may comprise a cell that expresses an MP2153, and that optionally has defective p21 or p53 function (e.g. p21 or p53 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 p21 or p53 modulating agents. In some embodiments of the invention, an apoptosis assay may be used as a secondary assay to test a candidate p21 or p53 modulating agents that is initially identified using a cell-free assay system. An apoptosis assay may also be used to test whether MP2153 function plays a direct role in apoptosis. For example, an apoptosis assay may be performed on cells that over- or under-express MP2153 relative to wild type cells. Differences in apoptotic response compared to wild type cells suggests that the MP2153 plays a direct role in the apoptotic response. Apoptosis assays are described further in US Pat. No. 6,133,437.

Cell proliferation and cell cycle assays. Cell proliferation may be assayed via bromodeoxyuridine (BRDU) incorporation. This assay identifies a cell population undergoing DNA synthesis by incorporation of BRDU into newly-synthesized DNA. Newly-synthesized DNA may then be detected using an anti-BRDU antibody (Hoshino *et al.*, 1986, Int. J. Cancer 38, 369; Campana *et al.*, 1988, J. Immunol. Meth. 107, 79), or by other means.

Cell proliferation is also assayed via phospho-histone H3 staining, which identifies a cell population undergoing mitosis by phosphorylation of histone H3. Phosphorylation of histone H3 at serine 10 is detected using an antibody specific to the phosphorylated form of the serine 10 residue of histone H3. (Chadlee, D.N. 1995, J. Biol. Chem 270:20098-105). Cell Proliferation may also be examined using [³H]-thymidine incorporation (Chen, J., 1996, Oncogene 13:1395-403; Jeoung, J., 1995, J. Biol. Chem. 270:18367-73). This assay allows for quantitative characterization of S-phase DNA syntheses. In this assay, cells synthesizing DNA will incorporate [³H]-thymidine into newly synthesized DNA. Incorporation can then be measured by standard techniques such as by counting of radioisotope in a scintillation counter (e.g., Beckman LS 3800 Liquid Scintillation Counter). Another proliferation assay uses the dye Alamar Blue (available from

Biosource International), which fluoresces when reduced in living cells and provides an indirect measurement of cell number (Voytik-Harbin SL et al., 1998, *In Vitro Cell Dev Biol Anim* 34:239-46). Yet another proliferation assay, the MTS assay, is based on in vitro cytotoxicity assessment of industrial chemicals, and uses the soluble tetrazolium salt, MTS. MTS assays are commercially available, for example, the Promega CellTiter 96[®] AQueous Non-Radioactive Cell Proliferation Assay (Cat.# G5421).

Cell proliferation may also be assayed by colony formation in soft agar (Sambrook et al., *Molecular Cloning*, Cold Spring Harbor (1989)). For example, cells transformed with MP2153 are seeded in soft agar plates, and colonies are measured and counted after two weeks incubation.

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

Involvement of a gene in the cell cycle may be assayed by flow cytometry (Gray JW et al. (1986) *Int J Radiat Biol Relat Stud Phys Chem Med* 49:237-55). Cells transfected with an MP2153 may be stained with propidium iodide and evaluated in a flow cytometer (available from Becton Dickinson), which indicates accumulation of cells in different stages of the cell cycle.

Accordingly, a cell proliferation or cell cycle assay system may comprise a cell that expresses an MP2153, and that optionally has defective p21 or p53 function (e.g. p21 or p53 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 p21 or p53 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 p21 or p53 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 MP2153 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 MP2153 relative to wild type cells. Differences in proliferation or cell cycle compared to wild type cells suggest that the MP2153 plays a direct role in cell proliferation or cell cycle.

Angiogenesis. Angiogenesis may be assayed using various human endothelial cell systems, such as umbilical vein, coronary artery, or dermal cells. Suitable assays include

Alamar Blue based assays (available from Biosource International) to measure proliferation; migration assays using fluorescent molecules, such as the use of Becton Dickinson Falcon HTS FluoroBlock cell culture inserts to measure migration of cells through membranes in presence or absence of angiogenesis enhancer or suppressors; and tubule formation assays based on the formation of tubular structures by endothelial cells on Matrigel® (Becton Dickinson). Accordingly, an angiogenesis assay system may comprise a cell that expresses an MP2153, and that optionally has defective p21 or p53 function (e.g. p21 or p53 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 p21 or p53 modulating agents. In some embodiments of the invention, the angiogenesis assay may be used as a secondary assay to test a candidate p21 or p53 modulating agents that is initially identified using another assay system. An angiogenesis assay may also be used to test whether MP2153 function plays a direct role in cell proliferation. For example, an angiogenesis assay may be performed on cells that over- or under-express MP2153 relative to wild type cells. Differences in angiogenesis compared to wild type cells suggest that the MP2153 plays a direct role in angiogenesis. U.S. Pat. Nos. 5,976,782, 6,225,118 and 6,444,434, among others, describe various angiogenesis assays.

Hypoxic induction. The alpha subunit of the transcription factor, hypoxia inducible factor-1 (HIF-1), is upregulated in tumor cells following exposure to hypoxia in vitro. Under hypoxic conditions, HIF-1 stimulates the expression of genes known to be important in tumour cell survival, such as those encoding glycolytic enzymes and VEGF. Induction of such genes by hypoxic conditions may be assayed by growing cells transfected with MP2153 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 MP2153, and that optionally has defective p21 or p53 function (e.g. p21 or p53 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 p21 or p53 modulating agents. In some embodiments of the invention, the hypoxic induction assay may be used as a secondary assay to test a candidate p21 or p53 modulating agents that is initially identified using

another assay system. A hypoxic induction assay may also be used to test whether MP2153 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 MP2153 relative to wild type cells. Differences in hypoxic response compared to wild type cells suggest that the MP2153 plays a direct role in hypoxic induction.

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

Cell-cell adhesion assays measure the ability of agents to modulate binding of cell adhesion proteins with their native ligands. These assays use cells that naturally or recombinantly express the adhesion protein of choice. In an exemplary assay, cells expressing the cell adhesion protein are plated in wells of a multiwell plate. Cells expressing the ligand are labeled with a membrane-permeable fluorescent dye, such as BCECF, and allowed to adhere to the monolayers in the presence of candidate agents. Unbound cells are washed off, and bound cells are detected using a fluorescence plate reader.

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).

Tubulogenesis. Tubulogenesis assays monitor the ability of cultured cells, generally endothelial cells, to form tubular structures on a matrix substrate, which generally simulates the environment of the extracellular matrix. Exemplary substrates include MatrigelTM (Becton Dickinson), an extract of basement membrane proteins containing laminin, collagen IV, and heparin sulfate proteoglycan, which is liquid at 4° C and forms a solid gel at 37° C. Other suitable matrices comprise extracellular components such as collagen, fibronectin, and/or fibrin. Cells are stimulated with a pro-angiogenic stimulant, and their ability to form tubules is detected by imaging. Tubules can generally be detected after an overnight incubation with stimuli, but longer or shorter time frames may also be used. Tube formation assays are well known in the art (e.g., Jones MK et al., 1999, Nature Medicine 5:1418-1423). These assays have traditionally involved stimulation with serum or with the growth factors FGF or VEGF. Serum represents an undefined source of growth factors. In a preferred embodiment, the assay is performed with cells cultured in serum free medium, in order to control which process or pathway a candidate agent modulates. Moreover, we have found that different target genes respond differently to stimulation with different pro-angiogenic agents, including inflammatory angiogenic factors such as TNF-alpha. Thus, in a further preferred embodiment, a tubulogenesis assay system comprises testing an MP2153's response to a variety of factors, such as FGF, VEGF, phorbol myristate acetate (PMA), TNF-alpha, ephrin, etc.

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Cell Migration. An invasion/migration assay (also called a migration assay) tests the ability of cells to overcome a physical barrier and to migrate towards pro-angiogenic signals. Migration assays are known in the art (e.g., Paik JH et al., 2001, J Biol Chem 276:11830-11837). In a typical experimental set-up, cultured endothelial cells are seeded onto a matrix-coated porous lamina, with pore sizes generally smaller than typical cell size. The matrix generally simulates the environment of the extracellular matrix, as described above. The lamina is typically a membrane, such as the transwell polycarbonate membrane (Corning Costar Corporation, Cambridge, MA), and is generally part of an upper chamber that is in fluid contact with a lower chamber containing pro-angiogenic stimuli. Migration is generally assayed after an overnight incubation with stimuli, but longer or shorter time frames may also be used. Migration is assessed as the number of cells that crossed the lamina, and may be detected by staining cells with hemotoxylin solution (VWR Scientific, South San Francisco, CA), or by any other method for determining cell number. In another exemplary set up, cells are fluorescently labeled and

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migration is detected using fluorescent readings, for instance using the Falcon HTS FluoroBlok (Becton Dickinson). While some migration is observed in the absence of stimulus, migration is greatly increased in response to pro-angiogenic factors. As described above, a preferred assay system for migration/invasion assays comprises testing an MP2153's response to a variety of pro-angiogenic factors, including tumor angiogenic and inflammatory angiogenic agents, and culturing the cells in serum free medium.

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

Primary assays for antibody modulators

For antibody modulators, appropriate primary assays test is a binding assay that tests the antibody's affinity to and specificity for the MP2153 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 MP2153-specific antibodies; others include FACS assays, radioimmunoassays, and fluorescent assays.

