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(54) **DNA MOLECULES ENCODING SPLICE VARIANTS OF THE HUMAN MELANOCORTIN 1 RECEPTOR PROTEIN**

DNA-MOLEKÜLE KODIERENDE SPLEISSVARIANTEN DES HUMANEN MELANOCORTIN-1-REZEPTORPROTEINS

MOLECULES D'ADN CODANT DES VARIANTS D'EPISSAGE DE LA PROTEINE HUMAINE DU RECEPTEUR DE MELANOCORTINE-1

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- **BONALDO FATIMA DE M ET AL: "NORMALIZATION AND SUBTRACTION: TWO APPROACHES TO FACILITATE GENE DISCOVERY" GENOME RESEARCH, COLD SPRING HARBOR LABORATORY PRESS, US, vol. 6, no. 9, 1 September 1996 (1996-09-01), pages 791-806, XP002039972 ISSN: 1088-9051 -& DATABASE EMBL [Online] 6 March 2002 (2002-03-06) BONALDO M.F. ET AL.: retrieved from EMBL Database accession no. bm701236 XP002236858**
- **BOX NEIL F ET AL: "Characterization of melanocyte stimulating hormone receptor variant alleles in twins with red hair." HUMAN MOLECULAR GENETICS, vol. 6, no. 11, 1997, pages 1891-1897, XP002236857 ISSN: 0964-6906**
- **TAN C P ET AL: "Molecular analysis of a new splice variant of the human melanocortin-1 receptor" FEBS LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 451, no. 2, 21 May 1999 (1999-05-21), pages 137-141, XP004259665 ISSN: 0014-5793**

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- **DATABASE GENBANK ACCESSION NO. AA778295, February 1998 HILLIER ET AL.: 'Homo sapiens cDNA clone', XP002905607**
- **DATABASE GENBANK ACCESSION NO. AI187892, October 1998 NCI-CGAP: 'Homo sapiens cDNA clone: Melanocyte Stimulating Hormone Receptor', XP002905608**
- **DATABASE GENBANK ACCESSION NO. AI123000, September 1998 NCI-CGAP: 'Homo sapiens cDNA clone: Melanocyte Stimulating Hormone Receptor', XP002905609**

Description

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priority to U.S. Serial No. 60/113,401, filed December 23, 1998.

FIELD OF THE INVENTION

[0002] The present invention relates to DNA molecules encoding splice variants of the melanocortin-1 receptor (MC-R1) protein belonging to the rhodopsin sub-family of G-protein coupled receptors, recombinant vectors comprising DNA molecules encoding MC-R1 splice variant proteins, recombinant host cells which contain a recombinant vector encoding MC-R1 splice variants, the human MC-R1 proteins encoded by the DNA molecule, and methods of identifying selective agonists and antagonists of MC-R1 splice variant proteins disclosed throughout this specification.

BACKGROUND OF THE INVENTION

[0003] Melanocortin receptors belong to the rhodopsin sub-family of G-protein coupled receptors (GPCR's). Five different subtypes are known. These melanocortin receptors bind and are activated by peptides such as α-, β-, or γ-melanocyte stimulating hormones (α-, β-, γ-MSH) derived from the pro-opiomelanocortin (POMC) gene. A wide range of physiological functions are believed to be mediated by melanocortin peptides and their receptors.

[0004] U.S. Patent No. 5,532,347, issued on July 2, 1996, to Cone and Mountjoy discloses and claims human and mouse DNA molecules which encode MC-R1 (also known in the art as α-MSH-R). The expressed human protein contains 317 amino acids.

[0005] U.S. Patent No. 5,849,871, issued on December 15, 1998, to Cone and Mountjoy discloses and claims human and mouse MC-R1. As noted in the previous paragraph, the expressed human protein contains 317 amino acid residues.

[0006] Mountjoy, et al. (1992, *Science* 257: 1248-1251) describe DNA molecules and the concomitant protein for human MC-R1 and human MC-R2.

[0007] Chhajlani, et al. (1992, *FEBS Letters* 309: 417-420) also disclose a human DNA molecule comprising an open reading frame which encodes human MC-R1.

[0008] Cone et al. (1996, *Recent Progress in Hormone Research* 51: 287-318) reviews the state of known mammalian melanocortin receptors, from MC-R1 through MC-R5.

[0009] Jackson (1997, *Human Molecular Genetics* 6: 1613-24) and Koppula, et al. (1997, *Human Mutation* 9:30-36) review the occurrence and potential significance of polymorphisms within the coding sequence of the human MC-R1 form A.

[0010] It is desirable to correlate *in vivo* data with *in vitro* biochemical activity of compounds.

[0011] It is also desirable to select compounds which activate one or more human melanocortin receptor proteins *in vitro.*

[0012] It is further desirable to discover new drugs which effect pathophysiological processes by modulating melanocortin receptor activity, followed by human clinical trials.

[0013] The present invention addresses and meets these needs by disclosing isolated nucleic acid molecules which express splice variants of human MC-R1, recombinant vectors which house these nucleic acid molecules, recombinant host cells which expresses these alternative forms of human MC-R1 and/or biologically active equivalents, and pharmacological properties of these human MC-R1 proteins.

SUMMARY OF THE INVENTION

[0014] The present invention relates to a series of isolated nucleic acid molecules (polynucleotides) which encode novel variants of the human melanocortin-1 receptor protein, referred to herein as MC-R1B proteins. The nucleic acid molecules of the present invention are substantially free from other nucleic acids. These isolated nucleic acid molecules encode a MC-R1 protein which contains an intracellular domain with an additional 65 amino acid residues in comparison to the previously disclosed human MC-R1, referred to herein also as MC-R1A. Therefore, the present invention relates to isolated nucleic acid molecules (polynucleotides) which encode a mRNA which expresses a novel human MC-R1 protein, these DNA molecules including but by no means being limited to DNA molecules comprising the nucleotide sequence disclosed herein as SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO: 11, SEQ ID NO:13, SEQ ID NO:16, SEQ ID NO:19, SEQ ID NO:22, and SEQ ID NO:25.

[0015] The present invention also relates to isolated nucleic acid molecules which represent human genomic clones which comprise at least a single intron within the open reading frame which encodes novel variants of human MC-R1B protein. Therefore, the present invention relates to isolated nucleic acid molecules (polynucleotides) which encode a RNA molecule which is spliced to generate a mRNA molecule which encodes a novel human MC-R1 protein variant,

these DNA molecules including but by no means being limited to DNA molecules comprising the nucleotide sequence disclosed herein as SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:21, and SEQ ID NO:24. To this end, the present invention also relates to the respective mRNA molecule generated from each of the DNA molecules depicted as SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:21, and SEQ ID NO:24.

[0016] The isolated nucleic acid molecules of the present invention comprise a 3' extension in the open reading frame which encodes a 65 amino acid COOH-terminal extension to known MC-R1. Therefore, the present invention relates to isolated nucleic acid molecules, both DNA and RNA molecules, that encode for a splice variant of known MC-R1 which encodes for this 65 amino acid COOH-terminal extension. The totality of nucleic acid molecules of the present invention, including genomic DNA, cDNA, RNA and mRNA, will be referred to herein as "MC-R1 splice variants", which will identify a disclosed nucleic acid molecule which encodes an protein with melanocortin 1 receptor activity in combination with this additional 3' exon which encodes a 65 amino acid COOH-terminal extension. These isolated nucleic acid molecules include but are by no means limited to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:18; SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO: 22, SEQ ID NO:24, and SEQ ID NO:25.

[0017] The present invention also relates to biologically active fragments or mutants of MC-R1 splice variants which encodes mRNA expressing a novel human MC-R1. Any such biologically active fragment and/or mutant of the MC-R1 splice variants disclosed herein will encode either a protein or protein fragment which at least substantially mimics the pharmacological properties of a wild-type MC-R1 protein and comprises at least a portion of the COOH terminal amino acid extension disclosed as SEQ ID NO:27. Any such polynucleotide includes but is not necessarily limited to nucleotide substitutions, deletions, additions, amino-terminal truncations and carboxy-terminal truncations such that these mutations encode mRNA which express a protein or protein fragment of diagnostic, therapeutic or prophylactic use and would be useful for screening for agonists and/or antagonists for MC-R1B function.

[0018] A preferred aspect of this portion of the present invention is set forth as SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:18; SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:24, and SEQ ID NO:25, human nucleic acid molecules which comprise the complete open reading frame for the MC-R1B proteins of the present invention.

[0019] The isolated nucleic acid molecules of the present invention may include a deoxyribonucleic acid molecule (DNA), such as genomic DNA and complementary DNA (cDNA), which may be single (coding or noncoding strand) or double stranded, as well as synthetic DNA, such as a synthesized, single stranded polynucleotide. The isolated nucleic acid molecule of the present invention may also include a ribonucleic acid molecule (RNA).

[0020] The present invention also relates to recombinant vectors and recombinant hosts, both prokaryotic and eukaryotic, which contain the substantially purified nucleic acid molecules disclosed throughout this specification, including but not limited to the isolated nucleic acid molecules as set forth in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:18; SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:24, and SEQ ID NO:25.

[0021] The present invention also relates to subcellular membrane fractions of the recombinant host cells (both prokaryotic and eukaryotic as well as both stably and transiently transformed cells) which contain the proteins encoded by the nucleic acids of the present invention. These subcellular membrane fractions will comprise either wild-type or mutant forms of the human melanocortin-1 receptor proteins which comprise the COOH-terminal extension at levels substantially above endogenous levels and hence will be useful in various assays described throughout this specification.

[0022] The present invention also relates to a substantially purified form of the COOH-terminal variants of human melanocortin-1 receptor protein, which comprises the amino acid sequences as disclosed in Figures 5A - 5F and as set forth in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:17, SEQ ID NO:20, SEQ ID NO:23, and SEQ ID NO:26. These MC-R1 proteins comprise a 65 amino acid extension at the COOH-terminus when compared to known human MC-R1 and are referred to throughout this specification as MC-R1B proteins or MC-R1 splice variant proteins.

[0023] The present invention also relates to biologically active fragments and/or mutants of the human MC-R1B proteins disclosed throughout this specification, including but not necessarily limited to amino acid substitutions, deletions, additions, amino terminal truncations and carboxy-terminal truncations such that these mutations provide for proteins or protein fragments of diagnostic, therapeutic or prophylactic use and would be useful for screening for agonists and/or antagonists for MC-R1B function.

[0024] The present invention also relates to isolated nucleic acid molecules which are fusion constructions expressing fusion proteins useful in assays to identify compounds which modulate wild-type vertebrate MC-R1B activity. A preferred aspect of this portion of the invention includes, but is not limited to, glutathione S-transferase (GST)-MC-R1B fusion constructs which include, but are not limited to, either the intracellular domain of human MC-1RB as an in-frame fusion at the carboxy terminus of the GST gene, or the extracellular and transmembrane ligand binding domain of MC-R1B fused to the amino terminus of GST, or the extracellular and transmembrane domain of MC-R1B fused to an immunoglobulin gene by methods known to one of ordinary skill in the art. Soluble recombinant GST-MC-R1B fusion proteins

may be expressed in various expression systems, including *Spodoptera frugiperda* (Sf21) insect cells (Invitrogen) using a baculovirus expression vector (pAcG2T, Pharmingen).

[0025] Therefore, the present invention relates to methods of expressing the human MC-R1B proteins disclosed herein and biological equivalents, assays employing these gene products, recombinant host cells which comprise DNA constructs which express these receptor proteins, and compounds identified through these assays which act as agonists or antagonists of MC-R1B activity.

[0026] The present invention also relates to polyclonal and monoclonal antibodies raised in response to either the human form of a MC-R1B protein, or a biologically active fragment thereof.

[0027] It is an object of the present invention to provide an isolated nucleic acid molecule which encodes a novel form of human MC-R1B, or human MC-R1B fragments, mutants or derivatives of the human MC-R1B proteins as set forth in Figures 5A - 5F and SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:17, SEQ ID NO:20, SEQ ID NO:23, and SEQ ID NO:26. Any such polynucleotide includes but is not necessarily limited to nucleotide substitutions, deletions, additions, amino-terminal truncations and carboxy-terminal truncations such that these mutations encode mRNA which express a protein or protein fragment of diagnostic, therapeutic or prophylactic use and would be useful for screening for agonists and/or antagonists for vertebrate MC-R I B function.

[0028] It is a further object of the present invention to provide the human MC-R1B proteins or protein fragments encoded by the nucleic acid molecules referred to in the preceding paragraph.

[0029] It is a further object of the present invention to provide recombinant vectors and recombinant host cells which comprise a nucleic acid sequence encoding these human MC-R1B proteins or biological equivalents thereof.

[0030] It is an object of the present invention to provide a substantially purified form of any of the human MC-R1B proteins, including but not limited to the proteins as set forth in Figures 5A - 5F and SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:17, SEQ ID NO:20, SEQ ID NO: 23, and SEQ ID NO:26.

[0031] It is an object of the present invention to provide for biologically active fragments and/or mutants of the human MC-R1B proteins disclosed herein, including but not necessarily limited to amino acid substitutions, deletions, additions, amino terminal truncations and carboxy-terminal truncations such that these mutations provide for proteins or protein fragments of diagnostic, therapeutic or prophylactic use.

[0032] It is also an object of the present invention to provide for MC-R1B-based assays to select for modulators of this receptor protein. These assays are preferably cell based assays whereby a DNA molecule encoding MC-R1B is transfected or transformed into a host cell tested wherein this recombinant host cell is allowed to grow for a time sufficient to express MC-R1B prior to use in various assays described herein.

[0033] Alternatively, an assay utilizing substantially purified membrane fractions from such a transfected host cell with a DNA vector encoding the MC-R1B protein, such that binding of test compounds in relation to a known MC-R1B ligand may be tested. To this end, it is a further object to provide for membrane preparations from host cells transfected or transformed with a DNA molecule encoding MC-R1B for use in assays to select for modulators of MC-R1B activity.

[0034] It is also an object of the present invention to provide for MC-R1B-based in-frame fusion constructions, methods of expressing these fusion constructs, biological equivalents disclosed herein, related assays, recombinant cells expressing these constructs, and agonistic and/or antagonistic compounds identified through the use of the nucleic acid encoding vertebrate MC-R1B protein as well as the expressed protein.

[0035] As used herein, "MC-R1 splice variants" and/or "MC-R1B splice variants", refers to a nucleic acid molecule which encodes a protein with melanocortin-1 receptor activity which comprises a 3' exon segment which encodes a 65 amino acid COOH-terminal extension identified in SEQ ID NO:27. Such nucleic acid molecules include but are not limited to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:18; SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:24, and SEQ ID NO:25.

[0036] As used herein, "MC-R1B" and/or "MC-R1 splice variant proteins" refers to the proteins translated from the MC-R1 splice variant nucleic acid molecules disclosed herein. These human MC-R1B proteins include but are not limited to SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:17, SEQ ID NO:20, SEQ ID NO:23, and SEQ ID NO:26.

[0037] As used herein, "GPCR"' refers to -- G-protein coupled receptor --.

[0038] The terms "isolated" and "purified" are used interchangeably to denote a nucleic acid, protein, membrane fraction and such which is substantially free from other like components.

[0039] Whenever used herein, the term "mammalian host" will refer to any mammal, including a human being.

BRIEF DECRIPTION OF THE FIGURES

[0040]

. Figure 1 shows a schematic representation of the human MC-R1 sequences. MC-RIMO (GenBank Accession #

X65634) and MC-R1CH (GenBank Accession # X67594) are also referred to herein as MC-R1A genes. The nucleotide sequence of mc1-8 (including a single intron) is disclosed in SEQ ID NO:21. The depicted ESTs are described in Example Section 1.

- Figure 2 shows the alternative splicing of the human MC-R1 gene. The MC-R1 A cDNA is as known in the art. The MC-R1 gene intron junctions are as shown, for example, in SEQ ID NO:21 (mc1-8). The MC-R1B cDNA shows the additional exon at the 3' end of the gene, which encodes a 65 amino acid extension, beginning with the Ser residue at amino acid 318. MC-R1A contains a Trp-317 residue while MC-R1B contains a Cys-317 residue. The dark boxes for MC-R1A and MC-R1B represent portions of the cDNA which encode transmembrane domains, while the dark boxes of the MC-R1 gene represent the two exons which encode for the MCR1B protein(s).
- Figure 3 shows the DNA sequence of the genomic clone, mc1-8 (SEQ ID NO:21). Large cap letters represent exon regions while small cap nucleotides represent the single intron of the MC-R1 gene.
- Figures 4A - 4B show the DNA and deduced amino acid sequence of the mc 1-8 genomic clone as a form A (SEQ ID Nos: 45 and 46) and form B (SEQ ID NOs: 21 and 23), illustrating spliced forms MCR1-A and MC-R1B.
- Figures 5A - 5F show the clustal alignment of amino acid sequences of various human MC-R1A and MCR1B clones.

DETAILED DESCRIPTION OF THE INVENTION

[0041] The present invention relates to isolated nucleic acid molecules (polynucleotide) which encode human melanocortin-1 receptor variant proteins referred to as MC-R1B proteins. The nucleic acid molecules of the present invention are substantially free from other nucleic acids. For most cloning purposes, DNA is a preferred nucleic acid.

[0042] The present invention relates to a series of isolated nucleic acid molecules (polynucleotide) which encodes mRNA which express novel splice variants of MC-R1, referred to as MC-R1B proteins. These DNA molecules comprise nucleotide sequences disclosed below.

- 1. MC-R1ESTc11

ATGGCTGTGC AGGGATCCCA GAGAAGACTT CTGGGCTCCC TCAACTCCAC CCCCACAGCC
ATCCCCCAGC TGGGGCTGGC TGCCAACCAG ACAGGAGCCC GGTGCCTGGA GGTGTCCATC
TCTGACGGGC TCTTCCTCAG CCTGGGGCTG GTGAGCTTGG TGGAGAACGC GCTGGTGGTG
GCCACCATCG CCAAGAACCG GAACCTGCAC TCACCCATGT ACTGCTTCAT CTGCTGCCTG
GCCTTGTCGG ACCTGCTGGT GAGCGGGAGC AACGTGCTGG AGACGGCCGT CATCCTCCTG
CTGGAGGCCG GTGCACTGGT GGCCCGGGCT GCGGTGCTGC AGCAGCTGGA CAATGTCATT
GACGTGATCA CCTGCAGCTC CATGCTGTCC AGCCTCTGCT TCCTGGGCGC CATCGCCGTG
GACCGCTACA TCTCCATCTT CTACGCACTG CGTTACCACA GCATCGTGAC CCTGCCGCGG
GCGCGGCAAG CCGTTGCGGC CATCTGGGTG GCCAGTGTCG TCTTCAGCAC GCTCTTCATC
GCCTACTACG ACCACGTGGC CGTCCTGCTG TGCCTCGTGG TCTTCTTCCT GGCTATGCTG
GTGCTCATGG CCGTGCTGTA CGTCCACATG CTGGCCCGGG CCTGCCAGCA CGCCCAGGGC
ATCGCCCGGC TCCACAAGAG GCAGCGCCCG GTCCACCAGG GCTTTGGCCT TAAAGGCGCT
GTCACCCTCA CCATCCTGCT GGGCATTTTC TTCCTCTGCT GGGGCCCCTT CTTCCTGCAT
CTCACACTCA TCGTCCTCTG CCCCGAGCAC CCCACGTGCG GCTGCATCTT CAAGAACTTC
AACCTCTTTC TCGCCCTCAT CATCTGCAAT GCCATCATCG ACCCCCTCAT CTACGCCTTC
CACAGCCAGG AGCTCCGCAG GACGCTCAAG GAGGTGCTGA CATGCTCCTG CTCTCAGGAC
CGTGCCCTCG TCAGCTGGGA TGTGAAGTCT CTGGGTGGAA GTGTGTGCCA AGAGCTACTC
CCACAGCAGC CCCAGGAGAA GGGGCCTTGT GACCAGAAAG CTTCATCCAC AGCCTTGCAG
CGGCTCCTGC AAAAGGAGGT GAAATCCCTG CCTCAGGCCA AGGGACCAGG TTTGCAGGAG
CCCCCCTAG (SEQ ID NO:1);

. 2. MC-R1ESTC11.6

ATGGCTGTGC AGGGATCCCA GAGAAGACTT CTGGGCTCCC TCAACTCCAC CCCCACAGCC
ATCCCCCAGC TGGGGCTGGC TGCCAACCAG ACAGGAGCCC GGTGCCTGGA GGTGTCCATC
TCTGACGGGC TCTTCCTCAG CCTGGGGCTG GTGAGCTTGG TGGAGAACGC GCTGGTGGTG
GCCACCATCG CCAAGAACCG GAACCTGCAC TCACCCATGT ACTGCTTCAT CTGCTGCCTG
GCCTTGTCGG ACCTGCTGGT GAGCGGGAGC AACGTGCTGG AGACGGCCGT CATCCTCCTG
CTGGAGGCCG GTGCACTGGT GGCCCGGGCT GCGGTGCTGC AGCAGCTGGA CAATGTCATT
GACGTGATCA CCTGCAGCTC CATGCTGTCC AGCCTCTGCT TCCTGGGCGC CATCGCCGTG

GACCGCTACA TCTCCATCTT CTACGCACTG CGTTACCACA GCATCGTGAC CCTGCCGCGG
GCGCGGCAAG CCGTTGCGGC CATCTGGGTG GCCAGTGTCG TCTTCAGCAC GCTCTTCATC
GCCTACTACG ACCACGTGGC CGTCCTGCTG TGCCTCGTGG TCTTCTTCCT GGCTATGCTG
GTGCTCATGG CCGTGCTGTA CGTCCACATG CTGGCCCGGG CCTGCCAGCA CGCCCAGGGC
ATCGCCCGGC TCCACAAGAG GCAGCGCCCG GTCCACCAGG GCTTTGGCCT TAAAGGCGCT
GTCACCCTCA CCATCCTGCT GGGCATTTTC TTCCTCTGCT GGGGCCCCTT CTTCCTGCAT
CTCACACTCA TCGTCCTCTG CCCCGAGCAC CCCACGTGCG GCTGCATCTT CAAGAACTTC
AACCTCTTTC TCGCCCTCAT CATCTGCAAT GCCATCATCG ACCCCCTCAT CTACGCCTTC
CACAGCCAGG AGCTCCGCAG GACGCTCAAG GAGGTGCTGA CATGCTCCTG CTCTCAGGAC
CGTGCCCTCG TCAGCTGGGA TGTGAAGTCT CTGGGTGGAA GTGTGTGCCA AGAGCTACTC
CCACAGCAGC CCCAGGAGAA GGGGCTTTGT GACCAGAAAG CTTCATCCAC AGCCTTGCAG
CGGCTCCTGC AAAAGGAGGT GAAATCCCTG CCTCAGGCCA AGGGACCAGG TTTGCAGGAG
CCCCCCTAG (SEQ ID NO:3);

. 3. MC-R1ESTc12

ATGGCTGTGC AGGGATCCCA GAGAAGACTT CTGGGCTCCC TCAACTCCAC CCCCACAGCC
ATCCCCCAGC TGGGGCTGGC TGCCAACCAG ACAGGAGCCC GGTGCCTGGA GGTGTCCATC
TCTGACGGGC TCTTCCTCAG CCTGGGGCTG GTGAGCTTGG TGAAGAACGC GCTGGTGGTG
GCCACCATCG CCAAGAACCG GAACCTGCAC TCACCCATGT ACTGCTTCAT CTGCTGCCTG
GCCTTGTCGG ACCTGCTGGT GAGCGGGAGC AACGTGCTGG AGACGGCCGT CATCCTCCTG
CTGGAGGCCG GTGCACTGGT GGCCCGGGCT GCGGTGCTGC AGCAGCTGGA CAATGTCATT
GACGTGATCA CCTGCAGCTC CATGCTGTCC AGCCTCTGCT TCCTGGGCGC CATCGCCGTG
GACCGCTACA TCTCCATCTT CTACGCACTG CGCTACCACA GCATCGTGAC CCTGCCGCGG
GCGCGGCAAG CCGTTGCGGC CATCTGGGTG GCCAGTGTCG TCTTCAGCAC GCTCTTCATC
GCCTACTACG ACCACGTGGC CGTCCTGCTG TGCCTCGTGG TCTTCTTCCT GGCTATGCTG
GTGCTCATGG CCGTGCTGTA CGTCCACATG CTGGCCCGGG CCTGCCAGCA CGCCCAGGGC
ATCGCCCGGC TCCACAAGAG GCAGCGCCCG GTCCACCAGG GCTTTGGCCT TAAAGGCGCT
GTCACCCTCA CCATCCTGCT GGGCATTTTC TTCCTCTGCT GGGGCCCCTT CTTCCTGCAT
CTCACACTCA TCGTCCTCTG CCCCGAGCAC CCCACGTGCG GCTGCATCTT CAAGAACTTC
AACCTCTTTC TCGCCCTCAT CATCTGCAAT GCCATCATCG ACCCCCTCAT CTACGCCTTC
CACAGCCAGG AGCTCCGCAG GACGCTCAAG GAGGTGCTGA CATGCTCCTG CTCTCAGGAC
CGTGCCCTCG TCAGCTGGGA TGTGAAGTCT CTGGGTGGAA GTGTGTGCCA AGAGCTACTC
CCACAGCAGC CCCAGGAGAA GGGGCTTTGT GACCAGAAAG CTTCATCCAC AGCCTTGCAG

CGGCTCCTGC AAAAGGAGGT GAAATCCCTG CCTCAGGCCA AGGGACCAGG TTTGCAGGAG
CCCCCCTAG (SEQ ID NO:5);

4. MC-R1ESTc2

ATGGCTGTGC AGGGATCCCA GAGAAGACTT CTGGGCTCCC TCAACTCCAC CCCCACAGCC
ATCCCCCAGC TGGGGCTGGC TGCCAACCAG ACAGGAGCCC GGTGCCTGGA GGTGTCCATC
TCTGACGGGC TCTTCCTCAG CCTGGGGCTG GTGAGCTTGG TGGAGAACGC GCTGGTGGTG
GCCACCATCG CCAAGAACCG GAACCTGCAC TCACCCATGT ACTGCTTCAT CTGCTGCCTG
GCCTTGTCGG ACCTGCTGGT GAGCGGGAGC AACGTGCTGG AGACGGCCGT CATCCTCCTG
CTGGAGGCCG GTGCACTGGT GGCCCGGGCT GCGGTGCTGC AGCAGCTGGA CAATGTCATT
GACGTGATCA CCTGCAGCTT CATGCTGTCC AGCCTCTGCT TCCTGGGCGC CATCGCCGTG
GACCGCTACA TCTCCATCTT CTACGCACTG TGCTACCACA GCATCGTGAC CCTGCCGCGG
GCGCGGCGAG CCGTTGCGGC CATCTGGGTG GCCAGTGTCG TCTTCAGCAC GCTCTTCATC
GCCTACTACG ACCACGTGGC CGTCCTGCTG TGCCTCGTGG TCTTCTTCCT GGCTATGCTG
GTGCTCATGG CCGTGCTGTA CGTCCACATG CTGGCCCGGG CCTGCCAGCA CGCCCAGGGC
ATCGCCCGGC TCCACAAGAG GCAGCGCCCG GTCCACCAGG GCTTTGGCCT TAAAGGCGCT
GTCACCCTCA CCATCCTGCT GGGCATTTTC TTCCTCTGCT GGGGCCCCTT CTTCCTGCAT
CTCACACTCA TCGTCCTCTG CCCCGAGCAC CCCACGTGCG GCTGCATCTT CAAGAACTTC
AACCTCTTTC TCGCCCTCAT CATCTGCAAT GCCATCATCG ACCCCCTCAT CTACGCCTTC
CACAGCCAGG AGCTCCGCAG GACGCTCAAG GAGGTGCTGA CATGCTCCTG CTCTCAGGAC
CGTGCCCTCG TCAGCTGGGA TGTGAAGTCT CTGGGTGGAA GTGTGTGCCA AGAGCTACTC
CCACAGCAGC CCCAGGAGAA GGGGCTTTGT GACCAGAAAG CTTCATCCAC AGCCTTGCAG
CGGCTCCTGC AAAAGGAGGT GAAATCCCTG CCTCAGGCCA AGGGACCAGG TTTGCAGGAG
CCCCCCTAG (SEQ ID NO:7);

. 5. MC R1ESTc4

ATGGCTGTGC AGGGATCCCA GAGAAGACTT CTGGGCTCCC TCAACTCCAC CCCCACAGCC
ATCCCCCAGC TGGGGCTGGC TGCCAACCAG ACAGGAGCCC GGTGCCTGGA GGTGTCCATC
TCTGACGGGC TCTTCCTCAG CCTGGGGCTG GTGAGCTTGG TGGAGAACGC GCTGGTGGTG
GCCACCATCG CCAAGAACCG GAACCTGCAC TCACCCATGT ACTGCTTCAT CTGCTGCCTG
GCCTTGTCGG ACCTGCTGGT GAGCGGGAGC AACGTGCTGG AGACGGCCGT CATCCTCCTG
CTGGAGGCCG GTGCACTGGT GGCCCGGGCT GCGGTGCTGC AGCAGCTGGA CAATGTCATT
GACGTGATCA CCTGCAGCTC CATGCTGTCC AGCCTCTGCT TCCTGGGCGC CATCGCCGTG
GACCGCTACA TCTCCATCTT CTACGCACTG CGCTACCACA GCATCGTGAC CCTGCCGCGG

GCGCGGCGAG CCGTTGCGGC CATCTGGGTG GCCAGTGTCG TCTTCAGCAC GCTCTTCATC
GCCTACTACG ACCACGCGGC CGTCCTGCTG TGCCTCGTGG TCTTCTTCCT GGCTATGCTG
GTGCTCATGG CCGTGCTGTA CGTCCACATG CTGGCCCGGG CCTGCCAGCA CGCCCAGGGC
ATCGCCCGGC TCCACAAGAG GCAGCGCCCG GTCCACCAGG GCTTTGGCCT TAAAGGCGCT
GTCACCCTCA CCATCCTGCT GGGCATTTTC TTCCTCTGCT GGGGCCCCTT CTTCCTGCAT
CTCACACTCA TCGTCCTCTG CCCCGAGCAC CCCACGTGCG GCTGCATCTT CAAGAACTTC
AACCTCTTTC TCGCCCTCAT CATCTGCAAT GCCATCATCG ACCCCCTCAT CTACGCCTTC
CACAGCCAGG AGCTCCGCAG GACGCTCAAG GAGGTGCTGA CATGCTCCTG CTCTCAGGAC
CGTGCCCTCG TCAGCTGGGA TGTGAAGTCT CTGGGTGGAA GTGTGTGCCA AGAGCGACTC
CCACAGCAGC CCCAGGAGAA GGGGCTTTGT GACCAGAAAG CTTCATCCAC AGCCTTGCAG
CGGCTCCTGC AAAAGGGGGT GAAATCCCTG CCTCAGGCCA AGGGACCAGG TTTGCAGGAG
CCCCCCTAG (SEQ ID NO:9);

. 6. MC-R1ESTc5

ATGGCTGTGC AGGGATCCCA GAGAAGACTT CTGGGCTCCC TCAACTCCAC CCCCACAGCC
ATCCCCCAGC TGGGGCTGGC TGCCAACCAG ACAGGAGCCC GGTGCCTGGA GGTGTCCATC
TCTGACGGGC TCTTCCTCAG CCTGGGGCTG GTGAGCTTGG TGAAGAACGC GCTGGTGGTG
GCCACCATCG CCAAGAACCG GAACCTGCAC TCACCCATGT ACTGCTTCAT CTGCTGCCTG
GCCTTGTCGG ACCTGCTGGT GAGCGGGAGC AACGTGCTGG AGACGGCCGT CATCCTCCTG
CTGGAGGCCG GTGCACTGGT GGCCCGGGCT GCGGTGCTGC AGCAGCTGGA CAATGTCATT
GACGTGATCA CCTGCAGCTC CATGCTGTCC AGCCTCTGCT TCCTGGGCGC CATCGCCGTG
GACCGCTACA TCTCCATCTT CTACGCACTG CGCTACCACA GCATCGTGAC CCTGCCGCGG
GCGCGGCAAG CCGTTGCGGC CATCTGGGTG GCCAGTGTCG TCTTCAGCAC GCTCTTCATC
GCCTACTACG ACCACGTGGC CGTCCTGCTG TGCCTCGTGG TCTTCTTCCT GGCTATGCTG
GTGCTCATGG CCGTGCTGTA CGTCCACATG CTGGCCCGGG CCTGCCAGCA CGCCCAGGGC
ATCGCCCGGC TCCACAAGAG GCAGCGCCCG GTCCACCAGG GCTTTGGCCT TAAAGGCGCT
GTCACCCTCA CCATCCTGCT GGGCATTTTC TTCCTCTGCT GGGGCCCCTT CTTCCTGCAT
CTCACACTCA TCGTCCTCTG CCCCGAGCAC CCCACGTGCG GCTGCATCTT CAAGAACTTC
AACCTCTTTC TCGCCCTCAT CATCTGCAAT GCCATCATCG ACCCCCTCAT CTACGCCTTC
CACAGCCAGG AGCTCCGCAG GACGCTCAAG GAGGTGCTGA CATGCTCCTG CTCTCAGGAC
CGTGCCCTCG TCAGCTGGGA TGTGAAGTCT CTGGGTGGAA GTGTGTGCCA AGAGCTACTC
CCACAGCAGC CCCAGGAGAA GGGGCTTTGT GACCAGAAAG CTTCATCCAC AGCCTTGCAG
CGGCTCCTGC AAAAGGAGGT GAAATCCCTG CCTCAGGCCA AGGGACCAGG TTTGCAGGAG
CCCCCCTAG (SEQ ID NO:11);