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

Primary assays for nucleic acid modulators

For nucleic acid modulators, primary assays may test the ability of the nucleic acid modulator to inhibit or enhance MP2153 gene expression, preferably mRNA expression. In general, expression analysis comprises comparing MP2153 expression in like
5 populations of cells (*e.g.*, two pools of cells that endogenously or recombinantly express MP2153) 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
10 MP2153 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
15 commonly detected with specific antibodies or antisera directed against either the MP2153 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*).

In some cases, screening assays described for small molecule modulators, particularly in assay systems that involve MP2153 mRNA expression, may also be used to
20 test nucleic acid modulators.

Secondary Assays

Secondary assays may be used to further assess the activity of MP2153-modulating agent identified by any of the above methods to confirm that the modulating agent affects
25 MP2153 in a manner relevant to the p21 or p53 pathway. As used herein, MP2153-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 MP2153.

30 Secondary assays generally compare like populations of cells or animals (*e.g.*, two pools of cells or animals that endogenously or recombinantly express MP2153) in the presence and absence of the candidate modulator. In general, such assays test whether treatment of cells or animals with a candidate MP2153-modulating agent results in changes in the p21 or p53 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 p21 or p53 or interacting pathways.

5 *Cell-based assays*

Cell based assays may use a variety of mammalian cell lines known to have defective p21 or p53 function (e.g. SAOS-2 osteoblasts, H1299 lung cancer cells, C33A and HT3 cervical cancer cells, HT-29, HCT116, and DLD-1 colon cancer cells, among others, available from American Type Culture Collection (ATCC), Manassas, VA). Cell
10 based assays may detect endogenous p21 or p53 pathway activity or may rely on recombinant expression of p21 or p53 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.

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Animal Assays

A variety of non-human animal models of normal or defective p21 or p53 pathway may be used to test candidate MP2153 modulators. Models for defective p21 or p53 pathway typically use genetically modified animals that have been engineered to mis-
20 express (e.g., over-express or lack expression in) genes involved in the p21 or p53 pathway. Assays generally require systemic delivery of the candidate modulators, such as by oral administration, injection, etc.

In a preferred embodiment, p21 or p53 pathway activity is assessed by monitoring neovascularization and angiogenesis. Animal models with defective and normal p21 or
25 p53 are used to test the candidate modulator’s affect on MP2153 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-
30 express the MP2153. 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.

In another preferred embodiment, the effect of the candidate modulator on MP2153 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 MP2153 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 maybe 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.

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.

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.

15

Diagnostic and therapeutic uses

Specific MP2153-modulating agents are useful in a variety of diagnostic and therapeutic applications where disease or disease prognosis is related to defects in the p21 or p53 pathway, such as angiogenic, apoptotic, or cell proliferation disorders. Accordingly, the invention also provides methods for modulating the p21 or p53 pathway in a cell, preferably a cell pre-determined to have defective or impaired p21 or p53 function (e.g. due to overexpression, underexpression, or misexpression of p21 or p53, or due to gene mutations), comprising the step of administering an agent to the cell that specifically modulates MP2153 activity. Preferably, the modulating agent produces a detectable phenotypic change in the cell indicating that the p21 or p53 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 p21 or p53 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 p21 or p53 function by administering a therapeutically effective amount of an MP2153 -modulating agent that modulates the p21 or p53 pathway. The invention further provides methods for modulating MP2153 function in a cell, preferably a cell pre-determined to have defective or impaired MP2153 function, by administering an MP2153 -modulating

agent. Additionally, the invention provides a method for treating disorders or disease associated with impaired MP2153 function by administering a therapeutically effective amount of an MP2153 -modulating agent.

5 The discovery that MP2153 is implicated in p21 or p53 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 p21 or p53 pathway and for the identification of subjects having a predisposition to such diseases and disorders.

10 Various expression analysis methods can be used to diagnose whether MP2153 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 p21 or p53 signaling that
15 express an MP2153, are identified as amenable to treatment with an MP2153 modulating agent. In a preferred application, the p21 or p53 defective tissue overexpresses an MP2153 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 MP2153 cDNA sequences as probes, can determine
20 whether particular tumors express or overexpress MP2153. Alternatively, the TaqMan® is used for quantitative RT-PCR analysis of MP2153 expression in cell lines, normal tissues and tumor samples (PE Applied Biosystems).

Various other diagnostic methods may be performed, for example, utilizing reagents such as the MP2153 oligonucleotides, and antibodies directed against an
25 MP2153, as described above for: (1) the detection of the presence of MP2153 gene mutations, or the detection of either over- or under-expression of MP2153 mRNA relative to the non-disorder state; (2) the detection of either an over- or an under-abundance of MP2153 gene product relative to the non-disorder state; and (3) the detection of perturbations or abnormalities in the signal transduction pathway mediated by MP2153.

30 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 MP2153 expression, the method comprising: a) obtaining a biological sample from the patient; b) contacting the sample with a probe for MP2153 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

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

I. *Drosophila* p21 screen

10 A dominant loss of function screen was carried out in *Drosophila* to identify genes that interact with the cyclin dependent kinase inhibitor, p21 (Bourne HR, et al., Nature (1990) 348(6297):125-132; Marshall CJ, Trends Genet (1991) 7(3):91-95). Expression of the p21 gene from GMR-p21 transgene (Hay, B. A., et al. (1994) Development 120:2121-2129) in the eye causes deterioration of normal eye morphology, resulting in reduced, rough eyes. Flies carrying this transgene were maintained as a stock (P 1025 F, genotype: y w; P{p21-pExp-gl-w[+]Hsp70(3'UTR)-5}). Females of this stock were crossed to a collection of males carrying piggyBac insertions (Fraser M *et al.*, Virology (1985) 145:356-361). Resulting progeny carrying both the transgene and transposons were scored for the effect of the transposon on the eye phenotype, i.e. whether the transposon enhanced or suppressed (or had no effect) the eye phenotype. All data was recorded and
15 all modifiers were retested with a repeat of the original cross, and the retests were scored at least twice. Modifiers of the eye phenotype were identified as members of the p21 pathway.

II. *Drosophila* p53 screen

25 The *Drosophila* p53 gene was overexpressed specifically in the wing using the vestigial margin quadrant enhancer. Increasing quantities of *Drosophila* p53 (titrated using different strength transgenic inserts in 1 or 2 copies) caused deterioration of normal wing morphology from mild to strong, with phenotypes including disruption of pattern and polarity of wing hairs, shortening and thickening of wing veins, progressive crumpling of the wing and appearance of dark "death" inclusions in wing blade. In a screen designed to
30 identify enhancers and suppressors of *Drosophila* p53, homozygous females carrying two copies of p53 were crossed to 5663 males carrying random insertions of a piggyBac transposon (Fraser M *et al.*, Virology (1985) 145:356-361). Progeny containing insertions were compared to non-insertion-bearing sibling progeny for enhancement or suppression

of the p53 phenotypes. Sequence information surrounding the piggyBac insertion site was used to identify the modifier genes. Modifiers of the wing phenotype were identified as members of the p53 pathway.

5 III. Analysis of Table 1

BLAST analysis (Altschul et al., *supra*) was employed to identify orthologs of *Drosophila* modifiers. The columns "MP2153 symbol", and "MP2153 name aliases" provide a symbol and the known name abbreviations for the Targets, where available, from Genbank. "MP2153 RefSeq_NA or GI_NA", "MP2153 GI_AA", "MP2153
10 NAME", and "MP2153 Description" provide the reference DNA sequences for the MP2153s as available from National Center for Biology Information (NCBI), MP2153 protein Genbank identifier number (GI#), MP2153 name, and MP2153 description, all available from Genbank, respectively. The length of each amino acid is in the "MP2153 Protein Length" column.

15 Names and Protein sequences of *Drosophila* modifiers of p21 or p53 from screen (Example I), are represented in the "Modifier Name" and "Modifier GI_AA" column by GI#, respectively.

Table 1

MP2153 symbol	MP2153 name aliases	MP2153 RefSeq_na: Locus Link	NA SE Q ID NO	MP2153 gi_aa	AA SE Q ID NO	MP2153 name (Locus Link)	MP2153 Description	MP2153 Protein length	Modifier	Modifier GI_AA
PACSIN1	KIAA1379, protein kinase C and casein kinase substrate in neurons 1	XM_166424.1	1	20555436	18	protein kinase C and casein kinase substrate in neurons 1	na	444	syndapin	7300664
PACSIN2	pacsin 2, protein kinase C and casein kinase substrate in neurons 2	NM_007229.1 XM_040131.2	2	6005826	19	protein kinase C and casein kinase substrate in neurons 2	cell shape and cell size control; vesicle-mediated transport; actin cytoskeleton organization and biogenesis; intracellular protein transport	486	syndapin	7300664

PAC3	SH3 domain-containing protein 6511, protein kinase C and casein kinase substrate in neurons 3	NM_016223.2	3	19224660	20	protein kinase C and casein kinase substrate in neurons 3	endocytosis; intracellular protein transport	424	syndapin	7300664
PSTPIP1	H-PIP, CD2BP1, PSTPIP, CD2BP1L, CD2BP1S, CD2 cytoplasmic tail-binding protein, proline-serine-threonine phosphatase interacting protein 1	NM_003978.2 XM_044569.8	4	20149528	21	proline-serine-threonine phosphatase interacting protein 1	cell adhesion; response to pest/pathogen/parasite; antimicrobial humoral response (sensu Vertebrata); signal transduction; inflammatory response	416	syndapin	7300664
PSTPIP2	MAYP, proline-serine-threonine phosphatase interacting protein 2	NM_024430.1	5	13270469	22	proline-serine-threonine phosphatase interacting protein 2	actin cytoskeleton organization and biogenesis; actin cytoskeleton organization and biogenesis	212	syndapin	7300664
LOC122888	similar to Polypyrimidine tract-binding protein (PTB) (Heterogeneous nuclear ribonucleoprotein I) (hnRNP I) (57 kDa RNA-binding protein (PPTB-1))	XM_063346.2	6	18597099	23	similar to Polypyrimidine tract-binding protein (PTB) (Heterogeneous nuclear ribonucleoprotein I) (hnRNP I) (57 kDa RNA-binding protein (PPTB-1))	na	591	CG2094	7302108

SRC	ASV, SRC1, Protooncogene SRC, Rous sarcoma, v-src avian sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog, v-src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (avian)	NM_005417.2	7	4885609	24	v-src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (avian)	V-src avian sarcoma viral oncogene homolog (Schmidt-Ruppin A-2), tyrosine kinase involved in cell proliferation, cell adhesion, and cytoskeletal organization, implicated in the progression of colon cancer and certain breast tumors	536	Src64B	7292520
HCK	JTK9, hemopoietic cell kinase	NM_002110.1 XM_009539.6	8	4504357	25	hemopoietic cell kinase	Hematopoietic cell kinase, Src family tyrosine kinase involved in signaling, phagocytosis and cell shape changes in myeloid cell types, and HIV-1 replication and spreading; mouse Hck mediates the development of encephalomyocarditis-induced diabetes	505	Src64B	7292520

FYN	FYN oncogene related to SRC, FGR, YES	NM_002037 .1	9	450382 3	26	FYN oncogene related to SRC, FGR, YES	Fyn proto- oncogene, a member of the Src family of tyrosine kinases, acts as an SH3/SH2 adapter protein in signal transduction pathways, plays a role in T-cell activation and neuronal development , may mediate integrin regulation of T-cell function	537	Src64B	729252 0
LCK	oncogene LCK, membr ane associated protein tyrosine kinase, lymphocyte- specific protein tyrosine kinase	NM_005356 .2	10	488544 9	27	lymphocyte- specific protein tyrosine kinase	Lymphocyte- specific protein tyrosine kinase, tyrosine kinase that is involved in T cell receptor signaling through Ras and MAPK pathways, activator of CASP8 in radiation- induced apoptosis; gene defect correlates with immunodeficiency plus CD4 lymphopenia	509	Src64B	729252 0

LYN	JTK8, Yamaguchi sarcoma viral (v-yes-1) related oncogene homolog, v-yes-1 Yamaguchi sarcoma viral related oncogene homolog	NM_002350.1	11	450505	28	v-yes-1 Yamaguchi sarcoma viral related oncogene homolog	Lyn protein tyrosine kinase, a non-receptor tyrosine kinase important in cytokine receptor- and IgE receptor-mediated signal transduction, regulates cell adhesion and apoptosis, plays a role in platelet activation and inflammatory responses	512	Src64B	7292520
BLK	MGC10442, BLK nonreceptor tyrosine kinase, B lymphoid tyrosine kinase	NM_001715.1 NM_032657	12	4502413	29	B lymphoid tyrosine kinase	B-lymphocyte tyrosine kinase, B-lymphocyte specific member of the Src family of tyrosine kinases that is involved in B-lymphocyte receptor-linked signal transduction	505	Src64B	7292520

FGR	SRC2, Oncogene FGR, Gardner-Rasheed feline sarcoma viral (v-fgr) oncogene, Gardner-Rasheed feline sarcoma viral (v-fgr) oncogene homolog	NM_005248.1	13	4885235	30	Gardner-Rasheed feline sarcoma viral (v-fgr) oncogene homolog	Gardner-Rasheed feline sarcoma viral (v-fgr) oncogene homolog, a member of the Src protein tyrosine kinase family, involved in the viral response, integrin signaling, exocytosis and inhibition of apoptosis, induced in B lymphocytes by Epstein-Barr virus	529	Src64B	7292520
TRAF5		NM_004619.2 NM_145759.1	14	11321603	31	TNF receptor-associated factor 5	TNF receptor-associated factor 5, member of a family of proteins that interact with the cytoplasmic domain of oligomerized TNF receptors, binds CD40 (TNFRSF5) and mediates signaling through activation of NF-kappaB and JNK pathways	557	CG3048	1.7E+07

TRAF 1		NM_005658 .2	15	503219 3	32	TNF receptor- associated factor 1	Tumor necrosis factor receptor (TNFR)- associated factor 1, part of a heteromeric complex that binds TNF receptors and mediates the effects of activation via intracellular signaling cascades, increased expression is associated with lymphoid malignancies	416	CG3048	1.7E+07
YES1	oncogene yes- 1, Yamaguchi sarcoma viral (v-yes- 1) oncogene homolog 1, v-yes-1 Yamaguchi sarcoma viral oncogene homolog 1	NM_005433 .2	16	488566 1	33	v-yes-1 Yamaguchi sarcoma viral oncogene homolog 1	Yamaguchi sarcoma viral oncogene homolog 1, a nonreceptor protein tyrosine kinase of the Src family, functions downstream of GM-CSF (CSF2), involved in disrupting cell-cell contacts; correspondin g gene is an oncogene associated with Yamaguchi sarcoma	543	Dr_yes1 S rc64B	072925 20
DKFZ p547 M236	DKFZp547 M236 DKFZp547 M236 hypothetical protein DKFZp547 M236	NM_018713 .1	17	892215 5	34	hypothetical protein DKFZp547M 236	Protein with low similarity to a region of metal transporters	485	CG5130 C G17723	729632 221357 035

IV. High-Throughput In Vitro Fluorescence Polarization Assay

Fluorescently-labeled MP2153 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 MP2153 activity.

V. High-Throughput In Vitro Binding Assay.

³³P-labeled MP2153 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 p21 or p53 modulating agents.

VI. Immunoprecipitations and Immunoblotting

For coprecipitation of transfected proteins, 3×10^6 appropriate recombinant cells containing the MP2153 proteins are plated on 10-cm dishes and transfected on the following day with expression constructs. The total amount of DNA is kept constant in each transfection by adding empty vector. After 24 h, cells are collected, washed once with phosphate-buffered saline and lysed for 20 min on ice in 1 ml of lysis buffer containing 50 mM Hepes, pH 7.9, 250 mM NaCl, 20 mM -glycerophosphate, 1 mM sodium orthovanadate, 5 mM p-nitrophenyl phosphate, 2 mM dithiothreitol, protease inhibitors (complete, Roche Molecular Biochemicals), and 1% Nonidet P-40. Cellular debris is removed by centrifugation twice at $15,000 \times g$ for 15 min. The cell lysate is incubated with 25 μ l of M2 beads (Sigma) for 2 h at 4 °C with gentle rocking.

After extensive washing with lysis buffer, proteins bound to the beads are solubilized by boiling in SDS sample buffer, fractionated by SDS-polyacrylamide gel electrophoresis, transferred to polyvinylidene difluoride membrane and blotted with the indicated antibodies. The reactive bands are visualized with horseradish peroxidase

coupled to the appropriate secondary antibodies and the enhanced chemiluminescence (ECL) Western blotting detection system (Amersham Pharmacia Biotech).

VII. Kinase assay

5 A purified or partially purified MP2153 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 $\mu\text{g/ml}$). 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
10 increasing assay throughput. A 96-well microtiter plate is employed using a final volume 30-100 μl . The reaction is initiated by the addition of ^{33}P -gamma-ATP (0.5 $\mu\text{Ci/ml}$) 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
15 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
20 defined by the amount of radioactivity detected following subtraction of the negative control reaction value (EDTA quench).

VIII. Expression analysis

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

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

30 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).

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
5 instrument.

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
10 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).

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
15 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
20 standard deviation of all normal samples (i.e., $\text{Tumor} - \text{average}(\text{all normal samples}) > 2 \times \text{STDEV}(\text{all normal samples})$).

A modulator identified by an assay described herein can be further validated for 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
25 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
30 available detection method.