. 7. MC-RIESTc6

ATGGCTGTGC AGGGATCCCA GAGAAGACTT CTGGGCTCCC TCAACTCCAC CCCCACAGCC
ATCCCCCAGC TGGGGCTGGC TGCCAACCAG ACAGGAGCCC GGTGCCTGGA GGTGTCCATC
TCTGACGGGC TCTTCCTCAG CCTGGGGCTG GTGAGCTTGG TGAAGAACGC GCTGGTGGTG
GCCACCATCG CCAAGAACCG GAACCTGCAC TCACCCATGT ACTGCTTCAT CTGCTGCCTG
GCCTTGTCGG ACCTGCTGGT GAGCGGGAGC AACGTGCTGG AGACGGCCGT CATCCTCCTG
CTGGAGGCCG GTGCACTGGT GGCCCGGGCT GCGGTGCTGC AGCAGCTGGA CAATGTCATT
GACGTGATCA CCTGCAGCTC CATGCTGTCC AGCCTCTGCT TCCTGGGCGC CATCGCCGTG
GACCGCTACA TCTCCATCTT CTACGCACTG CGCTACCACA GCATCGTGAC CCTGCCGCGG
GCGCGGCAAG CCGTTGCGGC CATCTGGGTG GCCAGTGTCG TCTTCAGCAC GCTCTTCATC
GCCTACTACG ACCACGTGGC CGTCCTGCTG TGCCTCGTGG TCTTCTTCCT GGCTATGCTG
GTGCTCATGG CCGTGCTGTA CGTCCACATG CTGGCCCGGG CCTGCCAGCA CGCCCAGGGC
ATCGCCCGGC TCCACAAGAG GCAGCGCCCG GTCCACCAGG GCTTTGGCCT TAAAGGCGCT
GTCACCCTCA CCATCCTGCT GGGCATTTTC TTCCTCTGCT GGGGCCCCTT CTTCCTGCAT
CTCACACTCA TCGTCCTCTG CCCCGAGCAC CCCACGTGCG GCTGCATCTT CAAGAACTTC
AACCTCTTTC TCGCCCTCAT CATCTGCAAT GCCATCATCG ACCCCCTCAT CTACGCCTTC
CACAGCCAGG AGCTCCGCAG GACGCTCAAG GAGGTGCTGA CATGCTCCTG CTCTCAGGAC
CGTGCCCTCG TCAGCTGGGA TGTGAAGTCT CTGGGTGGAA GTGTGTGCCA AGAGCTACTC
CCACAGCAGC CCCAGGAGAA GGGGCTTTGT GACCAGAAAG CTTCATCCAC AGCCTTGCAG
CGGCTCCTGC AAAAGGAGGT GAAATCCCTG CCTCAGGCCA AGGGACCAGG TTTGCAGGAG
CCCCCCTAG (SEQ ID NO:13);

8. mc1-3 (genomic)

ATGGCTGTGC AGGGATCCCA GAGAAGACTT CTGGGCTCCC TCAACTCCAC CCCCACAGCC
ATCCCCCAGC TGGGGCTGGC TGCCAACCAG ACAGGAGCCC GGTGCCTGGA GGTGTCCATC
TCTGACGGGC TCTTCCTCAG CCTGGGGCTG GTGAGCTTGG TGGAGAACGC GCTGGTGGTG
GCCACCATCG CCAAGAACCG GAACCTGCAC TCACCCATGT ACTGCTTCAT CTGCTGCCTG
GCCTTGTCGG ACCTGCTGGT GAGCGGGAGC AACGTGCTGG AGACGGCCGT CATCCTCCTG
CTGGAGGCCG GTGCACTGGT GGCCCAGGCT GCGGTGCTGC AGCAGCTGGA CAATGTCATT
GACGTGATCA CCTGCAGCTC CATGCTGTCC AGCCTCTGCT TCCTGGGCGC CATCGCCGCG
GACCGCTACA TCTCCATCTT CTACGCACTG CGCTACCACA GCATCGTGAC CCTGCCGCGG
GCGCGGCGAG CCGTTGCGGC CATCTGGGTG GCCAGTGTCG TCTTCAGCAC GCTCTTCATC
GCCTACTACG ACCACGTGGC CGTCCTGCTG TGCCTCGTGG TCTTCTTCCT GGCTATGCTG

GTGCTCATGG CCGTGCTGTA CGTCCACATG CTGGCCCGGG CCTGCCAGCA CGCCCAGGGC
ATCGCCCGGC TCCACAAGAG GCAGCGCCCG GTCCACCAGG GCTTTGGCCT TAAAGGCGCT
GTCACCCTCA CCATCCTGCT GGGCATTTTC TTCCTCTGCT GGGGCCCCTT CTTCCTGCAT
CTCACACTCA TCGTCCTCTG CCCCGAGCAC CCCACGTGCG GCTGCATCTT CAAGAACTTC
AACCTCTTTC TCGCCCTCAT CATCTGCAAT GCCATCATCG ACCCCCTCAT CTACGCCTTC
CACAGCCAGG AGCTCCGCAG GACGCTCAAG GAGGTGCTGA CATGCTCCTG gtgagcgcgg
tgcacgcggc tttaagtgtg ctgggcagag ggaggtggtg atattgtgtg gtctggttcc
tgtgtgaccc tgggcagttc cttacctccc tggtccccgt ttgtcaaaga ggatggacta
aatgatctct gaangtgttg aagcgcggac ccttctgggt ccagggaggg gtccctgcaa
aactccaggc aggacttctc accagcagtc gtggggaacg gaggaggaca tggggaggtt
gtggggcctc aggctccggg caccaggggc caacctcagg ctcctaaaga gacattttcc
gcccactcct gggacactcc gtctgctcca atgactgagc agcatccacc ccaccccatc
tttgctgcca gCTCTCAGGA CCGTGCCCTC GTCAGCTGGG ATGTGAAGTC TCTGGGTGGA
AGTGTGTGCC AAGAGCTACT CCCACAGCAG CCCCAGGAGA AGGGGCTTTG TGACCAGAAA
GCTTCATCCA CAGCCTTGCA GCGGCTCCTG CAAAAGGAGG TGAAATCCCT GCCTCAGGCC
AAGGGACCAG GTTTGCAGGA GCCCCCCTAG (SEQ ID NO:15);

9. mc1-3 (open reading frame)

ATGGCTGTGC AGGGATCCCA GAGAAGACTT CTGGGCTCCC TCAACTCCAC CCCCACAGCC
ATCCCCCAGC TGGGGCTGGC TGCCAACCAG ACAGGAGCCC GGTGCCTGGA GGTGTCCATC
TCTGACGGGC TCTTCCTCAG CCTGGGGCTG GTGAGCTTGG TGGAGAACGC GCTGGTGGTG
GCCACCATCG CCAAGAACCG GAACCTGCAC TCACCCATGT ACTGCTTCAT CTGCTGCCTG
GCCTTGTCGG ACCTGCTGGT GAGCGGGAGC AACGTGCTGG AGACGGCCGT CATCCTCCTG
CTGGAGGCCG GTGCACTGGT GGCCCAGGCT GCGGTGCTGC AGCAGCTGGA CAATGTCATT
GACGTGATCA CCTGCAGCTC CATGCTGTCC AGCCTCTGCT TCCTGGGCGC CATCGCCGCG
GACCGCTACA TCTCCATCTT CTACGCACTG CGCTACCACA GCATCGTGAC CCTGCCGCGG
GCGCGGCGAG CCGTTGCGGC CATCTGGGTG GCCAGTGTCG TCTTCAGCAC GCTCTTCATC
GCCTACTACG ACCACGTGGC CGTCCTGCTG TGCCTCGTGG TCTTCTTCCT GGCTATGCTG
GTGCTCATGG CCGTGCTGTA CGTCCACATG CTGGCCCGGG CCTGCCAGCA CGCCCAGGGC
ATCGCCCGGC TCCACAAGAG GCAGCGCCCG GTCCACCAGG GCTTTGGCCT TAAAGGCGCT
GTCACCCTCA CCATCCTGCT GGGCATTTTC TTCCTCTGCT GGGGCCCCTT CTTCCTGCAT
CTCACACTCA TCGTCCTCTG CCCCGAGCAC CCCACGTGCG GCTGCATCTT CAAGAACTTC
AACCTCTTTC TCGCCCTCAT CATCTGCAAT GCCATCATCG ACCCCCTCAT CTACGCCTTC
CACAGCCAGG AGCTCCGCAG GACGCTCAAG GAGGTGCTGA CATGCTCCTG CTCTCAGGAC

CGTGCCCTCG TCAGCTGGGA TGTGAAGTCT CTGGGTGGAA GTGTGTGCCA AGAGCTACTC
CCACAGCAGC CCCAGGAGAA GGGGCTTTGT GACCAGAAAG CTTCATCCAC AGCCTTGCAG
CGGCTCCTGC AAAAGGAGGT GAAATCCCTG CCTCAGGCCA AGGGACCAGG TTTGCAGGAG
CCCCCCTAG (SEQ ID NO:17);

. 10. mc1-6 (genomic)

ATGGCTGTGC AGGGATCCCA GAGAAGACTT CTGGGCTCCC TCAACTCCAC CCCCACAGCC
ATCCCCCAGC TGGGGCTGGC TGCCAACCAG ACAGGAGCCC GGTGCCTGGA GGTGTCCATC
TCTGACGGGC TCTTCCTCAG CCTGGGGCTG GTGAGCTTGG TGGAGAACGC GCTGGTGGTG
GCCACCATCG CCAAGAACCG GAACCTGCAC TCACCCATGT ACTGCTTCAT CTGCTGCCTG
GCCTTGTCGG ACCTGCTGGT GAGCGGGAGC AACGTGCTGG AGACGGCCGT CATCCTCCTG
CTGGAGGCCG GTGCACTGGT GGCCCGGGCT GCGGTGCTGC AGCAGCTGGA CAATGTCATT
GACGTGATCA CCTGCAGCTC CATGCTGTCC AGCCTCTGCT TCCTGGGCGC CATCGCCGTG
GACCGCTACA TCTCCATCTT CTACGCACTG CGCTACCACA GCATCGTGAC CCTGCCGCGG
GCGCGGCGAG CCGTTGCGGC CCTCTGGGTG GCCAGTGTCG TCTTCAGCAC GCTCTTCATC
GCCTACTACG ACCACGTGGC CGTCCTGCTG TGCCTCGTGG TCTTCTTCCT GGCTATGCTG
GTGCTCATGG CCGTGCTGTA CGTCCACATG CTGGCCCGGG CCTGCCAGCA CGCCCAGGGC
ATCGCCCGGC TCCACAAGAG GCAGCGCCCG GTCCACCAGG GCTTTGGCCT TAAAGGCGCT
GTCACCCCCA CCATCCTGCT GGGCATTTTC TTCCTCTGCT GGGGCCCCTT CTTCCTGCAT
CTCACACTCA TCGTCCTCTG CCCCGAGCAC CCCACGTGCG GCTGCATCTT CAAGAACTTC
AACCTCTTTC TCGCCCTCAT CATCTGCAAT GCCTTCATCG ACCCCCTCAT CTACGCCTTC
CACAGCCAGG AGCTCCGCAG GACGCTCAAG GAGGTGCTGA CATGCTCCTG CATGCTCCTG
gtgagcgcgg tgcacgcggc tttaagtgtg ctgggcagag ggaggtggtg atattgtgtg
gtctggttcc tgtgtgaccc tgggcagttc cttacctccc tggtccccgt ttgtcaaaga
ggatggacta aatgatctct gaangtgttg aagcgcggac ccttctgggt ccagggaggg
gtccctgcaa aactccaggc aggacttctc accagcagtc gtggggaacg gaggaggaca
tggggaggtt gtggggcctc aggctccggg caccaggggc caacctcagg ctcctaaaga
gacattttcc gcccactcct gggacactcc gtctgctcca atgactgagc agcatccacc
ccaccccatc tttgctgcca gCTCTCAGGA CCGTGCCCTC GTCAGCTGGG ATGTGAAGTC
TCTGGGTGGA AGTGTGTGCC AAGAGCTACT CCCACAGCAG CCCCAGGAGA AGGGGCTTTG
TGACCAGAAA GCTTCATCCA CAGCCTTGCA GCGGCTCCTG CAAAAGGAGG TGAAATCCCT
GCCTCAGGCC AAGGGACCAG GTTTGCAGGA GCCCCCCTAG (SEQ ID NO:18);

. 11. mc1-6 (open reading frame)

ATGGCTGTGC AGGGATCCCA GAGAAGACTT CTGGGCTCCC TCAACTCCAC CCCCACAGCC
ATCCCCCAGC TGGGGCTGGC TGCCAACCAG ACAGGAGCCC GGTGCCTGGA GGTGTCCATC
TCTGACGGGC TCTTCCTCAG CCTGGGGCTG GTGAGCTTGG TGGAGAACGC GCTGGTGGTG
GCCACCATCG CCAAGAACCG GAACCTGCAC TCACCCATGT ACTGCTTCAT CTGCTGCCTG
GCCTTGTCGG ACCTGCTGGT GAGCGGGAGC AACGTGCTGG AGACGGCCGT CATCCTCCTG
CTGGAGGCCG GTGCACTGGT GGCCCGGGCT GCGGTGCTGC AGCAGCTGGA CAATGTCATT
GACGTGATCA CCTGCAGCTC CATGCTGTCC AGCCTCTGCT TCCTGGGCGC CATCGCCGTG
GACCGCTACA TCTCCATCTT CTACGCACTG CGCTACCACA GCATCGTGAC CCTGCCGCGG
GCGCGGCGAG CCGTTGCGGC CCTCTGGGTG GCCAGTGTCG TCTTCAGCAC GCTCTTCATC
GCCTACTACG ACCACGTGGC CGTCCTGCTG TGCCTCGTGG TCTTCTTCCT GGCTATGCTG
GTGCTCATGG CCGTGCTGTA CGTCCACATG CTGGCCCGGG CCTGCCAGCA CGCCCAGGGC
ATCGCCCGGC TCCACAAGAG GCAGCGCCCG GTCCACCAGG GCTTTGGCCT TAAAGGCGCT
GTCACCCCCA CCATCCTGCT GGGCATTTTC TTCCTCTGCT GGGGCCCCTT CTTCCTGCAT
CTCACACTCA TCGTCCTCTG CCCCGAGCAC CCCACGTGCG GCTGCATCTT CAAGAACTTC
AACCTCTTTC TCGCCCTCAT CATCTGCAAT GCCTTCATCG ACCCCCTCAT CTACGCCTTC
CACAGCCAGG AGCTCCGCAG GACGCTCAAG GAGGTGCTGA CATGCTCCTG CTCTCAGGAC
CGTGCCCTCG TCAGCTGGGA TGTGAAGTCT CTGGGTGGAA GTGTGTGCCA AGAGCTACTC
CCACAGCAGC CCCAGGAGAA GGGGCTTTGT GACCAGAAAG CTTCATCCAC AGCCTTGCAG
CGGCTCCTGC AAAAGGAGGT GAAATCCCTG CCTCAGGCCA AGGGACCAGG TTTGCAGGAG
CCCCCCTAG (SEQ ID NO:19);

. 12. mc1-8 (genomic)

ATGGCTGTGC AGGGATCCCA GAGAAGACTT CTGGGCTCCC TCAACTCCAC CCCCACAGCC
ATCCCCCAGC TGGGGCTGGC TGCCAACCAG ACAGGAGCCC GGTGCCTGGA GGTGTCCATC
TCTGACGGGC TCTTCCTCAG CCTGGGGCTG GTGAGCTTGG TGGAGAACGC GCTGGTGGTG
GCCACCATCG CCAAGAACCG GAACCTGCAC TCACCCATGT ACTGCTTCAT CTGCTGCCTG
GCCTTGTCGG ACCTGCTGGT GAGCGGGAGC AACGTGCTGG AGACGGCCGT CATCCTCCTG
CTGGAGGCCG GTGCACTGGT GGCCCGGGCT GCGGTGCTGC AGCAGCTGGA CAATGTCATT
GACGTGATCA CCTGCAGCTC CATGCTGTCC AGCCTCTGCT TCCTGGGCGC CATCGCCGTG
GACCGCTACA TCTCCATCTT CTACGCACTG CGCTACCACA GCATCGTGAC CCTGCCGCGG
GCGCGGCGAG CCGTTGCGGC CCTCTGGGTG GCCAGTGTCG TCTTCAGCAC GCTCTTCATC
GCCTACTACG ACCACGTGGC CGTCCTGCTG TGCCTCGTGG TCTTCTTCCT GGCTATGCTG
GTGCTCATGG CCGTGCTGTA CGTCCACATG CTGGCCCGGG CCTGCCAGCA CGCCCAGGGC
ATCGCCCGGC TCCACAAGAG GCAGCGCCCG GTCCACCAGG GCTTTGGCCT TAAAGGCGCT

GTCACCCCCA CCATCCTGCT GGGCATTTTC TTCCTCTGCT GGGGCCCCTT CTTCCTGCAT
CTCACACTCA TCGTCCTCTG CCCCGAGCAC CCCACGTGCG GCTGCATCTT CAAGAACTTC
AACCTCTTTC TCGCCCTCAT CATCTGCAAT GCCTTCATCG ACCCCCTCAT CTACGCCTTC
CACAGCCAGG AGCTCCGCAG GACGCTCAAG GAGGTGCTGA CATGCTCCTG gtgagcgcgg
tgcacgcggc tttaagtgtg ctgggcagag ggaggtggtg atattgtgtg gtctggttcc
tgtgtgaccc tgggcagttc cttacctccc tggtccccgt ttgtcaaaga ggatggacta
aatgatctct gaangtgttg aagcgcggac ccttctgggt ccagggaggg gtccctgcaa
aactccaggc aggacttctc accagcagtc gtggggaacg gaggaggaca tggggaggtt
gtggggcctc aggctccggg caccaggggc caacctcagg ctcctaaaga gacattttcc
gcccactcct gggacactcc gtctgctcca atgactgagc agcatccacc ccaccccatc
tttgctgcca gCTCTCAGGA CCGTGCCCTC GTCAGCTGGG ATGTGAAGTC TCTGGGTGGA
AGTGTGTGCC AAGAGCTACT CCCACAGCAG CCCCAGGAGA AGGGGCTTTG TGACCAGAAA
GCTTCATCCA CAGCCTTGCA GCGGCTCCTG CAAAAGGAGG TGAAATCCCT GCCTCAGGCC
AAGGGACCAG GTTTGCAGGA GCCCCCCTAG (SEQ ID NO:21);

. 13. mc1-8 (open reading frame)

ATGGCTGTGC AGGGATCCCA GAGAAGACTT CTGGGCTCCC TCAACTCCAC CCCCACAGCC
ATCCCCCAGC TGGGGCTGGC TGCCAACCAG ACAGGAGCCC GGTGCCTGGA GGTGTCCATC
TCTGACGGGC TCTTCCTCAG CCTGGGGCTG GTGAGCTTGG TGGAGAACGC GCTGGTGGTG
GCCACCATCG CCAAGAACCG GAACCTGCAC TCACCCATGT ACTGCTTCAT CTGCTGCCTG
GCCTTGTCGG ACCTGCTGGT GAGCGGGAGC AACGTGCTGG AGACGGCCGT CATCCTCCTG
CTGGAGGCCG GTGCACTGGT GGCCCGGGCT GCGGTGCTGC AGCAGCTGGA CAATGTCATT
GACGTGATCA CCTGCAGCTC CATGCTGTCC AGCCTCTGCT TCCTGGGCGC CATCGCCGTG
GACCGCTACA TCTCCATCTT CTACGCACTG CGCTACCACA GCATCGTGAC CCTGCCGCGG
GCGCGGCGAG CCGTTGCGGC CCTCTGGGTG GCCAGTGTCG TCTTCAGCAC GCTCTTCATC
GCCTACTACG ACCACGTGGC CGTCCTGCTG TGCCTCGTGG TCTTCTTCCT GGCTATGCTG
GTGCTCATGG CCGTGCTGTA CGTCCACATG CTGGCCCGGG CCTGCCAGCA CGCCCAGGGC
ATCGCCCGGC TCCACAAGAG GCAGCGCCCG GTCCACCAGG GCTTTGGCCT TAAAGGCGCT
GTCACCCCCA CCATCCTGCT GGGCATTTTC TTCCTCTGCT GGGGCCCCTT CTTCCTGCAT
CTCACACTCA TCGTCCTCTG CCCCGAGCAC CCCACGTGCG GCTGCATCTT CAAGAACTTC
AACCTCTTTC TCGCCCTCAT CATCTGCAAT GCCTTCATCG ACCCCCTCAT CTACGCCTTC
CACAGCCAGG AGCTCCGCAG GACGCTCAAG GAGGTGCTGA CATGCTCCTG CTCTCAGGAC
CGTGCCCTCG TCAGCTGGGA TGTGAAGTCT CTGGGTGGAA GTGTGTGCCA AGAGCTACTC
CCACAGCAGC CCCAGGAGAA GGGGCTTTGT GACCAGAAAG CTTCATCCAC AGCCTTGCAG

CGGCTCCTGC AAAAGGAGGT GAAATCCCTG CCTCAGGCCA AGGGACCAGG TTTGCAGGAG CCCCCCTAG (SEQ ID NO:22);

. 14. mc-1-9 (genomic)

ATGGCTGTGC AGGGATCCCA GAGAAGACTT CTGGGCTCCC TCAACTCCAC CCCCACAGCC
ATCCCCCAGC TGGGGCTGGC TGCCAACCAG ACAGGAGCCC GGTGCCTGGA GGTGTCCATC
TCTGACGGGC TCTTCCTCAG CCTGGGGCTG GTGAGCTTGG TGGAGAACGC GCTGGTGGTG
GCCACCATCG CCAAGAACCG GAACCTGCAC TCACCCATGT ACTGCTTCAT CTGCTGCCTG
GCCTTGTCGG ACCTGCTGGT GAGCGGGAGC AACGTGCTGG AGACGGCCGT CATCCTCCTG
CTGGAGGCCG GTGCACTGGT GGCCCGGGCT GCGGTGCTGC AGCAGCTGGA CAATGTCATT
GACGTGATCA CCTGCAGCTC CATGCTGTCC AGCCTCTGCT TCCTGGGCGC CGTCGCCGTG
GACCGCTACA TCTCCATCTT CTACGCACTG CGCTACCACA GCATCGTGAC CCTGCCGCGG
GCGCGGCAAG CCGTTGCGGC CATCTGGGTG GCCAGTGTCG TCTTCAGCAC GCTCTTCATC
GCCTACTACG ACCACGTGGC CGTCCTGCTG TGCCTCGTGG TCTTCTTCCT GGCTATGCTG
GTGCTCATGG CCGTGCTGTA CGTCCACATG CTGGCCCGGG CCTGCCAGCA CGCCCAGGGC
ATCGCCCGGC TCCACAAGAG GCAGCGCCCG GTCCACCAGG GCTTTGGCCT TAAAGGCGCT
GTCACCCTCA CCATCCTGCT GGGCATTTTC TTCCTCTGCT GGGGCCCCTT CTTCCTGCAT
CTCACACTCA TCGTCCTCTG CCCCGAGCAC CCCACGTGCG GCTGCATCTT CAAGAACTTC
AACCTCTTTC TCGCCCCCAT CATCTGCAAC GCCATCATCG ACCCCCTCAT CTACGCCTTC
CACAGCCAGG AGCTCCGCAG GACGCTCAAG GAGGTACTGA CATGCTCCTG CATGCTCCTG
gtgagcgcgg tgcacgcggc tttaagtgtg ctgggcagag ggaggtggtg atattgtgtg
gtctggttcc tgtgtgaccc tgggcagttc cttacctccc tggtccccgt ttgtcaaaga
ggatggacta aatgatctct gaangtgttg aagcgcggac ccttctgggt ccagggaggg
gtccctgcaa aactccaggc aggacttctc accagcagtc gtggggaacg gaggaggaca
tggggaggtt gtggggcctc aggctccggg caccaggggc caacctcagg ctcctaaaga
gacattttcc gcccactcct gggacactcc gtctgctcca atgactgagc agcatccacc
ccaccccatc tttgctgcca gCTCTCAGGA CCGTGCCCTC GTCAGCTGGG ATGTGAAGTC
TCTGGGTGGA AGTGTGTGCC AAGAGCTACT CCCACAGCAG CCCCAGGAGA AGGGGCTTTG
TGACCAGAAA GCTTCATCCA CAGCCTTGCA GCGGCTCCTG CAAAAGGAGG TGAAATCCCT
GCCTCAGGCC AAGGGACCAG GTTTGCAGGA GCCCCCCTAG (SEQ ID NO:24);

. 15. mc1-8 (open reading frame)

ATGGCTGTGC AGGGATCCCA GAGAAGACTT CTGGGCTCCC TCAACTCCAC CCCCACAGCC
ATCCCCCAGC TGGGGCTGGC TGCCAACCAG ACAGGAGCCC GGTGCCTGGA GGTGTCCATC

TCTGACGGGC TCTTCCTCAG CCTGGGGCTG GTGAGCTTGG TGGAGAACGC GCTGGTGGTG
GCCACCATCG CCAAGAACCG GAACCTGCAC TCACCCATGT ACTGCTTCAT CTGCTGCCTG
GCCTTGTCGG ACCTGCTGGT GAGCGGGAGC AACGTGCTGG AGACGGCCGT CATCCTCCTG
CTGGAGGCCG GTGCACTGGT GGCCCGGGCT GCGGTGCTGC AGCAGCTGGA CAATGTCATT
GACGTGATCA CCTGCAGCTC CATGCTGTCC AGCCTCTGCT TCCTGGGCGC CGTCGCCGTG
GACCGCTACA TCTCCATCTT CTACGCACTG CGCTACCACA GCATCGTGAC CCTGCCGCGG
GCGCGGCAAG CCGTTGCGGC CATCTGGGTG GCCAGTGTCG TCTTCAGCAC GCTCTTCATC
GCCTACTACG ACCACGTGGC CGTCCTGCTG TGCCTCGTGG TCTTCTTCCT GGCTATGCTG
GTGCTCATGG CCGTGCTGTA CGTCCACATG CTGGCCCGGG CCTGCCAGCA CGCCCAGGGC
ATCGCCCGGC TCCACAAGAG GCAGCGCCCG GTCCACCAGG GCTTTGGCCT TAAAGGCGCT
GTCACCCTCA CCATCCTGCT GGGCATTTTC TTCCTCTGCT GGGGCCCCTT CTTCCTGCAT
CTCACACTCA TCGTCCTCTG CCCCGAGCAC CCCACGTGCG GCTGCATCTT CAAGAACTTC
AACCTCTTTC TCGCCCCCAT CATCTGCAAC GCCATCATCG ACCCCCTCAT CTACGCCTTC
CACAGCCAGG AGCTCCGCAG GACGCTCAAG GAGGTACTGA CATGCTCCTG CTCTCAGGAC
CGTGCCCTCG TCAGCTGGGA TGTGAAGTCT CTGGGTGGAA GTGTGTGCCA AGAGCTACTC
CCACAGCAGC CCCAGGAGAA GGGGCTTTGT GACCAGAAAG CTTCATCCAC AGCCTTGCAG
CGGCTCCTGC AAAAGGAGGT GAAATCCCTG CCTCAGGCCA AGGGACCAGG TTTGCAGGAG
CCCCCCTAG (SEQ ID NO:25).

[0043] The above-exemplified isolated DNA molecules encode polymorphisms of human MC-R1B, clones comprising an open reading frame which encodes an additional 65 amino acids (from residue 318 to 382; SEQ ID NO:27), as well as a substitution of a Cys-317 residue for the Trp-317 residue of the MC-R1A protein. More specifically, SEQ ID NOs: 1, 3, 5, 7, 9, 11, and 13 represent cDNA clones which contain 1149 nucleotides, with an open reading frame nucleotide 1 to nucleotide 1146, with a "TAG" termination codon from nucleotides 1147-1149. These open reading frames encode a human MC-R1B protein 382 amino acids in length, as shown in Figures 5A - 5F and as set forth in SEQ ID NOs: 2, 4, 6, 8, 10, 12, and 14, respectively.

[0044] The present invention also relates to MC-R1B genomic clones, the predicted open reading frames for these clones and the MC-R1B protein translated from the respective mRNA molecule of each genomic clone. This specification exemplifies, but is not necessarily limited to, MC-R1 polymorphic variations as disclosed in mc1-3 (SEQ ID NO:15), mc1-6 (SEQ ID NO:18), mc1-6 (SEQ ID NO:21), mc1-9 (SEQ ID NO:24). These DNA molecules represent human MC-R1B genomic clones which contain 1530 nucleotides, with an intron from nucleotides 951-1331 (see Example Section 1). The respective open reading frame of each of these genomic clones is disclosed in SEQ ID NO: 16 (mc1-3), SEQ ID NO: 19 (mc1-6), SEQ ID NO: 22 (mc1-6), and SEQ ID NO: 25 (mc1-9). Each of these open reading frames encodes a putative protein comprising 382 amino acids as disclosed in SEQ ID NO: 17 (pro-mc1-3), SEQ ID NO: 20 (pro-mc1-6), SEQ ID NO: 23 (pro-mc1-6), and SEQ ID NO: 25 (pro-mc1-9).

[0045] The present invention also relates to biologically active fragments or mutants of MC-R1 splice variants which encodes mRNA expressing a novel human MC-R1B. Any such biologically active fragment and/or mutant of the MC-R1 splice variants disclosed herein will encode either a protein or protein fragment which at least substantially mimics the pharmacological properties of a wild-type MC-R1 protein and comprises at least a portion of the COOH terminal amino acid extension disclosed as SEQ ID NO:27. Any such polynucleotide includes but is not necessarily limited to nucleotide substitutions, deletions, additions, amino-terminal truncations and carboxy-terminal truncations such that these mutations encode mRNA which express a protein or protein fragment of diagnostic, therapeutic or prophylactic use and would be useful for screening for agonists and/or antagonists for MC-R1 function.

[0046] A preferred aspect of this portion of the present invention is set forth as SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:18; SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:24, and SEQ ID NO:25, human nucleic acid molecules which comprise the complete open reading frame for the MC-R1 proteins of the present invention.

[0047] The isolated nucleic acid molecules of the present invention may include a deoxyribonucleic acid molecule (DNA), such as genomic DNA and complementary DNA (cDNA), which may be single (coding or noncoding strand) or double stranded, as well as synthetic DNA, such as a synthesized, single stranded polynucleotide. The isolated nucleic acid molecule of the present invention may also include a ribonucleic acid molecule (RNA), especially a mRNA molecule generated from a human MC-R1 splice variant genomic clone as disclosed in mc1-3 (SEQ ID NO:15), mc1-6 (SEQ ID NO:18), mc1-6 (SEQ ID NO:21), mc1-9 (SEQ ID NO:24) and their respective open reading frames, SEQ ID NO: 16 (mc1-3), SEQ ID NO: 19 (mc1-6), SEQ ID NO: 22 (mc1-6), and SEQ ID NO: 25 (mc1-9).

[0048] It is known that there is a substantial amount of redundancy in the various codons which code for specific amino acids. Therefore, this invention is also directed to those DNA sequences encode RNA comprising alternative codons which code for the eventual translation of the identical amino acid, as shown below:

- A=Ala=Alanine: codons GCA, GCC, GCG, GCU
- C=Cys=Cysteine: codons UGC, UGU
- D=Asp=Aspartic acid: codons GAC, GAU
- E=Glu=Glutamic acid: codons GAA, GAG
- F=Phe=Phenylalanine: codons UUC, UUU
- G=Gly=Glycine: codons GGA, GGC, GGG, GGU
- H=His=Histidine: codons CAC, CAU
- I=Ile=Isoleucine: codons AUA, AUC, AUU
- K=Lys=Lysine: codons AAA, AAG
- L=Leu=Leucine: codons UUA, UUG, CUA, CUC, CUG, CUU
- M=Met=Methionine: codon AUG
- N=Asp=Asparagine: codons AAC, AAU
- P=Pro=Proline: codons CCA, CCC, CCG, CCU
- Q=Gln=Glutamine: codons CAA, CAG
- R=Arg=Arginine: codons AGA, AGG, CGA, CGC, CGG, CGU
- S=Ser=Serine: codons AGC, AGU, UCA, UCC, UCG, UCU
- T=Thr=Threonine: codons ACA, ACC, ACG, ACU
- V=Val=Valine: codons GUA, GUC, GUG, GUU
- W=Trp=Tryptophan: codon UGG
- Y=Tyr=Tyrosine: codons UAC, UAU

[0049] Therefore, the present invention discloses codon redundancy which may result in differing DNA molecules expressing an identical protein. For purposes of this specification, a sequence bearing one or more replaced codons will be defined as a degenerate variation. Also included within the scope of this invention are mutations either in the DNA sequence or the translated protein which do not substantially alter the ultimate physical properties of the expressed protein. For example, substitution of valine for leucine, arginine for lysine, or asparagine for glutamine may not cause a change in functionality of the polypeptide.

[0050] It is known that DNA sequences coding for a peptide may be altered so as to code for a peptide having properties that are different than those of the naturally occurring peptide. Methods of altering the DNA sequences include but are not limited to site directed mutagenesis. Examples of altered properties include but are not limited to changes in the affinity of an enzyme for a substrate or a receptor for a ligand.

[0051] Any of a variety of procedures may be used to clone human MC-R1 splice variant, including but not limited to the procedure outlined in the Example sections. These methods include, but are not limited to, (1) a RACE PCR cloning technique (Frohman, et al., 1988, *Proc. Natl. Acad. Sci. USA* 85: 8998-9002). 5' and/or 3' RACE may be performed to generate a full-length cDNA sequence. This strategy involves using gene-specific oligonucleotide primers for PCR amplification of human MC-R1B cDNA. These gene-specific primers are designed through identification of an expressed sequence tag (EST) nucleotide sequence which has been identified by searching any number of publicly available nucleic acid and protein databases; (2) direct functional expression of the human MC-R1B cDNA following the construction of a human MC-R1B-containing cDNA library in an appropriate expression vector system; (3) screening a human MC-R1B-containing cDNA library constructed in a bacteriophage or plasmid shuttle vector with a labeled degenerate oligonucleotide probe designed from the amino acid sequence of the human MC-R1B protein; (4) screening a human MC-R1B-containing cDNA library constructed in a bacteriophage or plasmid shuttle vector with a partial cDNA encoding the human MC-R1B protein. This partial cDNA is obtained by the specific PCR amplification of human MC-R1B DNA fragments through the design of degenerate oligonucleotide primers from the amino acid sequence known for other kinases which are related to the human MC-R1B protein; (5) screening a human MC-R1B-containing cDNA library constructed in a bacteriophage or plasmid shuttle vector with a partial cDNA or oligonucleotide with homology to a mammalian MC-R1B protein. This strategy may also involve using gene-specific oligonucleotide primers for PCR amplification of human MC-

R1B cDNA identified as an EST as described above; or (6) designing 5' and 3' gene specific oligonucleotides using SEQ ID NO: 1 as a template so that either the full-length cDNA may be generated by known RACE techniques, or a portion of the coding region may be generated by these same known RACE techniques to generate and isolate a portion of the coding region to use as a probe to screen one of numerous types ofcDNA and/or genomic libraries in order to isolate a full-length version of the nucleotide sequence encoding human MC-R1B.

[0052] It is readily apparent to those skilled in the art that other types of libraries, as well as libraries constructed from other cell types-or species types, may be useful for isolating a human MC-R1B-encoding DNA or a human MC-R1B homologue. Other types of libraries include, but are not limited to, cDNA libraries derived from other human cells.

[0053] It is also readily apparent to those skilled in the art that suitable cDNA libraries may be prepared from cells or cell lines which have MC-R1B activity. The selection of cells or cell lines for use in preparing a cDNA library to isolate a cDNA encoding human MC-R1B may be done by first measuring cell-associated MC-R1B activity using any known assay available for such a purpose.

[0054] Preparation of cDNA libraries can be performed by standard techniques well known in the art. Well known cDNA library construction techniques can be found for example, in Sambrook et al., 1989, *Molecular Cloning: A Laboratory Manual;* Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Complementary DNA libraries may also be obtained from numerous commercial sources, including but not limited to Clontech Laboratories, Inc. and Stratagene.

[0055] It is also readily apparent to those skilled in the art that DNA encoding human MC-R1B may also be isolated from a suitable genomic DNA library. Construction of genomic DNA libraries can be performed by standard techniques well known in the art. Well known genomic DNA library construction techniques can be found in Sambrook, et al., *supra.*

[0056] In order to clone the human MC-R1B gene by one of the preferred methods, the amino acid sequence or DNA sequence of human MC-R1B or a homologous protein may be necessary. To accomplish this, the MC-R1B protein or a homologous protein may be purified and partial amino acid sequence determined by automated sequenators. It is not necessary to determine the entire amino acid sequence, but the linear sequence of two regions of 6 to 8 amino acids can be determined for the PCR amplification of a partial human MC-R1B DNA fragment. Once suitable amino acid sequences have been identified, the DNA sequences capable of encoding them are synthesized. Because the genetic code is degenerate, more than one codon may be used to encode a particular amino acid, and therefore, the amino acid sequence can be encoded by any of a set of similar DNA oligonucleotides. Only one member of the set will be identical to the human MC-R1B sequence but others in the set will be capable of hybridizing to human MC-R1B DNA even in the presence of DNA oligonucleotides with mismatches. The mismatched DNA oligonucleotides may still sufficiently hybridize to the human MC-R1B DNA to permit identification and isolation of human MC-R1B encoding DNA. Alternatively, the nucleotide sequence of a region of an expressed sequence may be identified by searching one or more available genomic databases. Gene-specific primers may be used to perform PCR amplification of a cDNA of interest from either a cDNA library or a population of cDNAs. An appropriate nucleotide sequence for use in a PCR-based method may be obtained from any of the identified MC-R1B splice variants described herein, either for the purpose of isolating overlapping 5' and 3' RACE products for generation of a full-length sequence coding for human MC-R1B, or to isolate a portion of the nucleotide sequence coding for human MC-R1B for use as a probe to screen one or more cDNA- or genomic-based libraries to isolate a full-length sequence encoding human MC-R1B or human MC-R1B-like proteins.

[0057] Included in the present invention are DNA sequences that hybridize to the nucleotide sequences of the various described MC-R1B splice variants (i.e., SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:18; SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO: 22, SEQ ID NO:24, and SEQ ID NO:25) under stringent conditions. By way of example, and not limitation, a procedure using conditions of high stringency is as follows: Prehybridization of filters containing DNA is carried out for 2 hours to overnight at 65°C in buffer composed of 6X SSC, 5X Denhardt's solution, and 100 μg/ml denatured salmon sperm DNA. Filters are hybridized for 12 to 48 hrs at 65°C in prehybridization mixture containing 100 μg/ml denatured salmon sperm DNA and 5-20 X 10^6 cpm of ^{32}P-labeled probe. Washing of filters is done at 37°C for 1 hr in a solution containing 2X SSC, 0.1 % SDS. This is followed by a wash in 0.1X SSC, 0.1% SDS at 50°C for 45 min. before autoradiography. Other procedures using conditions of high stringency would include either a hybridization step carried out in 5XSSC, 5X Denhardt's solution, 50% formamide at 42°C for 12 to 48 hours or a washing step carried out in 0.2X SSPE, 0.2% SDS at 65°C for 30 to 60 minutes.

[0058] Reagents mentioned in the foregoing procedures for carrying out high stringency hybridization are well known in the art. Details of the composition of these reagents can be found in, e.g., Sambrook et al., 1989, *Molecular Cloning: A Laboratory Manual;* Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. In addition to the foregoing, other conditions of high stringency which may be used are well known in the art.

[0059] The present invention also relates to a substantially purified forms of the human MC-R1B protein which comprise the amino acid sequences disclosed in Figures 5A - 5F and as set forth in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:17, SEQ ID NO:20, SEQ ID NO:23, and SEQ ID NO:26. These MC-R1 proteins comprise a 65 amino acid extension at the COOH-terminus when compared to known human MC-R1 and are referred to throughout this specification as MC-R1B proteins. The exemplified amino acid

sequences are listed below:

. 1. MC-R1ESTc11

MAVQGSQRRL LGSLNSTPTA IPQLGLAANQ TGARCLEVSI SDGLFLSLGL VSLVENALVV
ATIAKNRNLH SPMYCFICCL ALSDLLVSGS NVLETAVILL LEAGALVARA AVLQQLDNVI
DVITCSSMLS SLCFLGAIAV DRYISIFYAL RYHSIVTLPR ARQAVAAIWV ASVVFSTLFI
AYYDHVAVLL CLVVFFLAML VLMAVLYVHM LARACQHAQG IARLHKRQRP VHQGFGLKGA
VTLTILLGIF FLCWGPFFLH LTLIVLCPEH PTCGCIFKNF NLFLALIICN AIIDPLIYAF
HSQELRRTLK EVLTCSCSQD RALVSWDVKS LGGSVCQELL PQQPQEKGPC DQKASSTALQ
RLLQKEVKSL PQAKGPGLQE PP (SEQ ID NO:2);

. 2. MC-RIESTC11.6

MAVQGSQRRL LGSLNSTPTA IPQLGLAANQ TGARCLEVSI SDGLFLSLGL VSLVENALVV
ATIAKNRNLH SPMYCFICCL ALSDLLVSGS NVLETAVILL LEAGALVARA AVLQQLDNVI
DVITCSSMLS SLCFLGAIAV DRYISIFYAL RYHSIVTLPR ARQAVAAIWV ASVVFSTLFI
AYYDHVAVLL CLVVFFLAML VLMAVLYVHM LARACQHAQG IARLHKRQRP VHQGFGLKGA
VTLTILLGIF FLCWGPFFLH LTLIVLCPEH PTCGCIFKNF NLFLALIICN AIIDPLIYAF
HSQELRRTLK EVLTCSCSQD RALVSWDVKS LGGSVCQELL PQQPQEKGLC DQKASSTALQ
RLLQKEVKSL PQAKGPGLQE PP (SEQ ID NO:4);

. 3. MC-R1ESTc12

MAVQGSQRRL LGSLNSTPTA IPQLGLAANQ TGARCLEVSI SDGLFLSLGL VSLVKNALVV
ATIAKNRNLH SPMYCFICCL ALSDLLVSGS NVLETAVILL LEAGALVARA AVLQQLDNVI
DVITCSSMLS SLCFLGAIAV DRYISIFYAL RYHSIVTLPR ARQAVAAIWV ASVVFSTLFI
AYYDHVAVLL CLVVFFLAML VLMAVLYVHM LARACQHAQG IARLHKRQRP VHQGFGLKGA
VTLTILLGIF FLCWGPFFLH LTLIVLCPEH PTCGCIFKNF NLFLALIICN AIIDPLIYAF
HSQELRRTLK EVLTCSCSQD RALVSWDVKS LGGSVCQELL PQQPQEKGLC DQKASSTALQ
RLLQKEVKSL PQAKGPGLQE PP (SEQ ID NO:6);

. 4. MC-R1ESTc2

MAVQGSQRRL LGSLNSTPTA IPQLGLAANQ TGARCLEVSI SDGLFLSLGL VSLVENALVV
ATIAKNRNLH SPMYCFICCL ALSDLLVSGS NVLETAVILL LEAGALVARA AVLQQLDNVI
DVITCSFMLS SLCFLGAIAV DRYISIFYAL CYHSIVTLPR ARRAVAAIWV ASVVFSTLFI
AYYDHVAVLL CLVVFFLAML VLMAVLYVHM LARACQHAQG IARLHKRQRP VHQGFGLKGA
VTLTILLGIF FLCWGPFFLH LTLIVLCPEH PTCGCIFKNF NLFLALIICN AIIDPLIYAF
HSQELRRTLK EVLTCSCSQD RALVSWDVKS LGGSVCQELL PQQPQEKGLC DQKASSTALQ
RLLQKEVKSL PQAKGPGLQE PP (SEQ ID NO:8);

. 5. MC R1ESTc4

MAVQGSQRRL LGSLNSTPTA IPQLGLAANQ TGARCLEVSI SDGLFLSLGL VSLVENALVV
ATIAKNRNLH SPMYCFICCL ALSDLLVSGS NVLETAVILL LEAGALVARA AVLQQLDNVI
DVITCSSMLS SLCFLGAIAV DRYISIFYAL RYHSIVTLPR ARRAVAAIWV ASVVFSTLFI
AYYDHAAVLL CLVVFFLAML VLMAVLYVHM LARACQHAQG IARLHKRQRP VHQGFGLKGA
VTLTILLGIF FLCWGPFFLH LTLIVLCPEH PTCGCIFKNF NLFLALIICN AIIDPLIYAF
HSQELRRTLK EVLTCSCSQD RALVSWDVKS LGGSVCQERL PQQPQEKGLC DQKASSTALQ
RLLQKGVKSL PQAKGPGLQE PP (SEQ ID NO:10);

. 6. MC-R1ESTc5

MAVQGSQRRL LGSLNSTPTA IPQLGLAANQ TGARCLEVSI SDGLFLSLGL VSLVKNALVV
ATIAKNRNLH SPMYCFICCL ALSDLLVSGS NVLETAVILL LEAGALVARA AVLQQLDNVI
DVITCSSMLS SLCFLGAIAV DRYISIFYAL RYHSIVTLPR ARQAVAAIWV ASVVFSTLFI
AYYDHVAVLL CLVVFFLAML VLMAVLYVHM LARACQHAQG IARLHKRQRP VHQGFGLKGA
VTLTILLGIF FLCWGPFFLH LTLIVLCPEH PTCGCIFKNF NLFLALIICN AIIDPLIYAF
HSQELRRTLK EVLTCSCSQD RALVSWDVKS LGGSVCQELL PQQPQEKGLC DQKASSTALQ
RLLQKEVKSL PQAKGPGLQE PP (SEQ ID NO:12);

. 7. MC-R1ESTc6

MAVQGSQRRL LGSLNSTPTA IPQLGLAANQ TGARCLEVSI SDGLFLSLGL VSLVKNALVV
ATIAKNRNLH SPMYCFICCL ALSDLLVSGS NVLETAVILL LEAGALVARA AVLQQLDNVI
DVITCSSMLS SLCFLGAIAV DRYISIFYAL RYHSIVTLPR ARQAVAAIWV ASVVFSTLFI
AYYDHVAVLL CLVVFFLAML VLMAVLYVHM LARACQHAQG IARLHKRQRP VHQGFGLKGA
VTLTILLGIF FLCWGPFFLH LTLIVLCPEH PTCGCIFKNF NLFLALIICN AIIDPLIYAF
HSQELRRTLK EVLTCSCSQD RALVSWDVKS LGGSVCQELL PQQPQEKGLC DQKASSTALQ
RLLQKEVKSL PQAKGPGLQE PP (SEQ ID NO:14);

. 8. pro mc1-3

MAVQGSQRRL LGSLNSTPTA IPQLGLAANQ TGARCLEVSI SDGLFLSLGL VSLVENALVV
ATIAKNRNLH SPMYCFICCL ALSDLLVSGS NVLETAVILL LEAGALVAQA AVLQQLDNVI
DVITCSSMLS SLCFLGAIAA DRYISIFYAL RYHSIVTLPR ARRAVAAIWV ASVVFSTLFI
AYYDHVAVLL CLVVFFLAML VLMAVLYVHM LARACQHAQG IARLHKRQRP VHQGFGLKGA
VTLTILLGIF FLCWGPFFLH LTLIVLCPEH PTCGCIFKNF NLFLALIICN AIIDPLIYAF
HSQELRRTLK EVLTCSCSQD RALVSWDVKS LGGSVCQELL PQQPQEKGLC DQKASSTALQ
RLLQKEVKSL PQAKGPGLQE PP (SEQ ID NO:17);

. 9. pro mc1-6

MAVQGSQRRL LGSLNSTPTA IPQLGLAANQ TGARCLEVSI SDGLFLSLGL VSLVENALVV
ATIAKNRNLH SPMYCFICCL ALSDLLVSGS NVLETAVILL LEAGALVARA AVLQQLDNVI
DVITCSSMLS SLCFLGAIAV DRYISIFYAL RYHSIVTLPR ARQAVAAIWV ASVVFSTLFI
AYYDHVAVLL CLVVFFLAML VLMAVLYVHM LARACQHAQG IARLHKRQRP VHQGFGLKGA
VTLTILLGIF FLCWGPFFLH LTLIVLCPEH PTCGCIFKNF NLFLALIICN AIIDPLIYAF
HSQELRRTLK EVLTCSRSQD RALVSWDVKS LGGSVCQELL PQQPQEKGLC DQKASSTALQ
RLLQKEVKSL PQAKGPGLQE PP (SEQ ID NO:20);

. 10. pro mc1-8

MAVQGSQRRL LGSLNSTPTA IPQLGLAANQ TGARCLEVSI SDGLFLSLGL VSLVENALVV
ATIAKNRNLH SPMYCFICCL ALSDLLVSGS NVLETAVILL LEAGALVARA AVLQQLDNVI
DVITCSSMLS SLCFLGAIAV DRYISIFYAL RYHSIVTLPR ARRAVAALWV ASVVFSTLFI
AYYDHVAVLL CLVVFFLAML VLMAVLYVHM LARACQHAQG IARLHKRQRP VHQGFGLKGA
VTPTILLGIF FLCWGPFFLH LTLIVLCPEH PTCGCIFKNF NLFLALIICN AFIDPLIYAF

HSQELRRTLK EVLTCSCSQD RALVSWDVKS LGGSVCQELL PQQPQEKGLC DQKASSTALQ
RLLQKEVKSL PQAKGPGLQE PP (SEQ ID NO:23);

. 11. pro mc-1-9

MAVQGSQRRL LGSLNSTPTA IPQLGLAANQ TGARCLEVSI SDGLFLSLGL VSLVENALVV
ATIAKNRNLH SPMYCFICCL ALSDLLVSGS NVLETAVILL LEAGALVARA AVLQQLDNVI
DVITCSSMLS SLCFLGAVAV DRYISIFYAL RYHSIVTLPR ARQAVAAIWV ASVVFSTLFI
AYYDHVAVLL CLVVFFLAML VLMAVLYVHM LARACQHAQG IARLHKRQRP VHQGFGLKGA
VTLTILLGIF FLCWGPFFLH LTLIVLCPEH PTCGCIFKNF NLFLAPIICN AIIDPLIYAF
HSQELRRTLK EVLTCSCSQD RALVSWDVKS LGGSVCQELL PQQPQEKGLC DQKASSTALQ
RLLQKEVKSL PQAKGPGLQE PP (SEQ ID NO:26);

wherein M=Met (methionine), F=Phe (phenylalanine), L=Leu (leucine), I=Ile (isoleucine), V=Val (valine), S=Ser (serine), P=Pro (proline), T=Thr (threonine), A=Ala (alanine), Y=Tyr (tyrosine), H=His (histidine), Q=Gln (glutamine), N=Asn (asparagine), K=Lys (lysine), D=Asp (aspartic acid), E=Glu (glutamic acid); C=Cys (cysteine), W=Trp (tryptophan), R=Arg (arginine), and G=Gly (glycine).

[0060] These MC-R1B proteins comprise a 65 amino acid extension at the COOH-terminus when compared to known human MC-R1 and are referred to throughout this specification as MC-R1B proteins. More specifically, amino acid residue 317 of the MC-R1B proteins is Cys whereas the COOH-terminal amino acid residue 317 of known MC-R1A proteins is Trp. From amino acid residue 318 through the COOH-terminal amino acid at 382 of the MC-R1B proteins disclosed herein, the amino acid sequence is as set forth in SEQ ID NO:27, as shown below: SQD RALVSWDVKS LGGSVCQELL PQQPQEKGLC DQKASSTALQ RLLQKEVKSL PQAKGPGLQE pp (SEQ ID NO:27).

[0061] The present invention also relates to biologically active fragments and/or mutants of these human MC-R1B proteins comprising the amino acid sequence set forth as SEQ ID NO:2, including but not necessarily limited to amino acid substitutions, deletions, additions, amino terminal truncations and carboxy-terminal truncations such that these mutations provide for proteins or protein fragments of diagnostic, therapeutic or prophylactic use and would be useful for screening for agonists and/or antagonists for MC-R1B function.

[0062] Various preferred aspects of the invention represent human MC-R1B proteins as disclosed in Figures 5A - 5F and as set forth as SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:17, SEQ ID NO:20, SEQ ID NO:23, and SEQ ID NO:26, all of which comprise the 65 amino acid COOH-terminal extension as set forth in SEQ ID NO:27.

[0063] The present invention also relates to modified MC-R1B polypeptides which have amino acid deletions, additions, or substitutions but that still retain substantially the same biological activity as MC-R1B. It is generally accepted that single amino acid substitutions do not usually alter the biological activity of a protein (see, e.g., *Molecular Biology of the Gene,* Watson et al., 1987, Fourth Ed., The Benjamin/Cummings Publishing Co., Inc., page 226; and Cunningham & Wells, 1989, *Science* 244:1081-1085). Accordingly, the present invention includes isolated nucleic acid molecules and expressed MC-R1B proteins wherein one amino acid substitution is generated and which this protein retains substantially the same biological activity as wild-type MC-R1B. The present invention also includes isolated nucleic acid molecules and expressed MC-R1B proteins wherein two or more amino acid substitution is generated wherein this protein retains substantially the same biological activity as wild-type MC-R1B. In particular, the present invention includes embodiments where the above-described substitutions are conservative substitutions. In particular, the present invention includes embodiments where the above-described substitutions do not occur in the ligand-binding domain of MC-R1B.

[0064] Following expression of MC-R1B in a host cell, MC-R1B protein may be recovered to provide MC-R1B protein in active form. Several MC-R1B protein purification procedures are available and suitable for use. Recombinant MC-R1B protein may be purified from cell lysates and extracts by various combinations of, or individual application of salt fractionation, ion exchange chromatography, size exclusion chromatography, hydroxylapatite adsorption chromatography and hydrophobic interaction chromatography. In addition, recombinant MC-R1B protein can be separated from other cellular proteins by use of an immunoaffinity column made with monoclonal or polyclonal antibodies specific for full-length MC-R1B protein, or polypeptide fragments of MC-R1B protein.

[0065] The present invention also relates to isolated nucleic acid molecules which are fusion constructions expressing

fusion proteins useful in assays to identify compounds which modulate wild-type vertebrate MC-R1B activity. One aspect of this portion of the invention includes, but is not limited to, glutathione S-transferase (GST)-MC-R1B fusion constructs which include, but are not limited to, either the intracellular domain of MC-R1B as an in-frame fusion at the carboxy terminus of the GST gene or the extracellular and transmembrane ligand binding domain of MC-R1B fused to an GST or immunoglobulin gene by methods known to one of ordinary skill in the art. Recombinant GST-MC-RIB fusion proteins may be expressed in various expression systems, including *Spodoptera frugiperda* (Sf21) insect cells (Invitrogen) using a baculovirus expression vector (pAcG2T, Pharmingen).

[0066] The present invention also relates to subcellular membrane fractions from the recombinant host cells (both prokaryotic and eukaryotic as well as both stably and transiently transformed cells) which contain the nucleic acids of the present invention. These subcellular membrane fractions will comprise either wild-type or mutant forms of MC-R1B proteins at levels substantially above endogenous levels and hence will be useful in various assays described throughout this specification.

[0067] The present invention also relates to recombinant vectors and recombinant hosts, both prokaryotic and eukaryotic, which contain the substantially purified nucleic acid molecules disclosed throughout this specification. The nucleic acid molecules of the present invention encoding MC-R1B splice variants, in whole or in part, can be linked with other DNA molecules, i.e., DNA molecules to which the MC-R1B are not naturally linked, to form "recombinant DNA molecules" containing the receptor. The novel DNA sequences of the present invention can be inserted into vectors which comprise nucleic acids encoding a MC-R1B or a functional equivalent. These vectors may be comprised of DNA or RNA; for most cloning purposes DNA vectors are preferred. Typical vectors include plasmids, modified viruses, bacteriophage and cosmids, yeast artificial chromosomes and other forms of episomal or integrated DNA that can encode a MC-R1B. It is well within the purview of the skilled artisan to determine an appropriate vector for a particular gene transfer or other use.

[0068] To this end, the present invention also includes vectors containing an MC-R1B gene, host cells containing the vectors, and methods of making substantially pure MC-R1B protein comprising the steps of introducing the MC-R1B gene into a host cell, and cultivating the host cell under appropriate conditions such that MC-R1B is produced. The MC-R1B so produced may be harvested from the host cells in conventional ways. Therefore, the present invention also relates to methods of expressing the MC-R1B protein and biological equivalents disclosed herein, assays employing these gene products, recombinant host cells which comprise DNA constructs which express these receptor proteins, and compounds identified through these assays which act as agonists or antagonists of MC-R1B activity.

[0069] The cloned MC-R1B cDNA obtained through the methods described above may be recombinantly expressed by molecular cloning into an expression vector (such as pcDNA3.neo, pcDNA3.1, pCR2.1, pBlueBacHis2 or pLITMUS28) containing a suitable promoter and other appropriate transcription regulatory elements, and transferred into prokaryotic or eukaryotic host cells to produce recombinant MC-R1B. Techniques for such manipulations can be found described in Sambrook, et al., *supra,* are discussed at length in the Example section and are well known and easily available to the artisan of ordinary skill in the art.

[0070] A variety of mammalian expression vectors may be used to express recombinant MC-R1B in mammalian cells. Expression vectors are defined herein as DNA sequences that are required for the transcription of cloned DNA and the translation of their mRNAs in an appropriate host. Such vectors can be used to express eukaryotic DNA in a variety of hosts such as bacteria, blue green algae, plant cells, insect cells and animal cells. Specifically designed vectors allow the shuttling of DNA between hosts such as bacteria-yeast or bacteria-animal cells. An appropriately constructed expression vector should contain: an origin of replication for autonomous replication in host cells, selectable markers, a limited number of useful restriction enzyme sites, a potential for high copy number, and active promoters. A promoter is defined as a DNA sequence that directs RNA polymerase to bind to DNA and initiate RNA synthesis. A strong promoter is one which causes mRNAs to be initiated at high frequency. Expression vectors may include, but are not limited to, cloning vectors, modified cloning vectors, specifically designed plasmids or viruses. Commercially available mammalian expression vectors which may be suitable for recombinant MC-R1B expression, include but are not limited to, pcDNA3.neo (Invitrogen), pcDNA3.1 (Invitrogen), pCI-neo (Promega), pLITMUS28, pLITMUS29, pLITMUS38 and pLITMUS39 (New England Bioloabs), pcDNAI, pcDNAIamp (Invitrogen), pcDNA3 (Invitrogen), pMClneo (Stratagene), pXT1 (Stratagene), pSG5 (Stratagene), EBO-pSV2-neo (ATCC 37593) pBPV-1(8-2) (ATCC 37110), pdBPV-MMTneo(342-12) (ATCC 37224), pRSVgpt (ATCC 37199), pRSVneo (ATCC 37198), pSV2-dhfr (ATCC 37146), pUCTag (ATCC 37460), and IZD35 (ATCC 37565).

[0071] Also, a variety of bacterial expression vectors may be used to express recombinant MC-R1B in bacterial cells. Commercially available bacterial expression vectors which may be suitable for recombinant MC-R1B expression include, but are not limited to pCR2.1 (Invitrogen), pET11a (Novagen), lambda gt11 (Invitrogen), and pKK223-3 (Pharmacia).

[0072] In addition, a variety of fungal cell expression vectors may be used to express recombinant MC-R1B in fungal cells. Commercially available fungal cell expression vectors which may be suitable for recombinant MC-R1B expression include but are not limited to pYES2 (Invitrogen) and *Pichia* expression vector (Invitrogen).

[0073] Also, a variety of insect cell expression vectors may be used to express recombinant receptor in insect cells.

Commercially available insect cell expression vectors which may be suitable for recombinant expression of MC-R1B include but are not limited to pBlueBacIII and pBlueBacHis2 (Invitrogen), and pAcG2T (Pharmingen).

[0074] Expression of MC-R1B DNA may also be performed using *in vitro* produced synthetic mRNA. Synthetic mRNA can be efficiently translated in various cell-free systems, including but not limited to wheat germ extracts and reticulocyte extracts, as well as efficiently translated in cell based systems, including but not limited to microinjection into frog oocytes, with microinjection into frog oocytes being preferred.

[0075] To determine the MC-R1B cDNA sequence(s) that yields optimal levels of MC-R1B, cDNA molecules including but not limited to the following can be constructed: a cDNA fragment containing the full-length open reading frame for MC-R1B as well as various constructs containing portions of the cDNA encoding only specific domains of the protein or rearranged domains of the protein. All constructs can be designed to contain none, all or portions of the 5' and/or 3' untranslated region of a MC-R1B cDNA. The expression levels and activity of MC-R1B can be determined following the introduction, both singly and in combination, of these constructs into appropriate host cells. Following determination of the MC-R1B cDNA cassette yielding optimal expression in transient assays, this MC-R1B cDNA construct is transferred to a variety of expression vectors (including recombinant viruses), including but not limited to those for mammalian cells, plant cells, insect cells, oocytes, bacteria, and yeast cells,

[0076] Therefore, another aspect of the present invention includes host cells that have been engineered to contain and/or express DNA sequences encoding the MC-R1B. Such recombinant host cells can be cultured under suitable conditions to produce MC-R1B or a biologically equivalent form. Recombinant host cells may be prokaryotic or eukaryotic, including but not limited to, bacteria such as *E. coli,* fungal cells such as yeast, mammalian cells including, but not limited to, cell lines of human, bovine, porcine, monkey and rodent origin, and insect cells including but not limited to *Drosophila* and silkworm derived cell lines. Therefore, an expression vector containing DNA encoding a MC-R1B-like protein may be used for expression of MC-R1B in a recombinant host cell. Recombinant host cells may be prokaryotic or eukaryotic, including but not limited to bacteria such as *E. coli,* fungal cells such as yeast, mammalian cells including but not limited to cell lines of human, bovine, porcine, monkey and rodent origin, and insect cells including but not limited to Drosophila- and silkworm-derived cell lines. For instance, one insect expression system utilizes *Spodoptera frugiperda* (Sf21) insect cells (Invitrogen) in tandem with a baculovirus expression vector (pAcG2T, Pharmingen). Also, mammalian species which may be suitable and which are commercially available, include but are not limited to, L cells L-M(TK-) (ATCC CCL 1.3), L cells L-M (ATCC CCL 1.2), Saos-2 (ATCC HTB-85), 293 (ATCC CRL 1573), Raji (ATCC CCL 86), CV-1 (ATCC CCL 70), COS-1 (ATCC CRL 1650), COS-7 (ATCC CRL 1651), CHO-K1 (ATCC CCL 61), 3T3 (ATCC CCL 92), NIH/3T3 (ATCC CRL 1658), HeLa (ATCC CCL 2), C1271 (ATCC CRL 1616), BS-C-1 (ATCC CCL 26), MRC-5 (ATCC CCL 171), and CPAE (ATCC CCL 209). The expression vector may be introduced into host cells via any one of a number of techniques including but not limited to transformation, transfection, protoplast fusion, and electroporation. The expression vector-containing cells are individually analyzed to determine whether they produce MC-R1B protein. Identification of MC-R1B expressing cells may be done by several means, including but not limited to immunological reactivity with anti-MC-R1B antibodies, labeled ligand binding and the presence of host cell-associated MC-R1B activity.

[0077] The assays described herein as well as protein purification schemes can be carried out with cells that have been transiently or stably transfected or transformed with an expression vector which directs expression of MC-R1B. The expression vector may be introduced into host cells via any one of a number of techniques including but not limited to transformation, transfection, protoplast fusion, and electroporation. Transformation is meant to encompass a genetic change to the target cell resulting fmm an incorporation of DNA. Transfection is meant to include any method known in the art for introducing MC-R1B into the test cells. For example, transfection includes calcium phosphate or calcium chloride mediated transfection, lipofection, infection with a retroviral construct containing MC-R1B, and electroporation. The expression vector-containing cells are individually analyzed to determine whether they produce human MC-R1B protein. Identification of human MC-R1B expressing cells may be done by several means, including but not limited to immunological reactivity with anti-human MC-R1B antibodies, labeled ligand binding and the presence of host cell-associated human MC-R1B activity.

[0078] The specificity of binding of compounds showing affinity for MC-R1B is shown by measuring the affinity of the compounds for recombinant cells expressing the cloned receptor or for membranes from these cells. Expression of the cloned receptor and screening for compounds that bind to MC-R1B or that inhibit the binding of a known, radiolabeled ligand of MC-R1B to these cells, or membranes prepared from these cells, provides an effective method for the rapid selection of compounds with high affinity for MC-R1B. Such ligands need not necessarily be radiolabeled but can also be nonisotopic compounds that can be used to displace bound radiolabeled compounds or that can be used as activators in functional assays. Compounds identified by the above method are likely to be agonists or antagonists of MC-R1B and may be peptides, proteins, or non-proteinaceous organic molecules.

[0079] Melanocortin receptors belong to the odopsin sub-family of GPCR's. However, several features in the MC-R1B are shared with all other receptors and are absent in most other GPCR's, including the EN motif in TM1, the lack of Cys in the loop between TM2 and TM3 or between TM4 and TM5, the MxxxxxxxY motif in TM5, and the DPxxY motif in TM7. Since all melanocortin receptors lack Cys residues in the extracellular loops that are present in other members of the

odopsin sub-family, interhelical disulfide bond (e.g., between the Cys residues near the top of TM3 and TM5) may play the same function as interloop disulfide bond in most other GPCR's. Accordingly, the present invention is directed to methods for screening for compounds which modulate the expression of DNA or RNA encoding a MC-R1B protein as well as compounds which effect the function of the MC-R1B protein. Methods for identifying agonists and antagonists of other receptors are well known in the art and can be adapted to identify agonists and antagonists of MC-R1B. For example, Cascieri et al. (1992, *Molec. Pharmacol.* 41:1096-1099) describe a method for identifying substances that inhibit agonist binding to rat neurokinin receptors and thus are potential agonists or antagonists of neurokinin receptors. The method involves transfecting COS cells with expression vectors containing rat neurokinin receptors, allowing the transfected cells to grow for a time sufficient to allow the neurokinin receptors to be expressed, harvesting the transfected cells and resuspending the cells in assay buffer containing a known radioactively labeled agonist of the neurokinin receptors either in the presence or the absence of the substance, and then measuring the binding of the radioactively labeled known agonist of the neurokinin receptor to the neurokinin receptor. If the amount of binding of the known agonist is less in the presence of the substance than in the absence of the substance, then the substance is a potential agonist or antagonist of the neurokinin receptor. Where binding of the substance such as an agonist or antagonist to MC-R1B is measured, such binding can be measured by employing a labeled substance or agonist. The substance or agonist can be labeled in any convenient manner known to the art, e.g., radioactively, fluorescently, enzymatically.