WHAT IS CLAIMED IS:

1. A method of identifying a candidate p21 or p53 pathway modulating agent, said method comprising the steps of:
 - 5 (a) providing an assay system comprising a MP2153 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
 - 10 a candidate p21 or p53 pathway modulating agent.
2. The method of Claim 1 wherein the assay system comprises cultured cells that express the MP2153 polypeptide.
- 15 3. The method of Claim 2 wherein the cultured cells additionally have defective p21 or p53 function.
4. The method of Claim 1 wherein the assay system includes a screening assay comprising a MP2153 polypeptide, and the candidate test agent is a small molecule
- 20 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
- 25 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 a MP2153 polypeptide and the candidate test agent is an antibody.
- 30 8. The method of Claim 1 wherein the assay system includes an expression assay comprising a MP2153 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.
- 5 11. The method of Claim 1 additionally comprising:
(d) administering the candidate p21 or p53 pathway modulating agent identified in
(c) to a model system comprising cells defective in p21 or p53 function and, detecting a
phenotypic change in the model system that indicates that the p21 or p53 function is
restored.
- 10 12. The method of Claim 11 wherein the model system is a mouse model with defective
p21 or p53 function.
13. A method for modulating a p21 or p53 pathway of a cell comprising contacting a cell
15 defective in p21 or p53 function with a candidate modulator that specifically binds to a
MP2153 polypeptide, whereby p21 or p53 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
20 p21 or p53 function.
15. The method of Claim 13 wherein the candidate modulator is selected from the group
consisting of an antibody and a small molecule.
- 25 16. The method of Claim 1, comprising the additional steps of:
(e) providing a secondary assay system comprising cultured cells or a non-human
animal expressing MP2153 ,
(f) 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
30 derived therefrom, the system provides a reference activity; and
(g) 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
p21 or p53 pathway modulating agent,

and wherein the second assay detects an agent-biased change in the p21 or p53 pathway.

5 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.

10 19. The method of Claim 18 wherein the non-human animal mis-expresses a p21 or p53 pathway gene.

15 20. A method of modulating p21 or p53 pathway in a mammalian cell comprising contacting the cell with an agent that specifically binds a MP2153 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 p21 or p53 pathway.

20 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:

- 25 (a) obtaining a biological sample from the patient;
(b) contacting the sample with a probe for MP2153 expression;
(c) comparing results from step (b) with a control;
(d) determining whether step (c) indicates a likelihood of disease.

30 24. The method of Claim 23 wherein said disease is cancer.

SEQUENCE LISTING

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<120> MP2153S AS MODIFIERS OF THE p21 or p53 PATHWAY AND METHODS OF USE

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Ser Thr Ser Gln Ala Gly Asp Arg Gly Ser Val Ser Ser Tyr Asp Arg
340 345 350

Gly Gln Pro Tyr Ala Thr Glu Trp Ser Asp Asp Glu Ser Gly Asn Pro
355 360 365

Phe Gly Gly Ser Glu Thr Asn Gly Gly Ala Asn Pro Phe Glu Asp Asp
370 375 380

Ser Lys Gly Val Arg Val Arg Ala Leu Tyr Asp Tyr Asp Gly Gln Glu
385 390 395 400

Gln Asp Glu Leu Ser Phe Lys Ala Gly Asp Glu Leu Thr Lys Leu Gly
405 410 415

Glu Glu Asp Glu Gln Gly Trp Cys Arg Gly Arg Leu Asp Ser Gly Gln
420 425 430

Leu Gly Leu Tyr Pro Ala Asn Tyr Val Glu Ala Ile
435 440

<210> 20

<211> 424

<212> PRT

<213> Homo sapiens

<400> 20

Met Ala Pro Glu Glu Asp Ala Gly Gly Glu Ala Leu Gly Gly Ser Phe
1 5 10 15

Trp Glu Ala Gly Asn Tyr Arg Arg Thr Val Gln Arg Val Glu Asp Gly
20 25 30

His Arg Leu Cys Gly Asp Leu Val Ser Cys Phe Gln Glu Arg Ala Arg
35 40 45

Ile Glu Lys Ala Tyr Ala Gln Gln Leu Ala Asp Trp Ala Arg Lys Trp
50 55 60

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

305 310 315 320
 Asp Glu Val Thr Leu Thr Ser Ile Val Pro Thr Arg Asp Gly Thr Ala
 325 330 335
 Pro Pro Pro Gln Ser Pro Gly Ser Pro Gly Thr Gly Gln Asp Glu Glu
 340 345 350
 Trp Ser Asp Glu Glu Ser Pro Arg Lys Ala Ala Thr Gly Val Arg Val
 355 360 365
 Arg Ala Leu Tyr Asp Tyr Ala Gly Gln Glu Ala Asp Glu Leu Ser Phe
 370 375 380
 Arg Ala Gly Glu Glu Leu Leu Lys Met Ser Glu Glu Asp Glu Gln Gly
 385 390 395 400
 Trp Cys Gln Gly Gln Leu Gln Ser Gly Arg Ile Gly Leu Tyr Pro Ala
 405 410 415
 Asn Tyr Val Glu Cys Val Gly Ala
 420
 <210> 21
 <211> 416
 <212> PRT
 <213> Homo sapiens
 <400> 21
 Met Met Pro Gln Leu Gln Phe Lys Asp Ala Phe Trp Cys Arg Asp Phe
 1 5 10 15
 Thr Ala His Thr Gly Tyr Glu Val Leu Leu Gln Arg Leu Leu Asp Gly
 20 25 30
 Arg Lys Met Cys Lys Asp Met Glu Glu Leu Leu Arg Gln Arg Ala Gln
 35 40 45
 Ala Glu Glu Arg Tyr Gly Lys Glu Leu Val Gln Ile Ala Arg Lys Ala
 50 55 60
 Gly Gly Gln Thr Glu Ile Asn Ser Leu Arg Ala Ser Phe Asp Ser Leu
 65 70 75 80
 Lys Gln Gln Met Glu Asn Val Gly Ser Ser His Ile Gln Leu Ala Leu
 85 90 95