[0080] Therefore, the specificity of binding of compounds having affinity for MC-R1B is shown by measuring the affinity of the compounds for recombinant cells expressing the cloned receptor or for membranes from these cells. Expression of the cloned receptor and screening for compounds that bind to MC-R1B or that inhibit the binding of a known, radiolabeled ligand of MC-R1B to these cells, or membranes prepared from these cells, provides an effective method for the rapid selection of compounds with high affinity for MC-R1B. Such ligands need not necessarily be radiolabeled but can also be nonisotopic compounds that can be used to displace bound radiolabeled compounds or that can be used as activators in functional assays. Compounds identified by the above method are likely to be agonists or antagonists of MC-R1B and may be peptides, proteins, or non-proteinaceous organic molecules. Compounds may modulate by increasing or attenuating the expression of DNA or RNA encoding MC-R1B, or by acting as an agonist or antagonist of the MC-R1B receptor protein. These compounds that modulate the expression of DNA or RNA encoding MC-R1B or the biological function thereof may be detected by a variety of assays. The assay may be a simple "yes/no" assay to determine whether there is a change in expression or function. The assay may be made quantitative by comparing the expression or function of a test sample with the levels of expression or function in a standard sample. Kits containing MC-R1B, antibodies to MC-R1B, or modified MC-R1B may be prepared by known methods for such uses.

[0081] Therefore, the present invention relates to methods of expressing MC-R1B in recombinant systems and of identifying agonists and antagonists of MC-R1B. When screening compounds in order to identify potential pharmaceuticals that specifically interact with a target receptor, it is necessary to ensure that the compounds identified are as specific as possible for the target receptor. To do this, it is necessary to screen the compounds against as wide an array as possible of receptors that are similar to the target receptor. Thus, in order to find compounds that are potential pharmaceuticals that interact with receptor A, it is necessary not only to ensure that the compounds interact with receptor A (the "plus target") and produce the desired pharmacological effect through receptor A, it is also necessary to determine that the compounds do not interact with receptors B, C, D, etc. (the "minus targets"). In general, as part of a screening program, it is important to have as many minus targets as possible (see Hodgson, 1992, *Bio/Technology* 10:973-980, @ 980). MC-R1B proteins and the DNA molecules encoding this receptor protein have the additional utility in that they can be used as "minus targets" in screens designed to identify compounds that specifically interact with other G-protein coupled receptors. Due to homology to GPCRs, the MC-R1B of this invention is believed to function similarly to GPCRs and have similar biological activity. They are useful in understanding the biological and physiological effects and study to melanocortin active compounds in primates, followed by human clinical trials. More notable, MC-R1B agonists will be identified and evaluated for their effects on food intake, weight gain, and metabolic rate to identify novel-anti-obesity agents that are effective in primates. They may also be used to scan for monkey melanocortin agonists and antagonists; as in particular to test the specificity of identified ligands.

[0082] To this end, the present invention relates in part to methods of identifying a substance which modulates MC-R1B receptor activity, which involves:

- (a) combining a test substance in the presence and absence of a MC-R1B receptor protein, including but not limited to the MC-R1B proteins comprising the amino acid sequence as set forth in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:17, SEQ ID NO:20, SEQ ID NO: 23, and SEQ ID NO:26; and,
- (b) measuring and comparing the effect of the test substance in the presence and absence of the MC-R1B receptor protein.

[0083] In addition, several specific embodiments are disclosed herein to show the diverse type of screening or selection

assay which the skilled artisan may utilize in tandem with an expression vector directing the expression of the MC-R1B receptor protein. Methods for identifying agonists and antagonists of other receptors are well known in the art and can be adapted to identify agonists and antagonists of MC-R1B. Therefore, these embodiments are presented as examples and not as limitations. To this end, the present invention includes assays by which MC-R1B modulators (such as agonists and antagonists) may be identified. Accordingly, the present invention includes a method for determining whether a substance is a potential agonist or antagonist of MC-R1B that comprises:

- (a) transfecting or transforming cells with an expression vector that directs expression of MC-R1B in the cells, resulting in test cells;
- (b) allowing the test cells to grow for a time sufficient to allow MC-R1B to be expressed;
- (c) exposing the cells to a labeled ligand of MC-R1B in the presence and in the absence of the substance;
- (d) measuring the binding of the labeled ligand to MC-R1B; where if the amount of binding of the labeled ligand is less in the presence of the substance than in the absence of the substance, then the substance is a potential agonist or antagonist of MC-R1B.

[0084] The conditions under which step (c) of the method is practiced are conditions that are typically used in the art for the study of protein-ligand interactions: e.g., physiological pH; salt conditions such as those represented by such commonly used buffers as PBS or in tissue culture media; a temperature of about 4°C to about 55°C. The test cells may be harvested and resuspended in the presence of the substance and the labeled ligand. In a modification of the above-described method, step (c) is modified in that the cells are not harvested and resuspended but rather the radioactively labeled known agonist and the substance are contacted with the cells while the cells are attached to a substratum, e.g., tissue culture plates.

[0085] The present invention also includes a method for determining whether a substance is capable of binding to MC-R1B, i.e., whether the substance is a potential agonist or an antagonist of MC-R1B, where the method comprises:

- (a) transfecting or transforming cells with an expression vector that directs the expression of MC-R1B in the cells, resulting in test cells;
- (b) exposing the test cells to the substance;
- (c) measuring the amount of binding of the substance to MC-R1B;
- (d) comparing the amount of binding of the substance to MC-R1B in the test cells with the amount of binding of the substance to control cells that have not been transfected with MC-R1B;

wherein if the amount of binding of the substance is greater in the test cells as compared to the control cells, the substance is capable of binding to MC-R1B. Determining whether the substance is actually an agonist or antagonist can then be accomplished by the use of functional assays such as, e.g., the assay involving the use of promiscuous G-proteins described below.

[0086] The conditions under which step (b) of the method is practiced are conditions that are typically used in the art for the study of protein-ligand interactions: e.g., physiological pH; salt conditions such as those represented by such commonly used buffers as PBS or in tissue culture media; a temperature of about 4°C to about 55°C. The test cells are harvested and resuspended in the presence of the substance.

[0087] Chen et al. (1995, *Analytical Biochemistry* 226: 349-354) describe a colorometric assay which utilizes a recombinant cell transfected with an expression vector encoding a G-protein coupled receptor with a second expression vector containing a promoter with a cAMP responsive element fused to the LacZ gene. Activity of the overexpressed G-protein coupled receptor is measured as the expression and OD measurement of β-Gal. Therefore, another aspect of this portion of the invention includes a non-radioactive method for determining whether a substance is a potential agonist or antagonist of MC-R1B that comprises:

- (a) transfecting or transforming cells with an expression vector encoding MC-R1B, resulting in test cells;
- (b) transfecting or transforming the test cells of step (a) with an expression vector which comprises a cAMP-inducible promoter fused to a colorometric gene such a LacZ;
- (c) allowing the transfected cells to grow for a time sufficient to allow MC-R1B to be expressed;
- (d) harvesting the transfected cells and resuspending the cells in the presence of a known agonist of MC-R1B and/or in both the presence and absence of the test compound;
- (e) measuring the binding of the known agonist and test compound to overexpressed MC-R1B by a colorometric assay which measures expression off the cAMP-inducible promoter and comparing expression levels in the presence of the known agonist as well as in the presence and absence of the unknown substance so as to determine whether the unknown substance acts as either a potential agonist or antagonist of MC-R1B.

[0088] Additional methods of identifying agonists or antagonists include but are by no means limited to the following:

- I. (a) transfecting or transforming cells with a first expression vector which directs expression of MC-R1B and a second expression vector which directs the expression of a promiscuous G-protein, resulting in test cells;
  - (b) exposing the test cells to a substance that is a suspected agonist of MC-R1B;
  - (c) measuring the level of inositol phosphates in the cells;

  where an increase in the level of inositol phosphates in the cells as compared to the level of inositol phosphates in the cells in the absence of the suspected agonist indicates that the substance is an agonist of MC-R1B.
- II. (a) transfecting or transforming cells with a first expression vector which directs expression of MC-R1B and a second expression vector which directs the expression of a promiscuous G-protein, resulting in test cells;
  - (b) exposing the test cells to a substance that is an agonist of MC-R1B;
  - (c) subsequently or concurrently to step (b), exposing the test cells to a substance that is a suspected antagonist of MC-R1B;
  - (d) measuring the level of inositol phosphates in the cells;

  where a decrease in the level of inositol phosphates in the cells in the presence of the suspected antagonist as compared to the level of inositol phosphates in the cells in the absence of the suspected antagonist indicates that the substance is an antagonist of MC-R1B.
- III. the method of II wherein the first and second expression vectors of step (a) are replaced with a single expression vector which expresses a chimeric MC-R1B protein fused at its C-terminus to a promiscuous G-protein.

[0089] The above-described methods can be modified in that, rather than exposing the test cells to the substance, membranes can be prepared from the test cells and those membranes can be exposed to the substance. Such a modification utilizing membranes rather than cells is well known in the art and is described in, e.g., Hess et al., 1992, *Biochem. Biophys. Res. Comm.* 184:260-268. Accordingly, another embodiment of the present invention includes a method for determining whether a substance binds and/or is a potential agonist or antagonist of MC-R1B wherein membrane preparations from the test cells are utilized in place of the test cells. Such methods comprise the following and may utilized the physiological conditions as noted above:

- (a) transfecting or transforming cells with an expression vector that directs the expression of MC-R1B in the cells, resulting in test cells;
- (b) preparing membranes containing MC-R1B from the test cells and exposing the membranes to a ligand of MC-R1B under conditions such that the ligand binds to the MC-R1B in the membranes;
- (c) subsequently or concurrently to step (b), exposing the membranes from the test cells to a substance;
- (d) measuring the amount of binding of the ligand to the MC-R1B in the membranes in the presence and the absence of the substance;
- (e) comparing the amount of binding of the ligand to MC-R1B in the membranes in the presence and the absence of the substance where a decrease in the amount of binding of the ligand to MC-R1B in the membranes in the presence of the substance indicates that the substance is capable of binding to MC-R1B.

[0090] The present invention also relates to a method for determining whether a substance is capable of binding to MC-R1B comprising:

- (a) transfecting or transforming cells with an expression vector that directs the expression of MC-R1B in the cells, resulting in test cells;
- (b) preparing membranes containing MC-R1B from the test cells and exposing the membranes from the test cells to the substance;
- (c) measuring the amount of binding of the substance to the MC-R1B in the membranes from the test cells;
- (d) comparing the amount of binding of the substance to MC-R1B in the membranes from the test cells with the amount of binding of the substance to membranes from control cells that have not been transfected with MC-R1B, where if the amount of binding of the substance to MC-R1B in the membranes from the test cells is greater than the amount of binding of the substance to the membranes from the control cells, then the substance is capable of binding to MC-R1B.

[0091] A preferred embodiment of the present invention is determining various ligand binding affinities using ^{125}I-

labeled NDP-α-MSH as the labeled ligand in the presence of varying concentration of unlabeled ligands. The activation of the second messenger pathway may be determined by measuring the intracellular cAMP elicited by agonist at various concentration.

[0092] The present invention also relates to polyclonal and monoclonal antibodies raised in response to either the form of MC-R1B, or a biologically active fragment thereof. Polyclonal or monoclonal antibodies may be raised against MC-R1B or a synthetic peptide (usually from about 9 to about 25 amino acids in length) from a portion of MC-R1B, for instance as disclosed in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:17, SEQ ID NO:20, SEQ ID NO:23, and SEQ ID NO:26. Monospecific antibodies to MC-R1B are purified from mammalian antisera containing antibodies reactive against MC-R1B or are prepared as monoclonal antibodies reactive with MC-R1B using the technique of Kohler and Milstein (1975, *Nature* 256: 495-497). Monospecific antibody as used herein is defined as a single antibody species or multiple antibody species with homogenous binding characteristics for MC-R1B. Homogenous binding as used herein refers to the ability of the antibody species to bind to a specific antigen or epitope, such as those associated with MC-R1B, as described above. MC-R1B-specific antibodies are raised by immunizing animals such as mice, rats, guinea pigs, rabbits, goats, horses and the like, with an appropriate concentration of MC-R1B protein or a synthetic peptide generated from a portion of MC-R1B with or without an immune adjuvant.

[0093] Preimmune serum is collected prior to the first immunization. Each animal receives between about 0.1 mg and about 1000 mg of MC-R1B protein associated with an acceptable immune adjuvant. Such acceptable adjuvants include, but are not limited to, Freund's complete, Freund's incomplete, alum-precipitate, water in oil emulsion containing *Corynebacterium parvum* and tRNA. The initial immunization consists of MC-R1B protein or peptide fragment thereof in, preferably, Freund's complete adjuvant at multiple sites either subcutaneously (SC), intraperitoneally (IP) or both. Each animal is bled at regular intervals, preferably weekly, to determine antibody titer. The animals may or may not receive booster injections following the initial immunization. Those animals receiving booster injections are generally given an equal amount of MC-R1B in Freund's incomplete adjuvant by the same route. Booster injections are given at about three week intervals until maximal titers are obtained. At about 7 days after each booster immunization or about weekly after a single immunization, the animals are bled, the serum collected, and aliquots are stored at about -20°C.

[0094] Monoclonal antibodies (mAb) reactive with MC-R1B are prepared by immunizing inbred mice, preferably Balb/c, with MC-R1B protein. The mice are immunized by the IP or SC route with about 1 mg to about 100 mg, preferably about 10 mg, of MC-R1B protein in about 0.5 ml buffer or saline incorporated in an equal volume of an acceptable adjuvant, as discussed above. Freund's complete adjuvant is preferred. The mice receive an initial immunization on day 0 and are rested for about 3 to about 30 weeks. Immunized mice are given one or more booster immunizations of about 1 to about 100 mg of MC-R1B in a buffer solution such as phosphate buffered saline by the intravenous (IV) route. Lymphocytes, from antibody positive mice, preferably splenic lymphocytes, are obtained by removing spleens from immunized mice by standard procedures known in the art. Hybridoma cells are produced by mixing the splenic lymphocytes with an appropriate fusion partner, preferably myeloma cells, under conditions which will allow the formation of stable hybridomas. Fusion partners may include, but are not limited to: mouse myelomas P3/NS1/Ag 4-1; MPC-11; S-194 and Sp 2/0, with Sp 2/0 being preferred. The antibody producing cells and myeloma cells are fused in polyethylene glycol, about 1000 mol. wt., at concentrations from about 30% to about 50%. Fused hybridoma cells are selected by growth in hypoxanthine, thymidine and aminopterin supplemented Dulbecco's Modified Eagles Medium (DMEM) by procedures known in the art. Supernatant fluids are collected from growth positive wells on about days 14, 18, and 21 and are screened for antibody production by an immunoassay such as solid phase immunoradioassay (SPIRA) using MC-R1B as the antigen. The culture fluids are also tested in the Ouchterlony precipitation assay to determine the isotype of the mAb. Hybridoma cells from antibody positive wells are cloned by a technique such as the soft agar technique of MacPherson, 1973, Soft Agar Techniques, in *Tissue Culture Methods and Applications,* Kruse and Paterson, Eds., Academic Press.

[0095] Monoclonal antibodies are produced *in vivo* by injection of pristine primed Balb/c mice, approximately 0.5 ml per mouse, with about 2 x 10^6 to about 6 x 106 hybridoma cells about 4 days after priming. Ascites fluid is collected at approximately 8-12 days after cell transfer and the monoclonal antibodies are purified by techniques known in the art.

[0096] *In vitro* production of anti- MC-R1B mAb is carried out by growing the hybridoma in DMEM containing about 2% fetal calf serum to obtain sufficient quantities of the specific mAb. The mAb are purified by techniques known in the art.

[0097] Antibody titers of ascites or hybridoma culture fluids are determined by various serological or immunological assays which include, but are not limited to, precipitation, passive agglutination, enzyme-linked immunosorbent antibody (ELISA) technique and radioimmunoassay (RIA) techniques. Similar assays are used to detect the presence of MC-R1B in body fluids or tissue and cell extracts.

[0098] It is readily apparent to those skilled in the art that the above described methods for producing monospecific antibodies may be utilized to produce antibodies specific for MC-R1B peptide fragments, or full-length MC-R1B.

[0099] MC-R1B antibody affinity columns are made, for example, by adding the antibodies to Affigel-10 (Biorad), a gel support which is pre-activated with N-hydroxysuccinimide esters such that the antibodies form covalent linkages

with the agarose gel bead support. The antibodies are then coupled to the gel via amide bonds with the spacer arm. The remaining activated esters are then quenched with 1 M ethanolamine HCl (pH 8). The column is washed with water followed by 0.23 M glycine HCl (pH 2.6) to remove any non-conjugated antibody or extraneous protein. The column is then equilibrated in phosphate buffered saline (pH 7.3) and the cell culture supernatants or cell extracts containing full-length MC-R1B or MC-R1B protein fragments are slowly passed through the column. The column is then washed with phosphate buffered saline until the optical density (A_{280}) falls to background, then the protein is eluted with 0.23 M glycine-HCl (pH 2.6). The purified MC-R1B protein is then dialyzed against phosphate buffered saline.

[0100] The DNA molecules, RNA molecules, recombinant protein and antibodies of the present invention may be used to screen and measure levels of MC-R1B. The recombinant proteins, DNA molecules, RNA molecules and antibodies lend themselves to the formulation of kits suitable for the detection and typing of MC-R1B. Such a kit would comprise a compartmentalized carrier suitable to hold in close confinement at least one container. The carrier would further comprise reagents such as recombinant MC-R1B or anti-MC-R1B antibodies suitable for detecting MC-R1B. The carrier may also contain a means for detection such as labeled antigen or enzyme substrates or the like.

[0101] Pharmaceutically useful compositions comprising modulators of MC-R1B may be formulated according to known methods such as by the admixture of a pharmaceutically acceptable carrier. Examples of such carriers and methods of formulation may be found in Remington's Pharmaceutical Sciences. To form a pharmaceutically acceptable composition suitable for effective administration, such compositions will contain an effective amount of the protein, DNA, RNA, modified MC-R1B, or either MC-R1B agonists or antagonists including tyrosine kinase activators or inhibitors.

[0102] Therapeutic or diagnostic compositions of the invention are administered to an individual in amounts sufficient to treat or diagnose disorders. The effective amount may vary according to a variety of factors such as the individual's condition, weight, sex and age. Other factors include the mode of administration.

[0103] The pharmaceutical compositions may be provided to the individual by a variety of routes such as subcutaneous, topical, oral and intramuscular.

[0104] The term "chemical derivative" describes a molecule that contains additional chemical moieties which are not normally a part of the base molecule. Such moieties may improve the solubility, half-life, absorption, etc. of the base molecule. Alternatively the moieties may attenuate undesirable side effects of the base molecule or decrease the toxicity of the base molecule. Examples of such moieties are described in a variety of texts, such as Remington's Pharmaceutical Sciences.

[0105] Compounds identified according to the methods disclosed herein may be used alone at appropriate dosages. Alternatively, co-administration or sequential administration of other agents may be desirable.

[0106] The present invention also has the objective of providing suitable topical, oral, systemic and parenteral pharmaceutical formulations for use in the novel methods of treatment of the present invention. The compositions containing compounds identified according to this invention as the active ingredient can be administered in a wide variety of therapeutic dosage forms in conventional vehicles for administration. For example, the compounds can be administered in such oral dosage forms as tablets, capsules (each including timed release and sustained release formulations), pills, powders, granules, elixirs, tinctures, solutions, suspensions, syrups and emulsions, or by injection. Likewise, they may also be administered in intravenous (both bolus and infusion), intraperitoneal, subcutaneous, topical with or without occlusion, or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts.

[0107] Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

[0108] For combination treatment with more than one active agent, where the active agents are in separate dosage formulations, the active agents can be administered concurrently, or they each can be administered at separately staggered times.

[0109] The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal, hepatic and cardiovascular function of the patient; and the particular compound thereof employed. A physician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition. Optimal precision in achieving concentrations of drug within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the drug's availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of a drug.

[0110] The following examples are provided to illustrate the present invention without, however, limiting the same hereto.

EXAMPLE 1

Isolation and Characterization of Human MC-1R Splice Variants

[0111] *Expressed Sequence Tag (EST) Identification* - Genbank databases were monitored using the Tblastn search program (Altschul et al., 1990, *J. Mol. Biol.* 215:403-410) with amino acid sequence from human melanocortin receptor proteins. A human EST (GenBank accession # AI123000; dbEST Id #1881544; GenBank gi: 3538766; Clone Id: Image: 1509887 (3') deposited August 18, 1997) derived from five normalized and pooled cDNA libraries was identified with a significant homology score. EST AI123000 exhibited sequence identity (>90% at the DNA level) to the 3' end of the gene for the human MC-1R. The nucleotide sequence of EST AA123000 is as follows:

TTTTTGATGC TGAGTCACAT TTATTACCAG ACTTTCCTGG CCCCATGCTC ACAGGCACTG
GTCACTGAGT CAGGCATTTG CACGGGCTGT CTGCTTGGGC GACTGCTGCA GGAAAGCAGG
CTGAGGCCCA GTGCCCAGTC TGAGCCTTAG AACCGGCCCT CAGGAGGGTC CAGCCTCACA
CCACTAGGGG GGCTCCTGCA AACCTGGTCC CTTGGCCTGA GGAGGGATTT CACCTCCTTT
TGCAGGAGCC GCTGCAAGGC TGTTGGATGA AGCTTTCTGG TCACAAAGCC CCTTCTCCTG
GGGCTGCTGT GGGAGTAGCT CTTGGCACAC ACTTCCACCC AGAGACTTCA CATCCCAGCT
GACGAGGGCA CGGTCCTGAG AGCAGGAGCA CGTCAGCACC TCCTTGAGCG TCCTGCGACG
TCCTGGCTGT GGAAGGCGTA GATGAGGGGG TCGATGATGG CATTGCAGAT GATGAGGGCG
AGAAAGAGGT TGAAAGTTCT TGAAGATGCA GCCGACGTGG GGTGCTCGGG GCAGAGGACG
ATGAGTGTGA GATGCAGGAA GAGGGGGCCC CAGCAGAGGA GAAATTGCCA ACAGGATTGG
TGANGGTGAA GCNGCTTTTA AGCCANAGCC CT (SEQ ID NO:28).

[0112] An additional EST was subsequently deposited on October 13, 1998 with similar sequence identity to the 3' end of the human MC-R1 gene. The GenBank accession number of this EST is #AI187892 (dbEST Id #826102; GenBank gi: 1774101; Clone Id: Image:625984 (3')). The nucleotide sequence of EST AA 187892 is as follows:

AACAAACTTT GGTAAGTAGT GAATGGCAAA GGCTCAGGGG GTTTGCAGCA GGACCTCCTT
GGGGTCAGAT CTGCCAGCCT CGGGTTGNCT TTCAGACCCC TCATCGTCTA TGAGGCATCC
TGTAAGTGCA GCTGTGGCCA GGGCTTGCAT ATGCAATCAA TTCCTGATTC ACCTAGTTCT
TGGCAGGAAG AGAAAATACT CGTTAATCAG AGGACTAAAC AATCCAAAAG CGCATTCTCT
CTCTGGGAAT GGAATATAAT TTATATTTCT GTTGCTATTG AATTATCCTT CTAATTCCAC
TGGACTAAAC TTAATACCAG TAATACTAAA ATTTTGTTTT GGGCAAAGCG ACTTGAAGGA

GGAGTCAGTG GCGCACTAAT NGCTGACTGT GAAAAATAAA CACCTCTGAG ATCAAGAATC
CCACAGTGAG AGCTAGGATT TGAAGGTATC CAGAGATTGC AAAACTCTGT GACTAACAGC
AANTTTTTAA CCAGGGCAAA CCAAACCACT CCTACTTGGA CTTAAACCTC AATCATTTAG
ATTTCATTCC C (SEQ ID NO:29).

[0113] Additional searching of the dbEST subset of Genbank identified two other human ESTs with sequence identity to the human MC-R1R: The first is available under GenBank accession number #AA431397 and was isolated from human testis mRNA and entered on May 22,1997 (dbEST Id #1075968; GenBank gi: 2115105; Clone Id: Image:782133 (5')). The nucleotide sequence of EST AA431397 is as follows:

AAATGATCTC TGAAAGTGTT GAAGCGCGGA CCCTTCTGGG TCCCGGAGGG GTCCCTGCAA
AACTCCAGGC AGGACTTCTC ACCAGCAGTC GTGGGGAACC GAGGAGGACA TGGGGAGGTT
GTGGGGCCTC AGGCTCCGGG CACCAGGGGC CAACCTCAGG CTCCTAAAGA GACATTTTCC
GCCCACATCC TGGGACACTC CGTCTGCTCC AATGACTGAG CAGCATCCAC CCCACCCCAT
CTTTGCTGCC AGCTCTCAGG ACCGTGCGCT CGTCAGCTGG GATGTGAAGT CTCTGGGTGG
AAGTGTGTGC CAAGAGCTAC TCTCACAGCA GCCCCAGGAG AAGGGGCTTT GTGAC (SEQ ID NO:30).

[0114] Another EST is available under GenBank accession number #AA778295 and was isolated from human fetal heart mRNA and was entered into the database on February 5, 1998 (dbEST Id #1075968; GenBank gi: 2115105; Clone Id: Image:782133 (5')). The nucleotide sequence of EST AA431397 is as follows:

CGGGTGATGC TGAGTCACAT TTATTACCAG ACTTTCCTGG CCCCATGCTC ACAGGCACTG
GTCACTGAGT CAGGCATTTG CCAGGGCTGT CTGCTTGGGC GACTGCTGCA TGAAAGCAGG
CTGAGGCCCC AGTGCCCAGT CTGAGCCTTA GAACCGGCCC TCAGGAGGGC TCAGCCCTAT
ACCACTAGGG GGGCTCCTGC AAACCTGGTC CCTTGGCCTG AGGCAGGGAT TTCACCTCCT
TTTGCAGGAG CCGCTGCAAG GCT (SEQ ID NO:31).

[0115] DNA sequencing of both strands using dye terminator cycle sequencing ready reactions (Perkin Elmer-ABI), analyzed on a 377 ABI Prism cycle sequencer suggested that this EST may represent a portion of an alternatively spliced form of the human MC-R 1 gene, disclosed throughout this specification as an MC-R1B protein, containing 382 amino acids. The previously described MC-R1 protein containing 317 amino acids is referred to as MC-R1A (Mountjoy, et al., 1992, *Science* 257:1248-1251 [see also US Patent No. 5,532,347]; Chhajlani and Wikberg, 1992, *FEBS Letters* 309: 417-420). Figure 1 shows alignment of these ESTs in relation to the MC-R1A and MC-R1B genes.

[0116] *Cloning of the MC-R Spliced Variant MC-R1B) From Human Genomic DNA* - Touchdown PCR was performed with sheared human genomic DNA (0.5 mg; Clontech, Palo Alto, CA) in a GeneAmp 9700 PCR system (Perkin Elmer, Foster City, CA). Two sense primers, MC1R- 5'for1 (5'TCTCACACTCATCGTCCTCTGCCC3'; SEQ ID NO:32) and MC1R-5'for2 (5'CATCGCCTACTACGACCACGTGGC3'; SEQ ID NO:33), were designed based on the published sequence of human MC-1RA (*id*). The anti-sense primers, MC1R-3'rev1 (5'CGCTGCAAGGCTGTTGGATGAAGC3'; SEQ ID NO:34) and MC1R-3'rev2 (5'GTGGGAGTAGCTCTTGGCACACAC; SEQ ID NO:35) were derived from EST AI123000. An Advantage cDNA PCR kit (Clontech, Palo Alto, CA) was used in the PCR reactions essentially following the manufacturer's instructions. Two exceptions were the addition of 5% DMSO to the PCR reactions and PCR cycling as described below: 1) 94°C for I minute, 2) 5 cycles of 94°C for 30 seconds, 72°C for 3 minutes, 3) 5 cycles of 94°C for 30 seconds, 70°C for 3 minutes, 4) 20 cycles of 94°C for 30 seconds, 68°C for 3 minutes. Subsequent sequencing of the PCR products using BIG DYE terminator cycle sequencing Ready Reactions (Perkin Elmer, Foster City, CA) and analysis on a 377 ABI Prism cycle sequencer (Perkin Elmer, Foster City, CA) revealed the presence of a cryptic 381bp intron immediately upstream (at the C-terminal Trp-317 residue) of the TGA stop codon of the human MC-R1 gene. The nucleotide boundaries describing this intron using consensus splice junction sequences as a guide (Senapathy et al., 1990, *Meth. Enzymol.* 183: 252-278) are as follows. A conserved consensus splice donor site (A/C)AG/gt (nucleotides 950-952) was found which form the first two bases of the Trp triplet codon.

[0117] Figure 2 shows the alternative splicing of the two human forms of MC-R1, with the COOH-terminal regions of expressed protein shown as well as the splice junctions identified in the various genomic clones encoding human MC-R1B.

[0118] Figure 3 shows a representative genomic clone for human MC-R1B, the DNA sequence of the genomic clone, mcl-8 (SEQ ID NO:21). Large cap letters represent exon regions while small cap nucleotides represent the single intron of the MC-R1 gene. A conserved consensus splice acceptor site cag/R was identified at nucleotides 1330-1332. Formation of this splice junction results from the donor supplying TG and the acceptor supplying C to form the triplet codon for Cys (instead of the C-terminal amino Trp of the MC-R1A). The novel coding sequence giving rise to an additional 65 amino acids (not including the Trp-317 to Cys substitution) occurs as result of this splicing event.

[0119] Figures 4A - 4B show the nucleotide and amino acid sequence of the amino terminal portion of MC-R1A and MC-R1B forms of mc1-8, the 5' and 3' splice junction sequences, as well as the respective amino acid sequences of the carboxy terminal portions of MC-R1A and MC-R1B.

[0120] Overlapping PCR was then performed to generate a contiguous open reading frame (382 amino acids) devoid of the intron containing this novel carboxyl terminus. PCR products for exons I and II were produced each containing a small portion of the other exon. The primers for exon I were as follows:

- 1. mc1-like-1f (5'gggcccgaattcgccgccATGGCTGTGCAGGGATCCCAGAG3';SEQ ID NO:36); and,
- 2. mc1-like-1r (5'GGCACGGTCCTGAGAGCAGGAGCATGTCAGCACCTCCTTG3'; SEQ ID NO:37), and contained an EcoRI site and a Kozak sequence (GCC GCC) for optimum translation. The primers for exon II were as follows:

- 1. mcl-like-2f (5'CTGACATGCTCCTGCTCTCAGGACCGTGCCCTCGTCAGC3'; SEQ ID NO:38); and,
- 2. mcl-tike-2r (5'agtttagcggccgcCTAGGGGGGCTCCTGCAAACCTGG3'; SEQ ID NO:39), which contains a NotI site. The MCI-like open reading frame was then generated from exon I and II templates and primers mcl-like 1f and mcl-like 2r. The MC1-like ORF fragment was digested with EcoRI and NotI, gel-purified, ligated into pcDNA3 vector and transformed into SCS1 *E. coli* (Stratagene, La Jolla, CA). Each of the four exemplified genomic clones (mc1-3, mc1-6, mc1-8 and mc1-9) were isolated using the above disclosed methodology.

[0121] *Cloning of the MC-R Spliced Variant (MC-R1B) From Human Testes mRNA* - Full-length cDNA encoding MC-R1B was isolated from human testis poly $(A)^+$ mRNA (pool of 25 male caucasians). RT-PCR using 1 mg of testis mRNA was performed using the Advantage RT for PCR kit with MMLV reverse transcriptase (Clontech, Palo Alto, CA) essentially following the manufacturer's instructions. PCR was then conducted with the Advantage cDNA PCR kit (Clontech, Palo Alto, CA) essentially following the manufacturer's instructions (cycling conditions: 94°C for 1 min., 60°C for 2 min., 72°C for 2 min., 72°C for 10 min. The forward sense primer utilized (appending EcoR1 restriction site and optimized initiation sequence based on Kozak rules) was (5'GATCGAATTCGCCGCCATGGCTGTGCAGGGATCCCAGAGAAG3'; SEQ ID NO:40) while the reverse antisense primers were (5'GATCGAATTCCTAGGGGGGCTCCTGCAAACCTG3'; SEQ ID NO:41) or (5'GATCGAATTCGTGCCCAGTCTGAGCCTTAGAACCG3': SEQ ID NO:42). Amplified products were agarose gel-purified, digested with EcoR1 and ligated to the mammalian expression vector pcDNA-3.1 (-) (Invitrogen). This methodology was utilized to identify the MC-R1ESTc11, as well as the other cDNA clones,

EXAMPLE 2

Transient Expression of Human MC-R1B

[0122] Four 800 ml triple flasks (Nalge Nunc) containing 125 ml of Dulbecco's modified Eagle Medium (DMEM), (Gibco-BRL) supplemented with 10% fetal bovine serum (Sigma), L-glutamine (Gibco/BRL), and Pen/Strep (Gibco/BRL) were inoculated with COS 7 cells, and incubated for 4 days. The cells in each flask were collected by pouring off the media, adding 30 ml of trypsin/EDTA (0.05%, Gibco/BRL) to each flask and letting the flasks incubate at room temp for 2 min. Then the tyrpsin solution was removed, and the flasks incubated at 37°C for 10 minutes, 30 ml of DMEM added, and the cells collected. The cells were pelleted at 1000 rpm for 8 min., washed twice with Delbecco's PBS lacking Mg^{++} and Ca^{++} (Gibco/BRL). The cells were counted and resuspended to a density of 1.2 X 10^7/ml of PBS lacking Mg^{++} and Ca^{++}. DNA was introduced into the cells by electroporation; 0.85 ml of cells was mixed with 20 μg of MC-R1 expression plasmid, in an ice cold 0.4 cm cuvette (BioRad). The solution was electroporated with a BioRad Gene Pulsar electroporator set to 0.26 kV, 960 μFD. The cells from 30 electroporations were pooled into 1 liter of DMEM and dispensed 125 ml per triple flask and incubated at 37°C. Three days later the media from each flask was poured off, the cells were washed with 100 ml of Delbecco's PBS lacking Mg^{++} and Ca^{++}, and 30 ml of enzyme-free dissociation buffer (Gibco/BRL) added. After incubation at room temperature for 10 min., cells were collected, centrifuged at 1000 rpm for 10 min. at 4°C, and resuspended into 15 ml of membrane buffer (10 mM Tris pH 7.4, with proteinase inhibitors). A 500 x proteinase inhibitor solution contains Lxupeptin (Sigma) 2 μg/ml, Phosphoramidon (Sigma) 5 μM, Bacitracin (Sigma) 20 μg/ml, Aprotinin (Sigma) 2.5 μg/ml, and 0.05 M AEBSF (Pefabloc). Cells are disrupted with 10 strokes of a motor driven dounce, the homogenate transferred to 50 ml Falcon tubes and spun at 2200 rpm, 4°C for 10 min. The supernatant was transferred to 50 ml centrifuge tubes and spun at 18K for 20 min. in a Sorvall RC5B centrifuge. The membranes were resuspended into 0.6 ml of membrane buffer, passed 2 times through a 18 gauge needle and 5 times through a 25 gauge needle, aliquoted, frozen in liquid nitrogen, and stored at -80°C until needed.