Thr Leu Arg Glu Glu Leu Arg Ser Leu Glu Glu Phe Arg Glu Arg Gln
 100 105 110

Lys Glu Gln Arg Lys Lys Tyr Glu Ala Val Met Asp Arg Val Gln Lys
 115 120 125

Ser Lys Leu Ser Leu Tyr Lys Lys Ala Met Glu Ser Lys Lys Thr Tyr
 130 135 140

Glu Gln Lys Cys Arg Asp Ala Asp Asp Ala Glu Gln Ala Phe Glu Arg
 145 150 155 160

Ile Ser Ala Asn Gly His Gln Lys Gln Val Glu Lys Ser Gln Asn Lys
 165 170 175

Ala Arg Gln Cys Lys Asp Ser Ala Thr Glu Ala Glu Arg Val Tyr Arg
 180 185 190

Gln Ser Ile Ala Gln Leu Glu Lys Val Arg Ala Glu Trp Glu Gln Glu
 195 200 205

His Arg Thr Thr Cys Glu Ala Phe Gln Leu Gln Glu Phe Asp Arg Leu
 210 215 220

Thr Ile Leu Arg Asn Ala Leu Trp Val His Ser Asn Gln Leu Ser Met
 225 230 235 240

Gln Cys Val Lys Asp Asp Glu Leu Tyr Glu Glu Val Arg Leu Thr Leu
 245 250 255

Glu Gly Cys Ser Ile Asp Ala Asp Ile Asp Ser Phe Ile Gln Ala Lys
 260 265 270

Ser Thr Gly Thr Glu Pro Pro Ala Pro Val Pro Tyr Gln Asn Tyr Tyr
 275 280 285

Asp Arg Glu Val Thr Pro Leu Thr Ser Ser Pro Gly Ile Gln Pro Ser
 290 295 300

Cys Gly Met Ile Lys Arg Phe Ser Gly Leu Leu His Gly Ser Pro Lys
 305 310 315 320

Thr Thr Ser Leu Ala Ala Ser Ala Ala Ser Thr Glu Thr Leu Thr Pro
 325 330 335

Thr Pro Glu Arg Asn Glu Gly Val Tyr Thr Ala Ile Ala Val Gln Glu
 340 345 350

Ile Gln Gly Asn Pro Ala Ser Pro Ala Gln Glu Tyr Arg Ala Leu Tyr
 355 360 365

Asp Tyr Thr Ala Gln Asn Pro Asp Glu Leu Asp Leu Ser Ala Gly Asp
 370 375 380

Ile Leu Glu Val Ile Leu Glu Gly Glu Asp Gly Trp Trp Thr Val Glu
 385 390 395 400

Arg Asn Gly Gln Arg Gly Phe Val Pro Gly Ser Tyr Leu Glu Lys Leu
 405 410 415

<210> 22
 <211> 212
 <212> PRT
 <213> Homo sapiens

<400> 22

Met Asp Ala Ile His Lys Gln Lys Ser Leu Gln Phe Lys Lys Thr Met
 1 5 10 15

Asp Ala Lys Lys Asn Tyr Glu Gln Lys Cys Arg Asp Lys Asp Glu Ala
 20 25 30

Glu Gln Ala Val Ser Arg Ser Ala Asn Leu Val Asn Pro Lys Gln Gln
 35 40 45

Glu Lys Leu Phe Val Lys Leu Ala Thr Ser Lys Thr Ala Val Glu Asp
 50 55 60

Ser Asp Lys Ala Tyr Met Leu His Ile Gly Thr Leu Asp Lys Val Arg
 65 70 75 80

Glu Glu Trp Gln Ser Glu His Ile Lys Ala Cys Glu Ala Phe Glu Ala
 85 90 95

Gln Glu Cys Glu Arg Ile Asn Phe Phe Arg Asn Ala Leu Trp Leu His
 100 105 110

Val Asn Gln Leu Ser Gln Gln Cys Val Thr Ser Asp Glu Met Tyr Glu
 115 120 125

Gln Val Arg Lys Ser Leu Glu Met Cys Ser Ile Gln Arg Asp Ile Glu
 130 135 140

Tyr Phe Val Asn Gln Arg Lys Thr Gly Gln Ile Pro Pro Ala Pro Ile

36

Cys Lys Glu Thr Ala Asp Asn Thr Asp His Ser Leu Leu Pro Asn Leu
 145 150 155 160

Lys Gln Ser Asp Pro His Pro Glu Ala Pro Ile Asp Val Ile Glu Gly
 165 170 175

Glu Val Ile Ser Leu Glu Leu Pro Phe Gly Lys Val Thr Asn Leu Leu
 180 185 190

Met Leu Lys Gly Lys Asn Gln Ala Phe Ile Lys Met Ser Thr Glu Glu
 195 200 205

Ala Ala Asn Thr Met Ala Val Asn Ser Val Gln Ser Gly Asn Leu Ala
 210 215 220

Trp Thr Ala Pro Ala Ala Ala Val Asp Ala Gly Met Ala Met Ala Gly
 225 230 235 240

Gln Ser Leu Val Leu Arg Ile Ile Val Glu Asn Leu Phe Tyr Pro Thr
 245 250 255

Thr Leu Asp Val Leu His Gln Ile Phe Ser Lys Phe Gly Thr Val Lys
 260 265 270

Thr Ile Thr Phe Ile Lys Asp Asn Gln Phe Gln Ala Leu Leu Gln Tyr
 275 280 285

Thr Asp Pro Glu Asn Ala Gln His Thr Lys Leu Ser Leu Asp Trp Gln
 290 295 300

Asn Thr Tyr Asn Ala Cys His Thr Leu Cys Ile Asp Phe Ser Lys Leu
 305 310 315 320

Ile Ser Leu Asn Val Lys Tyr Asn Asn Asp Lys Ser Arg Asp Tyr His
 325 330 335

Ala Arg Thr Cys Pro Pro Gly Thr Ala Ser Pro Arg Trp Thr Arg His
 340 345 350

Gly Arg Gly Leu Arg Pro Phe Ser Ser Gln His Pro Arg Ser Pro Gly
 355 360 365

Pro Pro Ala Ile Pro Ser Ala Val Ala Ala Ala Ala Ala Gly Gln
 370 375 380

Ile Ala Ile Leu Gly Leu Ala Gly Thr Gly Asn Ser Val Leu Leu Arg
 385 390 395 400

Val Lys Ile Pro Phe Asn Lys Lys Glu Asn Ala Leu Val Gln Met Ala
405 410 415

Asp Gly Asn Gln Ala Gln Leu Ala Met Ser His Leu Asn Trp His Lys
420 425 430

Leu His Gly Lys Pro Ile Arg Ile Ser Ser His Gln Asn Val Gln Leu
435 440 445

Pro Arg Glu Gly Arg Glu Asp Gln Gly Leu Thr Lys Asp Tyr Gly Asn
450 455 460

Ser Pro Leu His Arg Phe Lys Lys Pro Gly Phe Lys Asn Phe Gln Asn
465 470 475 480

Ile Phe Pro Pro Ser Ala Thr Val His Leu Ser Asn Ile Pro Pro Ser
485 490 495

Val Ser Glu Glu Asp Leu Lys Val Leu Ser Ser Ser His Gly Gly Ile
500 505 510

Val Ile Gly Phe Lys Phe Phe Gln Lys Asn Arg Lys Met Ala Leu Ile
515 520 525

Gln Met Arg Ser Val Glu Glu Ala Val Gln Thr Pro Ile Ala Leu His
530 535 540

Asn His Asp Ile Trp Glu Asn His His Leu Arg Val Ser Phe Ser Lys
545 550 555 560

Ser Thr Ile Tyr Gly His Arg Pro Thr Thr Ala Gly Pro Pro Gly Asp
565 570 575

Asn Phe His His Ser Lys Lys Ser Asp Phe Lys Lys Gln Leu Lys
580 585 590

<210> 24

<211> 536

<212> PRT

<213> Homo sapiens

<400> 24

Met Gly Ser Asn Lys Ser Lys Pro Lys Asp Ala Ser Gln Arg Arg Arg
1 5 10 15

Ser Leu Glu Pro Ala Glu Asn Val His Gly Ala Gly Gly Gly Ala Phe

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

Glu Val Lys Leu Gly Gln Gly Cys Phe Gly Glu Val Trp Met Gly Thr
 275 280 285

Trp Asn Gly Thr Thr Arg Val Ala Ile Lys Thr Leu Lys Pro Gly Thr
 290 295 300

Met Ser Pro Glu Ala Phe Leu Gln Glu Ala Gln Val Met Lys Lys Leu
 305 310 315 320

Arg His Glu Lys Leu Val Gln Leu Tyr Ala Val Val Ser Glu Glu Pro
 325 330 335

Ile Tyr Ile Val Thr Glu Tyr Met Ser Lys Gly Ser Leu Leu Asp Phe
 340 345 350

Leu Lys Gly Glu Thr Gly Lys Tyr Leu Arg Leu Pro Gln Leu Val Asp
 355 360 365

Met Ala Ala Gln Ile Ala Ser Gly Met Ala Tyr Val Glu Arg Met Asn
 370 375 380

Tyr Val His Arg Asp Leu Arg Ala Ala Asn Ile Leu Val Gly Glu Asn
 385 390 395 400

Leu Val Cys Lys Val Ala Asp Phe Gly Leu Ala Arg Leu Ile Glu Asp
 405 410 415

Asn Glu Tyr Thr Ala Arg Gln Gly Ala Lys Phe Pro Ile Lys Trp Thr
 420 425 430

Ala Pro Glu Ala Ala Leu Tyr Gly Arg Phe Thr Ile Lys Ser Asp Val
 435 440 445

Trp Ser Phe Gly Ile Leu Leu Thr Glu Leu Thr Thr Lys Gly Arg Val
 450 455 460

Pro Tyr Pro Gly Met Val Asn Arg Glu Val Leu Asp Gln Val Glu Arg
 465 470 475 480

Gly Tyr Arg Met Pro Cys Pro Pro Glu Cys Pro Glu Ser Leu His Asp
 485 490 495

Leu Met Cys Gln Cys Trp Arg Lys Glu Pro Glu Glu Arg Pro Thr Phe
 500 505 510

Glu Tyr Leu Gln Ala Phe Leu Glu Asp Tyr Phe Thr Ser Thr Glu Pro

515 520 525

Gln Tyr Gln Pro Gly Glu Asn Leu
530 535

<210> 25
<211> 505
<212> PRT
<213> Homo sapiens

<400> 25

Met Gly Ser Met Lys Ser Lys Phe Leu Gln Val Gly Gly Asn Thr Phe
1 5 10 15

Ser Lys Thr Glu Thr Ser Ala Ser Pro His Cys Pro Val Tyr Val Pro
20 25 30

Asp Pro Thr Ser Thr Ile Lys Pro Gly Pro Asn Ser His Asn Ser Asn
35 40 45