EXAMPLE 3

Pharmacological Properties of Human MC-R1B

[0123] *Melanocortin Radioligand Binding Assay* - Binding reactions (total volume = 250 pl) contained MBB (50 mM Tris pH 7.2, 2 mM $CaCl_2$, 1 mM $MgCl_2$), 0.1% BSA, crude membranes prepared from cells expressing human MC-R1B receptor, 200 pM [^{125}I]-NDP αMSH (Amersham Corp.), and increasing concentrations of unlabelled test compounds dissolved in DMSO (DMSO final concentration = 2%). Reactions were incubated for 1 hour without shaking and then filtered through 96-well filter plates (Packard Corp.). Filters were washed three times with TNE buffer (50 mM Tris pH 7.4, 5 mM EDTA, 150 mM NaCl), dried and counted using Microscint-20 in a Topcount scintillation counter (Packard). Inhibitory concentration 50% (IC_{50} given in nM) is defined as the concentation of unlabeled melanocortin peptides which displaces 50% of the binding to the MC-1R expressing cell membranes. Non-specific binding was determined in the presence of 2 μM unlabelled NDP αMSH (Peninsula laboratories). COS-7 cells transiently expressing MC-R1B bound [^{125}I]-NDP-αMSH with high affinity and specificity (specific binding, defined as the difference in binding observed in the absence and presence of 1 μM unlabeled NDP-αMSH was >90% of total binding). Little, or no specific binding was observed in sham-transfected COS-7 cells. As shown below in Table 1, several melanocortin-derived peptides (amino acid sequence defined below in single letter IUPAC code) displaced the binding of [^{125}I]-NDP-αMSH potently indicating the presence of a high affinity binding site conferred by MC-1RB expression.

TABLE 1

Peptide	IC_{50} (nM)
αMSH	5
γMSH	5
NDP-αMSH	0.7
SHU-9119	0.7
MT-II	0.2
ACTH	5

[0124] *cAMP Functional Receptor Assay* - Receptor-mediated stimulation of cyclic AMP (cAMP) formation was assayed in COS-7 cells transfected with MC-1RB expression plasmids. Cells expressing MC-1RB were dissociated from tissue culture flasks by rinsing with Ca and Mg free phosphate buffered saline (Life Technologies, Gaithersburg, MD) and detached following 5 min. incubation with enzyme-free dissociation buffer (Specialty Media, Lavellette, NJ). Cells were collected by centrifugation and resuspended in Earle's Balanced Salt Solution (EBSS) (Life Technologies, Gaithersburg, MD) with additions of 10 mM HEPES pH 7.5, 5 mM $MgCl_2$, 1 mM glutamine and I mg/ml bovine serum albumin. Cells are counted and diluted to 2 to 4 x 10^6/ml. The phosphodiesterace inhibitor 3-isobutyl-1-methylxanthine was added at a concentration of 0.6 mM. Test peptides were diluted in EBSS with above additions and 10% DMSO; 0.1 vol of compounds added to 0.9 vol of cells. After room temperature incubation for 40 min., cells are lysed by incubation at 100°C for 5 min. to release accumulated cAMP. cAMP is measured in an aliquot of the cell lysate with the Amersham (Arlington Heights, IL) cAMP detection assay (RPA556). The amount of cAMP production which results from an unknown compound is compared to that amount of cAMP produced in response to αMSH which is defined as a 100 % agonist.

[0125] Previous studies (Mountjoy, et al., 1992, *Science* 257:1248-1251 [see also US Patent No. 5,532,347]; Chhajlani and Wikberg, 1992, *FEBS Letters* 309:417-420) has documented that activation of the MC-1RA isoform by melanocortin agonists results in an elevation of intracellular cAMP production through the coupling of G-proteins to activation of membrane-bound adenylate cyclase. Expression of MC-R1B protein transiently in COS-7 also gives a rise (-3-fold at maximum agonist concentration compared to background response measured in sham-transfected COS-7 cells) in intracellular cAMP formation specifically evoked by several melanocortin agonists or mixed agonists / antagonists including αMSH, MT-II, SHU-9119, γMSH, NDP-αMSH, and βMSH. This result indicates that MC-RIB cDNA encodes a functional receptor for melanocortins. The approximate rack order of potency of the above peptides in eliciting the cAMP response was MT-II> NDP-MSH> SHU-9119> αMSH> βMSH> γMSH.

[0126] The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims.

SEQUENCE LISTING

[0127]

. <110> APPLICANT: Merck & Co., Inc.

. <120> TITLE: DNA MOLECULES ENCODING SPLICE VARIANTS OF THE HUMAN MELANOCORTIN 1 RECEPTOR PROTEIN

. <130> DOCKET/FILE REFERENCE: 20367PCT

. <160> NUMBER OF SEQUENCES: 46

. <170> SOFTWARE: FastSEQ for Windows Version 3.0

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<213> ORGANISM:Homo sapien (human)

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225                 230                 235                 240
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Phe Phe Leu His Leu Thr Leu Ile Val Leu Cys Pro Glu His Pro Thr
            260                 265                 270
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    290                 295                 300
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cgtgccctcg tcagctggga tgtgaagtct ctgggtggaa gtgtgtgcca agagctactc    1020
ccacagcagc cccaggagaa ggggctttgt gaccagaaag cttcatccac agccttgcag    1080
cggctcctgc aaaaggaggt gaaatccctg cctcaggcca agggaccagg tttgcaggag    1140
ccccctag                                                            1149
```

. <210> SEQ ID NO:4
<211> LENGTH: 382
<212> TYPE: PRT
<213> ORGANISM:Homo sapien (human)

. <400> SEQ ID NO:4

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

```
Phe Phe Leu His Leu Thr Leu Ile Val Leu Cys Pro Glu His Pro Thr
            260                 265                 270
Cys Gly Cys Ile Phe Lys Asn Phe Asn Leu Phe Leu Ala Leu Ile Ile
        275                 280                 285
Cys Asn Ala Ile Ile Asp Pro Leu Ile Tyr Ala Phe His Ser Gln Glu
    290                 295                 300
Leu Arg Arg Thr Leu Lys Glu Val Leu Thr Cys Ser Cys Ser Gln Asp
305                 310                 315                 320
Arg Ala Leu Val Ser Trp Asp Val Lys Ser Leu Gly Gly Ser Val Cys
                325                 330                 335
Gln Glu Leu Leu Pro Gln Gln Pro Gln Glu Lys Gly Leu Cys Asp Gln
            340                 345                 350
Lys Ala Ser Ser Thr Ala Leu Gln Arg Leu Leu Gln Lys Glu Val Lys
        355                 360                 365
Ser Leu Pro Gln Ala Lys Gly Pro Gly Leu Gln Glu Pro Pro
    370                 375                 380
```

. <210> SEQ ID NO:5
<211> LENGTH: 1149
<212> TYPE: DNA
<213> ORGANISM:Homo sapien (human)

. <400> SEQ ID NO:5

```
atggctgtgc agggatccca gagaagactt ctgggctccc tcaactccac ccccacagcc      60
atcccccagc tggggctggc tgccaaccag acaggagccc ggtgcctgga ggtgtccatc     120
tctgacgggc tcttcctcag cctggggctg gtgagcttgg tgaagaacgc gctggtggtg     180
gccaccatcg ccaagaaccg gaacctgcac tcacccatgt actgcttcat ctgctgcctg     240
gccttgtcgg acctgctggt gagcgggagc aacgtgctgg agacggccgt catcctcctg     300
ctggaggccg gtgcactggt ggcccgggct gcggtgctgc agcagctgga caatgtcatt     360
gacgtgatca cctgcagctc catgctgtcc agcctctgct tcctgggcgc catcgccgtg     420
gaccgctaca tctccatctt ctacgcactg cgctaccaca gcatcgtgac cctgccgcgg     480
gcgcggcaag ccgttgcggc catctgggtg gccagtgtcg tcttcagcac gctcttcatc     540
gcctactacg accacgtggc cgtcctgctg tgcctcgtgg tcttcttcct ggctatgctg     600
gtgctcatgg ccgtgctgta cgtccacatg ctggcccggg cctgccagca cgcccagggc     660
atcgcccggc tccacaagag gcagcgcccg gtccaccagg gctttggcct taaaggcgct     720
gtcaccctca ccatcctgct gggcattttc ttcctctgct ggggcccctt cttcctgcat     780
ctcacactca tcgtcctctg ccccgagcac ccacgtgcg gctgcatctt caagaacttc     840
aacctctttc tcgccctcat catctgcaat gccatcatcg acccccctcat ctacgccttc     900
cacagccagg agctccgcag gacgctcaag gaggtgctga catgctcctg ctctcaggac     960
cgtgccctcg tcagctggga tgtgaagtct ctgggtggaa gtgtgtgcca agagctactc    1020
ccacagcagc cccaggagaa ggggctttgt gaccagaaag cttcatccac agccttgcag    1080
cggctcctgc aaaaggaggt gaaatccctg cctcaggcca agggaccagg tttgcaggag    1140
ccccctag                                                            1149
```

. <210> SEQ ID NO:6
<211> LENGTH: 382
<212> TYPE: PRT
<213> ORGANISM:homo sapien (human)

. <400> SEQ ID NO:6

```
Met Ala Val Gln Gly Ser Gln Arg Arg Leu Leu Gly Ser Leu Asn Ser
 1               5                  10                  15
Thr Pro Thr Ala Ile Pro Gln Leu Gly Leu Ala Ala Asn Gln Thr Gly
            20                  25                  30
```

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

. <210> SEQ ID NO:7
<211> LENGTH: 1149
<212> TYPE: DNA
<213> ORGANISM:Homo sapien (human)

. <400> SEQ ID NO:7

```
atggctgtgc agggatccca gagaagactt ctgggctccc tcaactccac ccccacagcc      60
atcccccagc tggggctggc tgccaaccag acaggagccc ggtgcctgga ggtgtccatc     120
tctgacgggc tcttcctcag cctggggctg gtgagcttgg tggagaacgc gctggtggtg     180
gccaccatcg ccaagaaccg gaacctgcac tcacccatgt actgcttcat ctgctgcctg     240
```

```
gccttgtcgg acctgctggt gagcgggagc aacgtgctgg agacggccgt catcctcctg     300
ctggaggccg gtgcactggt ggcccgggct gcggtgctgc agcagctgga caatgtcatt     360
gacgtgatca cctgcagctt catgctgtcc agcctctgct tcctgggcgc catcgccgtg     420
gaccgctaca tctccatctt ctacgcactg tgctaccaca gcatcgtgac cctgccgcgg     480
gcgcggcgag ccgttgcggc catctgggtg gccagtgtcg tcttcagcac gctcttcatc     540
gcctactacg accacgtggc cgtcctgctg tgcctcgtgg tcttcttcct ggctatgctg     600
gtgctcatgg ccgtgctgta cgtccacatg ctggcccggg cctgccagca cgcccagggc     660
atcgcccggc tccacaagag gcagcgcccg gtccaccagg gctttggcct taaaggcgct     720
gtcaccctca ccatcctgct gggcattttc ttcctctgct ggggcccctt cttcctgcat     780
ctcacactca tcgtcctctg ccccgagcac cccacgtgcg gctgcatctt caagaacttc     840
aacctctttc tcgccctcat catctgcaat gccatcatcg acccccctcat ctacgccttc     900
cacagccagg agctccgcag gacgctcaag gaggtgctga catgctcctg ctctcaggac     960
cgtgccctcg tcagctggga tgtgaagtct ctgggtggaa gtgtgtgcca agagctactc    1020
ccacagcagc cccaggagaa ggggctttgt gaccagaaag cttcatccac agccttgcag    1080
cggctcctgc aaaaggaggt gaaatccctg cctcaggcca agggaccagg tttgcaggag    1140
ccccctag                                                            1149
```

. <210> SEQ ID NO:8
<211> LENGTH: 382
<212> TYPE: PRT
<213> ORGANISM:Homo sapien (human)

. <400> SEQ ID NO:8

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

```
Phe Phe Leu His Leu Thr Leu Ile Val Leu Cys Pro Glu His Pro Thr
            260                 265                 270
Cys Gly Cys Ile Phe Lys Asn Phe Asn Leu Phe Leu Ala Leu Ile Ile
        275                 280                 285
Cys Asn Ala Ile Ile Asp Pro Leu Ile Tyr Ala Phe His Ser Gln Glu
    290                 295                 300
Leu Arg Arg Thr Leu Lys Glu Val Leu Thr Cys Ser Cys Ser Gln Asp
305                 310                 315                 320
Arg Ala Leu Val Ser Trp Asp Val Lys Ser Leu Gly Gly Ser Val Cys
                325                 330                 335
Gln Glu Leu Leu Pro Gln Gln Pro Gln Glu Lys Gly Leu Cys Asp Gln
            340                 345                 350
Lys Ala Ser Ser Thr Ala Leu Gln Arg Leu Leu Gln Lys Glu Val Lys
        355                 360                 365
Ser Leu Pro Gln Ala Lys Gly Pro Gly Leu Gln Glu Pro Pro
    370                 375                 380
```

. <210> SEQ ID NO:9
<211> LENGTH: 1149
<212> TYPE: DNA
<213> ORGANISM:Homo sapien (human)

. <400> SEQ ID NO:9

```
atggctgtgc agggatccca gagaagactt ctgggctccc tcaactccac ccccacagcc      60
atcccccagc tggggctggc tgccaaccag acaggagccc ggtgcctgga ggtgtccatc     120
tctgacgggc tcttcctcag cctggggctg gtgagcttgg tggagaacgc gctggtggtg     180
gccaccatcg ccaagaaccg gaacctgcac tcacccatgt actgcttcat ctgctgcctg     240
gccttgtcgg acctgctggt gagcgggagc aacgtgctgg agacggccgt catcctcctg     300
ctggaggccg gtgcactggt ggcccgggct gcggtgctgc agcagctgga caatgtcatt     360
gacgtgatca cctgcagctc catgctgtcc agcctctgct tcctgggcgc catcgccgtg     420
gaccgctaca tctccatctt ctacgcactg cgctaccaca gcatcgtgac cctgccgcgg     480
gcgcggcgag ccgttgcggc catctgggtg gccagtgtcg tcttcagcac gctcttcatc     540
gcctactacg accacgcggc cgtcctgctg tgcctcgtgg tcttcttcct ggctatgctg     600
gtgctcatgg ccgtgctgta cgtccacatg ctggcccggg cctgccagca cgcccagggc     660
atcgcccggc tccacaagag gcagcgcccg gtccaccagg gctttggcct taaaggcgct     720
gtcaccctca ccatcctgct gggcattttc ttcctctgct ggggcccctt cttcctgcat     780
ctcacactca tcgtcctctg ccccgagcac cccacgtgcg gctgcatctt caagaacttc     840
aacctctttc tcgccctcat catctgcaat gccatcatcg acccccctcat ctacgccttc     900
cacagccagg agctccgcag gacgctcaag gaggtgctga catgctcctg ctctcaggac     960
cgtgccctcg tcagctggga tgtgaagtct ctgggtggaa gtgtgtgcca agagcgactc    1020
ccacagcagc cccaggagaa ggggctttgt gaccagaaag cttcatccac agccttgcag    1080
cggctcctgc aaaaggggat gaaatccctg cctcaggcca agggaccagg tttgcaggag    1140
ccccctag                                                            1149
```

. <210> SEQ ID NO:10
<211> LENGTH: 382
<212> TYPE: PRT
<213> ORGANISM:Homo sapien (human)

. <400> SEQ ID NO:10

```
Met Ala Val Gln Gly Ser Gln Arg Arg Leu Leu Gly Ser Leu Asn Ser
 1               5                  10                  15
Thr Pro Thr Ala Ile Pro Gln Leu Gly Leu Ala Ala Asn Gln Thr Gly
            20                  25                  30

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

. <210> SEQ ID NO:11
<211> LENGTH: 1149
<212> TYPE: DNA
<213> ORGANISM:Homo sapien (human)

. <400> SEQ ID NO:11

```
atggctgtgc agggatccca gagaagactt ctgggctccc tcaactccac ccccacagcc      60
atcccccagc tggggctggc tgccaaccag acaggagccc ggtgcctgga ggtgtccatc     120
tctgacgggc tcttcctcag cctggggctg gtgagcttgg tgaagaacgc gctggtggtg     180
gccaccatcg ccaagaaccg gaacctgcac tcacccatgt actgcttcat ctgctgcctg     240

gccttgtcgg acctgctggt gagcgggagc aacgtgctgg agacggccgt catcctcctg     300
ctggaggccg gtgcactggt ggcccgggct gcggtgctgc agcagctgga caatgtcatt     360
gacgtgatca cctgcagctc catgctgtcc agcctctgct tcctgggcgc catcgccgtg     420
gaccgctaca tctccatctt ctacgcactg cgctaccaca gcatcgtgac cctgccgcgg     480
gcgcggcaag ccgttgcggc catctgggtg gccagtgtcg tcttcagcac gctcttcatc     540
gcctactacg accacgtggc cgtcctgctg tgcctcgtgg tcttcttcct ggctatgctg     600
gtgctcatgg ccgtgctgta cgtccacatg ctggcccggg cctgccagca cgcccagggc     660
atcgcccggc tccacaagag gcagcgcccg gtccaccagg gctttggcct taaaggcgct     720
gtcaccctca ccatcctgct gggcattttc ttcctctgct ggggcccctt cttcctgcat     780
ctcacactca tcgtcctctg ccccgagcac cccacgtgcg gctgcatctt caagaacttc     840
aacctctttc tcgccctcat catctgcaat gccatcatcg acccccctcat ctacgccttc     900
cacagccagg agctccgcag gacgctcaag gaggtgctga catgctcctg ctctcaggac     960
cgtgccctcg tcagctggga tgtgaagtct ctgggtggaa gtgtgtgcca agagctactc    1020
ccacagcagc cccaggagaa ggggctttgt gaccagaaag cttcatccac agccttgcag    1080
cggctcctgc aaaaggaggt gaaatccctg cctcaggcca agggaccagg tttgcaggag    1140
ccccctag                                                            1149
```

<210> SEQ ID NO:12
<211> LENGTH: 382
<212> TYPE: PRT
<213> ORGANISM:Homo sapien (human)

<400> SEQ ID NO:12

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

Phe Phe Leu His Leu Thr Leu Ile Val Leu Cys Pro Glu His Pro Thr
            260                 265                 270
Cys Gly Cys Ile Phe Lys Asn Phe Asn Leu Phe Leu Ala Leu Ile Ile
        275                 280                 285
Cys Asn Ala Ile Ile Asp Pro Leu Ile Tyr Ala Phe His Ser Gln Glu
    290                 295                 300
Leu Arg Arg Thr Leu Lys Glu Val Leu Thr Cys Ser Cys Ser Gln Asp
305                 310                 315                 320
Arg Ala Leu Val Ser Trp Asp Val Lys Ser Leu Gly Gly Ser Val Cys
                325                 330                 335
Gln Glu Leu Leu Pro Gln Gln Pro Gln Glu Lys Gly Leu Cys Asp Gln
            340                 345                 350
Lys Ala Ser Ser Thr Ala Leu Gln Arg Leu Leu Gln Lys Glu Val Lys
        355                 360                 365
Ser Leu Pro Gln Ala Lys Gly Pro Gly Leu Gln Glu Pro Pro
    370                 375                 380
```

. <210> SEQ ID NO:13
<211> LENGTH: 1149
<212> TYPE: DNA
<213> ORGANISM:Homo sapien (human)

. <400> SEQ ID NO:13

```
atggctgtgc agggatccca gagaagactt ctgggctccc tcaactccac ccccacagcc      60
atcccccagc tggggctggc tgccaaccag acaggagccc ggtgcctgga ggtgtccatc     120
tctgacgggc tcttcctcag cctggggctg gtgagcttgg tgaagaacgc gctggtggtg     180
gccaccatcg ccaagaaccg gaacctgcac tcacccatgt actgcttcat ctgctgcctg     240
gccttgtcgg acctgctggt gagcgggagc aacgtgctgg agacggccgt catcctcctg     300
ctggaggccg gtgcactggt ggcccgggct gcggtgctgc agcagctgga caatgtcatt     360
gacgtgatca cctgcagctc catgctgtcc agcctctgct tcctgggcgc catcgccgtg     420
gaccgctaca tctccatctt ctacgcactg cgctaccaca gcatcgtgac cctgccgcgg     480
gcgcggcaag ccgttgcggc catctgggtg gccagtgtcg tcttcagcac gctcttcatc     540
gcctactacg accacgtggc cgtcctgctg tgcctcgtgg tcttcttcct ggctatgctg     600
gtgctcatgg ccgtgctgta cgtccacatg ctggcccggg cctgccagca cgcccagggc     660
atcgcccggc tccacaagag gcagcgcccg gtccaccagg gctttggcct taaaggcgct     720
gtcaccctca ccatcctgct gggcattttc ttcctctgct ggggcccctt cttcctgcat     780
ctcacactca tcgtcctctg ccccgagcac cccacgtgcg gctgcatctt caagaacttc     840
aacctctttc tcgccctcat catctgcaat gccatcatcg acccccctcat ctacgccttc     900
cacagccagg agctccgcag gacgctcaag gaggtgctga catgctcctg ctctcaggac     960
cgtgccctcg tcagctggga tgtgaagtct ctgggtggaa gtgtgtgcca agagctactc    1020
ccacagcagc cccaggagaa ggggctttgt gaccagaaag cttcatccac agccttgcag    1080
cggctcctgc aaaaggaggt gaaatccctg cctcaggcca agggaccagg tttgcaggag    1140
ccccctag                                                            1149
```

. <210> SEQ ID NO:14
<211> LENGTH: 382
<212> TYPE: PRT
<213> ORGANISM:Homo sapien (human)

. <400> SEQ ID NO:14

```
Met Ala Val Gln Gly Ser Gln Arg Arg Leu Leu Gly Ser Leu Asn Ser
 1               5                  10                  15
Thr Pro Thr Ala Ile Pro Gln Leu Gly Leu Ala Ala Asn Gln Thr Gly
            20                  25                  30
```

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

. <210> SEQ ID NO:15
<211> LENGTH: 1530
<212> TYPE: DNA
<213> ORGANISM:Homo sapien (human)

. <400> SEQ ID NO:15

```
atggctgtgc agggatccca gagaagactt ctgggctccc tcaactccac ccccacagcc      60
atcccccagc tggggctggc tgccaaccag acaggagccc ggtgcctgga ggtgtccatc     120
tctgacgggc tcttcctcag cctggggctg gtgagcttgg tggagaacgc gctggtggtg     180
gccaccatcg ccaagaaccg gaacctgcac tcacccatgt actgcttcat ctgctgcctg     240
```

```
gccttgtcgg acctgctggt gagcgggagc aacgtgctgg agacggccgt catcctcctg     300
ctggaggccg gtgcactggt ggcccaggct gcggtgctgc agcagctgga caatgtcatt     360
gacgtgatca cctgcagctc catgctgtcc agcctctgct tcctgggcgc catcgccgcg     420
gaccgctaca tctccatctt ctacgcactg cgctaccaca gcatcgtgac cctgccgcgg     480
gcgcggcgag ccgttgcggc catctgggtg gccagtgtcg tcttcagcac gctcttcatc     540
gcctactacg accacgtggc cgtcctgctg tgcctcgtgg tcttcttcct ggctatgctg     600
gtgctcatgg ccgtgctgta cgtccacatg ctggcccggg cctgccagca cgcccagggc     660
atcgcccggc tccacaagag gcagcgcccg gtccaccagg gctttggcct taaaggcgct     720
gtcaccctca ccatcctgct gggcattttc ttcctctgct ggggcccctt cttcctgcat     780
ctcacactca tcgtcctctg ccccgagcac cccacgtgcg gctgcatctt caagaacttc     840
aacctctttc tcgccctcat catctgcaat gccatcatcg acccccctcat ctacgccttc     900
cacagccagg agctccgcag gacgctcaag gaggtgctga catgctcctg gtgagcgcgg     960
tgcacgcggc tttaagtgtg ctgggcagag ggaggtggtg atattgtgtg gtctggttcc    1020
tgtgtgaccc tgggcagttc cttacctccc tggtccccgt ttgtcaaaga ggatggacta    1080
aatgatctct gaangtgttg aagcgcggac ccttctgggt ccagggaggg gtccctgcaa    1140
aactccaggc aggacttctc accagcagtc gtggggaacg gaggaggaca tggggaggtt    1200
gtggggcctc aggctccggg caccaggggc caacctcagg ctcctaaaga gacattttcc    1260
gcccactcct gggacactcc gtctgctcca atgactgagc agcatccacc ccaccccatc    1320
tttgctgcca gctctcagga ccgtgccctc gtcagctggg atgtgaagtc tctgggtgga    1380
agtgtgtgcc aagagctact cccacagcag ccccaggaga aggggctttg tgaccagaaa    1440
gcttcatcca cagccttgca gcggctcctg caaaaggagg tgaaatccct gcctcaggcc    1500
aagggaccag gtttgcagga gccccccctag                                    1530
```

. <210> SEQ ID NO:16
<211> LENGTH: 1149
<212> TYPE: DNA
<213> ORGANISM:Homo sapien (human)

. <400> SEQ ID NO:16

```
atggctgtgc agggatccca gagaagactt ctgggctccc tcaactccac ccccacagcc      60
atcccccagc tggggctggc tgccaaccag acaggagccc ggtgcctgga ggtgtccatc     120
tctgacgggc tcttcctcag cctggggctg gtgagcttgg tggagaacgc gctggtggtg     180
gccaccatcg ccaagaaccg gaacctgcac tcacccatgt actgcttcat ctgctgcctg     240
gccttgtcgg acctgctggt gagcgggagc aacgtgctgg agacggccgt catcctcctg     300
ctggaggccg gtgcactggt ggcccaggct gcggtgctgc agcagctgga caatgtcatt     360
gacgtgatca cctgcagctc catgctgtcc agcctctgct tcctgggcgc catcgccgcg     420
gaccgctaca tctccatctt ctacgcactg cgctaccaca gcatcgtgac cctgccgcgg     480
gcgcggcgag ccgttgcggc catctgggtg gccagtgtcg tcttcagcac gctcttcatc     540
gcctactacg accacgtggc cgtcctgctg tgcctcgtgg tcttcttcct ggctatgctg     600
gtgctcatgg ccgtgctgta cgtccacatg ctggcccggg cctgccagca cgcccagggc     660
atcgcccggc tccacaagag gcagcgcccg gtccaccagg gctttggcct taaaggcgct     720
gtcaccctca ccatcctgct gggcattttc ttcctctgct ggggcccctt cttcctgcat     780
ctcacactca tcgtcctctg ccccgagcac cccacgtgcg gctgcatctt caagaacttc     840
aacctctttc tcgccctcat catctgcaat gccatcatcg acccccctcat ctacgccttc     900
cacagccagg agctccgcag gacgctcaag gaggtgctga catgctcctg ctctcaggac     960
cgtgccctcg tcagctggga tgtgaagtct ctgggtggaa gtgtgtgcca agagctactc    1020
ccacagcagc cccaggagaa ggggctttgt gaccagaaag cttcatccac agccttgcag    1080
cggctcctgc aaaaggaggt gaaatccctg cctcaggcca agggaccagg tttgcaggag    1140
ccccccctag                                                          1149
```

. <210> SEQ ID NO:17
<211> LENGTH: 382
<212> TYPE: PRT
<213> ORGANISM:Homo sapien (human)

. <400> SEQ ID NO:17

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

. <210> SEQ ID NO:18
<211> LENGTH: 1540
<212> TYPE: DNA
<213> ORGANISM:Homo sapien (human)

. <400> SEQ ID NO:18

```
atggctgtgc agggatccca gagaagactt ctgggctccc tcaactccac ccccacagcc      60
atcccccagc tggggctggc tgccaaccag acaggagccc ggtgcctgga ggtgtccatc     120
tctgacgggc tcttcctcag cctggggctg gtgagcttgg tggagaacgc gctggtggtg     180
gccaccatcg ccaagaaccg gaacctgcac tcacccatgt actgcttcat ctgctgcctg     240
gccttgtcgg acctgctggt gagcgggagc aacgtgctgg agacggccgt catcctcctg     300
ctggaggccg gtgcactggt ggcccgggct gcggtgctgc agcagctgga caatgtcatt     360
gacgtgatca cctgcagctc catgctgtcc agcctctgct tcctgggcgc catcgccgtg     420
gaccgctaca tctccatctt ctacgcactg cgctaccaca gcatcgtgac cctgccgcgg     480
gcgcggcgag ccgttgcggc cctctgggtg gccagtgtcg tcttcagcac gctcttcatc     540
gcctactacg accacgtggc cgtcctgctg tgcctcgtgg tcttcttcct ggctatgctg     600
gtgctcatgg ccgtgctgta cgtccacatg ctggcccggg cctgccagca cgcccagggc     660
atcgcccggc tccacaagag gcagcgcccg gtccaccagg gctttggcct taaaggcgct     720
gtcaccccca ccatcctgct gggcattttc ttcctctgct ggggcccctt cttcctgcat     780
ctcacactca tcgtcctctg ccccgagcac cccacgtgcg gctgcatctt caagaacttc     840
aacctctttc tcgccctcat catctgcaat gccttcatcg acccccctcat ctacgccttc     900
cacagccagg agctccgcag gacgctcaag gaggtgctga catgctcctg catgctcctg     960
gtgagcgcgg tgcacgcggc tttaagtgtg ctgggcagag ggaggtggtg atattgtgtg    1020
gtctggttcc tgtgtgaccc tgggcagttc cttacctccc tggtccccgt ttgtcaaaga    1080
ggatggacta aatgatctct gaangtgttg aagcgcggac ccttctgggt ccagggaggg    1140
gtccctgcaa aactccaggc aggacttctc accagcagtc gtggggaacg gaggaggaca    1200
tggggaggtt gtggggcctc aggctccggg caccaggggc caacctcagg ctcctaaaga    1260
gacattttcc gcccactcct gggacactcc gtctgctcca atgactgagc agcatccacc    1320
ccaccccatc tttgctgcca gctctcagga ccgtgccctc gtcagctggg atgtgaagtc    1380
tctgggtgga agtgtgtgcc aagagctact cccacagcag ccccaggaga aggggctttg    1440
tgaccagaaa gcttcatcca cagccttgca gcggctcctg caaaaggagg tgaaatccct    1500
gcctcaggcc aagggaccag gtttgcagga gccccctag                           1540
```

. <210> SEQ ID NO:19
<211> LENGTH: 1149
<212> TYPE: DNA
<213> ORGANISM:Homo sapien (human)

. <400> SEQ ID NO:19

```
atggctgtgc agggatccca gagaagactt ctgggctccc tcaactccac ccccacagcc      60
atcccccagc tggggctggc tgccaaccag acaggagccc ggtgcctgga ggtgtccatc     120
tctgacgggc tcttcctcag cctggggctg gtgagcttgg tggagaacgc gctggtggtg     180
gccaccatcg ccaagaaccg gaacctgcac tcacccatgt actgcttcat ctgctgcctg     240
gccttgtcgg acctgctggt gagcgggagc aacgtgctgg agacggccgt catcctcctg     300
ctggaggccg gtgcactggt ggcccgggct gcggtgctgc agcagctgga caatgtcatt     360
gacgtgatca cctgcagctc catgctgtcc agcctctgct tcctgggcgc catcgccgtg     420
gaccgctaca tctccatctt ctacgcactg cgctaccaca gcatcgtgac cctgccgcgg     480
gcgcggcgag ccgttgcggc cctctgggtg gccagtgtcg tcttcagcac gctcttcatc     540
gcctactacg accacgtggc cgtcctgctg tgcctcgtgg tcttcttcct ggctatgctg     600
gtgctcatgg ccgtgctgta cgtccacatg ctggcccggg cctgccagca cgcccagggc     660
atcgcccggc tccacaagag gcagcgcccg gtccaccagg gctttggcct taaaggcgct     720
gtcaccccca ccatcctgct gggcattttc ttcctctgct ggggcccctt cttcctgcat     780
ctcacactca tcgtcctctg ccccgagcac cccacgtgcg gctgcatctt caagaacttc     840
aacctctttc tcgccctcat catctgcaat gccttcatcg acccccctcat ctacgccttc     900
cacagccagg agctccgcag gacgctcaag gaggtgctga catgctcctg ctctcaggac     960
cgtgccctcg tcagctggga tgtgaagtct ctgggtggaa gtgtgtgcca agagctactc    1020
ccacagcagc cccaggagaa ggggctttgt gaccagaaag cttcatccac agccttgcag    1080
cggctcctgc aaaaggaggt gaaatccctg cctcaggcca agggaccagg tttgcaggag    1140
cccccctag                                                           1149
```

. <210> SEQ ID NO:20
<211> LENGTH: 382
<212> TYPE: PRT
<213> ORGANISM:Homo sapien (human)

. <400> SEQ ID NO:20

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

. <210> SEQ ID NO:21
<211> LENGTH: 1530
<212> TYPE: DNA
<213> ORGANISM:Homo sapien (human)

. <400> SEQ ID NO:21