Thr Pro Gly Ile Arg Glu Ala Gly Ser Glu Asp Ile Ile Val Val Ala
50 55 60

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

Gly Asp Gln Met Val Val Leu Glu Glu Ser Gly Glu Trp Trp Lys Ala
85 90 95

Arg Ser Leu Ala Thr Arg Lys Glu Gly Tyr Ile Pro Ser Asn Tyr Val
100 105 110

Ala Arg Val Asp Ser Leu Glu Thr Glu Glu Trp Phe Phe Lys Gly Ile
115 120 125

Ser Arg Lys Asp Ala Glu Arg Gln Leu Leu Ala Pro Gly Asn Met Leu
130 135 140

Gly Ser Phe Met Ile Arg Asp Ser Glu Thr Thr Lys Gly Ser Tyr Ser
145 150 155 160

Leu Ser Val Arg Asp Tyr Asp Pro Arg Gln Gly Asp Thr Val Lys His
165 170 175

Tyr Lys Ile Arg Thr Leu Asp Asn Gly Gly Phe Tyr Ile Ser Pro Arg
180 185 190

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

Leu Glu Arg Gly Tyr Arg Met Pro Arg Pro Glu Asn Cys Pro Glu Glu
 450 455 460

Leu Tyr Asn Ile Met Met Arg Cys Trp Lys Asn Arg Pro Glu Glu Arg
 465 470 475 480

Pro Thr Phe Glu Tyr Ile Gln Ser Val Leu Asp Asp Phe Tyr Thr Ala
 485 490 495

Thr Glu Ser Gln Tyr Gln Gln Gln Pro
 500 505

<210> 26
 <211> 537
 <212> PRT
 <213> Homo sapiens

<400> 26

Met Gly Cys Val Gln Cys Lys Asp Lys Glu Ala Thr Lys Leu Thr Glu
 1 5 10 15

Glu Arg Asp Gly Ser Leu Asn Gln Ser Ser Gly Tyr Arg Tyr Gly Thr
 20 25 30

Asp Pro Thr Pro Gln His Tyr Pro Ser Phe Gly Val Thr Ser Ile Pro
 35 40 45

Asn Tyr Asn Asn Phe His Ala Ala Gly Gly Gln Gly Leu Thr Val Phe
 50 55 60

Gly Gly Val Asn Ser Ser Ser His Thr Gly Thr Leu Arg Thr Arg Gly
 65 70 75 80

Gly Thr Gly Val Thr Leu Phe Val Ala Leu Tyr Asp Tyr Glu Ala Arg
 85 90 95

Thr Glu Asp Asp Leu Ser Phe His Lys Gly Glu Lys Phe Gln Ile Leu
 100 105 110

Asn Ser Ser Glu Gly Asp Trp Trp Glu Ala Arg Ser Leu Thr Thr Gly
 115 120 125

Glu Thr Gly Tyr Ile Pro Ser Asn Tyr Val Ala Pro Val Asp Ser Ile
 130 135 140

Gln Ala Glu Glu Trp Tyr Phe Gly Lys Leu Gly Arg Lys Asp Ala Glu

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

Gly Leu Ile Cys Lys Ile Ala Asp Phe Gly Leu Ala Arg Leu Ile Glu
 405 410 415

Asp Asn Glu Tyr Thr Ala Arg Gln Gly Ala Lys Phe Pro Ile Lys Trp
 420 425 430

Thr Ala Pro Glu Ala Ala Leu Tyr Gly Arg Phe Thr Ile Lys Ser Asp
 435 440 445

Val Trp Ser Phe Gly Ile Leu Leu Thr Glu Leu Val Thr Lys Gly Arg
 450 455 460

Val Pro Tyr Pro Gly Met Asn Asn Arg Glu Val Leu Glu Gln Val Glu
 465 470 475 480

Arg Gly Tyr Arg Met Pro Cys Pro Gln Asp Cys Pro Ile Ser Leu His
 485 490 495

Glu Leu Met Ile His Cys Trp Lys Lys Asp Pro Glu Glu Arg Pro Thr
 500 505 510

Phe Glu Tyr Leu Gln Ser Phe Leu Glu Asp Tyr Phe Thr Ala Thr Glu
 515 520 525

Pro Gln Tyr Gln Pro Gly Glu Asn Leu
 530 535

<210> 27
 <211> 509
 <212> PRT
 <213> Homo sapiens

<400> 27

Met Gly Cys Gly Cys Ser Ser His Pro Glu Asp Asp Trp Met Glu Asn
 1 5 10 15

Ile Asp Val Cys Glu Asn Cys His Tyr Pro Ile Val Arg Leu Asp Gly
 20 25 30

Lys Gly Arg Leu Leu Ile Arg Asn Gly Ser Glu Val Arg Asp Pro Leu
 35 40 45

Val Thr Tyr Glu Gly Ser Asn Pro Pro Ala Ser Pro Leu Gln Asp Asn
 50 55 60

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

Gly Phe Glu Lys Gly Glu Pro Leu Arg Ile Leu Glu Gln Ser Gly Glu
 85 90 95

Trp Trp Lys Ala Gln Ser Leu Thr Thr Gly Gln Glu Gly Phe Ile Pro
 100 105 110

Phe Asn Phe Val Ala Lys Ala Asn Ser Leu Glu Pro Glu Pro Trp Phe
 115 120 125

Phe Lys Asn Leu Ser Arg Lys Asp Ala Glu Arg Gln Leu Leu Ala Pro
 130 135 140

Gly Asn Thr His Gly Ser Phe Leu Ile Arg Glu Ser Glu Ser Thr Ala
 145 150 155 160

Gly Ser Phe Ser Leu Ser Val Arg Asp Phe Asp Gln Asn Gln Gly Glu
 165 170 175

Val Val Lys His Tyr Lys Ile Arg Asn Leu Asp Asn Gly Gly Phe Tyr
 180 185 190

Ile Ser Pro Arg Ile Thr Phe Pro Gly Leu His Glu Leu Val Arg His
 195 200 205

Tyr Thr Asn Ala Ser Asp Gly Leu Cys Thr Arg Leu Ser Arg Pro Cys
 210 215 220

Gln Thr Gln Lys Pro Gln Lys Pro Trp Trp Glu Asp Glu Trp Glu Val
 225 230 235 240

Pro Arg Glu Thr Leu Lys Leu Val Glu Arg Leu Gly Ala Ala Gln Phe
 245 250 255

Gly Glu Val Trp Met Gly Tyr Tyr Asn Gly His Thr Lys Val Ala Val
 260 265 270

Lys Ser Leu Lys Gln Gly Ser Met Ser Pro Asp Ala Phe Leu Ala Glu
 275 280 285

Ala Asn Leu Met Lys Gln Leu Gln His Gln Arg Leu Val Arg Leu Tyr
 290 295 300

Ala Val Val Thr Gln Glu Pro Ile Tyr Ile Ile Thr Glu Tyr Met Glu
 305 310 315 320

Asn Gly Ser Leu Val Asp Phe Leu Lys Thr Pro Ser Gly Ile Lys Leu
 325 330 335

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

Ala Phe Ile Glu Glu Arg Asn Tyr Ile His Arg Asp Leu Arg Ala Ala
 355 360 365

Asn Ile Leu Val Ser Asp Thr Leu Ser Cys Lys Ile Ala Asp Phe Gly
 370 375 380

Leu Ala Arg Leu Ile Glu Asp Asn Glu Tyr Thr Ala Arg Glu Gly Ala
 385 390 395 400

Lys Phe Pro Ile Lys Trp Thr Ala Pro Glu Ala Ile Asn Tyr Gly Thr
 405 410 415

Phe Thr Ile Lys Ser Asp Val Trp Ser Phe Gly Ile Leu Leu Thr Glu
 420 425 430

Ile Val Thr His Gly Arg Ile Pro Tyr Pro Gly Met Thr Asn Pro Glu
 435 440 445

Val Ile Gln Asn Leu Glu Arg Gly Tyr Arg Met Val Arg Pro Asp Asn
 450 455 460

Cys Pro Glu Glu Leu Tyr Gln Leu Met Arg Leu Cys Trp Lys Glu Arg
 465 470 475 480

Pro Glu Asp Arg Pro Thr Phe Asp Tyr Leu Arg Ser Val Leu Glu Asp
 485 490 495

Phe Phe Thr Ala Thr Glu Gly Gln Tyr Gln Pro Gln Pro
 500 505

<210> 28
 <211> 512
 <212> PRT
 <213> Homo sapiens

<400> 28

Met Gly Cys Ile Lys Ser Lys Gly Lys Asp Ser Leu Ser Asp Asp Gly
 1 5 10 15

Val Asp Leu Lys Thr Gln Pro Val Arg Asn Thr Glu Arg Thr Ile Tyr
 20 25 30

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

275	280	285
Glu Glu Ala Asn Leu Met Lys Thr Leu Gln His Asp Lys Leu Val Arg		
290	295	300
Leu Tyr Ala Val Val Thr Arg Glu Glu Pro Ile Tyr Ile Ile Thr Glu		
305	310	315
Tyr Met Ala Lys Gly Ser Leu Leu Asp Phe Leu Lys Ser Asp Glu Gly		
325	330	335
Gly Lys Val Leu Leu Pro Lys Leu Ile Asp Phe Ser Ala Gln Ile Ala		
340	345	350
Glu Gly Met Ala Tyr Ile Glu Arg Lys Asn Tyr Ile His Arg Asp Leu		
355	360	365
Arg Ala Ala Asn Val Leu Val Ser Glu Ser Leu Met Cys Lys Ile Ala		
370	375	380
Asp Phe Gly Leu Ala Arg Val Ile Glu Asp Asn Glu Tyr Thr Ala Arg		
385	390	395
Glu Gly Ala Lys Phe Pro Ile Lys Trp Thr Ala Pro Glu Ala Ile Asn		
405	410	415
Phe Gly Cys Phe Thr Ile Lys Ser Asp Val Trp Ser Phe Gly Ile Leu		
420	425	430
Leu Tyr Glu Ile Val Thr Tyr Gly Lys Ile Pro Tyr Pro Gly Arg Thr		
435	440	445
Asn Ala Asp Val Met Thr Ala Leu Ser Gln Gly Tyr Arg Met Pro Arg		
450	455	460
Val Glu Asn Cys Pro Asp Glu Leu Tyr Asp Ile Met Lys Met Cys Trp		
465	470	475
Lys Glu Lys Ala Glu Glu Arg Pro Thr Phe Asp Tyr Leu Gln Ser Val		
485	490	495
Leu Asp Asp Phe Tyr Thr Ala Thr Glu Gly Gln Tyr Gln Gln Gln Pro		
500	505	510
<210> 29		
<211> 505		
<212> PRT		