```
atggctgtgc agggatccca gagaagactt ctgggctccc tcaactccac ccccacagcc      60
atcccccagc tggggctggc tgccaaccag acaggagccc ggtgcctgga ggtgtccatc     120
tctgacgggc tcttcctcag cctggggctg gtgagcttgg tggagaacgc gctggtggtg     180
gccaccatcg ccaagaaccg gaacctgcac tcacccatgt actgcttcat ctgctgcctg     240
gccttgtcgg acctgctggt gagcgggagc aacgtgctgg agacggccgt catcctcctg     300
ctggaggccg gtgcactggt ggcccgggct gcggtgctgc agcagctgga caatgtcatt     360
gacgtgatca cctgcagctc catgctgtcc agcctctgct tcctgggcgc catcgccgtg     420
gaccgctaca tctccatctt ctacgcactg cgctaccaca gcatcgtgac cctgccgcgg     480
gcgcggcgag ccgttgcggc cctctgggtg gccagtgtcg tcttcagcac gctcttcatc     540
gcctactacg accacgtggc cgtcctgctg tgcctcgtgg tcttcttcct ggctatgctg     600
gtgctcatgg ccgtgctgta cgtccacatg ctggcccggg cctgccagca cgcccagggc     660
atcgcccggc tccacaagag gcagcgcccg gtccaccagg gctttggcct taaaggcgct     720
gtcaccccca ccatcctgct gggcattttc ttcctctgct ggggcccctt cttcctgcat     780
ctcacactca tcgtcctctg ccccgagcac cccacgtgcg gctgcatctt caagaacttc     840
aacctctttc tcgccctcat catctgcaat gccttcatcg acccccctcat ctacgccttc     900
cacagccagg agctccgcag gacgctcaag gaggtgctga catgctcctg gtgagcgcgg     960
tgcacgcggc tttaagtgtg ctgggcagag ggaggtggtg atattgtgtg gtctggttcc    1020
tgtgtgaccc tgggcagttc cttacctccc tggtccccgt ttgtcaaaga ggatggacta    1080
aatgatctct gaangtgttg aagcgcggac ccttctgggt ccagggaggg gtccctgcaa    1140
aactccaggc aggacttctc accagcagtc gtggggaacg gaggaggaca tggggaggtt    1200
gtggggcctc aggctccggg caccaggggc caacctcagg ctcctaaaga gacattttcc    1260
gcccactcct gggacactcc gtctgctcca atgactgagc agcatccacc ccaccccatc    1320
tttgctgcca gctctcagga ccgtgccctc gtcagctggg atgtgaagtc tctgggtgga    1380
agtgtgtgcc aagagctact cccacagcag ccccaggaga aggggctttg tgaccagaaa    1440
gcttcatcca cagccttgca gcggctcctg caaaaggagg tgaaatccct gcctcaggcc    1500
aagggaccag gtttgcagga gccccccctag                                    1530
```

. <210> SEQ ID NO:22
<211> LENGTH: 1149
<212> TYPE: DNA
<213> ORGANISM:Homo sapien (human)

. <400> SEQ ID NO:22

```
atggctgtgc agggatccca gagaagactt ctgggctccc tcaactccac ccccacagcc      60
atcccccagc tggggctggc tgccaaccag acaggagccc ggtgcctgga ggtgtccatc     120
tctgacgggc tcttcctcag cctggggctg gtgagcttgg tggagaacgc gctggtggtg     180
gccaccatcg ccaagaaccg gaacctgcac tcacccatgt actgcttcat ctgctgcctg     240
gccttgtcgg acctgctggt gagcgggagc aacgtgctgg agacggccgt catcctcctg     300
ctggaggccg gtgcactggt ggcccgggct gcggtgctgc agcagctgga caatgtcatt     360
gacgtgatca cctgcagctc catgctgtcc agcctctgct tcctgggcgc catcgccgtg     420
gaccgctaca tctccatctt ctacgcactg cgctaccaca gcatcgtgac cctgccgcgg     480
gcgcggcgag ccgttgcggc cctctgggtg gccagtgtcg tcttcagcac gctcttcatc     540
gcctactacg accacgtggc cgtcctgctg tgcctcgtgg tcttcttcct ggctatgctg     600
gtgctcatgg ccgtgctgta cgtccacatg ctggcccggg cctgccagca cgcccagggc     660
atcgcccggc tccacaagag gcagcgcccg gtccaccagg gctttggcct taaaggcgct     720
gtcaccccca ccatcctgct gggcattttc ttcctctgct ggggcccctt cttcctgcat     780
ctcacactca tcgtcctctg ccccgagcac cccacgtgcg gctgcatctt caagaacttc     840
aacctctttc tcgccctcat catctgcaat gccttcatcg acccccctcat ctacgccttc     900

cacagccagg agctccgcag gacgctcaag gaggtgctga catgctcctg ctctcaggac     960
cgtgccctcg tcagctggga tgtgaagtct ctgggtggaa gtgtgtgcca agagctactc    1020
ccacagcagc cccaggagaa ggggctttgt gaccagaaag cttcatccac agccttgcag    1080
cggctcctgc aaaaggaggt gaaatccctg cctcaggcca agggaccagg tttgcaggag    1140
ccccccctag                                                          1149
```

. <210> SEQ ID NO:23
<211> LENGTH: 382
<212> TYPE: PRT
<213> ORGANISM:Homo sapien (human)

. <400> SEQ ID NO:23

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

Gln Glu Leu Leu Pro Gln Gln Pro Gln Glu Lys Gly Leu Cys Asp Gln
            340                 345                 350
Lys Ala Ser Ser Thr Ala Leu Gln Arg Leu Leu Gln Lys Glu Val Lys
        355                 360                 365
Ser Leu Pro Gln Ala Lys Gly Pro Gly Leu Gln Glu Pro Pro
    370                 375                 380
```

. <210> SEQ ID NO:24
<211> LENGTH: 1540
<212> TYPE: DNA
<213> ORGANISM:Homo sapien (human)

. <400> SEQ ID NO:24

```
atggctgtgc agggatccca gagaagactt ctgggctccc tcaactccac ccccacagcc      60
atcccccagc tggggctggc tgccaaccag acaggagccc ggtgcctgga ggtgtccatc     120
tctgacgggc tcttcctcag cctggggctg gtgagcttgg tggagaacgc gctggtggtg     180
gccaccatcg ccaagaaccg gaacctgcac tcacccatgt actgcttcat ctgctgcctg     240
gccttgtcgg acctgctggt gagcgggagc aacgtgctgg agacggccgt catcctcctg     300
ctggaggccg gtgcactggt ggcccgggct gcggtgctgc agcagctgga caatgtcatt     360
gacgtgatca cctgcagctc catgctgtcc agcctctgct tcctgggcgc cgtcgccgtg     420
gaccgctaca tctccatctt ctacgcactg cgctaccaca gcatcgtgac cctgccgcgg     480
gcgcggcaag ccgttgcggc catctgggtg gccagtgtcg tcttcagcac gctcttcatc     540
gcctactacg accacgtggc cgtcctgctg tgcctcgtgg tcttcttcct ggctatgctg     600
gtgctcatgg ccgtgctgta cgtccacatg ctggcccggg cctgccagca cgcccagggc     660
atcgcccggc tccacaagag gcagcgcccg gtccaccagg gctttggcct taaaggcgct     720
gtcaccctca ccatcctgct gggcattttc ttcctctgct ggggccccct cttcctgcat     780
ctcacactca tcgtcctctg ccccgagcac cccacgtgcg gctgcatctt caagaacttc     840
aacctctttc tcgccccat catctgcaac gccatcatcg accccctcat ctacgccttc     900
cacagccagg agctccgcag gacgctcaag gaggtactga catgctcctg catgctcctg     960
gtgagcgcgg tgcacgcggc tttaagtgtg ctgggcagag ggaggtggtg atattgtgtg    1020
gtctggttcc tgtgtgaccc tgggcagttc cttacctccc tggtccccgt ttgtcaaaga    1080
ggatggacta aatgatctct gaangtgttg aagcgcggac ccttctgggt ccagggaggg    1140
gtccctgcaa aactccaggc aggacttctc accagcagtc gtggggaacg gaggaggaca    1200
tggggaggtt gtggggcctc aggctccggg caccaggggc caacctcagg ctcctaaaga    1260
gacattttcc gcccactcct gggacactcc gtctgctcca atgactgagc agcatccacc    1320
ccacccccatc tttgctgcca gctctcagga ccgtgccctc gtcagctggg atgtgaagtc    1380
tctgggtgga agtgtgtgcc aagagctact cccacagcag ccccaggaga aggggctttg    1440
tgaccagaaa gcttcatcca cagccttgca gcggctcctg caaaaggagg tgaaatccct    1500
gcctcaggcc aagggaccag gtttgcagga gccccccctag                         1540
```

. <210> SEQ ID NO:25
<211> LENGTH: 1149
<212> TYPE: DNA
<213> ORGANISM:Homo sapien (human)

. <400> SEQ ID NO:25

```
atggctgtgc agggatccca gagaagactt ctgggctccc tcaactccac ccccacagcc      60
atcccccagc tggggctggc tgccaaccag acaggagccc ggtgcctgga ggtgtccatc     120
tctgacgggc tcttcctcag cctggggctg gtgagcttgg tggagaacgc gctggtggtg     180
gccaccatcg ccaagaaccg gaacctgcac tcacccatgt actgcttcat ctgctgcctg     240
gccttgtcgg acctgctggt gagcgggagc aacgtgctgg agacggccgt catcctcctg     300
ctggaggccg gtgcactggt ggcccgggct gcggtgctgc agcagctgga caatgtcatt     360
gacgtgatca cctgcagctc catgctgtcc agcctctgct tcctgggcgc cgtcgccgtg     420
gaccgctaca tctccatctt ctacgcactg cgctaccaca gcatcgtgac cctgccgcgg     480
gcgcggcaag ccgttgcggc catctgggtg gccagtgtcg tcttcagcac gctcttcatc     540
```

```
gcctactacg accacgtggc cgtcctgctg tgcctcgtgg tcttcttcct ggctatgctg     600
gtgctcatgg ccgtgctgta cgtccacatg ctggcccggg cctgccagca cgcccagggc     660
atcgcccggc tccacaagag gcagcgcccg gtccaccagg gctttggcct taaaggcgct     720
gtcaccctca ccatcctgct gggcattttc ttcctctgct ggggcccctt cttcctgcat     780
ctcacactca tcgtcctctg ccccgagcac cccacgtgcg gctgcatctt caagaacttc     840
aacctctttc tcgccccccat catctgcaac gccatcatcg acccccctcat ctacgccttc     900
cacagccagg agctccgcag gacgctcaag gaggtactga catgctcctg ctctcaggac     960
cgtgccctcg tcagctggga tgtgaagtct ctgggtggaa gtgtgtgcca agagctactc    1020
ccacagcagc cccaggagaa ggggctttgt gaccagaaag cttcatccac agccttgcag    1080
cggctcctgc aaaaggaggt gaaatccctg cctcaggcca agggaccagg tttgcaggag    1140
ccccccctag                                                           1149
```

. <210> SEQ ID NO:26
<211> LENGTH: 382
<212> TYPE: PRT
<213> ORGANISM:Homo sapien (human)

. <400> SEQ ID NO:26

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

```
Cys Asn Ala Ile Ile Asp Pro Leu Ile Tyr Ala Phe His Ser Gln Glu
    290                 295                 300
Leu Arg Arg Thr Leu Lys Glu Val Leu Thr Cys Ser Cys Ser Gln Asp
305                 310                 315                 320
Arg Ala Leu Val Ser Trp Asp Val Lys Ser Leu Gly Gly Ser Val Cys
                325                 330                 335
Gln Glu Leu Leu Pro Gln Gln Pro Gln Glu Lys Gly Leu Cys Asp Gln
            340                 345                 350
Lys Ala Ser Ser Thr Ala Leu Gln Arg Leu Leu Gln Lys Glu Val Lys
        355                 360                 365
Ser Leu Pro Gln Ala Lys Gly Pro Gly Leu Gln Glu Pro Pro
    370                 375                 380
```

. <210> SEQ ID NO:27
<211> LENGTH: 65
<212> TYPE: PRT
<213> ORGANISM:Homo sapien (human)

. <400> SEQ ID NO:27

```
Ser Gln Asp Arg Ala Leu Val Ser Trp Asp Val Lys Ser Leu Gly Gly
 1               5                  10                  15
Ser Val Cys Gln Glu Leu Leu Pro Gln Gln Pro Gln Glu Lys Gly Leu
            20                  25                  30
Cys Asp Gln Lys Ala Ser Ser Thr Ala Leu Gln Arg Leu Leu Gln Lys
        35                  40                  45
Glu Val Lys Ser Leu Pro Gln Ala Lys Gly Pro Gly Leu Gln Glu Pro
    50                  55                  60
Pro
65
```

. <210> SEQ ID NO:28
<211> LENGTH: 632
<212> TYPE: DNA
<213> ORGANISM:Homo sapien (human)

. <400> SEQ ID NO:28

```
tttttgatgc tgagtcacat ttattaccag actttcctgg ccccatgctc acaggcactg      60
gtcactgagt caggcatttg cacgggctgt ctgcttgggc gactgctgca ggaaagcagg     120
ctgaggccca gtgcccagtc tgagccttag aaccggccct caggagggtc cagcctcaca     180
ccactagggg ggctcctgca aacctggtcc cttggcctga ggagggattt cacctccttt     240
tgcaggagcc gctgcaaggc tgttggatga agctttctgg tcacaaagcc ccttctcctg     300
gggctgctgt gggagtagct cttggcacac acttccaccc agagacttca catcccagct     360
gacgagggca cggtcctgag agcaggagca cgtcagcacc tccttgagcg tcctgcgacg     420
tcctggctgt ggaaggcgta gatgaggggg tcgatgatgg cattgcagat gatgagggcg     480
agaaagaggt tgaaagttct tgaagatgca gccgacgtgg ggtgctcggg gcagaggacg     540
atgagtgtga gatgcaggaa gaggggccc cagcagagga gaaattgcca acaggattgg      600
tganggtgaa gcngctttta agccanagcc ct                                   632
```

. <210> SEQ ID NO:29
<211> LENGTH: 551
<212> TYPE: DNA
<213> ORGANISM:Homo sapien (human)

. <400> SEQ ID NO:29

aacaaacttt ggtaagtagt gaatggcaaa ggctcagggg gtttgcagca ggacctcctt 60

ggggtcagat ctgccagcct cgggttgnct ttcagacccc tcatcgtcta tgaggcatcc 120
tgtaagtgca gctgtggcca gggcttgcat atgcaatcaa ttcctgattc acctagttct 180
tggcaggaag agaaaatact cgttaatcag aggactaaac aatccaaaag cgcattctct 240
ctctgggaat ggaatataat ttatatttct gttgctattg aattatcctt ctaattccac 300
tggactaaac ttaataccag taatactaaa attttgtttt gggcaaagcg acttgaagga 360
ggagtcagtg gcgcactaat ngctgactgt gaaaaataaa cacctctgag atcaagaatc 420
ccacagtgag agctaggatt tgaaggtatc cagagattgc aaaactctgt gactaacagc 480
aantttttaa ccagggcaaa ccaaaccact cctacttgga cttaaacctc aatcatttag 540
atttcattcc c 551

. <210> SEQ ID NO:30
<211> LENGTH: 355
<212> TYPE: DNA
<213> ORGANISM:Homo sapien (human)

. <400> SEQ ID NO:30

aaatgatctc tgaaagtgtt gaagcgcgga cccttctggg tcccggaggg gtccctgcaa 60
aactccaggc aggacttctc accagcagtc gtggggaacc gaggaggaca tggggaggtt 120
gtggggcctc aggctccggg caccaggggc caacctcagg ctcctaaaga gacattttcc 180
gcccacatcc tgggacactc cgtctgctcc aatgactgag cagcatccac cccaccccat 240
ctttgctgcc agctctcagg accgtgcgct cgtcagctgg gatgtgaagt ctctgggtgg 300
aagtgtgtgc caagagctac tctcacagca gccccaggag aaggggcttt gtgac 355

. <210> SEQ ID NO:31
<211> LENGTH: 263
<212> TYPE: DNA
<213> ORGANISM:Homo sapien (human)

. <400> SEQ ID NO:31

cgggtgatgc tgagtcacat ttattaccag actttcctgg ccccatgctc acaggcactg 60
gtcactgagt caggcatttg ccagggctgt ctgcttgggc gactgctgca tgaaagcagg 120
ctgaggcccc agtgcccagt ctgagcctta gaaccggccc tcaggagggc tcagccctat 180
accactaggg gggctcctgc aaacctggtc ccttggcctg aggcagggat ttcacctcct 240
tttgcaggag ccgctgcaag gct 263

. <210> SEQ ID NO:32
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM:Artificial Sequence

. <220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

. <400> SEQ ID NO:32
tctcacactc atcgtcctct gccc 24

. <210> SEQ ID NO:33
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM:Artificial Sequence

. <220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

. <400> SEQ ID NO:33
catcgcctac tacgaccacg tggc 24

. <210> SEQ ID NO:34
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM:Artificial Sequence

. <220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

. <400> SEQ ID NO:34
cgctgcaagg ctgttggatg aagc 24

. <210> SEQ ID NO:35
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM:Artificial Sequence

. <220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

. <400> SEQ ID NO:35
gtgggagtag ctcttggcac acac 24

. <210> SEQ ID NO:36
<211> LENGTH: 41
<212> TYPE: DNA
<213> ORGANISM:Artificial Sequence

. <220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

. <400> SEQ ID NO:36
gggcccgaat tcgccgccat ggctgtgcag ggatcccaga g 41

. <210> SEQ ID NO:37
<211> LENGTH: 40
<212> TYPE: DNA
<213> ORGANISM:Artificial Sequence

. <220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

. <400> SEQ ID NO:37
ggcacggtcc tgagagcagg agcatgtcag cacctccttg 40

. <210> SEQ ID NO:38
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM:Artificial Sequence

. <220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

. <400> SEQ ID NO:38
ctgacagtgct cctgctctca ggaccgtgcc ctcgtcagc 39

. <210> SEQ ID NO:39
<211> LENGTH: 38
<212> TYPE: DNA
<213> ORGANISM:Artificial Sequence

. <220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

. <400> SEQ ID NO:39
agtttagcgg ccgcctaggg gggctcctgc aaacctgg 38

. <210> SEQ ID NO:40
<211> LENGTH: 42
<212> TYPE: DNA
<213> ORGANISM:Artificial Sequence

. <220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

. <400> SEQ ID NO:40
gatcgaattc gccgccatgg ctgtgcaggg atcccagaga ag 42

. <210> SEQ ID NO:41
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM:Artificial Sequence

. <220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

. <400> SEQ ID NO:41
gatcgaattc ctaggggggc tcctgcaaac ctg 33

. <210> SEQ ID NO:42
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM:Artificial Sequence

. <220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

. <400> SEQ ID NO:42
gatcgaattc gtgcccagtc tgagccttag aacg 35

. <210> SEQ ID NO:43
<211> LENGTH: 317
<212> TYPE: PRT
<213> ORGANISM:Homo sapien (human)

. <400> SEQ ID NO:43

Met Ala Val Gln Gly Ser Gln Arg Arg Leu Leu Gly Ser Leu Asn Ser
1 5 10 15

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

. <210> SEQ ID NO:44
<211> LENGTH: 317
<212> TYPE: PRT
<213> ORGANISM:Homo sapien (human)

. <400> SEQ ID NO:44

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

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

. <210> SEQ ID NO:45
<211> LENGTH: 962
<212> TYPE: DNA
<213> ORGANISM:Homo sapien (human)

. <400> SEQ ID NO:45

```
atggctgtgc agggatccca gagaagactt ctgggctccc tcaactccac ccccacagcc      60
atcccccagc tggggctggc tgccaaccag acaggagccc ggtgcctgga ggtgtccatc     120
tctgacgggc tcttcctcag cctggggctg gtgagcttgg tggagaacgc gctggtggtg     180
gccaccatcg ccaagaaccg gaacctgcac tcacccatgt actgcttcat ctgctgcctg     240
gccttgtcgg acctgctggt gagcgggagc aacgtgctgg agacggccgt catcctcctg     300
ctggaggccg gtgcactggt ggcccgggct gcggtgctgc agcagctgga caatgtcatt     360
gacgtgatca cctgcagctc catgctgtcc agcctctgct tcctgggcgc catcgccgtg     420
gaccgctaca tctccatctt ctacgcactg cgctaccaca gcatcgtgac cctgccgcgg     480
gcgcggcgag ccgttgcggc cctctgggtg gccagtgtcg tcttcagcac gctcttcatc     540
gcctactacg accacgtggc cgtcctgctg tgcctcgtgg tcttcttcct ggctatgctg     600
gtgctcatgg ccgtgctgta cgtccacatg ctggcccggg cctgccagca cgcccagggc     660
atcgccccgc tccacaagag gcagcgcccg gtccaccagg gctttggcct taaaggcgct     720
gtcaccccca ccatcctgct gggcattttc ttcctctgct ggggcccctt cttcctgcat     780
ctcacactca tcgtcctctg ccccgagcac cccacgtgcg gctgcatctt caagaacttc     840
aacctctttc tcgccctcat catctgcaat gccttcatcg acccccctcat ctacgccttc     900
cacagccagg agctccgcag gacgctcaag gaggtgctga catgctcctg gtagcttggt     960
ga                                                                    962
```

. <210> SEQ ID NO:46
<211> LENGTH: 297

<212> TYPE: PRT
<213> ORGANISM:Homo sapien (human)

. <400> SEQ ID NO:46

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

1. . A purified nucleic acid molecule encoding a human melanocortin 1 receptor protein, wherein the human melanocortin-1 receptor protein comprises a carboxy terminal region having the amino acid sequence as set forth in SEQ ID NO:27.

2. . A purified nucleic acid molecule of claim 1 wherein the nucleic acid molecule is selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:18; SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:24, and SEQ ID NO:25.

3. . A purified nucleic acid molecule encoding human MC-R1B protein wherein the nucleic acid molecule encodes a protein comprising an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:17, SEQ ID NO:20, SEQ ID NO:23, and SEQ ID NO:26.

4. . An expression vector for the expression of a human MC-R1B protein in a recombinant host cell wherein the expression vector comprises a DNA molecule which encodes the amino acid sequence of claim 1.

5. . An expression vector of claim 4 which is a eukaryotic expression vector.

6. . An expression vector of claim 4 which is a prokaryotic expression vector.

7. . A host cell which expresses a recombinant human MC-R1B protein wherein said host cell contains the expression vector of claim 4.

8. . A host cell which expresses a recombinant human MC-R1B protein wherein said host cell contains the expression vector of claim 5.

9. . A host cell which expresses a recombinant human MC-R1B protein wherein said host cell contains the expression vector of claim 6.

10. . A host cell of claim 7 wherein said human MC-R1B protein is overexpressed from said expression vector.

11. . A host cell of claim 8 wherein said human MC-R1B protein is overexpressed from said expression vector.

12. . A host cell of claim 9 wherein said human MC-R1B protein is overexpressed from said expression vector.

13. . A subcellular membrane fraction obtained from the host cell of claim 10 which fraction contains recombinant human MC-R1B protein.

14. . A subcellular membrane fraction obtained from the host cell of claim 11 which fraction contains recombinant human MC-R1B protein.

15. . A subcellular membrane fraction obtained from the host cell of claim 12 which fraction contains recombinant human MC-R1B protein.

16. . A purified nucleic acid molecule encoding human MC-R1B protein wherein the nucleic acid molecule encodes a protein consisting of an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:17, SEQ ID NO:20, SEQ ID NO:23, and SEQ ID NO:26.

17. . A purified human melanocortin 1 receptor protein which comprises a carboxy terminal amino acid domain as set forth in SEQ ID NO:27.

18. . A purified human melanocortin 1 receptor protein of claim 17 which comprises the amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:17, SEQ ID NO:20, SEQ ID NO:23, and SEQ ID NO:26.

19. . A method for determining whether a substance is capable of binding to human MC-R1B comprising:

. (a) providing test cells by transfecting cells with an expression vector of claim 4;
. (b) exposing the test cells to the substance;
. (c) measuring the amount of binding of the substance to MC-R1B;
. (d) comparing the amount of binding of the substance to MC-R1B in the test cells with the amount of binding of the substance to control cells that have not been transfected with MC-R1B.

20. . A method for determining whether a substance is capable of activating MC-R1B comprising:

. (a) providing test cells by transfecting cells with an expression vector of claim 4;
. (b) exposing the test cells to the substance;
. (c) measuring the amount of accumulated intracellular cAMP;
. (d) comparing the amount of cAMP in the test cells in response to the substance with the amount of cAMP in test cells that have not been exposed to the substance.

21. . A method of identifying a substance which modulates MC-R1B receptor activity, comprising:

. (a) combining a test substance in the presence and absence of a MC-R1B receptor protein wherein said MC-R1B receptor protein comprises the amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:17, SEQ ID NO:20, SEQ ID NO:23, and SEQ ID NO:26.; and,

. (b) measuring and comparing the effect of the test substance in the presence and absence of the MC-R1B receptor protein.

22. . A method for determining whether a substance is a potential agonist or antagonist of MC-R1B comprising:

. (a) transfecting or transforming cells with an expression vector of claim 4 that directs expression of MC-R1B in the cells, resulting in test cells;

. (b) allowing the test cells to grow for a time sufficient to allow MC-R1B to be expressed;

. (c) exposing the cells to a labeled ligand of MC-R1B in the presence and in the absence of the substance;

. (d) measuring the binding of the labeled ligand to MC-R1B; where if the amount of binding of the labeled ligand is less in the presence of the substance than in the absence of the substance, then the substance is a potential agonist or antagonist of MC-R1B.

23. . A method for determining whether a substance is capable of binding to MC-R1B comprising:

. (a) transfecting or transforming cells with an expression vector of claim 4 that directs the expression of MC-R1B in the cells, resulting in test cells;

. (b) exposing the test cells to the substance;

. (c) measuring the amount of binding of the substance to MC-R1B;

. (d) comparing the amount of binding of the substance to MC-R1B in the test cells with the amount of binding of the substance to control cells that have not been transfected with MC-R1B;

wherein if the amount of binding of the substance is greater in the test cells as compared to the control cells, the substance is capable of binding to MC-R1B.

24. . A method for determining whether a substance is capable of binding to MC-R1B comprising:

. (a) transfecting or transforming cells with an expression vector of claim 4 that directs the expression of MC-R1B in the cells, resulting in test cells;

. (b) preparing membranes containing MC-R1B from the test cells and exposing the membranes to a ligand of MC-R1B under conditions such that the ligand binds to the MC-R1B in the membranes;

. (c) subsequently or concurrently to step (b), exposing the membranes from the test cells to a substance;

. (d) measuring the amount of binding of the ligand to the MC-R1B in the membranes in the presence and the absence of the substance;

. (e) comparing the amount of binding of the ligand to MC-R1B in the membranes in the presence and the absence of the substance where a decrease in the amount of binding of the ligand to MC-R1B in the membranes in the presence of the substance indicates that the substance is capable of binding to MC-R1B.

25. . A method for determining whether a substance is capable of binding to MC-R1B comprising:

. (a) transfecting or transforming cells with an expression vector of claim 4 that directs the expression of MC-R1B in the cells, resulting in test cells;

. (b) preparing membranes containing MC-R1B from the test cells and exposing the membranes from the test cells to the substance;

. (c) measuring the amount of binding of the substance to the MC-R1B in the membranes from the test cells;

. (d) comparing the amount of binding of the substance to MC-R1B in the membranes from the test cells with the amount of binding of the substance to membranes from control cells that have not been transfected with MC-R1B, where if the amount of binding of the substance to MC-R1B in the membranes from the test cells is greater than the amount of binding of the substance to the membranes from the control cells, then the substance is capable of binding to MC-R1B.

26. . A method of identifying agonists of MC-R1B comprising:

. (a) transfecting or transforming cells with a first expression vector of claim 4 which directs expression of MC-R1B and a second expression vector which directs the expression of a promiscuous G-protein, resulting in test cells;
. (b) exposing the test cells to a substance that is a suspected agonist of MC-R1B;
. (c) measuring the level of inositol phosphates in the cells;

where an increase in the level of inositol phosphates in the cells as compared to the level of inositol phosphates in the cells in the absence of the suspected agonist indicates that the substance is an agonist of MC-R1B.

27. . A method of identifying antagonists of MC-R1B comprising:

. (a) transfecting or transforming cells with a first expression vector of claim 4 which directs expression of MC-R1B and a second expression vector which directs the expression of a promiscuous G-protein, resulting in test cells;
. (b) exposing the test cells to a substance that is an agonist of MC-R1B;
. (c) subsequently or concurrently to step (b), exposing the test cells to a substance that is a suspected antagonist of MC-R1B;
. (d) measuring the level of inositol phosphates in the cells;

where a decrease in the level of inositol phosphates in the cells in the presence of the suspected antagonist as compared to the level of inositol phosphates in the cells in the absence of the suspected antagonist indicates that the substance is an antagonist of MC-R1B.

28. . A method of identifying antagonists of MC-R1B as recited in claim 27 wherein the first and second expression vectors of step (a) are replaced with a single expression vector which expresses a chimeric MC-R1B protein fused at its C-terminus to a promiscuous G-protein.

29. . An antibody that binds specifically to MC-R1B protein wherein the MC-R1B receptor protein comprises the amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:17, SEQ ID NO:20, SEQ ID NO:23, and SEQ ID NO:26.

Revendications

1. . Molécule d'acide nucléique purifiée codant une protéine de récepteur de la mélanocortine-1 humaine, la protéine de récepteur de la mélanocortine-1 humaine comprenant une région carboxy terminale de séquence d'acides aminés comme présenté dans SEQ ID N° 27.

2. . Molécule d'acide nucléique purifiée selon la revendication 1, la molécule d'acide nucléique étant choisie dans le groupe constitué de SEQ ID N° 1, SEQ ID N° 3, SEQ ID N° 5, SEQ ID N° 7, SEQ ID N° 9, SEQ ID N° 11, SEQ ID N° 13, SEQ ID N° 15, SEQ ID N° 16, SEQ ID N° 18, SEQ ID N° 19, SEQ ID N° 21, SEQ ID N° 22, SEQ ID N° 24 et SEQ ID N° 25.

3. . Molécule d'acide nucléique purifiée codant la protéine MC-R1B humaine, la molécule d'acide nucléique codant une protéine comprenant une séquence d'acides aminés choisie dans le groupe constitué de SEQ ID N° 2, SEQ ID N° 4, SEQ ID N° 6, SEQ ID N° 8, SEQ ID N° 10, SEQ ID N° 12, SEQ ID N° 14, SEQ ID N° 17, SEQ ID N° 20, SEQ ID N° 23 et SEQ ID N° 26.

4. . Vecteur d'expression pour l'expression d'une protéine MC-R1B humaine dans une cellule hôte recombinante, le vecteur d'expression comprenant une molécule d'ADN qui code la séquence d'acides aminés selon la revendication 1.

5. . Vecteur d'expression selon la revendication 4 qui est un vecteur d'expression eucaryote.

6. . Vecteur d'expression selon la revendication 4 qui est un vecteur d'expression procaryote.

7. . Cellule hôte qui exprime une protéine MC-R1B humaine recombinante, ladite cellule hôte comprenant le vecteur d'expression selon la revendication 4.

8. . Cellule hôte qui exprime une protéine MC-R1B humaine recombinante, ladite cellule hôte contenant le vecteur d'expression selon la revendication 5.

9. . Cellule hôte qui exprime une protéine MC-R1B humaine recombinante, ladite cellule hôte contenant le vecteur d'expression selon la revendication 6.

10. . Cellule hôte selon la revendication 7, ladite protéine MC-R1B humaine étant surexprimée par ledit vecteur d'expression.

11. . Cellule hôte selon la revendication 8, ladite protéine MC-R1B humaine étant surexprimée par ledit vecteur d'expression.

12. . Cellule hôte selon la revendication 9, ladite protéine MC-R1B humaine étant surexprimée par ledit vecteur d'expression.

13. . Fraction de membrane sub-cellulaire obtenue à partir de la cellule hôte selon la revendication 10, laquelle fraction contenant la protéine MC-R1B humaine recombinante.

14. . Fraction de membrane sub-cellulaire obtenue à partir de la cellule hôte selon la revendication 11, laquelle fraction contenant la protéine MC-R1B humaine recombinante.

15. . Fraction de membrane sub-cellulaire obtenue à partir de la cellule hôte selon la revendication 12, laquelle fraction contenant la protéine MC-R1B humaine recombinante.