<213> Homo sapiens

<400> 29

Met Gly Leu Val Ser Ser Lys Lys Pro Asp Lys Glu Lys Pro Ile Lys
 1 5 10 15

Glu Lys Asp Lys Gly Gln Trp Ser Pro Leu Lys Val Ser Ala Gln Asp
 20 25 30

Lys Asp Ala Pro Pro Leu Pro Pro Leu Val Val Phe Asn His Leu Thr
 35 40 45

Pro Pro Pro Pro Asp Glu His Leu Asp Glu Asp Lys His Phe Val Val
 50 55 60

Ala Leu Tyr Asp Tyr Thr Ala Met Asn Asp Arg Asp Leu Gln Met Leu
 65 70 75 80

Lys Gly Glu Lys Leu Gln Val Leu Lys Gly Thr Gly Asp Trp Trp Leu
 85 90 95

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

Val Ala Arg Val Glu Ser Leu Glu Met Glu Arg Trp Phe Phe Arg Ser
 115 120 125

Gln Gly Arg Lys Glu Ala Glu Arg Gln Leu Leu Ala Pro Ile Asn Lys
 130 135 140

Ala Gly Ser Phe Leu Ile Arg Glu Ser Glu Thr Asn Lys Gly Ala Phe
 145 150 155 160

Ser Leu Ser Val Lys Asp Val Thr Thr Gln Gly Glu Leu Ile Lys His
 165 170 175

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

Ile Thr Phe Pro Ser Leu Gln Ala Leu Val Gln His Tyr Ser Lys Lys
 195 200 205

Gly Asp Gly Leu Cys Gln Arg Leu Thr Leu Pro Cys Val Arg Pro Ala
 210 215 220

Pro Gln Asn Pro Trp Ala Gln Asp Glu Trp Glu Ile Pro Arg Gln Ser
 225 230 235 240

Leu Arg Leu Val Arg Lys Leu Gly Ser Gly Gln Phe Gly Glu Val Trp
 245 250 255

Met Gly Tyr Tyr Lys Asn Asn Met Lys Val Ala Ile Lys Thr Leu Lys
 260 265 270

Glu Gly Thr Met Ser Pro Glu Ala Phe Leu Gly Glu Ala Asn Met Met
 275 280 285

Lys Ala Leu Gln His Glu Arg Leu Val Arg Leu Tyr Ala Val Val Thr
 290 295 300

Lys Glu Pro Ile Tyr Ile Val Thr Glu Tyr Met Ala Arg Gly Cys Leu
 305 310 315 320

Leu Asp Phe Leu Lys Thr Asp Glu Gly Ser Arg Leu Ser Leu Pro Arg
 325 330 335

Leu Ile Asp Met Ser Ala Gln Ile Ala Glu Gly Met Ala Tyr Ile Glu
 340 345 350

Arg Met Asn Ser Ile His Arg Asp Leu Arg Ala Ala Asn Ile Leu Val
 355 360 365

Ser Glu Ala Leu Cys Cys Lys Ile Ala Asp Phe Gly Leu Ala Arg Ile
 370 375 380

Ile Asp Ser Glu Tyr Thr Ala Gln Glu Gly Ala Lys Phe Pro Ile Lys
 385 390 395 400

Trp Thr Ala Pro Glu Ala Ile His Phe Gly Val Phe Thr Ile Lys Ala
 405 410 415

Asp Val Trp Ser Phe Gly Val Leu Leu Met Glu Val Val Thr Tyr Gly
 420 425 430

Arg Val Pro Tyr Pro Gly Met Ser Asn Pro Glu Val Ile Arg Asn Leu
 435 440 445

Glu Arg Gly Tyr Arg Met Pro Arg Pro Asp Thr Cys Pro Pro Glu Leu
 450 455 460

Tyr Arg Gly Val Ile Ala Glu Cys Trp Arg Ser Arg Pro Glu Glu Arg
 465 470 475 480

Pro Thr Phe Glu Phe Leu Gln Ser Val Leu Glu Asp Phe Tyr Thr Ala
 485 490 495

Thr Glu Arg Gln Tyr Glu Leu Gln Pro
 500 505

<210> 30
 <211> 529
 <212> PRT
 <213> Homo sapiens

<400> 30

Met Gly Cys Val Phe Cys Lys Lys Leu Glu Pro Val Ala Thr Ala Lys
 1 5 10 15

Glu Asp Ala Gly Leu Glu Gly Asp Phe Arg Ser Tyr Gly Ala Ala Asp
 20 25 30

His Tyr Gly Pro Asp Pro Thr Lys Ala Arg Pro Ala Ser Ser Phe Ala
 35 40 45

His Ile Pro Asn Tyr Ser Asn Phe Ser Ser Gln Ala Ile Asn Pro Gly
 50 55 60

Phe Leu Asp Ser Gly Thr Ile Arg Gly Val Ser Gly Ile Gly Val Thr
 65 70 75 80

Leu Phe Ile Ala Leu Tyr Asp Tyr Glu Ala Arg Thr Glu Asp Asp Leu
 85 90 95

Thr Phe Thr Lys Gly Glu Lys Phe His Ile Leu Asn Asn Thr Glu Gly
 100 105 110

Asp Trp Trp Glu Ala Arg Ser Leu Ser Ser Gly Lys Thr Gly Cys Ile
 115 120 125

Pro Ser Asn Tyr Val Ala Pro Val Asp Ser Ile Gln Ala Glu Glu Trp
 130 135 140

Tyr Phe Gly Lys Ile Gly Arg Lys Asp Ala Glu Arg Gln Leu Leu Ser
 145 150 155 160

Pro Gly Asn Pro Gln Gly Ala Phe Leu Ile Arg Glu Ser Glu Thr Thr
 165 170 175

Lys Gly Ala Tyr Ser Leu Ser Ile Arg Asp Trp Asp Gln Thr Arg Gly
 180 185 190

Asp His Val Lys His Tyr Lys Ile Arg Lys Leu Asp Met Gly Gly Tyr
 195 200 205

Tyr Ile Thr Thr Arg Val Gln Phe Asn Ser Val Gln Glu Leu Val Gln
 210 215 220

His Tyr Met Glu Val Asn Asp Gly Leu Cys Asn Leu Leu Ile Ala Pro
 225 230 235 240

Cys Thr Ile Met Lys Pro Gln Thr Leu Gly Leu Ala Lys Asp Ala Trp
 245 250 255

Glu Ile Ser Arg Ser Ser Ile Thr Leu Glu Arg Arg Leu Gly Thr Gly
 260 265 270

Cys Phe Gly Asp Val Trp Leu Gly Thr Trp Asn Gly Ser Thr Lys Val
 275 280 285

Ala Val Lys Thr Leu Lys Pro Gly Thr Met Ser Pro Lys Ala Phe Leu
 290 295 300

Glu Glu Ala Gln Val Met Lys Leu Leu Arg His Asp Lys Leu Val Gln
 305 310 315 320

Leu Tyr Ala Val Val Ser Glu Glu Pro Ile Tyr Ile Val Thr Glu Phe
 325 330 335

Met Cys His Gly Ser Leu Leu Asp Phe Leu Lys Asn Pro Glu Gly Gln
 340 345 350

Asp Leu Arg Leu Pro Gln Leu Val Asp Met Ala Ala Gln Val Ala Glu
 355 360 365

Gly Met Ala Tyr Met Glu Arg Met Asn Tyr Ile His Arg Asp Leu Arg
 370 375 380

Ala Ala Asn Ile Leu Val Gly Glu Arg Leu Ala Cys Lys Ile Ala Asp
 385 390 395 400

Phe Gly Leu Ala Arg Leu Ile Lys Asp Asp Glu Tyr Asn Pro Cys Gln
 405 410 415

Gly Ser Lys Phe Pro Ile Lys Trp Thr Ala Pro Glu Ala Ala Leu Phe
 420 425 430

Gly Arg Phe Thr Ile Lys Ser Asp Val Trp Ser Phe Gly Ile Leu Leu

435 440 445
 Thr Glu Leu Ile Thr Lys Gly Arg Ile Pro Tyr Pro Gly Met Asn Lys
 450 455 460
 Arg Glu Val Leu Glu Gln Val Glu Gln Gly Tyr His Met Pro Cys Pro
 465 470 475 480
 Pro Gly Cys Pro Ala Ser Leu Tyr Glu Ala Met Glu Gln Thr Trp Arg
 485 490 495
 Leu Asp Pro Glu Glu Arg Pro Thr Phe Glu Tyr Leu Gln Ser Phe Leu
 500 505 510
 Glu Asp Tyr Phe Thr Ser Ala Glu Pro Gln Tyr Gln Pro Gly Asp Gln
 515 520 525
 Thr
 <210> 31
 <211> 557
 <212> PRT
 <213> Homo sapiens
 <400> 31
 Met Ala Tyr Ser Glu Glu His Lys Gly Met Pro Cys Gly Phe Ile Arg
 1 5 10 15
 Gln Asn Ser Gly Asn Ser Ile Ser Leu Asp Phe Glu Pro Ser Ile Glu
 20 25 30
 Tyr Gln Phe Val Glu Arg Leu Glu Glu Arg Tyr Lys Cys Ala Phe Cys
 35 40 45
 His Ser Val Leu His Asn Pro His Gln Thr Gly Cys Gly His Arg Phe
 50 55 60
 Cys Gln His Cys Ile Leu Ser Leu Arg Glu Leu Asn Thr Val Pro Ile
 65 70 75 80
 Cys Pro Val Asp Lys Glu Val Ile Lys Ser Gln Glu Val Phe Lys Asp
 85 90 95
 Asn Cys Cys Lys Arg Glu Val Leu Asn Leu Tyr Val Tyr Cys Ser Asn
 100 105 110

Ala Pro Gly Cys Asn Ala Lys Val Ile Leu Gly Arg Tyr Gln Asp His
 115 120 125

Leu Gln Gln Cys Leu Phe Gln Pro Val Gln Cys Ser Asn Glu Lys Cys
 130 135 140

Arg Glu Pro Val Leu Arg Lys Asp Leu Lys Glu His Leu Ser Ala Ser
 145 150 155 160

Cys Gln Phe Arg Lys Glu Lys Cys Leu Tyr Cys Lys Lys Asp Val Val
 165 170 175

Val Ile Asn Leu Gln Asn His Glu Glu Asn Leu Cys Pro Glu Tyr Pro
 180 185 190

Val Phe Cys Pro Asn Asn Cys Ala Lys Ile Ile Leu Lys Thr Glu Val
 195 200 205

Asp Glu His Leu Ala Val Cys Pro Glu Ala Glu Gln Asp Cys Pro Phe
 210 215 220

Lys His Tyr Gly Cys Ala Val Thr Asp Lys Arg Arg Asn Leu Gln Gln
 225 230 235 240

His Glu His Ser Ala Leu Arg Glu His Met Arg Leu Val Leu Glu Lys
 245 250 255

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

Gln Lys Glu Ser Lys Ile Gln Gln Leu Ala Glu Thr Ile Lys Lys Leu
 275 280 285

Glu Lys Glu Phe Lys Gln Phe Ala Gln Leu Phe Gly Lys Asn Gly Ser
 290 295 300

Phe Leu Pro Asn Ile Gln Val Phe Ala Ser His Ile Asp Lys Ser Ala
 305 310 315 320

Trp Leu Glu Ala Gln Val His Gln Leu Leu Gln Met Val Asn Gln Gln
 325 330 335

Gln Asn Lys Phe Asp Leu Arg Pro Leu Met Glu Ala Val Asp Thr Val
 340 345 350

Lys Gln Lys Ile Thr Leu Leu Glu Asn Asn Asp Gln Arg Leu Ala Val
 355 360 365

Leu Glu Glu Glu Thr Asn Lys His Asp Thr His Ile Asn Ile His Lys
 370 375 380

Ala Gln Leu Ser Lys Asn Glu Glu Arg Phe Lys Leu Leu Glu Gly Thr
 385 390 395 400

Cys Tyr Asn Gly Lys Leu Ile Trp Lys Val Thr Asp Tyr Lys Met Lys
 405 410 415

Lys Arg Glu Ala Val Asp Gly His Thr Val Ser Ile Phe Ser Gln Ser
 420 425 430

Phe Tyr Thr Ser Arg Cys Gly Tyr Arg Leu Cys Ala Arg Ala Tyr Leu
 435 440 445

Asn Gly Asp Gly Ser Gly Arg Gly Ser His Leu Ser Leu Tyr Phe Val
 450 455 460

Val Met Arg Gly Glu Phe Asp Ser Leu Leu Gln Trp Pro Phe Arg Gln
 465 470 475 480

Arg Val Thr Leu Met Leu Leu Asp Gln Ser Gly Lys Lys Asn Ile Met
 485 490 495

Glu Thr Phe Lys Pro Asp Pro Asn Ser Ser Ser Phe Lys Arg Pro Asp
 500 505 510

Gly Glu Met Asn Ile Ala Ser Gly Cys Pro Arg Phe Val Ala His Ser
 515 520 525

Val Leu Glu Asn Ala Lys Asn Ala Tyr Ile Lys Asp Asp Thr Leu Phe
 530 535 540

Leu Lys Val Ala Val Asp Leu Thr Asp Leu Glu Asp Leu
 545 550 555

<210> 32
 <211> 416
 <212> PRT
 <213> Homo sapiens

<400> 32

Met Ala Ser Ser Ser Gly Ser Ser Pro Arg Pro Ala Pro Asp Glu Asn
 1 5 10 15

Glu Phe Pro Phe Gly Cys Pro Pro Thr Val Cys Gln Asp Pro Lys Glu

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

Ile Thr Asn Val Thr Arg Arg Cys His Glu Ser Ala Cys Gly Arg Thr
 275 280 285

Val Ser Leu Phe Ser Pro Ala Phe Tyr Thr Ala Lys Tyr Gly Tyr Lys
 290 295 300

Leu Cys Leu Arg Leu Tyr Leu Asn Gly Asp Gly Thr Gly Lys Arg Thr
 305 310 315 320

His Leu Ser Leu Phe Ile Val Ile Met Arg Gly Glu Tyr Asp Ala Leu
 325 330 335

Leu Pro Trp Pro Phe Arg Asn Lys Val Thr Phe Met Leu Leu Asp Gln
 340 345 350

Asn Asn Arg Glu His Ala Ile Asp Ala Phe Arg Pro Asp Leu Ser Ser
 355 360 365

Ala Ser Phe Gln Arg Pro Gln Ser Glu Thr Asn Val Ala Ser Gly Cys
 370 375 380

Pro Leu Phe Phe Pro Leu Ser Lys Leu Gln Ser Pro Lys His Ala Tyr
 385 390 395 400

Val Lys Asp Asp Thr Met Phe Leu Lys Cys Ile Val Glu Thr Ser Thr
 405 410 415

<210> 33
 <211> 543
 <212> PRT
 <213> Homo sapiens

<400> 33

Met Gly Cys Ile Lys Ser Lys Glu Asn Lys Ser Pro Ala Ile Lys Tyr
 1 5 10 15

Arg Pro Glu Asn Thr Pro Glu Pro Val Ser Thr Ser Val Ser His Tyr
 20 25 30

Gly Ala Glu Pro Thr Thr Val Ser Pro Cys Pro Ser Ser Ser Ala Lys
 35 40 45

Gly Thr Ala Val Asn Phe Ser Ser Leu Ser Met Thr Pro Phe Gly Gly
 50 55 60

Ser Ser Gly Val Thr Pro Phe Gly Gly Ala Ser Ser Ser Phe Ser Val
 65 70 75 80

Val Pro Ser Ser Tyr Pro Ala Gly Leu Thr Gly Gly Val Thr Ile Phe
 85 90 95

Val Ala Leu Tyr Asp Tyr Glu Ala Arg Thr Thr Glu Asp Leu Ser Phe
 100 105 110

Lys Lys Gly Glu Arg Phe Gln Ile Ile Asn Asn Thr Glu Gly Asp Trp
 115 120 125

Trp Glu Ala Arg Ser Ile Ala Thr Gly Lys Asn Gly Tyr Ile Pro Ser
 130 135 140

Asn Tyr Val Ala Pro Ala Asp Ser Ile Gln Ala Glu Glu Trp Tyr Phe
 145 150 155 160

Gly Lys Met Gly Arg Lys Asp Ala Glu Arg Leu Leu Leu Asn Pro Gly
 165 170 175

Asn Gln Arg Gly Ile Phe Leu Val Arg Glu Ser Glu Thr Thr Lys Gly
 180 185 190

Ala Tyr Ser Leu Ser Ile Arg Asp Trp Asp Glu Ile Arg Gly Asp Asn
 195 200 205

Val Lys His Tyr Lys Ile Arg Lys Leu Asp Asn Gly Gly Tyr Tyr Ile
 210 215 220

Thr Thr Arg Ala Gln Phe Asp Thr Leu Gln Lys Leu Val Lys His Tyr
 225 230 235 240

Thr Glu His Ala Asp Gly Leu Cys His Lys Leu Thr Thr Val Cys Pro
 245 250 255

Thr Val Lys Pro Gln Thr Gln Gly Leu Ala Lys Asp Ala Trp Glu Ile
 260 265 270

Pro Arg Glu Ser Leu Arg Leu Glu Val Lys Leu Gly Gln Gly Cys Phe
 275 280 285

Gly Glu Val Trp Met Gly Thr Trp Asn Gly Thr Thr Lys Val Ala Ile
 290 295 300

Lys Thr Leu Lys Pro Gly Thr Met Met Pro Glu Ala Phe Leu Gln Glu
 305 310 315 320

Ala Gln Ile Met Lys Lys Leu Arg His Asp Lys Leu Val Pro Leu Tyr
 325 330 335

Ala Val Val Ser Glu Glu Pro Ile Tyr Ile Val Thr Glu Phe Met Ser
 340 345 350

Lys Gly Ser Leu Leu Asp Phe Leu Lys Glu Gly Asp Gly Lys Tyr Leu
 355 360 365

Lys Leu Pro Gln Leu Val Asp Met Ala Ala Gln Ile Ala Asp Gly Met
 370 375 380

Ala Tyr Ile Glu Arg Met Asn Tyr Ile His Arg Asp Leu Arg Ala Ala
 385 390 395 400

Asn Ile Leu Val Gly Glu Asn Leu Val Cys Lys Ile Ala Asp Phe Gly
 405 410 415

Leu Ala Arg Leu Ile Glu Asp Asn Glu Tyr Thr Ala Arg Gln Gly Ala
 420 425 430

Lys Phe Pro Ile Lys Trp Thr Ala Pro Glu Ala Ala Leu Tyr Gly Arg
 435 440 445

Phe Thr Ile Lys Ser Asp Val Trp Ser Phe Gly Ile Leu Gln Thr Glu
 450 455 460

Leu Val Thr Lys Gly Arg Val Pro Tyr Pro Gly Met Val Asn Arg Glu
 465 470 475 480

Val Leu Glu Gln Val Glu Arg Gly Tyr Arg Met Pro Cys Pro Gln Gly
 485 490 495

Cys Pro Glu Ser Leu His Glu Leu Met Asn Leu Cys Trp Lys Lys Asp
 500 505 510

Pro Asp Glu Arg Pro Thr Phe Glu Tyr Ile Gln Ser Phe Leu Glu Asp
 515 520 525

Tyr Phe Thr Ala Thr Glu Pro Gln Tyr Gln Pro Gly Glu Asn Leu
 530 535 540

<210> 34

<211> 240

<212> PRT

<213> Homo sapiens

<400> 34

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