16. . Molécule d'acide nucléique purifiée codant la protéine MC-R1B humaine, la molécule d'acide nucléique codant une protéine consistant en une séquence d'acides aminés choisie dans le groupe constitué de SEQ ID N° 2, SEQ ID N° 4, SEQ ID N° 6, SEQ ID N° 8, SEQ ID N° 10, SEQ ID N° 12, SEQ ID N° 14, SEQ ID N° 17, SEQ ID N° 20, SEQ ID N° 23 et SEQ ID N° 26.

17. . Protéine de récepteur de la mélanocortine 1 humaine purifiée qui comprend un domaine d'acides aminés carboxy terminal comme présenté dans SEQ ID N° 27.

18. . Protéine de récepteur de la mélanocortine 1 humaine purifiée selon la revendication 17 qui comprend la séquence d'acides aminés choisie dans le groupe constitué de SEQ ID N° 2, SEQ ID N° 4, SEQ ID N° 6, SEQ ID N° 8, SEQ ID N° 10, SEQ ID N° 12, SEQ ID N° 14, SEQ ID N° 17, SEQ ID N° 20, SEQ ID N° 23 et SEQ ID N° 26.

19. . Procédé pour déterminer si une substance est capable de se lier à la protéine MC-R1B humaine comprenant les étapes consistant à :

- (a) fournir des cellules de test en transfectant des cellules avec un vecteur d'expression selon la revendication 4 ;
- (b) exposer les cellules de test à la substance ;
- (c) mesurer la quantité de liaison de la substance à MC-R1B ;
- (d) comparer la quantité de liaison de la substance à MC-R1B dans les cellules de test à la quantité de liaison de la substance à des cellules de contrôle qui n'ont pas été transfectées avec MC-R1B.

20. . Procédé pour déterminer si une substance est capable d'activer MC-R1B comprenant les étapes consistant à :

- (a) fournir des cellules de test en transfectant des cellules avec un vecteur d'expression selon la revendication 4 ;
- (b) exposer les cellules de test à la substance ;
- (c) mesurer la quantité d'AMP_c intracellulaire accumulée ;
- (d) comparer la quantité d'AMP_c dans les cellules de test en réponse à la substance à la quantité d'AMP_c dans les cellules de test qui n'ont pas été exposées à la substance.

21. . Procédé d'identification d'une substance qui module l'activité du récepteur MC-R1B, comprenant les étapes consistant à :

- (a) associer une substance test en présence et en l'absence d'une protéine de récepteur MC-R1B, ladite protéine de récepteur MC-R1B comprenant la séquence d'acides aminés choisie dans le groupe constitué de SEQ ID

N° 2, SEQ ID N° 4, SEQ ID N° 6, SEQ ID N° 8, SEQ ID N° 10, SEQ ID N° 12, SEQ ID N° 14, SEQ ID N° 17, SEQ ID N° 20, SEQ ID N° 23 et SEQ ID N° 26 ; et

. (b) mesurer et comparer l'effet de la substance test en présence et en l'absence de la protéine de récepteur MC-R1B.

22. . Procédé pour déterminer si une substance est un agoniste ou un antagoniste potentiel de MC-R1B comprenant les étapes consistant à :

. (a) transfecter ou transformer des cellules avec un vecteur d'expression selon la revendication 4 qui dirige l'expression de MC-R1B dans les cellules, pour obtenir des cellules de test ;
. (b) laisser les cellules de test croître pendant une durée suffisante pour permettre l'expression de MC-R1B ;
. (c) exposer les cellules à un ligand marqué de MC-R1B en présence et en l'absence de la substance ;
. (d) mesurer la liaison du ligand marqué à MC-R1B ;

où, si la quantité de liaison du ligand marqué est moins élevée en présence de la substance qu'en l'absence de la substance, alors la substance est un agoniste ou un antagoniste potentiel de MC-R1B.

23. . Procédé pour déterminer si une substance est capable de se lier à MC-R1B, comprenant les étapes consistant à :

. (a) transfecter ou transformer des cellules avec un vecteur d'expression selon la revendication 4 qui dirige l'expression de MC-R1B dans les cellules, pour obtenir des cellules de test ;
. (b) exposer les cellules de test à la substance ;
. (c) mesurer la quantité de liaison de la substance à MC-R1B ;
. (d) comparer la quantité de liaison de la substance à MC-R1B dans les cellules de test à la quantité de liaison de la substance à des cellules de contrôle qui n'ont pas été transfectées avec MC-R1B ;

dans lequel, si la quantité de liaison de la substance est plus élevée dans les cellules de test que dans les cellules de contrôle, la substance est capable de se lier à MC-R1B.

24. . Procédé pour déterminer si une substance est capable de se lier à MC-R1B, comprenant les étapes consistant à :

. (a) transfecter ou transformer des cellules avec un vecteur d'expression selon la revendication 4 qui dirige l'expression de MC-R1B dans les cellules, pour obtenir des cellules de test ;
. (b) préparer des membranes contenant MC-R1B à partir des cellules de test et exposer les membranes à un ligand de MC-R1B dans des conditions telles que le ligand se lie à MC-R1B dans les membranes ;
. (c) pendant ou après l'étape (b), exposer les membranes des cellules de test à une substance ;
. (d) mesurer la quantité de liaison du ligand à MC-R1B dans les membranes en présence et en l'absence de la substance;
. (e) comparer la quantité de liaison du ligand à MC-R1B dans les membranes en présence et en l'absence de la substance, où une diminution de la quantité de liaison du ligand à MC-R1B dans les membrane en présence de la substance indique que la substance est capable de se lier à MC-R1B.

25. . Procédé pour déterminer si une substance est capable de se lier à MC-R1B, comprenant les étapes consistant à :

. (a) transfecter ou transformer des cellules avec un vecteur d'expression selon la revendication 4 qui dirige l'expression de MC-R1B dans les cellules, pour obtenir des cellules de test ;
. (b) préparer des membranes contenant MC-R1B à partir des cellules de test et exposer les membranes issues des cellules de test à la substance ;
. (c) mesurer la quantité de liaison de la substance à MC-R1B dans les membranes issues des cellules de test ;
. (d) comparer la quantité de liaison de la substance à MC-R1B dans les membranes issues des cellules de test à la quantité de liaison de la substance à des membranes issues de cellules de contrôle qui n'ont pas été transfectées avec MC-R1B, où, si la quantité de liaison de la substance à MC-R1B dans les membranes issues des cellules de test est supérieure à la quantité de liaison de la substance aux membranes issues des cellules de contrôle, la substance est capable de se lier à MC-R1B.

26. . Procédé d'identification d'agonistes de MC-R1B comprenant les étapes consistant à :

. (a) transfecter et transformer des cellules avec un premier vecteur d'expression selon la revendication 4 qui

dirige l'expression de MC-R1B et un second vecteur d'expression qui dirige l'expression d'une protéine G poly-réactive, pour obtenir les cellules de test ;

. (b) exposer les cellules de test à une substance qui est un agoniste supposé de MC-R1B ;

. (c) mesurer le niveau d'inositol phosphates dans les cellules ;

où une augmentation du niveau d'inositol phosphates dans les cellules comparativement au niveau d'inositol phosphates dans les cellules en l'absence de l'agoniste supposé indique que la substance est un agoniste de MC-R1B.

27. . Procédé pour identifier des antagonistes de MC-R1B comprenant les étapes consistant à :

. (a) transfecter ou transformer des cellules avec un premier vecteur d'expression selon la revendication 4 qui dirige l'expression de MC-R1B et un second vecteur d'expression qui dirige l'expression d'une protéine G poly-réactive, pour obtenir les cellules de test ;

. (b) exposer les cellules de test à une substance qui est un agoniste de MC-R1B ;

. (c) après ou pendant l'étape (b), exposer les cellules de test à une substance qui est un antagoniste supposé de MC-R1B ;

. (d) mesurer le niveau d'inositol phosphates dans les cellules;

où une diminution du niveau d'inositol phosphates dans les cellules en présence de l'antagoniste supposé comparativement au niveau d'inositol phosphates dans les cellules en l'absence de l'antagoniste supposé indique que la substance est un antagoniste de MC-R1B.

28. . Procédé pour identifier des antagonistes de MC-R1B comme décrit dans la revendication 27, dans lequel le premier et le second vecteur d'expression de l'étape (a) sont remplacés par un seul vecteur d'expression qui exprime une protéine MC-R1B chimérique fusionnée à son extrémité C-terminale à une protéine G poly-réactive.

29. . Anticorps qui se lie spécifiquement à une protéine MC-R1B, la protéine de récepteur MC-R1B comprenant la séquence d'acides aminés choisie dans le groupe constitué de SEQ ID N° 2, SEQ ID N° 4, SEQ ID N° 6, SEQ ID N° 8, SEQ ID N° 10, SEQ ID N° 12, SEQ ID N° 14, SEQ ID N° 17, SEQ ID N° 20, SEQ ID N° 23 et SEQ ID N° 26.

Patentansprüche

1. . Gereinigtes Nukleinsäuremolekül, codierend für ein humanes Melanocortin 1 - Rezeptorprotein, wobei das humane Melanocortin 1-Rezeptorprotein eine carboxyterminale Region mit der in SEQ-ID-Nr. 27 angegebenen Aminosäuresequenz umfasst.

2. . Gereinigtes Nukleinsäuremolekül nach Anspruch 1, wobei das Nukleinsäuremolekül aus der Gruppe ausgewählt ist, die aus SEQ-ID-Nr. 1, SEQ-ID-Nr. 3, SEQ-ID-Nr. 5, SEQ-ID-Nr. 7, SEQ-ID-Nr. 9, SEQ-ID-Nr. 11, SEQ-ID-Nr. 13, SEQ-ID-Nr. 15, SEQ-ID-Nr. 16, SEQ-ID-Nr. 18, SEQ-ID-Nr. 19, SEQ-ID-Nr. 21, SEQ-ID-Nr. 22, SEQ-ID-Nr. 24 und SEQ-ID-Nr. 25 besteht.

3. . Gereinigtes Nukleinsäuremolekül, codierend für ein humanes MC-R1B-Protein, wobei das Nukleinsäuremolekül für ein Protein codiert, das eine Aminosäuresequenz umfasst, welche aus der Gruppe ausgewählt ist, die aus SEQ-ID-Nr. 2, SEQ-ID-Nr. 4, SEQ-ID-Nr. 6, SEQ-ID-Nr. 8, SEQ-ID-Nr. 10, SEQ-ID-Nr. 12, SEQ-ID-Nr. 14, SEQ-ID-Nr. 17, SEQ-ID-Nr. 20, SEQ-ID-Nr. 23 und SEQ-ID-Nr. 26 besteht.

4. . Expressionsvektor zur Expression eines humanen MC-R1B-Proteins in einer rekombinanten Wirtszelle, wobei der Expressionsvektor ein DNA-Molekül umfasst, welches für die Aminosäuresequenz von Anspruch 1 codiert.

5. . Expressionsvektor nach Anspruch 4, welcher ein eukaryotischer Expressionsvektor ist.

6. . Expressionsvektor nach Anspruch 4, welcher ein prokaryotischer Expressionsvektor ist.

7. . Wirtszelle, welche ein rekombinantes humanes MC-R1B-Protein exprimiert, wobei die Wirtszelle den Expressionsvektor nach Anspruch 4 enthält.

8. . Wirtszelle, welche ein rekombinantes humanes MC-R1B-Protein exprimiert, wobei die Wirtszelle den Expressi-

onsvektor nach Anspruch 5 enthält.

9. . Wirtszelle, welche ein rekombinantes humanes MC-R1B-Protein exprimiert, wobei die Wirtszelle den Expressionsvektor nach Anspruch 6 enthält.

10. . Wirtszelle nach Anspruch 7, wobei das humane MC-R1B-Protein von dem Expressionsvektor überexprimiert wird.

11. . Wirtszelle nach Anspruch 8, wobei das humane MC-R1B-Protein von dem Expressionsvektor überexprimiert wird.

12. . Wirtszelle nach Anspruch 9, wobei das humane MC-R1B-Protein von dem Expressionsvektor überexprimiert wird.

13. . Subzelluläre Membranfraktion, erhalten aus der Wirtszelle nach Anspruch 10, wobei die Fraktion rekombinantes humanes MC-R1B-Protein enthält.

14. . Subzelluläre Membranfraktion, erhalten aus der Wirtszelle nach Anspruch 11, wobei die Fraktion rekombinantes humanes MC-R1B-Protein enthält.

15. . Subzelluläre Membranfraktion, erhalten aus der Wirtszelle nach Anspruch 12, wobei die Fraktion rekombinantes humanes MC-R1B-Protein enthält.

16. . Gereinigtes Nukleinsäuremolekül, codierend für ein humanes MC-R1B-Protein, wobei das Nukleinsäuremolekül für ein Protein codiert, das aus einer Aminosäuresequenz besteht, welche aus der Gruppe ausgewählt ist, die aus SEQ-ID-Nr. 2, SEQ-ID-Nr. 4, SEO-ID-Nr. 6, SEQ-ID-Nr. 8, SEQ-ID-Nr. 10, SEQ-ID-Nr. 12, SEQ-ID-Nr. 14, SEQ-ID-Nr. 17, SEQ-ID-Nr. 20, SEQ-ID-Nr. 23 und SEQ-ID-Nr. 26 besteht.

17. . Gereinigtes humanes Melanocortin 1-Rezeptorprotein, das eine carboxyterminale Aminosäuredomäne wie in SEQ-ID-Nr. 27 angegeben umfasst.

18. . Gereinigtes humanes Melanocortin 1-Rezeptorprotein nach Anspruch 17, das die Aminosäuresequenz umfasst, welche aus der Gruppe ausgewählt ist, die aus SEQ-ID-Nr. 2, SEQ-ID-Nr. 4, SEQ-ID-Nr. 6, SEQ-ID-Nr. 8, SEQ-ID-Nr. 10, SEQ-ID-Nr. 12, SEQ-ID-Nr. 14, SEQ-ID-Nr. 17, SEQ-ID-Nr. 20, SEQ-ID-Nr. 23 und SEQ-ID-Nr. 26 besteht.

19. . Verfahren zur Feststellung, ob eine Substanz zur Bindung an humanes MC-R1B in der Lage ist, umfassend:

- . (a) Bereitstellen von Testzellen durch Transfektion von Zellen mit einem Expressionsvektor nach Anspruch 4;
- . (b) Aussetzen der Testzellen der Substanz;
- . (c) Messen des Ausmaßes der Bindung der Substanz an MC-R1B;
- . (d) Vergleichen des Ausmaßes der Bindung der Substanz an MC-R1B in den Testzellen mit dem Ausmaß der Bindung der Substanz an Kontrollzellen, die nicht mit MC-R1 B transfiziert wurden.

20. . Verfahren zur Feststellung, ob eine Substanz zur Aktivierung von MC-R1 B in der Lage ist, umfassend:

- . (a) Bereitstellen von Testzellen durch Transfektion von Zellen mit einem Expressionsvektor nach Anspruch 4;
- . (b) Aussetzen der Testzellen der Substanz;
- . (c) Messen des Menge von akkumuliertem intrazellulären cAMP;
- . (d) Vergleichen der Menge von cAMP in den Testzellen als Reaktion auf die Substanz mit der Menge von cAMP in Testzellen, die nicht der Substanz ausgesetzt wurden.

21. . Verfahren zur Identifizierung einer Substanz, welche MC-R1B-Rezeptoraktivität moduliert, umfassend:

- . (a) Kombinieren einer Testsubstanz in Anwesenheit und Abwesenheit eines MC-R1B-Rezeptorproteins, wobei das MC-R1B-Rezeptorprotein die Aminosäuresequenz umfasst, welche aus der Gruppe ausgewählt ist, die aus SEQ-ID-Nr. 2, SEQ-ID-Nr. 4, SEQ-ID-Nr. 6, SEQ-ID-Nr. 8, SEQ-ID-Nr. 10, SEQ-ID-Nr. 12, SEQ-ID-Nr. 14, SEQ-ID-Nr. 17, SEQ-ID-Nr. 20, SEQ-ID-Nr. 23 und SEQ-ID-Nr. 26 besteht; und
- . (b) Messen und Vergleichen der Wirkung der Testsubstanz in Anwesenheit und Abwesenheit des MC-R1B-Rezeptorproteins.

22. . Verfahren zur Feststellung, ob eine Substanz ein potentieller Agonist oder Antagonis von MC-R1 B ist, umfassend:

. (a) Transfizieren oder Transformieren von Zellen mit einem Expressionsvektor nach Anspruch 4, der die Expression von MC-R1B in den Zellen steuert, welches Testzellen ergibt;
. (b) Wachsen lassen der Testzellen für einen ausreichenden Zeitraum, um die Expression von MC-R1B zu erlauben;
. (c) Aussetzen der Zellen einem markierten Liganden von MC-R1B in Anwesenheit und in Abwesenheit der Substanz;
. (d) Messen der Bindung des markierten Liganden an MC-R1B;

wobei die Substanz ein potentieller Agonist oder Antagonist von MC-R1B ist, wenn das Ausmaß der Bindung des markierten Liganden in Anwesenheit der Substanz geringer ist als in Abwesenheit der Substanz.

23. . Verfahren zur Feststellung, ob eine Substanz zur Bindung an MC-R1B in der Lage ist, umfassend:

. (a) Transfizieren oder Transformieren von Zellen mit einem Expressionsvektor nach Anspruch 4, der die Expression von MC-R1B in den Zellen steuert, welches Testzellen ergibt;
. (b) Aussetzen der Testzellen der Substanz;
. (c) Messen des Ausmaßes der Bindung der Substanz an MC-R1B;
. (d) Vergleichen des Ausmaßes der Bindung der Substanz an MC-R1B in den Testzellen mit dem Ausmaß der Bindung der Substanz an Kontrollzellen, die nicht mit MC-R1B transfiziert wurden;

wobei die Substanz zur Bindung an MC-R1B in der Lage ist, wenn das Ausmaß der Bindung der Substanz in den Testzellen größer als in den Kontrollzellen ist.

24. . Verfahren zur Feststellung, ob eine Substanz zur Bindung an MC-R1B in der Lage ist, umfassend:

. (a) Transfizieren oder Transformieren von Zellen mit einem Expressionsvektor nach Anspruch 4, der die Expression von MC-R1B in den Zellen steuert, welches Testzellen ergibt;
. (b) Herstellen von Membranen, die MC-R1B enthalten, aus den Testzellen und Aussetzen der Membranen einem Liganden von MC-R1B unter solchen Bedingungen, dass der Ligand an das MC-R1B in den Membranen bindet;
. (c) nach oder gleichzeitig mit Schritt (b) Aussetzen der Membranen aus den Testzellen einer Substanz;
. (d) Messen des Ausmaßes der Bindung des Liganden an das MC-R1B in den Membranen in Anwesenheit und Abwesenheit der Substanz;
. (e) Vergleichen des Ausmaßes der Bindung des Liganden an MC-R1B in den Membranen in Anwesenheit und Abwesenheit der Substanz, wobei eine Abnahme des Ausmaßes der Bindung des Liganden an MC-R1B in den Membranen in Anwesenheit der Substanz anzeigt, dass die Substanz zur Bindung an MC-R1B in der Lage ist.

25. . Verfahren zur Feststellung, ob eine Substanz zur Bindung an MC-R1B in der Lage ist, umfassend:

. (a) Transfizieren oder Transformieren von Zellen mit einem Expressionsvektor nach Anspruch 4, der die Expression von MC-R1B in den Zellen steuert, welches Testzellen ergibt;
. (b) Herstellen von Membranen, die MC-R1B enthalten, aus den Testzellen und Aussetzen der Membranen aus den Testzellen der Substanz;
. (c) Messen des Ausmaßes der Bindung der Substanz an das MC-R1B in den Membranen aus den Testzellen;
. (d) Vergleichen des Ausmaßes der Bindung der Substanz an MC-R1B in den Membranen aus den Testzellen mit dem Ausmaß der Bindung der Substanz an Membranen aus Kontrollzellen, die nicht mit MC-R1B transfiziert wurden, wobei die Substanz zur Bindung an MC-R1B in der Lage ist, wenn das Ausmaß der Bindung der Substanz an MC-R1B in den Membranen aus den Testzellen größer als das Ausmaß der Bindung der Substanz an die Membranen aus den Kontrollzellen ist.

26. . Verfahren zur Identifizierung von Agonisten von MC-R1B, umfassend:

. (a) Transfizieren oder Transformieren von Zellen mit einem ersten Expressionsvektor nach Anspruch 4, der die Expression von MC-R1B steuert, und einem zweiten Expressionsvektor, der die Expression eines promiskuitiven G-Proteins steuert, welches Testzellen ergibt;
. (b) Aussetzen der Testzellen einer Substanz, die ein mutmaßlicher Agonist von MC-R1B ist;
. (c) Messen des Niveaus von Inositphosphaten in den Zellen;

wobei eine Erhöhung des Niveaus von Inositphosphaten in den Zellen im Vergleich zu dem Niveau von Inositptiosphaten in den Zellen in Abwesenheit des mutmaßlichen Agonisten anzeigt, dass die Substanz ein Agonist von MC-R1B ist.

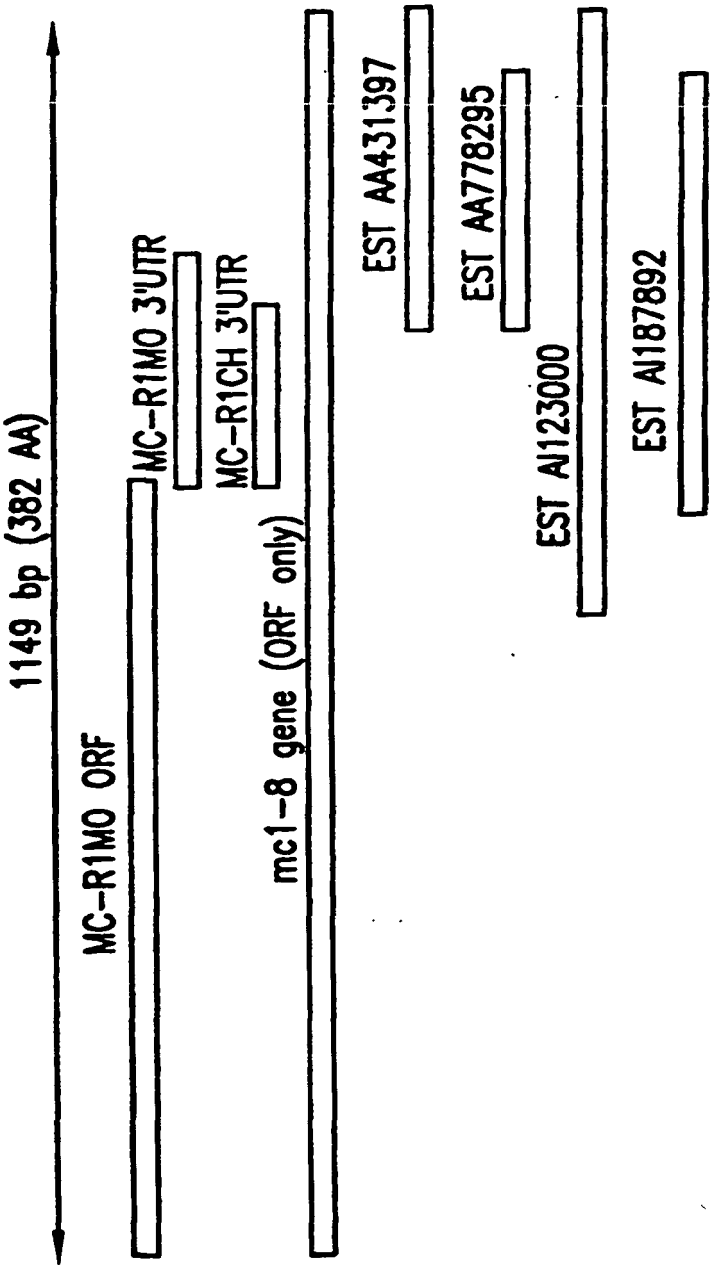
27. . Verfahren zur Identifizierung von Antagonisten von MC-R1B, umfassend:

. (a) Transfizieren oder Transformieren von Zellen mit einem ersten Expressionsvektor nach Anspruch 4, der die Expression von MC-R1B steuert, und einem zweiten Expressionsvektor, der die Expression eines promiskuitiven G-Proteins steuert, welches Testzellen ergibt;
. (b) Aussetzen der Testzellen einer Substanz, die ein Agonist von MC-R1B ist;
. (c) nach oder gleichzeitig mit Schritt (b) Aussetzen der Testzellen einer Substanz, die ein mutmaßlicher Antagonist von MC-R1B ist;
. (d) Messen des Niveaus von Inositphosphaten in den Zellen;

wobei eine Abnahme des Niveaus von Inositphosphaten in den Zellen in Anwesenheit des mutmaßlichen Antagonisten im Vergleich zu dem Niveau von Inositphosphaten in den Zellen in Abwesenheit des mutmaßlichen Antagonisten anzeigt, dass die Substanz ein Antagonist von MC-R1B ist.

28. . Verfahren zur Identifizierung von Antagonisten von MC-R1B nach Anspruch 27, wobei die ersten und zweiten Expressionsvektoren von Schritt (a) durch einen einzigen Expressionsvektor ersetzt sind, welcher ein chimäres MC-R1B-Protein exprimiert, das an seinem C-Terminus mit einem promiskuitiven G-Protein fusioniert ist.

29. . Antikörper, der spezifisch an ein MC-R1B-Protein bindet, wobei das MC-R1B-Rezeptorprotein die Aminosäuresequenz umfasst, welche aus der Gruppe ausgewählt ist, die aus SEO-ID-Nr. 2, SEQ-ID-Nr. 4, SEQ-ID-Nr. 6, SEQ-ID-Nr. 8, SEQ-ID-Nr. 10, SEQ-ID-Nr. 12, SEQ-ID-Nr. 14, SEQ-ID-Nr. 17, SEQ-ID-Nr. 20, SEQ-ID-Nr. 23 und SEQ-ID-Nr. 26 besteht.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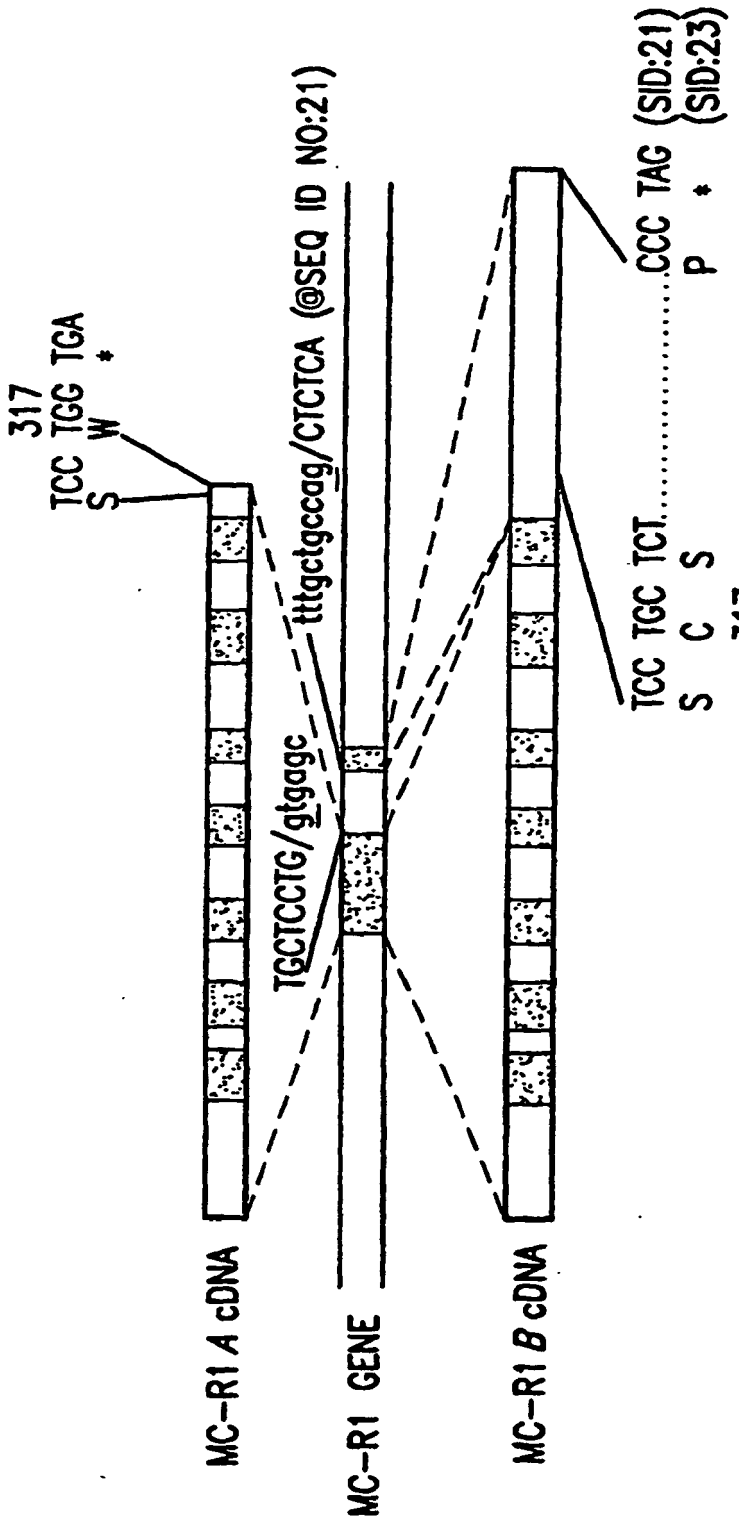
MC-R1MO ORF
MC-R1MO 3'UTR
MC-R1CH 3'UTR
mc1-8 gene (ORF only)
EST AA431397
EST AA778295
EST AI123000
EST AI187892

FIG.1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S W *
TGCTCCTG/gtgagc
tttgctgccag/CTCTCA (@SEQ ID NO:21)
TCC TGC TCT.....CCC TAG (SID:21)
S C S P * (SID:23)
317
MC-R1 A cDNA
MC-R1 GENE
MC-R1 B cDNA

FIG.2

ATGGCTGTGC AGGGATCCCA GAGAAGACTT CTGGGCTCCC TCAACTCCAC CCCCACAGCC ATCCCCCAGC
TGGGGCTGGC TGCCAACCAG ACAGGAGCCC GGTGCCTGGA GGTGTCCATC TCTGACGGGC TCTTCCTCAG
CCTGGGGCTG GTGAGCTTGG TGGAGAACGC GCTGGTGGTG GCCACCATCG CCAAGAACCG GAACCTGCAC
TCACCCATGT ACTGCTTCAT CTGCTGCCTG GCCTTGTCGG ACCTGCTGGT GAGCGGGAGC AACGTGCTGG
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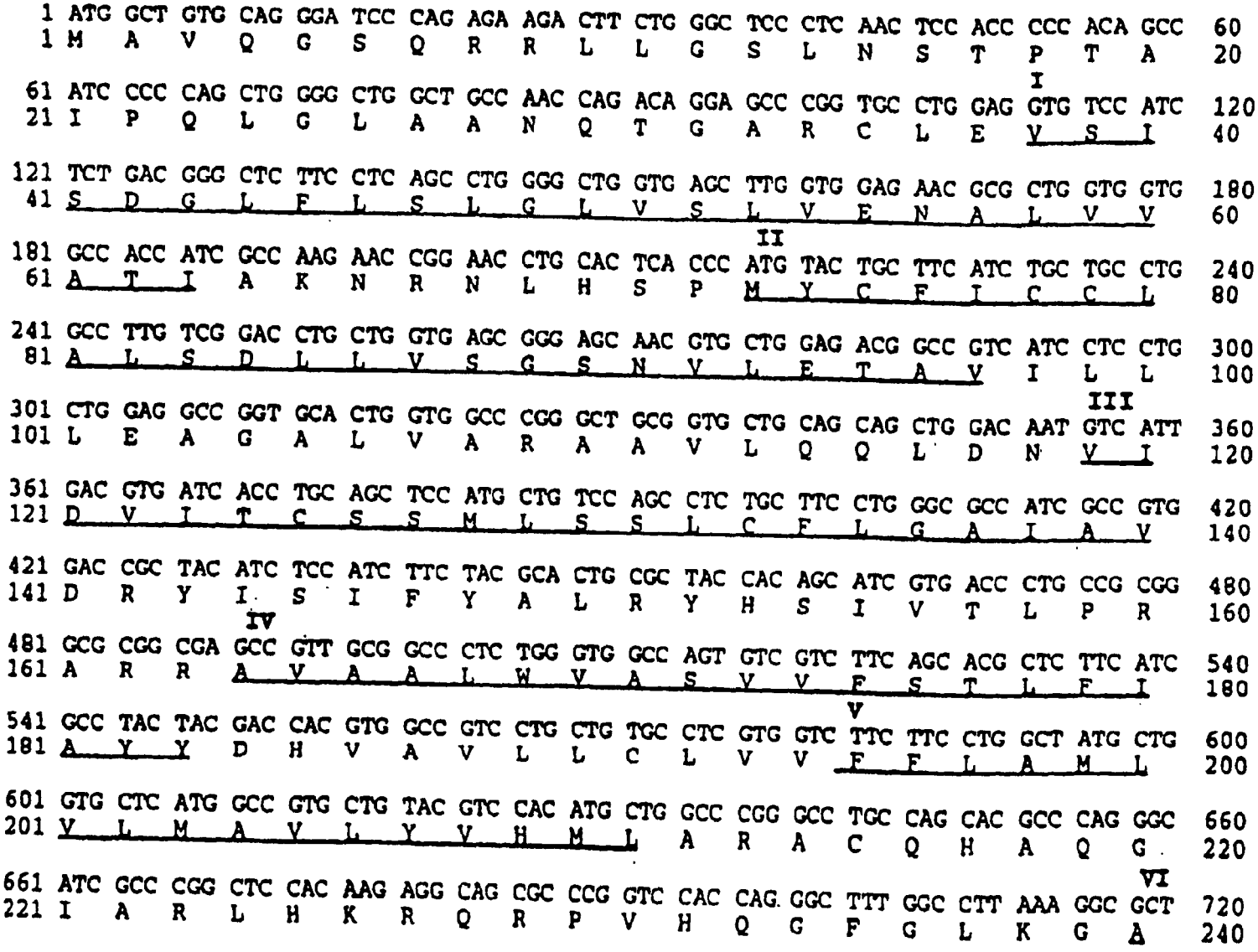
FIG.3

EP 1 140 968 B9 (W1B1)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1 M A V Q G S Q R R L L G S L N S T P T A 20
I
61 ATC CCC CAG CTG GGG CTG GCT GCC AAC CAG ACA GGA GCC CGG TGC CTG GAG GTG TCC ATC 120
21 I P Q L G L A A N Q T G A R C L E V S I 40
121 TCT GAC GGG CTC TTC CTC AGC CTG GGG CTG GTG AGC TTG GTG GAG AAC GCG CTG GTG GTG 180
41 S D G L F L S L G L V S L V E N A L V V 60
II
181 GCC ACC ATC GCC AAG AAC CGG AAC CTG CAC TCA CCC ATG TAC TGC TTC ATC TGC TGC CTG 240
61 A T I A K N R N L H S P M Y C F I C C L 80
241 GCC TTG TCG GAC CTG CTG GTG AGC GGG AGC AAC GTG CTG GAG ACG GCC GTC ATC CTC CTG 300
81 A L S D L L V S G S N V L E T A V I L L 100
III
301 CTG GAG GCC GGT GCA CTG GTG GCC CGG GCT GCG GTG CTG CAG CAG CTG GAC AAT GTC ATT 360
101 L E A G A L V A R A A V L Q Q L D N V I 120
361 GAC GTG ATC ACC TGC AGC TCC ATG CTG TCC AGC CTC TGC TTC CTG GGC GCC ATC GCC GTG 420
121 D V I T C S S M L S S L C F L G A I A V 140
421 GAC CGC TAC ATC TCC ATC TTC TAC GCA CTG CGC TAC CAC AGC ATC GTG ACC CTG CCG CGG 480
141 D R Y I S I F Y A L R Y H S I V T L P R 160
IV
481 GCG CGG CGA GCC GTT GCG GCC CTC TGG GTG GCC AGT GTC GTC TTC AGC ACG CTC TTC ATC 540
161 A R R A V A A L W V A S V V F S T L F I 180
V
541 GCC TAC TAC GAC CAC GTG GCC GTC CTG CTG TGC CTC GTG GTC TTC TTC CTG GCT ATG CTG 600
181 A Y Y D H V A V L L C L V V F F L A M L 200
601 GTG CTC ATG GCC GTG CTG TAC GTC CAC ATG CTG GCC CGG GCC TGC CAG CAC GCC CAG GGC 660
201 V L M A V L Y V H M L A R A C Q H A Q G 220
VI
661 ATC GCC CGG CTC CAC AAG AGG CAG CGC CCG GTC CAC CAG GGC TTT GGC CTT AAA GGC GCT 720
221 I A R L H K R Q R P V H Q G F G L K G A 240

FIG.4A

```
721 GTC ACC CCC ACC ATC CTG CTG GGC ATT TTC TTC CTC TGC TGG GGC CCC TTC TTC CTG CAT  780
241 V   T   P   T   I   L   L   G   I   F   F   L   C   W   G   P   F   F   L   H    260
                                                                          VII

781 CTC ACA CTC ATC GTC CTC TGC CCC GAG CAC CCC ACG TGC GGC TGC ATC TTC AAG AAC TTC  840
261 L   T   L   I   V   L   C   P   E   H   P   T   C   G   C   I   F   K   N   F    280

841 AAC CTC TTT CTC GCC CTC ATC ATC TGC AAT GCC TTC ATC GAC CCC CTC ATC TAC GCC TTC  900
281 N   L   F   L   A   L   I   I   C   N   A   F   I   D   P   L   I   Y   A   F    300

901 CAC AGC CAG GAG CTC CGC AGG ACG CTC AAG GAG GTG CTG ACA TGC TCC TG/gt...ag/CT
301 H   S   Q   E   L   R   R   T   L   K   E   V   L   T   C   S                    316
```

MC-R1 *form A*

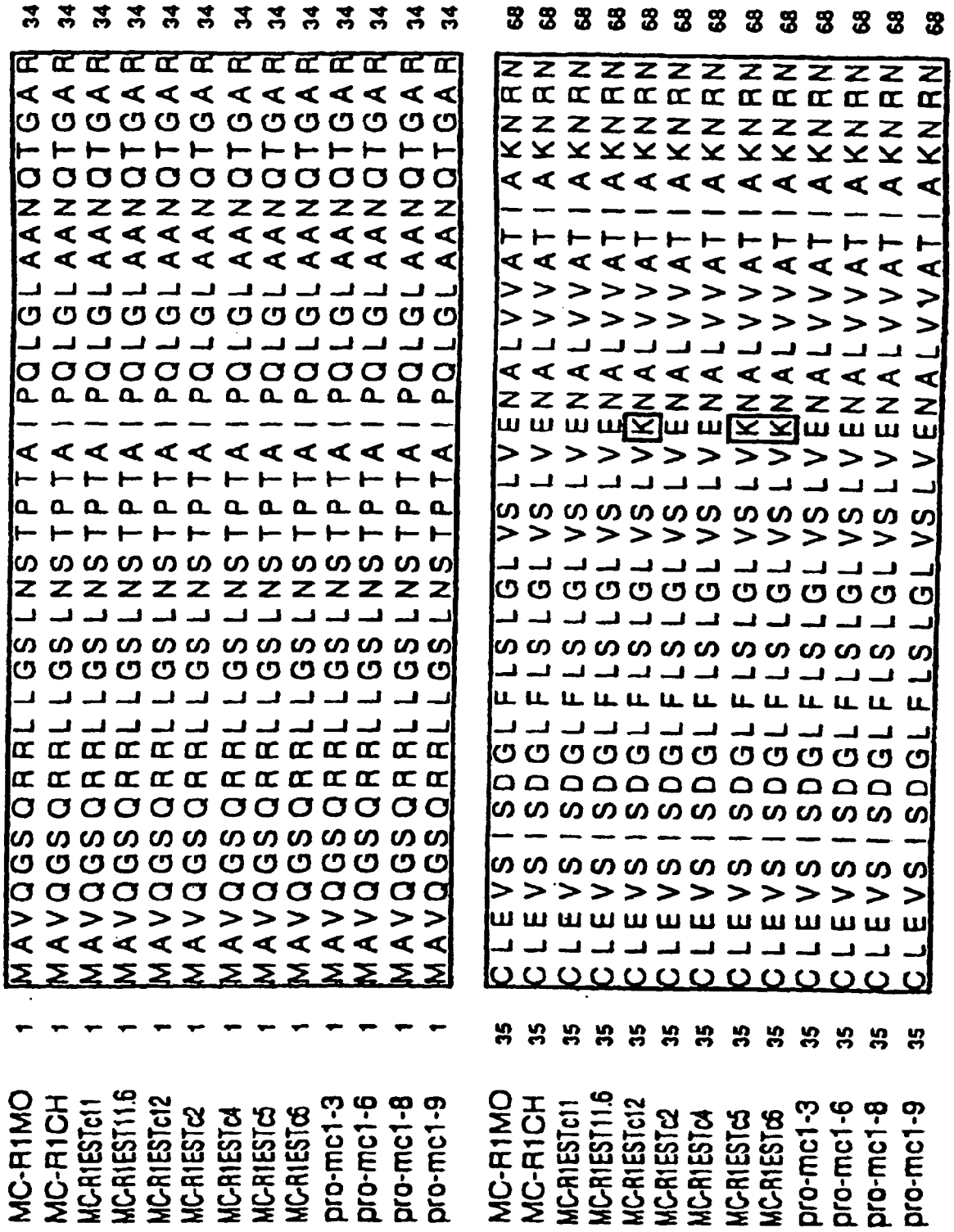
```
    TGG TGA  (SEQ ID NO:45)
317 W   *    (SEQ ID NO:46)
```

MC-R1 *form B*

```
    TGC TCT CAG GAC CGT GCC CTC GTC AGC TGG GAT GTG AAG TCT CTG GGT GGA AGT GTG TGC
317 C   S   Q   D   R   A   L   V   S   W   D   V   K   S   L   G   G   S   V   C

    CAA GAG CTA CTC CCA CAG CAG CCC CAG GAG AAG GGG CTT TGT GAC CAG AAA GCT TCA TCC
337 Q   E   L   L   P   Q   Q   P   Q   E   K   G   L   C   D   Q   K   A   S   S

    ACA GCC TTG CAG CGG CTC CTG CAA AAG GAG GTG AAA TCC CTG CCT CAG GCC AAG GGA CCA
357 T   A   L   Q   R   L   L   Q   K   E   V   K   S   L   P   Q   A   K   G   P

    GGT TTG CAG GAG CCC CCC TAG      (SEQ ID NO:21)
377 G   L   Q   E   P   P   *  382  (SEQ ID NO:23)
```

FIG.4B

EP 1 140 968 B9 (W1B1)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MC-R1ESTc4 1 MAVQGSQRRLLGSLNSTPTAIPQLGLAANQTGAR 34
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pro-mc1-8 1 MAVQGSQRRLLGSLNSTPTAIPQLGLAANQTGAR 34
pro-mc1-9 1 MAVQGSQRRLLGSLNSTPTAIPQLGLAANQTGAR 34
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MC-R1CH 35 CLEVSISDGLFLSLGLVSLVENALVVATIAKNRN 68
MC-R1ESTc11 35 CLEVSISDGLFLSLGLVSLVENALVVATIAKNRN 68
MC-R1EST11.6 35 CLEVSISDGLFLSLGLVSLVENALVVATIAKNRN 68
MC-R1ESTc12 35 CLEVSISDGLFLSLGLVSLVKNALVVATIAKNRN 68
MC-R1ESTc2 35 CLEVSISDGLFLSLGLVSLVENALVVATIAKNRN 68
MC-R1ESTc4 35 CLEVSISDGLFLSLGLVSLVENALVVATIAKNRN 68
MC-R1ESTc5 35 CLEVSISDGLFLSLGLVSLVKNALVVATIAKNRN 68
MC-R1ESTc6 35 CLEVSISDGLFLSLGLVSLVKNALVVATIAKNRN 68
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pro-mc1-8 35 CLEVSISDGLFLSLGLVSLVENALVVATIAKNRN 68
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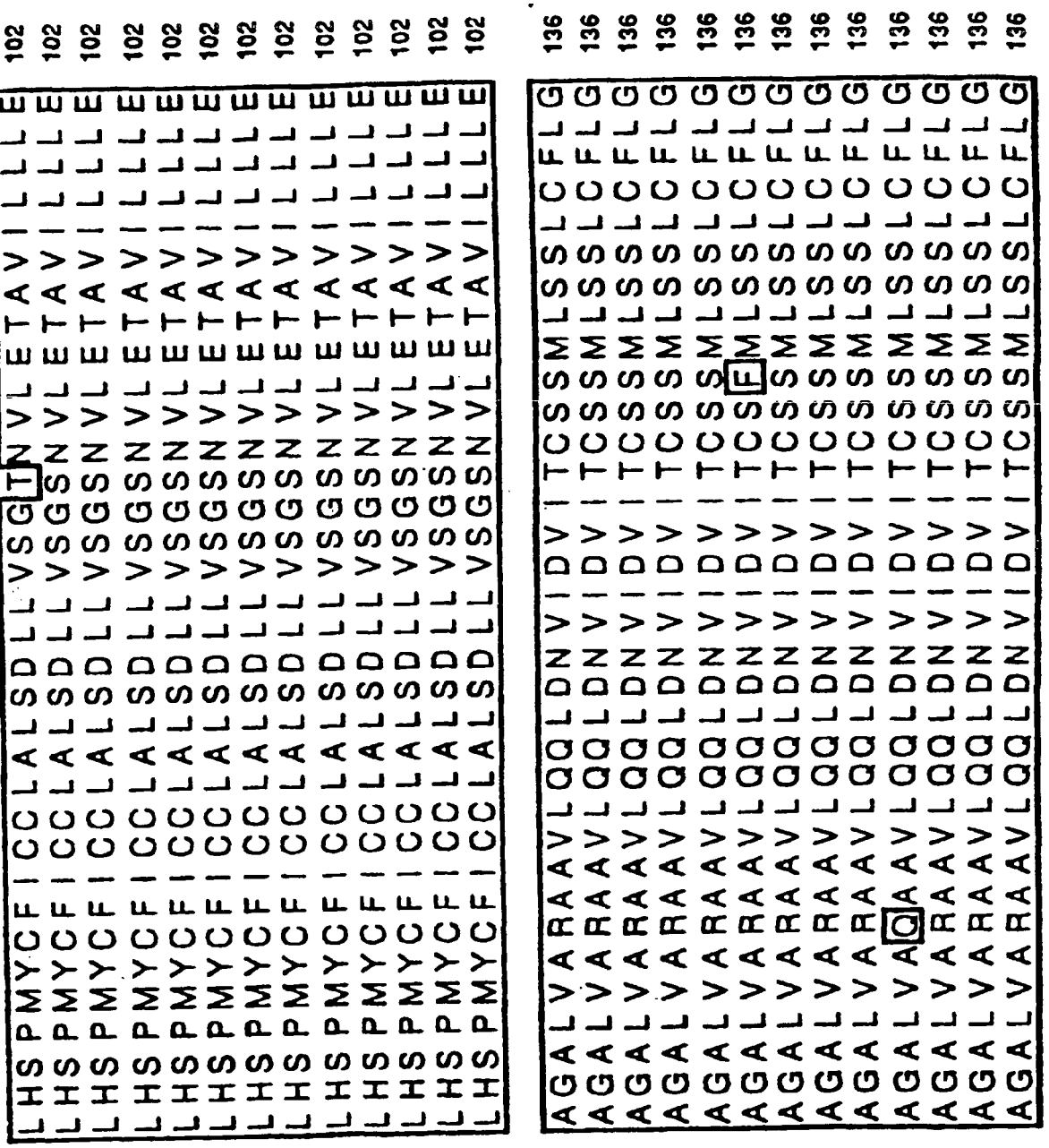
FIG.5A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pro-mc1-8 69 LHSPMYCFICCLALSDLLVSGGSNVLETAVILLLE 102
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MC-R1CH 103 AGALVARAAVLQQLDNVIDVITCSSMLSSLCFLG 136
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MC-R1ESTc12 103 AGALVARAAVLQQLDNVIDVITCSSFMLSSLCFLG 136
MC-R1ESTc2 103 AGALVARAAVLQQLDNVIDVITCSSMLSSLCFLG 136
MC-R1ESTc4 103 AGALVARAAVLQQLDNVIDVITCSSMLSSLCFLG 136
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MC-R1ESTc6 103 AGALVARAAVLQQLDNVIDVITCSSMLSSLCFLG 136
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pro-mc1-6 103 AGALVARAAVLQQLDNVIDVITCSSMLSSLCFLG 136
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FIG.5B

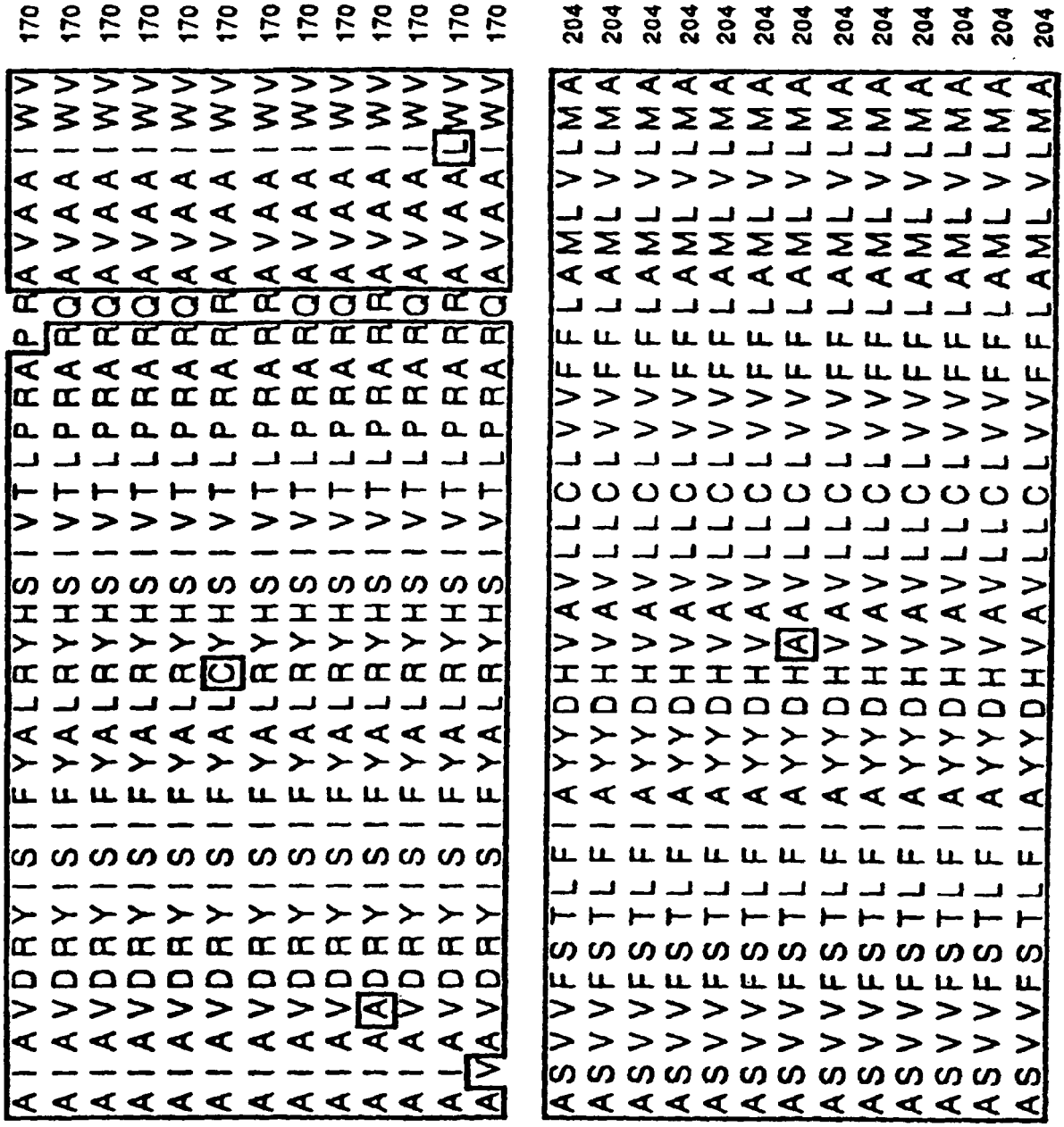
MC-R1MO 137 AIAVDRYISIFYALRYHSIVTLPRAPRAVAAIWV 170
MC-R1CH 137 AIAVDRYISIFYALRYHSIVTLPRARQAVAAIWV 170
MC-R1ESTc11 137 AIAVDRYISIFYALRYHSIVTLPRARQAVAAIWV 170
MC-R1EST11.6 137 AIAVDRYISIFYALRYHSIVTLPRARQAVAAIWV 170
MC-R1ESTc12 137 AIAVDRYISIFYALRYHSIVTLPRARQAVAAIWV 170
MC-R1ESTc2 137 AIAVDRYISIFYALCYHSIVTLPRARRAVAAIWV 170
MC-R1ESTc4 137 AIAVDRYISIFYALRYHSIVTLPRARRAVAAIWV 170
MC-R1ESTc5 137 AIAVDRYISIFYALRYHSIVTLPRARQAVAAIWV 170
MC-R1ESTc6 137 AIAVDRYISIFYALRYHSIVTLPRARQAVAAIWV 170
pro-mc1-3 137 AIADDRYISIFYALRYHSIVTLPRARRAVAALWV 170
pro-mc1-6 137 AIAVDRYISIFYALRYHSIVTLPRARQAVAAIWV 170
pro-mc1-8 137 AIAVDRYISIFYALRYHSIVTLPRARRAVAALWV 170
pro-mc1-9 137 AVADRYISIFYALRYHSIVTLPRARQAVAAIWV 170
MC-R1MO 171 ASVVFSTLFIAYYDHVAVLLCLVVFFLAMLVLMA 204
MC-R1CH 171 ASVVFSTLFIAYYDHVAVLLCLVVFFLAMLVLMA 204
MC-R1ESTc11 171 ASVVFSTLFIAYYDHVAVLLCLVVFFLAMLVLMA 204
MC-R1EST11.6 171 ASVVFSTLFIAYYDHVAVLLCLVVFFLAMLVLMA 204
MC-R1ESTc12 171 ASVVFSTLFIAYYDHVAVLLCLVVFFLAMLVLMA 204
MC-R1ESTc2 171 ASVVFSTLFIAYYDHVAVLLCLVVFFLAMLVLMA 204
MC-R1ESTc4 171 ASVVFSTLFIAYYDHAAVLLCLVVFFLAMLVLMA 204
MC-R1ESTc5 171 ASVVFSTLFIAYYDHVAVLLCLVVFFLAMLVLMA 204
MC-R1ESTc6 171 ASVVFSTLFIAYYDHVAVLLCLVVFFLAMLVLMA 204
pro-mc1-3 171 ASVVFSTLFIAYYDHVAVLLCLVVFFLAMLVLMA 204
pro-mc1-6 171 ASVVFSTLFIAYYDHVAVLLCLVVFFLAMLVLMA 204
pro-mc1-8 171 ASVVFSTLFIAYYDHVAVLLCLVVFFLAMLVLMA 204
pro-mc1-9 171 ASVVFSTLFIAYYDHVAVLLCLVVFFLAMLVLMA 204

FIG.5C

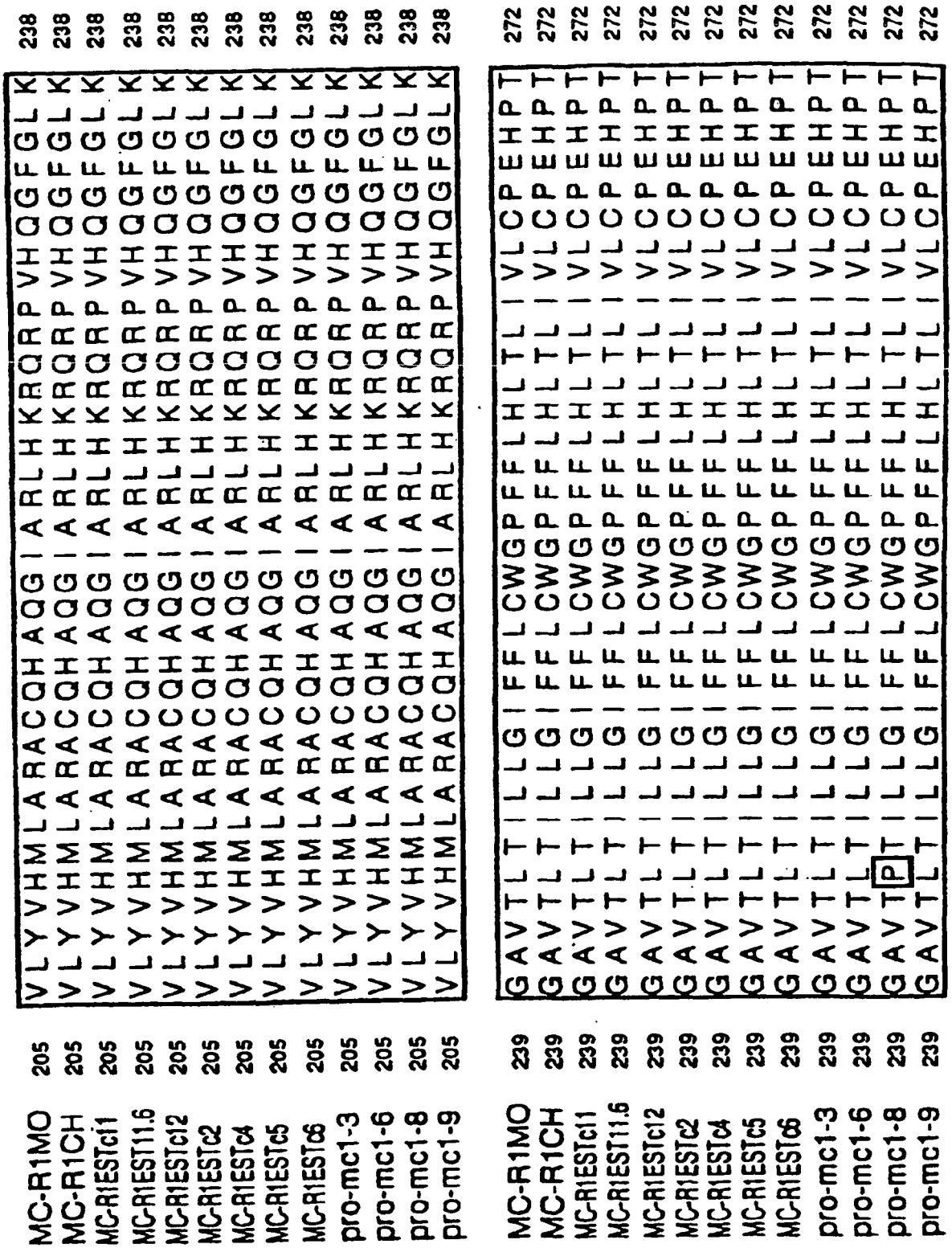
MC-R1MO 205 VLYVHMLARACQHAQGIARLHKRQRPVHQGFGLK 238
MC-R1CH 205 VLYVHMLARACQHAQGIARLHKRQRPVHQGFGLK 238
MC-R1ESTc11 205 VLYVHMLARACQHAQGIARLHKRQRPVHQGFGLK 238
MC-R1EST11.6 205 VLYVHMLARACQHAQGIARLHKRQRPVHQGFGLK 238
MC-R1ESTc12 205 VLYVHMLARACQHAQGIARLHKRQRPVHQGFGLK 238
MC-R1ESTc2 205 VLYVHMLARACQHAQGIARLHKRQRPVHQGFGLK 238
MC-R1ESTc4 205 VLYVHMLARACQHAQGIARLHKRQRPVHQGFGLK 238
MC-R1ESTc5 205 VLYVHMLARACQHAQGIARLHKRQRPVHQGFGLK 238
MC-R1ESTc6 205 VLYVHMLARACQHAQGIARLHKRQRPVHQGFGLK 238
pro-mc1-3 205 VLYVHMLARACQHAQGIARLHKRQRPVHQGFGLK 238
pro-mc1-6 205 VLYVHMLARACQHAQGIARLHKRQRPVHQGFGLK 238
pro-mc1-8 205 VLYVHMLARACQHAQGIARLHKRQRPVHQGFGLK 238
pro-mc1-9 205 VLYVHMLARACQHAQGIARLHKRQRPVHQGFGLK 238
MC-R1MO 239 GAVTLTILLGIFFLCWGPFFLHLTLIVLCPEHPT 272
MC-R1CH 239 GAVTLTILLGIFFLCWGPFFLHLTLIVLCPEHPT 272
MC-R1ESTc11 239 GAVTLTILLGIFFLCWGPFFLHLTLIVLCPEHPT 272
MC-R1EST11.6 239 GAVTLTILLGIFFLCWGPFFLHLTLIVLCPEHPT 272
MC-R1ESTc12 239 GAVTLTILLGIFFLCWGPFFLHLTLIVLCPEHPT 272
MC-R1ESTc2 239 GAVTLTILLGIFFLCWGPFFLHLTLIVLCPEHPT 272
MC-R1ESTc4 239 GAVTLTILLGIFFLCWGPFFLHLTLIVLCPEHPT 272
MC-R1ESTc5 239 GAVTLTILLGIFFLCWGPFFLHLTLIVLCPEHPT 272
MC-R1ESTc6 239 GAVTLTILLGIFFLCWGPFFLHLTLIVLCPEHPT 272
pro-mc1-3 239 GAVTLTILLGIFFLCWGPFFLHLTLIVLCPEHPT 272
pro-mc1-6 239 GAVTLTILLGIFFLCWGPFFLHLTLIVLCPEHPT 272
pro-mc1-8 239 GAVTPTILLGIFFLCWGPFFLHLTLIVLCPEHPT 272
pro-mc1-9 239 GAVTLTILLGIFFLCWGPFFLHLTLIVLCPEHPT 272

FIG.5D

MC-R1MO	273	CGCIFKNFNLFLALIICNAIIDPLIYAFHSQELR	306
MC-R1CH	273	CGCIFKNFNLFLALIICNAIIDPLIYAFHSQELR	306
MC-R1ESTc11	273	CGCIFKNFNLFLALIICNAIIDPLIYAFHSQELR	306
MC-R1EST11.6	273	CGCIFKNFNLFLALIICNAIIDPLIYAFHSQELR	306
MC-R1ESTc12	273	CGCIFKNFNLFLALIICNAIIDPLIYAFHSQELR	306
MC-R1ESTc2	273	CGCIFKNFNLFLALIICNAIIDPLIYAFHSQELR	306
MC-R1ESTc4	273	CGCIFKNFNLFLALIICNAIIDPLIYAFHSQELR	306
MC-R1ESTc5	273	CGCIFKNFNLFLALIICNAIIDPLIYAFHSQELR	306
MC-R1ESTc6	273	CGCIFKNFNLFLALIICNAIIDPLIYAFHSQELR	306
pro-mc1-3	273	CGCIFKNFNLFLALIICNAIIDPLIYAFHSQELR	306
pro-mc1-6	273	CGCIFKNFNLFLALIICNAIIDPLIYAFHSQELR	306
pro-mc1-8	273	CGCIFKNFNLFLALIICNAFIDPLIYAFHSQELR	306
pro-mc1-9	273	CGCIFKNFNLFLAPIICNAIIDPLIYAFHSQELR	306

MC-R1MO	307	RTLKEVLTCSW SEQ ID NO:43	317
MC-R1CH	307	RTLKEVLTCSW SEQ ID NO:44	317
MC-R1ESTc11	307	RTLKEVLTCSCSQDRALVSWDVKSLGGSVCQELL	340
MC-R1EST11.6	307	RTLKEVLTCSCSQDRALVSWDVKSLGGSVCQELL	340
MC-R1ESTc12	307	RTLKEVLTCSCSQDRALVSWDVKSLGGSVCQELL	340
MC-R1ESTc2	307	RTLKEVLTCSCSQDRALVSWDVKSLGGSVCQELL	340
MC-R1ESTc4	307	RTLKEVLTCSCSQDRALVSWDVKSLGGSVCQERL	340
MC-R1ESTc5	307	RTLKEVLTCSCSQDRALVSWDVKSLGGSVCQELL	340
MC-R1ESTc6	307	RTLKEVLTCSCSQDRALVSWDVKSLGGSVCQELL	340
pro-mc1-3	307	RTLKEVLTCSCSQDRALVSWDVKSLGGSVCQELL	340
pro-mc1-6	307	RTLKEVLTCSRSQDRALVSWDVKSLGGSVCQELL	340
pro-mc1-8	307	RTLKEVLTCSCSQDRALVSWDVKSLGGSVCQELL	340
pro-mc1-9	307	RTLKEVLTCSCSQDRALVSWDVKSLGGSVCQELL	340

FIG.5E

MC-R1ESTc11	341	PQQPQEKGPCDQKASSTALQRLLQKEVKSLPQAK	374
MC-R1EST11.6	341	PQQPQEKGLCDQKASSTALQRLLQKEVKSLPQAK	374
MC-R1ESTc12	341	PQQPQEKGLCDQKASSTALQRLLQKEVKSLPQAK	374
MC-R1ESTc2	341	PQQPQEKGLCDQKASSTALQRLLQKEVKSLPQAK	374
MC-R1ESTc4	341	PQQPQEKGLCDQKASSTALQRLLQKGVKSLPQAK	374
MC-R1ESTc5	341	PQQPQEKGLCDQKASSTALQRLLQKEVKSLPQAK	374
MC-R1ESTc6	341	PQQPQEKGLCDQKASSTALQRLLQKEVKSLPQAK	374
pro-mc1-3	341	PQQPQEKGLCDQKASSTALQRLLQKEVKSLPQAK	374
pro-mc1-6	341	PQQPQEKGLCDQKASSTALQRLLQKEVKSLPQAK	374
pro-mc1-8	341	PQQPQEKGLCDQKASSTALQRLLQKEVKSLPQAK	374
pro-mc1-9	341	PQQPQEKGLCDQKASSTALQRLLQKEVKSLPQAK	374

MC-R1ESTc11	375	GPGLQEPP	SEQ ID NO:2	382
MC-R1EST11.6	375	GPGLQEPP	SEQ ID NO:4	382
MC-R1ESTc12	375	GPGLQEPP	SEQ ID NO:6	382
MC-R1ESTc2	375	GPGLQEPP	SEQ ID NO:8	382
MC-R1ESTc4	375	GPGLQEPP	SEQ ID NO:10	382
MC-R1ESTc5	375	GPGLQEPP	SEQ ID NO:12	382
MC-R1ESTc6	375	GPGLQEPP	SEQ ID NO:14	382
pro-mc1-3	375	GPGLQEPP	SEQ ID NO:17	382
pro-mc1-6	375	GPGLQEPP	SEQ ID NO:20	382
pro-mc1-8	375	GPGLQEPP	SEQ ID NO:23	382
pro-mc1-9	375	GPGLQEPP	SEQ ID NO:26	382

FIG.5F